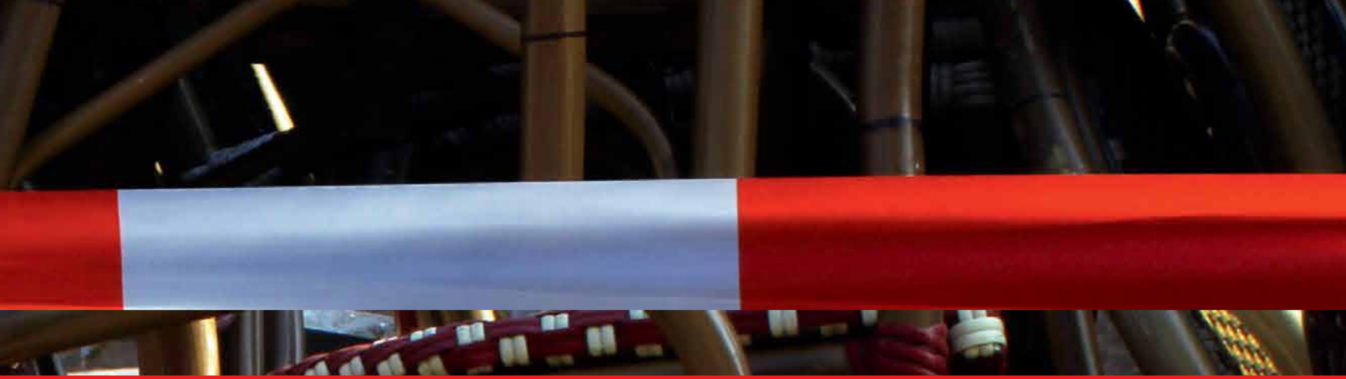

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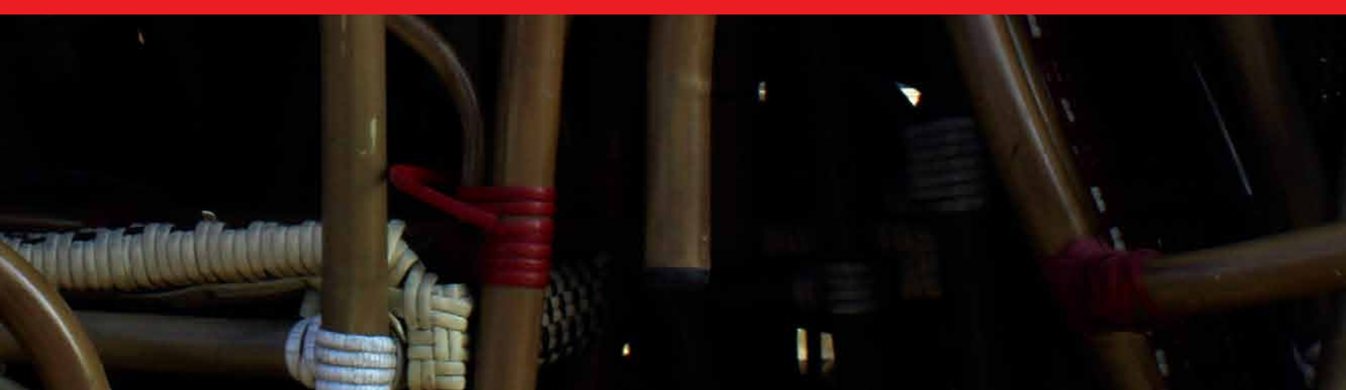

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Meet the editor

Márcia Aparecida Sperança is an associate professor at the Center for Natural and Human Sciences, Universidade Federal do ABC (UFABC), Brazil. After obtaining a Ph.D. in the Biology of Parasite–Host Interaction from the Parasitology Department, Biomedical Institute of the University of São Paulo, Brazil, Dr. Sperança worked as an assistant professor and researcher at Marilia Medical School, Brazil. Her scientific experience is in diagnosis, molecular biology, and epidemiology of arboviruses, the bacteria *Helicobacter pylori*, malaria parasites, Chagas disease, leishmaniasis, and COVID-19. Since 2009, Dr. Sperança has been the head of the Laboratory of Pathogenic Agents at UFABC, an institution with multi and interdisciplinary academic proposals.

Contents

Preface

Epidemics and pandemics, caused by infectious agents, constitute the greatest challenges to global public health, being an important factor in the evolution of societies throughout history, with repercussions on health, social, economic, and cultural policies [1]. The infectious agents that cause most epidemics and pandemics are the result of zoonoses, where animals are reservoirs of pathogenic agents or intermediate hosts. The emergence, re-emergence, and spread of these diseases are associated with disorderly urbanization, lack of basic sanitation, climate change, and environmental degradation.

Based on humanity's past experiences, different populations around the world have ways of identifying and preventing diseases transmitted by different types of microorganisms, transmitted through different routes. A classic example of learning after the occurrence of epidemic periods is the history of smallpox, a zoonotic disease that produced epidemic outbreaks for centuries, with high lethality wherever it went. In the 18th century, it was observed that people who milked cows and, at some point, had pustules on their hands caused by the *vaccinia virus* that infected cows, were not affected by smallpox. In 1796, Dr. Edward Jenner, based on this observation, carried out the classic experiment of injecting part of the lesion on the hand of a milkmaid infected with the *vaccinia virus* into a child's skin. After several days of mild smallpox symptoms, the child recovered and it was then that Dr. Jenner injected a human smallpox lesion into the skin of the same child who had no symptoms, demonstrating that he was protected. In this experiment, immunization was discovered, which was called vaccination, in honor of the use of the *vaccinia virus* [2].

Section 1 of this book includes three chapters that present a literature review and discuss epidemics and climate aspects, the relationship of epidemics with socio-cultural interactions, and health policies involving vaccines, which are the most effective means of infectious disease prevention. Section 2 includes two chapters that address the educational and preparedness aspects of zoonotic and viral diseases.

The new coronavirus SARS-CoV-2, which causes severe acute respiratory syndrome (SARS), known as COVID-19, is the most recent pandemic. Since its identification in China in December 2019, the virus has caused millions of cases and thousands of deaths worldwide. The structure of China's healthcare system allowed for rapid recognition of COVID-specific characteristics, whose etiological agent was identified using biotechnological tools, within a month. Following the identification of SARS-CoV-2, specific molecular diagnostic tests were developed and the forms of transmission and spread of the virus were also quickly described. SARS-CoV-2 is a coronavirus transmitted through the air from respiratory secretions. Clinical signs of COVID-19 during the early period of transmission in 2020 ranged from absence of symptoms to cough, runny nose, fever, body, and joint pain, and in the most serious cases, to a severe, potentially lethal, acute respiratory syndrome affecting the lungs. Maintenance of virus circulation due to different SARS-Cov-2 transmission control policies adopted across the globe, associated with a crescent number of asymptomatic infections and related to natural evolution of the virus and vaccine protection, contributed to a decrease in COVID-19 mortality. SARS-CoV-2 is the third emerging zoonotic coronavirus since 2002 when SARS-CoV emerged in China. In 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia [3]. Thus, there is a risk of new coronavirus emergence, and experiences in diagnosis, treatment, and control of this group of viruses are of great importance. Section 3 includes two chapters on the contribution of the COVID-19 pandemic on preparedness for future pandemics, and Section 4 includes two chapters on its prevention and treatment based on the acquired experience.

Social distancing is one control strategy for air-transmitted pathogens such as SARS-CoV-2. In a digitalized world, during the pandemic of the century, new tools have been developed for quality medical care and humanized guidance for people at a distance. Section 5 includes three chapters discussing digital devices for health care.

Epidemiological studies are of central importance to prevent diseases and Section 6 includes two chapters on an investigation of human and animal diseases considering epidemiological aspects and prevention.

I am grateful to all authors for their trust and important contributions and to IntechOpen for once more allowing me to serve as a book, contributing positively to public health worldwide.

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Section 1

Climate Society and Health

Chapter 1

Effects of Climate Change on Epidemic Propagation and Community Preparedness: A Review

Jaiye Dukiya

Abstract

Climate change is the twenty-first-century driver of global epidemic outbreak distribution. An early warning system for effective community preparedness is the antidote if the SDGs will not be a mirage. This study review adopted the search engine secondary method of data collection and descriptive content analysis in conjunction with the other in-depth interview survey reported by recent studies on climate change-induced health challenges and opinion survey on community participation in disease monitoring and control. Proper grassroots dissemination of climate change reality and the attendant intrusion of new diseases that are not amenable to existing medical and tradomedical approaches are imperative, hence the need for contingency planning by all the stakeholders. There is also the need to adopt real-time geospatial analysis techniques and environmental safeguard policy at all levels for disease monitoring and disseminating information to relevant policy makers and implementing agencies.

Keywords: climate change, community preparedness, disease monitoring, early warning, ecological changes, environmental safeguards, InVEST

1. Introduction

The issue of an epidemic outbreak is not new to the human race globally, while the phrase climate change has also become a domiciliary word, and even though the scientific definition seems even milder, its impacts across the world are disastrous, alarming, becoming frightening as its episodes are threatening the continuous existence of human race. Scientific research on its atmospheric variation over the past 50 years has shown a steady increase in atmospheric carbon dioxide (CO_2) due to anthropogenic activities. The observable verifications soar if the projected climate variables go above the bounds for which a country's operation is patterned. In that case, the least desirable environmental cataclysm demanding management and adaption will erupt [1]. The only problematic and shocking about the whole issue is the convincing assurance that anthropogenic phenomena warm and change the atmosphere more than any recorded modern history [2]. In fact, oxidized gases like nitrous oxide (N_2O) and even halocarbons have been substituted continually for chlorofluorocarbons (CFCs) in refrigerants in the atmosphere [3]. Regrettably, the agricultural sector happens to be one of the culprits that also exacerbates the GHG that propagates a series of epidemiologies in the face of resilient and unsustainable community health security across developing countries and sub-Saharan countries in particular. Hence, the need for the development of integrated global, national and community preparedness as advocated for by the WHO in the COVID-19 pandemic.

2. Review of literature

2.1 Concept of climate change and global warming

Climate change can be seen as the deviations that occur in the already established knowledge of the atmospheric condition of places over two to three decades. Researchers often use statistical approaches to ascertain whether changes in climate are not probably within the range of natural adjustment and mere coincidental; since the probability that the increase in atmospheric warming since 1950 is not occasioned by natural forces is less than one percent (1%). Climate change can be seen as a momentous long-range modification of the global climate as it relates to the interconnected system of the wind, sun, ocean, precipitations, general terrain and anthropogenic activities. The analysis of the global climate can be addressed using the cybernetics system-of-system approach, where the whole globe is seen as a single system. A change in the Land Surface Temperature (LST) in Yucon Territory that led to the glacial melting will eventually affect the Atlantic Ocean tidal rise and tsunami activities in the southern hemisphere. Again, the industrialization and over-dependence on fossil fuel of EU and USA is the bane of climate change and its attendant natural disaster in Africa and other developing countries.

Climate variability connotes a planetary system capricious in a climate that ranges in months and decades. Climate variability occasioned by the activities of atmospheric get streams like the inter tropical convergence zone (ITCZ) in the tropics and the El-Nino in regions of the world for more than 2 years are significant natural climate anomalies. Anthropologist, Biodiversity Conventions, and Sustainable Eco-developments uses global ecological services (ES) maps to assess the global trends of ecological variability for SDG policy formation. The proposition that there are no climate change occurrences may be difficult to stand amidst myriad avalanche visual and sensor-based evidence data on heat waves, dwindling ice cap and tsunamis across the world. Global warming is the continuous slow increase in the average temperature of the earth's atmosphere as a result of the increase trapping of the re-radiated energy (heat) emitted by the earth from the incoming sun radiant energy. The re-radiated and emitted heat does not get to the outer space but trapped at the lower altitude. The excess greenhouse gas as a result of anthropogenic activities now trapped more than required surface temperature for the sustenance of life forms including humans, (see **Figures 1** and **2**).

Heat is energy and when added to the global climate systems that are interconnected, changes occur. And since two-thirds of the earth's surface is covered with ocean, it gets heated up, leading to much evapotranspiration. Also, intensive-energy storms like typhoons, tornadoes, hurricanes, and cyclones are on the increase globally, while the Arctic and Antarctica ice-caps are fast striking in coverage. All these directly lead to global ecological modification and migrations of multivariate disease vectors, as reported by many studies [4–7]. The geographical temperature, rainfall and humidity distribution dynamics and population dynamics are closely related to

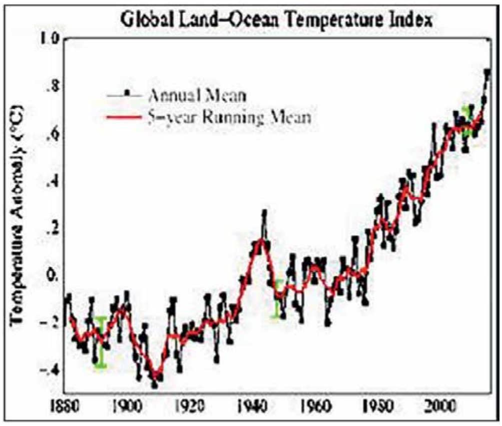

Figure 1.
Global land-ocean temperature index and greenhouse effect (Source: NASA and Center for Climate and Energy Solutions).

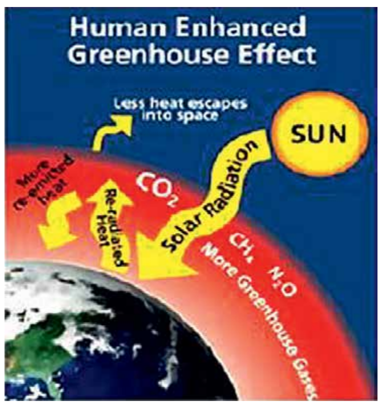

Figure 2.
Global land-ocean temperature index and greenhouse effect (Source: NASA and Center for Climate and Energy Solutions).

the patterns of – insect vectors metabolism and migratory activities globally. Even Measles epidemics, for example, that are cyclic, recurring whenever the proportion of susceptible individuals reaches a suitable threshold, are temperature-related.

2.2 The concept of InVEST and disease control

Integrated Valuation of Ecosystem Services and Tradeoffs (InVEST) is an integrated software package for mapping and valuing nature goods and services that sustain human existence., and it is a tool initially developed by the Natural Capital Project [8] to demonstrate ecosystem productivity function at a given place and time. InVEST has been used in Baoxing County by the Chinese local government to integrate ecosystem services into their Land Use Master Plan with better results than past projects. The tool helps evaluate the impacts of ecosystems modification, leading to dwindling in ecosystem service provision to people or as a seascape [9]. The models explained both service provision types, activities locations and the beneficiaries. A change in climate invariably modifies the functionality of local biotic microorganisms that are made to relocate while new ones replace them forcefully, hence the invasion of seemingly strange microorganisms and diseases.

2.3 The concept of EMP and ESG and epidemic control

An Environmental Management Plan (EMP) is a planning approach that accounts for a specific environmental monitoring statement comprising measured variables, sampling locations, threshold tolerances and remediation. In epidemic monitoring and surveillance, there is the need to watch the atmospheric pollutant tolerance level benchmarked in the Kyoto Protocol to the United Nations Framework Convention on Climate Change (UNFCCC), including even hydrofluorocarbons (HFCs), perfluorocarbons (PFCs), and Sulfur hexafluoride (SF6). Ecological balances in both climatic variables and the food chain require the strategic implementation of environmental management, mitigation measures, monitoring programs, cost estimates, resource requirements, budget and institutional arrangements. The creation of new and dynamic ecological niches that favor certain microbe and the emergence of certain signals are what epidemiologists should look for in any given locality. This is where early warning signals comes from, and professional in that area of specialty are to disseminate the warning to the relevant agency for policy formation.

2.4 Critical habitats and epidemiology control

The doctrine of critical habitat is very jamming in epidemiological control as it relates to critical specific ecological locations with huge biodiversity functional value to the community. They include habitats with endangered, endemic resistive range species sites and ecological convergence zones of evolutionary processes with relevant socioeconomic or cultural values to the community or the nation.

Significant conversion or degraded ecology may be in the form of (i) acute shrinking of habitat functionality caused by natural or human-induced land use changes or (ii) critical change in the habitat food chain that endangers the existence of some native species. This is the basis for the invasion of alien species that are non-native to existing flora and fauna, which significantly thread the biodiversity due to their ability to spread rapidly and out-compete native species. Transboundary impacts of biodiversity distortions are impacts that extend to multiple countries beyond the host country but may not be global in nature.

Plants were the first known hosts for viruses, and plant viruses have been a focus of research over the years when viruses were more ecological in nature, and most of the work done in plant virology has been molecular [10]. But of late, rodents are known as hosts to many viruses that are inimical to human health, while unique habitat distortions and species niche expurgation have been associated with the emergence of zoonotic diseases [11].

For instance, Ebola is transmitted into the human body system through contact with blood, secretions, or other bodily fluids of host animals such as fruit bats, monkeys and forest antelope in the rainforest. It was first observed in 1976 in Nzara, South Sudan, and in Yambuku, Democratic Republic of the Congo, near the Ebola River. The forest fruit bats of the Pteropodidae family were thought to be the natural Ebola virus hosts.

Zoonotic disease studies on the post-West African Ebola Virus Disease (WAEVD) outbreak reveals that changes in land uses and vegetative cover are a significant contributing factor to emerging infectious diseases (EIDs). The general idea is that

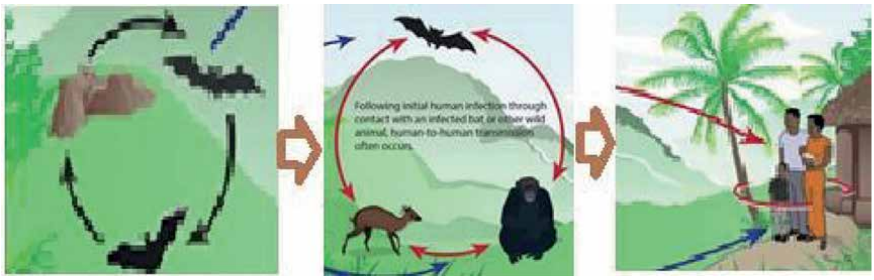

Figure 3.
Ebola and other virus zoonosis cycle (Source: Modified after Centres for Disease Control (CDC)).

zoonosis occurs when there is an interface between at least one pathogen and two host species, which may be human and another host animal species, as illustrated in **Figure 3**. In fact, for many centuries, Zoonoses have been acknowledged, and over 200 cases have been diagnosed including Ebola, SARS and HIV [12, 13].

As inner core forest-dependent bat species lose habitat, they migrated to the secondary human-modified landscape in search for new habitats and food in already almost bat saturated areas. When a particular environmental stresses such as; reduced food and nutrition, extreme weather conditions, reduced shelter, and increased competition, there will be compromised immunological systems in wildlife and humans. There is therefore the need to carry out community safety advocacy on major development in any community.

2.5 Environmental safe guards (ESG) and indigenous peoples

Community health and safety refers to all conscious efforts in protecting and safeguarding the local communities from the adverse effects of developmental project-related hazards emanating from ecological transformation and curtailing the spread of communicable diseases from workforce to the host communities. Major construction sites during or after decommissioning are potential sources of biohazards in the form of communicable diseases like HIV/AIDS and bilharzias. The present climate change push factors have led to global and regional migration of workers in search of juicy jobs, but are host to malaria parasites like Sika that may overwhelm local resilient levels. Proper monitoring and management of health and safety impacts of major projects will help in creating positive community environmental perception and preparedness. This is where the principle of inclusive planning becomes relevant in policy formation and implementation. Large projects that will significantly affect the ecological setting of a locality must be participatory, and there must be robust contingency planning in place for effective sustainability and disease surveillance.

Key aspects of protecting local communities from project-related disease hazards are summarized below:

i. Assess the weather-related changes and identify disease-related vectors and potential impacts on the safety of the communities.

ii. Establish mitigation and adaptation strategies that are commensurate with the perceived risks, hazards, and propagation. These approaches should strengthen the community resilience level far beyond their hitherto vulnerability levels.

iii. Conduct an assessment of the Vulnerability and Capacity Analysis of the community and the levels of their exposure to weather related hazards.

iv. Manage vector habitats to avoid or minimize the exacerbation of impacts caused by them on the environment such as water bodies and drought that could result from significant changes to vegetation cover, topography, and hydrologic regimes

v. Have community-based emergency prevention, preparedness, and response arrangements in place if the consequences of emergency events are imminent with local authorities, and focus on the following:

a. Define specific emergency response procedures.

b. Trained emergency response teams.

c. Define emergency contacts and communication systems/protocols.

d. Establish integration of local and regional emergency and health authorities.

e. Permanently stationed emergency equipment.

f. Define protocols for ambulance and other emergency vehicle services.

g. Designate evacuation routes and meeting points.

h. Conduct drills (annual or more frequently as necessary).

Going by the dynamic terrain of the global ecological system as a result of human-induced climate change variability and the increasing challenges of exotic pathogens [14], Various rubrics models of integrated risk-based, disease-targeted surveillance and participatory surveillance have emerged in response to the global pandemic phases [15–17]. Therefore, much of such models focus on both veterinary and human epidemiology that are technically associated with risk and risk factors that border on how to better account for disease propagation.

3. Methodological approach

The study adopted the search engine secondary method of data collection and descriptive content analysis in conjunction with the other in-depth interview survey reported by recent studies on climate change-induced health challenges and opinion survey on community participation in disease monitoring and control and Non-governmental interventions. Major deduction was made toward achieving the sustainable development goals (SDGs) targets 3 and 13 that address good health and well-being; and Climate action in the country.

4. Discussion

4.1 Global diseases weather tolerance distribution

Generally, many scientists have jettisoned what was once a basic preposition in infectious disease modeling: that a vector's ability to flourish and infest communities has a direct linear relationship with increasing temperature. While the nonlinear models explained the relationship between warming and propagation within a range of time and place better. Excessive heat beyond the tolerance levels of vectors and pathogens do slow down transmission thereby leading to decline in disease spread. Studies have revealed that many mosquito-borne viruses get to the topmost between the range of 23°C and 26°C before dropping as temperature increases especially in the West Nile [18–22]. While hitherto cool, higher elevated areas that attenuated their propagation can become vulnerable with increased temperature; see **Figure 4** for the global spatial coverage of malaria outbreak.

Also, according to Marcia Castro, Professor of Demography and chair of the Department of Global Health and Population at the Harvard T.H. Chan School of Public Health, malaria transmission in the highlands that are hitherto cool will increase over time and will become more susceptible to the mosquito vector staying longer than just a few months due to the influence of climate change. Warming weather generally catalyzes tropical disease pathogen propagation like the Zika virus in the *Aedes aegypti* mosquito that now migrated from Africa/Asia eastward to the Pacific since the year 2007, with more than 80 reported cases from other countries. For instance, in 2015, about 1.5 million people were infected in Brazil before spreading elsewhere in America. In fact, another modeling study has postulated that in a worst-case scenario, 1.3 billion more people will be living in locations with temperatures that are conducive for Zika transmission by 2050.

The Centre for Disease Control (CDC) approximated the number of Lyme cases treated in the United States at about 476,000 per year on average between 2010 and

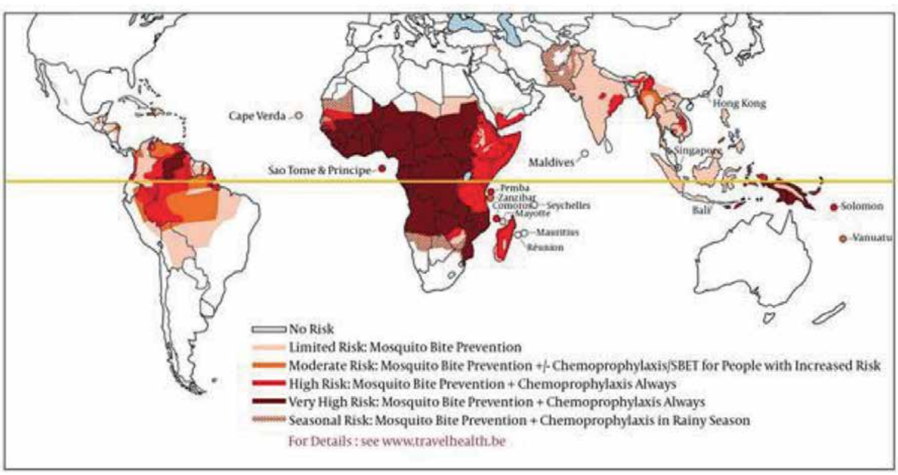

Figure 4.
Worldwide distribution of Malaria outbreak in 2019 (Source: WHO).

2018, a significant increase above the annual average of 329,000 reported by the insurance claims between 2005 and 2010. This increase is in consonant with the increase in the spatial distribution of Lyme-bearing ticks and other diseases.

Infectious diseases caused by pathogen that develops in the environment or in an intermediate host are significantly influenced by climatic parameters that often have a direct association with the growth of the pathogens as their incubation can be aborted under unfavorable temperature; where, for instance, 18°C is the temperature tolerance for tropical Plasmodium falciparum and 20°C is for the Japanese encephalitis virus to increase reproduction rate [23, 24]. Climate change has therefore created a conducive habitat for the lone star tick, a vector for ehrlichiosis to thrive in New England that was initially limited to the southern United States.

4.2 Pathogenic habitat analysis

Globally, the significant consequences of the continuous spread of vector-borne infectious diseases where West Nile fever is now a common mosquito-borne ailment in the United States since 1999, along with other pathogens like Dengue and Chikungunya spreading into Europe as well. Critical aspects of a vector's lifecycle, such as its growth, reproductive capacity, and biting rates, are temperature dependent, and for Sam Telford, professor of infectious disease and global health at the Cummings School of Veterinary Medicine at Tufts University, "drought is death," for those vectors.

Diseases spread are generally associated with the environmental factors and biophysical state of a given locality. For example, temperature surges often force communities to be exposed to unwholesome water sources that can cause waterborne diseases, especially in arid and semi-arid regions [25]. A high rate of humidity prevents the body from sweating, resulting in fungal skin diseases, but modern advances in Remote Sensing and GIS have significantly assisted in comprehending the relationships between disease dispersal and geospatial dynamics as a complement to disease location and outbreak forecasting [26]. Real-time information on environmental factors has been veritable in identifying the habitats of disease vectors based on their ecology and the terrain configuration together with the land use/land cover dynamics. Geospatial analyses are significant veritable tools in understanding the relationship between disease dispersion and environmental factors, in addition to locating and forecasting outbreaks of diseases [26, 27].

Under the [28] survey program, it was found that about 8 in every 10 directors of local health acknowledged the existence of climate change, but less than 5% of health departments organizing climate change impacts education in their area. Also, only about 8.4% have adequate resources for residents' protection against climate impact-related ailments. Although about 6 out of every 10 Americans are aware of climate change, this gap is a major challenge that calls for more innovative, cost-effective collaborations within local communities on early warning and preparedness.

4.3 Epidemiology monitoring and early warning systems

Monitoring and surveillance is used interchangeably in this context meaning a systematic continuous process of watching, collection of data, analyzing, interpretation, and dissemination of relevant results output on the latent health challenges for policy formation and implementation. Such result output should be disseminated to all the relevant stakeholders for effective disease prevention and control [29]. Historically, infectious diseases predicting outbreaks based on climate data can be traced to the work of Gill and Roger [30, 31] who developed an early warning system for malaria based on rainfall in India. Their approach demonstrated how an early warning system could be developed from weather variables like temperature, rainfall, humidity and winds for the incidence of diseases such as pneumonia, smallpox, leprosy and tuberculosis (TB). Presently, there exist myriad earth resources data from space-borne satellites and ground-based sensors that are easily accessible at relatively low cost, enhancing the assessment of the correlation of climate-related disease outbreaks. More so, advances in epidemiological and statistical modeling have allowed apparent associations to be tested explicitly.

Surveillance generally requires coordinated networks of relevant actors, free flow of information for disease prevention activities, control measures and epidemiological investigations. In fact, it requires contingency planning in which scenarios for tactical operations are established in relation to the dynamic environmental factors on a continuous basis from the local to the international, which may follow a cyclic process as in **Figure 5**.

While monitoring, according to Akhtar and White [32], is the supervision of the occurrences of specific or general health events overtime within a given community which is the most common objective of surveillance. According to them, data from the system can be used to compute the incidences and prevalence of those health events. Surveillance objectives will generally include the following:

Figure 5.
A conceptual basis for disease monitoring as a self-correcting cycle.

i. monitoring the trend of health events,

ii. supplying researchers with trending issues,

iii. appraise the effectiveness interventions,

iv. predict trends of future disease,

v. disseminates real-time information on health issues to policymakers,

vi. awaken the need for the integration of health stakeholders

Early warning is wide and multistage in approach involving many actors from the grassroots to complex digital simulation models. It always involves active engagement in crisis prevention, and the first approach is the prediction of when, why, where, and how epidemic crises will emerge. It is the act of troubleshooting latent problem in a community, the cause, how eminent, and the way forward. Early warning deals with the origin and the causes that empower community preparedness and not the symptoms. Early warning should be near real-time evaluation mechanism of risky phenomena in a highly vulnerable community that are likely to accelerate or trigger epidemic outbreak that is embedded in the UN Humanitarian Early Warning System (HEWS).

Quantitative Early Warning System (QnEWS), as against qualitative Early Warning System, employs systematic collection and processing of empirical information according to a given set of criteria with the aim of isolating the factors that contribute or influence the outbreak of problems, and ascertain the antecedent contextual structures, events and processes that can cause the outbreak of epidemic or violence using threshold patterns, causal or procedural model [33]. An early warning system such as in **Figure 6** can be developed for an infectious disease only if the disease is epidemic-prone.

5. Conclusion and recommendation

Anthropogenic activities have negatively impacted the finite Mother Earth, thereby threatening the existence of man. The Ozone layer depletion directly impacts human health through climatic extremes, heat waves, air pollution, sea-level rise, drought, global epidemic, socioeconomic and political conflicts and food insecurity. The emergence of strange epidemic disease is the most devastating as it is boundaryless, and rendering existing innovations obsolete. The devastating impact of infectious diseases on human health and livelihood is intrinsically linked to complex stressors or drivers such as poor access to clean water and food, inadequate public health infrastructure and services, political instability and conflicts, drug resistance virus mutations, and population upsurge [See 35, 36]. The modification of vector–pathogen habitats has now led to epidemic disease dynamism in the twenty-first century. The world has experienced cases of SARX variants, HIV, Ebola, Lassa fever, ZIKV, COVID-19, etc., which raises the question "Who-is-free," or "Are-we-ready." The time to re-strategize and embrace integrated disease is now.

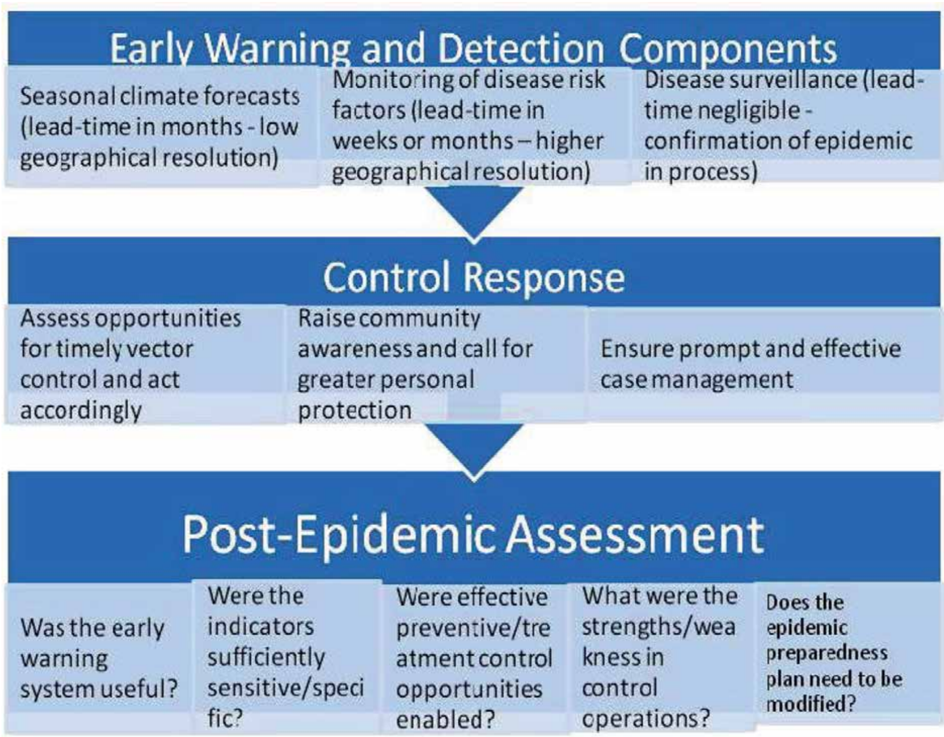

Figure 6.
Framework for developing early warning systems for climate-sensitive diseases (Source: After WHO [34]).

i. The following are therefore recommendations as a way forward;

ii. The law of polluters pay should be vigorously applies at the international and national level as this will check the activities of those countries that pay lip service to eco-friendly development.

iii. Contingency planning should be incorporated and implemented at all levels of health service delivery in the face of dynamic migrating Virus-Borne diseases (VBD).

iv. Inclusive planning in the spirit of 'leave-no-one-behind' of the SDGs target should be fully advocated at all levels for local community capacity development and preparedness as emphasized in [37].

v. Policy on ecological preservation/conservation should be a priority at every governmental level, while encouraging all forms of eco-developments, [see 38].

vi. Real-time geospatial analysis technology should be embraced at all levels for disease monitoring and dissemination of information to relevant policymakers and implementing agencies [as in 39].

vii. COP-28 and other subsequent ones should create a session on climate change and epidemic diseases across the globe.

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Chapter 2

Trans-Frontier Socio-Cultural Interactions and Learning for Epidemic Preparedness and Control

Dennis Chirawurah, Stephen Apanga and Niagia Santuah

Abstract

West Africa's extensive migratory activities and unregulated cross-border community interactions between countries pose challenges to epidemic preparedness and control. Understanding of the nature of these activities and interactions is therefore necessary for epidemic preparedness planning and response. We used a qualitative cross-sectional study to conduct focused group discussions and key informant interviews in contiguous border communities in Ghana and Burkina Faso to assess if and how cross border interactions compromise or facilitate management of public health emergencies. Knowledge and perception of the severity of epidemics in Ghana and Burkina Faso is high, and existing local networks and institutions have the capacity to effectively respond to public health emergencies when properly mobilized. Managing cross-border community interactions and interrelationships and respectful cross-cultural dialog among the multiplicity of stakeholders within and between the two countries is sine qua non for constructing a robust and responsive architecture for effective epidemic preparedness and control.

Keywords: Burkina Faso, COVID-19, epidemic, Ghana, migration

1. Introduction

West Africa is a beehive of activity. The sub region's colonial past and haphazard partitioning into different political and linguistic boundaries has done little to curtail cross border movement of people, products and services [1–4]. Besides, the rather liberal Economic Community of West African States (ECOWAS) Protocol (A/P.1/5/79) on free movement of persons, residence and establishment bolsters free trans-border movements [3].

Over time, the people have self-identified as one people, from one ancestry with a common destiny. Different tribes that have found themselves dispersed across the borders of countries have not resisted the lure of reconnecting. This is particularly so of the Kasena in Ghana and Burkina Faso who are sparsely distributed across contiguous communities between the two countries. Whereas these cross border movements – most of them unofficial - have fostered strong community bonds that may augur well for regional peace and security [5], they could also compromise the ability of health authorities to effectively respond to emergency situations. This leaves a wide room for speculation. What is the nature of these interactions and how do they strengthen cross border collaboration or weaken concerted action in cases of emergency such as the Ebola outbreak in West Africa and the global Coronavirus pandemic (COVID 19) that dismantled borders and devastated populations across the globe?

By August 2020, COVID-19 had spread across more than 200 countries infecting over 30 million people with close to 1 million deaths [6]. At about the same time, Ghana recorded 108,226 active COVID-19 cases with 874 deaths [7] whereas Burkina Faso's active cases were 13,625 with 169 deaths at the same time [8]. The pandemic wreaked considerable economic and social costs, bringing down Ghana's GDP by 27.9%, pushing 3.8 million Ghanaians into temporal poverty [9], and plunging the Burkinabe national economy into recession, compromising its ability to service its external debt [6]. Similarly, the 2013–2016 Ebola virus disease (EVD) outbreak in West Africa was the biggest in history. Having peaked at 28,646 infections and 11,323 deaths, it surpassed all previous outbreaks put together. Guinea, Liberia, and Sierra Leone bore the brunt of the 2015 Ebola outbreak that ravaged countries across West Africa [10, 11]. But Ebola did not enter Ghana. The setting up of a West African Ebola Response Center in Ghana to coordinate regional effort, and other national emergency response actions to combat the disease, are well documented. Yet what cross border communities, such as those between Ghana and Burkina Faso, did or did not do that stopped Ebola from crossing the border into Ghana, is relatively unexplored. Not all public health emergencies can be prevented, which means it is better to be prepared to handle them when they arise [10]. Though the importance of small cross-border trade and cross-cultural learning as a means of economic survival cannot be emphasized enough, challenges remain [5]. Sustained action by national and international partners to support wide-ranging epidemic control measures is critical, but solving basic operational problems to contain an epidemic largely requires a local approach and initiative [12]. To date, cross border trade, cultural and agricultural interactions and interrelationships among Kasena communities in Ghana and Burkina Faso are more of the norm than the exception [13]. This provides a unique opportunity to examine the nature and scope of these networks and cross border interactions and how they influence effective prevention and control of public health emergencies.

1.1 Cross border movements in ECOWAS

Migration is movement from a person's usual residence across borders, either within States or between them [14]. But at the mention of the word migration, at least three other terms come to mind – Mobility, Translocality and Itinerant worker. Whereas Mobility is a relationship in which the world is lived and understood [15] translocality describes movements, among others, of people, goods and services across space and time with differing magnitudes [16]. An Itinerant worker moves from their usual place of residence to engage in short-term business transactions in another State or in a different part of the same State. Itinerant cross-border traders have built loose networks in the process of frequent trade mobility [5].

The Social Network theory can be used to explain cross border interactions. According to Killick, the importance of networks rank among the most important explanatory factors for migration [17]. Thus, the central role played by networks in cross-border mobility cannot be emphasized enough. Migrant networks go beyond borders as "sets of interpersonal ties that bring together migrants, non-migrants and former migrants in networks of kinship, friendship and common ancestry [17].

Cross-border trade in West Africa is therefore big business, and the flow of trade is determined by a complex web of relationships [5]. These movements happen within the legal regime of the ECOWAS Protocol (A/P.1/5/79) on Free Movement of Persons, Residence and Establishment. The protocol makes specific provisions for intra-regional movement with right "to enter, reside and establish in the territory of Member-states". Females dominate informal cross-border trade and they have diverse socio-economic and cultural variables. They also differ in the volume and value of businesses, types of buying and selling activities, travel destinations and types of markets they operate in [18]. These cross-border trade movements are cyclical [16], and the kind of trade they engage in has strengthened social and economic bonds and has remained largely unchanged over a long period of time in spite of the boundaries created [19]. Itinerant traders, especially women, involved in Informal Cross-Border Trade are invisible within the framework of the ECOWAS protocol on Free Movement of Goods and Services across borders [20]. Attempts to remedy the situation through the ECOWAS Common Approach on Migration (2008), ECOWAS Gender and Migration Framework and Plan of Action (2015-2020) yielded limited results. The traders continue to be confronted with formal and informal rules and regulations that are not supportive of their local knowledge and practices [5]. They argue that this disrupts building new alliances and the creation of visions that are liberatory [21]. The ECOWAS protocol has failed to consider the socio-cultural composition of the itinerant traders' worldviews on trade and free movement. According to Ref. [15], what migrants experience and think has been a lower research priority, to the extent that many of the realities of social life have been largely neglected. Bangu's [5] research on border posts and informal entry points between Ghana, Togo and Burkina Faso, to determine the lived experiences of itinerant female traders, confirmed [22] report that informal cross-border business transactions potentially improve lives and livelihoods, especially of people living close to border communities. He however concluded that there is limited documented research on itinerant cross-border traders' lived experiences and social realities in the context of the ECOWAS Protocol. The situation is much more uncertain about how these cross border interactions influence the management of public health emergencies, especially the two most recent epidemics, Ebola in West Africa and the global coronavirus pandemic (COVID-19). This paper focuses on what we can learn from these cross-border interactions and interrelationships for epidemic preparedness and control in the future. Specifically,

1. what is the nature of evidence of cross border interactions between Ghana and Burkina Faso?

2. what basic knowledge about Ebola and COVID-19 do people have?

3. what networks and institutions exist for preventing or effectively responding to public health emergencies?

4. what capacities exist for preventing or managing public health emergencies?

5. what are the pathways for effectively responding to or controlling public health emergencies?

2. Methodological approach

The studies were conducted in selected contiguous Kasem-speaking communities in the Kasena Nankana Municipality in the Upper East region of Ghana; and

Kasem-speaking communities in the Commune Urbaine de Pô in the Nahouri Province in the Centre-sud region of Burkina Faso. Navrongo Municipal is one of the 15 districts in the Upper East Region. The Kasena in Ghana and Burkina Faso speak the Kasem language, share common cultural practices with common historical origins and linguistic affinity [23]. Though Ghana and Burkina Faso share common colonial history, Gold Coast, as Ghana was then known, was administered by the British using Indirect Rule whereas the French used Assimilation in now Burkina Faso [24]. A typographical error in respect of the spelling of "Yoo" in Burkina Faso and "Yua" in Ghana is said to be responsible for the current distribution of the Kasena in their current homeland straddling the two countries. The major occupation of the Kasena both in Ghana and Burkina Faso is agriculture, basically on subsistence basis with up to 96% of the population engaged in it. The rest is typically engaged in the informal sector of cross border trading, hunting, and cottage industry. Nearly nine out of 10 persons in the study area are said to be living below the poverty line [25].

2.1 Study area in Ghana

The Kasena Nankana East Municipal Assembly (KNMA), formerly Kasena-Nankana District, came into existence when the former Kasena-Nankana District, created in 1988, was split into two in 2008. Kasena-Nankana East was elevated to a municipal status in 2012 and renamed Kasena Nankana Municipal Assembly. The Municipal Assembly has a total land area of 767km^2 and a population of 134,018, comprising 48.8% male and 51.2% female as at 2021. Geographically, KNMA in Ghana is located on 10.8955° N, 1.0921° W. The Municipality was created by the Local Government Instrument (L.I) 1855 of 2007. It shares boundaries with Kasena-Nankana West to the west in Ghana, and Commune Urbaine de Pô and Commune de Tiébélé to the north in Burkina Faso.

2.2 Study area in Burkina Faso

Nahouri is one of the 45 Provinces of Burkina Faso and is located in the Centre-Sud administrative region with Pô as the capital. With a current population of 155,463, women constitute 52%. On healthcare, the Province has 19 health and social promotion centres (Centres de santé et de promotion sociale), 3 doctors and 67 nurses as at 2011. Temperatures range from 25 to 40°C. However, cold and dry Harmattan is also characteristic of the Province around December to March each year. In Burkina Faso, the geographical coordinates of Commune Urbaine de Pô are 11.1697° N, 1.1450° W°. The dominant ethnic groupings in the Province include Kasena and Nankana with most people being multi-lingual as a result of long history of coexistence, interactions and inter-marriages. About 95% of households in the Nahouri Province have no access to toilet facilities and about 90% dispose of their rubbish in a heap outside the house. Also, 68% of households fetch their drinking water from either pond, dug outs or dams and only about 16.3% have access to standpipes or boreholes.

In Burkina Faso, data were collected from the communities of Adong, Dakola, Kayaa and Pô, whereas in Ghana, data were collected from Manyoro, Paga, Pindaa, and Wanjagenia.

2.3 Research design

Research design refers to the systematic plan used for answering the research questions of a study, from conception to data collection and analysis [26]. In order to arrive at a better understanding of the research purpose, the two studies adopted embedded mixed methods, that is, using a combination of qualitative and quantitative approaches for data collection.

> *"Whereas quantitative or deductive researchers go out in search of data to match a theory, qualitative or inductive researchers go out hoping to find a theory that explains their data from observations and intuitive understandings gained in the field" (Merriam, 1997, 1998, as cited in [27].*

The first study assessed community interactions during the Ebola outbreak of 2015 while the second assessed community perceptions of COVID-19 after the relaxation of restrictions including the reopening of Ghana's borders with Burkina Faso in June 2020. The studies were cross-sectional and non-experimental, using a descriptive case study design complemented by non-participant observation. According to [26] case study is an empirical investigation of phenomena in their natural context. Considering the objectives of the studies, there was the need to describe the nature of cross border social networking and how these influence communities' capacity to prepare and respond to emergency situations.

2.4 Research methods

The primary data collection methods were Key Informant Interviews and Focus Group Discussions, which elicited information from people regarded as repositories of information. Semi-structured interviews were used to guide key informant interviews and focus group discussions because they provide considerable flexibility for the researcher to survey respondents while maintaining the basic structure of the interview. Although this was a guided conversation between researchers and interviewees, there was the need for be considerable flexibility for the researchers.

2.4.1 Focus group discussion

Focus Group Discussions (FGDs) enable researchers obtain in-depth information that can be analyzed for perceptions, attitudes, feelings and beliefs about issues pertaining to the objectives of a study [27]. Cross section of Focus Group discussants:

- Clan/Lineage Heads, Elders, Thought Leaders/Opinion Leaders (women and men)

- Trade associations, farmer associations, community networks, youth groups

These were prioritized ahead of others to compose the focus group discussions because, by virtue of their positions and traditional roles, they are endowed with important information about the community, its traditions and belief systems and practices. The focus groups also served as a pool from which key informants were identified and followed up later in the research. The use of Focus Group Discussion as a method allowed for the observation of group dynamics, discussions, and first-hand insights into the behavior, attitudes, and opinions of community stakeholders such as thought leaders, chiefs and indigenous institutional functionaries on issues relating to cross border movements and interactions and how these affect the delivery of public health interventions.

2.4.2 Key informant interviews

This requires careful selection of participants considered to be the most knowledgeable on the subject. Key Informant Interviews (KIIs) allowed the researchers to probe respondents and guide the interviews according to the respondent's answers [28]. Key Informant Interviews is one of the methods that make up for the limitations of Observation as a method of data collection, whether structured or unstructured. The indirect approach to conducting interviews enables the researcher to obtain answers, which the respondents may not consciously be aware.

2.5 Sampling and inclusion criteria

Community traditional leaders were earmarked for in-depth interviews. Additional key informants were obtained through snowballing or identified from focus group discussants. Participants for the KIIs and FGDs were selected based on a predetermined inclusion criteria. Respondents aged 18 years and above, traditional authorities, opinion leadership, local political actors, civil society organizations, immigration officers and traders met the inclusion criteria.

2.6 Data collection instruments

- Focus group discussion guide
- Semi-structured interview guide
- Digital audio recorder
- Digital camera

2.7 Analytical approach

Audio recordings were transcribed and translated into English and coded before using the conventional content analysis approach to analyze the qualitative data. This was suitable for these studies given that existing research literature on cross border interactions in the study area is limited. Conventional content analysis steps were used in the data analysis during which transcripts were first read through to achieve immersion and obtain a sense of the whole. Codes were derived from the text, by first highlighting the exact words from the text that captured key thoughts or concepts which were then grouped into themes. The qualitative data was then analyzed quantitatively to get both an understanding of people's perspectives and feelings as well as the general distribution of opinion among study respondents on key variables. This allowed the transcribed data to be organized, analyzed and visualized for presentation.

2.8 Ethical considerations

Ethical issues surrounding the study were considered and addressed first by assuring participants that the research was purely for academic and public health purposes and not to assess their competencies, legality or profitability of their cross-border dealings. Secondly, the consent of all participants was sought before interviews were conducted. An assurance was given to those who declined to participate or discontinued the process after the interview got under way. Participants were also educated to decline answering questions that they were not comfortable with. And as way of deepening confidentiality, participants were assured that their personal details and private information will not be exposed in the report.

3. Results and interpretation

3.1 Evidence of cross border interactions

Contiguous communities between Ghana and Burkina Faso regularly cross the border to reconnect with their kith and kin because they see themselves as one people separated by an artificial border:

> *"When you come here, we say 'a member of our household has come', and when we also come to your home, you'd say a member of your household has come. So now that you are here, when someone asks me, I would say 'a member of our household has come to trace the family ancestry'. What is more edifying than that?"* - key informant, Commune de Tiébélé, Burkina Faso.

The two studies uncovered considerable cross border movements and activities between Ghana and Burkina Faso:

> *"We have our farms several kilometers across the border into Burkina Faso where our Ancestors lived and farmed long before the colonial period. We still cross over to farm without any difficulties"* – Key Informant from Pindaa in the Navrongo Municipality of Ghana.

A key informant from Adong in the Commune Urbaine de Pô in Burkina Faso confirmed this information:

> *"The people of Pindaa have their farms deep inside our territory where they have cultivated till date without any dispute with us. In the same way, our people regularly cross the border into Pindaa [in Ghana] to have their children vaccinated during national immunization days. They have not been turned away before because we are one people".*
>
> *"During the off-farming season here, our people go to Ghana and farm and on their return they buy agrochemicals [because the agrochemicals are cheaper in Ghana]"* – Key informant from Pô of the Commune Urbaine de Pô in Burkina Faso.

Most of the cross-border movements involved the use of unapproved and unmanned routes, thus circumventing the closure of Ghana's borders with Burkina Faso during the COVID-19 period.

3.2 Basic knowledge about Ebola and COVID-19

The epidemiology of the Ebola disease was well known to most study participants with 83% mentioning correctly at least one country that was affected by Ebola in West Africa. Knowledge of the epidemiology of COVID-19 was varied, with many people not knowing how it started or where it came from. However, all participants said COVID-19 pandemic had affected all countries. Twenty-eight of forty three respondents or almost two-thirds (65.1%) were able to mention at least three ways of preventing the spread of COVID-19. Knowledge about Ebola and COVID-19 was high among community members and this augurs well for effective prevention and control measures in health emergency situations.

3.3 Public health emergency response networks

The two studies also identified a network of individuals and organizations that are involved in emergency/disaster prevention/response work in both countries. Distinct to Burkina Faso were Action sociale and the Armed forces, whereas those peculiar to Ghana were the National Disaster Management Organization (NADMO) and the National Commission on Civic Education (NCCE). For obvious reasons, the health sector, including the ministries of health, doctors, hospitals, health directorates, health workers, health volunteers, veterinary officers and environmental health workers, were deeply involved in the Ebola and COVID-19 response in both countries. With regard to COVID-19, a woman at Kayaa in the Commune Urbaine de Pô in Burkina Faso stated that *"the doctors, if you seek early treatment from them, they can prevent you from dying from the disease"*. Critical structures common to both countries were research institutions, transport operators especially long-distance truck drivers (whose work was curtailed during COVID-19), the Red Cross and Red Crescent Society, border security, district assemblies, traditional and religious leaders, media and information services. Both Ghana and Burkina Faso have a decentralized system of government that can serve as the basic infrastructure for managing epidemics at the local level. Under Burkina Faso's le Code Général des Collectivités Territoriales (CGCT), the Conseiller heads the Conseils Villageois de Développement (CVD). This is the equivalent of Ghana's local government system and the District Assembly with the Assembly member who chairs the Unit Committee. The CVDs or Unit Committees can be the first line personnel at the community level who can be trained to conduct disease surveillance to support the health system. A network of institutions therefore exists in both Ghana and Burkina Faso that can be mobilized in cases of health emergencies.

3.4 Capacity for managing public health emergencies

For Ebola and COVID-19, like any other disaster with devastative impact on victims and the entirety of communities, there is the need for capacity to prevent or respond effectively to possible outbreaks. Respondents identified and emphasized the need for communities and organizations within each country to work collaboratively towards the management of any emergency.

Knowledge was identified as a bedrock to curbing Ebola and COVID-19. A focus group discussant from Dakola in the Commune Urbaine de Pô in Burkina Faso asked a rhetorical question:

> *"Knowledge differs from individual to individual, from community to community and from country to country. So should we not find a way to learn from each other?"*

Thus, cross-cultural learning and unity of purpose are key for effective handling of public health emergencies. Participants' idea of working together spans sharing of information, skills and experiences, sharing or pooling resources together, taking collective decisions and distribution of tasks, and building of trust among parties. Nearly all respondents (98.6%) agreed that networking among cross-border communities and organizations is critical for the prevention of Ebola. A Key Informant from Wanjagenia in the Navrongo Municipality in Ghana emphasized the rationale for people to work together; *"The destructive nature of the disease* [Ebola] *and the speed at which it spreads makes collaboration a must".* A focus group discussant from Kayaa in the Commune Urbaine de Pô in Burkina Faso was more specific; *"We also need to form joint task forces, effective border checks and screening, real time communication, and sharing of new technology in the fight against Ebola".*

The capacity and opportunity for Ghana and Burkina Faso to collaborate to respond to emergencies is huge but challenges, mainly of mistrust and bureaucratic bottlenecks, remain that need to be addressed.

Inadequate training of health staff and volunteers, scarcity of logistics such as hand gloves, veronica buckets, nose masks, overalls, detergents, as well as the language barrier and poor road network were mentioned as key challenges to effective collaboration to combat public health emergencies such as Ebola and COVID-19.

The capacity of persons, communities and organizations to effectively deal with challenges of disease prevention and control - though currently weak – is crucial as it underpins the ability to mobilize, deploy and judiciously use both human and material resources.

3.5 Pathways to effective epidemic response

The studies found several ways through which the capacities of individuals, organizations and communities can be strengthened to prevent or effectively respond to an outbreak of Ebola in Ghana. Of these, training of health workers, volunteers and Red Cross officials in Ebola prevention and treatment was highlighted.

Continuous education and sensitization of the general public also ranked high as 87% and 92% of respondents of the Ebola and COVID-19 studies respectively highlighted them. Sustainable financing was however identified as the pivot to addressing most of the challenges;

> *"All the logistics needed, once there's money, they can be acquired in order for work to be effectively done"* – A focus group discussant from Adongo in the Commune Urbaine de Pô in Burkina Faso.

The use of social networks and indigenous knowledge was also identified as a key strategy for effectively managing cross border activities.

> *"We ordinary community members should not be left out. Day in day out we see people pass through our communities in and out of the country. So if any disease is coming it will affect us first. We can also be trained to screen people most of whom are arriving without travel or medical health records"* – Focus group discussant, Nahouri, Commune Urbaine de Pô, Burkina Faso.

Within and between Ghana and Burkina Faso, pathways to effective management of public health emergencies are many and varied.

4. Conclusions

People in the West African subregion are known for their extensive cross border activities, mostly using unregulated routes. This study sought to illuminate understanding about how these cross-border interactions and interrelationships between Ghana and Burkina Faso specifically, compromise or facilitate management of public health emergencies, using the Ebola outbreak in West Africa and the global coronavirus pandemic (COVID-19) as case studies. We found that knowledge and perception of the severity of epidemics was high but challenges of human and material resources remain. There also exists a myriad of local networks and institutions that have the capacity to effectively respond to public health emergencies but they are not efficiently mobilized both within and between countries. Collaboration at different levels is key, but managing cross-border community interactions and interrelationships requires respectful dialog among the multiplicity of stakeholders identified. Given the porous nature of the borders between Ghana and Burkina Faso in particular, and West Africa generally, inter-country networking and cross-cultural learning are sine qua non for constructing a robust and responsive architecture for effective epidemic preparedness and control in West Africa.

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Author contribution

Dennis Chirawurah: Development of the concept and design of the study, team lead for field data collection, revision and approval of Book Chapter final draft.

Stephen Apanga: Design of study instruments, supervision of field data collection and data interpretation, revision and approval of Book Chapter final draft.

Niagia Santuah: Contribution to data collection and interpretation, drafting of the study report and literature search, revision and approval of Book Chapter final draft.

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Chapter 3

The Perception of the Effectiveness of Vaccines between Myth and Reality

Alessandra Cecilia Jacomuzzi

Abstract

The perception of the risk of a vaccine and its effectiveness has always been the subject of study. The human mind, in fact, tends to underestimate the effectiveness of a vaccine and overestimate its risk. But where does this problem come from and how does the human being think when he is talking about a vaccine? In this chapter, I intend to review the main studies on the efficacy of the vaccine. I also intend to deepen the studies on the perception of risk to highlight what are the strategies of thought adopted by the human beings when they must reason on these issues.

Keywords: vaccine, thought psychology, cognitive bias, risk perception, efficacy and effectiveness vaccine

1. Introduction

Nowadays, the opportunity of getting vaccinated to lower the risk of contracting various diseases still tends to be seen by many people as an obligation that comes to undermines the rights of human beings rather than being an advantage. And yet, the history of humankind should have taught us that vaccines, far from being a dangerous tool to be demonised, are one of humankind's most important progresses. Today more than ever, after years of pandemic, we can only be aware of the fact that vaccines are the most important weapon people can use against viruses [1, 2].

Looking back over human history we can see a time when there were no vaccines. A time when people could not even imagine it could be possible to develop such a weapon to help people in the fight against disease. At that time the only weapon at the disposal of human beings was isolation. Once a person or a group of people had contracted an infectious, incurable or fatal disease, there was no other way of fighting it other than isolating people. That isolation, while protecting humankind from infection, did not however eradicate the disease and its spreading. Furthermore, isolation made it impossible to help the sick, left in this way to face their fateful destiny alone.

In 1796, however, a breakthrough was made in that sense by a British physician Edward Jenner. That year the world's population had to fight a terrible, lethal virus: smallpox. This caused an endemic disease to develop that soon became the leading cause of death in many geographical areas, including Europe. The British physician Jenner started with the consideration that once a person had contracted the virus, if

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they were able to survive, they turned out to be immune to the disease. In the particular case of smallpox, the physician noted that milkmaids who had come into contact with bovine smallpox turned out to be immune to smallpox.

Starting with this consideration he thought of injecting bovine smallpox pus into a human being in the hope of thus making them immune to the disease. On 14 May 1796, the physician took material from a pustule on a bovine afflicted with smallpox and injected it into an 8-year-old boy. The reason for him choosing an 8-year-old boy as the subject of his test is unknown. However, today we can state that he made the right choice. Indeed, children are generally less vulnerable and this could have been advantageous since the test involved direct contact with the virus [3].

What happened on the days following the inoculation of the pus into the boy was something that appeared very similar to a miracle. The child, in fact, started developing the symptoms of the disease. After a few days, he recovered. Some months later, Jenner injected blood taken from another man afflicted with smallpox into the boy. The boy did not fall ill. No symptoms appeared. The boy had become immune to the disease. In 1796 Jenner had managed to chalk up the greatest point in the match against viruses. The history of smallpox confirms this. In 1979, in fact, the WHO declared smallpox to be permanently defeated and today it is no longer necessary to be vaccinated against smallpox (source: https://www.epicentro.iss.it/, website of the Italian National Health Institute). Going back over the essential stages that led to defeating the smallpox epidemic produces an authentic sense of relief. Indeed, the invention of vaccines permitted fighting the development of infection and slowing down the progression of epidemics.

Inspite of this, in several countries so-called “anti-vax” movements are present and well-established. Furthermore, the recent COVID-19 epidemic led the world’s entire population to question the usefulness and importance of vaccines. And yet, there is a very strong emotion that accompanies every thought about vaccination: fear. Fear due to the feeling that inoculating foreign matter into our body, at a time of well-being, may lead to negative consequences. Fear in itself is an emotion that has developed for the survival of the species [4–26]. Without fear, human beings would be less attentive to difficulties and dangerous situations, they would be unable to develop strategies to overcome them and sometimes they would be unable to find helpful solutions for survival. However, at a historical time such as the one we have experienced, and are still experiencing, dominated by total uncertainty about the future, the risk is that fear may become a negative emotion that prevents distinguishing a subjective danger from the actual objective danger and fog the mind preventing it from seeing the real benefits of vaccination. This is why it is crucial, and urgent, to understand how the human mind thinks of the efficacy of a vaccine and, above all, what information the human mind uses when it has to choose between two different vaccines.

2. Relative and absolute risk reduction

The concept of vaccine efficacy (VE) is regularly used in medical statistics. In order to understand it you need to know not only two fundamental concepts but also above all the difference between them. These concepts are relative risk reduction (RRR) and absolute risk reduction (ARR). Indeed, the formula to calculate vaccine efficacy is the following: $VE = (1 - RR) \times 100$ where RR is the value of relative risk reduction, that is the reduction in the risk of infection between the vaccinated population and the non-vaccinated population of a specific group of subjects in a trial [26–28].

Let us look at an example taken from reality to better understand what we are talking about. As the starting point, let us take the two articles presenting the vaccine efficacy data related to the vaccine for COVID-19 developed by Pfizer [29] and that related to the vaccine for COVID-19 developed by Moderna [30] when we were at the height of the pandemic. In that same year, we all discussed specific data reported by the media, that is a rate of vaccine efficacy of 95% for the Pfizer vaccine. How was this number arrived at, which from merely a media and communicative perspective had a very strong impact?

The calculation to arrive at this figure is the following. The starting point was the total number of subjects who took part in the Pfizer vaccine trial, that is 34,922 persons. Of these, 17,411 were subjected to the vaccine and 17,511 received the placebo. Only 8 people in the vaccinated group got infected while 162 in the non-vaccinated group got infected. The estimate of the probability of getting infected for the group of vaccinated subjects was therefore calculated through the ratio 8/17411 that is 0.046. In the group of non-vaccinated subjects, instead, this estimate is given by the ratio 162/17511 that is 0.925. Given these two probability estimates, the vaccine efficacy is generally calculated by using the ratio. In this case, therefore, 0.046/0.925 = 0.05. This figure given as a percentage has become that 5% in the reduction of the probability of getting infected from which derives the 95% communicated to the media [11, 12].

In itself, the figure of 95% would therefore be the correct number to be communicated to the general public. The basic problem is that a probability of this type, given as a percentage, was misunderstood by the world's population. For what reason? Because when our mind is faced with a figure of 95% of vaccine efficacy it intuitively interprets it in terms of frequency. That is, in this specific case, if the Pfizer vaccine has an estimated efficacy of 95% it means that of 100 persons exposed to the virus, only 5 will contract it. But this certainty is, in actual fact, misleading.

Let us go back over the calculation that led to the figure of 95%. That which has been calculated is what in medical statistics is defined as RRR, a proportional reduction in relative risk, in other words, an estimate based solely on the population that took part in the trial and not the world's population. This specification, far from being superfluous, is fundamental when it is necessary to choose a vaccine. Indeed, the absolute risk reduction, therefore that measurement that allows us to quantify the difference between the risk of disease between vaccinated and non-vaccinated subjects in absolute terms is much smaller. In the case of the Pfizer vaccine, the absolute risk reduction is given by the difference between the probability of getting infected between the two groups, of vaccinated and non-vaccinated subjects: 0.925–0.046 = 0.879. The value of 0.879 is much lower than the 95% of efficacy communicated by all the media. Therefore, we tend to consider 95% as an absolute risk reduction while the figure is actually lower.

3. Misunderstandings about the vaccine efficacy figure

The inability to comprehend the concept of vaccine efficacy just like the lack of knowledge of the two concepts, relative risk reduction and absolute risk reduction, has repercussions on the daily life of the world's population. To understand what we are talking about, let us start by analysing a tangible case: the recent COVID-19 pandemic. The decision to talk about this case is due to the fact that it is the most recent pandemic condition that people have had to face. Furthermore, the emergency led the world's entire population to reflect about vaccines.

People regularly hear talk about vaccine efficacy in the media, and the media tends to give numbers as a percentage. And yet, given the delicate nature of the choice to be made, the information about a vaccine should be gathered by interviewing doctors, especially general practitioners. These doctors are indeed those assigned by the government system to be intermediaries between the pharmaceutical companies, governments, and the general public in a medical setting. However, at least in the case of the COVID-19 vaccine, the information was mostly collected through media channels and spread over social networks. This meant that in terms of vaccine efficacy the world's population encountered a single value, given as a percentage, for each vaccine. This value, as we have seen, expresses an efficacy based on a relative risk reduction, that is a reduction in risk proportional to the sample that took part in the trial. The problem is that this index of efficacy is intuitively and erroneously interpreted by the general population as an index of absolute risk reduction. And this is because of the very operation of our mind.

In 2021 two different types of vaccine, developed by different pharmaceutical companies, were chiefly distributed in Europe. In countries where both vaccines were distributed to the population, controversies arose immediately. For example, in Italy, the two vaccines available in early 2021 were the one developed by Pfizer in partnership with BioNtech (trade name: Cominarty) and the one developed by AstraZeneca (trade name: Vaxzevria). The former is of American and German origin, the latter is of British origin born from the partnership between Oxford University and the pharmaceutical company. Controversies about vaccines in Italy are clearly nothing new. And yet, in this case, the controversy had a very peculiar nature since it started not from the general population but from a group of doctors. In February 2021, in fact, a group of doctors in Rome stated they did not want to accept the vaccination reserved for them with the vaccine developed by Astrazeneca. This one proved to have a much lower declared efficacy than the one developed by the Pfizer pharmaceutical company, administered to their senior colleagues. From then on, we witnessed a succession of fear, scepticism and rejection of the Astrazeneca vaccine. These emotions were also fed by additional communications about the side effects of this vaccine and by suspensions then followed by the authorisation for its administration by EMA. The controversy that fed the debates about vaccine efficacy not only in Italy but also in the rest of Europe was due to the apparent existence of first-class vaccines (such as Pfizer, BioNtech or Moderna) whose declared efficacy was around 95% and second-class vaccines (such as Astrazeneca or Janssen of the Johnson & Johnson group) whose efficacy was around 65–70% [31].

Now, when someone reads that there are two vaccines whose efficacy is 95% in one case and 65% in the other, they immediately think that one vaccine is able to create a greater immunity barrier than the other. Interpreted in this way, however, the figure would seem to have been obtained from a mere difference in efficacy of the two vaccines, which in actual fact is not correct. The problem at the origin of the misunderstanding however is difficult to solve since it depends on the way our mind reasons. Faced with a vaccine efficacy of 95% we think that what they are communicating is a figure that tells us that given 100 people subjected to the vaccine only 5 will fall ill; or, to put a more positive spin on it, given 100 people exposed to the virus 95 will be immune.

4. Human reasoning in the presence of efficacy expressed as a percentage

Several studies [4–24, 26–28, 32–34] have demonstrated that the human mind finds difficulty in interpreting medical statistics relating to vaccine efficacy.

This difficulty is part of the many traps of our thinking that lead us to make mistakes when we have to take decisions or when we need to calculate the probability that an event may occur [30]. These traps are such for all human beings and are part of the very workings of our reasoning. For example, Daniel Kahneman, Nobel Prize winner for economic sciences in 2002, famous for the study of these traps, performed an interesting test. He presented a riddle that throughout history has managed to drive thousands of students of the finest American universities crazy. The riddle at issue is the following: *A baseball bat and a ball cost 1 dollar and 10 cents. The bat costs one dollar more than the ball, how much does the ball cost?* In this case, the answer that comes naturally is 10 cents. However, let us try doing the maths. If the ball cost 10 cents, the price of the baseball bat plus the ball would be 1 dollar and 1o plus 10 cents, that is one dollar and 20. Here then our intuitive, fast thinking leads us in the wrong direction. Another pioneer in studies into the psychology of reasoning, as well as a psychologist who conducted one of the first and most important investigations into the psychology of reasoning is Peter Wason (1924–2003). In 1966, he managed to devise a riddle capable of revealing the fallacy of deductive reasoning. In actual fact what Wason managed to discover with his experiment was not entirely new. Indeed, Aristotle had talked about the problem of deductive reasoning when he introduced what was called *affirmation of the consequent*, that is:

If A then B
B
Therefore: A

This method of reasoning is quite common in human beings and the fact that it had been isolated already in antiquity simply means that it is a matter of a way of reasoning that has always been based on the manner of thinking of human beings. And yet, Wason's research stands out for two factors. The first is that his experiment has been replicated a great many times and always gives the same result. The second is that one of the variants of the experiment presented by Wason demonstrates that this type of fallacious deductive reasoning is affected by the context. Therefore, depending on the contextual information within which the deductive reasoning has to be carried on, this may or may not lead us to error.

The traps of our reasoning are many, but the merit of the psychology of reasoning is of having discovered and explained many of them. In fact, the only chance the human being has of not falling into these traps is the fact of knowing them. One of these, when talking about vaccination, is the one that leads us to remain anchored to a concept of disease that prevents us from bearing in mind all the variables in the very concept of efficacy. It has, in fact, been demonstrated that when the human mind has to reason in terms of vaccines and vaccine efficacy it tends to take no account whatsoever of the factor related to the control population, that is the subjects who are administered a placebo. Faced with information containing data related to sick people and vaccinated or non-vaccinated healthy people, the information that will be taken into consideration will concern the number of vaccinated sick people, the number of vaccinated people or non-vaccinated sick people. However, the control group is not taken into consideration. This means that intuitively when our mind hears talk about vaccine efficacy it thinks it is a matter of efficacy in terms of an absolute risk reduction, that is the reduction in the risk of falling ill if you get vaccinated. However, since the figure presented by the media concerns the relative risk reduction one then runs into a basic misunderstanding leading to overestimate the efficacy and not seeing its immediate application. Furthermore, other studies, conducted into the perception of the efficacy of vaccines for COVID-19, have demonstrated that people tend to identify the figure of vaccine efficacy with the rate of non-mortality among vaccinated people. This is clearly incorrect and over the long term can lead to overestimating efficacy itself [2]. This type of problem in the methods of reasoning has necessarily affected the choice of vaccine and as a result people's daily lives.

5. Repercussions of the mechanisms of reasoning on vaccine choice

We have seen how in Italy in 2021 there was great controversy surrounding the first two vaccines that were distributed: Pfizer and Astrazeneca. This controversy, far from being solely Italian, presented itself in other European countries and in Canada. There were plenty of repercussions and EMA, just like several countries such as Canada for example, opted for an albeit temporary suspension of Astrazeneca. This suspension was requested solely due to an issue concerning the side effects of the vaccine. And yet, if we ask the person in the street about this matter, we will hear that the Astrazeneca vaccine was withdrawn because it was not as effective as the others. From this perspective we can state that the reasoning intuitively conducted by the human mind regarding the concept of vaccine efficacy led to an incorrect interpretation of the figure. In fact, that 65% of efficacy compared to the 95% of Pfizer remained fixed in people's minds. And through an anchoring bias, it meant that the whole history of the Astrazeneca vaccine remained tied to the concept of a vaccine that failed to provide sufficient coverage. This misunderstanding was the reason that triggered the many controversies that broke out in 2021. Moreover, it led many people to refuse the vaccine, or not get the booster, thereby slowing down the process of coming out of the pandemic. In a recent study, the misunderstandings and false myths about vaccines are mostly attributed to an incorrect conception of the concept of risk reduction. This concept is at the base of the related concept of vaccine efficacy. Indeed, the latter is indicated as a relative risk reduction. This has the disadvantage of only considering the subjects who took part in the trial, it is however understood as a figure regarding coverage on the basis of sick people in the world's entire population. The media, moreover, generally publish the figure related to relative risk reduction.

A recent study demonstrates that human reasoning is such as to chiefly conceive the concept of relative risk reduction. Hence, therefore, the proliferation of misunderstandings about the usefulness or lack of one vaccine rather than another or of any vaccine in general. An even more important problem is that in order to choose a vaccine the general population bases itself on what the media publish and on the opinion of the general practitioners. This category of doctors, however, does not seem to be exempt from implementing the common strategies of reasoning that lead to misunderstanding the concept of efficacy. More than the general practitioners it seems that the oncologists, mostly called on to decide in the case of pharmacological therapies and surgery, are facilitated in correctly interpreting the data related to vaccine efficacy. However, they too are only able to interpret it correctly if a greater amount of information is presented.

The concept of efficacy, moreover, is only conceivable within the broader medical statistics founded by Greenwood and his successors [33]. Moreover, studies into vaccine availability, already in the last century, have highlighted how the manner of presenting the data affects their interpretation [35]. And in a historical context such as the current one a manner of presenting data that is not very clear can become very dangerous.

6. Conclusions

Several studies have highlighted that approximately 66% of the world's population uses the internet. These users spend many hours a day on the web [36]. It is clear that the twenty-first century has been marked by the development of digital technology. However, it is necessary to bear in mind that the development of digital technologies, just as their understanding by most of the world's population, underwent a drastic change as regards speed starting in 2020. The pandemic that marked human history brought about an acceleration in the development of digital technology, on the one hand, and in its use, on the other hand. What was a privilege just for some generations has become a worldwide means of communication for everyone. Very small children just like the elderly have learned what the web is, what digital registration is and what a cloud is, but above all what digital communication is. Today, information about vaccine efficacy comes not only from accredited means of communication but also above all from social media. It means our devices keep us constantly connected with all the other human beings, and unfortunately, give everyone a voice on sensitive subjects such as the choice of a vaccine.

So, therefore, it becomes increasingly more urgent to be able to understand what the themes, concepts and notions are on which our mind can lead our reasoning astray. Vaccine efficacy is one of these themes. It is necessary to be able to provide information as correct as possible explaining to the general public what the above-mentioned 95% of efficacy of the Pfizer vaccine means. To do that I believe it is desirable, since we are talking about vaccine efficacy, to explain that the efficacy of a vaccine corresponds to the extent of the relative risk reduction. That is the risk reduction calculated solely on the population that took part in the trial. This figure is a ratio between the two possibilities of risk reduction, that of the vaccinated subjects and that of the non-vaccinated subjects. We cannot then think in terms of frequency that 95% of efficacy corresponds to a probability that of 100 persons 95 turn out to be immune to the virus. Furthermore, it is important to clarify that the figure on the efficacy of the vaccine does not take account of the variables that were not able to be calculated in the trial. Among these, for example, the length of time for which the vaccine is able to remain active or the exposure to the risk of infection of the population. The latter variable is indeed subject to change depending on the areas and persons involved.

Today the pandemic is over, but our way of reasoning in terms of vaccine efficacy still remains the same. This is why it has become important and urgent to manage to implement more precise and accurate communication. Furthermore, it becomes important to permit general practitioners, called upon to provide help in making decisions about vaccines, to understand what information is actually useful to this end. From this perspective, while the development of the vaccines COVID-19 permitted considerable progress, it seems instead that at the level of communication and understanding of vaccines, the general public has still remained very far behind.

Conflict of interest

"The authors declare no conflict of interest."

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Section 2

Zoonotic and Viral Diseases

Chapter 4

The Significance of Education in the Preparedness for Zoonotic Diseases

Natalia Uribe Corrales

Abstract

Zoonotic diseases can potentially cause different illnesses in humans and animals, ranging from mild to severe manifestations and resulting in fatalities. Regrettably, the public and governmental bodies often lack awareness regarding the significance of many zoonoses. Neglected zoonotic diseases, including Leptospirosis, Chagas disease, Leishmaniasis, and various parasitic and virus infections, are particularly concerning. In different contexts, diverse educational strategies address the intricate interplay between human health, animal health, and the environment. By fostering recognition of zoonotic diseases, communities can better understand the underlying dynamics and develop effective prevention, control, and mitigation strategies for improving their health.

Keywords: infectious diseases, knowledge, pedagogy, public health, training

1. Introduction

Zoonoses, which encompass infectious diseases transmitted between animals and humans, pose significant challenges to public health. These diseases can range from illnesses in humans and animals, varying from mild to severe manifestations and even fatalities [1]. Notably, zoonoses constitute a substantial portion of Emerging Infectious Diseases (EIDs), accounting for 60.3% of reported cases according to recent studies [1–3].

Regrettably, many zoonoses remain unfamiliar to both the public and the public and governmental bodies, cognition of their significance. Consequently, numerous zoonotic diseases, such as Leptospirosis, Chagas disease, Leishmaniasis, and various parasitic infections, are often neglected [4]. These diseases predominantly affect low and middle-income countries (LMICs), particularly regions where communities reside near livestock populations.

To address the complex interplay between human health, animal health, and the environment, the concept of "One Health" has emerged as a pivotal theoretical framework. The One Health approach acknowledges the interconnectedness of public health in humans, animal health, and the environment, emphasizing the necessity for a multidisciplinary and collaborative practice [5, 6]. By recognizing the intricate relationships between these domains, the One Health approach seeks to elucidate the

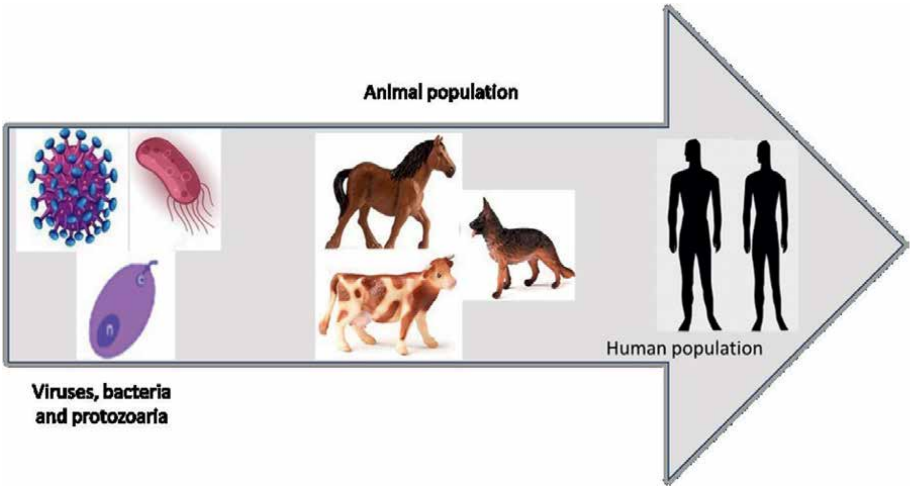

Figure 1.
Dissemination process of zoonotic diseases.

underlying dynamics of zoonotic diseases and develop effective prevention, control, and mitigation strategies.

By conducting a comprehensive exploration of noteworthy zoonotic diseases, their epidemiological characteristics, and the potential impact of education, this chapter aims to shed light on how knowledge dissemination can contribute to enhancing awareness and implementing effective biosecurity measures among the population. Furthermore, it seeks to underscore the significance of informed policy making, emphasizing the imperative for interdisciplinary collaboration in safeguarding public health within our increasingly interconnected world (**Figure 1**).

2. Some important zoonotic diseases

Zoonotic diseases are a significant concern due to their potential to spread from animals to humans.

2.1 Bacteria

2.1.1 Brucellosis

Brucellosis, a bacterial zoonotic disease, is the most prevalent and noteworthy zoonosis. It is acknowledged as both a re-emerging and neglected ailment [7, 8]. In endemic regions, the incidence rate of brucellosis stands at 10%, with a low fatality rate. However, the World Health Organization (WHO) estimates that a considerable proportion of cases go unreported, resulting in only half a million cases being officially registered annually. Moreover, the number of unreported instances exhibiting unspecified clinical symptoms is 10 times higher. Consequently, brucellosis represents a paramount concern in the realm of public health [9]. Notably, individuals across all age and gender groups are susceptible to brucellosis, necessitating the implementation of control measures in humans focused on curtailing animal infections through vaccination and comprehensive care initiatives [7–9].

The causative agent of brucellosis is a bacterium known as Brucella, encompassing distinct species that affect a broad range of susceptible hosts. Noteworthy among these species are *Brucella abortus, Brucella melitensis, Brucella suis, Brucella ovis, Brucella canis, Brucella neotomae*, and *Brucella microti* [10].

Brucellosis can be transmitted through horizontal and vertical routes; this organism exhibits higher concentrations in the uterine region of pregnant animals, with aborted fetuses, placental membranes, and uterine discharges serving as the primary sources of infection. Moreover, the transmission of the disease from infected animals to newborns can transpire through milk contaminated with Brucella organisms. These microorganisms can persist for extended periods, particularly in cold and moist environments. Animals contract the infection by ingesting feed and water that has been contaminated or by meeting aborted fetuses, fetal membranes, and uterine discharges. Additionally, infected bulls can spread disease between herds through natural mating or artificial insemination [11].

Infected animals exhibit various clinical signs, particularly related to reproductive failures, such as abortion and the birth of weak offspring that serve as carriers within the herd. The clinical manifestations and numerous complications of brucellosis in different animal species primarily manifest in the reproductive tract. The disease's incubation period can vary from 2 weeks to several months. Calves can become infected early, but clinical symptoms may only become apparent as they mature. Late abortions in pregnant animals lead to weak calves, reduced fertility, retention of fetal membranes, endometritis, and diminished milk production. The abortion rate in susceptible herds can range from 30 to 80% [7, 9, 12, 13].

The zoonotic significance of brucellosis is experiencing a notable escalation due to various factors, including the substantial growth in the global trade of animal products, rapid deforestation, unregulated and unsustainable development practices, urbanization, intensive farming methods, migratory or nomadic animal husbandry, and increased international travel and tourism [9].

2.1.2 Leptospirosis

This disease poses an epidemic threat, particularly in the aftermath of heavy rainfall [14]. Leptospirosis is caused by the bacterium Leptospira interrogans, which has more than 200 serologic variants and is pathogenic to humans and animals [15]. The primary transmission mode for humans is direct contact with the urine of infected animals or a urine-contaminated environment [14].

Leptospirosis can manifest in diverse clinical presentations, ranging from mild illness to severe and occasionally fatal disease. The symptoms of Leptospirosis often overlap with those of other infectious diseases, such as influenza, dengue, and viral hemorrhagic fevers. Common signs and symptoms include fever, headache, myalgia, jaundice, renal failure, hemorrhage, myocarditis with arrhythmias, meningitis/meningoencephalitis, and pulmonary hemorrhage with respiratory loss [16].

Diagnosing Leptospirosis involves a combination of serology, clinical presentation, and epidemiological data. Serologic tests are commonly utilized to detect specific antibodies in the patient's blood, aiding in confirming the infection. However, it is essential to consider the patient's symptoms, travel history, occupational exposure, and potential contact with animals or contaminated environments when diagnosing [17].

In recent years, an increasing number of cases of Leptospirosis have been documented in various countries within the Middle East. Both human and animal cases have been reported [18], highlighting the widespread nature of this zoonotic disease [19]. Human Leptospirosis often involves individuals working in occupations such as farming and rice field labor, as well as travelers and plumbers. Additionally, Leptospirosis in children and adults who have met infected livestock or contaminated water has been recorded [16].

While animal cases encompass a variety of species, livestock are commonly affected by Leptospirosis. Furthermore, there have been reports of direct detection of Leptospirosis in water resources, underscoring the potential for waterborne transmission of the disease [17, 19].

Preventive measures are crucial to mitigate the health and economic consequences of Leptospira infection in the community. These measures include a comprehensive understanding of the disease's epidemiology, raising public awareness about the risks and prevention methods, and implementing vaccination programs for domestic animals and high-risk populations.

2.2 Viruses

2.2.1 Influenza

The avian influenza virus (AIV) is classified within the family Orthomyxoviridae and the genus Influenza virus A [20]. Wild aquatic birds, specifically ducks, gulls, and shorebirds, serve as this virus's primary hosts and natural reservoirs. Consequently, the wide geographic distribution and circulation of AIV can be attributed to these bird species [21].

Various factors have contributed to the increased spread and occurrence of AIV outbreaks globally. These factors include the expansion of international trade, intensified poultry production practices, climate alteration, bird migration patterns, human mobility, and the rapid growth of the global population [22]. Many countries engage in commercial farming practices involving high-density poultry populations and bird rearing in free-range environments, such as backyards and rooftops [23]. Consequently, backyard birds have emerged as an intermediary host for AIV transmission, affecting commercial poultry and human populations, primarily because backyard farms often lack adequate biosecurity measures, given their outdoor enclosures [20, 23].

Bird-to-human transmission of avian influenza has predominantly resulted from direct contact with infected backyard birds and through slaughtering and de-feathering. In terms of specific sources of exposure, the reported cases of human infections have been attributed to interactions with backyard poultry (70%), domestically bred birds (26%), slaughtered poultry (14%), or deceased birds (4%) [24].

Notably, avian influenza viruses have sporadically crossed over to infect other mammalian species. Among these, pigs play a significant epidemiological role in the evolutionary dynamics of novel influenza viruses due to their susceptibility to avian and human influenza viruses, facilitating viral reassortment and the emergence of new strains [20].

2.2.2 Rabies

Rabies is an acute viral infection caused by lyssaviruses, capable of infecting all terrestrial mammals. The primary transmission mode is through infected animals' saliva, typically from bites, although scratches and organ transplants can facilitate transmission in rare cases [25]. This disease has a profound global impact, with an estimated annual death toll of 59,000 individuals attributed to dog-mediated rabies. Alarmingly, approximately 40% of these fatalities occur in children under the age of 15 years [26], disproportionately affecting impoverished and underserved communities. Developing countries in Africa and Asia bear the heaviest burden of this disease [10]. Consequently, rabies presents significant global social and public health challenges and a substantial economic burden estimated at $8.6 billion annually [27].

The World Health Organization (WHO), in collaboration with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (WOAH), has set a vision to eliminate dog-mediated rabies by the year 2030 [25]. This ambitious goal aligns with broader global objectives, such as poverty alleviation and the reduction of childhood mortality, as outlined in the Millennium Development Goals. While achieving this target by 2030 poses a significant challenge for specific regions, it is noteworthy that many of these areas consistently try to enhance their capacity to combat rabies [26, 28].

Rabies presents itself in two distinct forms: encephalitic (furious or classical) and paralytic (dumb) rabies. The encephalitic form, which is more prevalent, is observed in approximately 80% of patients. Among these cases, a significant proportion, ranging from 50 to 80%, exhibit classic symptoms such as hydrophobia and aerophobia, which are unique to rabies [3, 29]. This presentation typically progresses to severe flaccid paralysis, coma, and death due to multiple organ failures. In contrast, paralytic rabies manifests with pronounced muscle weakness early in the disease course [30].

The incubation periods for both encephalitic and paralytic rabies are comparable, from 2 weeks to several months. The typical incubation period in humans ranges from 2 to 3 months [31]. Regrettably, there is no recognized or approved treatment for rabies once clinical symptoms have manifested. Nevertheless, palliative care is advised for individuals afflicted with rabies to alleviate suffering and potentially extend survival time temporarily (references [32] and [33]). However, it is essential to note that effective pre-and post-exposure prophylaxis measures are available [30, 31].

2.3 Protozoa

2.3.1 Chagas disease

This disease is caused by the parasite *Trypanosoma cruzi* (*T. cruzi*) is a zoonotic infection primarily prevalent in Latin American countries [32]. This disease is estimated to affect 8 to 11 million people worldwide. Chagas disease carries significant health implications, with approximately 20 to 30% of infected individuals developing a chronic form of the infection that can lead to fatal heart or gastrointestinal diseases [34, 35].

Transmission of Chagas disease occurs through various means. The most common transmission mode is through contact with the feces or urine of the reduviid bug, also known as the triatomine bug or kissing bug, which serves as the intermediate host for the parasite. Vertical transmission from mother to fetus is another route of infection. Additionally, the disease can be transmitted through blood transfusions, organ transplants from infected individuals, or consumption of contaminated food or drinks [36, 37].

The clinical symptoms of Chagas disease can be diverse, but significant complications often include cardiomegaly (enlargement of the heart), gastrointestinal disorders, and, in some cases, peripheral neuropathy. The chronic form of the disease can have severe consequences, potentially leading to life-threatening conditions [32, 37].

Despite the significant impact of Chagas disease on public health, no vaccination is currently available for its prevention. Consequently, controlling the disease relies on vector control, which involves reducing the population of triatomine bugs and improving housing conditions to minimize contact with the bugs [34].

Efforts to combat Chagas disease also involve blood and organ screening to prevent transmission through transfusions and transplants. Public health initiatives focus on raising awareness about the disease, promoting early detection and treatment, and implementing preventive measures to reduce exposure to the vector and contaminated sources. Likewise, developing an effective vaccine would be a significant breakthrough in the fight against Chagas disease, offering long-term protection and contributing to its eventual eradication [34, 35, 37].

2.3.2 Leishmaniasis

Leishmaniasis, a vector-borne disease, represents the most marginalized condition of its kind and can be attributed to various obligate intracellular protozoan species belonging to the Leishmania genus. These parasites are transmitted between mammalian hosts primarily through phlebotomine sandflies. Regarding disease epidemiology, dogs play a pivotal role among domestic animals [38].

The diseases can be classified into two distinct types based on the primary reservoir hosts responsible for human infection: zoonosis and anthroponosis. Zoonosis is an infectious disease that primarily affects animals but can be transmitted to humans, whereas anthroponosis denotes a naturally occurring condition primarily affecting humans [38, 39]. The majority of Leishmania species are implicated in zoonotic transmission. Infected animal reservoir hosts are often introduced into humans, leading to spillover events and subsequent zoonotic diseases. Within humans, twenty-two *Leishmania* species belonging to the subgenera *L. (Leishmania), L. (Mundinia),* and *L. (Viannia)* have been identified.

Leishmaniases encompass a wide range of clinical presentations, encompassing self-healing localized or multiple cutaneous lesions, mucosal lesions, and potentially life-threatening visceral forms. Although specific species or subgenera are often associated with conditions, these manifestations are not exclusive to a single species [10]. Cutaneous Leishmaniasis (CL) often results in self-resolving skin lesions that leave permanent scars. However, certain species can lead to more severe pathologies, including mucocutaneous (MCL), diffuse (DCL), or disseminated (DL) cutaneous leishmaniases. Visceral Leishmaniasis (VL), known as kala-azar, represents the most severe form of Leishmaniasis and can be fatal if left untreated. Prominent clinical indicators include non-tender splenomegaly, with or without hepatomegaly, and individuals with pre-existing health conditions may develop post-kala-azar dermal Leishmaniasis (PKDL) because of treatment [25].

Additionally, environmental changes and socioeconomic factors, such as inadequate housing and sanitation, malnutrition, and population mobility, significantly influence the dynamics of vector-borne diseases. These anthropogenic factors often lead to alterations in the composition and behavior of sand fly vectors.

2.3.3 Toxoplasmosis

Toxoplasma gondii is an apicomplexan parasite widely recognized as one of the most significant zoonotic protozoan infections due to its pathogenicity during gestation in various animal species, including humans. Its definitive host is domestic cats and other felids [40, 41].

In the feline population, the life cycle of T. gondii is typically sustained through their predation of rodents, such as mice. For instance, a study conducted on a cat population in southern Poland revealed that 68.8% of the animals tested seropositive for T. gondii, with a notably higher prevalence observed in older cats (> 1 year) (83.5%) compared to younger cats (48.3%), as well as in cats dwelling outdoors as opposed to indoors (69.7% vs. 16.7%) [42]. The presence of T. gondii infection in marine mammals has raised concerns regarding the potential role of reptiles (e.g., turtles, crocodiles, snakes), amphibians (e.g., frogs, toads), and fish as sources of infection [43].

Dogs and cats, particularly those exhibiting feral behavior, significantly threaten biodiversity. However, it should be noted that predation can also transmit parasites, some of which may possess zoonotic potential, posing risks not only to our companion animals but also to human health [44]. Nonetheless, despite the potential for zoonotic transmission, most research and efforts have primarily focused on the impact of predation on conservation [41].

Regarding Toxoplasmosis, the parasite Toxoplasma gondii can be vertically transmitted to various intermediate host species, including humans. Given that farm animals serve as sources of infection for humans and reservoirs of T. gondii for wildlife, it has been suggested that efforts be directed toward minimizing T. gondii infections in livestock, particularly in the case of pigs [40–42].

3. Educational strategies

3.1 Description of the condition

To address the prevention of human diseases is necessary to first focus on addressing what is happening in the animal kingdom. In the years past, most of the numerous main human epidemics infectious diseases that caused morbidity and mortality worldwide are transmitted from animal to human either directly or indirectly through products of animal origin [45], so a better and more precise knowledge and understanding with a solid awareness of the implications of zoonotic diseases to public health may result to improvement in surveillance and intervention systems for prevention and control [46, 47].

3.2 The influence of educational initiatives on the prevention and management of zoonotic diseases

The efficacy of preventive and control measures against zoonotic diseases is contingent upon disseminating accurate and timely information through awareness, education, and knowledge-sharing mechanisms. The promotion of awareness concerning these diseases relies on the effective utilization of information, communication, education, and technology transfer, in conjunction with the recognition, investigation, collaboration, advancement of diagnostic techniques, the deployment of surveillance tools, the application of epidemiological practices, and the utilization of molecular biology methodologies [48].

It is imperative to foster awareness and educate the public about zoonotic diseases' risk factors and potential reservoirs. This approach facilitates a comprehensive comprehension of pathogen diversity, reservoir specificity, and the development of preventive and control strategies for such conditions. Notable instances showcasing the effectiveness of awareness campaigns include the general awareness among European populations regarding the risk of human infection associated with prion-contaminated beef meat (linked to bovine spongiform encephalopathy), as well as similar awareness initiatives observed in North America [25].

3.3 Some health education initiatives around the world

Health education initiatives play a significant role in disease control, although they are often overshadowed by more prominent intervention programs [2]. These initiatives can adopt various formats and have been implemented worldwide.

In the past, community education efforts primarily relied on pamphlets, community health workers who would disseminate information to village communities, and radio and television advertisements. Posters have traditionally been employed to convey health-related information to school-aged children. However, in today's increasingly digital era that fosters interactive experiences, signs often need to be revised to engage children effectively. Consequently, over the past two decades, numerous endeavors have been made to deliver health education through media such as cartoons, films, radio programs, comic books, and cultural performances [34, 46, 49].

The Meena Communication Initiative (MCI) is an exemplary health education program which emerged as a pioneering Education Entertainment (EE) project in Southeast Asia in 1991 [50]. This project created at least seven episodes, focusing on public health topics such as handwashing, worm prevention, and pediatric diarrheal disease [33].

A study in Nepal in 2002 revealed that 96% of children who engaged with the Meena media reported implementing at least one behavioral change, with handwashing being the most frequently mentioned change [49]. Meena was regarded as the most efficacious strategy ever devised by UNICEF, as even young adults in their late twenties continued to recollect the lessons imparted by Meena regarding handwashing and hygiene [2, 33, 50].

Another educational program is "The Magic Glasses," a 12-minute cartoon explicitly developed for implementation in Hunan province, China. This animated production revolves around a child bestowed with special glasses enabling him to perceive the larvae and eggs of soil-transmitted helminths within his village. As he explores the community and witnesses the impact of worm infestation on places and individuals, he resolves to educate his fellow villagers about these parasites and methods to prevent infection [51].

The positive reception from children underscores the effectiveness of this tool in imparting knowledge to schoolchildren on averting soil-transmitted helminth infections. In the group of students exposed to the video intervention, there was a 50% reduction in disease prevalence compared to the control group, which received a poster containing essential information on soil-transmitted helminths. Furthermore, there was a noticeable increase in handwashing behavior among children in the intervention group after using the bathroom and before meals [52].

Snakes and Ladders have been utilized in various studies conducted in Asia and Africa to assess the effectiveness of health education interventions targeting schistosomiasis, *Taenia solium*, and *Taenia saginata*. To gauge the efficacy of this game as an intervention tool, students who had yet to receive any prior educational interventions were requested to complete a pre- and post-game questionnaire. Before laying the competition, students were presented with a questionnaire consisting of 10 fill-in-the-blank questions. Subsequently, after engaging in the game, they were provided with a post-game questionnaire containing the same set of questions as the pre-game questionnaire. The analysis revealed an 18.5% increase in correct answers between the pre- and post-game questionnaires, indicating that even a brief period of interaction with the game could enhance knowledge acquisition [53, 54].

Juma Na Kichocho is a comic book designed to educate children in Zanzibar, Africa, about schistosomiasis and malaria. While malaria had been a topic covered in routine health education at local schools, no such educational efforts had been directed toward schistosomiasis. The comic book is a child-friendly medium through which information on symptoms, transmission, life cycles, and control measures of both diseases is presented. Before distributing the comic books, students were administered a pre-exposure knowledge, attitudes, and practices (KAP) questionnaire. Subsequently, the comic books were distributed alongside a 30-minute presentation delivered by a health educator from the Helminth Control Laboratory Unguja. Over the following year, teachers were encouraged to incorporate comic booklets into their school health education curriculum. The initiative culminated in administering a post-exposure questionnaire to assess the participants' KAP. The results obtained from the post-questionnaire indicated a no significant increase or decrease was observed in schistosomiasis-related knowledge [2, 55].

"The Vicious Worm" is a computer program specifically developed to facilitate the educational process surrounding the topic of *Taenia solium*, a parasitic infection. The program's primary objective is to disseminate comprehensive information about the transmission, diagnosis, risk factors, prevention, and control measures associated with the disease. Each of these aspects is further subdivided into relevant subsections, encompassing hand hygiene practices, safe procurement and preparation of uninfected pork, pig husbandry techniques, the life cycle of *Taenia solium*, appropriate slaughtering methods, and meat inspection protocols. Upon accessing all the informational sections, users are given a quiz within a virtual schoolhouse designed to assess their comprehension of the acquired knowledge. The initial evaluation of this program took place in Tanzania, East Africa, involving 79 participants from the agriculture and health sectors. Notably, all subjects scored 70% or higher on the pretest before engaging with the program. After a session lasting approximately one and a half hours, all participants displayed a significant improvement in knowledge, as demonstrated by their post-program assessment results [56].

A subsequent follow-up assessment was conducted 2 weeks after the utilization of the program, revealing that all participants achieved higher scores than their initial baseline scores. Furthermore, a secondary follow-up evaluation involving the same participants was conducted 1 year later. Although the results demonstrated a decline from the 2-week post-test scores, they remained superior to the original baseline scores. Moreover, it was observed that 82% of the participants (50 individuals) had engaged with the Vicious Worm program on multiple occasions, either for personal learning or to facilitate knowledge sharing with others [55, 56].

Mobile health applications and programs, designed to monitor health, manage doctors' appointments, and facilitate virtual consultations with healthcare professionals, are anticipated to benefit individuals in low- and middle-income countries (LMICs). This is attributed to the fact that mobile internet usage is the primary means of accessing the Internet for a significant portion of the population in LMICs [57].

Numerous Mobile Health applications allow users to access disease-specific information and track symptoms. An advantage of these applications is that they facilitate the dissemination of essential training materials and medical information to community health workers. To illustrate, during the 2014 Ebola outbreak in Nigeria, the Adandach Group developed a mobile tutorial for healthcare professionals. This tutorial provided comprehensive insights into the causes, diagnostic methods, transmission pathways, and field treatment of Ebola. Equipped with this knowledge, previously uninformed healthcare workers were able to enhance their self-protection measures and safeguard the well-being of patients visiting their clinics [2, 8].

Amidst the Covid-19 pandemic, numerous applications were created to monitor potential virus symptoms, perform contact tracing, and issue notifications. Utilizing such apps could prove valuable in managing future outbreaks of Ebola or other pandemics. While these applications may possess limited practicality for most zoonotic diseases, they have the potential to serve as a reporting mechanism for identifying cases. Furthermore, in conjunction with this program, numerous similar initiatives have been implemented in various countries, leveraging similar technology to furnish healthcare workers with current resources and facilitate communication with patients residing in remote areas [58].

3.4 Significant impact of modest outcomes

The efficacy of theoretical and practical instruction within the educational setting has been demonstrated in fostering comprehension of the phenomenon of disease transmission in a circular manner, wherein diseases are transmitted between animals and humans and back to animals. Noteworthy investigations have revealed that theoretical lectures can enhance knowledge of zoonoses and equip the populace with preventive measures, as evidenced by **Tables 1** and **2** findings. These findings substantiate an overall increase in general awareness, suggesting that adolescents possess the necessary resources to address such diseases when adequately informed effectively [6, 59].

The acquisition of proficiencies and aptitudes in health prevention and zoonotic diseases holds paramount significance in equipping future generations to safeguard themselves against present and forthcoming infectious diseases [60]. Implementing corrective measures should commence with health prevention initiatives within educational institutions and integrating early education principles. Furthermore, specific investigations reveal that health education and hygiene instruction should be more valued, particularly among children and adolescents. Nevertheless, several authors have demonstrated that health education alone can serve as an effective preventive measure against zoonoses such as toxocariasis and others [61].

Within this framework, recognizing the risk associated with zoonotic diseases is essential for implementing effective prevention strategies. However, the public's inadequate comprehension of zoonotic illnesses presents a significant concern. The limited understanding observed in this study regarding zoonotic diseases is not unexpected, as regrettably, these subjects are absent from the curricula of numerous educational institutions worldwide [25, 62].

Adolescents' population	Percentage of adolescents who do not know about zoonoses before educational intervention. Germany, Slovenia, Friuli Venezia Giulia, Carinthia (n = 656)	Percentage of adolescents who do not know about zoonoses after educational intervention. Germany, Slovenia, Friuli Venezia Giulia, Carinthia (n = 338)
Can pets like dogs and cats become sick like humans?	11.89%	9,97%
Must dogs be given medication against intestinal worms at least once a year?	23,78%	8,54%
Is it worthwhile to vaccinate dogs against rabies and other diseases?	8,69%	3,32%
Many diseases that affect humans come from animals.	28,96%	20,47%
Zoonoses are diseases transmitted from animals to humans.	32,16%	15,18%
Can pet animals transmit diseases to humans	31,40%	9,48%
Can humans transmit diseases to animals?	59,91%	34,52%

Modified from "What Do Adolescents Know About One-Health and Zoonotic Risks? A School-Based Survey in Italy, Austria, Germany, Slovenia, Mauritius, and Japan" [59].

Table 1.
Knowledge about general zoonoses in adolescents.

Adolescents' population	Percentage of adolescents who do not know about these zoonoses before educational intervention. (n = 315)	Percentage of adolescents who do not know about these zoonoses after educational intervention. (n = 315)
Rabies	87,30%	19,36%
Brucellosis	85,07%	31,74%
Leptospirosis	86,98%	57,14%
Bartonella's	86,66%	51,42%
Leishmaniasis	74,60%	39,68%
Giardiasis	70,79%	41,58%
Toxoplasmosis	79,68%	38,09%
Toxocariasis	89,52%	49,52%
Ancylostomiasis	78,41%	44,12%
Scabies	66,98%	25,39%
Dermatophytosis	71,11%	24,44%

Modified from "Improving the knowledge of high school students about zoonotic diseases from pets in Medellín-Colombia" [6].

Table 2.
Knowledge about zoonotic diseases in high school students.

4. Conclusions

Zoonotic diseases prevail in various contexts, highlighting the need to develop diverse strategies to enhance knowledge about these diseases. Many zoonoses continue to pose significant challenges for low- and middle-income countries, resulting in illnesses and even fatalities. However, considerable potential exists to leverage advancements in children's programming by integrating health education messages into widely popular cartoons and media, addressing this pressing issue.

Various health education interventions exhibit varying levels of effectiveness, with a select few demonstrating enduring impacts on their recipients. This presents numerous opportunities to enhance and broaden educational programs, increasing their effectiveness across different countries.

Given the perpetual struggle between our species and the potentially fatal zoonotic diseases, it is imperative to incorporate the One Health concept into school curricula. As Isaac Asimov astutely remarked, "Education is something you cannot finish," emphasizing the ongoing battle against pathogens that never ceases.

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Chapter 5

Preparedness for Viral Outbreaks: Making Accurate Predictions from the Outset

Ana Cascon and William F. Shadwick

Abstract

An epidemic of an unknown virus introduces extreme uncertainty and can, as we found in 2020, easily lead to panic reactions. Only data subjected to mathematical analysis—statistical analysis above all else at the outset—can give a quick understanding of the seriousness of the situation and provide the means for immediate contingency planning. To understand the Covid-19 crisis, we used Extreme Value Theory (EVT) techniques that extract information from the tails of distributions, where the information about 'catastrophic events' resides. We describe how the information so obtained gave us the predictive power essential for contingency planning very early in the Covid-19 pandemic. We also describe the epidemiological model we developed, which extends the initial statistical work and gives a complete toolkit for predicting the behaviour of a viral outbreak in time to be effective in dealing with it. Finally, we talk briefly about the importance of a readily accessible worldwide population and disease database to aid in the preparation for future emergencies.

Keywords: predictive power, mathematical models, extreme value statistics, data based, small data sets, creation of international database

1. Introduction

> *'It doesn't matter how beautiful your theory is, it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong.'*
>
> —*Richard P. Feynman [1]*

One of the main qualities of human beings is the ability to transform the unknown into something manageable, predictable and ultimately controllable. We are surrounded by examples of this, from the astronomical observations of the ancients and millennia of using plants for medicinal purposes to the whole body of empirical knowledge leading to the science we depend on today for all of modern medicine and technology.

For this, we have used observations and experiments, constantly testing our knowledge of how nature works. When this process develops to the level of a theory

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of why or how things occur, we must verify that our theory is capable of making useful predictions.

Theories which are incapable of prediction have no value in this enterprise, as Feynman so memorably said.

The same empirical knowledge that was used to guide cannon balls into enemy fortifications—then transformed into laws by Isaac Newton—now allows us to send spacecraft to the moon. Because the laws make predictions whose accuracy can be tested, those tests tell us the theory is not accurate enough to send probes to the outer planets—for that, we need Einstein's refinements. And those, in turn, have had their accuracy proved by observation and experiment.

The same process applies equally to biology and medicine. When a new virus appears, we try all imaginable ways to understand how to deal with it, using models and laboratory experiments and trying new, and old, medicines.

The danger of making assumptions before observing and experimenting is well illustrated by the occurrence of an outbreak of the common cold, a coronavirus, in an Antarctic base after 17 weeks of complete isolation [2]. This example is of particular importance here, since many of the models that have been developed to understand viruses make assumptions about the spread of diseases and, in particular, means for preventing that spread that have never been proven.

That these models have never been validated by testing their predictions against real data was somehow not considered at the outset of the Covid-19 pandemic when they were used to guide public policy.

The most important thing we can do at the beginning of an epidemic is the most basic of all. Make observations and collect and study the primary data, which is the number of infections, the proportion of those that require hospitalisation and the proportion that result in death.

The essential tool in this phase is the statistical analysis of those observations to make provisions for the burden on the medical system. We should do this because it works. And because the fear that hospitals would be overwhelmed led to disastrous public policy decisions almost everywhere.

2. Application of statistics to the virus threat

2.1 What are the right tools? The statistics of the 'extreme values'

When observing natural phenomena, like the daily maximum temperature in summer, the severity of earthquakes, or deaths caused by viruses, we always have a large cluster of data around the average, the mean value, and we have the 'tails', data that is far from the mean.

Averages, as the name indicates, describe 'the status quo'. No hospital is worried about seeing the average number of patients showing up in the emergency department. The tail of the distribution of hospital admissions, the departure from the average, on the other hand, is what we need to understand to be prepared for bad times.

In a viral epidemic, with rapidly growing numbers of hospital admissions, the important information about daily admissions is how much bigger they are likely to be than the ones we have already observed. That's what we need to be able to predict.

We are prepared for average-strength earthquakes, with evacuation plans and reinforced buildings, as well as for average years of influenza and other virus infections with hospital capacity, medical supplies and staff capability for the average disease seasons.

To deal with exceptional cases, such as an epidemic of infections with a previously unknown virus, we have to turn to the area of probability and statistics, which is designed to make predictions about events far from the average.

That subject is called Extreme Value Theory. It is what insurance companies use to attempt to set the correct premiums for earthquake insurance or damage from hurricanes, knowing as they do that an event worse than those already observed can be expected to happen someday.

That's completely analogous to our hospital admissions problem. On 3 March 2020, New York City recorded its first Covid-19 hospital admission. On 13 March, 145 Covid-19 patients were admitted, and by 19 March the daily number had ballooned to 571. Two days later, Governor Cuomo made his fateful 'Pause' order, shutting down the city and the state. He had been advised by Imperial College modellers that 'unless drastic measures were taken—intensive care units would have 30 Covid patients for every available bed' [3, 4].

In the event, by the end of March, admissions had peaked at 1835 in a single day and began to subside.

The question that the mayor and governor would have liked the answer to on 19 March, when the then frightening level of 571 daily admissions had been reached, were: How many admissions should we expect on a day that exceeds 571, the largest number at that point?

Imperial College modellers did not know how to answer [5]. For that, we need statistics.

2.2 The statistics of 'How much worse can it get?'

On 19 March 2020, when 571 Covid-19 patients were admitted, everyone would have liked to know the answer to this question.

Of course, nobody can give an exact answer—but using statistics, we can give the answer on average. In other words, it is perfectly possible to answer the question: 'Over the days when more than 571 people are admitted, what will the average admissions be?' On 19 March 2020, our answer would have been 1246. Over the next 2 months, there were 34 days with more than 571 admissions, but their average never exceeded our estimate by more than 15%.

To provide these answers, we use a variant of the subject called Extreme Value Theory (EVT).

Unfortunately, for NYC and the rest of the world that was affected by Covid-19, there is no possibility of conventional EVT [6] addressing a problem with so little data. EVT has largely been applied to actuarial or financial problems where huge data sets of observations are available.

As it turns out, we discovered a new approach to EVT that we have been using for many years to make good predictions about the tails of even very small data sets. We proved, too late to help New York in 2020, that our methods provide reliable estimates of the size of Covid-19 outbreaks from the outset in NYC and elsewhere to the endemic phase. Now our methods have been available for almost 2 years and should be in use to help deal with the ongoing Covid-19 crisis.

2.3 The mathematical idea

From the outset, there was significant controversy about the degree to which Covid-19 was unprecedented, especially as the public policy responses were unprecedented [7]. Headline numbers of deaths appeared worldwide with no context, no reference to normal seasonal mortality.

Was Covid-19 an average epidemic, or were these numbers far above average? But what does it mean to be 'far above the average'? We saw many discussions about the 'departure from the average number of deaths or the average over the most recent five years,' but the average does not convey the variability of the historical record. Even worse was the assumption that the standard deviation from the 5-year average was a useful indicator of what was happening in the spring of 2020.

When we started considering this problem in April 2020, we used our standard approach of working purely with data, making no assumptions. We compared weekly Covid-19 deaths in 2020 with weekly deaths from all causes over the same period from all previous years where the data was available [8].

Working with no assumptions gives us a unique window into the problem of virus infections. We look at the information given by the data, which is what already happened, and find an estimative of what is likely to happen on average. We cannot possibly say what will happen on a certain day or how large or small it is going to be, but we can say what is likely to happen. Enough to make predictions, which is the hallmark of good science.

2.4 Immediate evaluation of the seriousness of the threat

It's easy to calculate the difference between the 5-year average weekly deaths in England and Wales in the second week of April (10,520) and the number of deaths recorded in the second week of April 2020 (18,516). The fact that deaths recorded in this particular week were 76% above the 5-year average conveys absolutely no information.

To make any meaningful inference about the deaths in the second week of April 2020, you needed to know how much variability there is in the weekly death data.

To exemplify what can be done at the first level, when we have deaths' data but not likely enough data related to a new virus, we will mention two studies we did.

I like to say we wanted to know if this new virus was something that comes from Mars and is so completely unforeseeable, or if it could be seen as a consequence of changes in life.

The critical question to ask is how likely it is that the maximum number of weekly deaths observed so far will be exceeded, and if it is, what the average excess will be [9].

To verify the accuracy of our tools, we did a test of the robustness of the method using weekly Brazilian data to see if the 2016 peak was predictable by looking at the 'in-sample' period from January 2001 to the end of 2015. The worst week in the in-sample period was 26,172 in June 2015.

The key question is how bad the situation can get if this maximum from June 2015 is exceeded. According to our analysis, if the situation got worse, the average excess deaths would be 28,629. Indeed, in June 2016, a new record week was recorded. The number of deaths was 28,709. In 2016, 2017 and 2018, there were 33 weeks exceeding the previous maximum of 26,172, and the average number of deaths in those weeks was 26,989—only 6% lower than our prediction.

We proceeded with the same study for Brazil using weekly data from 2001 to 2018 [10], and for some European countries, Denmark, the Netherlands, Sweden and the UK., the records we have start in 2007, 1995, 2000 and 2010, respectively [11]. Using this data until the end of 2019 did allow us to make predictions for 2020 that were in very good agreement with reality.

What we found out is the number of deaths in 2020 was indeed high, but predictable, that is, compatible with what has been seen before.

2.5 Bounds on growth for hospital admissions: an essential tool for contingency planning

As soon as we had some data about Covid-19, we could do some estimations of the growth of the virus. We used all the data available, which was not a lot, but we managed to create bounds of growth that have been proven to be predictive.

The method we are going to describe here can be used for all sorts of planning: infections, deaths, hospitalisations, hospital beds, equipment and personnel.

As we already described, the idea is to use a statistical technique for making estimates far from the mean. We observed Covid-19 waves separated by only 3 weeks, so our standard approach during the endemic phase has been to use 3 weeks of hospital admissions data to estimate bounds on growth for the next few weeks.

At the outset of the epidemic, or in any new epidemic, we may have even less data available. For example, as we discussed in Section 2.1, on 19 March 2020, 2 days before Governor Cuomo's 'Pause' order went into effect, we would have had only 17 days of hospital admissions to advise the governor what to expect—and it would have been enough.

As we described before, the idea is to take the sample maximum and find Level 1, the average number of admissions conditional on exceeding this maximum. This calculation gives us our first bound on cumulative admissions, which is linear growth at Level 1 admissions per day.

Level 2 is the calculated average conditional on exceeding Level 1, and Level 3 is the calculated average conditional on exceeding Level 2. Linear growth at Level 2 and Level 3 admissions per day will be used once the Level 1 growth bound is exceeded by 10% or more.

Note that as long as average admissions over K days are less than or equal to Level 1, then simple arithmetic means that the sum of those admissions over K days must be less than or equal to K times L1—exactly the result of linear growth at L1 admissions per day. We can see in the sample below (**Figure 1**), which was based on 21 days of hospital admissions in England until 5 December, that the hospitalisations were well within the bounds. When we made this estimate, the UK government was being pressured to 'cancel Christmas' by its scientific advisors who had vastly overestimated the impact of the Omicron variant [12].

It is very important to note that we have been making accurate predictions, as illustrated above, in real time for English hospitalisations since November 2021. A more detailed description of our predictions, with the EVT bands for the beginning of the waves and including the epidemiological model that we describe below, can be seen in [13].

2.6 An epidemiological study of viral growth that makes accurate predictions

We have shown that the epidemic curve of cumulative events in viral outbreaks is a Gompertz function. This is a 'first law of virus dynamics' that is analogous to the observation by Galileo that projectiles follow parabolic paths. It does not explain why that's the path followed—but it allows accurate predictions to be made. A Gompertz function fit to observed data can be projected forward to predict future growth—at first for a few days and then for weeks at a time.

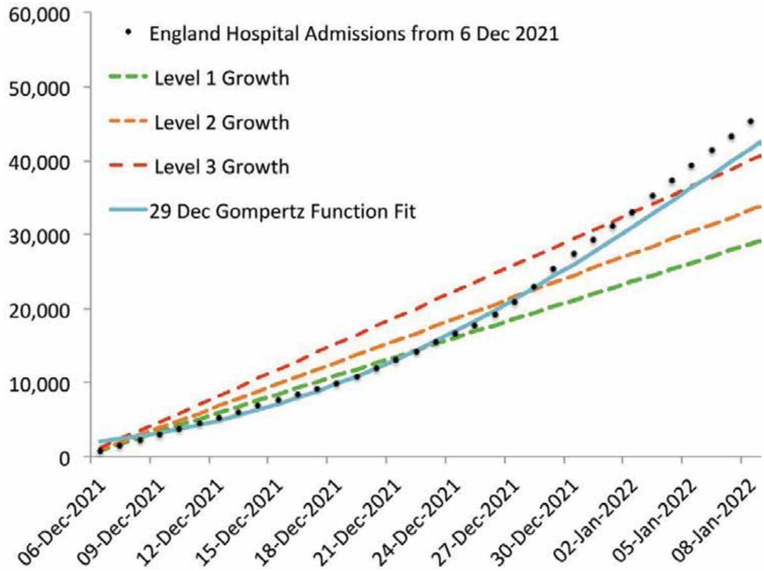

Figure 1.
The 29 December 2021 Gompertz function fit's prediction errors never exceeded 9.2%. The level 3 bound was only breached in the first week of January, after our target level of predictive power had been achieved.

Not only does this model correctly describe the Covid-19 outbreaks, but also all the viral outbreaks of the past for which we have been able to obtain data, and most recently, the monkeypox epidemic (**Figure 2**).

In cases such as monkeypox, the initial outbreak leads to a series of Gompertz function 'approximations' (fits made by non-linear regression from observed data) which rapidly converge to their final form. In cases such as Covid-19, the Spanish

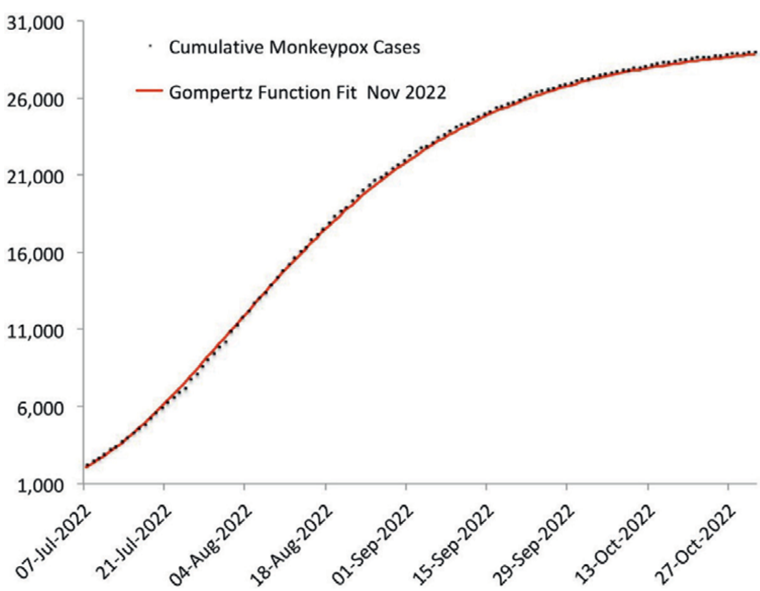

Figure 2.
Cumulative US monkeypox cases, July to November 2022.

influenza pandemic or seasonal influenza, the initial Gompertz function growth is followed by a linear growth.

These two modes alternate, creating what everyone knows as the seasonal influenza cycle and what was observed initially as successive 'waves' of Covid-19 outbreaks.

This model is a stark contrast to the 'state of the art' compartmental models, whose proponents are careful to explain that their models are producing 'scenarios' and not predictions [14].

Our model, which was published on 26 December 2021 [15], was discovered by working with data from viral outbreaks, with no assumptions and with the goal of making predictions that were accurate enough to be useful during an epidemic. As we have said before, a mathematical model must be able to make accurate predictions to be valid.

Previous attempts to use the Gompertz function to predict the course of the Covid-19 outbreak, such as Michael Levitt's [16], failed this test because their authors missed the significance of the transition to linear growth—indicating endemic disease.

There is no way to predict the timing of this transition, so it was never possible to predict the outbreak fully simply by identifying the final Gompertz function fit.

Once the transition is made, linear extrapolation gives excellent predictions until the next outbreak. This is marked by a sharp increase in the slope of the line of best fit. At that time, we use the statistical techniques described above on the most recent 21 data points to provide bounds on the growth of the new outbreak. This gives excellent predictions until the next Gompertz function phase is sufficiently well established. This typically takes 3 to 4 weeks.

During the Gompertz function growth phase, a series of Gompertz function fits to cumulative admissions data allows us to make predictions by extrapolating forward along the fitted curve. The prediction errors become smaller and remain smaller for longer as the outbreak progresses. Typically, within about 2 weeks, prediction errors remain below 25% for at least a week out of the sample, and in 3 to 4 weeks, the errors will remain below 10% for at least that long. Our growth bounds are created when we detect a transition from linear growth to the next Gompertz function outbreak phase. They are intended to contain cumulative admissions until the Gompertz function fits' prediction errors remain below 10% for at least a week.

We refer again to [13] for a full description of the complete process.

For the first time since March 2020, a combination of our model with the EVT methods presented here provides a means to navigate successive waves of Covid-19 with reliable projections for the short- to medium-term future.

All Covid-19 events, cases, hospitalisations, ICU admissions and deaths can be forecast accurately, first for a few days and then for weeks at a time with increasing precision as outbreaks progress.

To develop our model, we were greatly inspired by what we saw in the annual cycle of endemic influenza—something that records of the Portuguese National Health Service show clearly.

In brief, the problem of forecasting Covid-19, and other viruses, is reduced to:

1. Using EVT to provide bounds on growth over the period (approximately 3 weeks) before the Gompertz function's predictive power develops;

2. Identifying the switch to Gompertz function growth;

3. Identifying the end of the outbreak and return to linear growth.

2.7 Two ongoing applications

We have been making accurate real-time predictions of Covid-19 hospital admissions in England since November 2021 (as we indicated in subsection 2.5). They have, as our model established, continued to alternate between Gompertz function growth and linear growth [17].

To anticipate demand on the health system, each time we detect a transition from linear growth to a new outbreak, we use our statistical analysis to provide linear growth bounds.

The most recent outbreak in England was detected using the data up to 21 July 2023, when we observed a strong departure from the linear trend that had been present for many weeks. **Figure 3** shows the growth bounds we estimated then as well as the most recent Gompertz function fit.

We have also been following Covid-19 hospital admissions in Florida and the predictions of the CDC Centre for Forecasting and Outbreak Analytics [18].

We detected the beginning of what seems likely to be a small outbreak in Florida from the CDC data for hospital admissions up to 14 July 2023.

Figure 4 shows the prediction that the CDC made on 14 July and the daily admissions from 15 July to 18 August 2023.

Figure 5 shows the growth bound we established then, together with cumulative hospital admissions and cumulative admissions from the CDC's predicted daily values.

As of 18 August, cumulative Covid-19 hospital admissions were 15.6% lower than our linear growth bound.

They were more than 52% above the level the CDC predicted. We know what Feynman would say.

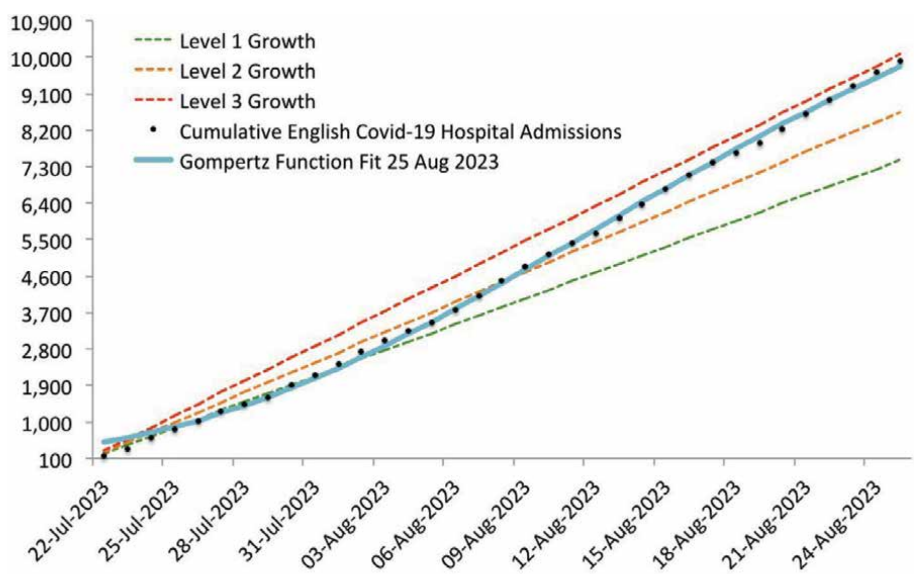

Figure 3.
Growth bounds in English hospitalisations, July to august 2023.

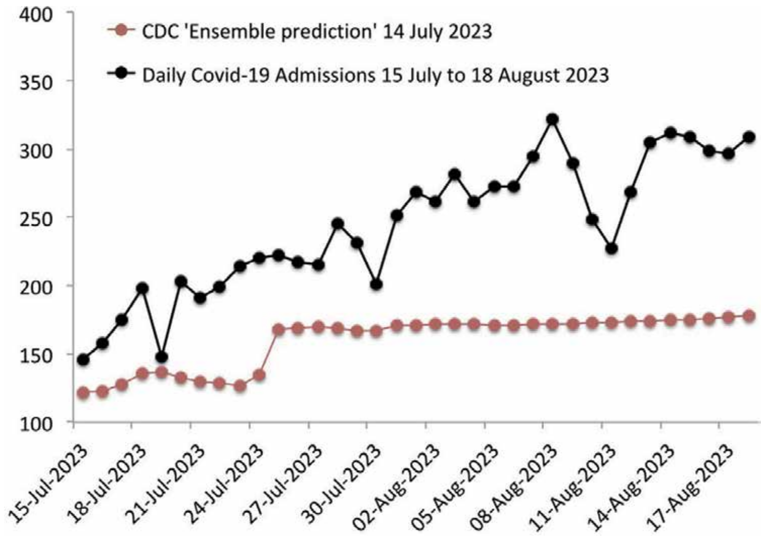

Figure 4.
Prediction made by CDC on 14 July 2023 for daily admissions from 15 July to 18 August 2023.

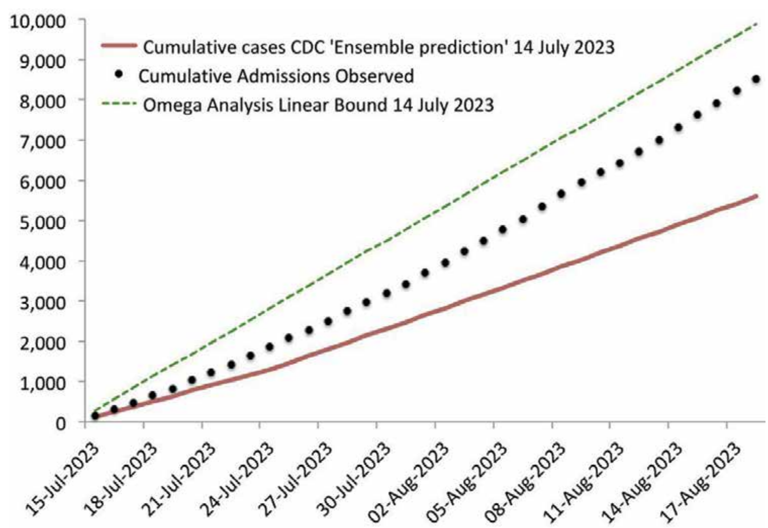

Figure 5.
Shows the growth bound established on 14 July 2023, together with cumulative hospital admissions and cumulative admissions from the CDC predicted daily values.

To allow the readers to test their own statistical tools, we are annexing a table with the Florida Covid-19 hospital admissions from 15 July to 21 August 2023, data that was used to build our Florida graphs. **Figure 4** illustrates our point that the CDC prediction is very poor when verified against the data. In **Figure 5**, we draw the statistical bounds that are calculated, finding the average excess conditional on what has been already observed (**Figure 6**).

Florida	Hospital Admissions	cumulative
15/07/23	146	146
16/07/23	158	304
17/07/23	175	479
18/07/23	198	677
19/07/23	148	825
20/07/23	203	1028
21/07/23	191	1219
22/07/23	199	1418
23/07/23	214	1632
24/07/23	220	1852
25/07/23	222	2074
26/07/23	217	2291
27/07/23	215	2506
28/07/23	245	2751
29/07/23	231	2982
30/07/23	201	3183
31/07/23	251	3434
01/08/23	268	3702
02/08/23	261	3963
03/08/23	282	4245
04/08/23	261	4506
05/08/23	272	4778
06/08/23	272	5050
07/08/23	295	5345
08/08/23	326	5671
09/08/23	292	5963
10/08/23	251	6214
11/08/23	228	6442
12/08/23	269	6711
13/08/23	305	7016
14/08/23	316	7332
15/08/23	310	7642
16/08/23	300	7942
17/08/23	299	8241
18/08/23	314	8555
19/08/23	303	8858
20/08/23	302	9160
21/08/23	393	9553

Figure 6.
Florida hospital admissions from 15 July to 21 August 2023.

3. Conclusion

Only data, subjected to mathematical analysis—statistical analysis above all else at the outset—can give a quick understanding of the seriousness of the situation and provide the means for immediate contingency planning.

Acknowledgements

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Appendix

A. A small note about our epidemiological model discoveries

It is important to stress the necessity of building models that relate to actual data. For us, this means two things: no assumptions about the facts and verifying that the model is actually able to make predictions.

In our epidemiological model, we studied different viruses, in different countries and different time periods. We always used our scientific standard of applying the theory to part of the data, and then we verified that the model has significant predictive power for epidemics, from cholera in 1853 to the Spanish Flu in 1918 and Ebola in 2014, to the acute phase of annual outbreaks of endemic influenza and the Covid-19 pandemic. See Ref. [19] for a non-technical version of our model for the accurate prediction of Covid-19.

B. The importance of a readily accessible population and disease database

One important piece of information that did allow us to fully build the model was influenza's data that we obtained from the Portuguese medical service. The Portuguese data describe cases of influenza that were severe enough that the patients would look for a doctor, who would then diagnose the cases, and a very good database was created. These data show the complete cycle of influenza and give us a blueprint to follow. A good reference for the seasonality of influenza is the work of Hope-Simpson [20].

As mathematicians, we had no idea of the difficulty of obtaining data about viruses. We discovered that the WHO collects data from all countries, writes reports with its conclusions, but does not carry a database.

It makes us think of Tycho Brahe and of all the men who devoted their lives to observing and recording the sky. It makes us think of all the discoveries that were made possible by his work.

A database of observations is a repository of knowledge. It is where scientists can look for patterns, for information on where to base theories and then test them.

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Section 3

Contributions of SARS-CoV-2

Chapter 6

The Impact of COVID-19 on Educationists' Preparedness to Encounter a Future Pandemic

Musa A. Alghamdi

Abstract

It is believed that pandemics such as COVID-19 affect the social, economic, and educational lives of people. Educationists and students were heavily impacted by the coronavirus and the protocols that were applied by governments. In this study, the researcher aims to investigate the preparedness of Second language (SL) educationists in higher education to encounter any pandemic breakout in the future. The study tries to investigate the SL educationists' preparedness by answering two questions. The first question focuses on the extent to which SL educators are ready to encounter future pandemics. The second question will be: How does the COVID-19 experience affect their readiness to encounter educational challenges in teaching SL in the future? This study aims to apply a qualitative study to collect data from educationists who work for higher education in Saudi Arabia. Seven people have been interviewed to collect data to carry out this study. The results showed that the teachers are ready to encounter three domains of challenges during any future Pandemic. These domains showed that teachers can encounter technical challenges in any future Pandemic, adjust their teaching methods to accommodate online learning, and provide their students with emotional support.

Keywords: future pandemic, COVID-19, teachers' preparedness, coronavirus, teachers' beliefs, self-efficacy, social cognitive theory

1. Introduction

The coronavirus disease that emerged in 2019 (COVID-19) has spread quickly to different parts of the world. It had severely caused a huge impact on all sides of life. It has various influences on worldwide socioeconomic domains. Education was not far from the effect of COVID-19 [1, 2]. The traditional approach to education around the world utilizes the face-to-face mode, where the interaction between the learners and their teachers occurs in the same place and time. Because of the onset of COVID-19, the education system employed technical-based and online platforms to teach their students. In this phase, the learners and teachers were obliged to be in different places and sometimes at different times to teach and learn. As well, we have noticed that schools were locked and students, as part of society, were locked down in their houses. Students all over the world attended their classes remotely from home. Teachers taught their classes online, using all the possible technology to contact and teach their courses. In other words, most countries implemented online learning technologies. According to the Organization of Economic Co-operation and Development (OECD) [3], about 1.7 billion students in educational establishments all over the world used online learning to overcome the complications of COVID-19. In fact, besides the psychological and social hardship, learners and educators encountered a number of technical-related difficulties (such as internet connection or dealing with technical faults during class time) [1].

2. Literature review

2.1 The importance of teachers' beliefs

Nespor [4] claims that the weakly regulated nature of the numerous difficulties confronted by teachers is caused by teachers' beliefs playing the foremost part in describing tasks and choosing approaches because beliefs can be flexibly employed to new problems. He proposed that it appears.

> *"likely that some crucial experience or some particularly influential teacher produces a richly-detailed episodic memory that later serves the student as an inspiration and a template for his or her own teaching practices" (p. 320).*

Certainly, it looks like 'beliefs are far more influential than knowledge in determining how individuals organize and define tasks and problems and are stronger predictors of behaviour' ([5] p. 311).

2.2 The social cognitive theory (SCT)

The Social Cognitive Theory (SCT) is a psychological framework that places significant emphasis on the influence of cognitive, behavioral, and social contexts on how people behave. The psychological theory, Social Cognitive Theory, was formulated by the renowned psychologist Albert Bandura during the 1980s [6]. It has gained significant recognition as a fundamental principle within the field of contemporary psychology.

The fundamental of the Social Cognitive Theory (SCT) is that human behavior is influenced by the dynamic interplay between individual elements, such as ideas, beliefs, attitudes, and values, and the resulting behavior. This implies that behavior is not just determined by intrinsic variables but is also influenced by extrinsic circumstances.

The Social Cognitive Theory (SCT) places significant emphasis on the concept of self-efficacy, which refers to people's confidence in their own capability to achieve success. Based on the theoretical framework, individuals who possess a robust sense of self-efficacy are inclined to engage in demanding endeavors and demonstrate perseverance when confronted with impediments.

According to Bandura [6–8], the Social Cognitive Theory posits that the presence of self-efficacy, which refers to an individual's belief in their capability to successfully execute a specific behavior, is necessary for the attainment of a desired outcome. Behavioral shifts as well as persistence are influenced by two key factors: the first one is the anticipated results of practicing a particular habit and the second factor is one's perceived capability to carry out the necessary actions. Hence, self-efficacy expectations exhibit significant variability contingent upon the specific task and contextual factors [9]. Strategies targeting self-efficacy have been found to effectively mitigate feelings, such as anxiousness and discomfort, as demonstrated by Bandura's seminal works in Refs. [7, 8].

Finally, SCT emphasizes the role of reinforcement in learning. According to the theory, people are more likely to repeat behaviors that are rewarded than those that are punished. This means that positive reinforcement is an effective way to promote desired behaviors.

2.3 Defining and measuring self-efficacy beliefs

Teacher self-efficacy has been characterized as "a teacher's assessment of his or her own skills to achieve the intended levels of learner involvement and achievement, even among challenging or unmotivated learners' [10]. The concept of educational beliefs is wide and for investigation reasons it has been redefined into more detailed sub-types [5]. These sub-types include beliefs about self-assurance to affect learners' performance (teacher efficacy), beliefs about the nature of knowledge (epistemological beliefs), belief about perceptions of one-self (self-concept), and belief about self-confidence to accomplish particular responsibilities (self-efficacy). The latter is the most important type that relates to the current research.

According to Bandura [8], who defined the concept, 'perceived self-efficacy refers to beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments' (p. 3). Self-efficacy is specific to certain behaviors and encompasses two sections. These two sections are efficacy expectations and outcome expectations. Efficacy expectations relate to belief in individual aptitude to influence a conduct, while outcome expectations believe in that the behavior will lead to a certain outcome. As a consequence, mechanisms for the purpose of self-efficacy normally contain two methods to measure these two sections.

According to Bandura [6], self-efficacy beliefs were found in reaction to four different information. The most influential inspiration on self-efficacy is "enactive experience" in which self-efficacy for a behavior is improved by effectively doing the behavior. The second is "vicarious experience" in which other alike individuals are perceived to perform a behavior efficaciously. The third is verbal persuasion, which inspires efforts that foster efficacy through success. Fourth, physiological states such as stress may play a significant role in individual self-efficacy.

2.4 Teachers' beliefs, practices, and attitudes towards technology

Belief systems exhibit a dynamic and porous nature, rendering them subject to modification in response to new experiential insights. In deeper consideration, the assumptions that teachers have about how to instruct and educate students might be seen as their beliefs [5]. Belief systems of individuals are shaped via their own experiences and often consist of a network of interconnected and interdependent beliefs, rather than isolated and singular ones [11]. Prior research has indicated that there is an interaction between the various ideas held by instructors [12, 13] or a combination of these beliefs with others [14]. Additionally, there is an intricate link between educators' beliefs and practices, as well as the processes that underlie their relationships with one another [15]. Several investigations have posited that instructors possess the ability to understand the occurrences they face and subsequently determine choices regarding their methods of instruction depending on their points of view [5, 16, 17].

Consequently, their actions and routines are influenced by their individualized beliefs regarding teaching [18]. Nevertheless, it has been demonstrated by several research that the presence of positive views or attitudes does not necessarily ensure the successful implementation of innovative practices [19, 20].

The teachers' beliefs play a role in their acceptance and use of technology in their realm. A number of investigations provide evidence suggesting that the beliefs held by educators have a significant influence on how willing they are to embrace and incorporate innovative changes into their curriculum [19, 21, 22].

According to the findings of Zacharia [23], educators who possess favorable views towards computer simulations are more inclined to integrate technology into their instructional practices. In a comparable way, Stylianidou et al. [22] posited that opinions held by instructors exert a favorable impact on their implementation of innovative techniques. The instructors under study have comparable resources, although they held divergent perspectives about pedagogy and technological instruments. The authors discovered that the teachers who participated in the study exhibited diverse approaches in incorporating these tools within their teaching environments, influenced by their individual beliefs. This implies that the views of educators on new technologies can significantly impact their decision-making processes and ultimately shape the manner in which computer innovations are implemented within educational institutions. In contrast, Kriek and Stols [24] have posited that educators' every pre-existing attitude and belief can serve as a hindrance to the integration of technology in the classroom. Furthermore, additional investigations have shown that despite the majority of educators exhibiting favorable attitudes and views towards technological advances in education, only a relatively small percentage of teachers actually put these innovations into practice [25, 26].

2.5 Challenges that teachers encountered during the COVID-19

During the COVID-19, the educators encountered a number of challenges that did not help them to perform their teaching practices in the proper way. The previous literature revealed that the difficulties that the educators encountered during the COVID-19 can be divided into three groups. The first difficulty the educator faced was the technical issues. The second one was psychological and emotional problems. The third one was the pedagogical difficulties.

First, on the level of technology, the educators have encountered problems of internet connections [27]. Because the COVID-19 suddenly spread around the world, the educators did not have enough time to get training and attend any workshop to deal with different new technologies, applications, and platforms. Such lack of training prevented teachers from choosing the proper education technologies. As well, teachers tended to use different platforms and free ones such as Google Classroom and WhatsApp [28]. Moreover, Purwanto et al. [29] investigated and have shown that educators encountered a challenge of lack of technological skills. Gurung [30] investigated the difficulties that Indian educators faced during the COVID-19. The researcher finds two technology-related reasons that prevented the Indian educators from adopting online learning. These reasons are the electricity and network supply in their areas. The second reason relates to the educators' lack of knowledge about technology. They pointed out that it can be understood that some educators are still not able to meet the Technological Pedagogical Content Knowledge (TPACK) framework that works to integrate technology, pedagogy, and content.

Second, on the psychology and emotional level, the previous studies discussed two areas where the COVID-19 had an impact on the psychology and emotional state of the learners and teachers. The first area relates to the teachers' psychological, mental, and emotional health. Concerns with COVID-19 are examined in a research conducted by Lacomba-Trejo et al. [31]. The findings revealed that educators are more likely to experience anxiety and depression and have a lower degree of happiness and resilience.

The other area that was affected by COVID-19 was the learners' motivation and how it makes it difficult for the educators to motivate their learners. As widely agreed among the researchers, an individual who possesses a high level of motivation consistently demonstrates outstanding achievement [32, 33]. Individuals with a high level of motivation consistently exhibit loyalty and dedication towards their assigned tasks and obligations [29]. On the other hand, lack of motivation diminishes learners' enthusiasm and hinders their ability to do well in their classroom activities and examinations [32]. Gurung [29] finds that more than half of the participants agreed that the COVID-19 lowered their students' motivation. In other words, the study found that the educators were unable to motivate their learners in online classrooms because of a lack of human interaction and an inability to get to know them on a deeper level. Gustiani [34] states that learners' expected motivation to acquire new information and their interest in trying out a novel teaching technique were the primary factors that kept them motivated in their online courses. Extrinsic factors like government mandates and natural phenomena also played a role in raising the level of motivation among the participants [33]. However, the researcher mentioned that deficient external resources also contributed to the phenomenon of amotivation, or the absence of motivation. Moreover, Pokhrel and Chhetri [35] maintain that during COVID-19 online learning, learners who have an intrinsic motive to learn do not have as much trouble because they do not need as much help and direction. On the other hand, learners who struggle with studying have a harder time.

Third, the COVID-19 had an impact on pedagogical practices in educational environment. This impact can be recognized via two challenges. First, through the ability of the teachers to adopt the new teaching mode. Second, through the assessment challenges that educators encountered during the COVID-19. Most governments had shut down schools, training institutions, and college and university sites as part of their shutdown and social distancing tactics in response to the COVID-19 Pandemic. Thus, teachers were obliged to change the mode of teaching from face-to-face mode to the online ones. The pedagogical impact of such closure appears from two sides. First, the teachers' readiness to deal with the new online teaching method. Pokhrel and Chhetri [35] state that one of the pedagogical challenges that teachers encountered during COVID-19 was that they were not prepared to implement new changes and teach online, instead of teaching on-campus. In the same vein, Gurung [29] finds that the participants raised the same problem of adopting the online teaching during COVID-19.

3. Methodology

3.1 Qualitative paradigm

Creswell [36] confirmed that researchers consider qualitative approach to be the best approach to widen our understanding of any social environment. The qualitative approach helps us to see the targeted environment from the inside via collection of the participants' points of view and their thoughts [37]. Thus, this study uses the qualitative paradigm to explore the aimed setting and informants and to find an answer for research questions.

The aim of this research paper is to find out the readiness of the Second language teachers (SLTs) in higher education to encounter any Pandemic and how the experience of COVID-19 plays a role in their preparedness. The study used an inductive qualitative approach for inquiry using the semi-structured interview to collect the data from seven SLTs who work in Second language institutions. The research works answer two main questions: To what extent are the Second language educationists ready to encounter future pandemics to teach Second language skills? How does the COVID-19 experience affect their readiness to encounter educational challenges in teaching SL in the future? In order to achieve this study's aim, a qualitative research is applied. Qualitative paradigm is typically suitable to collect data from small samples. Moreover, the sample size was small due to the unique nature of the project and the aim of exploring detailed individual experiences. It is known that in qualitative studies, it is not aimed to measure and quantify the result. Its elementary advantage is to provide a comprehensive account and study of a research subject [38].

3.2 Instrumentation

Face-to-face semi-structured interviews were employed in this investigation. The interview included seven questions meant to elicit thought and discussion about what they experienced being college-level language instructors throughout the COVID-19 pandemic. As well as, their readiness to encounter any pandemic in the future. Interviews were recorded electronically with each participant's permission. Respondents were made aware and ensured of their confidentiality during the entire process.

3.3 Objectives

The objectives of the research paper are:

1. To study the readiness of English as a foreign language (EFL) teachers to encounter various challenges that may have occurred by a future Pandemic.

2. To study how COVID-19 pandemic has changed teachers' attitudes towards online learning.

3. To study the level of technical-related teachers' preparedness.

4. To study the level of psychological and emotional-related teachers' preparedness.

3.4 Sample

Seven EFL instructors were planned to interview to collect their opinions to answer the research question of this study. These informants teach in the English Language Institute in Saudi Arabia during the COVID-19 pandemic (**Table 1**).

Participants' information		
Instructor's name	**Gender**	**Years of experience**
Mr. Yousef	M	15
Dr Haifa	F	12
Mr. Mohammed	M	15
Mr. Raed	M	9
Ms. Wafa	F	13
Mr. Hassan	M	12
Ms. Fatimah	F	10

Table 1.
Participants' information.

3.5 Research questions

1. To what extent are the Second language educationists ready to encounter future pandemics to teach Second language skills?

2. How does the COVID-19 experience affect their readiness to encounter educational challenges in teaching SL in the future?

4. Analysis

Thematic analysis was utilized to uncover themes and patterns and to categorize sections of information [39]. The first three transcripts were analyzed by the researcher, and a system for coding was devised. Throughout the procedure, the researcher studied the connections between the starting codes and sketched out the probable codes [36]. The researcher was conscious of the possible bias in data interpretation because he was identified as a college EFL instructor. As a result, the researcher was mindful to minimize the effect of his personal experiences, beliefs, and preferences by delivering lengthy explanations and direct quotes [40].

5. Findings

In this qualitative investigation, the thematic analysis was applied to answer the research questions. This thematic analysis explored the readiness of teachers to encounter future pandemics. The analysis revealed three main themes. The three major themes from the thematic analysis were revealed. These themes include teachers are ready for technical challenges, ready to adjust their teaching methods to accommodate online learning, and ready to provide their students with emotional support.

5.1 Ready for technical challenges

All informants interviewed addressed that although they encountered technical difficulties in their online classroom during COVID-19, they insisted that they are now having experience that may help them to overcome all the past technical challenges they may encounter in a future online classroom.

Mr. Mohammed mentioned that:

> *"I am now able to easily utilize technology to create virtual learning environments. I feel I am prepared to use technology to create virtual learning environments for my students. I can now effectively use different video conferencing tools, online learning platforms, and other digital tools to facilitate remote learning. These skills were not easy when I first was asked to move to online classroom during COVID-19. I think I have learnt a lot".*

In the same vein, Mr. Yousef states the same:

> *"I believe that I am and the other teachers here are now gain a lot of experience that will help us in the future to encounter any problem that will enforce us to teach through online technologies. Our experience during COVID-19 was difficult but provide us with all skills to use those applications and platforms."*

Both Mr. Mohammed and Mr. Yousef believe that they have all potential skills and abilities to teach under any future Pandemic circumstances. The power they have is not only depending on their technical skills as Mr. Yousef mentioned but in their belief in their abilities. This finding is in line with what previous studies proved about the connection between teachers' beliefs and thoughts and how that affects their practices in their classrooms [12–15]. In addition, the point of view of the informants above may relate to the Bandura [6] self-efficacy beliefs, in which they believe in their capabilities to deal with the courses' needs for teaching their students in any future difficulties. This belief reflects what Bandura [6] named as "efficacy expectations and outcome expectations", which relates to an individual's belief in his/her ability to impact a behavior and expecting that the behavior will lead to a certain outcome. According to Bandura [8], individuals tend to develop beliefs regarding their capabilities, predict the probable impacts of future actions, establish personal objectives, and devise alternative strategies that may lead to expected benefits. Furthermore, this finding supports the finding of Refs. [19, 21, 22] which found that the beliefs held by teachers have an important impact on how keen they are to embrace and integrate advanced changes into their teaching practices.

In addition, although Mr. Raed believed that the COVID-19 experience has expanded not only the teachers' but also the institutions' power to face any future difficulty that obliges them to depend on internet-based classrooms. He highlighted the need for more improvement and development.

> *"COVID-19 has given a gigantic challenge and opportunity to the educators to be ready to face any such challenge in the future. Though likely to be tough time Educators have made significant strides in adapting to the challenges posed by the COVID-19 pandemic, but readiness varies widely. Many institutions and educators have improved their online learning capabilities, but universal access to technology and comprehensive teacher training remains uneven. Yet there is room for further preparedness and resilience-building to better face future pandemics."*

Mr. Raed pointed to another factor that may affect the readiness of the educationists to face a future Pandemic. He raised the role of the institution that may play a positive or negative role in staff preparedness. This point agrees with the Bandura's Self Cognitive theory [8] that takes into consideration the outsider factors' (e.g. Community) role to affect the self-efficacy in individuals what in turn will affect their future behavior.

5.2 Adjust teaching and assessment methods to accommodate online learning

Ms. Wafa was asked about her preparedness for any future difficulty that may oblige teachers to teach online. She stated that the previous COVID-19 era experience helped her with skills that she needs to find the suitable teaching practices and methods that help her and her learners in online learning.

> *"I believe that my experience that I gained from COVID-19 period will help me to be ready to adjust my teaching methods to accommodate virtual learning if necessary…".*

In the same vein, Ms. Fatimah mentions that:

> *"Diverse learning needs will make teaching more complicated. Fair online assessments and academic integrity will be hard to maintain. Educators have to adapt technology-based curricula and implementing flexible assessments. Education should emphasize digital literacy and adoptable curricula must be made available."*

Ms. Fatimah highlights the challenges that educators face in a pandemic era. She raised the challenge of the varied learning needs during online learning. She mentions two difficulties that a teacher may encounter. These are maintaining fair online assessments and academic integrity. To meet these challenges, she proposes that teachers must adapt curricula learning and implement flexible assessments that may suit online education.

Dr. Haifa states that:

> *"teachers learn a lot of skills during COVID-19. I am sure that most of the staff are now able to prepare the curricula and assessment tasks that are suitable for online learning as well as can help their learners to go smoothly during online learning."*

Dr. Haifa suggests that teachers have learned a variety of skills during the COVID-19 pandemic. She emphasizes how teachers have adapted to the changes brought about by the COVID-19. These skills include the ability to create curricula and assessment tasks learners need during online learning. This suggests that teachers have had to become more tech-savvy and knowledgeable about online learning platforms in order to be able to effectively teach their students. Additionally, it implies that teachers have had to become more creative in their teaching methods in order to engage their students in an online environment.

5.3 Provide emotional support

Teachers in the semi-structured interview have focused not only on their preparedness to apply technical tools but also on their role to support their learners psychologically and emotionally. Dr. Haifa mentions how much important it is that the teachers need to be ready to help their students and support them emotionally:

> *"Teachers should foster a sense of community among their students, even when they are learning remotely. This could include setting up virtual study groups, encouraging*

> *students to connect with each other online, and providing support and guidance to students who are struggling. This will help to improve learners' psychological sates and foster their emotional feelings during a pandemic."*

Mr. Hassan pointed to the importance of supporting learners. He pointed to the difficulty of balancing teaching with the emotional and psychological support during COVID-19.

> *"Moreover, as a teacher, I faced additional pressures, such as balancing my professional and personal lives while working from home, addressing students' emotional well-being during a stressful time".*

The pressures faced by teachers during the pandemic are significant and complex. This example shows that not only did they have to balance their professional and personal lives, but they also had to address students' emotional well-being in an extremely trying time. The stress of having to juggle both roles on top of adapting teaching methods and navigating new technologies put immense pressure on teachers, which can be difficult for many people to manage successfully.

He then added that.

> *"The hard experience I encountered during COVID-19 provide equipped me with a further step and more knowledge about how to encourage my learners in the time they are away from my normal classroom."*

Mr. Hassan reflects his resilience and determination to continue to provide a quality education to their students, despite the challenges posed by the COVID-19. It also shows his commitment to finding new ways to engage and motivate their learners, even when they are not able to be in the same physical space. The speaker's experience has enabled them to gain a deeper understanding of how best to support their students emotionally and psychologically, and this will likely be beneficial in any future situation.

6. Conclusion

In conclusion, the COVID-19 pandemic has had a profound impact on the preparedness of educationists to encounter a future Pandemic. The pandemic has highlighted the need for educationists to be better prepared to respond to a future Pandemic, including the need for more resources, better communication, and improved collaboration between stakeholders. Educationists must also be prepared to adapt to the changing needs of students and families, as well as the changing landscape of education. By taking the necessary steps to prepare for a future Pandemic, educationists can ensure that they are better equipped to respond to any future health crisis.

In this paper, the findings showed that the teachers have shown their readiness to encounter all those predicted challenges they may encounter during any future Pandemic. The findings showed that teachers are ready to encounter mainly three challenges. These challenges are technical challenges, providing their students with emotional and psychological support, adjusting their teaching methods to accommodate online learning.

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Chapter 7

A Review of COVID-19 Vaccines, Immunogenicity, Safety, and Efficacy toward Addressing Vaccine Hesitancy, Inequity, and Future Epidemic Preparedness

Sao Puth and Vandara Loeurng

Abstract

This chapter provides an update on COVID-19 vaccines, emphasizing their immunogenicity, safety, efficacy, and potential impact on vaccine hesitancy, inequity, and future epidemic preparedness. Various vaccine types, such as mRNA-based, DNA-based, viral vector, inactivated, and protein subunit vaccines, are explored, evaluating their mechanisms and advantages in eliciting robust immune responses. Safety is thoroughly assessed using clinical trials and real-world data to address hesitancy concerns. Strategies for equitable distribution are discussed to achieve widespread coverage and overcome barriers. Lessons drawn from the pandemic serve as a roadmap for proactive measures aimed at bolstering epidemic preparedness, highlighting the critical role of global cooperation and equitable vaccine distribution in safeguarding public health worldwide.

Keywords: COVID-19 vaccine, immunogenicity, safety, efficacy, vaccine hesitancy, vaccine inequity, and future epidemic preparedness

1. Introduction

On January 30, 2020, the World Health Organization (WHO) officially declared the outbreak of novel coronavirus disease 2019 (COVID-19) as a global pandemic. This declaration was made in response to the highly transmittable and pathogenic nature of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA virus [1]. Since then, COVID-19 has caused more than 6 million deaths worldwide [2], resulting in significant economic losses globally [3]. Despite efforts to control the pandemic, it is still ongoing as China continues to report high numbers of cases. Concerns are rising that the "Zero COVID" policies implemented in China may not effectively contain the spread of COVID-19 [4]. Furthermore, scientific evidence suggests that climate changes, such as global warming, rapid population growth,

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urban expansion, and deforestation, are bringing human habitation closer to livestock and wildlife, potentially serving as hosts for future pandemic pathogens [5].

Since the onset of the disease, vaccines and vaccination strategies have continuously evolved, gaining particular attention in the wake of the COVID-19 outbreak. Notable advancements have been made in the development of novel vaccine technologies, resulting in the creation of effective vaccines against various diseases [6, 7]. Specifically addressing the ongoing global pandemic caused by the SARS-CoV-2 virus, COVID-19 vaccines have been swiftly developed and distributed, serving as a crucial tool in the fight against the pandemic [8–10]. Clinical trials have demonstrated that these vaccines effectively prevent severe illness, hospitalization, and death. Furthermore, they possess the potential to slow down virus transmission and reduce the emergence of new variants (**Tables 1**–**3**). The widespread administration of vaccines is vital in safeguarding vulnerable populations, including the elderly and individuals with underlying health conditions [10]. Compared to natural infection, vaccination plays a prominent role in saving humanity from various COVID-19 variants, including the recent surge of the Omicron variant and aiding in the recovery from the global economic crisis (**Tables 1**–**3**).

While COVID-19 vaccines offer numerous benefits, they also have limitations regarding their immunogenicity, safety, and effectiveness. Vaccine hesitancy is a concern, as individuals may refuse vaccination due to apprehensions about the immunogenicity, safety, and efficacy of the vaccines [61–65]. The efficacy rates of COVID-19 vaccines vary among different types, and emerging virus variants can impact their effectiveness. For instance, mRNA vaccines have demonstrated higher efficacy rates compared to viral vector and inactivated virus vaccines (**Table 3**). Extensive research and monitoring have been conducted to ensure the safety of COVID-19 vaccines with most reported adverse events being mild and temporary (**Table 2**). However, rare cases of severe adverse events, such as blood clots, have been associated with some vaccines, leading to temporary suspensions in vaccine distribution and increased surveillance [65, 66].

Overall, COVID-19 vaccines induce immunogenicity by stimulating the production of neutralizing antibodies and cellular immune responses (**Table 1**). While the inactivated COVID-19 vaccines may exhibit slightly lower immunogenicity compared to certain other formed vaccines, they still prove effective in reducing the severity of COVID-19 and providing protection against severe outcomes (**Table 3**). Despite the development and approval of multiple vaccines, there remains a significant challenge of inequitable access to vaccines, particularly in low- and middle-income countries (LMICs) [67]. Additionally, logistical obstacles such as cold chain storage and vaccine distribution have hindered efficient delivery in certain regions [68].

At this juncture, it is crucial for us to reflect upon the valuable lessons learned during the COVID-19 pandemic spanning the past 3 years. It is imperative that we contemplate how to prepare better and effectively respond to future challenges. In addition to implementing measures like social distancing, it is essential to have a comprehensive understanding of vaccine technologies and the immunogenicity, safety, and efficacy of vaccines. The objective of this chapter is threefold: (1) To examine and reflect upon recent advancements in vaccine technologies, focusing on the immunogenicity, safety, and efficacy of approved COVID-19 vaccines; (2) To provide critical insights aimed at addressing gaps in vaccine inequity, ensuring that access to vaccines is fair and equitable for all; (3) To provide critical insights and recommendations for preparedness and control measures in response to potential future pandemics. By addressing these aspects, we aim to enhance our preparedness

Approved vaccines	Developers (Companies or Institutions)	Vaccines' immunogenicity
Sinovac - inactivated (CoronaVac)	Developed by Sinovac Biotech, a Chinese biopharmaceutical company	After receiving two doses of the Sinovac (CoronaVac) vaccine, individuals aged 18 to 59 [11] or children/adolescents aged 3 to 17 [12] exhibited a robust immune response to SARS-CoV-2. This immune response effectively neutralized the alpha, beta, gamma, delta, and omicron variants, although there may be some reduced efficacy against certain variants [13]. Furthermore, when individuals were given a booster dose of the same vaccine between twenty-four and thirty weeks after the second dose, the levels of neutralizing antibodies and T-cell responses significantly increased against the Delta and Omicron variants of concern [14].
Bharat Biotech (BBV152) - inactivated (Covaxin)	Developed by Bharat Biotech, an Indian biotechnology company	The BBV152 vaccine induced strong immune responses, both in the form of neutralizing antibodies and cell-mediated immune responses, which remained at high levels for 3 months after the second vaccination in healthy adults and adolescents (aged 12–65 years) [15]. Furthermore, the effectiveness of Covaxin against various variant lineages, including B.1.617.2 (Delta, India), B.1.617.2.1 (Delta Plus, India), B.1.351 (Beta, South Africa), B.1.1.7 (Alpha, UK), and B.1.1.529 (Omicron), was also investigated [16]. The findings of the study demonstrated the persistence of these immune responses for up to 12 months following vaccination.
Sinopharm (BBIBP-CorV)	Developed by the Beijing Institute of Biological Products, a subsidiary of Sinopharm, a Chinese state-owned company	The Sinopharm vaccine exhibits the ability to trigger the production of neutralizing antibodies upon completion of the two-dose regimen of individuals between the ages of 18 to 59 [17, 18]. Furthermore, a booster dose has been shown to reverse the decline of antibodies, thereby enhancing cellular immune responses, including T-cell responses [19].
Wuhan Institute of Biological Products (Sinopharm)	Another inactivated vaccine developed by the Wuhan Institute of Biological Products, another subsidiary of Sinopharm	Refer to Sinopharm produced by BBIBP-CorV
Covovax	Developed by Novavax, an American vaccine development company, in collaboration with the Serum Institute of India	A study [20] identified Covovax as a promising candidate for a booster dose after various priming dose regimens. The study observed that administering a third dose of Covovax after the second dose of BBIBP-CorV, AZD1222, BNT162b2, or CoronaVac/AZD1222, within a time interval of 3–10 months, resulted in strong immunogenicity and exhibited a good safety profile. The Covovax vaccine stimulated the production of antibodies and triggered cellular immune responses, including the activation of T cells. Overall, these findings suggest that Covovax has the potential to be an effective booster dose, providing enhanced immune protection to individuals who have previously received different priming dose regimens.

Approved vaccines	Developers (Companies or Institutions)	Vaccines' immunogenicity
Soberana 02	Developed by the Finlay Vaccine Institute in Cuba	In a Phase 3 study [21], involving 100 volunteers aged 19–80 years, it was reported that two doses of Soberana 02 (SOBERANA 02–25 μg) were administered. Half of the volunteers received a third dose of the corresponding SOBERANA 02, while the other half received a heterologous dose of SOBERANA Plus. The study found that SOBERANA 02 was safe and immunogenic in individuals aged 19–80 years, leading to the production of neutralizing antibodies and specific T-cell responses. The highest immune responses were observed in the group that received the heterologous three-dose protocol. These immune responses are crucial for protecting against COVID-19 and reducing the severity of symptoms.
Abdala	Developed by the Center for Genetic Engineering and Biotechnology in Cuba	The Abdala vaccine is found to induce substantial humoral immune responses against SARS-CoV-2 among adults 19–80 years of age after third dose of vaccination [22]. In addition, Abdala vaccine also stimulated the production of specific IgG antibodies against the RBD of SARS-CoV-2, as well as ACE2 inhibition titers and neutralizing antibodies in healthy children and adolescents with age (3–11 years, or 12–18 years old) [23].
Oxford-AstraZeneca (Vaxzevria, Covishield)	Developed by the University of Oxford and AstraZeneca	Extensive data and studies have been conducted on the immunogenicity of the Oxford-AstraZeneca vaccine [24–28]. Clinical trials and real-world data have shown that the vaccine elicits a robust immune response, including producing antibodies and activating cellular immune responses [25, 26]. The vaccine stimulates the production of neutralizing antibodies that target the spike protein of the SARS-CoV-2 virus [24–28]. These antibodies are crucial for preventing infection and reducing the severity of COVID-19 symptoms. Additionally, the vaccine activates T-cell responses, which play a role in recognizing and destroying virus-infected cells. Studies have demonstrated that the Oxford-AstraZeneca vaccine induces strong responses after the completion of the two-dose regimen. It is effective in reducing the risk of severe disease, hospitalization, and death due to COVID-19 [29].
Johnson & Johnson (Janssen)	Developed by Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson	Similar to Oxford-AstraZeneca mentioned above. The vaccine stimulates the production of neutralizing antibodies and activates cellular immune responses, including T-cell responses [30, 31]. Clinical trial has shown that the Johnson & Johnson vaccine induces strong immune responses after a single dose [32]. It has effectively reduced severe disease, hospitalization, and death due to COVID-19. Additionally, the vaccine has shown effectiveness against multiple virus variants, including the Alpha and Beta variants [33, 34].

Approved vaccines	Developers (Companies or Institutions)	Vaccines' immunogenicity
Sputnik Light, the first component of Sputnik V	Developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia	Sputnik Light vaccine induces strong humoral and cellular immune responses after the completion of the single-dose regimen [35]. Sputnik Light is also a leading booster shot that has demonstrated efficacy in preventing COVID-19 and reducing the risk of severe disease, hospitalization, and death. The vaccine has also shown effectiveness against different variants of the SARS-CoV-2 virus, including the Alpha, Gamma, and Omicron variants [36].
CanSinoBIO (Convidecia)	Developed by CanSino Biologics in China	CanSinoBIO vaccine induces strong immune responses after a single dose [37]. In addition, a booster shot is recommended for the highest and high-priority-use groups at 4–6 months after completion of the primary dose [38]. It has demonstrated efficacy in preventing COVID-19 and reducing the risk of severe disease and hospitalization [38].
Covishield	The name given Oxford-AstraZeneca vaccine when manufactured by the Serum Institute of India	Like the AstraZeneca vaccine [24–28], Covishield induces strong antibody responses upon completing the two-dose regimen. Furthermore, a recent study demonstrated that individuals who received either homologous or heterologous boosting with COVISHIELD™ or COVAXIN® after being initially primed with COVISHIELD™ or COVAXIN® exhibited immunogenic and safe responses. Among the four combinations assessed, the most potent immune response was observed in those who received a heterologous boost with COVISHIELD™ following a COVAXIN® prime [39].
Pfizer-BioNTech COVID-19 Vaccine (Comirnaty)	Developed by Pfizer and BioNTech	Pfizer-BioNTech vaccine generates high levels of neutralizing antibodies after the completion of the two-dose regimen [40]. These antibodies specifically target the spike protein of the SARS-CoV-2 virus. The vaccine has also been shown to activate strong T-cell responses, contributing to the overall immune response against the virus [41]. Clinical trials and real-world data have shown that the Pfizer-BioNTech vaccine has high efficacy in preventing COVID-19 infection, severe disease, hospitalization, and death [42]. The vaccine has also demonstrated effectiveness against Omicron variant of the SARS-CoV-2 virus and the immunogenicity of the Pfizer-BioNTech vaccine has been studied across various populations, including different age groups [43].
Moderna COVID-19 Vaccine (mRNA-1273)	Developed by Moderna	According to Ref. [44, 45], the Moderna COVID-19 vaccine (mRNA-1273) exhibits high immunogenicity as an mRNA-based vaccine encoding the spike protein of SARS-CoV-2. It generates a robust immune response with neutralizing antibodies that block the spike protein, preventing viral entry into human cells. The vaccine also induces a strong cellular immune response involving T-cells, contributing to its effectiveness against COVID-19

Approved vaccines	Developers (Companies or Institutions)	Vaccines' immunogenicity
		and its variants. Its immunogenicity has been critical in preventing severe illness, hospitalization, and fatalities, playing a crucial role in mitigating the global pandemic impact.
Zydus Cadila (ZyCoV-D)	Zydus Cadila	The Zydus Cadila COVID-19 vaccine, ZyCoV-D, had received emergency use authorization in India [46]. It is a DNA-based vaccine using a plasmid DNA platform to deliver the spike protein's genetic code from the SARS-CoV-2 virus. ZyCoV-D vaccine was reported to induce strong humoral and cellular immune responses in animal models [47].
Novavax (NVX-CoV2373)	Novavax	Novavax vaccine induces a strong immune response, including the production of neutralizing antibodies and the activation of cellular immune responses [48]. Clinical trials have demonstrated that the Novavax vaccine generates robust antibody responses after the completion of the two-dose regimen. The vaccine has shown efficacy in preventing COVID-19 infection, reducing the severity of the disease, and preventing hospitalization [49]. Additionally, the Novavax vaccine has shown effectiveness against different variants of the SARS-CoV-2 virus, including the Omicron variant, and after booster shots (3rd or 4th doses) resulted in enhanced cross-reactive immunity to SARS-CoV-2 variants [50].
Medicaga	Medicaga & GSK	Medicago vaccine induces a strong immune response, including the production of neutralizing antibodies and the activation of cellular immune responses after the completion of the two-dose regimen [51]. The vaccine has shown efficacy in preventing COVID-19 infection, reducing the severity of disease caused by the Delta variant [52].

Table 1.
A comprehensive review of the immunogenic characteristics exhibited by approved COVID-19 vaccines.

Approved vaccines	Developers (Companies or Institutions)	Vaccines' safety and side-effect profile
Sinovac - inactivated (CoronaVac)	Developed by Sinovac Biotech, a Chinese biopharmaceutical company	Overall, Sinovac vaccine has been found to have a good safety profile [53]. Frequently reported side effects of the CoronaVac vaccine include mild to moderate pain or tenderness at the injection site, fatigue, headache, muscle pain, and fever. These side effects are typically temporary and tend to subside within a few days. The majority of adverse reactions or events were observed in less than 10% of individuals who received the CoronaVac vaccine.
Bharat Biotech (BBV152) - inactivated (Covaxin)	Developed by Bharat Biotech, an Indian biotechnology company	Comprehensive safety evaluations have been conducted, and the vaccine has been found to be safe for people aged 18 and above. There are no serious

Approved vaccines	Developers (Companies or Institutions)	Vaccines' safety and side-effect profile
		adverse events were reported [15], and there are no safety concerns raised in an interim analysis [54].
Sinopharm (BBIBP-CorV)	Developed by the Beijing Institute of Biological Products, a subsidiary of Sinopharm, a Chinese state-owned company	WHO has recommended its use for people aged 18 and above [17]. The most common side effects experienced after the first dose of the vaccine were injection site pain and fatigue. Similarly, injection site pain and fatigue were also the most common side effects reported after the second dose. These side effects were more commonly observed in individuals aged 49 years or younger compared to those over the age of 49. Additionally, females were more likely to experience these side effects than males [55].
Wuhan Institute of Biological Products (Sinopharm)	Another inactivated vaccine developed by the Wuhan Institute of Biological Products, another subsidiary of Sinopharm	Refer to Sinopharm produced by BBIBP-CorV
Covovax	Developed by Novavax, an American vaccine development company, in collaboration with the Serum Institute of India	Based on the WHO's report [56], the Covovax vaccine has been proven to be both safe and effective for individuals aged 12 and above, but it is not recommended for those younger than 12 years of age. Although very rare, some serious adverse events of myocarditis and pericarditis have been observed after vaccination, typically occurring within a few days. However, it is essential to note that these cases were generally mild.
Soberana 02	Developed by the Finlay Vaccine Institute in Cuba	A phase 3 study [21] showed that this vaccine exhibits a favorable safety profile and could serve as an appealing choice for incorporation into COVID-19 vaccination programs. The incidence of serious and severe adverse events (AE) was exceedingly rare and occurred at comparable rates between the placebo and vaccine recipients. Although there were slightly more solicited AEs in the vaccine group, they were primarily localized reactions and mostly mild and temporary in nature.
Abdala	Developed by the Center for Genetic Engineering and Biotechnology in Cuba	Abdala vaccine was safe, encompassing a diverse range of participants spanning from 3 to 80 years old [22, 23]. Most adverse reactions to the vaccine were mild and localized to the injection site, resolving within 24–48 hours. No severe adverse events directly linked to the vaccine were reported.
Oxford-AstraZeneca (Vaxzevria, Covishield)	Developed by the University of Oxford and AstraZeneca	Overall, the Oxford-AstraZeneca vaccine has been found to have a good safety profile. Common side effects include pain or tenderness at the injection site, fatigue, headache, muscle pain, fever, and flu-like symptoms [24, 25]. These side effects are generally mild to moderate in severity and resolve on their own within a few days. Through phase 1/2 and 3 trials, no serious adverse events or deaths that were treatment-associated occurred in ChAdOx1 nCoV-19 recipients [24–26]. However, following the administration of this vaccine, there have been

Approved vaccines	Developers (Companies or Institutions)	Vaccines' safety and side-effect profile
		reports of an exceptionally uncommon and unfavorable occurrence known as Thrombosis with Thrombocytopenia Syndrome (TTS) [29]. This syndrome is characterized by atypical and severe instances of blood clotting, coupled with reduced platelet levels. The occurrence of TTS is infrequent.
Johnson & Johnson (Janssen)	Developed by Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson	Similar to Oxford-AstraZeneca mentioned above. There was found to have a good safety profile and common side effects include fatigue, headache, myalgia, and injection-site pain [30]. A rare serious adverse event is the "thrombosis with thrombocytopenia syndrome" and "Guillain-Barre Syndrome" reported [34].
Sputnik Light, the first component of Sputnik V	Developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia	Safety was confirmed by real-world data and clinical trials; Sputnik Light demonstrates a favorable safety profile [36]. The majority of reported adverse reactions were mild (66.4% of all vaccines), with only a small percentage classified as moderate (5.5%) [35]. Notably, no serious adverse events were recorded following vaccination with Sputnik Light [36].
CanSinoBIO (Convidecia)	Developed by CanSino Biologics in China	The CanSinoBIO vaccine has been found to be safe and effective, with common side effects primarily related to solicited systemic or injection-site reactions, which were reported as mild or moderate. Redness and swelling at the injection site were observed in less than 10% of Ad5-nCoV recipients and less than 2% of placebo recipients [37]. However, there have been rare reports of Thrombosis with Thrombocytopenia Syndrome (TTS) occurring approximately 3–30 days after receiving the Ad5-nCoV vaccine. While a plausible link between the vaccine and TTS is suspected, further evidence is necessary to confirm this association [38]. The vaccine is recommended for individuals aged 18 and above [38].
Covishield	The name given Oxford-AstraZeneca vaccine when manufactured by the Serum Institute of India	Refer to Oxford-AstraZeneca developed by University of Oxford mentioned above.
Pfizer-BioNTech COVID-19 Vaccine (Comirnaty)	Developed by Pfizer and BioNTech	Overall, the Pfizer-BioNTech vaccine has demonstrated a favorable safety and side-effect profile [40, 57]. Common side effects include pain at the injection site, fatigue, and headache [40]. These side effects are usually mild to moderate in severity and resolve within a few days. Serious adverse events following vaccination with the Pfizer-BioNTech vaccine are very rare. A very rare serious adverse event is myocarditis, which is mainly observed in young males aged 18–35 after the second dose [57]. Typically, these cases of myocarditis occur within a few days after vaccination, and they are generally mild in nature, responding well to conservative treatment. Moreover, they tend to be

Approved vaccines	Developers (Companies or Institutions)	Vaccines' safety and side-effect profile
		less severe with more favorable outcomes compared to classical myocarditis or myocarditis related to COVID-19 [57].
Moderna COVID-19 Vaccine (mRNA-1273)	Developed by Moderna	The Moderna vaccine has shown a good safety profile, with common side effects including pain or swelling at the injection site, fatigue, headache, and myalgia [45]. These side effects are generally mild to moderate in severity and resolve within a few days. Like Pfizer-BioNTech, myocarditis, an extremely infrequent and serious adverse event, is primarily observed in young males aged 18–35 after receiving the second dose [58].
Zydus Cadila (ZyCoV-D)	Zydus Cadila	The DNA vaccine, ZyCoV-D, was safely administered intradermally using a needle-free injection system with a 28-day interval between each of the three doses. It has demonstrated safety in both phases I/II [46] and phase III trials [59].
Novavax (NVX-CoV2373)	Novavax	Novavax vaccine demonstrated a generally favorable safety profile [49, 50]. Although very rare, serious adverse events of myocarditis and pericarditis have been observed. Typically, these cases occurred within a few days after vaccination and were generally mild in severity [56].
Medicaga	Medicaga & GSK	Regarding the Medicaga vaccine, no reports of related severe adverse events were recorded, and the reactogenicity was generally mild to moderate and of short duration [51].

Table 2.
A comprehensive review of the safety profiles demonstrated by approved COVID-19 vaccines.

Approved vaccines	Developers (Companies or Institutions)	Vaccines' efficacy against symptomatic COVID-19
Sinovac - inactivated (CoronaVac)	Developed by Sinovac Biotech, a Chinese biopharmaceutical company	The efficacy of the Sinovac vaccine has been reported to vary across different studies and settings. Overall, the vaccine has shown efficacy in reducing the risk of symptomatic COVID-19, hospitalization, and severe disease. The effectiveness of the Sinovac vaccine in preventing symptomatic COVID-19 has been reported to range from around 50.7% to 83.5% in different studies [53].
Bharat Biotech (BBV152) - inactivated (Covaxin)	Developed by Bharat Biotech, an Indian biotechnology company	The Bharat Biotech vaccine has shown efficacy in preventing symptomatic COVID-19 and its associated complications. The Bharat Biotech vaccine has reported an efficacy rate of 77·8% in preventing symptomatic COVID-19 [60].

Approved vaccines	Developers (Companies or Institutions)	Vaccines' efficacy against symptomatic COVID-19
Sinopharm (BBIBP-CorV)	Developed by the Beijing Institute of Biological Products, a subsidiary of Sinopharm, a Chinese state-owned company	Based on a substantial multi-country Phase 3 trial, it has been demonstrated that administering two doses of the vaccine at an interval of 21 days results in an efficacy of 79% against symptomatic COVID-19, starting from 14 days after the second dose [17].
Wuhan Institute of Biological Products (Sinopharm)	Another inactivated vaccine developed by the Wuhan Institute of Biological Products, another subsidiary of Sinopharm	Refer to Sinopharm produced by BBIBP-CorV
Covovax	Developed by Novavax, an American vaccine development company, in collaboration with the Serum Institute of India	The NVX-CoV2373 vaccine, at least 7 days after administered in a two-dose regimen to adult participants, provided 89.7% protection against symptomatic COVID-19 and demonstrated high efficacy against the B.1.1.7 variant [49].
Soberana 02	Developed by the Finlay Vaccine Institute in Cuba	Two doses of the Soberana 02 vaccine demonstrated an efficacy rate of 69.7% in preventing symptomatic COVID-19 [21].
Abdala	Developed by the Center for Genetic Engineering and Biotechnology in Cuba	According to the preliminary data from the phase 3 trials, the Abdala vaccine demonstrated an efficacy rate of around 92.28% in preventing symptomatic COVID-19 [22].
Oxford-AstraZeneca (Vaxzevria, Covishield)	Developed by the University of Oxford and AstraZeneca	Based on the primary analysis of data from trial participants who received two standard doses of the AstraZeneca vaccine, the efficacy against symptomatic SARS-CoV-2 infection was found to be 72% [29]. The inter-dose interval varied from about 4–12 weeks. Notably, vaccine efficacy tended to be higher when the interval between doses was longer.
Johnson & Johnson (Janssen)	Developed by Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson	According to data gathered from the United States, the two-dose vaccine regimen, administered at a 2-month interval, exhibited a remarkable efficacy of 94% in preventing symptomatic infections. On the other hand, the single-dose vaccine showed a lower efficacy rate of 72% [34].
Sputnik Light, the first component of Sputnik V	Developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia	The Sputnik Light vaccine has demonstrated a noteworthy efficacy of 80% against symptomatic COVID-19 infections [36].
CanSinoBIO (Convidecia)	Developed by CanSino Biologics in China	The CanSinoBIO vaccine has shown an overall efficacy rate of 64% in preventing symptomatic COVID-19 [37].
Covishield	The name given Oxford-AstraZeneca vaccine when manufactured by the Serum Institute of India	Refer to Oxford-AstraZeneca developed by University of Oxford mentioned above.

Approved vaccines	Developers (Companies or Institutions)	Vaccines' efficacy against symptomatic COVID-19
Pfizer-BioNTech COVID-19 Vaccine (Comirnaty)	Developed by Pfizer and BioNTech	Real-world studies have shown that the Pfizer-BioNTech vaccine boasts an efficacy rate of approximately 91.2% in preventing symptomatic COVID-19 after completing the full vaccination regimen [42]. This effectiveness has been observed across various age groups and has exhibited promising results against different COVID-19 variants, including the Omicron variant [43].
Moderna COVID-19 Vaccine (mRNA-1273)	Developed by Moderna	After the recommended two-dose regimen, the Moderna vaccine has demonstrated an impressive efficacy rate of 98.1% in preventing symptomatic COVID-19 [42].
Zydus Cadila (ZyCoV-D)	Zydus Cadila	Following the administrating of the third dose at 28 days, the ZyCoV-D vaccine has exhibited an efficacy rate of 66.6% in preventing symptomatic COVID-19 [59].
Novavax (NVX-CoV2373)	Novavax	The Novavax vaccine has displayed an efficacy rate of 89.7% in preventing symptomatic COVID-19 at least 7 days after the second dose [49].
Medicago	Medicago & GSK	As per the joint announcement from Medicago and GSK regarding phase 3 results, the Medicago vaccine showcased an efficacy rate of 75.3% in preventing symptomatic COVID-19 [52].

Table 3.
A comprehensive review of the effectiveness of approved COVID-19 vaccines in preventing symptomatic COVID-19.

and response capabilities, ultimately striving for more effective control and management of future health crises.

2. Overview of SARS-CoV-2 and its biology

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belonging to the coronavirus family, has led to outbreaks of various diseases. This family of viruses includes common viruses responsible for ailments ranging from common colds to more severe conditions like severe acute respiratory syndrome (SARS), which caused an outbreak in 2003 [69], as well as middle east respiratory syndrome (MERS), which caused an outbreak in 2012 [70]. The most recent outbreak occurred in 2019 with the emergence of SARS-CoV-2 [1], resulting in significant global health impacts [2] and economic consequences [3].

SARS-CoV-2 is an enveloped virus characterized by its positive-sense single-stranded RNA genome. The genome of SARS-CoV-2 contains instructions for the production of four primary structural proteins: spike glycoprotein (S), envelope protein (E), membrane protein (M), and nucleoprotein (N) [71]. These four structural proteins come together to encapsulate the viral genetic material (RNA), forming a complete virus capable of replication, transmission, and disease onset (**Figures 1** and **2**).

The virus exhibits a spherical shape and displays spike-like projections on its surface, which gives it a crown-like appearance (**Figure 1**). These projections are composed of the glycoprotein spike (S protein), consisting of two subunits, S1 and S2, and play a crucial role in receptor recognition and fusion with the host cell membrane [72, 73]. Specifically, SARS-CoV-2 attaches to host cells by utilizing its spike protein to bind to the angiotensin-converting enzyme 2 (ACE2) receptor located on the surface of human cells. Upon entering the host cell, the viral RNA genome is released and serves as a template for the synthesis of viral proteins. The viral RNA is then replicated, packaged into new virus particles, and subsequently released from the host cell to infect other cells, leading to the development of novel coronavirus disease 2019 (COVID-19) (**Figure 2**). In the absence of prevention or treatment, SARS-CoV-2 primarily targets the respiratory tract and can cause symptoms ranging from mild to severe respiratory illness [74]. It is worth noting that the virus can also infect other organs, including the skin, kidneys, endocrine organs, and eyes [75]. The severity of COVID-19 disease can vary widely and is influenced by factors such as age, underlying health conditions, and viral load [76].

Mounting an effective immune response to SARS-CoV-2 infection plays a crucial role in controlling the virus and mitigating the development of severe disease [77–80]. Vaccination, in particular, elicits the production of antibodies targeting the S proteins, which have been shown to generate neutralizing antibodies capable of impeding the virus from infecting host cells. Additionally, T cells are activated, enabling them to identify and eliminate infected cells (**Table 1**).

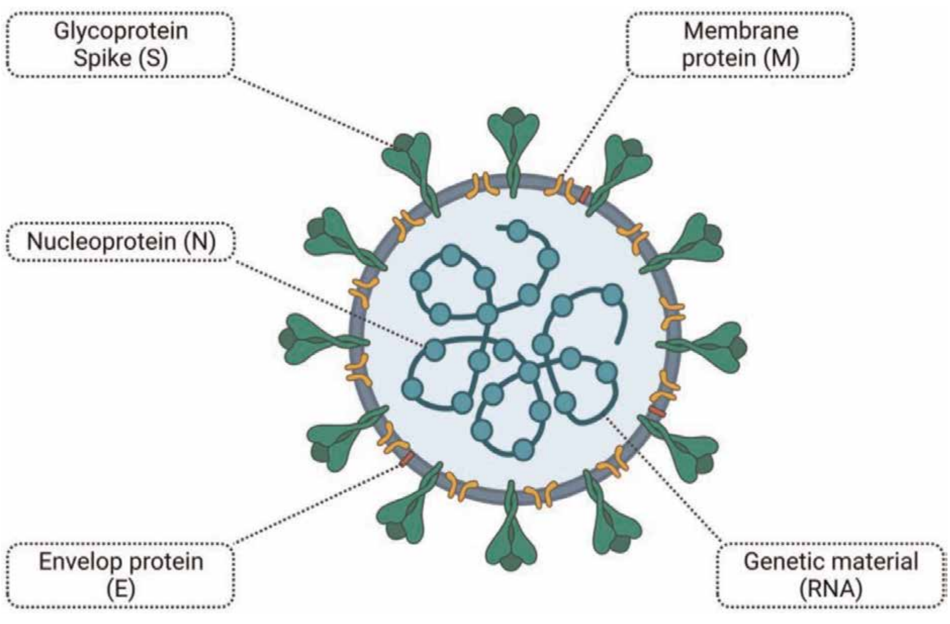

Figure 1.
The structural representation of SARS-CoV-2. This visual depiction was obtained from biorender (https://www.biorender.com).

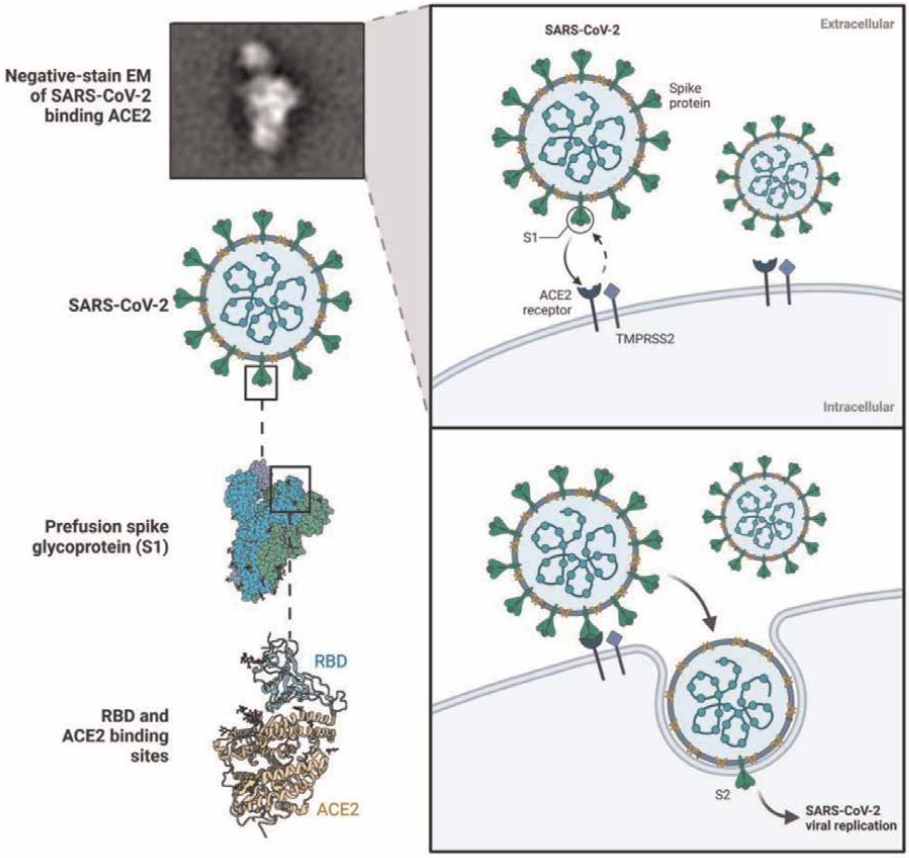

Figure 2.
The portrayal of SARS-CoV-2's entry into host cells via the ACE2 receptor. This visual representation illustrates the simulated steps and mechanisms involved in the recognition and entry of host cells through ACE2-mediated pathways by the prefusion spike glycosylation (S1). This visual depiction was obtained from biorender (https://www.biorender.com).

Like all viruses, including SARS-CoV-2, there are numerous mutations that can give rise to new variants with distinct characteristics. These characteristics can include rapid transmission, increased disease severity, or resistance to vaccines and treatments [81, 82]. These altered versions of the virus are commonly referred to as "variants". Some variants have shown higher transmissibility and may be linked to an elevated risk of severe illness [83–85]. The emergence of these variants highlights the critical need for ongoing surveillance and research to comprehend the evolution and dissemination of the virus [81]. The Omicron variant of SARS-CoV-2, initially identified in South Africa, was reported to the WHO on November 24, 2021, as a novel variant [84].

3. An update of COVID-19 vaccines

Recent advancements in vaccine technology have led to the development of various vaccines available in the market (**Figure 3**) [6, 7]. These vaccines consist of several crucial components. First, they contain an antigen, which can be in the form of a live-attenuated or killed virus, or a specific protein derived from the virus. The presence of the antigen enables our bodies to recognize and combat the disease if we

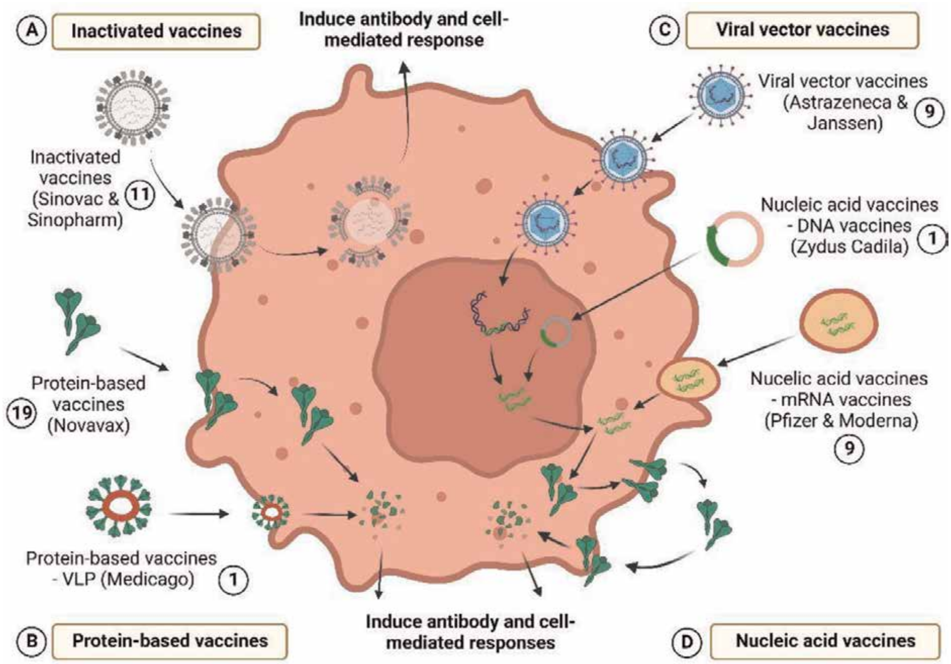

Figure 3.
An overview of the approved COVID-19 vaccines. Fifty approved COVID-19 vaccines were obtained from the COVID-19 vaccine tracker (https://covid19.trackvaccines.org/), with data updated until December 2, 2022, and accessed on June 19, 2023. The vaccine platforms are classified into four main categories, based on their vaccine technologies. Each vaccine platform as a representative example was illustrated for its immunogenic mechanisms. (A) inactivated vaccines (11 vaccines), (B) protein-based vaccines (19 protein vaccines & 1 VLP vaccine), (C) viral vector vaccines (9 vaccines), and (D) nucleic acid vaccines (9 mRNA vaccines & 1 DNA vaccine). This visual depiction was produced using a biorender (https://www.biorender.com).

come into contact with it in the future. Second, vaccines include an adjuvant, which assists in enhancing our immune response and improving the effectiveness of the vaccine. Additionally, vaccines are formulated with preservatives to maintain their efficacy over time, and stabilizers to prevent mechanical failures during storage and transportation. It is important to note that all the ingredients used in vaccines, as well as the vaccines themselves, undergo thorough testing and monitoring to ensure their safety and efficacy [7].

Up until December 2, 2022, a significant milestone has been reached with the approval of 50 vaccines by at least one country. Additionally, the WHO has granted Emergency Use Listing (EUL) to 11 vaccines, benefiting a total of 201 countries [86]. This remarkable progress showcases the global efforts in combating the COVID-19 pandemic. The extensive pursuit of vaccine development is evident in the reported 821 vaccine trials. Currently, there are 242 vaccine candidates undergoing clinical trials at various stages of progress. Among them, 66 vaccines are in Phase 1 trials, indicating their initial safety and dosage assessments. Phase 2 trials involve 72 vaccines, evaluating their effectiveness in larger populations. Furthermore, 92 vaccines are in Phase 3 trials, which involve large-scale testing to determine their overall efficacy. Notably, 50 vaccines have already received authorization, indicating their successful completion of clinical trials and regulatory approval. These crucial vaccine trials are being conducted in 80 countries worldwide, highlighting the widespread collaboration and dedication in the pursuit of effective COVID-19 vaccines (**Figure 4**).

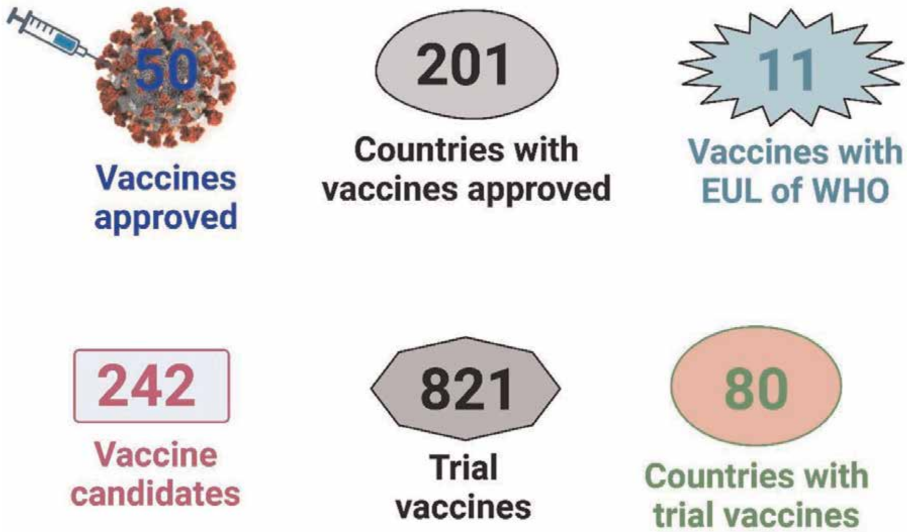

Figure 4.
An overview of the present scenario concerning COVID-19 vaccines available in the market. The figure was adopted from the COVID-19 vaccine tracker (https://covid19.trackvaccines.org/), with data updated until December 2, 2022, and accessed on June 19, 2023. This visual depiction was produced using a biorender (https://www.biorender.com).

Furthermore, the authorized COVID-19 vaccines encompass a diverse array of types, showcasing advancements in medical technology. These include mRNA, DNA, viral vectors, inactivated or killed viruses, and protein-based subunit vaccines (**Figure 3**). mRNA vaccines, such as the notable ones developed by Pfizer-BioNTech and Moderna, harness the power of genetic material to initiate an immune response within the body. Similarly, DNA vaccines like Zydus Cadila utilize genetic material to stimulate the immune system's defenses. Viral vector vaccines, such as the well-known ones manufactured by AstraZeneca and Johnson & Johnson, take advantage of a modified virus as a delivery system to transport genetic material and activate the immune response. By utilizing this approach, these vaccines can effectively trigger the body's defense mechanisms against the virus. Inactivated or killed virus vaccines, exemplified by the commendable efforts of Sinovac or Sinopharm, employ viruses that have been rendered inactive or killed to provoke an immune response. Through this method, the immune system becomes primed to recognize and combat the virus should an actual infection occur. Protein subunit vaccines, including the notable ones produced by Novavax or Medicago, employ specific proteins derived from the virus itself. By introducing these viral proteins into the body, an immune response is triggered, enabling the immune system to develop defenses against the virus. Collectively, these various COVID-19 vaccine platforms have demonstrated their efficacy in generating neutralizing antibodies and stimulating cell-mediated responses, as depicted in **Figure 3** and referenced in **Tables 1**–**3**.

4. The immunogenicity of COVID-19 vaccines

Vaccine immunogenicity refers to the capacity of a vaccine to stimulate an immune response within the body. The primary objective of vaccination is to activate the immune system, prompting it to recognize and counter specific components of a pathogen, such as a virus, while avoiding the onset of the actual disease [87]. Upon administration of the vaccine, the immune response is triggered, leading to the activation of various immune cells, including B cells. The immune system identifies the foreign components within the vaccine as antigens and initiates an immune response against them. B cells are responsible for producing antibodies that can neutralize the pathogen or mark it for elimination by other immune cells. T cells, comprising helper T cells and killer T cells, play a crucial role in coordinating and executing the immune response [88].

Vaccine immunogenicity is evaluated through clinical trials, wherein researchers measure the production of specific antibodies, such as neutralizing antibodies, in the blood of vaccinated individuals (**Table 1**). These antibodies are designed to recognize and bind to the specific components of the targeted pathogen that the vaccine aims to address. The presence of these antibodies indicates that the vaccine has successfully stimulated an immune response. The level and quality of the immune response induced by a vaccine can vary based on several factors, including the vaccine type, the antigens it contains, the dosage, and the vaccination schedule [89]. High immunogenicity is desirable as it suggests that the vaccine effectively triggers a robust immune response and provides protection against the specific pathogen being targeted [90].

Table 1 provides a comprehensive analysis of the immunogenicity of approved COVID-19 vaccines. Overall, these vaccines have been shown to elicit strong immune responses, including the generation of neutralizing antibodies and virus-specific T cells which are effective in reducing the risk of severe disease, hospitalization, and death due to COVID-19.

5. The safety of COVID-19 vaccines

Vaccine safety encompasses the comprehensive evaluation of potential risks and adverse effects associated with the administration of a vaccine. This evaluation involves rigorous testing throughout clinical trials and ongoing monitoring following its approval and widespread use [2]. Before entering clinical trials, vaccines typically undergo preclinical testing, including laboratory studies and animal testing to assess their safety and effectiveness. This initial evaluation helps identify any potential safety concerns and informs the decision to proceed with human trials. Subsequently, vaccines progress through various phases of clinical trials involving human participants. These trials thoroughly examine the vaccine's safety, immunogenicity, and efficacy. Throughout these trials, vaccine safety is closely monitored, and participants are carefully observed for any adverse reactions or side effects [91–93].

Table 2 provides a comprehensive analysis of the safety profile of approved COVID-19 vaccines, which has been extensively studied in both clinical trials and real-world settings. Most of the reported adverse events have been mild and temporary, such as localized pain at the injection site and low-grade fever [92]. Although rare, there have been reports of more severe adverse events, including anaphylaxis [93]. However, it is important to note that the occurrence of such serious adverse events is very low [93]. Overall, the risk of experiencing severe adverse events from the vaccines is significantly lower compared to the risk of severe illness resulting from COVID-19 (**Table 2**).

6. The efficacy of COVID-19 vaccines

Vaccine efficacy is a measurement of the effectiveness of a vaccine in disease or infection prevention, determined through controlled clinical trials under controlled conditions. This measure quantifies the reduction in disease incidence among vaccinated individuals in comparison to their unvaccinated counterparts, offering insights into the vaccine's capacity to protect against a specific pathogen. Clinical trials randomly assign participants to receive either the vaccine or a placebo, monitoring the occurrence of the targeted disease or infection in both groups [94]. By comparing the incidence rates, researchers can calculate the vaccine's efficacy, expressed as a percentage that represents the reduced risk of developing the disease among vaccinated individuals.

Table 3 provides an efficacy review analysis of approved COVID-19 vaccines in preventing symptomatic COVID-19. Clinical trials and real-world data have demonstrated that all COVID-19 vaccines effectively protect against severe illness, hospitalization, and mortality. When it comes to preventing symptomatic COVID-19, mRNA vaccines have demonstrated notably higher efficacy rates compared to other types of vaccines (**Table 3**) [94].

7. Opinions on immunogenicity, safety, and efficacy toward filling gaps of vaccine hesitancy

The evaluation of COVID-19 vaccines takes into account important factors such as immunogenicity, safety, and efficacy. A thorough review of these factors for authorized COVID-19 vaccines reveals that various vaccine platforms, including inactivated vaccines, viral vector vaccines, mRNA vaccines, DNA vaccines, and protein-based vaccines, demonstrate strong immunogenicity by eliciting neutralizing antibodies and cellular immune responses (**Table 1**). Moreover, studies have demonstrated that these vaccines are both safe and effective in preventing symptomatic cases of COVID-19 (**Tables 2** and **3**).

In terms of immunogenicity, both the recommended two-dose regimen and a single dose of the Johnson & Johnson vaccine have been shown to elicit strong immune responses in clinical trials and real-world data (**Table 1**). These responses include the production of neutralizing antibodies and the activation of T-cell responses, which are important for combating the SARS-CoV-2 virus. While the level of immunogenicity may vary among different vaccine platforms, overall, vaccines have proven effective in reducing the severity of COVID-19 symptoms and preventing hospitalization and mortality (**Table 3**).

When it comes to safety, robust monitoring systems have been implemented to continuously evaluate the side effects of vaccines [53, 92, 93]. Most adverse events have been mild and temporary, including symptoms like pain at the injection site, fatigue, or low-grade fever (**Table 2**). These mild to moderate side effects have been observed across various vaccine platforms and generally resolve on their own within a few days. Serious adverse events are exceedingly rare [53], and the benefits of vaccination in preventing severe COVID-19 far outweigh the potential risks. However, ensuring vaccine safety remains a top priority, and ongoing surveillance plays a critical role in promptly addressing any emerging safety concerns [53].

In terms of efficacy, COVID-19 vaccines have shown remarkable effectiveness in preventing both the incidence and severity of COVID-19 [94] (**Table 3**). Vaccination has proven to be highly successful in reducing hospitalizations and fatalities, even in the presence of emerging variants of concern. However, breakthrough infections can still occur, particularly with new variants like "Omicron," underscoring the need for ongoing surveillance, booster doses, and the development of updated vaccines to address viral mutations. Continued vigilance and adaptation are crucial to ensure the continued effectiveness of COVID-19 vaccination efforts according to a report [95].

Furthermore, the prime-boost vaccination strategy has demonstrated its potency, safety, and effectiveness in combating COVID-19 (**Tables 2** and **3**). In addition, studies have shown that heterologous prime-boost vaccination using combinations of an inactivated vaccine, AstraZeneca, Pfizer, and Moderna vaccines can be even more potent compared to homologous prime-boost vaccination using any single vaccine alone [96, 97]. The implementation of homologous or heterologous prime-boost vaccination strategies has been observed. In Cambodia, for instance, a homologous or heterologous prime-boost vaccination approach has been implemented, with inactivated vaccines used as the priming vaccine and viral vector or mRNA vaccines as the boosting vaccine. Encouragingly, no adverse events have been reported, and the vaccinated population in Cambodia has experienced a significant reduction in mortality [98]. These findings further emphasize the overall convenience and benefits of COVID-19 vaccination strategies.

8. Opinions on immunogenicity, safety, and efficacy toward filling gaps of vaccine inequity

In the global context, the impact of COVID-19 vaccines is influenced by the administration of numerous approved vaccines worldwide, as illustrated in **Figures 4** and **3**. A staggering 13.47 billion vaccine doses have been administered globally, with an average of 70.3% of the world population having received at least one dose and 93,683 doses being administered daily [8]. However, it is concerning that only 32.2% of individuals in low and middle-income countries (LMICs) have received at least one vaccine dose, primarily utilizing vaccines with lower prominence [8]. These statistics highlight the existence of a "vaccine inequity" gap between LMICs and developed nations.

The "vaccine inequity" observed among LMICs can be attributed to several crucial factors. These include the inability of these countries to manufacture their own vaccines, limited budgets to purchase advanced vaccines like Pfizer or Moderna [7], and concerns regarding the immunogenicity, safety, and efficacy of lower-profile vaccines, which may lead to vaccine hesitancy [61–65]. In light of these challenges, it is important to emphasize that the available vaccines, as outlined in **Tables 2** and **3**, have demonstrated overall safety and effectiveness, particularly in reducing hospitalizations and deaths. Therefore, individuals are encouraged to receive any vaccines that are accessible and affordable to help mitigate the impact of COVID-19.

COVAX and vaccine diplomacy are crucial strategies that have significant impacts on achieving equitable distribution of vaccines. By pooling resources and coordinating with vaccine manufacturers, COVAX aims to provide vaccines to LMICs that may otherwise struggle to secure sufficient doses. This initiative helps bridge the gap between nations with ample resources and those facing financial and logistical challenges. In addition, to effectively address vaccine inequity, it is also crucial to establish

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comprehensive vaccine surveillance systems that monitor the immunogenicity, safety profile, and efficacy of vaccines in regional countries. Taking inspiration from the UK report released by the UK Health Security Agency on October 21, 2021 [95], implementing such surveillance systems can provide valuable insights and help ensure that vaccines are being administered effectively and safely in different regions. This approach would significantly enhance trust in vaccine uptake within these countries and serve as essential documentation for future vaccine research and development. In Cambodia, for instance, a range of vaccines, including inactivated vaccines (Sinovax & Sinopharm), mRNA vaccines (Pfizer & Moderna), and viral vector vaccines (Astrazeneca & Janssen), are being used [7, 98]. It would be highly beneficial if Cambodia also conducts evaluation reports similar to the UK case [95]. These reports will be invaluable for future vaccine research and development in Cambodia, providing insights into which vaccine-based platforms offer long-lasting protective and therapeutic efficacy for the country's geographic and regional populations. Additionally, the reports will bolster efforts to enhance vaccine production capabilities, enabling better preparedness for future pandemics and ensuring the availability, safety, effectiveness, and affordability of vaccines in Cambodia.

In the global context, furthermore, as the UK holds the presidency of the G7, it should also consider conducting a comprehensive study in line with the research conducted by Edward J Mills and Gilmar Reis [99]. This study would involve head-to-head clinical trials comparing vaccines such as Pfizer, Moderna, Astrazeneca, Sputnik V, and Sinopharm, among others. The aim of this study would be to accumulate data and establish trust in the immunogenicity, safety, and efficacy of these vaccines. Including lower-profile vaccines in the study would have a significant impact on many LMICs, maximizing vaccine uptake in those regions. Importantly, such a study would contribute to shaping a better global solution regarding the prioritization of vaccine production, determining who should be offered the vaccine and establishing guidelines for booster shots, both in LMICs and developed nations. Moreover, it would enhance preparedness and control measures for future pandemic threats, ensuring a more effective response.

In cases where certain lower-profile vaccines are not approved for use in the UK, conducting a head-to-head study becomes limited. However, it is crucial to consider alternative approaches such as a collective report from G7 and G20 countries, along with data from LMICs. This would provide a more comprehensive analysis of vaccines' immunogenicity, safety, and efficacy. Additionally, the inclusion of vaccines like the DNA vaccine (Zydus Candila) from India, VLP (Medicago) from Canada, and Novavax (USA) (**Figure 3**) should be considered. Another valuable approach would be to develop a methodology that combines data from separate studies to estimate the immunogenicity, safety, and efficacy of different vaccines. This approach would enhance the credibility and reliability of the findings.

9. Opinions on immunogenicity, safety and efficacy toward future epidemic preparedness and control

This report presents an update on the current landscape of COVID-19 vaccines, emphasizing their immunogenicity, safety, and efficacy in the context of filling gaps of vaccine hesitancy, vaccine inequity, and future epidemic preparedness and control. The development and widespread administration of vaccines have played a crucial role in mitigating the impact of the ongoing COVID-19 pandemic [9, 10]. With numerous vaccines receiving emergency use authorization, the knowledge gained from their development and deployment can significantly contribute to future epidemic preparedness and control efforts [100]. The remarkable speed at which vaccines were developed and distributed globally highlights the potential for expediting vaccine development in response to emerging infectious diseases. Through collaborative endeavors involving governments, researchers, and pharmaceutical companies, we can further enhance vaccine production, distribution, and ensure equitable access, thus strengthening global preparedness against future epidemics [7].

Furthermore, it is crucial for LMICs to prioritize the enhancement of laboratory capacities to enable prompt and accurate diagnosis of infectious diseases [101]. This can be achieved by investing in infrastructure, equipment, and training for laboratory personnel. By strengthening laboratory capabilities, LMICs can effectively contribute to epidemic prevention, detection, and control. It is also important for LMICs to allocate resources to support research and development initiatives focused on combating epidemics [7]. This entails providing financial support to local research institutions, fostering collaborations with international partners, and conducting studies on the local epidemiology of infectious diseases, actively practice in non-pandemic times through one health concept [101]. To ensure reliable and standardized testing, it is imperative to establish well-equipped laboratories, provide comprehensive training to laboratory staff, and implement robust quality control measures [7]. Additionally, addressing vaccine hesitancy is paramount. This can be accomplished through transparent communication, accessible education, and community engagement. Public health campaigns should prioritize disseminating accurate information, dispel myths and misinformation, and address concerns in order to enhance vaccine acceptance among the population.

10. Conclusion

In summary, the utilization of COVID-19 vaccines has demonstrated their effectiveness in mitigating the impact of the pandemic, showcasing favorable immunogenicity, safety, and efficacy against the virus. These valuable insights gained from developing and deploying vaccines can be invaluable for future epidemic preparedness and control. To ensure successful vaccination strategies in future outbreaks and epidemics, it is imperative to prioritize factors such as maintaining public trust, promoting equitable access to vaccines, and continuing research and development efforts. By applying these lessons, we can strengthen our readiness to effectively address and control potential future epidemics.

Conflict of interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this chapter.

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Section 4

Prevention and Treatment Devices

Chapter 8

Filtration Efficiency Assessment of Decontaminated FFP2 Masks for Safe re-Use: Study Conducted as Part of the COVID-19 Response Plan at HASSAN II University Hospital in Morocco

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Abstract

During COVID-19, healthcare workers were at risk of infection and needed protection. Unfortunately, crisis-related mask shortages are forcing hospitals to look for ways to reuse masks after decontamination. The study aimed to assess the effectiveness of decontaminated FFP2 masks using moist heat or hydrogen peroxide. It compared the filtration efficiency, chemical composition, and structural changes of these masks with new FFP2 masks. This evaluation was carried out through techniques like scanning electron microscopy, Fourier transform infrared spectroscopy, and thermogravimetric analysis. The finding indicates that the analysis of the chemical composition and structure of the filter media did not exhibit significant alterations or structural deformations. Remarkably, the breathing resistance tests verified that decontaminated FFP2 masks yielded consistent results, differing only by 10 Pa compared to the EN149 standard. Furthermore, the chemical analysis revealed that the filter media in decontaminated masks remained unaltered, with no detectable chemical derivatives found in their components.

Keywords: COVID-19, FFP2 mask, shortage, decontamination, reuse

1. Introduction

The outbreak of the novel coronavirus disease (COVID-19) pandemic has raised urgent concerns about distributing and using personal protective equipment (PPE) among healthcare workers responsible for patient care. In response to this crisis, the World Health Organization (WHO) has warned of increased demand and potential shortages of PPE. The rapid influx of infected patients and the global impact of the epidemic have placed enormous strains on supply chains, leading to the loss of critical equipment, such as ventilators, and the units needed for patient care, such as FFP2 single-use ventilators. This interruption in the supply chain also affects single-use PPE

FFP2 masks are essential in personal protective equipment in healthcare [1–4]. These masks are designed to effectively filter particles in the 0.4–0.6 μm range with 94% efficiency. These are usually recommended for respiratory protection [2]. Traditionally, these masks are intended for single use to prevent possible microbial and viral contamination. However, due to the recent COVID-19 pandemic, there has been a significant shortage of these masks, and various decontamination methods are being investigated to assess their potential for reuse. As a result, a rapidly growing need exists to explore the potential for reusing these masks to alleviate mask shortages and optimally protect healthcare workers.

Several efforts have been made globally to address the shortage of FFP2 masks and provide compelling evidence of their potential for safe reuse. Various methods have been documented, including dry and moist heat, hydrogen peroxide vapor, ozone, and UV irradiation. Studies conducted in this area have introduced approaches to assess the filtration efficiency of masks after decontamination according to the established criteria [5–7]. Nonetheless, there are concerns that these processes may affect the filtration performance of masks, especially when working with hydrogen peroxide vapor [8].

However, implementing a reuse protocol presupposes the availability of a simple, safe reprocessing method adapted to the hospital environment and considering both logistics and human factors. These requirements, especially the availability and simplicity of the supply chain in hospitals in Morocco, led to the selection of reprocessing methods based on moist heat and vaporized hydrogen peroxide, which are most commonly used in the COVID-19 pandemic. This study investigates the structural and chemical changes of FFP2 masks after exposure to the chosen treatment method. Specifically, to mitigate environmental hazards, we tested solely on the new Duckbill brand FFP2 masks widely used in Moroccan hospitals. These masks have undergone up to four reprocessing cycles using each method. The primary purpose of this protocol is to analyze the filtration and mechanical properties of decontaminated FFP2 masks.

2. Materials and method

2.1 Filtering mechanisms

The FFP2 masks can filter out foreign particles by intercepting them within various layers of the mask, using physical mechanisms that can be either mechanical or electrostatic [9]. Particles typically traverse the mask in a laminar flow, allowing the airflow to bypass obstacles such as fibers easily. Mechanical entrapment of particles on fiber surfaces can occur when the inertia of the particles is sufficient to deviate from the aerodynamic trajectory or when suspended particles do not follow the laminar flow and interact with air molecules, resulting in a disordered, random

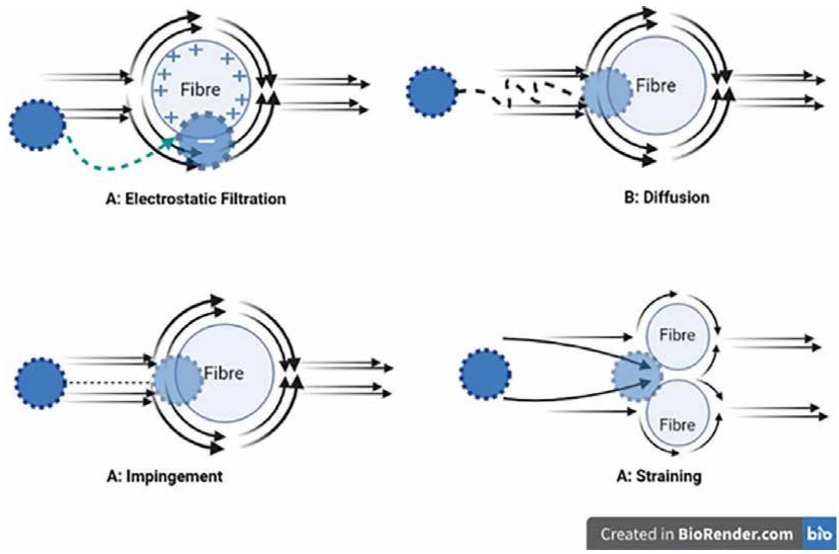

Figure 1.
Functional mechanisms of FFP2 filter media.

trajectory. This vibratory motion increases the probability that the particles get into the fibers and remain suspended due to Van der Waals's weak molecular interaction. Generally, this mechanism helps trap airborne particles with a diameter of around 0.1 μm, **Figure 1** [10, 11].

When the fibers contain significant electrical charges, an electrostatic process can capture the particles, whatever their charge be [11]. During this process, the fibers can attract particles with inherent charges *via* Coulomb forces and neutral polar particles [e.g., small water droplets] *via* dielectrophoresis forces. These latter result from the interaction between polarized objects and electric gradients. The filtration efficiency of most FFP2 masks is achieved through a combination of mechanical and electrostatic influences. The assessment of the filtration efficiency of these masks encompasses a series of tests and parameters in line with the established industry standards.

2.2 Measurements of respiratory mask efficiency

Standards provide a set of measurable parameters for assessing the effectiveness of respirators. When examining the reusability of respirators, studies often focus on specific parameters such as breathing resistance, aerosolization tests, and leakage tests. In our research, we have expanded these parameters and have included additional measures commonly assessed in the manufacturing field for this specific type of filter. The parameters considered in this study are.

2.2.1 Measure 1: respiratory resistance

The ISO EN 149 standard incorporates a parameter that includes two essential measurements: inhalation and breathing resistance. This test takes place over 3 minutes and provides respiratory efficiency and resistance values by applying two separate flow rates. The first, simulating inhalation, was set at 95 l/min and 0.2 m/s, while the second, simulating expiration, was set at 160 l/min and 0.34 m/s.

2.2.2 Measure 2: the lifetime and respiratory comfort

This parameter is mainly related to the effectiveness of the respirator, which is designed to establish a secure seal between the respirator and the wearer's face. If the seal is inadequate, the contaminated air will take the path of least resistance through the seal face leak. An improper seal will therefore affect the level of protection provided to the wearer. This can affect the product's life, which is generally estimated to be between 4 and 8 hours [12].

2.2.3 Measure 3: the quality of distribution and the intermingling of fibers

The best-known manufacturing process for FFP2 masks' nonwoven fabrics is the melting process that gives fine fibers. The fibers' fineness is usually between 0.6 and 10 μm for the melt-blown and 1 to 50 μm for the spunbond. This parameter is essential to obtain a high filtering efficiency.

2.2.4 Measure 4: chemical structure

Typically, the layers and filter media of the masks under study are predominantly polypropylene. However, subjecting polypropylene to elevated temperatures can lead to material degradation and a decline in its mechanical properties. This study highlighted the formation of oxidation products such as hydroperoxides and various carbonyl products during its degradation. They can influence the filtering performance of our masks, which results in the appearance of derivatives of chemical compounds. In this study, we have proceeded to chemical characterization to explore the changes in the molecular structure of the filter media. It is important to note that some common thermoplastics, such as polypropylene (PP), have a low thermal degradation plateau [13–15].

2.2.5 Measure 5: moisture saturation

Moisture accumulation reduces the filtering efficiency of FFP2 masks. Therefore, each type of mask has a maximum usage time that depends on the ability of its materials to absorb moisture [16]. In this work, we have considered this parameter, which can affect the filtration efficiency of our masks, mainly as we use a decontamination protocol based on moist heat [13, 14].

2.3 Testing protocol

2.3.1 FFP2 mask decontamination protocols

The masks were split into two groups for testing. The first group underwent moist heat sterilization, while the second group was treated with hydrogen peroxide containing silver ions. Specifically, the first group was subjected to an autoclave cycle at 121°C for 20 minutes, followed by a drying period of 15 minutes. To ensure the sterilization performance validation, we have used multiparametric tests and Bowie–Dick penetration tests as required by international standards and guidelines (SO 17665). The second sample of masks was exposed to a decontamination cycle using hydrogen peroxide doped with 12% silver ions at a rate of 6 ml per m^3 for 10 minutes and a contact time of one hour on a 27 m^3 enclosure. For this purpose, we have used a rotating nozzle micro-nebulizer to generate particles smaller than 5 μm to ensure smooth penetration.

2.3.2 Samples studied

The samples analyzed are FFP2 (Duckbill)-type masks. The composition of the layers and the filter media is generally based on polypropylene. These masks have been exposed to moist heat sterilization and hydrogen peroxide doped with silver ions. The parts of the samples studied are the inner and outer layers (spunbond) of the mask and the intermediate filter media (melt-blown). The protocol used takes into account a maximum of four reuses of the FFP2 mask. Indeed, the protocol consists of performing decontamination tests on 20 new masks to protect the manipulators during the study. This protocol also includes the analysis of a control sample of FFP2 masks without any exposure to any reprocessing procedure.

2.3.3 Analysis methods

2.3.3.1 Respiratory resistance test

Respiratory resistance testing consists of physical tests to measure pressure according to the standard ISO EN 149 test. This test consists of measuring the resistance to airflow through the whole respirator at various flow rates designed to represent the peak inhalation and exhalation rates of a wearer during work of low to moderate intensity [including peak flow rates of 95 lpm, minute volume of 30 lpm, and 160 lpm, minute volume of 50 lpm]. The maximum permitted breathing resistance is 3.0 mbar. We used a motorized differential pressure sensor adapted to the test forces and standard accessories for fixing and holding FFP2 masks on the test device to perform the test.

2.3.3.2 Scanning electron microscopy (SEM)

The morphological properties, distribution quality, and fibers' intermingling have been studied by Quanta 200 FEI equipped with EDX probe with software Genesis 2000i and 15 kV accelerating voltage. The samples were mounted on adhesive tape and a water-coated nozzle to improve electrical conductivity. The samples included in this type of analysis are the filter media (melt-blown) and the external and internal layers (spunbond) of the FFP2 masks that are the object of this study.

2.3.3.3 Fourier transforms infrared spectroscopy (FTIR)

The chemical structure changes of the reprocessed masks are characterized by examining the FTIR spectra. These spectra were obtained using Spectrometer FT-IR Nicolet iS50, piloted, and recorded in the frequency range between 450 and 4000 cm^{-1} using a resolution of 4 cm^{-1} with a sampling frequency of 16 scans. The samples included in this type of analysis are the filter media of the masks (melt-blown).

2.3.3.4 Thermogravimetric analysis (TGA)

To observe possible moisture saturation in the layers of the FFP2 masks, the thermogravimetric behavior of our samples was studied. This was done on a Q500 TGA device. The samples of approximately 10 mg were heated from 25 to 500°C at a heating rate of 10°C/min under 20 ml/min of nitrogen current. The samples examined for this type of analysis are the filter media of the masks FFP2 (melt-blown).

2.3.4 Analysis interpretation

All of the above tests were carried out on decontaminated and control samples. Using an empirical analytical method, the data acquired were evaluated to study the impact of the decontamination procedure on the filtering efficiency and filter media material (melt-blown, spunbond) of the FFP2 masks.

3. Results

3.1 Respiratory resistance

Respiratory resistance tests (inhalation and exhalation) were carried out on our samples after they had undergone various decontamination cycles to study the filtration efficiency of our masks after exposure to reprocessing processes. The test includes a motorized differential pressure sensor adapted to test forces and standard accessories for fixing and holding FFP2 masks on the test device. We have reported the results in **Table 1**.

These findings show that the breathing resistance of the new FFP2 mask is 340 Pa on exhalation and 350 Pa on inhalation. The deviation from the EN149 standard of −/+ 50 Pa may be due to faulty storage or exposure to humidity or radiation [17, 18]. As these types of masks are electret type of filters, they must be stored under the manufacturer's recommended conditions. We have already studied the effects of mask storage. It has been reported that for a stock of over 10 years for certain masks, 10% no longer meet the efficiency criteria and are below the standard [19]. However, with this defect, the filtration efficiency is relatively high or consistently above 90%.

For FFP2 masks that underwent a single cycle of hydrogen peroxide and silver ion disinfection or a steam heat autoclave cycle, performing respiratory resistance has remained constant with a slight difference of 10 Pa in comparison with the witness FFP2, a slight difference of 0.02% at inspiration.

FFP2 masks that underwent two to four cycles of disinfection by steam autoclaving showed a decrease in the order of 20 Pa on inspiration and expiration compared to the witness FFP2 masks. The uncertainty on this means of experimentation adopted in our study is +/− 0.01, which leads us to conclude that the proposed reprocessing techniques are acceptable. Indeed, the results obtained on the respiratory resistance test allow the possible reuse of three FFP2 masks according to the EN149 standard [20].

Masks sample	Expiratory resistance [Pa] 160 l/min–0.34 m/s	Inspiratory resistance [Pa] 95 l/min–0.2 m/s
Witness FFP2	340	350
H_2O_2/Ag^+ FFP2	340	340
One steam cycle FFP2	360	320
Two steam cycle FFP2	330	330
Three steam cycle FFP2	330	330
Four steam cycle FFP2	330	330

Table 1.
Respiratory resistance results according to EN149 standard.

3.1.1 Scanning electron microscopy (SEM)

The quality of distribution and the intermingling of the fibers on the surface is evaluated using Quanta 200 FEI equipped with an EDAX probe and Genesis 2000i software with an acceleration of 15 kV voltage. Sectional views are taken to observe the organization of the fibers on the thickness and the different fiber mixtures in the filtering media (melt-blown) and the external layers of the FFP2 masks (spunbond).

The magnification ranged from x200 to x400. The resolution of the images received is 2048 x 1536 pixels, always the pixel as the conversion unit for measuring the fiber diameter. Many types of FFP2 respirator masks are currently commercialized. These are composed according to a standard manufacturing process of two polypropylene spunbond protective layers and two or more melt-blown filtering layers. Each of these layers will be studied separately.

We have grouped the fiber thickness and diameter data in **Table 2** and **Figure 2** (SEM). They detail the various operating procedures explained in the method section. The aim here is to get an idea of the structural characteristics of the layers studied and to point out any structural changes in the SEM of the exposed masks compared with the FFP2 control mask.

Melt-blown layers are less compact than spunbond layers in the FFP2 mask manufacturing process, yielding the smaller fibers required for FFP2 mask filtration efficiency [21, 22]. This section observes a change in fiber diameters, especially since the reprocessing method adopted is steam heat. The latter can also influence the compactness of the filter media, which can become clogged due to dryness during autoclaving of FFP2 masks and, subsequently, an increase in pressure drop and the permeance of melt-blown layers [23–25].

Fiber diameter control seems more challenging to judge from **Figure 2**, which shows the fiber diameter distribution of the melt-blown and spunbond samples of our FFP2 masks in this study. It offers a wide disparity in fiber diameters within the same sample, particularly for filter media, a feature of melt-blown products [24].

Masks sample	Layers studied	Thickness [mm]	Fiber diameter [µm]
Witness FFP2	Melt-blown	[20]	[3–5]
	Spunbond	[20]	[15–20]
H_2O_2/Ag^+ FFP2	Melt-blown	[20]	[3–5]
	Spunbond	[20]	[15–20]
One steam cycle FFP2	Melt-blown	[22]	[4–5]
	Spunbond	[20]	[17–20]
Two steam cycle FFP2	Melt-blown	[22.5]	[4–5]
	Spunbond	[21]	[18–20]
Three steam cycle FFP2	Melt-blown	[22.7]	[4.5–5]
	Spunbond	[22]	[18–20]
Four steam cycle FFP2	Melt-blown	[22.7]	[4.5–5]
	Spunbond	[22.5]	[18.520]

Table 2.
Structural characteristics of FFP2 mask monolayers per reprocessing cycle.

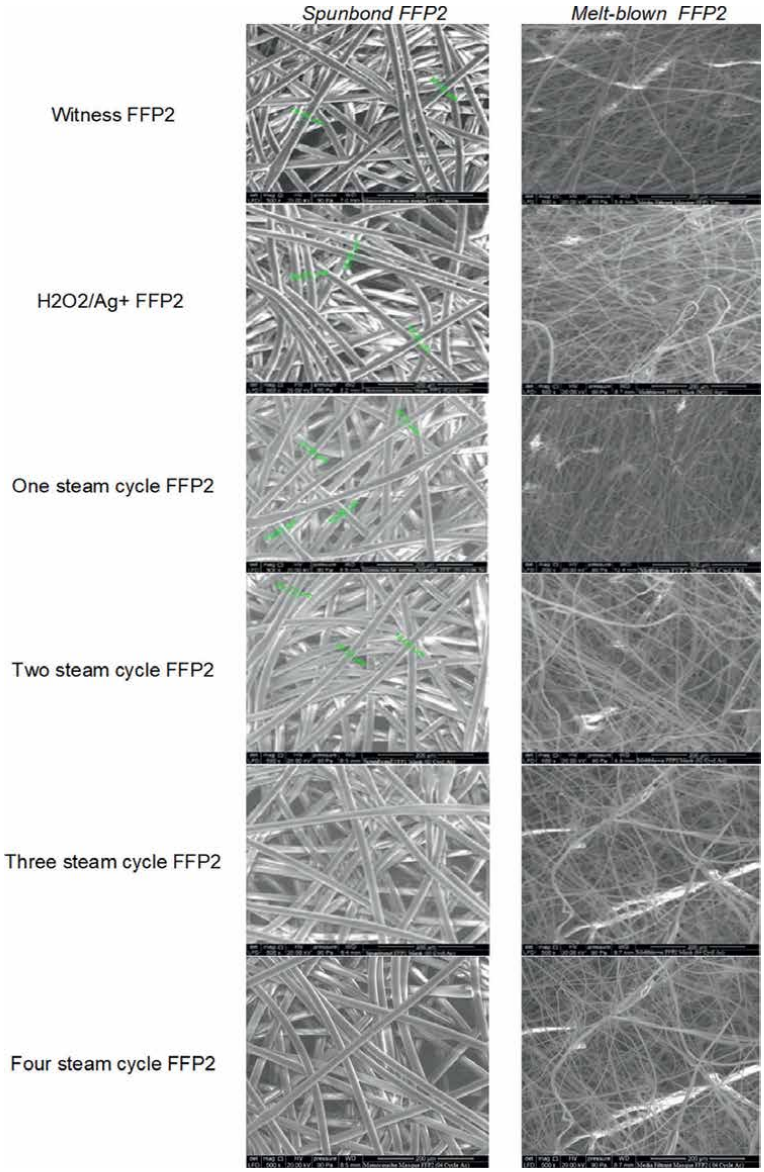

Figure 2.
SEM images of the melt-blown and spunbond composing FFP2 masks per reprocessing cycle.

In contrast to the samples exposed to steam heat autoclaving, which increased in diameter from 0.5 to 3.5 μm in the spunbond layers and from 2 to 2.5 mm in thickness, our results reveal that the diameter of the fibers in samples treated with hydrogen peroxide and silver ions remains constant compared to that of the control samples, which can be explained by the saturation of moisture in the samples studied **Figure 2** and **Table 2**.

Results obtained in this way lead us to conclude that our masks have changed little structurally, and the parameters obtained in the respiratory resistance tests confirm this hypothesis since they have decreased, especially for FFP2 masks subjected to steam heat treatment cycles.

3.1.2 Fourier transform infrared spectroscopy (FTIR)

IR absorption spectroscopy aims to determine the difference in chemical structure between reprocessed and control samples, with the protocol characterizing only the melt-blown filter media, by examining changes in molecular structure. Below are the spectrograms illustrating the chemical structure of the samples tested **Figure 3**.

All observed predominant bands are characteristic isotactic vibrational bands (iPP) [26, 27]. The FTIR spectrum of our samples shows a strong C-H stretching vibration band of the alkane from 2841 to 2955 cm^{-1}, and the C-H bend represents the peak at 1380 and 1454 cm^{-1}.

The emergence of a band at 1725 cm^{-1} occurred in all samples, and this signal in the spectra reflects a carbonyl group (C = O) derived from the polyester group [27]. This suggests that the structure of the samples analyzed also contains a PET thermoplastic polymer. Tests confirmed the use of a mixture of PP and PET polymers in the melt-blown layers of FFP2 masks as protection against harmful bioaerosol particles [26].

The spectra obtained from the samples shown in **Figure 3** were similar; no new peaks were detected, meaning there were no reactions or interactions between the materials during reprocessing our FFP2 masks compared with the control samples.

3.1.3 Thermogravimetric analysis (TGA)

The ATG purpose here is to observe any moisture saturation in the layers of FFP2 masks, mainly as we use a moist heat reprocessing method described above. On the one hand, this parameter can influence the performance of the filter media and, on the other, cause bacterial proliferation during storage in unfavorable environments [10, 28]. This thermogravimetric analysis may also show a cross-linking or decomposition reaction of polypropylene at low temperatures and a degradation of the filtering capacity of our masks exposed to a moist heat reprocessing method.

ATG curves for FFP2 H2O2/Ag+, FFP2 single-cycle, and FFP2 three-cycle steam autoclave showed degradation at 315°C compared to FFP2 Witness and FFP2 four-cycle and FFP2 two-cycle steam autoclave samples, which showed degradation at 360°C.

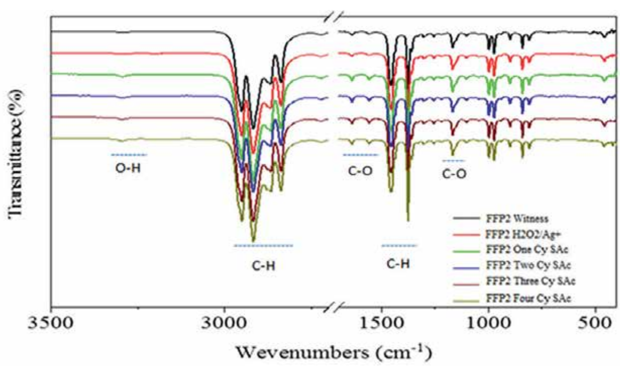

Figure 3.
FTIR spectra of the melt-blown layers of FFP2 masks per reprocessing cycle.

The impact of moisture saturation on our reprocessed samples was observed for FFP2 masks that were recycled two to four times, lengthening degradation over time compared to the FFP2 control. The breakdown temperature of FFP2 H2O2/Ag + is higher (320°C) than FFP2 Witness, although polypropylene is resistant to hydrogen peroxide at room temperature [29].

We attribute the weight loss in our samples to the depolymerization of the PP structure [30]. The thermogravimetric analysis results confirm that our FFP2 masks give specific stability to the filter layers with moist heat reprocessing with a sterilization plate not exceeding 125°C. At this temperature value, our TGA curves confirm this stability in **Figure 4**.

This result indicates that our mask reprocessing methods do not induce measurable chemical reactions such as cross-linking or polypropylene chain splitting (**Table 3**).

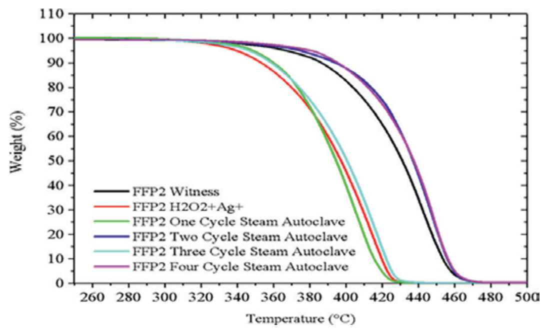

Figure 4.
Thermogravimetric analysis curves of the layers composing FFP2 masks per reprocessing cycle.

Masks sample	Respiratory resistance results	Structural characteristics (SEM)		Chemical structure FTIR	Moisture saturation TGA	Reuse Interpretation
		Thickness [mm]	Fiber diameter [µm]			
H_2O_2/Ag^+ FFP2	ER/340	[20]	[3–5]	undetected chemical residues	unobserved filter disability	Compliant
	IR/340	[20]	[15–20]			
One steam cycle FFP2	ER/360	[22]	[4–5]	undetected chemical residues	unobserved filter disability	Compliant
	IR/320	[20]	[17–20]			
Two steam cycle FFP2	ER/330	[22.5]	[4–5]	undetected chemical residues	unobserved filter disability	Compliant
	IR/330	[21]	[18–20]			
Three steam cycle FFP2	ER/330	[22.7]	[4.5–5]	undetected chemical residues	unobserved filter disability	Compliant
	IR/330	[22]	[18–20]			
Four steam cycle FFP2	ER/330	[22.7]	[4.5–5]	undetected chemical residues	unobserved filter disability	Compliant
	IR/330	[22.5]	[18.5–20]			

ER: Expiratory resistance, IR: Inspiratory resistance.

Table 3.
Reuse compliance according to results obtained of FFP2 mask monolayers per reprocessing cycle.

4. Discussion

Within the guidelines for personal protection in healthcare establishments, particularly regarding respiratory protection, the use of FFP2 masks and similar mask categories is traditionally recommended for single use. However, the scarcity of personal protective equipment (PPE) during this pandemic and the need to maintain a safe working environment for healthcare professionals have highlighted the need to look for innovative solutions to PPE shortages.

The reprocessing protocols proposed for FFP2 masks or other respiratory protection still pose problems and technical difficulties linked to logistical conditions and to the limits of risk management in the collection and reprocessing chain [28]. Based on data from the literature and existing resources, it adopted two protocols for reprocessing FFP2 masks in this study. The first involved hydrogen peroxide doped with silver ions, while the second used moist heat, described as a widely recognized technique in hospital sterile processing systems [28].

The work undertaken enabled us to assess the feasibility of reprocessing and reusing FFP2 masks, to manage a shortage. The results obtained during the first reprocessing, based on hydrogen peroxide and silver ions, enabled us to conclude that there was no influence on performing the masks tested. Characterization tests confirm the chemical and structural stability of our samples. The presence of silver ions at low doses seems insignificant to cause an effect on the electrostatic filtration provided by the electrical charge of the cast iron ("electret") used in this type of mask. Another study using the same reprocessing method concluded that the mechanical integrity and performance of the FFP2 are maintained after exposure to 10 or 20 cycles of hydrogen peroxide [5].

The problem of SARS-CoV inactivation has also been widely documented; indeed, there is a vast scientific record of research into the inactivation of viruses and bacterial spores using hydrogen peroxide [31, 32]. And recently, a report submitted to the US FDA by a Columbus-based company, Battelle, has showed that vaporized hydrogen peroxide (HPV) can safely sterilize N-95 FFRs. In its study, the company used spores of the bacterium *Geobacillus Stearothermophilus*, as a biological indicator to contaminate N-95 FFRs (contaminated by either liquid droplets or exposure to an aerosol) [5].

Regarding the second method of reprocessing FFP2 masks using moist heat, the results appear reassuring for four reuses. Indeed, no structural changes or deformation of the integrity of our samples on a 121°C sterilization plate was detected. A study carried out under the same conditions confirms these results: an *Staphylococcus epidermidis* permeability test and filtration tests showed no significant difference before and after five cycles of moist heat decontamination [14, 33]. Another study used moist heat decontamination in real-world testing and reported a moderate influence on integrating the tested masks at 60°C and 80% relative humidity [34]. In comparison, another study revealed that decontamination tests by autoclaving at 134°C in Dutch hospitals resulted in mask deformation and loss of elastic strength [35].

The limitation of this work is that we did not validate the removal of the SARS-CoV-2 virus by autoclaving but relied on multiparameter chemical indicators to show the performance of the sterilization load on already biologically valid autoclaves. However, a recent study has indicated that a sterilization cycle, such as ours (15 minutes at 121°C), removed the SARS-CoV-2 [35].

5. Conclusion

We have extensively tested the reuse of respirator masks during this pandemic period. Various procedures have been proposed, and given the variability of the results obtained, it is likely that the success of decontamination is closely linked to mask models and their intrinsic structure. The results of our experiments show that the proposed reprocessing techniques, based on moist heat or hydrogen peroxide, did not influence the functionality of the Duckbill FFP2 masks tested.

According to our results, in the event of an acute shortage of FFP2 masks, these simple processes, which are available in hospitals, economical, and quick to implement, can guarantee the safe reuse of the type of FPP2 masks tested.

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Conflict of interest

The author[s] declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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Chapter 9

Interplay between Inhaled Ibuprofenate, SARS-CoV-2, Vasoplegic Pulmonary Vascular Dysfunction, Pneumonia and CARDS

Christian Carlos Zurita-Lizza, Ignacio Rodriguez-Sanchez and Pablo Alexis Doreski

Abstract

In this manuscript, we will describe the possible mechanisms of action of inhaled sodium ibuprofenate in hypertonic saline formulation-NaIHS, focusing primarily on vasoplegic pulmonary vascular dysfunction leading to severe pneumonia and Coronavirus Disease 2019-associated acute respiratory distress syndrome. We will address the anti-inflammatory, immunomodulatory and antiangiogenic therapeutic effects of NaIHS, which together would exert their action through the negative modulation of local inflammatory mediators, pro-inflammatory cytokines and inflammatory pathways. In such a manner, NaIHS may reverse pulmonary vasoplegia and may thereby restore hypoxic pulmonary vasoconstriction, correcting the uncoupling of the ventilation-perfusion ratio and vasoplegic intrapulmonary shunting and, above all, it may reverse severe hypoxaemia. We will also describe the potential virucidal effects of NaIHS on Severe Acute Respiratory Syndrome-Coronavirus 2. Likewise, we will mention the evidence obtained from the potential adjuvant treatment with NaIHS in two observational cohort studies done in Argentina, the most recent of them with 5146 patients, concluding that NaIHS reduces mortality by 48.7%, although randomised clinical trials are still needed to confirm these data.

Keywords: NaIHS, SARS-CoV-2, pulmonary vascular dysfunction, virucidal effect, severe pneumonia and CARDS

1. Introduction

Coronavirus Disease 2019 (COVID-19) sepsis with a respiratory starting point is a vascular pathology of immuno-inflammatory aetiology secondary to Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) infection, characterised mainly by endothelitis with generalised endothelial dysfunction, occlusive thromboinflammation, massive cytokine release, renin-angiotensin system (RAS) imbalance, metabolic dysfunction with oxidative stress and reactive oxygen species (ROS) release and respiratory or multi-organ dysfunction [1, 2].

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) derived from propionic acid and poorly soluble in water, acting as a reversible and non-selective inhibitor of cyclooxygenase 1 and 2 (COX) [3], with still poorly understood COX-independent effects [3]. The hydrosoluble NaIHS formulation administered by inhalation bears the following characteristics: high ionic strength and micrometric or nanometric size, thus achieving a high concentration in the pulmonary biophase since, being hydrosoluble, NaIHS requires a dose 10 times lower compared to traditional orally administered ibuprofen to achieve its therapeutic effect and would also have a high pulmonary volume of distribution, thus obtaining a high therapeutic safety and equal pharmacological effect at very low NaIHS doses of 150 mg/day, distributed in 3 aerosolisations of 50 mg every 8 hours (with the possibility of increasing the dose if necessary), using special nebulisation devices that avoid aerosolisation and contagion of health personnel [4].

NaIHS has a history of successful therapeutic use in chronic lung diseases such as cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis and chronic obstructive pulmonary disease (COPD); thanks to its anti-inflammatory, immunomodulatory, mucolytic, antiangiogenic and bactericidal effects [4]. In addition, NaIHS has a virucidal effect in vitro on viruses enveloped with a bilayer membrane, including the Coronaviridae family [4].

After the SARS-CoV-2 pandemic declaration in March 2020 by the World Health Organisation (WHO), in June 2020 [4], a group of researchers: Doreski, PA; Garcia, NH; Beltramo, DM et al. in Argentina developed the idea of using NaIHS in moderate and severe COVID-19 pneumonia [4], in the modality of compassionate use and covered by the Declaration of Helsinki [4, 5]. Accordingly, it was approved for emergency use in several Argentine provinces and its phase II clinical trial (Pegasus trial) was approved in July 2021 by the Drug, Food and Technology National Administration of Argentina (ANMAT) [4–6]. Two observational multi-centre cohort studies of heterogeneous populations have been conducted in Argentina with NaIHS: the first study analysed data from 383 patients (15% mechanically ventilated), drawing statistically significant conclusions from both groups studied about decreased mortality, shorter hospital stay, improvement of clinical signs and rapid reversal of hypoxaemia [5]; and the second study, recently in May 2022, analysed data from 5146 patients, conducted with the approval of the Institutional Review Board of the National Bureau of Economic Research (NBER) of Harvard and Columbia Universities, concluded that NaIHS reduces mortality by 48.7% [6]. However, some studies are still needed to confirm these emerging data.

2. Therapeutic effects of NaIHS and pathophysiological mechanisms of SARS-CoV-2 involved in pulmonary circulation

2.1 Anti-inflammatory and immunomodulatory therapeutic effects.

2.1.1 Pulmonary vasoplegia

In a recently published article, we have postulated nitric oxide (NO) overproduction as the most important possible determinant in the production of pulmonary vasoplegia, through overexpression and dysregulation of NO-generating enzymes involving indoleamine-2-3-dioxygenase-1 (IDO) and inducible NO synthase (iNOS) [7], producing NO from the amino acids L-tryptophan as substrate in the former and from L-arginine in the latter, respectively. This would occur at the endothelial and mononuclear levels [7]. NO is the main vasoplegic mediator of experimental sepsis, with NO overproduction in COVID-19 possibly being the main responsible for pulmonary vasoplegia and a further determinant of endothelial injury by oxidative stress from ROS generation [7]. The rapid reversal of hypoxaemia observed in the studies mentioned in the introduction may be caused by the therapeutic effect of NaIHS [7], which has led us to consider, on one hand, a pharmacokinetic link with gaseous NO, given that in anaerobiosis, its elimination half-life is as short as 1 to 5 seconds and the production of injury is concentration-dependent in the micromolar range, due to its hyperproduction [7]; and on the other hand, a pharmacodynamic link, since patients with severe vasoplegic pneumonia and COVID-19-associated acute respiratory distress syndrome (CARDS) may respond favourably to NaIHS therapeutics [7], whereas inhaled vasodilator therapeutics such as NO, prostaglandins, prostacyclins and milrinone may lead to a marked deterioration [8]. Patients with acute respiratory distress syndrome (ARDS) and pulmonary hypertension may favourably respond to inhaled vasodilators, although more studies are still needed [8]. Pathophysiologically, pulmonary vasoplegia involving large heterogeneous lung areas presents in about 80% of the cases as severe vasoplegic pneumonia or CARDS [8], favourably responding to NaIHS [7], 100% oxygen supplementation, high flow nasal cannula (HNFC), continuous positive airway pressure (CPAP) and non-invasive mechanical ventilation (NIV) or requiring early invasive mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO) [8], on a case-by-case and personalised basis. Pulmonary vasoplegia may lead to pulmonary vascular dysfunction with loss of physiological sympathetic hypoxic pulmonary vasoconstriction (HPV), producing a decoupling of the ventilation-perfusion (V/Q) ratio and a significant right-to-left vasoplegic intrapulmonary shunting with mixed venous blood of approximately 50% or higher [1, 8]. Furthermore, pulmonary vasoplegia may lead to an increase in pulmonary blood flow that may not allow for the time necessary for adequate alveolar-capillary gas exchange, generating severe hypoxaemia and acute respiratory failure [1]. This is to say that alveolar ventilation is preserved, with preserved lung compliance and low lung elastance, but pulmonary perfusion is altered, leading to inadequate gas exchange [8] and furthermore, as a consequence of the above, a significant increase in physiological dead space. It should be clearly stated that the differential diagnosis between severe vasoplegic pneumonia and CARDS is extremely difficult, given the possibility of overlap between both pathological entities, with highly heterogeneous clinical, gasometric (normo- or hypercapnic) and imaging presentation [1, 8]. Lung imaging studies evidence the coexistence of predominantly vasoplegic areas and minor vasoconstricted areas [1], as a consequence of the possible hyperproduction of NO in the predominantly vasoplegic areas [7], which may override the RAS imbalance in the vasoconstricted areas [1]. RAS imbalance would lead to down-regulation of angiotensin-converting enzyme 2 (ACE2) of the RAS axis with vasodilator effect and up-regulation of angiotensin II (Ang II) of the RAS axis with vasoconstrictor effect [1], thus promoting a pathological increase in the vasoconstrictor effect of RAS with increased circulating Ang 2 [1].

2.1.2 Main pathophysiological mechanisms that may lead to NO hyperproduction and possible therapeutic response using NaIHS

IDO overexpression and activation with consequent activation of the IDO-kynurenine pathway may lead to NO hyperproduction in anaerobiosis [2]. Such overexpression and activation may be due to the positive modulation of the following inflammatory pathways through COX2 [9], nuclear factor kappa light chain enhancer of activated B cells (NF-kB) [2], signal transducer and activator of transcription 3 (STAT3) [2], toll-like receptor 4 (TLR4) [2] and the pro-inflammatory cytokines interferon gamma (IFN-γ) [2, 9], being this one the most important [2, 9], interleukin-1 beta (IL-1β) [9], tumour necrosis factor alpha (TNF-α) [9] and IL-6 [2]. NaIHS may indirectly inhibit IDO [9] by negatively modulating all the inflammatory pathways and pro-inflammatory cytokines mentioned above [10].

RAS imbalance would occur through the down-regulation of ACE2 of the anti-inflammatory RAS axis and the up-regulation of Ang II of the pro-inflammatory RAS axis [1]. ACE2 down-regulation would promote iNOS overexpression and induction, decreased expression of endothelial synthase (eNOS), which would exert a regulatory function on iNOS and endothelial protective effect, and increased vascular smooth muscle reactivity to NO [1]. Ang II up-regulation would also promote iNOS overexpression and induction, through the activation of NF-kB, which would interact with the Ang type 1 receptor (ATR1) and activate nicotinamide adenine dinucleotide phosphate complex 2 (NADPH-oxidase) and, also through (ATR1), generating oxidative stress and ROS [10]. In addition, RAS imbalance would increase the release of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6 and others, which would lead as well to iNOS induction and overexpression [1, 10]. NaIHS may reverse RAS imbalance through direct inhibition of COX2, NF-kB and transforming growth factor-beta 1 (TGF-β1) [10], and it may thereby restore ACE2 up-regulation of the anti-inflammatory RAS axis and Ang II down-regulation of the pro-inflammatory RAS axis [11]. It should be noted that ibuprofen does not produce ACE2 overexpression in both uninfected and SARS-CoV-2 infected patients and does not promote viral entry, but only restore the RAS imbalance caused by COVID-19 [12].

Possible inhibition of the vasopressor response by blocking calcium entry into vascular smooth muscle cells, generated by iNOS induction [13]. iNOS induction and overexpression would be triggered by activation of the inflammatory pathways COX2 and NF-kB and by the pro-inflammatory cytokines IL-1β, TNF-α and IL-6 [13]. NaIHS may restore the vasopressor response by reversing the blockade of calcium influx, through negative modulation of the inflammatory pathways and the pro-inflammatory cytokines mentioned above [10].

The mononuclear pro-inflammatory cytokine storm syndrome would be amplified by a positive feedback loop between STAT3, NF-kB and IL-6 [14], further amplifying the immuno-inflammatory response and thus promoting iNOS overexpression and induction [14]. NaIHS would prevent the generation of the positive feedback loop mentioned above, through the negative modulation of all its components [10].

The Warburg effect would be activated as a consequence of anaerobic cellular metabolism and possible positive modulation by M1 macrophages, via the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway [15]. Hypoxaemia generates mitochondrial dysfunction and oxidative stress, forcing cells to opt for an alternative metabolic pathway (Warburg effect) to more rapidly and efficiently obtain the energy needed [15]; that is to say that cellular aerobic glycolysis (Krebs or tricarboxylic acid cycle) is blocked and the Warburg effect would be activated, characterised by impaired aerobic glycolysis with lactate production, fatty acid synthesis and glutaminolysis and in this way, the Warburg effect would promote iNOS induction and overexpression [15]. NaIHS may reverse hypoxaemia [7] and may negatively modulate the PI3K/AKT/mTOR pathway [16], and it may thereby inhibit the Warburg effect [7].

In conclusion, NaIHS may indirectly inhibit IDO and iNOS enzymes and may thus prevent the hyperproduction of NO as a generator of pulmonary vasoplegia, as explained in each case above [7]. NaIHS may reverse pulmonary vasoplegia and restore HPV and may thus correct the V/Q ratio and vasoplegic intrapulmonary shunting [7] but most of all, it may be able to reverse severe hypoxaemia [7] and acute respiratory failure where possible in severe vasoplegic pneumonia and CARDS.

2.1.3 Vasodilation and pulmonary oedema

The activation of local inflammatory mediators such as prostaglandins (mainly prostaglandin E2), prostacyclins (prostaglandin I2), bradykinins and the afore-mentioned NO produces vasodilation with increased capillary permeability and

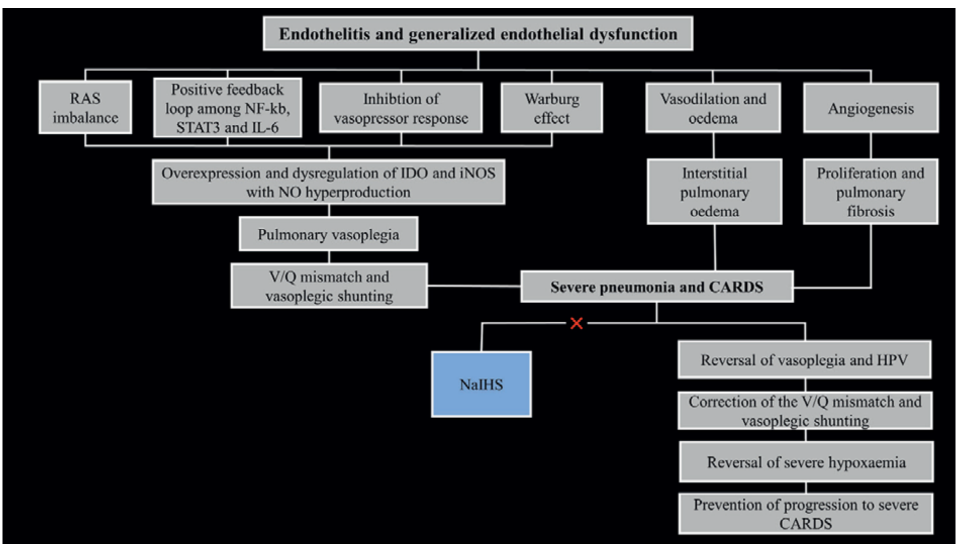

Figure 1.
Potential therapeutic effects of NaIHS on pulmonary vascular dysfunction in COVID-19.
Endothelitis and generalised endothelial dysfunction caused by the respiratory SARS-CoV-2 infection may lead, at the pulmonary level, to NO hyperproduction, by the possible overexpression and dysregulation of iNOS and IDO [7]; through the following mechanisms such as RAS imbalance [1, 10], positive feedback loop among NF-kB, STAT3 and IL-6 [14], the loss of the vasopressor effect [13] and the activation of the Warburg effect [15]; NO hyperproduction may cause pulmonary vasoplegia and the loss of HPV [7], this pulmonary vascular dysfunction may lead to the V/Q mismatch and the vasoplegic pulmonary shunting [8]. This alteration of gas exchange added to vasodilation with pulmonary oedema and angiogenesis may all together [5, 7, 8] produce severe vasoplegic pneumonia and CARDS. One arm shows preliminary evidence after the treatment with NaIHS, which may revert pulmonary vasoplegia and HPV, correcting the V/Q mismatch, vasoplegic shunting and severe hypoxaemia [7]; and it may also prevent the progression of severe pneumonia and CARDS. The other arm shows preliminary evidence without treatment with NaIHS.

mixed interstitial pulmonary oedema, at the onset of severe vasoplegic pneumonia and CARDS, showing the characteristic tomographic pattern of ground-glass opacity [5, 7].

NaIHS, by direct inhibition of COX-2, would inhibit all of the above-mentioned local inflammatory mediators and thus prevent vasodilation and pulmonary oedema [5, 7]. In the particular case of bradykinin, it is worth mentioning that NaIHS, through the aforementioned COX2-dependent mechanism, may produce two effects: on one hand, it may lead to down-regulation of the bradykinin B2 receptor [17] and on the other hand, it may promote ACE2 up-regulation [11]; hence, NaIHS may prevent bradykinin action, negatively modulating the des-arginine 9-bradykinin (des-Arg 9-BK) pathway and producing down-regulation of the bradykinin B1 receptor [1].

2.1.4 Pulmonary angiogenesis

In severe vasoplegic pneumonia and CARDS, angiogenesis is found, which is of great importance in the progression to the proliferative and fibrotic stages of CARDS and also in the subsequent post-COVID-19 pulmonary fibrotic sequelae [5]. NaIHS, through direct inhibition of COX-2, may negatively modulate vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [18] and by COX-independent effect, it may inhibit hypoxia-inducible factor-1 alpha (HIF-1α) [19], thereby inhibiting angiogenesis and pulmonary fibrosis see **Figures 1** and **2**. [18, 19].

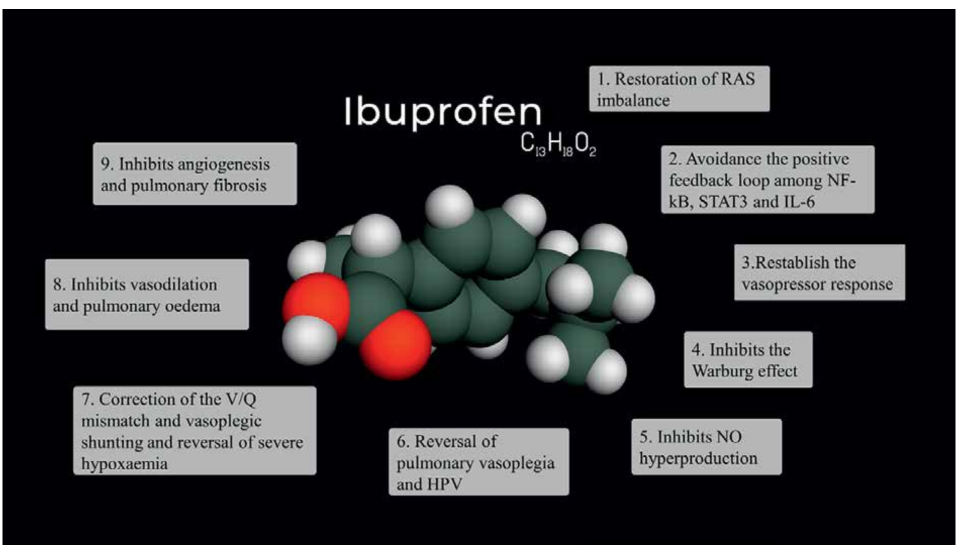

Figure 2.
Potential therapeutic effects of NaIHS on vasoplegic pneumonia and CARDS.
1. *Restoration of RAS imbalance [10, 11];* **2.** *Inhibition of positive feedback loop [10] among NF-kB [10], STAT3 [10] and IL-6 [10];* **3.** *Restoration of the vasopressor response [7];* **4.** *Inhibition of Warburg effect [7, 16];* **5.** *Prevention of NO hyperproduction [7];* **6.** *Reversal of pulmonary vasoplegia and restoration of HPV [7];* **7.** *Correction of the V/Q mismatch and vasoplegic shunting and thus, reversal of severe hypoxemia [7];* **8.** *Inhibition of vasodilation and pulmonary oedema [5, 7] and* **9.** *Inhibition of angiogenesis [18, 19] (**Table 1**).*

Therapeutic targets	Mechanisms of action	Therapeutic effects
1. RAS imbalance	Inhibition of COX2-dependent effect	Inhibition of COX2, NF-kB and TGF-β1
2. Positive feedback loop among NF-kB, STAT3 and IL-6	Inhibition of COX2-dependent effect	Inhibition of NF-kB, STAT3 and IL-6
3. Inhibition of the vasopressor response	Inhibition of COX2-dependent effect	Inhibition of COX2, NF-kB, IL-1β, TNF-α and IL-6
4. Warburg effect	Inhibition of COX2-dependent effect	Inhibition of PI3K/AKT/mTOR
5. IDO	Inhibition of COX2-dependent effect	Indirect inhibition of IDO by Inhibition of COX2, STAT3, NF-kB, TLR4, IFN-γ, IL-1β, TNF-α and IL-6
6. Pulmonary vasoplegia	Inhibition of COX2-dependent effect	Indirect inhibition of iNOS and IDO by inhibition of COX2, STAT3, NF-kB, TLR4, TGF-β1, IFN-γ, IL-1β, TNF-α, IL-6 and PI3K/AKT/mTOR
7.Vasodilation and interstitial pulmonary oedema	Inhibition of COX2-dependent effect	Inhibition of prostaglandins, prostacyclins, NO and bradykinins
8. Angiogenesis	Inhibibition of COX2-dependent and COX-independent effects	Inhibition of VEGF, bFGF and HIF-1α
9.V/Q mismatch and vasoplegic pulmonary shunting	Inhibition of COX2-dependent effect	Indirect inhibition of iNOS and IDO by inhibition of COX2, STAT3, NF-kB, TLR4, TGF-β1, IFN-γ, IL-1β, TNF-α, IL-6 and PI3K/AKT/mTOR

1. *Restoration of the RAS imbalance [10, 11] by inhibition of COX2 [10], NF-kB [10], and TGF-β1[10];* **2.** *Avoidance of the positive feedback loop among STAT3 [10], NF-kB [10] and mainly IL-6 [10];* **3.** *Restoration of the vasopressor response by inhibition of NF-kB [10], COX2 [10], TNF-α [10], IL-1β [10] and IL-6 [10];* **4.** *Inhibition of the Warburg effect via inhibition of PI3K/AKT/mTOR [16];* **5.** *Indirect inhibition of IDO [9] by inhibition of COX2 [10], NF-kB [10], STAT3 [10], TLR4 [10], IFN-γ [10], IL-1β [10], TNF-α [10] and IL-6 [10];* **6.** *Reversal of pulmonary vasoplegia by indirect inhibition of iNOS and IDO [7] by inhibition of COX2 [10], NF-kB [10], STAT3 [10], TLR4 [10], TGF-β1 [10], IFN-γ [10],IL-1β [10], TNF-α [10] and IL-6 [10];* **7.** *Inhibition of vasodilation and interstitial pulmonary oedema by inhibition of COX2 [7, 10]: inhibition of prostaglandins [5], prostacyclins [5], NO [7], bradykinins [17] and, by up-regulation of ACE2 [11] inhibition of bradykinins [1];* **8.** *Inhibition of angiogenesis by inhibition of COX2-dependent effect [18]: VEGF and bFGF [18] and by inhibition of COX-independent effect [19], inhibition of HIF-1α [19] and* **9.** *Correction of the V/Q mismatch and the vasoplegic pulmonary shunting by indirect inhibition of iNOS and IDO [7] by inhibition of COX2 [10], STAT3 [10], NF-kB [10], IFN-γ [10], TGF-β1 [10], IL-1β [10], TNF-α [10], IL-6 [10] and PI3K/AKT/mTOR [16].*

Table 1.
Potential therapeutic effects of NaIHS on the main vascular pathophysiological mechanisms secondary to SARS-CoV-2 infection.

3. NaIHS potential virucidal effects on SARS-CoV-2

The binding of the Spike glycoprotein of the SARS-CoV-2 to the pulmonary ACE2 receptor anchored to the plasmatic membrane of type 2 pneumonocytes requires proteolytic cleavage by the host of the S1 and S2 subunits, with the fusion of both membranes and subsequent viral endocytosis.

3.1 Mechanisms that might prevent SARS-CoV-2 endocytosis

Kringle-containing transmembrane protein 1 (KREMEN1) receptor: It has been recently described as one of the new receptors for SARS-CoV-2 but being these receptors less efficient compared to the classical ACE2 receptor [20]. It has been hypothesised that the binding of protein S and KREMEN1, with subsequent internalisation of SARS-CoV-2, might depend on the activation of protein S by transmembrane protease serine 2 (TMPRSS2) or cathepsin L [20]. NaIHS may inhibit the Wingless/Int-1/beta-catenin (Wnt/β-catenin) pathway [16], given its agonist effect on peroxisome proliferator-activated receptor gamma (PPAR-γ) and through this effect [16], it might negatively modulate KREMEN1 gene expression [21]. In addition, NaIHS might inhibit the action of the KREMEN1 receptor through possible negative modulation of TMPRSS2 [10–12] and cathepsin L [10], which will be further developed.

AXL tyrosine kinase coreceptor: The ACE2 receptor, typically described for SARS-CoV-2 binding, in the absence of inflammation is only present in the lung at a density of less than 0.1% and, in the presence of inflammation, the resulting downregulation may further reduce its density, leading to the suggestion of other receptors and co-receptors for SARS-CoV-2, such as AXL [22]. By the direct inhibition of COX2-dependent effect, NaIHS may negatively modulate the synthesis and expression of the AXL coreceptor and may also induce its proteolytic degradation [23].

NaIHS may inhibit in vitro disintegrin and metalloproteinase domain 17 (ADAM 17) [11], by the direct inhibition of COX2, avoiding the excision of ACE2 from the pulmonary membrane and preventing dysregulation of the RAS towards inflammation, contributing to the protective anti-inflammatory effect mentioned above [11].

NaIHS may inhibit in vitro TMPRSS2 [10–12] through an indirect COX2-dependent anti-androgenic effect [10], which may inhibit hepatic glucuronidation of testosterone, via inhibition of UDP-glucuronosyltransferase and UGT2B15 and thus lead to transcriptional repression and expression of testosterone [10]. This decrease in testosterone would be related to the inhibition of TMPRSS2 transcription and expression, given that TMPRSS2 expression is regulated by androgens [10], being frequent in males with hypogonadism and mainly in those over 60 years of age [10]. Moreover, NaIHS might indirectly inhibit poly (ADP-ribose) polymerase 1 (PARP1) by a COX2-independent effect, since PARP1 inhibition may negatively modulate TMPRSS2 transcription and expression [12].

NaIHS may prevent the reorganisation of actin filaments, impeding the interaction between the viral S1 protein and host actin [4] by the inhibition of the synthesis and release of the cytokine IL-1βand the negative modulating of the rock kinase A (RhoA) pathway, through a COX2-dependent effect [24]. NaIHS may also inhibit the activation of Rho GTPase and its alternatively spliced isoform Ras-related C3 botulinum toxin substrate 1b (RAC1b), through a COX-independent effect [5].

NaIHS may negatively modulate the protease cathepsin L by the inhibition of the synthesis and release of cytokine IL-6 [10] and through the possible negative modulation of all the components of the positive feedback loop aforementioned, among IL-6 [10], NF-kB [10] and STAT3 [10], preventing protein S cleavage and subsequent endosomal viral endocytosis [10].

3.2 Mechanisms that might inhibit SARS-CoV-2 replication

SARS-CoV-2 uses the host cellular interactome for its replication.

NaIHS inhibits in silico [25] and may inhibit in vitro [26, 27] the SARS-CoV-2 main protease (Mpro).

NaIHS may inhibit in silico PTGS2EI gene expression by direct inhibition of prostaglandin-endoperoxide synthase 2 (PTGS2) and it may inhibit in silico the

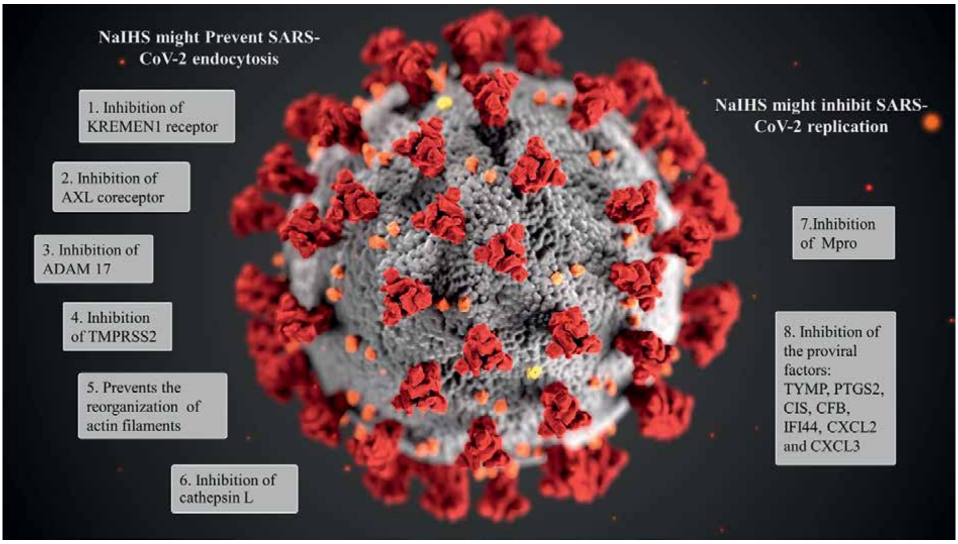

Figure 3.
Potential virucidal effects of NaIHS that might avoid endocytosis and replication bySARS-CoV-2.
1. *Inhibition of KREMEN1 receptor [10–12, 16, 21];* **2.** *Inhibition of AXL coreceptor [23];* **3.** *Inhibition of ADAM 17 [11];* **4.** *Inhibition of TMPRSS2 [10–12];* **5.** *Inhibition of the reorganisation of actin filaments [4, 24];* **6.** *Inhibition of cathepsin L [10];* **7.** *Inhibition of Mpro in silico [25] and in vitro [26, 27];* **8.** *Inhibition of the pro-viral factors TYMP, PTGS2, CIS, CFB, IFI44, CXCL2 and CXCL3 [28].*

Therapeutic targets	Mechanisms of action	Therapeutic effects
1. KREMEN1 receptor	Inhibition of COX2-dependent and COX-independent effects	Prevention of SARS-CoV-2 endocytosis
2. AXL coreceptor	Inhibition of COX2-dependent effect	Prevention of SARS-CoV-2 endocytosis
3. ADAM 17	Inhibition of COX2-dependent effect	Prevention of SARS-CoV-2 endocytosis
4. TMPRSS2	Inhibition of COX2-dependent and COX-independent effects	Prevention of SARS-CoV-2 endocytosis
5. Actin	Inhibition of COX2-dependent and COX-independent effects	Prevention of SARS-CoV-2 endocytosis
6. Cathepsin L	Inhibition of COX2-dependent effect	Prevention of SARS-CoV-2 endocytosis
7. Mpro	Inhibition in silico and in vitro	Inhibition of SARS-CoV-2 replication
8. Pro-viral factors: TYMP, PTGS2, CIS, CFB, IFI44, XAF1, CXCL2 and CXCL3	Inhibition in silico	Inhibition of SARS-CoV-2 replication

1. *KREMEN1 receptor: NaIHS inhibits the Wnt/β catenin pathway [16] and through this effect, it might negatively modulate KREMEN1 gene expression [21] and might also inhibit the action of the KREMEN1 receptor through possible negative modulation of TMPRSS2 [10–12] and cathepsin L [10];* **2.** *AXL coreceptor: the direct inhibition of COX2, may negatively modulate the synthesis and expression of the AXL corecetor [23] and may also induce its proteolytic degradation [23];* **3.** *ADAM 17: inhibition by the direct inhibition of COX2 [11];* **4.** *TMPRSS2: indirect inhibition by antiandrogenic effect (COX2-dependent effect) [10, 11] and it might indirectly inhibit PARP1 (COX-independent effect) [12];* **5.** *Actin: by the inhibition of the synthesis and release of IL-1β and the negative modulation of the RhoA pathway (COX2-dependent effect) [24] and, the inhibition of the RhoGTPase and RAC1b (COX-independent effects) [5];* **6.** *Cathepsin L: negative modulation by the inhibition of IL-6 [10] and the inhibition of the positive feedback loop among IL-6 [10], NF-kB [10] and STAT3 [10];* **7.** *Mpro inhibition in silico [25] and in vitro [26, 27];* **8.** *Inhibition in silico of the proviral-factors: TYMP, PTGS2, C1S, CFB, IFI44, XAF1, CXCL2 and CXCL3 [28].*

Table 2.
NaIHS potential virucidal effect on SARS-CoV-2.

expression of 8 important proviral factors: TYMP, PTGS2, C1S, CFB, IFI44, XAF1, CXCL2 and CXCL3 (**Figure 3**) (**Table 2**) [28].

4. Conclusion

With the ongoing emergence of new variants and sub-variants of concern due to immune escape secondary to SARS-CoV-2 mutations, not only are vaccines and their booster doses necessary and vital but also the urgent need for effective medical treatments, which are currently very few and controversial. Therefore, in addition to testing new drugs against SARS-CoV-2, we believe it is essential to reuse known drugs such as ibuprofen, with over 50 years of experience in clinical practice, effective, economical, universally accessible and therapeutically safe.

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Section 5

Digital Health Humanized Tools

Chapter 10

Telemedicine and Competency-Based Training to Maximize Resources in the Face of a Pandemic, without Losing Humanization

Luis Alberto Camputaro, Alejandro Jose Duarte Cuellar, Carlos Gabriel Alvarenga Cardoza and Francisco Jose Alabí Montoya

Abstract

The COVID-19 pandemic has exposed global concerns about healthcare system capacity. The World Health Organization sets readiness standards for pandemics, but disparities in healthcare infrastructure and a shortage of medical professionals hinder responses. The pandemic has overwhelmed healthcare systems worldwide, leading to a shortage of healthcare workers. Countries like Mexico, Colombia, and Peru have recruited temporary healthcare professionals to address the shortage. Even countries with relatively high doctor-to-patient ratios, such as El Salvador, struggle to find Critical Care Medicine specialists. El Salvador's response includes the 2020 inauguration of El Salvador Hospital (ESH), using telemedicine to connect specialists with non-specialists in intensive care. Competence-based training is crucial in rapidly educating a large healthcare workforce, with a course tailored to local needs—however, the pandemic challenges humanizing patient care due to limited family interactions. Telemedicine offers emotional support and spiritual accompaniment through video calls. The Social Work Unit at HES helps maintain patient-family communication, with post-discharge surveys assessing humanitarian support effectiveness. In summary, the COVID-19 pandemic has exposed healthcare system challenges, necessitated innovative training, emphasized telemedicine's role, and promoted efforts to maintain humanized care while assessing patient satisfaction.

Keywords: pandemics, healthcare systems, COVID-19, telemedicine, humanization

1. Introduction

1.1 Pandemics and the capacity of healthcare systems

The definition of a pandemic, as outlined by the World Health Organization (WHO), involves the global dispersion of a novel ailment [1]. According to WHO's standards, an effective healthcare system necessitates an approximate ratio of 4 beds per 1000 inhabitants, along with 23 doctors, nurses, and obstetricians per every 10,000 residents, to deliver comprehensive essential healthcare services [2]. However, WHO's data from 2018 reveals that the number of doctors per 10,000 inhabitants stands at 12.3, displaying notable disparities across countries and regions [3].

Given this data, it appears improbable for a healthcare system to be adequately equipped with the requisite number of beds and appropriately trained medical and paramedical professionals, essential for an effective response to a pandemic.

The worldwide progress of COVID-19 has inundated healthcare systems on a global scale and continues to be the main driving force behind the current scarcity of skilled human personnel. According to records from the Pan American Health Organization in September 2020, approximately 570,000 healthcare professionals in the Americas have been infected with COVID-19, leading to 2500 deaths [4].

1.2 The deficiency of physicians and specialists in critical care medicine

In reaction, various nations, such as Mexico, Colombia, Peru, Guyana, Trinidad and Tobago, among others, have enlisted healthcare practitioners, even retired ones, to temporarily join the public sector.

The primary methods employed by healthcare personnel to combat the pandemic, in addition to their unwavering dedication to their work, include (a) Education in personal cleanliness and strict adherence to procedures concerning the wearing and removal of Personal Protective Gear. (b) Instruction in the recognition and management of specimens, cases, and contacts, as well as the proficient use of medical apparatus, such as ventilators and monitors.

Healthcare experts across 20 countries in the Latin American and Caribbean Region (often referred to as the LAC Region) have expressed their concerns regarding deficiencies in infrastructure, personal protective gear, and the absence of assistance [5].

Within the realm of Intensive Care Medicine, this shortfall has prompted the expedited training of doctors from diverse specialties through rapid (sometimes online) courses. Nonetheless, this approach provides a partial remedy, as the provision of intensive care necessitates comprehensive training.

Even in the case of El Salvador, which proudly touts a proportion of 16.36 medical professionals per every 10,000 residents [6], along with 1.2 healthcare facilities for every 1000 residents [7], it has not evaded this particular dilemma.

1.3 El Salvador Hospital

The inauguration of the El Salvador Hospital (ESH) transpired on June 22, 2020. This hospital stands as the Central American region's pinnacle in terms of bed capacity and cutting-edge technological equipment. It houses medical and technological resources suitable for 105 Intensive Care Unit beds and 295 Intermediate Care Unit

Beds. Furthermore, the hospital possesses the capacity to extend its infrastructure to include an additional 1000 ICU beds and 1000 beds for general patient care. In addition, HES is equipped with supplementary facilities such as radiology and imaging centers, a dedicated dining area, pharmaceutical services, departments specializing in anesthesiology and inhalation therapy, a clinical laboratory, a blood bank, and social support services. Moreover, it offers two designated relaxation zones for healthcare staff.

An advanced information technology framework, supported by a fiber optic network, interconnects all areas of the hospital, granting access to each patient's medical records and electronic prescriptions, resulting in a 90% reduction in paper usage.

The primary strategy of ESH revolves around telemedicine and is implemented through a Central Monitoring Center where intensive care medicine specialists monitor and oversee the care of hospitalized patients (**Table 1** and **Figures 1** and **2**). Non-specialized physicians in intensive care medicine, such as general practitioners and internists, are responsible for carrying out the hands-on care activities. The Intensivist guides these healthcare providers in updating the clinical, hemodynamic, and respiratory status of patients.

In response to the shortage of intensive care medicine specialists, the objective has been to train approximately 1000 healthcare professionals in basic life support measures for COVID-19 patients.

Sector	Intensive care unit	Intermediate care unit	General ward
Supervise Doctor*	Nine (9) ICU Medical Specialists	Five (5) ICU Medical Specialists	Nine (9) Internal Medicine Medical Specialists
Physician Supervisor in Hospital Department	Single Monitor Expert (total 9)	Single Monitor Expert (total 5)	Single Monitor Expert (total 9)
Attending physician	12 General practitioners per coordinator (total 108)	15 General practitioners per coordinator (total 75)	13 General practitioners per coordinator (total 117)
Number of beds available per hospitalization area	143	104	721

Monitoring room single physical space, physically separated from the hospitalization area.

Table 1.
Distribution of medical personnel to cover assistance for COVID-19 patients.

Figure 1.
Monitoring center El Salvador Hospital.

Figure 2.
Intermediate care area monitoring detail.

2. Competence-based training, an alternative to preparing health personnel in a short time

An expedited training approach, formulated around the framework of concise courses, was opted for, aiming to rapidly educate a substantial workforce within a condensed timeframe. This pedagogical approach, rooted in competency-driven education, seeks to convey fundamental understanding and industry-relevant proficiencies while fostering students' enthusiasm for continued education [8]. A couple of instances of these educational methodologies include Foundational Crucial Assistance (FCA, Critical Care Medicine Society) and Progressive Trauma Life Sustenance (PTLS, American College of Surgical Specialists). However, the implementation of such courses, which cater to a limited number of individuals every 48 hours and do not delve into precise particulars concerning severe COVID-19 treatment, demands an excessive allocation of time and resources that is unfeasible within the current healthcare emergency context. Hence, a novel course, tailored to local requisites, was devised under the overarching principle of "training professionals from practical experience to theoretical understanding."

2.1 Course design

Within the initial week, a diagnostic process was undertaken, comprising the following steps:

Collaborating with Monitoring Specialists to identify areas for enhancement in executing hands-on tasks.

Convening personnel from the Teaching and Research sectors, including Intensive Care Physicians, Nursing Graduates, and Respiratory Technicians, to formulate an optimal skills training approach through practical workshops. This was achieved through the examination of "lessons learned," exchanged via a WhatsApp group.

Synergy was fostered with the Medical Emergency System (SEM), an entity affiliated with the Ministry of Health of El Salvador, well-versed in CPR and rescue operations. Likewise, collaboration extended to the personnel from the Andalusian Health System (SAMU), a contingent of 30 professionals from Sevilla, Spain, extensively trained in COVID-19 management, who were partaking in a health-focused collaborative endeavor at the hospital.

From these collaborative efforts emerged the course "Fundamentals of Life Support in COVID-19 Patients." Noteworthy for its original design and alignment with the discerned needs in patient care, this course was uniquely tailored.

The course is structured around four stations, each spanning 50 minutes, with topics encompassing:

1. Patient's Clinical Assessment

2. Respiratory Assistance

3. Heart Rhythm Irregularities and Cardiac Revival (CPR)

4. Medication Science and Infusion Devices.

In preparation for each workshop, a conceptual structure was established, providing the groundwork for instructors to lead their instructional sessions (**Table 2**). Moreover, instructors were provided with anatomical replicas, simulated respiratory devices, infusion apparatus, and commonly used drug formulations, all of which were utilized to enhance practical training for students.

2.2 Strategy for the course implementation

Given the substantial number of students slated for training (approximately 1000), encompassing a variety of roles including doctors, community service medical doctors, nurses, and respiratory technicians, and considering the workshop's knowledge-building nature, the following approach was adopted:

Twenty participants were assigned to each group, with a maximum of five individuals per station (totaling four stations). This design ensured optimal utilization of the instructional session, bordering on a personalized experience.

Two sessions were conducted per day—morning and afternoon—each accommodating 40 participants, resulting in a combined total of 80 participants per day. Over a week, this format enabled the training of approximately 400 professionals from Monday to Friday (**Table 3**).

This system, which facilitated the instruction of 80 participants daily, was supported by eight expert instructors, along with assistants (comprising 3–4 members) stationed at each station. These assistants were responsible for monitoring completion times, ensuring the administration of pre-post achievement tests (as described

Training session with a respiratory therapist instructor **Oxygen therapy and management of the airway** 1. Various ventilation support systems: venturi system, non-rebreather mask, high-flow oxygen, orotracheal tube. 2. PaO_2/FiO_2 ratio calculation. 3. Saturation monitoring. 4. Identifying the indicators of ventilation strategy "failure." 5. Assessment of artificial airways: venturi system, high-flow oxygen, CPAP, orotracheal tube. 6. Operating and programming ventilators, understanding alarm signals, and grasping the adjustment-maladjustment concept. 7. Analysis of arterial blood gases. 8. Utilizing the prone position in patient care.	**Training session with a degree in nursing** **Intravenous medication session** 1. Intravenous drug types. 2. Methods of packaging. 3. Approaches to dilution. 4. Modes of administration: quantity, injection, ongoing delivery. 5. Computation of infusions in mg/kg. 6. Application of infusion pumps.
Training session with emergency physician specialist **Cardiopulmonary resuscitation** 1. Identification of potentially fatal cardiac rhythms. 2. Methodical strategy for Cardiopulmonary Arrest (CPA). 3. Order of medications to administer. 4. Quantity of personnel. Duration of 5. Cardiopulmonary resuscitation (CPR). 6. DNR principle (Do Not Intervene Directive).	**Training session with ICU specialist** **Clinical evaluation (top to bottom)** 1. Neurological assessment: conscious, agitated, agog, under anesthesia (Check pupils). 2. Hemodynamic assessment: BP, heartbeat, peripheral perfusion, urination rhythm. 3. Respiratory assessment: at ease, uneasy. Adapting to mechanical ventilation. Evaluate respiratory exertion. 4. Abdominal area: swollen, sore. 5. Medication administration: Kind and quantity during the examination. 6. Dietary assistance: consumes/does not consume. Endures/does not endure. Glucose level. Inducing bowel movement. 7. Well-being: Patient orientation (Head support, lower limbs). Discomfort.

Table 2.
Conceptual content of the COVID-19 patient life support fundamentals course workshops.

	Commission 1	Commission 2	Instructors
Morning shift 08:00–12:00 hs	20 students	20 students	4 (1 per station)
Afternoon shift 13:00–17:00 hs	20 students	20 students	4 (1 per station)
Total students/shift	40	40	
Total instructors/shift			8

Table 3.
Number of students and instructors per day.

below), and orchestrating breaks that allowed for refreshments and meals for both instructors and collaborative staff.

The course implementation adhered to the ensuing protocol:

1. Assistants: oversee completion of the pre-test.

2. Medical Coordinator's welcome address to participants: provide an overview of the course's structure, detail station timings, and outline the roles of collaborators.

3. Participant distribution: each group consists of five members (totaling 20 participants), specifically designed to ensure the inclusion of a doctor, community service medical doctor, nurse, and respiratory technician. This approach aimed to cultivate a transdisciplinary team-oriented environment.

4. Closing remarks by the coordinator: highlighting the undertaken efforts and encouraging the exchange of newfound knowledge. Each session concluded with applause directed toward the instructors and assistants, followed by reciprocal applause from them to the participants. This practice served as a motivating gesture, acknowledging the exertion invested throughout the 4-hour course.

5. Assistants: verify completion of the post-test.

Because of the attributes of the program crafted by the HES Department of Education and Research, it garnered the official approval of the Ministry of Health in El Salvador, along with the backing of the following entities: 1. Universidad José Matias Delgado in El Salvador, thus attaining the status of a University Program; 2. The Central American and Caribbean Consortium of Intensive Therapy (COCECATI), expanding its reach on an international scale; 3. The Latin American Council for Neurointensive Care (CLaNI).

2.3 Program assessment

Assessment of Course Utility: A pre-post analogical-visual knowledge perception survey, structured as a "before and after" comparison, was formulated. In this survey, students rated various domains identified as areas with potential for improvement in care. Participants were assigned scores on a scale of 0–10 before and after completing the course. The survey tool was transitioned into a digital format to streamline the process. Tablets were utilized and equipped with online pre-post testing capabilities. This facilitated the real-time recording of responses, ensuring anonymity and centralizing data collection. This approach effectively curbed the risk of data loss and registration inaccuracies. Assistants were entrusted with overseeing the pre- and post-tests to guarantee an unequivocal reception rate of 100%.

During the period spanning from August 17th to August 21st, August 24th to August 28th, and September 7th to September 11th of the year 2020 (which comprises 15 working days), a total of 981 professionals underwent training. This training encompassed the entirety of professionals dedicated to caring for COVID-19 patients, namely doctors, medical doctors specializing in community service, nurses, and respiratory therapy technicians. The gender distribution among these professionals was 66.3% female and 33.7% male, with an average age of 29.92 years and a standard deviation of 5.82 years.

Out of the 981 professionals who received training, 44.9% were doctors, 42.9% were nurses, 7% were respiratory therapy technicians, and 5.2% were community service medical doctors who expressed their interest in participating in this educational initiative.

The comparative analysis between the results of the assessments conducted before and after the training exhibited a significant discrepancy in the perception of knowledge across all areas. This was confirmed through a Mann-Whitney U test with a p-value < .0001, as illustrated in **Table 4**.

An inventive approach to train healthcare personnel in managing critical COVID-19 patients was successfully conceptualized and executed. The training initiative achieved full coverage of HES's COVID-19 patient management team. Its effectiveness, centered around a competency-based pedagogical framework, was measured through the assessment of knowledge perception in 10 distinct domains. These encompassed proficiencies in organizing emergency care, and identification of available medications and equipment within the institution, among others [9].

	Item	Concept	Score	
			Pre-test	Post-test
1	Airway Oxygen Therapy and Respiratory Assistance	*How much do you consider your knowledge about* management of venturi mask	6.39	8.75
		How much do you consider your knowledge about management of Non-Rebreather Mask	6.42	8.80
		How much do you consider your knowledge about management of High-Flow Nasal Cannula	5.24	8.68
		How much do you consider your knowledge about management of artificial airway (Orotracheal tube)	5.12	8.38
		How much do you consider your knowledge about management of ventilator	4.70	8.24
2	Cardiology	*How much do you consider your knowledge about* cardiopulmonary resuscitation	6.32	8.84
		How much do you consider your knowledge about arrhythmia detection	5.40	8.55
3	Drugs	*How much do you consider your knowledge about* titratable intravenous drug use	5.69	8.53
		How much do you consider your knowledge about the use of infusion pumps	5.88	8.75
4	Therapeutic intensity	*How much do you consider your knowledge about* the handling of moderate-gravely sick patient	6.07	8.52
	Mean		5.72	8.60
	Dst		0.59	0.19
	Median		5.78	8.61
	r		4.70–6.42	8.24–8.84

Table 4.
Pre- and post-course perception of knowledge scores by domain. Mean, Dst., med, and r. Mann. Mann-Whitney U test p < .0001.

The integration between the monitoring center and the hands-on staff was substantially improved, enhancing communication coherence, and bestowing a higher degree of autonomy to the latter group, allowing the use of telemedicine as a strategy in the absence of specialized hand resources.

3. Maintaining humanization in patient care in the context of isolation due to a pandemic

3.1 Telemedicine

As we previously mentioned, and like the rest of the world, our healthcare system had to overcome the lack of trained workers during the COVID-19 pandemic [5]. The use of telemedicine turned out to be a fundamental tool for dealing with this scarcity [10]. Telemedicine avoided the loss of qualified personnel and maintained the bond between families and their loved ones.

Telemedicine is the delivery of health services via remote telecommunications; this includes interactive consultative and diagnostic services. A multidisciplinary team is needed to achieve the goals set forward by telemedicine [11].

Satisfactory results have been reported with telemedicine, which is great at providing healthcare services as well as facilitating communication between the patient and his family [12].

3.2 The intensive care unit

Since the 1970s, the Intensive Care Unit (ICU) has been defined as the hospital unit providing continuous surveillance and care to acutely ill patients who require uninterrupted medical and nursing care, in addition to specialized human resources and equipment [13].

Admission to an ICU is a stressful event, both for the patient and his family. They perceive the environment as an aggressive and threatening space because it represents the risk of the patient dying [14].

Furthermore, the family structure is deeply changed by the estrangement of one of its members [15]. Notably, family involvement in patient care provides emotional support to the patient reducing both anxiety and depression [16, 17].

Healthcare workers have made efforts to improve comfort for patients and their families, both during hospitalization and in early convalescence. An example of this effort is the more flexible visiting hours [18–20].

The COVID-19 pandemic was declared a public health emergency by the World Health Organization and is the largest global health crisis at the moment [21]. Due to the nature of the disease, interactions between patients and their families have been limited. In addition, they needed to maintain isolation, and contact protocols did not allow for family visits, face-to-face medical reports, and the usual interactions with the nursing staff. The social fear caused by the pandemic enhanced the usual symptoms of anxiety, depression, and post-traumatic stress already prevalent in ICU patients. This environment further complicates the grieving process [22, 23].

The environment created by the COVID-19 pandemic has highlighted the importance of a global approach when attending to the patient's needs.

3.3 Maintaining humanization in patient care in the context of isolation due to a pandemic

Humanizing care implies considering all the dimensions of a person (biological, mental, spiritual, and social). Addressing the spiritual needs of a person means giving emotional support as well as listening and is not the practice of religion.

Different studies show a connection between spirituality and physical and mental health [24].

For these reasons, our hospital provides spiritual accompaniment to patients and their families. As of November 2020, spiritual visits are made to patients every 15 days to listen to their existential concerns, support them spiritually, and give them comfort. These visits are always conducted with absolute respect for the patient and his beliefs. As of March 2021, family members of the patient can participate in these spiritual visits if they so choose.

These support sessions are carried out through video calls. During these video calls, concerns, fears, and uncertainties are heard, to discover the existential meaning of the moment and give spiritual comfort.

3.4 The Social Work Unit

The mission of the Social Work Unit in our hospital is to create a bridge between doctors, patients, and family members in a professional, timely, and decisive manner. Among the objectives of the Social Work, Unit is to help the emotional state of patients during their hospital stay by facilitating communication with their families through video calls, giving daily updates to each family member about the health status of their loved one, and coordinating patient discharge, among others.

3.5 Contact with discharged patients

The social work unit sends a list of confirmed discharged patients and their contact information (phone number and email). Subsequently, the contact information is incorporated into the electronic telephone book of the ORH, together with the information related to the survey (password, discharge date, patient name, and telephone number).

Each patient receives a greeting message and an invitation to participate in the survey for patient satisfaction after discharge. If, after 24 hours, there is no response, a second message is sent.

Finally, in coordination with the Quality Organizational Unit (QOU), the results are monitored monthly. All this is registered in the Integrated Management Information System (SIIG-eTAB of the Ministry of Health (MINSAL).

3.6 Satisfaction survey to assess the effectiveness of humanitarian support

The QUO works with the Social Work Unit to collect data from discharged patients. With patient-collected data (WhatsApp number and email), an electronic record is created with the patient's name, discharge date, telephone number, and password to access the survey.

Algorithm.

1. Each patient receives the following message: "Hello. We greet you from El Salvador Hospital. We are interested in knowing the opinion of the person who received our services during hospital admission; for this, we invite you to participate in a survey about the services received. If you agree to participate in the survey, please say yes."

2. If no response is received that day, a new message is sent: Would you like to participate in the post-discharged patient satisfaction survey from El Salvador Hospital?

3. If the person answers yes, 4 messages are sent:

   - You can take the survey anytime you deem convenient or request support from a person you trust. It is recommended that you copy the password and then paste it for entry, the password is:

   - A message with the password to access the survey is sent.

   - A message stating: "Avoid typing the password letter by letter, it is better to copy it completely. Then we invite you to enter our survey website and paste the password in the indicated place." Site link: encuestas.salud.gov.sv/index.php/371221?lang=es

4. If the respondent expresses difficulty in carrying out the survey procedure, then assistance is provided so that the respondent can participate on the day and time they deem convenient; guidance is provided via text message or phone call.

5. If no other option is available, support is given to assist in the participation of the survey, sending question by question and subsequently registering it with the password assigned to the respondent.

6. Daily activity related to the survey is recorded:

   - The number of discharges reported by social workers.

   - The number of discharged people registered with a telephone number or email.

   - The number of discharged people to whom the message was sent.

   - Number of people who agreed to participate in the survey.

7. In coordination with the Quality Organizational Unit, monthly monitoring of the results of citizen participation in the survey is carried out, which is registered in the MINSAL's integrated management information system.

8. The results are periodically published in the transparency portal: https://www.transparencia.gov.sv/institutions/hes

	Domains	Percentage perceived from 0 to 100
1	Staff treatment	
2	Perceived staff knowledge	
3	Clarity of the information received regarding your health situation during your stay	
4	Privacy	
5	Recommendations or instructions provided by the staff to be followed at home for your care and treatment	
6	Interest shown by healthcare workers when attending requests and complaints	
7	Therapy duration	
8	Facility comfort.	

Table 5.
Domains are evaluated as the perception of care during hospital admission.

	January	February	March	April	May	Total
Number of phone calls	13.090	9.143	10.388	12.387	13.285	58.297

Table 6.
Number of phone calls and/or video calls done by social work.

The respondent analyzed Eight domains and scored from 0 to 100%. Corresponding "0%" to the worst impression and "100%" to the best-perceived impression (**Table 5**).

From January 1 to May 31, 2021, 58,297 telephone and/or video calls were made to relatives of those admitted to El Salvador Hospital (**Table 6**).

These calls had the following objectives:

1. To inform relatives about the patient's condition.

2. Video calls between patients and relatives for emotional support.

3. Informed consent request for special procedures.

4. Hospital discharge management:

    a. Discharge destination (home, rehabilitation);

    b. Treatment;

    c. Follow-up plan.

A total of 2865 discharges were reported by the social work unit, of which 2019 were contacted with 1500 agreeing to participate in the survey.

The MINSAL's integrated management information system (SIIG-eTAB) recorded a total of 859 completed surveys during the study period, which is 30% of the discharges reported by Social Work.

	January	February	March	April	May	Average (5 months)
General perception (average 8 domains)	89.5	89.8	92.5	92.4	93.3	91.4
Hospital wards (average 8 domains)	90.07	89.62	91.76	93.06	93.73	91.6
ICU (average 8 domains)	89.95	90.53	95.14	92.78	93.83	92.4
IMCU (average 8 domains)	88.35	89.27	90.63	91.25	92.22	90.3

Table 7.
Overall satisfaction and level of care. Average of eight domains and scored from 0 to 100%. Corresponding "0%" to the worst impression and "100%" to the best-perceived impression.

The patient satisfaction survey shows an average from January to May of 91.6% for the Wards, 92.4% for the ICU, and 90.3% for the IMCU.

Discharged patients, on average, perceived higher service quality in March to May compared to January and February. Notably, from March to May, opportunities for improvement in care were evaluated and implemented **Table 7**, Acknowledging that some readers will not be experts in your field of research.

4. Conclusions

4.1 Telemedicine as a strategy in pandemic times

The COVID-19 pandemic exposed vulnerabilities in healthcare systems globally, particularly concerning healthcare workforce and infrastructure. The shortage of doctors and specialists in critical care medicine has become a critical issue in several countries. In response, innovative strategies were developed, like the creation of the El Salvador Hospital (ESH), a cutting-edge medical facility designed to combat the pandemic. Telemedicine also emerged as a vital tool for managing the scarcity of trained healthcare workers while maintaining the connection between patients and their families.

4.2 Competence-based training

To address the urgent need for trained healthcare professionals, a competence-based training program was introduced, rapidly educating a substantial workforce within a condensed timeframe. This program was specifically designed to impart foundational knowledge, job-specific skills, and motivation to students. Through this initiative, healthcare professionals could efficiently manage COVID-19 patients, resulting in a significant improvement in their knowledge perception.

4.3 Maintaining humanization in patient care

The COVID-19 pandemic imposed restrictions on patient-family interactions, challenging the humanization of patient care. However, efforts were made to address this issue through telemedicine, which helped maintain connections between patients and their families. Additionally, the El Salvador Hospital introduced spiritual accompaniment for patients and families through video calls, recognizing the importance of addressing patients' spiritual needs. The Social Work Unit played a crucial role in facilitating communication between patients and their families during hospitalization and in early convalescence.

The satisfaction survey results indicated that the implementation of these initiatives had a positive impact on patient care, with higher service quality perceived in the later months of the study period.

In conclusion, the COVID-19 pandemic forced healthcare systems to adapt rapidly to address challenges related to healthcare workforce shortages and maintaining humanization in patient care. The innovative approaches described in this study, such as the competence-based training program and the use of telemedicine, provide valuable insights into addressing similar challenges in future healthcare emergencies. The focus on maintaining a holistic approach to patient care, including spiritual support and communication with families, highlights the importance of addressing patients' emotional and social needs during a pandemic. These strategies can serve as a model for other healthcare systems aiming to enhance their preparedness for similar crises in the future.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Appendices and nomenclature

WHO	World Health Organization
ESH	El Salvador Hospital
SII-eTAB	Integrated Management Information System
MINSAL	El Salvador Ministry of Health
QUO	Quality Organizational Unit

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Chapter 11

Expanding Health Access in Haiti through Telemedicine

Vladimir Berthaud

Abstract

This chapter, per the author, describes the telemedicine technology, reviews relevant literature, analyzes the benefits and limitations, and highlights specific challenges and opportunities for its implementation in Haiti. It describes potential applications of telemedicine for attenuating workforce shortage, advancing healthcare access, equity, and inclusion, as well as improving clinical outcomes and education of medical providers in resource-poor settings. More specifically, the chapter proposes to leverage the pool of Haitian health professionals abroad for the development and sustainability of well-structured telemedicine programs while encouraging the continuous support of existing ventures. Stretching out limited healthcare dollars to optimize the well-being of Haitians represents the overarching goal of this endeavor. The author hopes to disseminate and replicate this model in other low- and middle-income countries.

Keywords: AMHE (Association Médicale Haïtienne à l'Etranger or Haitian Medical Association Abroad), GRAHN (Groupe de Reflexion et d'Action pour une Haiti Nouvelle or Think Tank and Action Group for a New Haiti), healthcare access, clinical outcome, cost-effectiveness, PEPFAR (President's Emergency Program for AIDS relief), HIV, comorbidities, telemedicine, global equity

1. Introduction

With the most worrisome health indicators in the Americas, inadequate healthcare budget, fragile infrastructure, alarming shortage of healthcare professionals, and limited access to primary and specialty medical services, Haiti stands very far from meeting the healthcare needs of its ever-growing population and achieving sustainable development [1]. Moreover, Haiti exports 85% of its physicians, the largest proportion in the world. But a few encouraging trends of progress had emerged recently, albeit underrecognized. Indeed, since 1990, infant and maternal mortality had halved (but the rates remain three and five times higher than the regional average), and life expectancy had increased by 6 years to 64.3 years, largely attributed to better control of infectious diseases. During the past 12 years, these small gains had been threatened by rampant violence, numerous accidents, and major disasters. Nonetheless, amidst these dark clouds, the watchful observer discerns few patches of blue sky. For instance, in partnership with private and international organizations, the Haitian Ministry of Health had deployed noteworthy efforts to eliminate the imported cholera epidemic for three and a half years, curb the scourge of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), expand vaccination coverage nationwide, and build capacity for tuberculosis (TB) control. Plenty of room for skepticism abounds as cholera is re-emerging and the incidence of tuberculosis in Haiti remains the highest in Americas. The accelerated deterioration of the social fabric, inaccessibility to clean water, and breakdown in hygiene probably contribute to the resurgence of cholera. Deeply entrenched TB risk factors, such as poverty, malnutrition, low educational attainment, and overcrowding, greatly explain this underperformance. Meanwhile, public health experts recognize the tremendous challenges posed by the climbing prevalence of cardiovascular diseases in Haiti, the excess morbidity and mortality from ischemic heart disease, stroke, lower respiratory infections, diabetes, the jump in cancer cases, and chronic renal failure, as well as the historic neglect of oral health and societal discrimination against behavioral disorders [1]. Given this heart-wrenching landscape, the exploration of telemedicine in Haiti as an innovative solution to mitigate the workforce shortage, increase healthcare access, and improve targeted health outcomes, clearly deserves the utmost consideration. This book chapter intends to stimulate in-depth thinking and open the forum for discussion on global equity and inclusion showcasing Haiti.

2. Background

The Haitian Institute of Statistics and Informatics estimates the population of Haiti at 11887456 inhabitants in 2021. However, only 19.28% of the population had accessed ambulatory healthcare services in 2021, as compared to 30.7% in 2017, a troubling downward trend contrasting with skyrocketing unmet needs. No other country in the Americas displays such a critical workforce shortage as illustrated in the following indicators. In 2021, Haiti disposed of 9.91 medical personnel (physicians, nurses, midwives, and nurses' aides) per 10,000 population [2]. At 6.3 per 10,000 population, Haiti exhibits the lowest density of physicians in the Americas, nearly fourfold lower than the minimum recommended by the World Health Organization (WHO) [1], and with an operational and investment healthcare budget allocation of 4.2% and 2.6% of the national budget in 2021, far below the 15% benchmark recommended by WHO. For the past four decades, about 85% of Haiti medical graduates had been leaving the country to pursue better opportunities for themselves and their families. About 80% of Haiti's public health workforce practice in urban areas, while over half of the population resides in rural localities. Nowadays, essential hypertension and diabetes account for the majority of outpatient visits in Haiti, while the incidence of cancer keeps rising [2]. On a hopeful note, Haiti had implemented a fruitful public-private partnership model to control the major epidemics of HIV/AIDS and tuberculosis, eradicate the imported cholera epidemic for three and a half years, and expand immunization coverage, notwithstanding the recurrent natural disasters, pervasive political instability, and collapsing economy.

3. Overview of the literature on telemedicine in Haiti

A scant body of literature on the use of telemedicine in Haiti had primarily reported isolated projects for diabetic foot care, pediatric emergencies, dermatology, radiology, military operations, and disaster relief [3]. In a case study of hybrid telemedicine for diabetic foot care by Olayele et al., the investigators engaged a nurse practitioner (NP) from a Chicago wound care clinic to travel to Haiti twice a month [4]. During the 90 to 120-minute telemedicine sessions, the NP presented the clinical cases and transmitted related health documents to physicians in Chicago *via* CISCO WebEx platform. Then, the consulting physicians dispatched their recommendations for medical care and teaching points for staff education. The team followed 44 patients with diabetic foot ulcer in 1226 total visits between April 1, 2014 and March 31, 2015. The authors identified bidirectional language translation as the major barrier. Most of the participants reported improved knowledge of wound care, and 90% of them considered the acquired information as a helpful tool to better manage their patients with diabetic foot. Unfortunately, this study did not clearly mention the geographic location of the hospital in Haiti. More recently, Kamaratos-Sevdalis et al. published a qualitative review of 12 English-language studies of telehealth services for diabetic foot infection from around the world [5]. Based on pre-established criteria, they selected five randomized trials, three case reports, three cohort studies, and one survey for analysis. Sample sizes varied widely from one to 1199. In short, the study results suggest a good acceptance rate of telehealth for diabetic foot care and possibly similar or better outcomes. The interpretation of these findings calls for caution because they derive from short-term follow-up data and require validation in better designed long-term randomized controlled trials or large prospective cohort studies. On their side, Flaherty and colleagues from the University of Florida, Gainesville, USA, evaluated the cost-effectiveness of a nighttime telemedicine and medication delivery service for children ages zero to nine years living in the hilly town of Gressier, near Port-au-Prince, urban Jacmel and three surrounding rural areas in the southeast of Haiti, from July 2019 to June 2021 [6]. The National Bioethics Committee of Haiti and the University of Florida Institutional Review Board (IRB) approved the study protocol. The study participants gave IRB-authorized informed consent/assent prior to enrollment. As the main outcome measure, the clinical investigators chose disability-adjusted life years (DALY) averted by treating pre-emergency conditions such as acute respiratory, gastrointestinal, and cutaneous diseases. The study results showed potential benefits from these innovative interventions as compared with using the hospital emergency department. However, the authors themselves acknowledged three main study limitations: missing provider/institutional costs of hospital emergency in the analysis, exclusion of patients with nighttime symptoms evolving slowly enough not to warrant routine primary care in the morning, and the reliance on a particular methodology that could have introduced recall bias in data collection and lead to underestimation of the outcome measure. Furthermore, using Health Insurance Portability and Accountability Act (HIPAA) compliant platform and the approval of University of California, Los Angeles (UCLA) institutional review board (IRB)-approved English and Haitian creole informed consent, Cutler et al. carried out the first known teledermatology research project in Haiti [7]. The study setting occupied a philanthropic clinic in the town of Petit-Goave, serving local and neighboring rural communities, 42 miles from the capital of Haiti. The study enrolled 101 participants in March 2015, with a mean age of 26 years (range 0–92) and a male-to-female ratio of one to two. The clinical investigators selected the study format based upon prior trial runs. First, a Haitian primary care provider in Petit-Goave examined the participants at the local clinic, proposed a working diagnosis and treatment plan, photographed each subject with an iPhone 6, and formatted the picture with the application Photogene four to achieve a resolution of 1024 and a configuration of 300 × 300 DPI. Subsequently, the Haitian primary care provider uploaded the images to a smartphone via encrypted platform, scanned, and forwarded them along the consultation request forms, using unique patient codes, to six board-certified dermatologists in Los Angeles, California, for review, diagnosis, and recommended treatment plan. Whenever the consultants changed the treatment plan, the Haitian staff contacted the patients in concern to ensure they received the correct therapy. The concordance between the primary care provider and the dermatologist reached 68.9%. The elapsed time between initial case upload and reading of the dermatology consultation by the Haitian primary care provider and volunteer United States-based medical students averaged 1.67 days only. Atopic dermatitis, including prurigo nodularis and eczema, and fungal infections accounted for the majority of diagnoses, 39% and 18%, respectively. Acne, bacterial infections, and pigment disorders represented 10%, 9%, and 7% each, while other various pathologies constituted the remaining 16% of the total cases. However, atopic dermatitis also made up 46.7% of the discordant diagnoses. Although this study demonstrated the feasibility of teledermatology in rural areas, it did not adjust for confounders that might have biased the dermatologists' impressions, for example, the clinical presentation and diagnosis formulated by the Haitian primary care provider. During Operation Uphold Democracy in 1995, the United States military troops deployed in Haiti experimented 30 asynchronous telemedicine consultations between Walter Reed Army Medical Center in Washington, D.C., and Haiti [8]. The most common consultations concerned dermatology, radiology, and surgery [8]. The results of this limited experience indicated that the consultations generated a significant change in treatment plan half of the time. In a retrospective study of telemedicine consultations conducted by the United States military in Haiti during this second troops occupation, Walters et al. found an effect of telemedicine on diagnosis, treatment, and overall patient health status of 30%, 32%, and 70%, respectively [9]. Not too long ago, in the aftermath of the 2010 earthquake, a few non-governmental organizations and private health entities launched some, short-term, unstructured telemedicine initiatives for primary care, and mental health in Haiti. In general, the organizers reported very few of them in non-peer-reviewed publications, using rather a plain narrative format.

Yet, an embryo of telemedicine already exists in Haiti. It consists essentially in telestroke, telesurgery, teleradiology, and telepathology, representing less than 1% use. By comparison, in Latin America, 2015 data emanating from the World Health Organization (WHO) Global Survey on eHealth and the 2017 survey of hospitals across nine diverse countries discovered a range of telemedicine use from 25% of hospitals in Colombia to 65% in Chile before the COVID-19 pandemic [1]. In the context of rising costs of energy from crude oil and natural gas on the international market, soaring shortage of electricity, potable water, internet service, and transportation, compounded by galloping inflation, dismal gross domestic product (GDP) of $1176.8 per capita [10], harrowing national budget and trade deficit, and scarce investment in sustainable development, creative solutions for cost-effective, and outcome-driven healthcare delivery models become highly desirable in Haiti once the right conditions exist.

4. Telemedicine technology

The terms telemedicine and telehealth are not interchangeable. Telehealth encompasses a broad range of remote healthcare technology applications, including patient education, administration, and collaboration, as well as telemedicine. Depending on the backdrop, conditions, and populations, telemedicine comprises various modalities: real-time service *via* live video, voice, and data conferencing; store and forward, involving data capture in digital files on a computer or mobile device followed by secure transmission for later analysis, interpretation, and sharing. A third modality consists in remote monitoring *via* patient data collection from wearable sensors and other devices, and subsequent transmission to monitoring systems and health care professionals to track patient health [1]. Two distinguished peer-reviewed journal articles by Dorsey and Topol [11] and Tuckson et al. [12] had depicted a comprehensive synopsis of telemedicine modalities and challenges. A paper by Daniel and Sulmasy, elaborated policy recommendations for the use of telemedicine in primary care setting on behalf of the American College of Physicians (ACP) [13]. Two months later, ACP issued a full Position Paper in the Annals of Internal Medicine. The authors reviewed evidence-based advantages of telemedicine regarding access of health services, clinical outcomes, and costs of treating patients outside of traditional healthcare settings and at home, versus potential barriers, operational, regulatory, and licensing challenges. The paper described the ACP positions on the adoption and practice of telemedicine in great detail. This book chapter focuses on synchronous telemedicine, i.e., real-time interactive audio-video, supplemented as necessary, with asynchronous telemedicine, i.e., secure electronic transmission of patient's medical information (medical history and physical exam findings, radiographs, laboratory, and pathology results) for expert evaluation and recommendations outside of real time. Network performance remains essential to any successful telemedicine program, especially when using real-time video and voice. Network reliability, resiliency, and diversity play a central role to ensuring the delivery of quality care in an increasingly connected environment. Selection of the right internet and wide area network (WAN) service provider, internet and WAN connections that offer high bandwidth and availability, as well as minimal latency turns out crucial. Expressed in Mbps or Gbps, bandwidth represents the measure of both the capacity of data connection and the amount of data delivered through it. Many cloud-based high-definition videoconference platforms function fully on a modest bandwidth of just 1.5 Mbps, 6% of the 25-Mbps federal commission communication (FCC) standard. In fact, zoom video software requires only 1.5 Mbps [14], as do other widely used videoconferencing platforms, such as Webex (Cisco Systems) and GoToMeeting (LogMeIn) [1]. One can realize effective high-definition communication by simply using smartphones and laptops over land and wireless connections and over a range of bandwidths. The U.S. Federal Communications Commission recommends a broadband connection of 10 Mbps for a small practice and 100 Mbps to one Gbps for a large one [1, 15]. Measured in milliseconds, latency describes the lag time for a data packet to travel to a destination either one way or round trip. High-quality videoconferencing usually requires a latency of 150 milliseconds. Additionally, high availability and robust security stand as critical elements for telemedicine applications to support compliance with security, privacy, and confidentiality [1, 16–19]. About 60% of Haiti's population subscribes to mobile phones [20]. According to the 2016–2017 "Enquête Mortalité, Morbidité et Utilisation des Services" (EMMUS VI), the daily utilization of internet service in urban and rural areas is nearly similar (25.0% vs. 29.2%) in spite of disparate access to electricity, 76% vs. 17% [1, 21].

5. Potential applications of telemedicine to advance global equity and inclusion in Haiti

Telemedicine could alleviate the physician workforce shortage and clinic overcrowding, enhance continuity care, and streamline health information management. In essence, program implementation should aim at overcoming major technical, operational, financial, procedural, and human barriers (**Table 1**) [1].

Technical barriers: One of the initial steps of telemedicine utilization involves the selection of appropriate space in a designated health center with dependable access to electricity and internet service for the establishment of secure broadband connection and storage of telemedicine equipment: high-resolution monitor, desktop computer, high-definition camera, and microphone, as well as digital stethoscopes, otoscopes, ophthalmoscopes, portable electrocardiographic machine, and handheld ultrasound, etc. Electricity and internet access constitute some of the greatest roadblocks [1]. However, one can partially overcome them by resorting to green technology such as wind turbines, solar panels (already in use by Partners in Health (PIH) and Zanmi Lasante in the Central Plateau of Haiti for over 8 years), and satellite communications (widely utilized by The Study Group on Kaposi's Sarcoma and Opportunistic Infections, known under the French acronym as Les Centres GHESKIO, in Port-au-Prince). Access to the designated space for telemedicine and patients' charts should be restricted to responsible personnel using door locks, proximity cards, keypads, or biometrics. Many Haitians in Haiti and abroad master the telemedicine technology. For instance, Eng. Samuel

Technical	Scarce electric grid and power supply Unreliable or non-existing internet service Low broadband penetration
Operational	Suboptimal organization of patients' charts Space constraint for telemedicine session Deficient roads and transportation service Recurrent work stoppage due to a cascade of strikes and civil protests
Financial	Inadequate accessibility to funding for telemedicine equipment, software, maintenance, and sustainability Frequent payment interruptions for salaries, intrants, and utilities
Procedural	Little to nonexistent telemedicine policies and legal framework Restricted availability of mutually agreed standard operating procedures Undefined credentialing process for licensures and privileges
Human	*Locally-specific*: Absence of telemedicine integration into the national health care plan Lack of leadership engagement and stakeholders buy-in Reluctance of patients and medical providers to adopt the new format Increased burden on personnel at overcrowded and understaffed clinics Low educational attainment and health literacy level of patients *Provider-specific*: Lack of cultural competence of foreign telemedicine consultants Conflicting schedules and competing priorities for the consultants Absence of incentives for telemedicine providers *Patient-provider related*: Limited patient-provider relationship and continuity of care Cross-border language barriers

Table 1.
Major barriers to telemedicine in Haiti.

Pierre, PhD., internationally known as an award-winner expert in information technology, mobile communication, fiber optics, cloud computing, and department chair at Polytechnic Institute of Montreal, is leading an avant-gardist project, Pôle d Innovation et de Dévelopment du Grand Nord (PIGraN), to provide long-distance education from kindergarten to graduate studies, cutting-edge healthcare including telemedicine, along sustainable agricultural, and economic development in Northern Haiti.

Operational barriers: Complete medical history, medication lists, laboratory tests, and radiographic results should gradually integrate patients' electronic health records (EHR). Telemedicine offers the opportunity to develop and implement a robust and user-friendly EHR system. As a matter-of-fact, in the Central Plateau of Haiti, Partners in Health (PIH) and Zanmi Lasante are utilizing a web-based medical record system linking remote areas in rural Haiti and University Hospital of Mirebalais. Through this system, PIH and Zanmi Lasante provide a wide array of medical, educational, social, and economic services aiming at health equity and social justice, while promoting scientific advancement. Sharing similar goals, The Study Group on Kaposi's Sarcoma and Opportunistic Infections, known as Les Centres GHESKIO, in Port-au-Prince, had implemented a solid electronic database for healthcare delivery, education, and training, research and social services nationwide, focusing on marginalized populations. GHESKIO focuses on promoting scientific independence through multilateral collaboration. Under the sponsorship of the United States Centers for Diseases Control and Prevention (CDC) and the Haitian Ministry of Health, The President's Emergency Plan for AIDS Relief (PEPFAR) program is operating a national network of HIV electronic database for healthcare delivery, monitoring, evaluation, and reports. The CDC had brought a significant contribution in the formation of epidemiologists, field workers, HIV providers, and health administrators, as well as uplifting laboratory capacity and infectious diseases surveillance in Haiti. As telemedicine is moving from hospitals and ambulatory health centers to homes and mobile devices, the nature of the telemedicine visit will keep changing. Broadband expansion could stimulate this ongoing technological transformation. Telemedicine visits may become shorter and more frequent by using diverse communication methods with different providers. Any chosen space for telemedicine in Haiti and abroad should ensure the protection of patients' privacy and confidentiality and safeguard the telemedicine equipment. However, frequent strikes and civil unrest may continue impeding not only telemedicine operations but also the general provision of healthcare services, with grave consequences on people with acute and chronic illnesses.

Financial barriers: Contingent upon the technology adopted and the intervention used, the cost of a telemedicine program varies substantially. Quite often the initial costs of space retrofitting, acquiring the necessary medical equipment, telemedicine hardware, software, and medical equipment for telemedicine, and setting up a robust electronic health records (EHR) system, and establishing communication modalities could reach substantial amounts and become unaffordable for resource-poor countries. Further, maintenance and continuous upgrade of the telemedicine system, as well as staff training, will add up to the operating budget. In Haiti, the unstable political climate and persistent insecurity make it hard to attract potential donors and generate confidence in volunteer telemedicine consultants. Moreover, for a country with uncertain future, strapped for cash, entangled in foreign debt, and overwhelmed by high priorities, the public and private sectors would probably take a cautious approach to investing in new healthcare projects, such as telemedicine. Hence, the prior demonstration of clear clinical advantages of telemedicine usage may help sway stakeholders. In that regard, what does the published peer-reviewed literature indicate?

Depending on the clinical setting, randomized and observational studies of the clinical impact of telemedicine had yielded conflicting results. For example, the observational study by Nassar et al., including 3355 intensive care units (ICU) patients in a network of seven Veterans Administration (VA) hospitals failed to demonstrate shortened hospital length of stay or decreased mortality rates when applying telemedicine for critically ill patients [22]. In a different hospital setting, a retrospective cohort study, Monkowski et al. analyzed the impact of inpatient infectious disease telemedicine consultation service on hospital and patient outcomes [23]. The study reviewed data on 244 patients, 73 in the pre-infectious disease telemedicine group, year 2012, and 171 in the infectious disease telemedicine group, year 2014. Mean age was 65 for the pre-tele group and 58 for the tele group. More immunosuppressed patients belonged to the tele group (23% vs. 12%). Study results showed that infectious disease telemedicine significantly reduced hospital length of stay, the median number of days patients received antibiotics, and the average antibiotic cost per hospitalized patient day, $14.53 in 2012 vs. $11.25 in 2014, all important performance indicators of antimicrobial stewardship. Cantor et al. reviewed 28 randomized controlled trials and 14 observational studies to evaluate the effectiveness and harms of various telehealth interventions supplementing in-person maternal health care of 44,894 women [24]. The telemedicine interventions included phone, web, and mobile applications. Maternal health areas involved general maternal care, postpartum depression, gestational diabetes, gestational hypertension, breastfeeding, and other conditions, such as smoking cessation and weight gain. This qualitative review found essentially similar clinical outcomes and patient satisfaction between in-person care and maternal telehealth. Berthaud et al. implemented a stepwise hybrid model of telemedicine provided by board-certified infectious diseases physicians to improve clinic attendance and viral suppression for 516 HIV-positive inmates in Tennessee prisons as follows: in-person clinic only, 2004–2010, at the central prison in Nashville; hybrid 1, 2011–2013: 50% in-person clinic followed by 50% telemedicine at the same central prison and on the same day; hybrid 2, 2014–2016: 50% live clinic at the central prison and 50% telemedicine at the Meharry Medical College campus in Nashville, on alternate week; telemedicine only clinic sessions, 2017–2018: at the Meharry Medical College campus [25]. For the in-person clinic, the inmates were all seen at a central penitentiary clinic in Nashville. Clinic attendance increased from 50% in 2004 to 90% in 2017–2018, while HIV viral suppression rose from 30% to 90%. The telemedicine program improved all channels of communication, patient-provider relationship and continuity of care, linkage, and engagement of inmates in transition, and offered opportunity to train medical students and residents, as well as inmates and prison staff [25]. Salgia et al. examined the educational impact of Veterans Administration distance learning case-based and didactic program for treatment of chronic hepatitis C in Michigan, Indiana, east-central Illinois, and northwestern Ohio, from June 2011 to September 2012 [26]. The Specialty Care Access Network-Extension of Community Healthcare Outcomes (SCAN-ECHO) program was developed to transfer subspecialty knowledge to physicians, nurse practitioners, and physician assistants, modeled after the Project ECHO created at the University of New Mexico for treatment of chronic hepatitis C. The investigators surveyed 51 providers anonymously using an electronic instrument. They achieved a response rate of only 47% with 96% completion [27]. The results demonstrated that primary care providers considered case-based and didactic sessions as equally important and that the distance videoconferencing learning program improved healthcare delivery.

In summary, this body of research contributes to advancing our knowledge on the feasibility, favorable clinical advantages and cost-effectiveness of telemedicine in diverse clinical settings, and the potential to reduce barriers to accessing specialty care for underserved populations. Therefore, the author of this book chapter hypothesizes that telemedicine could reduce emergency department visits, hospital admissions, and enhance the management of chronic comorbidities in Haiti, leading to more productive lives, sizeable return on investment, and reduced financial barriers.

Procedural barriers: To the best of the author's knowledge, no legislative framework exists to regulate the practice of telemedicine in Haiti. This shortcoming underscores the importance of memoranda of agreement (MOA) between international providers or healthcare organizations and local Haitian healthcare entities. Prior to starting a telemedicine program, the partners involved should develop mutually agreed upon standard operating protocols. The quality of care should reflect evidence-based guidelines adapted to the local context. Policies should address medical negligence and malpractice, as well as liability insurance to protect vulnerable populations. Two-way channels of communication should remain widely open. Providers should have ample opportunity to review patients' charts within a reasonable time period prior to the telemedicine session. Encrypted e-mail with two-level authentication factors is preferred for the transmission of patients private and confidential health information. Patients would need to sign approved informed consent, and the medical providers would have to sign confidentiality agreement in order to confirm their engagement into a professionally responsible patient-provider relationship. At the local clinic, a physician or a mid-level provider should present the clinical case and perform a brief physical exam as necessary. The telemedicine consultants should use the opportunity to educate patients, medical teams, and stakeholders. They should forward their final consultation reports, including teaching points, in a timely manner, utilizing clear, concise language, and relevant references [1]. Finally, this author strongly encourages the telemedicine consultants to deploy their best effort to follow the same patients at subsequent sessions, thereby ensuring continuity of care and reinforcing patient-provider relationship.

Human barriers: Leadership engagement is paramount for the application of telemedicine. It requires basic knowledge of operations and identification of top-priority domains of application. The leadership vision should preferably align with the national and local strategic healthcare plan, but sometimes it could outpace them. Leadership should promote community awareness and convince national and international stakeholders of the potential benefits of telemedicine for the appropriate populations and locations. Prior to inception, this author strongly recommends identifying a telemedicine champion to spearhead an outreach campaign and build up partnerships. Patient education, confidence, engagement, and satisfaction remain indispensable for ultimate program success. Outcome-driven incentives may serve as acceptable enablers. Key performance indicators should measure specific clinical outcomes, patient's health improvement and satisfaction, providers satisfaction, and cost-effectiveness. The national HIV care model in Haiti teaches us that successful engagement (99%), retention (80%), and treatment adherence (73% viral suppression) stand in the realm of possibility for a disease-specific, organized, accountable, and supportive healthcare delivery system [2]. Lessons learned from the Haitian national HIV program inform prospective telemedicine volunteers about the importance of education, respect, condemnation of stigma and discrimination, and promotion of self-centered care.

6. Modalities and domains

6.1 Consolidation and expansion

6.1.1 Evolving medical and surgical specialties

As described in the background section, since the mid-1990s, few peer-reviewed papers about various telemedicine experiences in Haiti had been published in scientific journals. They relate particularly to dermatology, pediatric emergency, diabetic foot care, military deployment, and disaster relief. While most of these short-term experiments dwindled, new and more enduring projects emerged and strove to dispense invaluable services in different regions of Haiti. Therefore, the fundamental goal should emphasize consolidation and expansion of these impactful telemedicine services such as telestroke, telesurgery, teleradiology, and telepathology [1]. For example, telestroke can help quickly determine a patient eligibility for lifesaving thrombolytic treatment or neurosurgery. Telesurgery enables a surgeon in Haiti to perform robotic surgery remotely and can eliminate the barriers of distance in the delivery of high-quality surgical care. Teleradiology allows physicians to share digital imaging and interpretation remotely. Telepathology consists in the transfer of high-resolution microscopic pictures for reading and diagnosis [1]. Among illustrations of telesurgery/teleradiology programs in Haiti, one can mention the following: Bernard Mevs Hospital in partnership with University of Miami and Project MediShare, Mirebalais University Hospital in collaboration with Harvard University, and the longstanding partnership between Bienfaisance Hospital in Pignon and various academic medical centers in the United States. Teleradiology and telepathology open the prospect for applying machine learning (ML) and artificial intelligence (AI) to refine clinical decision-making capacity. However, before the application of AI and ML one should install proper oversight measures to protect the rights and well-being of patients, including a code of ethics and regulations, determination of data ownership, and processes for transparency, accountability, and elimination of algorithm bias. Then, the telemedicine clinic or hospital should pilot and validate the data output prior to dissemination and final application. These variants of telemedicine can upgrade the training of Haitian physicians and nurses in Haiti, as well as enriching the experience of international consultants. They can incorporate graduate residency training programs, reduce technological gaps, health inequities, and open doors for collaborative research, information sharing, and propagation of best practices.

6.2 Implementation and upscaling: chronic infections and comorbidities of public health importance

6.2.1 The use of telemedicine in infectious diseases

In general, randomized clinical trials of telemedicine use in infectious disease have demonstrated positive health outcomes for patients with HIV, chronic hepatitis C, and tuberculosis, as well as patient satisfaction and successful longitudinal mentorship. Experience with acute skin and soft tissue infections, respiratory, and urinary tract infections have shown favorable results. Thus, in a narrative appraisal of 29 peer-reviewed publications, Parmar et al. summarized the use of telemedicine technologies in the management of acute infectious diseases (14 papers), human immunodeficiency virus/HIV (2 papers), chronic hepatitis C/HCV (9 papers), and active pulmonary tuberculosis (4 papers) [28, 29]. Total sample size reached 3990, ranging from one to 1201. Study designs included case reports, cross-sectional and observational studies, randomized trials, and prospective and retrospective cohorts. Telemedicine facilitated the acute treatment and follow-up of patients with bacteremia, acute respiratory, urinary tract, soft tissue, and skin infections after hospital discharge. Published literature consistently demonstrates positive clinical outcomes for the treatment of HIV, chronic hepatitis C, and tuberculosis using telemedicine. In general, patients constantly report high levels of satisfaction. In a prospective study conducted from February 2012 to August 2015, Wood et al. analyzed the impact of teleconsultation and longitudinal mentorship to community HIV providers on medical care and education [30]. The University of Washington and Mountain West Education and Training Center (MW AETC) developed and implemented this program with the goal of reinforcing community provider capacity to deliver the latest, evidence-based HIV treatment. The program used cloud-based technology adapted to mobile device and computer to connect the participants with a multidisciplinary specialist panel in real time. It enrolled a cohort of 40 community HIV providers at 11 clinical sites, followed the Extension of Community Healthcare Outcomes (ECHO) model, and administered 172 ECHO sessions through 553 case presentations. The University of Washington tracked and evaluated program performance through periodic self-assessment of HIV care knowledge. The study results revealed significant increase in the knowledge and confidence of the participants and showed potential to promote workforce development and expand access to high-quality HIV care. In different geographic regions, Zolfo et al. described a hybrid telemedicine model sponsored by the Institute of Tropical Medicine, Antwerp (ITMA), Belgium, combining E-mail and web support to assist more than 170 healthcare professionals in 40 low- and middle-income countries in the provision of HIV care and continuing medical education [31]. Participants included alumni physicians of ITMA and their colleagues working in HIV clinics. During the initial 24 months (April 2003-March 2005), the participants requested 342 telemedicine consultations from 17 different countries. The majority of them originated from Uganda, Mozambique, Rwanda, and Cambodia. Diagnosis and treatment of opportunistic infections, antiretroviral side effects, and antiretroviral resistance represented the most common topics addressed in teleconsultations. This collaborative activity showed how telemedicine can provide effective clinical support in low-resource settings at an affordable cost. In Barcelona, Spain, León et al. performed a two-year prospective, randomized study to compare standard HIV care with an internet-based model encompassing the entire spectrum of management of chronic HIV infection, designated virtual hospital, and comprising virtual consultations, telepharmacy, virtual library, and virtual community [32]. They randomized subjects with computer and broadband access to either virtual hospital (Arm 1) or standard of care (Arm 2). After 1 year of monitoring, participants crossed-over to the other arm. In the first year, the study enrolled 83 subjects, 42 in Arm 1 and 41 in Arm 2. The study investigators did not detect any significant statistical difference between virtual hospital and standard of care in treatment adherence, viral load suppression, CD4+ T-cell count, quality of life, or psychological questionnaires. In 219, the Infectious Diseases Society of America (IDSA), the world's largest organization of infectious diseases specialists had published an authoritative position statement on telehealth and telemedicine as they apply to the practice of infectious diseases [33]. The paper laid out an informative telehealth toolkit for consideration when developing and executing a telehealth program. In its position statement, the IDSA supports the use of telehealth in HIV and tuberculosis management, antimicrobial stewardship, outpatient antimicrobial therapy, and infection prevention and control. IDSA reiterates the special challenges to confront in telemedicine practice (patient satisfaction, reimbursement, licensure, and liability). Finally, the consensus paper recommends proper application of telehealth in clinical care, education, and research in an ethical manner.

6.2.2 Telemedicine opportunities for chronic infections and comorbidities in Haiti

For several decades, Haiti had adopted an exemplary model of public-private-international and academic cooperation for the prevention and treatment of HIV. The author would encourage the perpetuation of this successful model that had brought down the HIV prevalence from 3.2% in the mid-1990s to 1.9% in 2021, in spite of chronic political strife and social upheaval. Nonetheless, telemedicine could boost the success of PEPFAR and other HIV programs in Haiti. Given the current epidemiological picture of chronic diseases in Haiti, the implementation and upscaling of telemedicine in Haiti should focus on the management of chronic comorbidities: asthma/chronic obstructive pulmonary disease (COPD), essential hypertension, hyperlipidemia, diabetes mellitus, and behavioral disorders. The author of this chapter discusses the latter in the next section. During the past 40 years, Haiti had become dependent on import to feed its population. Consequently, cheaper high-fat, high-calorie, high-salt nutriments had become more accessible and affordable than healthy locally grown organic foods, raising the risks of cardiovascular diseases, and diabetes. Stress due to worsening food insecurity, growing food desert, political and gang violence, unemployment, precarity of life, and hopelessness further exacerbate these chronic conditions and the burden of behavioral disorders. The relentless deterioration of the environment and sanitary conditions, coupled with tobacco and alcohol abuse, and provide a fertile ground for the rising prevalence of chronic respiratory diseases. In term of implementation, first of all, the telemedicine programs should prioritize promotion of healthy lifestyles and disease prevention: good nutritional habits and weight management, environmental and personal hygiene, accident/injury prevention (especially for the widespread motorcycle riders), smoking and drinking cessation, adoption of responsible sexual behavior, and appropriate contraceptive methods. Although the incidence of cancer is escalating in Haiti and considering the limited access to expensive diagnostic and treatment tools (chemotherapy, biologics, and radiation), special telemedicine programs on the prevention of some of the more prevalent types of malignancies such as cervical, breast, and prostate cancer, deserve considerable attention. Nonetheless, a multidisciplinary oncology telemedicine consultation team can still play a role in alleviating the sufferings of people with cancer if they support a patient assistance program (laboratory and pharmaceuticals). Such a program could also embrace artificial intelligence and machine learning for diagnostic pathology and radiographic interpretation once they fulfill the necessary requirements.

6.3 Mental health

6.3.1 Applications of telemedicine in mental health

Mental health affects people worldwide. The COVID-19 pandemic had driven the use of telemedicine for mental health care and demonstrated promising results, but long-term outcomes remain undetermined. In general, the COVID-19 pandemic proves that tele mental health can substitute in-person care for assessment and treatment of diverse behavioral disorders, especially attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, major depression and anxiety disorders, and post-traumatic disorder (PTSD). However, tele mental health existed before COVID-19. A paper by Garcia-Lizana et al. summarized the results of earlier studies of the evaluation of telepsychiatry (1997–May 2008) [34]. After excluding studies with sample sizes lower than 10, the authors analyzed 620 articles, including 10 randomized controlled trials. They found inadequate evidence of the effectiveness of telepsychiatry in the management of mental illnesses. Later, an extensive review comprising 30 randomized controlled trials on the intermediate outcomes and health outcomes of tele mental health and four cost analysis studies by Bashshur et al. examined the empirical evidence of telemedicine interventions in mental disorders [35]. The review found empirical evidence of the potential for tele mental health to accomplish long-term management of mental illnesses through monitoring, surveillance, promotion, prevention, and biopsychosocial treatment programs. According to the study findings, basic telephone appears the preferred technology. Tele mental health found acceptance across lifespan, improved medication adherence, mental healthcare in primary care setting, and clinical outcomes for patients with comorbid medical conditions. Notably, it delivered effective treatment for depression and anxiety disorders, especially cognitive behavioral therapy. Cost-effectiveness analysis revealed that tele mental health programs need a threshold of 250 consultations to achieve cost-effectiveness. Lau et al. conducted a systematic review and meta-analysis to evaluate the efficacy of therapist-supported internet-based cognitive behavior therapy for stress, anxiety, and depressive symptoms among postpartum women [36]. The study found that therapist-supported internet-based cognitive behavior therapy significantly improves stress, anxiety, and depressive symptoms among postpartum women with small to large effects. Rightly so, the authors underlined five major shortcomings of their study: sampling bias as most of the participants self-selected, the use of self-reported outcomes, the inclusion of a small number of trials affecting subgroup analyses, the report of different effect sizes by diverse sessions of internet-based cognitive behavioral therapy, and the evaluation of only short-term benefits.

6.3.2 Opportunities for Haiti

Mental health remains taboo in Haiti and among Haitian expatriates as the country suffers a dearth of mental health professionals (23 psychiatrists and 124 psychologists for the entire country of 11,887,456 inhabitants, practicing almost exclusively in the metropolitan area of Port-au-Prince). Meanwhile, a certainly much greater but unknown number of North American-trained mental health professionals of Haitian descent live in the United States and Canada. Many of them, previously educated in Haiti, very familiar with the nuances and distinctive features of Haitian culture, could significantly contribute to a culturally and linguistically-appropriate tele mental health program earning rapidly the trust of mental health patients and Haitian providers. The Haitian American Psychiatric Association, born in 1984, and quite active in community outreach and education programs stands out well-suited to accomplish this mission. Telemedicine can facilitate mental health service utilization, reduce stigmatization, promote patient privacy and confidentiality, and ease their discomfort with the mental health service delivery system in Haiti.

7. Conclusion

Telemedicine presents important limitations. First and foremost, it does not constitute a panacea for a weak healthcare infrastructure nor does it replace traditional in-person visits provided by well-trained personnel in a well-rounded healthcare system. The substantial absence of direct physical examination and the diminished patient-provider relationship may jeopardize the clinical acumen of the telemedicine consultant and erode patient trust. Nonetheless, telemedicine offers an interesting alternative to advance global equity in healthcare. Second, patients' rights and privacy concerns always require strict protection still a work in progress for telemedicine. Third, preventive medicine, including community awareness, workforce education, and technical assistance, should form the backbone of telemedicine in low- and middle-income countries. Meanwhile, the expansion of smartphones and telemedicine throughout the world in the COVID-19 era opens new perspectives to attenuate the geographic and social digital divide and reduce global health equities. The spotlight on Haiti exemplifies how low- and middle-income countries can customize telemedicine to improve healthcare access. So far, whether or not upscaling of telemedicine will affect the expatriation of medical graduates to rich countries remains unanswered. Paradoxically, the emigration of physicians from resource-poor nations could also serve as a stepping stone to reconnect with and give back to their homeland. In fact, many of them had organized their own national networks of health professionals abroad. By twinning with their affiliated healthcare institutions, medical and nursing schools, and nongovernmental organizations, they can develop and implement long-term telemedicine programs to benefit their native countries.

The Association of Haitian Physicians Abroad, better known under its French acronym, AMHE or Association Médicale Haïtienne à l'Etranger (Haitian Medical Association Abroad), founded in 1972, defined by its obligation to the homeland, and composed essentially of health professionals of Haitian origin, could play a major role in telemedicine initiatives between North America and Haiti. To accomplish this endeavor, AMHE would leverage its rich experience in Haiti, including medical and surgical services, HIV and tuberculosis programs, medical education, and residency training. The initial step would consist in identifying a pool of potential volunteers among retirees and active professionals. Next, they would form a steering committee to spearhead one or two pilot projects funded by AMHE members and possibly sponsored by United States Agency for International Development (USAID), other US/Canada government agencies, international, or philanthropic organizations, and individual donors. Subsequent to performance evaluation and quality improvement, the telemedicine program would expand to advance global health equity and inclusion. In the aftermath of the 2010 earthquake in Haiti, a group of eminent professionals of Haitian descent living primarily in North America and Europe created the Groupe de Reflexion et d'Action pour une Haiti Nouvelle (GRAHN), or Think Tank and Action Group for a New Haiti. This worldwide organization appeals to Haitian citizenry and friendship in the construction of a new Haiti grounded in science, technology, equity, and social justice. In fact, GRAHN's Institut des Sciences, des Technologies, et des Etudes Avancées (ISTEAH) or Institute of Sciences, Technologies, and Advanced Studies shows a proven track record in preparing local Haitians and government and private employees to earn fully accredited masters and doctors degrees using long-distance learning and the free expertise of foreign and Haitian academicians. As healthcare and education constitute the pillars of GRAHN and AMHE, the two organizations had joined forces to build the AMHE-GRAHN community health care center of excellence, a component of Pole d 'Innovation du Grand Nord (PIGraN), or Innovation Pole of the Greater North. The center will provide free or low-cost, high-quality care in primary and reproductive health, preventive medicine, infectious diseases, mental health, and ophthalmology. The use of information technology, communication, and telemedicine will represent the cornerstone of the AMHE-GRAHN community health center. Thus, fiber optic cable for high-speed internet access and videoconferencing will wire all the offices. This will facilitate the implementation of telemedicine consultations to support medical providers at the health center and throughout Haiti under the auspices of health professionals from AMHE and GRAHN. Toward that end, the Montreal Nurses and Nurse's Aides Association, a GRAHN affiliate, will shoulder this effort. Based on previous experience at similar centers, telemedicine may offer a wider spectrum of medical expertise, surveillance, and assistance. In the near future, smartphone technology will bring health counseling and medical care to disenfranchised populations wherever they might live in Haiti. Bridging the technological gap will enable children born in remote villages of Haiti to pursue undergraduate and graduate studies while accessing excellent healthcare without living their villages. Moving forward, the AMHE-GRAHN collaborative enterprise may attenuate poverty by fostering education, healthcare, creating wealth, sustainable, and equitable development. As a tenet of social justice and recognizing healthcare as a basic human right, the allocation of global healthcare resources should prioritize the sickest and neediest people around the world rather than the wealthiest ones.

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Chapter 12

WhatsApp as a Humanized Communication Tool during SARS-CoV-2 Monitoring

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Abstract

Due to the COVID-19 pandemic, Universities studied safe ways to return to activities, which pointed out that the effective biosecurity measures were the use of masks, social distancing, personal hygiene, and monitoring programs by testing and isolation of contaminated individuals. Not only monitoring and testing itself but also the entire community orientation process is essential for the successful mitigation of SARS-CoV-2 infections. The aim of this study was the development of communication tools for monitoring SARS-CoV-2 by testing a Brazilian University community, during the gradual return to face-to-face activities, from May 2021 to December 2022. The tests were performed by RTqPCR, in a laboratory with biosafety level 2, using saliva samples self-collected, on dry cotton, in a dry collection tube, wrapped in a 70% isopropyl alcohol wipe, transported in an envelope with individual epidemiological and symptoms data, and maintained at room temperature until analysis. The results were delivered by a health professional by email and WhatsApp which was a humanized channel constituted to receive doubts and anxieties, as well as contact and guidance regarding the biosafety protocols adopted at the university, and health issues in general, which subsidized the monitoring by providing a rich and detailed collection of data.

Keywords: epidemiological surveillance, mass testing, SARS-CoV-2, RTqPCR, saliva sample, humanized disease communication

1. Introduction

In December 2019, a series of pneumonia cases caused by a then-unknown virus was linked to the fish and seafood market in Wuhan, China. When the pneumonia's cause was identified, the new coronavirus was described [1]. On February 11, 2020, the World Health Organization (WHO) named the disease caused by SARS-CoV-2 as COVID-19 (coronavirus disease 2019) [2]. Exactly 1 month later, on March 11 2020, the WHO declared COVID 19 pandemic, reporting 118,000 cases in 114 countries and 4291 deaths [3]. By the end of 2022, more than 700 million cases and almost 7 million deaths from COVID-19 had been recorded worldwide [4].

Due to the pandemic, nonessential activities were restricted in 2020. Realizing it to be unsustainable to maintain restricted activities for long periods, educational institutions and universities, in particular, began to study safe ways to return to activities. Several studies point out that the biosecurity measures that were sustained as effective were the use of masks, social distancing, personal hygiene, in addition to monitoring programs by testing and the isolation of contaminated individuals, whether in a university environment [5–16], school environment [17], health [18, 19] or work [11, 20].

In educational institutions, there was great concern about the possibility of high transmission rates among students, the community of workers, and individuals around them [8, 12]. However, it was observed that, with the sanitary measures adopted, the occurrence of transmission of SARS-CoV-2 was minimized internally, in educational institutions [13], while sanitary measures were maintained, with a lower incidence of contamination when compared to the surroundings [9, 17]. An important example was the conditions for monitoring SARS-CoV-2, associated with the sanitary measures adopted by Delaware State University, which is a publicly funded university for the black community, which made the university environment protective for a historically vulnerable population, becoming not only an educational space but also one of the social securities [12].

Monitoring by testing is a rich source of epidemiological information, capable of helping to understand the impact of vaccination, emergence and behavior of variants, time of infection, prediction/detection of outbreaks, community guidance, and development of protocols, among others [8, 11, 17, 20]. Testing and isolating confirmed cases are the most effective way to control virus dissemination. Different institutions have implemented various forms of testing, whether on demand (of symptomatic people or people who have had contact with the virus), random monitoring, or even universal and high-frequency testing [7, 9, 19]. A model developed in research on regular testing in the university environment to control the virus points out that 96% of infections could be prevented with routine testing [5]. In a survey conducted by the University of California, 90% of respondents reported that they would not feel comfortable working knowing that their colleagues were not being regularly tested [14].

For monitoring by testing to be carried out efficiently on a large scale, four steps must be organized: collection of biological material, carrying out the test in the laboratory, dissemination of results, and result-based transmission control measures. The gold standard method for detecting SARS-CoV-2 corresponds to the collection of nasal and oropharyngeal secretions, with a test performed by reverse transcription and real-time polymerase chain reaction (RTqPCR), with at least two virus markers. The infrastructure needed to carry out the gold standard test includes specialized personnel for sample collection, storage, and transport conditions with refrigeration at least −20°C, and a laboratory with level III biosafety, so that the contaminated sample is not a source of transmission to the professionals involved. This level of infrastructure comes with a high cost and, in underdeveloped countries such as Brazil, is available only in a few health institutions, making mass testing difficult.

Several studies have pointed to the presence of SARS-CoV-2 in saliva [8, 10, 21], making it possible to use it as a sample for RTqPCR. Systematic reviews have indicated that this type of material presents similar accuracy to nasal and oropharyngeal secretions [15, 21], with the advantage that its collection does not require the presence of health professionals (cheapening, simplifying, and reducing risks during collection) and is less invasive and more comfortable [10, 22], thus increasing the likelihood of people joining mass testing [14]. These facilities have led several testing programs that started with the collection of nasal and oropharyngeal secretions to adhere to the use of saliva in their samples [12, 17, 22]. Despite the aforementioned facilities, some laboratories reported difficulties in working with saliva due to sample quality, excess viscosity, or insufficient quantity [14]. In addition, most studies that use saliva as a sample require 2 mL of saliva, which is a large amount that must be transported quickly in a refrigerated environment and in appropriate biosafety conditions. Therefore, in institutions that are not in the health area, it is difficult to obtain the necessary infrastructure for sample collection, even though self-collection of saliva.

An alternative for obtaining biological samples to use the gold standard diagnostic method for detecting SARS-CoV-2 was developed by our research group using self-collected saliva on dry cotton with a 0.5 cm diameter and transported in temperature environment in blood collection tubes without additives, wrapped with 70% ethanol tissue and a transport system with seal-type envelopes containing a label with the information of the individuals [21]. This system was successfully used to monitor SARS-CoV-2 in the community of Universidade Federal do ABC (UFABC). Once the issue of the diagnosis of SARS-CoV-2 has been resolved, another essential step in monitoring the virus consists of disclosing the results and control measures taken after learning of positive cases. In a community as diverse as the university, made up of undergraduate and graduate students, outsourced workers (security, cleaning, food promotion, gardening, transportation, etc.), workers with technical administrative activities, teachers, and researchers, it is important to report positive cases in a humanized and individualized way. The objective of this study was the development of communication tools for monitoring SARS-CoV-2 by testing in the UFABC community, during the gradual return to face-to-face activities, from May 2021 to December 2022.

2. Monitoring of SARS-CoV-2 in a university community

2.1 Saliva and community information data collection

The saliva sample collection kit comprises a plastic safety envelope with a printed form to be filled in with the subject's data; a dry collection tube; 2 wipes with 70% isopropyl alcohol; and a flexible rod with a sterile hydrophilic cotton tip and a diameter of 0.5 cm. This material is packaged in another sealed safety plastic envelope. The outer envelope is labeled with instructions on filling out the form and collecting the material, in addition to a *QR code* for accessing the "monitora COVID" (Monitoring COVID) WhatsApp. The content of both the label external to the kit, and the form to be completed, evolved throughout the test to improve the data collected about the subject and facilitate the location of people and organization of delivery of results.

The kits contained different colors and symbols, but they differ only in relation to the content of the form. They were classified into public workers and interns (symbol is a pink circle); undergraduate students (symbol is a light blue pentagon); researchers – graduate, scientific initiation, external researchers, etc. (symbol is a green rectangle); outsourced workers; and external public (the symbol is an orange diamond).

In all kits, the information requested was date and time of collection, institutional localization, demographical data, residence address, data on vaccination, symptoms presented in the week, and whether the individual had contact anyone who tested positive for SARS-CoV-2 and where. In the public employee's kit, it was add the area of work, immediate superior, professional category, institutional identification, and if there was any face-to-face interaction. In the undergraduate student kit, was add academic record, which course/subject you are studying, and which room and laboratory you attended. In the researchers' kit, was add category (graduate, postdoc, external researcher, or others) and name of advisor/supervisor. Finally, in the kit for outsourced workers or external public, was add company name, category; and if external, the contact person at UFABC.

To carry out the test, just follow the steps indicated on the envelope, also described in the institutional orientation video prepared together with the university's communication team (available at https://youtu.be/-bJpdROUMZU). In short, the person must fill out the form; clean their hands and the area with one of the alcohol wipes; take the swab with cotton to the mouth and soak it in saliva; deposit the rod inside the dry tube; close it; wrap the tube with the second alcohol wipe; deposit the tube wrapped in the tissue inside the plastic bag; seal it; and, finally, deposit it in one of the collection boxes scattered around the campus. The collection boxes containing the kits were collected twice a day and transported to the agent pathogen laboratory, where the material would be analyzed.

The fact that the sample is collected on cotton and in small quantities, also because it is involved in 70% isopropyl alcohol, allows the sample to remain viable for until 2 weeks at room temperature, and the collection boxes can be handled by workers without risk of contamination, which was crucial to facilitate and reduce the cost of transporting the material. At the time of analysis, these samples can be handled in a laboratory with biosafety level 2 (SBL2).

2.2 Diagnosis of SARS-CoV-2 and disclosure of positive results

The extraction of nucleic acids was performed according to the protocol developed by our research group with a TRIZOL-type reagent prepared with reagents obtained from the national market [21]. The diagnosis of SARS-CoV-2 was carried out according to a protocol developed by our research group and has been used in the monitoring of the virus in the UFABC community since May 2021. The test is performed by reverse transcription and chain reaction of the real-time polymerase (RTqPCR), using reagents for the detection of SARS-CoV-2 by TaqMan with three different markers (genes that encode the envelope proteins – E; nucleocapsid – N; and RNA Polymerase – RdRp), from acids nucleic acids obtained from self-collected saliva on a sterile cotton ball. Nucleic acid samples from individuals who test positive for SARS-CoV-2 are stored for further study.

The disclosure of positive results was carried out in two different ways according to the number of positive individuals and the period of epidemic waves in the region. Thus, when the test started, the subjects who tested positive were contacted via telephone by a health professional who, in addition to informing the result, provided guidance on the protocols to be followed, on health issues, questioned their general condition, and clarified any doubts that might arise. In some situations, telephone contact was not possible, so the immediate supervisor was contacted, so that the person could be located and properly oriented.

In addition to this contact by the health professional, emails were sent, with a copy to the boss and/or supervisor, formalizing the result and passing on the protocols to be followed in writing. At the beginning of week 32 of monitoring, on January 17, 2022, the new tool, WhatsApp "Monitora Corona UFABC", was used, in which the results and guidelines are delivered by a psychology professional. As there was a great diversity of profiles in the community, each conversation was adapted so that the language and content were accessible to the interlocutors. However, as a backdrop to the dialog, a kind of script was developed with topics to be addressed:

- Call the person, wait for them to answer, and then say that they tested positive for SARS-Cov-2;
- Ask about your health status at the moment and if you have been contaminated other times;
- Question whether the person resides alone or accompanied and provide guidance on the contagion of the virus;
- Guidance on the biosafety protocols to be followed (isolation, distancing, ventilation, use of masks, and hygiene);
- Advise on medical care to be sought;
- Guidance on vaccination (which group could already be vaccinated at the time, how many doses, and when they could be vaccinated after being infected);
- Advise on the protocols for attending the university in person;
- Welcome doubts and anxieties;
- Solve possible doubts regarding the registration (data not filled in or unintelligible).

It is important to emphasize that this script was used as a basis and was not always strictly followed but adapted to the needs of each subject and each pandemic period. An interesting and illustrative example was given regarding the issue of vaccination. In early 2022, there were still many questions about who could be vaccinated, at what time, how many doses, and types of vaccine, among others. Over the course of the year, these doubts diminished until they disappeared.

2.3 UFABC institutional actions and incidence of SARS-CoV-2 during pandemic and community monitoring

On March 13, 2020, the UFABC suspended face-to-face academic and administrative activities, with the suspension extended indefinitely on the 25th of the same month. In June 2020, the university administration established the UFABC Planning and Management Actions Committee regarding coronavirus. The purpose of this committee was to study the conditions of return and offer subsidies so that the necessary measures could be taken regarding the resumption of face-to-face activities at UFABC. As a result of this committee, the Monitoring and Testing Center was created, which monitored the epidemiological situation of the university community through weekly tests on people who have justification to attend. Testing took place from May 2021 to December 2022, completing 80 weeks of community monitoring. Just over 51,000 tests were performed with 1800 positive results, corresponding to 1364 infections in 1128 people (**Figure 1**).

The blue bars correspond to the total number of tests performed in each epidemiological week. The red line corresponds to the percentage of positive tests for SARS-CoV-2.

The tested community was made up of civil servants, whether administrative technicians or teachers; workers in a situation of outsourcing various contracts such as concierge, surveillance, maintenance, cleaning, and gardening; researchers, mostly graduate students; and undergraduate students. Although the collection could be carried out autonomously, in the first weeks of testing, health professionals were in person at the testing sites for proper guidance and to resolve possible doubts. In addition, the university's communication team made videos available instructing the material collection procedure (https://youtu.be/-bJpdROUMZU).

At first, the idea was to develop a platform that would serve both as a database for epidemiological monitoring and as a tool for delivering test results. However, there was an understanding that, as this is a new and delicate topic, the tests whose results were positive for SARS-CoV-2 should be delivered in a personalized way.

Between epidemiological weeks 30 and 31, there was a recess period from December 18, 2021 to January 9, 2022, when there was a significant increase in infected people. Therefore, on the return from recess, in the week of January 10 to 16, 2022, the monitoring and testing core detected 43 positive cases, when the accumulated result for the previous 30 weeks totaled only 51 cases.

Faced with this significant increase, it was necessary to rethink the results delivery strategy, as telephone contact, in addition to being limited to synchronous conversations, cannot be carried out concurrently by the same professional, demanding much time and resources. In view of this, it was thought of delivering these results via Information and Communication Technology (ICT), specifically via WhatsApp web, a tool in which it would be possible to contact several people simultaneously, in addition to enabling asynchronous communication and automatic recording of the collected data.

At the beginning of June 2022, all servers and university workers were to return in person, as well as a partial return of students. This moment corresponded to the beginning of a new wave of contamination in the community. In the middle of June, we had, in epidemiological week number 54, a peak of 116 positive cases. As there

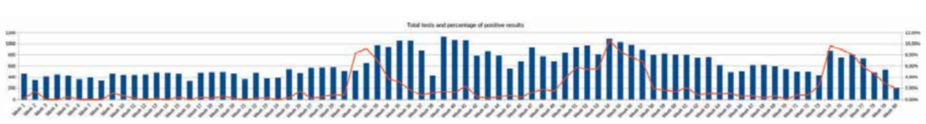

Figure 1.
Total tests and percentage of positive results.

was only one professional responsible for delivering results via WhatsApp, and a large number of positive cases, it was necessary, once again, to rethink the logic.

It was observed that, in this new epidemiological moment, doubts were concentrated much more around practical and bureaucratic issues (such as those related to removal from face-to-face activities) and less on issues related to health. Therefore, it was understood that the WhatsApp communication channel should become secondary to the informative email; thus, the delivery of results was prioritized via email, and the WhatsApp number no longer was used to call people to inform positive results but it was passed on to the community as a space to solve doubts related to testing. However, despite the non-prioritization of delivering positive results via WhatsApp, given the cooling of this new wave and as far as the professionals involved were able, the choice for communication via this channel persisted, which was more direct with the infected person.

To keep the tests within the limits of the laboratory's capacity for analysis of pathogenic agents, at the time of the mass return of the community, in June 2022, the monitoring public was restricted to only outsourced workers and public servants. However, throughout the second semester, it was observed that the testing of workers was not reaching the capacity of the laboratory, making it possible, from the academic recess, in September, to resume testing of students and researchers, even if without wide disclosure of this fact.

2.4 Monitoring of SARS-CoV-2 in the different phases of the plan for the gradual resumption of face-to-face activities in the UFABC

Throughout the community monitoring period (between May 2021 and December 2022), UFABC administration presented several changes to the biosafety protocol, according to the epidemiological period experienced and the public policies in place at each moment.

There was a more restricted moment, when there was limited access to the campus, mandatory use of masks, and mandatory weekly testing. Throughout 2022, the classes were gradually taught face-to-face again, reaching totality in the third quarter. In June 2022, the university workers returned en masse. In September, the positive result for SARS-CoV-2 in the monitoring and testing at UFABC is no longer sufficient

Date	Federal	State	Municipal	UFABC
January 2020		Establishes the State Public Health Emergency Operations Center (COE-SP) of the São Paulo State Health Department and takes related measures (SS No. 13, of 1/29/2020)		
February 2020	Declares Public Health Emergency of National Importance (ESPIN) due to Human Infection by the new Coronavirus (2019-nCoV) Ordinance No. 188, of 2.3.2020			

Date	Federal	State	Municipal	UFABC
March 2020			Emergency period (Municipal Decree 21.111 SBC and 17.317, STA)	Suspends the academic and administrative activities of the University (ORDINANCE No. 378/2020 - REIT (11.01))
April 2020		Adds to Decree No. 64.881, of March 22, 2020 (which decrees quarantine in the State), an article recommending the use of masks by the population (No. 64.949, of 4/23/2020)		Establishes authorization for Emergency Continuing Studies (ECE) in Undergraduate and Graduate Studies (RESOLUTION No. 239/2020 - CONSEPE (11.99))
May 2020		Provides for the general and mandatory use of face protection masks, preferably non-professional ones, in public spaces, inside establishments, among others (N° 64.959, of 5/4/2020).	Establishes the obligation to wear masks (DECREE No. 21.157, of 06.05.20, SBC and Municipal Decree 17.370 STA)	
July 2020	Amends Law No. 13,979, of February 6, 2020, to provide for the mandatory use of personal protective masks for circulation in public and private spaces accessible to the public, on public roads and public transport, on the adoption of asepsis measures in places of public access, including public transport, and on the provision of sanitizing products to users during the validity of measures to deal with the public health emergency of international importance resulting from the COVID-19 pandemic (Law No. 19 of 7/2/2020)			Regulates the mandatory use of face protection masks on UFABC premises while the situation resulting from the COVID-19 pandemic persists (ORDINANCE No. 595/2020 - REIT (11.01)).

Date	Federal	State	Municipal	UFABC
November 2020				Art. 1st Approve the Plan for the gradual resumption of face-to-face activities at UFABC (DECISORARY ACT No. 188/2020 - CONSUNI (11.00.06))
January 2021			Beginning of return to face-to-face classes (DECREE No. 15.568 - STA)	
July 2021		Beginning of return to face-to-face classes (DECREE No. 65,849)	Return of face-to-face classes (DECREE No. 21.652 SBC;)	
March 2022				Suspends the Plan for the Gradual Resumption of On-site Activities at UFABC. Resumption of face-to-face activities in June 2022 (RESOLUTION No. 217/2022 - CONSUNI (11.00.06)).
April 2022	Declares the closure of the Public Health Emergency of National Importance (ESPIN) as a result of human infection with the new coronavirus (2019-nCoV) and revokes Ordinance GM/MS No. 188, of February 3, 2020 (Ordinance No. 913, of 4.22.			
September 2022				Updates biosafety guidelines and standards on campuses, in order to ensure the necessary safety conditions for carrying out face-to-face activities – need for a medical certificate for removal (ORDINANCE No. 2800/2022 - REIT (11.01)).

Date	Federal	State	Municipal	UFABC
October 2022				Updates biosecurity guidelines and standards on campuses, in order to guarantee the necessary safety conditions for carrying out face-to-face activities - Optional use of mask (ORDINANCE N° 2880 and 2882/2022 - REIT (11.01))
December 2022				Suspends, indefinitely, the activities of the UFABC Monitoring and Testing Center (ORDINANCE No. 2997/2022 - REIT (11.01)).

Main biosecurity measures adopted by the federal, state, municipal governments (of the municipalities in which the university is located), and by UFABC, respectively. Data were obtained from: https://www.planalto.gov.br/ccivil_03/Portaria/quadro_portaria.htm; https://www.saobernardo.sp.gov.br/web/transparencia/legislacao-relacionada; https://www3.santoandre.sp.gov.br/coronavirus/?page_id=90; https://www.saopaulo.sp.gov.br/coronavirus/legislacao/; https://www.ufabc.edu.br/acesso-a-informacao/boletim-de-servico.

Table 1.
Main biosecurity measures adopted by the government and UFABC.

for removal from face-to-face activities (requiring a medical certificate). At the end of October, mask wearing is no longer mandatory. At the end of December, the monitoring and testing center was demobilized.

It was possible to observe that the change in protocols, whether within the university or public policies (**Table 1**), had an impact on the community's behavior regarding testing. The formation of two, almost opposites, main groups stand out: one that, as the biosecurity measures were softened, felt more comfortable resuming their pre-pandemic behaviors; and a second group that, when they felt the community biosecurity measures decreased, started to reinforce their individual care, in an attempt to preserve protection against the virus.

By correlating the fluctuation in the number of tests performed and the protocol changes, some issues are observed: during 2021, at the time of greater restriction of access to the campus, the number of tests performed was more stable (average of 448 tests per week, with a standard deviation of 68), while in 2022, there was a much greater fluctuation in the number of tests (average of 757 weekly tests, with a standard deviation rising to 211) following important changes in biosafety protocols.

At the beginning of 2022, it was observed that the peak of the first wave occurred in the testing period, at which time there was also a progressive increase in the number of tests performed. Around April, we saw a drop in the number of tests, and this drop may have some correlation with the suspension of the "gradual plan to resume face-to-face activities at UFABC," approved by the superior council on March 31, 2022. In June, occurred the mass return of university workers, a period that corresponds to both the increase in tests carried out and the second wave of infection that occurred during the testing period.

At the beginning of September 2022 occurred the school recesses and a simultaneous drop in test taking. At the end of the recess (September 19, 2022), the end of administrative removals (automatic to the positive result of internal testing) was announced. At the end of October, the mandatory use of masks finished. In November, the third wave of infection began, which corresponded to a return to the increase in the number of tests carried out, which, this time, will jointly reduce the number of positive results.

The divergence of information disclosed, whether in the municipal, state, or federal public sphere, or in the private sphere, about the pandemic, also proved to be an important obstacle to community orientation and, consequently, the dissemination of correct, updated, and adequate information.

One of the main obstacles was related to the medical advice received by the community, both in the public and private networks. Several diagnoses were given based only on clinical examinations; misguided guidelines regarding the time and form of transmission of the virus; and lack of knowledge about the different types of tests available on the market, also leading to inadequate guidelines.

The lack of testing carried out in the health network also had a relevant impact on how the community received information about the positive result at UFABC. At first, the difficulty in obtaining tests meant that there was a greater demand for the test at the University, including by people who were not part of the community, making guidance and acceptance of the anxieties of the people involved valuable.

When antigen tests become more popular, including being used by almost all Brazilians public health system (SUS – Sistema Unico de Saúde) primary care facilities and made available in pharmacies to the general public, there was a mismatch of information regarding positive and negative results. As RTqPCR is more sensitive than the antigen test, there would be no sense in the latter being used as a counterproof of the former. However, the ease of access to the antigen test and the lack of adequate disclosure of its real effectiveness made the question continually arise "my test was negative outside UFABC, your test must be flawed."

There was also much difficulty in guiding the community regarding the importance of biosafety measures and the severity of the disease, as the government was already talking about the post pandemic moment, in which people should resume their normal activities and behaviors, now without risk. This situation is reinforced by the lack of testing and the high number of false negatives caused by inadequate testing. With regard to the severity of the disease, specifically, the advancement of vaccination and the consequent decrease in hospitalizations and, mainly, deaths, contributed with the message of "there is no more risk." The deletion of information regarding the existence of a long COVID and post-COVID is noted, leading the population to view SARS-CoV-2 as just another endemic virus, with which we must live without major consequences.

Despite the obstacles mentioned above, there are indications that, due to the monitoring carried out, the UFABC community, especially with regard to workers, remained more oriented and protected than the average population, showing little evidence of internal SARS-CoV-2 transmission.

2.5 Comparing the experience of UFABC community SARS-CoV-2 monitoring among other strategies around the world

When reviewing monitoring and testing, studies are concentrated in Europe, North America, and Central Asia. The scarcity of publications in South America and

India could, for example, be correlated with their high infection rates, suggesting low adherence to pandemic monitoring practices. However, Australia and New Zealand are countries that have high adherence to biosafety protocols and have not published literature on the subject [19].

Although there is an understanding that the best strategy is universal and high-frequency testing, many institutions do not have the financial conditions to carry it out [7], and, although testing has proven to be an essential instrument for mitigating contamination, it is not enough, needing to be complemented with the other measures already mentioned, such as the use of masks and ventilated environments [9].

It is interesting to note that, although universities and schools were called to resume their activities, the testing of students was controversial, especially at the beginning of the pandemic (2020), sometimes discouraged by the North American Centers for Disease Control and Prevention (CDC), or simply not advising about it [6, 17]. However, researchers had already warned that, without monitoring and testing, there would be a high probability of outbreaks [6], which in fact happened at the end of 2020. Several North American colleges and universities had outbreaks of COVID-19, thus deciding to initiate monitoring and testing programs [7, 8]. However, it is estimated that only approximately 6% of large American colleges and universities were able to implement mass testing in their communities, one of the causes being the high cost involved [7].

In the United Kingdom, for example, although the government at the time also did not recommend it, some universities implemented monitoring and testing of asymptomatic people to reduce transmission on campus. Cambridge University organized weekly RT-PCR pool testing; the University of Nottingham had weekly testing added to sentinel monitoring; University of East Anglia had a testing program that was known to virtually eliminate COVID-19 from its campus; and the University of Southampton implemented RT-LAMP testing in saliva samples, which monitored students and staff [16].

One way to make RTqPCR testing cheaper and faster is to combine collections from several individuals into a single sample, the so-called pooling test [22]. Studies have shown that samples with high viral load in an individual PCR test (CT $<$ 28) were detected after combining 5 or 10 samples; however, when the viral load decreases, there is an increase in the frequency of false negatives, especially in pools of 10 samples. Furthermore, subjects with CT $>$ 31 could not be detected in pools of 10, and CT $>$ 33 were not detected in pools of 5 [10]. Although there is this important loss of sensitivity of the test, a study carried out in Japan comparing individual RTqPCR and by combining several samples, suggests that, in a scenario of budget constraints when choosing more tests with less sensitivity, the probability of success of curbing the virus is larger [10]. However, it should be noted that, in a scenario such as that of UFABC, in which the incidence of positives reached more than 10% of the tests, pooling is no longer an interesting strategy, as it could lead to the need to retest all samples.

In the United States, Boston University carried out more than 500,000 COVID-19 tests in its monitoring [13]; Delaware *State University (publicly funded historically Black university*) tested twice a week, performing RTqPCR for all university students and workers between August 2020 and April 2021 [12]; at Berkeley, University of California, performed RTqPCR testing on almost 5000 participants [14]; and 18 university residential campuses in Connecticut performed monitoring, ranging from antigen testing, pooling PCR, or individual testing [6]. Duke University implemented mandatory testing twice a week for students residing on campus; Clemson University conducted its testing with volunteers; Olivet Nazarene University, in Illinois,

		Frequency	Type of sample and test
UK	Cambridge	Weekly	Pool RTPCR
	Nottingham	Weekly	Sentinel
	Southampton		RT-LAMP
U.S	Massachusetts		PCR
	Delaware	Twice a week	RTPCR
	Connecticut		Pool PCR, individual PCR or antigen
	North Caroline	Twice a week	
	Illinois	Twice a week	Pool RTPCR

Table 2.
Summary of types and frequency of SARS-CoV-2 testing at UK and US universities.

performed a pooling PCR test once or twice a week [5]. **Table 2** summarize some types and frequency of testing carried out in UK and US universities.

There is a complexity to be evaluated to ascertain the ideal frequency of testing, weekly testing, for example, may be sufficient to detect most infections but, perhaps, not enough to stop new contaminations [6, 20]. The model developed by the University of California suggests that when the prevalence of the virus is less than 1% of the population, universal and biweekly testing is sufficient to contain an outbreak [14]. In studies carried out on 18 residential campuses in Connecticut, it was evaluated that each week added per student implied a decrease of 0.0014 positive cases per student per week [6].

The testing carried out at UFABC proposed a weekly frequency to its participants, with a new sample when presented results were considered inconclusive. In the case of positives, at first a new sample was called after 14 days. For contractual reasons, some outsourced workers could not be removed for 14 consecutive days, requiring a new test after 7 days in symptomatic cases, or 5 days when asymptomatic. Monitoring these workers was essential for tracking the behavior of the virus over time. When the tests often started to come back negative before 14 days, it was decided to reduce the quarantine (and retest) from 2 weeks to 10 days.

It should be noted that, during the period of restricted access to the campus, there were members of the community who attended the University on time; in these cases, the recommended testing frequency was “whenever you are on campus, without exceeding one test per week.” However, in some specific situations, there was flexibility in allowing, or even requesting, more frequent testing, usually referring to suspected infection or viral load monitoring, as the dynamics of the virus changes greatly among the different variants [8]. This closer contact, as mentioned, was fundamental for the development of more accurate and effective protocols to combat the infection.

It was observed during monitoring, and corroborated by the results of other studies, that disease symptoms or severity are not associated with the viral load detected in the tests performed, that is, asymptomatic or pre-symptomatic subjects can present high viral loads, thus transmitting the virus [10]. Thus, testing and isolating symptomatic people is no longer interesting, leading to the need to test asymptomatic subjects so that it is possible to break the chain of transmission [5, 15, 16, 20]. In a North American emergency care unit, the transition from testing symptomatic to asymptomatic patients took, in a period of 7 months, from one of the highest prevalences of infection in the country to one of the lowest [18].

Research indicates that random testing of asymptomatic individuals has not been effective in containing outbreaks, whereas universal testing during the COVID-19 wave was effective in containing transmission in the workplace [19]. In universities, it was also found that random or voluntary testing was less effective than sample selection based on monitoring, for example [15].

It was observed that, in several situations, the budget difficulty was circumvented with strategies that restricted the number of people tested and/or reduced the sensitivity of the tests, as in the case of pooling, or with inappropriate use of antigen tests (which had been developed to use symptomatic screening, with confirmation by RTqPCR of negative results). The development of the testing protocol by the laboratory of pathogenic agents at UFABC managed to make the testing process cheaper and simpler.

Starting with the use of local inputs, passing through the use of simple and everyday materials, such as a plastic safety envelope (used by the post office), alcohol wipes (often used in the restaurant business, for hand hygiene), and flexible rods for babies. Paying special attention to these last two items because cotton was responsible for preserving the saliva sample, an essential factor for lowering the entire logistics of transport and pretest storage; also, allowing collection in small quantities contributes not only to ease for the user but also to a reduction in the contamination probability (both from the people who manipulate it and from the sample itself, thus protected from the action of RNases, for example). In this way, it was possible to structure a simple, autonomous test, accessible to a diverse public, with a molecular test of high sensitivity and specificity, using the SL 2 laboratory, in a university that does not have courses in the health area, therefore having a small number of professionals in the field area.

Although, given the effectiveness of vaccines, some institutions dismantled their testing programs [20], even after vaccination progressed, the rate of infection, hospitalization, and death from SARS-CoV-2 was still considered high, as the vaccine does not block transmission of the virus. Therefore, it is relevant to continue tracking, by testing, infected people who are asymptomatic or pre symptomatic, as while the virus circulates, new variants tend to emerge [10].

However, as mentioned, there is some difficulty in following through monitoring and testing amidst the erasure of the importance and severity of the consequences of SARS-CoV-2 infection. In monitoring a university in the United Kingdom, for example, there was a decline in participation in weekly testing from 58–5% of students [15]. At UFABC, it was possible to observe a decrease in adherence to testing, especially when administrative leave for employees and allowed absences for students ceased, and medical certificates were requested. In contact via WhatsApp, this became a recurring theme, whether from people questioning the reason for monitoring without automatic removal or from people inquiring about the need for testing with "the end of the pandemic."

2.6 Communication strategies used on SARS-CoV-2 monitoring and testing programs

In the literature review carried out on monitoring and testing programs, few mentions were made regarding the communication of test results, as well as the orientation of the people involved. **Table 3** summarizes some forms of communication adopted by monitoring carried out in the United Kingdom and the United States.

According to Kola et al.'s study [23], training in psychosocial support and mental health is now recommended for workers who make contact with those infected during

		Communication channel		Observations
		Positive result	**negative result**	
UK	University I	Email	Email	Multiple students encouraging testing
	University II	Telephone by health professionals	Texting	
U.S	Illinois	Own app	Own app	Add-on via email
	Boston	Telephone by health professionals	Email	Isolation of positives and their contacts
	Delaware	Email	Email	Guided to seek teleassistance
	NY	Telephone	Telephone	Advised to seek care in severe cases
	Clemson (rural area)	Telephone by health professionals	Email and texting	
	California	Telephone by health professionals and email	Email	Inconclusive contacted via telephone for new collection

References: United Kingdom I [15]; United Kingdom II [16]; Illinois [8]; Boston [13]; Delaware [12]; NY [11]; Clemson (rural area) [7]; California [14].

Table 3.
Communication used in tests carried out in the United Kingdom and United States.

infectious disease control, as it has proven essential to build a safe relationship with the community, strengthen their engagement in the adoption of biosafety protocols, and recognize the need for physical or mental health care.

Studies point to the pertinence of mental health interventions in the course of an infection, from the initial stages. Objective information about the disease – such as mode of transmission, course of infection, symptoms, quarantine and vaccines – is essential both for the promotion of mental health and for the population's literacy. Furthermore, it is understood that access to mental health can and should be complemented by information and communication technology (ICT) when face-to-face interaction is limited [24].

In research carried out focused on the response of middle and low-income countries to the pandemic, the creation of several programs based on previous humanitarian emergencies added to the peculiar characteristics of COVID-19 was raised. In China, for example, guidelines were created that suggested a decentralized and territorialized organization that included mental health support. In Lebanon, South Africa, Kenya, Uganda, India, and the Maldives, government action plans were created that highlighted the promotion of mental health for people in quarantine and frontline workers, and that ensured continuity of care for people already diagnosed with psychiatric issues [23].

As mentioned, and, as observed in North American and European teaching environments [17], the monitoring and testing measures implemented at UFABC led to the development of biosafety protocols and community guidance capable of making the monitored environment safer than the surroundings. There is an increase in positive cases in moments after socialization outside the school environment, such as holidays and vacations. Infections are detected but without leaving signs of large virus transmission chains, even pointing to lower infection rates than in situations where protective measures are not adopted [17].

Thus said, not only monitoring and testing itself but also the entire community orientation process is essential for the successful mitigation of SARS-CoV-2 infections. Although this consequence has been pointed out in several studies, there are few publications that dedicate space in their writings to mention or detail this process of guiding their audience.

3. Conclusions

WhatsApp web "monitor COVID" proved to be a valuable tool for contacting the community, providing a two-way street, in which health professionals have access to the public who, in turn, also have access to the professional, regardless of having tested positive for SARS-CoV-2. Thus, a humanized channel was constituted to receive the doubts and anxieties of the community, as well as contact and guidance regarding the biosafety protocols adopted at the university, and health issues in general. It is interesting to note that, unlike telephone contact, conversations carried out via WhatsApp are recorded for later consultation if necessary, and, unlike contact via email, it is possible to have a fluid conversation, bringing the interlocutors closer together and avoiding communication failures. Furthermore, this close contact with the community subsidized the monitoring by providing a rich and detailed collection of data.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

SBL2	biosafety level 2
CDC	Centers for Disease Control and Prevention
ICT	information and communication technology
RTqPCR	reverse transcription and chain reaction of the real-time polymerase
UFABC	Universidade Federal do ABC
WHO	World Health Organization

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Section 6

Epidemiology and Disease Prevention

Chapter 13

In-Hospital Mortality of Acute Myocardial Infarction

Lucas Ferrero

Abstract

Acute myocardial infarction (AMI), commonly referred to as a heart attack, is a life-threatening condition that occurs when blood flow to a part of the heart is blocked, resulting in damage to the heart muscle. According to the World Health Organization (WHO), it is one of the leading causes of death worldwide, with an estimated 8.9 million deaths in 2019, which represents 16% of the total deaths in the world. Early diagnosis and appropriate management of AMI are crucial for reducing morbidity and mortality. Since the 1960's, extraordinary progress has been made in its diagnosis and treatment, impressively reducing the in-hospital mortality of these patients from 26.7 to 7.2% in the latest reports of in-hospital mortality of AMI. In addition, each tool applied for the prevention and treatment of coronary disease has modified the mortality rates of the different types of coronary syndrome by changing the population that suffers from them. Nevertheless, some tools for risk stratification in patients with AMI still remain.

Keywords: acute myocardial infarction, mortality, epidemiology, evolution, Killip–Kimball classification, prognostic markers

1. Introduction

Coronary heart disease and its main complication, acute myocardial infarction (AMI), are major causes of morbidity and mortality worldwide. Its pathophysiology has been known for more than a century, but the bases of its treatment were established only a few decades ago. Despite advancements in the treatment and management of AMI, it remains a leading cause of mortality and morbidity globally [1].

In-hospital mortality, which refers to deaths that occur during hospitalization, is an important measure of the quality of care provided to AMI patients. Understanding the factors associated with in-hospital mortality is crucial for improving outcomes for AMI patients. This chapter aims to provide a comprehensive overview of the current knowledge on in-hospital mortality from AMI, including the risk factors, prognostic markers, diagnosis, and management, which have undergone great changes and advances in the last 60 years.

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2. Epidemiology

The epidemiology of in-hospital mortality from acute myocardial infarction is important to understand the burden of this disease on healthcare systems and patients.

Acute myocardial infarction is a common cause of hospitalization and death worldwide. The incidence of AMI varies by country and region, with the higher rates reported in developed countries. According to a study by the World Health Organization, approximately 100 million people worldwide suffer from AMI each year, and around 9 million die from this disease, which in 2019 represented 16% of the total deaths in the world [1].

Over the past few decades, there have been significant changes in the epidemiology of AMI. While the incidence of AMI should have declined due to improvements in the healthcare system and the development of new treatments for atherosclerosis factors, the worldwide incidence of AMI is expected to rise due to aging populations and an increase in risk factors such as obesity, diabetes, and hypertension, which will be discussed in the following paragraphs. The Global Burden of Disease (GBD) Study 2019 is an ongoing multinational collaboration to provide comparable and consistent estimates of population health over time. It shows that the prevalence of total cardiovascular disease (CVD) nearly doubled from 1990 (271 million) to 2019 (523 million), and the number of CVD deaths steadily increased from 12.1 million in 1990, reaching 18.6 million in 2019 [2].

With the advent of new drugs and procedures, the cost of treatment for a person suffering from AMI has multiplied in the recent years. Because of this, a disparity in the quality of care has been created among populations with socioeconomic differences, both between countries and within each country. These healthcare disparities begin to be an important discussion in the preparation of the different medical care guidelines. Both non-governmental institutions such as the WHO and those responsible for the health of each government should advocate for the right of every person to receive the best possible treatment in order to achieve equality in the population.

3. Risk factors

The risk factors for cardiovascular disease are diverse and multifactorial. Some risk factors are modifiable, while others are non-modifiable. Identifying these risk factors is crucial for developing effective prevention and management strategies for patients suffering from AMI.

Non-modifiable risk factors include age (the elderly are at greater risk), gender (men have a higher incidence of AMI up to age 60), family history, and genetics. Inside this category, the greatest change to consider in the last decades is the aging of the world population, which occurs mainly in the developed countries [3].

Modifiable risk factors are those that can be modified or controlled through lifestyle changes or medical interventions. These risk factors include smoking, physical inactivity, an unhealthy diet, hypertension, diabetes, obesity, dyslipidemia, and psychosocial factors such as stress, anxiety, and depression. Over the last five decades, there have been significant changes in the presence of these risk factors among the world's populations. Besides the decline in the prevalence of smoking in many countries, all other cardiovascular risk factors have increased in most countries of the world, both developed and developing [4]. According to the GBD Study 2019, here are some estimates of the global prevalence of some major cardiovascular risk factors in 2019 [5]:

- Tobacco use: 1.3 billion people (16.8% of the population).
- Unhealthy diet: 2.5 billion people (32.4% of the population).
- Obesity: 672 million people (8.7% of the population).
- Physical inactivity: 1.6 billion people (20.6% of the population).
- Harmful use of alcohol: 2 billion people (25.9% of the population).
- Diabetes: 463 million people (6% of the population).

These numbers may vary depending on how each risk factor is defined and measured.

4. Prognostic markers

Throughout the history of medicine and in each pathology that afflicts the human being, researchers have made an effort to predict the outcome, and for this, specific data are sought to guide us in this effort. Generally, the marker that prevails and is standardized in the largest number of medical centers is usually the easiest to determine. Risk stratification in patients suffering from AMI is a fundamental part of treatment decision-making, since drugs and procedures are not free of complications. Among the dozens of prognostic markers of in-hospital mortality, there are two that remain among the most reliable and used within the coronary unit: the ventricular ejection fraction measurement and the Killip and Kimball classification. This is mainly due to the ease of their determination and the fact that they represent the impact of myocardial ischemia and necrosis on cardiac function as a pump.

4.1 Ejection fraction

Ejection fraction (EF) refers to the percentage of blood that is ejected from the left ventricle with each heartbeat. It is a measure of the heart's pumping ability and is commonly assessed using echocardiography or other imaging techniques. The normal range for FE is 50–70%.

The use of ejection fraction as a marker for prognosis in cardiovascular disease has a long history. The concept of EF was first introduced in the early twentieth century by Frank and Starling. Then, in the 1950s and 1960s, advances in imaging technology, such as the advent of echocardiography, allowed for non-invasive measurement of EF in patients with cardiovascular disease. Researchers quickly recognized the potential of EF as a prognostic marker, and numerous studies were conducted in the following decades to investigate the relationship between EF and outcomes in patients with various forms of heart disease. The importance of fractional ejection in the prognosis of AMI lies in its ability to predict the risk of adverse outcomes, including heart failure, recurrent myocardial infarction, and death. Patients with a low EF are at higher risk and may benefit from more aggressive management strategies, such as early revascularization, aggressive medical therapy, and closer monitoring. On the other hand, patients with a preserved EF may have a lower risk of complications and may be managed with less aggressive strategies [6].

In addition to its prognostic value, EF is also an important parameter for assessing the response to treatment in patients with AMI. An improvement in EF following revascularization or other interventions is associated with a better prognosis and may guide ongoing management decisions.

4.2 Killip and Kimball classification

One of the first advances in the treatment of AMI was the creation of the coronary unit proposed by the researchers Killip and Kimball in 1967, who also introduced the classification that bears their names and clinically divides patients with acute myocardial infarction according to the degree of heart failure on hospital admission (**Table 1**) [7].

The Killip and Kimball (KK) classification was revalidated by multiple trials over the years [7–12], which remains current despite multiple advances in the treatment of patients with AMI. This validity is not common in areas of medicine with such radical and important changes as emergency cardiology.

Although the correlation between greater heart failure and greater mortality was maintained, the overall and group mortality of patients with AMI has decreased considerably, as it can be seen in **Table 2** and **Figure 1**.

In addition to what can be observed in the decrease in mortality rates, the incidence of presentation of the different groups of KK has evolved since their initial presentation.

Group	Definition
A	Patient without clinical signs of heart failure.
B	Patient who presented rales on lung auscultation, R3 on cardiac auscultation, or jugular venous distention on hospital admission.
C	Patient admitted with acute pulmonary edema.
D	Patient admitted with cardiogenic shock (SBP < 90 mmHg and signs of peripheral hypoperfusion).

Table 1.
Killip and Kimball classification.

KK Group	Original KK trial (1967) [7]	GISSI Trial (1987) [8]	KK in AMI (2001) [9]	KK meta-analysis (2003) [10]	CAMI – NSTEMI (2018) [11]	KK in Argentina (2022) [12]
A	6%	6%	2%	3%	3%	3.5%
B	17%	15%	7%	9%	9%	6.9%
C	38%	30%	19%	14%	12%	25%
D	81%	17%	Not included		31%	57.1%
Total	27.6%	8.7%	—	—	5.92%	7.2%

Table 2.
Comparison of mortality rates according to the KK classification.

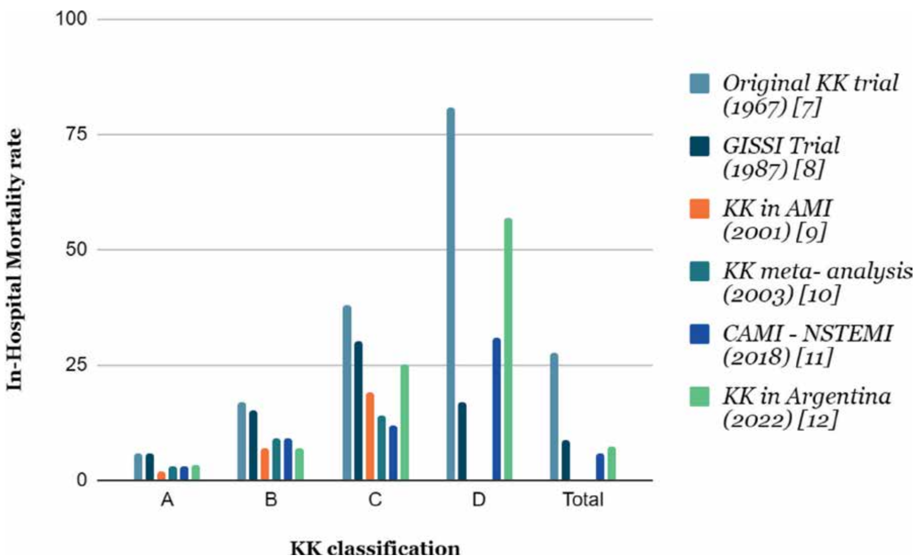

Figure 1.
Comparison of mortality rates according to the KK classification.

Cardiogenic shock presentation (KK group D) is more frequent in patients with ST-segment elevation myocardial infarction (STEMI) compared to patients with non-ST-segment elevation myocardial infarction (NSTEMI), but the overall incidence is declining. The differences between the two AMI subtypes may be due to differences in their pathophysiology: Patients with STEMI have acute occlusion of a coronary artery with sudden ischemia and immediate impairment in function of the affected area of myocardium, which, of sufficient magnitude, can cause such a drop in ejection fraction to cause a drop in blood pressure and the installation of a state of cardiogenic shock, while patients with NSTEMI usually have a gradual progression of coronary obstruction, which allows the myocardium to adapt and not suddenly lose a large percentage of its contractile strength. The increasingly lower incidence of cardiogenic shock in patients with AMI is mainly due to the intention of rapid revascularization that international guidelines demand.

Groups B and C of the KK classification have a higher incidence among patients with NSTEMI, who usually have chronic myocardial ischemia before suffering the acute event, while group A (without heart failure) dominates the world of AMIs today in most of the world. Among the reasons that can be included, in addition to the advances in coronary reperfusion, is the greater and faster access to treatment for an increasing part of the world population [12].

5. Risk scores

The timely assessment and management of patients with AMI are critical to reducing morbidity and mortality. Risk stratification is an essential part of the evaluation of patients with AMI, as it helps identify those who are at a higher risk of complications and mortality. Several risk scores have been developed to predict the risk of adverse outcomes in patients with AMI, including the “Global Registry of Acute Coronary Events” (GRACE), “Thrombolysis in Myocardial Infarction”

(TIMI), and "Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines" (CRUSADE) scores [13–15].

The GRACE risk score is a well-established tool that predicts the risk of death and major cardiovascular events in patients with AMI. The score is based on eight clinical variables, including age, heart rate, blood pressure, serum creatinine, Killip class, cardiac arrest at admission, ST-segment deviation, and elevated cardiac enzymes. The score ranges from 1 to 372, with higher scores indicating a higher risk of adverse outcomes [13].

Similarly, the TIMI risk score is another widely used tool for risk stratification in patients with AMI. The score is based on seven clinical variables, including age, heart rate, systolic blood pressure, Killip class, ST-segment deviation, cardiac arrest at admission, and the presence of three or more risk factors for coronary artery disease. The score ranges from 0 to 7, with higher scores indicating a higher risk of adverse outcomes. Both scores have been validated in several large cohorts of patients with AMI and have been shown to be strong predictors of mortality and other adverse outcomes [14].

On the other hand, the CRUSADE risk score is a newer tool that was developed specifically for patients with non-ST-segment elevation acute coronary syndrome, which includes unstable angina and NSTEMI. The score is based on eight clinical variables, including age, heart rate, systolic blood pressure, serum creatinine, Killip class, cardiac arrest at admission, the presence of ST-segment deviation, and the use of glycoprotein IIb/IIIa inhibitors. The score ranges from 1 to 100, with higher scores indicating a higher risk of bleeding complications, and it is used as an antagonist to balance the risks and benefits of anticoagulant treatment in each patient [15].

6. Evolution of AMI diagnostic criteria

Over the past century, the diagnostic criteria for AMI have changed multiple times, driven by advances in technology, changes in our understanding of the pathophysiology of the disease, and a growing recognition of the importance of an early and accurate diagnosis.

The diagnosis of AMI has been a challenge for clinicians throughout the history of medicine, with early descriptions of the disease dating back to ancient times. However, it was not until the twentieth century that significant progress was made in understanding the pathophysiology of AMI and developing effective diagnostic tools. The early diagnostic criteria for AMI were based on clinical presentation, ECG findings (such as ST-segment elevation or depression), and serum biomarkers such as glutamic-oxaloacetic transaminase (GOT), lactate dehydrogenase (LDH), and glutamic pyruvic transaminase (GPT). Then, these general biomarkers of damage were replaced with creatine kinase (CK) and its MB isoenzyme (CK-MB). However, these were also limited by their lack of specificity and sensitivity, as CK and CK-MB can be elevated in other conditions [16].

In the 1980s, the use of troponin as a biomarker for AMI diagnosis began to gain acceptance. Troponin is a cardiac-specific protein that is released into the bloodstream in response to myocardial injury. Unlike CK and CK-MB, troponin is highly specific for myocardial injury and is not affected by skeletal muscle injury. The introduction of troponin led to the development of the Universal Definition of Myocardial Infarction, a consensus document of The Joint European Society of Cardiology and

The American College of Cardiology, which was first published in 2000 and has been revised several times since then. The Universal Definition established the use of troponin as the preferred biomarker for AMI diagnosis and defined a rise or fall in troponin levels as a key diagnostic criterion [17].

More recently, high-sensitivity troponin assays have become available, which allow for an even earlier and more accurate diagnosis of AMI. These assays can detect very small amounts of troponin in the bloodstream, allowing diagnosis within a few hours of symptom onset and, furthermore, the diagnosis of small infarcts that would not be recognized with the use of less sensitive markers [18].

This is how patients diagnosed with AMI have changed throughout history, mainly due to progress in the detection of increasingly sensitive and specific biomarkers. In summary, currently a large number of patients who decades ago were not considered to have AMI are diagnosed with this pathology and therefore treated in a better way.

7. Evolution of AMI treatment

The treatment of AMI has undergone significant evolution over the past few decades, with advances in medical technology and research leading to the improved outcomes for patients.

The treatment of AMI has undergone significant evolution over the past few decades, with advances in medical technology and research leading to the improved outcomes for patients. In the past, treatment for AMI was primarily focused on managing symptoms and reducing the risk of complications. However, with the introduction of new therapies and interventions, the goal of treatment has shifted to restoring blood flow to the affected area of the heart as quickly as possible. One of the most significant advancements in AMI treatment has been the widespread adoption of percutaneous coronary intervention (PCI), also known as angioplasty. This procedure involves inserting a catheter into the blocked coronary artery and inflating a small balloon to open the artery and restore blood flow. This is often accompanied by the placement of a stent, a small metal mesh tube that helps keep the artery open. The use of PCI has been shown to significantly reduce the risk of death and major complications in patients with AMI. In addition, advances in technology and techniques have made PCI safer and more effective, with faster procedural times and lower complication rates [19].

Another important development in AMI treatment is the use of pharmacological therapies to prevent and treat blood clots. Antiplatelet and anticoagulant medications, such as aspirin and heparin, can help prevent the formation of blood clots that can lead to a new or more severe AMI. Newer agents, such as P2Y12 inhibitors and direct oral anticoagulants, have also been developed and shown to be effective in reducing the risk of recurrent events [20].

In addition, cardiac rehabilitation programs have become an important component of AMI treatment, helping patients recover and reduce their risk of future cardiovascular events. These programs typically include exercise, dietary counseling, and lifestyle modifications and have been shown to improve quality of life and reduce the risk of death and hospitalization [21].

Overall, the evolution of AMI treatment has been marked by significant improvements in patient outcomes and quality of life. With continued research and development, it is likely that new and even more effective therapies will be developed to further improve the management of this serious condition.

8. Mortality rate according to the type of AMI

There are two main types of AMI: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). STEMI is characterized by a complete blockage of a coronary artery, while NSTEMI involves a partial blockage. The incidence of these two types of AMI has changed differently over time [22].

In the past, the incidence of STEMI was higher than that of NSTEMI. However, over the past few decades, this trend has been reversed [23]. The increase in NSTEMI incidence can be attributed to a variety of factors. In particular, the use of high-sensitivity cardiac troponin assays has allowed for earlier detection of myocardial injury, leading to a more frequent diagnosis of NSTEMI. Additionally, the increasing prevalence of risk factors such as diabetes and obesity, associated with greater and longer survival of patients with atherosclerotic disease, may be contributing to the rise in NSTEMI incidence.

The treatment and prognosis are also different between STEMI and NSTEMI, and as such, it is important to examine mortality trends separately. For most of human history, the mortality rate associated with AMI was high, with STEMI having a significantly higher mortality rate compared to NSTEMI. However, the advances in medical technology and treatments mentioned above have led to significant improvements in outcomes for both types of AMI, with the mortality rates of these AMI subtypes equalizing and even reversing, according to some surveys.

According to an English study examining long-term trends in incidence and case fatality rates at the AMI hospital, by 2005, the odds of dying within 1 year after discharge were 50% lower among STEMI patients in comparison with those admitted in 1997, and a nonsignificant trend toward lower odds of dying within 1 year of hospitalization was noted among patients with NSTEMI [24].

In the English study previously mentioned, mortality from NSTEMI remained higher than STEMI. These can also be seen in the results of a small Argentine survey, represented in **Table 3** and **Figure 2** [12].

The higher death rates in STEMI patients may have resulted from the fact that those patients were older, had a greater burden of cardiovascular comorbidities, and were more likely to have 3-vessel coronary disease or not revascularizable disease. This also may explain why doctors may have been less aggressive in managing NSTEMI patients due to concerns about adverse effects, culminating in the underutilization of effective cardiac medications and PCI as well as greater delays in the time to receipt of PCI in patients with NSTEMI.

KK Group	STEMI In-Hospital death/ total (mortality rate)	NSTEMI In-Hospital death/ total (mortality rate)	All AMI In-Hospital death/ total (mortality rate)
A	0/47 (0%)	4/65 (6%)	4/112 (3.5%)
B	0/11 (0%)	2/18 (11%)	2/29 (6.9%)
C	0/0	1/4 (25%)	1/4 (25%)
D	4/7 (57%)	0/0	4/7 (57.1%)
Total	4/65 (6.1%)	7/87 (8%)	11/152 (7.2%)

Table 3.
Comparison of mortality rates according to the KK classification and type of AMI.

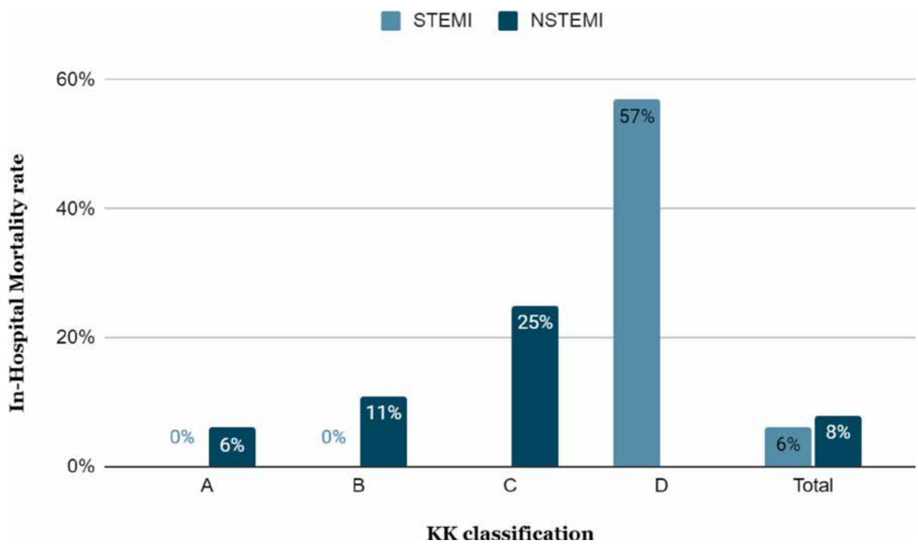

Figure 2.
Comparison of mortality rates according to the KK classification and type of AMI.

In conclusion, in addition to showing an increase in the representation of NSTEMI among patients with AMI, the above allows us to assume that the differences in mortality in hospitalized patients with STEMI and NSTEMI are strongly related to the clinical characteristics of the patients and less to the presence (or absence) of ST segment elevation. Therefore, by modifying the populations (affected by progress in the treatment of risk factors, the diagnosis of AMI, and its treatment), the mortality of patients with AMI changed to the point where currently the mortality of NSTEMI is equal to or higher than STEMI.

9. Perspectives on the future of AMI mortality

As we have already established, the in-hospital mortality of patients with AMI has been decreasing over the last 50 years thanks to advances in the prevention, diagnosis, and treatment of these patients, but many challenges still arise. An example of adversity to overcome is the inequality between populations with higher incomes and the most deprived population, which are not only exposed to more environmental risk factors but also do not usually have access to the new treatments that scientific progress constantly provides, both in the treatment of these risk factors (such as atherosclerosis) and in the treatment of patients suffering from AMI [25].

Looking ahead, there are several promising areas of research that may further improve the outlook for AMI patients. These include the development of new medications and therapies that target specific mechanisms involved in the pathophysiology of AMI, as well as advances in precision medicine that can help tailor treatments to individual patients based on their genetic and clinical characteristics.

Overall, while significant progress has been made in the prevention and treatment of AMI, there is still much work to be done to reduce the morbidity and mortality associated with this condition, particularly in underserved populations. Continued investment in research, prevention efforts, and access to quality healthcare will be essential to improving the outlook for AMI patients in the future.

10. Conclusion

Years of research and scientific progress added knowledge and tools for its treatment, considerably lowering the mortality rates, but the Killip and Kimball classification and fraction ejection measurement continue to be a prognostic marker of in-hospital mortality, retaining their clinical importance decades after their first implementation. Its ability to predict the risk of adverse outcomes, guide risk stratification, and assess the response to treatment makes it a valuable tool for clinicians managing patients with this life-threatening condition. Understanding the importance of prognostic markers in the context of AMI can help clinicians make informed decisions and improve patient outcomes.

Continued efforts to improve prevention, early detection, and personalized management strategies for all patients with AMI are crucial in reducing mortality rates and addressing disparities in outcomes between AMI subtypes.

Conflict of interest

The authors declare no conflict of interest.

Thanks

I want to thank my family for accompanying me and being a pillar both in my professional career and in my personal life, and to my wife for her patience and permanent support.

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Chapter 14

Multivariate and Epidemiological Analysis of a Complex Problem: Bovine Abortion

Paula Gädicke and Alvaro Ruiz

Abstract

Bovine abortion generates economic losses in herds. When finding its causes, only infectious elements are usually analysed, and a diagnosis is obtained for nearly half of the cases. It is necessary to handle the problem in its multicausality by considering both infectious and non-infectious elements and to identify the causal patterns that affect each herd. This is the only way to achieve a significant reduction of the problem. There are epidemiological tools to suitably characterise the problem and identify the different factors that may be involved. This multivariate approach can serve as a model of analysis for other problems with compound causes.

Keywords: epidemiology, bovine, abortion, multivariate, economic

1. Introduction

One of the challenges that the dairy industry faces is the occurrence of bovine abortion, which reduces the amount of milk that can be obtained and the number of possible replacements for the herd. This serious problem affects the productivity and profitability of dairy farms [1], as it reduces the potential number of heifers for replacement and milk production and increases the costs associated with feeding, treatments, insemination and premature culling of animals. It also constitutes a challenge for the veterinary profession [1, 2].

The studies that examine bovine abortion vary in many aspects, such as the epidemiological indicators and definitions they use. They also differ in how they present their results, how they calculate risk factors, and especially how they define important events. It is necessary to clearly distinguish between factors at the animal and herd levels, which may be associated with different production systems [3].

The most commonly used methodologies for quantifying abortions in epidemiological studies on the subject are characterisation using the proportion of abortions and crude and specific abortion density rates, while survival analysis is used to identify periods of greatest risk and describe the abortion risk function. Modifications have been made to this method to consider abortions that are repeated from one period to another [3].

2. Bovine abortion as a syndrome

A syndrome is understood as a set of phenomena that characterise a specific situation. In the context of bovine abortion, a combination of several factors is required for foetal death to occur, which implies different types of causal mechanisms, which can act independently or interact with each other [4]. In addition, there may be a long interval between exposure to the cause of the abortion and its observation [3].

There are several published studies that report different aetiologies of abortion, especially those of an infectious nature. However, there is not enough information that addresses the bovine abortion syndrome in an integral manner, despite numerous studies demonstrating its multifactorial aetiology [5]. Infectious agents can be responsible for decreased ovulation rates, fertilisation, embryonic survival, foetal and perinatal survival; however, some signs of reproductive diseases may be similar to genetic abnormalities, the effect of toxins or physical trauma [2].

Depending on the predominant aetiology or combinations thereof in a herd or geographic region, the foetal survival curve will have different patterns. When analysing foetal survival curves—for example, if a peak is obtained in the curve at a stage of gestation—a predominant abortion mechanism can be suspected; bi- or trimodal curves may indicate more than one aetiology or their combination [6]. In addition, the foetal survival curve for cows with different characteristics (age and history of previous abortions) may vary within the same farm by showing a similar shape but at a different level [7]; however, very good quality data is needed to estimate these effects.

In general, research addressing the issue of bovine abortion at the national level focuses on the study of a particular pathology and does not analyse the presentation of these diseases in relation to herd or animal factors. It is necessary for study designs to allow inferences to be made to the general population, or to specific strata thereof; it is also important that they allow for the joint analysis of factors and infer causal relationships rather than statistical associations, for which prospective studies with adequate comparison groups are required [8].

3. Epidemiological tools for bovine abortion quantification

To clearly explain the abortion indicators used in a study, it is necessary to have the following aspects defined as precisely as possible [1]: definition of an abortion case, period at risk of aborting, technique used to diagnose pregnancy and the cow's status at each control check, identification of cows and date of service or artificial inseminations and their repetitions, identification of cows that have been diagnosed pregnant, date of previous delivery, date of termination of the risk period or follow-up of each cow.

It is necessary to resort to the inspection and interpretation of reproductive records in order to detect unnoticed abortions and thus ensure that the numerator of abortion epidemiological indicators reflects the reality of the herd. It is useful to perform an analysis of intervals between artificial insemination or heat repetitions, as there could have been a foetal death if heat or insemination is repeated more than 42 days after the last insemination/heat, since repetitions close to 21 days may correspond to no conception or embryonic death before the maternal recognition period [9]. Repetitions between 21 and 42 days would correspond to embryonic and not foetal mortalities, provided that heat detection is perfect. The interpartum interval less than 260 days or short lactations, that is, less than 8 months, may be indicators that the cow dried up earlier than due, among other causes, due to cessation of gestation. It is also important to review the gestation status of cows that have already been diagnosed as pregnant and that present heat, since the presentation of heat behaviour can be normal in approximately 5% of pregnant cows [10].

Studies analysing the occurrence of SAB agree that there is little accuracy in the gestational age assigned to abortions because the occurrence of the event can be much earlier than the physical manifestation in the cow: return to cyclicity or expulsion of the foetus [11]. This means that most early abortions are not observed, and late ones are observed. In addition, the lack of etiological diagnosis is a problem in most of the cases that are analysed. There are biases from when abortion samples are sent to diagnostic laboratories, to the fact that most of the causes sought as diagnosis are infectious [9]. In designing studies that quantify this syndrome or identify risk factors, the population at risk, event definitions and analytical procedures to be used should be clearly established, since the main inconsistencies when making comparisons between studies are given by these inaccuracies. In addition, clarity should be given to possible associated biases that may exist, for example, to the selection pressure exerted on herds by eliminating cows that have aborted. On the other hand, studies should take into account that the risk of abortion is higher in early gestation [12] and that only considering those abortions that are visually detected underestimates the actual amount produced.

Descriptive epidemiology provides useful tools for defining and quantifying a situation and understanding the nature of a problem. The most commonly used indicators for quantifying abortions in a herd are the proportion of abortions, the incidence of abortions and, for quantitative analysis, survival analysis.

3.1 Proportional abortions rate (PAR)

This is the indicator that requires more general information and is the one that is most frequently used. This should be calculated considering in the numerator the abortions that occurred and in the denominator, the total number of pregnancies in a given period, for example, during 1 year. It can be used in crude form (based on all females) or stratified by age, breed, production level, etc. [13]. Although this measure is objective and provides information about the subgroup of animals where the problem is concentrated, it says nothing about its dynamics. It can be very useful for characterising the herd in a general way or for making evaluations after some intervention; however, it is not the appropriate tool for detecting causal associations in problem herds. This indicator has no bias with respect to the distribution of risk in gestation; it can be determined for a cohort or in a contemporary life table, where it is quantified for each interval of the risk period. The PA should be calculated according to the conditional probability that a cow will not abort before 260 days of gestation [1].

3.2 Abortion incidence rates (TIA)

This is the most appropriate morbidity indicator for characterising the dynamics of an event occurrence since it indicates the number of new events in defined populations and periods. In the numerator are counted new cases of abortion that occur within a given period within a group of animals that are at risk of this happening. The incidence rate can have a bias regarding the representation of risk in periods that are overrepresented by cows in gestational states not normally associated with any risk of abortion [1].

The choice of statistical model for studying a disease is directly related to the assumptions that must be met in them according to the biology of the problem. The results of statistical analysis are a function of the data and assumptions used; therefore, it is necessary to analyse whether the assumptions of the chosen model make sense with the true population structure of the variable studied since if different assumptions are made about the data, the results will be different [14]. The distribution of abortion occurrence time is not symmetrical and is commonly bi- or trimodal [15], so it is not appropriate to analyse it with linear regression [16].

Survival models are appropriate for analysing this type of data, which allow the characterisation of abortion events as a function of the time at which they occur by estimating the foetal survival function and the risk function of a foetus dying. It is a very useful tool for studying the association between different factors and the risk of an event occurring, in this case, abortion, adjusting the different times at risk in which different animals contribute during the observation time [8]. Logistic regression models can be used to analyse the probability of a cow aborting. It is possible to form a multivariable model to jointly analyse the effect of different factors [8]. The indicators of survival models and logistic regression models can be interpreted as risk indicators; however, if information on the timing of abortion is available, survival models use a more adjusted denominator in risk indicators [17].

Given the possible lack of a temporal relationship between abortion and the cause that produced it, it is difficult to obtain precise data on the occurrence of abortions to find a causal association. This leads to the need to try to maintain farm records of possible abortion risk factors so that a thorough retrospective farm analysis can be performed when an abortion occurs. To implement an effective disease surveillance system, at least the following is needed: to have an adequate monitoring method that allows the rapid detection of events of interest, to define and evaluate results in relation to time, to establish a criterion that allows concluding that the indicators obtained in a herd or area are higher than expected. It is usual for monitoring the risk of abortion in a calendar period to be done through PA and/or TIA [11]. A traditional alternative is to establish the Endemic Curve and the Endemic Index of abortion presentation with retrospective data [13].

4. Frequency and risk factors of bovine abortion, the case of central south of Chile

Bovine abortion is an important topic in herd management. There are several determinants that give rise to a loss of gestation. Quantifying abortion occurrence using means of observed abortions underestimates the real situation since observed foetal losses are approximately 20% of the total foetal losses. Frequency estimations of cumulative foetal loss after pregnancy diagnosis in dairy cattle that includes observed and unobserved losses vary from 3.6% to 10.6% [3].

The authors used historical data from 77 dairy farms in southern Chile (Bio-Bio, Los Lagos and Los Ríos regions) that were collected over a period of 5 years (2001–2005) [3]; the data consisted of 44,959 lactations from 20,977 cows. Moreover, the authors evaluated the farm management practices by administering a questionnaire to

127 farms. The farms were chosen based on the owners' consent and the availability of high-quality electronic records verified by practitioners who advised the farms.

To calculate the observed, inferred and total abortions, we used two measures: the *Proportional Abortion Rate (PAR)* and the *Density Incidence Rate (DIR)*. These measures show the frequency distribution of abortions in different populations and time periods [3]. The association between the DIR and individual lactation characteristics (number of lactations, year of beginning lactation and trimester of gestation in which the abortion occurred) was assessed using a conditional logistic regression model. A forward approach was used for including variables in model building, and the likelihood ratio test was used for assessing the goodness of fit of the models. One-way interactions and confounding variables were also tested. To investigate the association between herd management and lactation factors and the occurrence of abortion events [3], the authors applied a hierarchical logistic regression model with a random intercept. This model allowed us to account for the clustering of cows within herds and to estimate the variability in the abortion risk across herds.

A common problem in the study of abortion rates in livestock is the reliance on farmers' own records, which often underestimate the actual number of cases. This can lead to inaccurate estimates of the prevalence and impact of abortion on animal health and productivity. A considerable number of possible cases of abortion might be recovered by analysing the reproductive records in more detail. If we had analysed observed abortions only, we would have detected just 17.8% of total cases. We found a PAR for general abortion of 11.6% and a DIR of 1.7% per cow-month. General abortions were highest in first parity cows (PAR: 14.6%, and DIR: 1.9% per cow-month). The frequency of non-observed abortions decreased as the gestation period progressed, while the frequency of observed abortions increased with the gestation time. The foetal period around 40 days (corresponding to 82 gestation days) was the most critical for the risk of abortion [3]. These results suggest that different factors may affect the occurrence and detection of abortions at different stages of pregnancy. Such patterns of occurrence are different from those found in other production systems worldwide. The PAR in studies that included both observed and unobserved foetal losses varies widely, from 3.6% to 10.6% [1] and 10.2% [18]; our findings (11.6%) are at the upper limit of that report [3].

For parity and trimesters of gestation, we found different patterns of occurrence than in other production systems around the world and some evidence suggesting some potential factors associated. A previous abortion in the same lactation was observed in 9.2% of the cows that aborted, lower than the value for the general population (12.6%). A lower proportion of aborted cows was observed for cows with a history of abortion in the same lactation by parity 1, 2, 3, ≥4: 9.9%, 9.6%, 9.0% and 7.7%, respectively, compared with cows without a history of abortion by parity: 12.3%, 11.6%, 11.3% and 10.9%, respectively. Furthermore, for observed abortion cases, we found an increased trend across gestation that could nonetheless be associated with the fact that it is easier to observe an aborted foetus or signs of the cow in late gestation [12].

We observed that the probability of finding any type of abortion was lower during the second and third trimesters, with respect to the first gestational trimester. Previous studies showed that the highest risk of abortion for cows occurred during the first trimester, and it was related to the rate of twins and damage due to palpation [10]. In contrast, others reported a peak in incidence during the second trimester [19]. These differences may reflect variations in the detection time between studies.

A cow with an unobserved abortion would likely be detected sooner in herds with better oestrus detection; therefore, it might be a reflection of better management practices as well [12]. In addition, depressed progesterone secretion during the early foetal period and cows carrying twins [18] could influence abortions in this period, as well as excessive loss of body condition during early lactation related to metabolic and infectious diseases [19].

Other reports [7, 11] found a higher proportion of abortions than our study in cows with a history of previous occurrence of abortions. Our findings can be interpreted as a consequence of immunity protection for some infectious components. Protection against the recurrence of abortion would be expected in some infectious diseases like brucellosis, *Campylobacter fetus*, leptospirosis, BVDV infection and IBR infection [19, 20]. Although the studied herds were brucellosis-free, the other agents are prevalent abortion causes in southern Chile [21]. Vaccines against common infectious diseases do not seem to be a solution for reducing the incidence of abortions in a herd, except for the use of the Leptospira vaccine in special conditions of the herd. The above suggests an infectious and non-infectious component in the causal network [5].

The results from studies based on reported cases of abortion should be approached with care due to potential biases such as only analysing the cases of abortion submitted to the lab or searching mainly for a limited number of infectious agents. A definitive diagnosis is not always possible in veterinary diagnostic laboratories. In fact, only 30–55% of submissions result in a clear diagnosis [22]. This could imply a bias if the diagnosed causes of abortions (which occur in late gestation and are then observed) are extended to all gestational losses (early and late). Serological studies have been complemented with other analyses which were not totally successful in identifying an etiologic cause.

The role of common infections causing abortion in a region, as investigated by serology, was inconclusive, while additional etiological diagnoses were made in 31% of foetuses analysed by pathology and microbiology. When associations were found between the serologic results of the dams and the histologic lesions in the foetus, the results of the laboratory tests and the epidemiological investigation suggested that multiple pathogens were involved in the bovine abortion cases. Therefore, the hypothesis of a single etiological agent could not be confirmed. However, histologic lesions were found in only 62% of the analysed foetuses [22].

Based on the information regarding infectious causes and considering the above bias, the principal infectious agents reported as causing abortion in countries with a pasture-based system for milk production have been the following: In Argentina: brucellosis, *C. fetus*, *Escherichia coli*, bovine herpes virus, BVDV, neosporosis (NEO) [23, 24].

There are management measures in herds related to the level of abortions that could be grouped as factors associated with infectious diseases, production system intensity and nutritional aspects [3]. A tap drinking system for cows was found to reduce the likelihood of abortion in herds (OR: 0.74) compared to a herd that does not have a tap drinking water system for cows. The presence of some contaminants, such as nitrites, has been reported in southern Chile, which can reach groundwater through leaching and thus contaminate drinking water. On the other hand, a possible cause could be related to the transmission of some infectious diseases, like leptospirosis (serovars of *Leptospira interrogans* and *Leptospira borgpepetseni*), which is endemic in the area [25]. We adjusted the effect of vaccination against leptospirosis with the interaction term, and our findings support the idea that leptospirosis participates in the network of factors related to Bovine Abortion Syndrome (BAS). Also, we found a positive association between the practice of rodent control in food storage and the proportion of abortion in herds (OR: 1.61). However, one should not conclude that vaccination decreases the risk of abortion, but rather it is a consequence of high-level abortions in the herd. Another interesting finding [26] was the absence of a protective effect against abortion by *using vaccines* against other common diseases that cause abortion, such as BVDV, IBR and *Neospora caninum*. Although these agents are prevalent in the south of Chile and other neighbouring countries [21], the results contradict the common belief that vaccination programmes are effective for controlling abortion problems in herds [27, 28]. This highlights the complexity of the issue and the need for further research to understand the underlying factors and develop effective prevention strategies.

It is interesting to note that certain management practices were found to be associated with a decreased risk of abortions in herds. For example, the *use of a bull versus artificial insemination only* was associated with a lower risk of abortion (OR: 0.73). This may be related to improved reproductive efficiency, such as oestrous detection [29]. The results of [22] showed that abortion did not have a significant effect ($p > 0.05$) on the total amount of milk produced by the cows until 120 days after giving birth. This is consistent with previous research that reported a positive relationship between abortion and milk production around the time of artificial insemination for single pregnancies [26]. A potential reason for the discrepancy between the results is that one of the investigations only accounted for the mortality of embryos and foetuses, whereas the others also considered the foetal stage. This implies that the former study had a narrower scope and a different definition of pregnancy loss than the latter ones, which could affect the comparison and interpretation of the findings. Moreover, higher milk production has been reported as a significant factor for the rise in the twinning rate, and twin-bearing cows have a higher chance of losing their pregnancy [26].

It is interesting to note that the exclusive use of pasture for cows was associated with an increased risk of abortion (OR: 1.87) [26]. This could be related to mineral supplementation in cows (OR: 0.56). Although dairy farms in the area studied still adopt relatively extensive production systems, those not using any supplement may be related to low-yielding herds, which have the worst reproductive performance and nutritional problems. Cows with better body conditions have better reproductive performance than those with poor body condition [30]. Additionally, vitamin and mineral deficiencies have been described as being related to reproductive diseases, and cows fed with an adequate grass supply show better reproductive performance [31]. The β-carotene plasma level affects the corpus luteum function, and plasma levels of β-carotene in cows are affected by their feed [32].

Fresh plants have more carotene than preserved ones. Carotenoids in feedstuffs like hay, straw, fodder, etc., lose a lot of their content during the preservation and storage process [33]. For this reason, it would be very interesting to analyse the carotenoid plasma level and the metabolic, energy and protein balance at the cow level and its relation to abortion to elucidate the possible role of nutritional aspects in the incidence of abortion.

According to the results of [26], the problem of Bovine Abortion Syndrome (BAS) in the stratum studied, which includes medium to large dairy herds from southern Chile, is significant. The study also revealed that there is a large underestimation of abortion rates caused by only analysing farmers' records of abortion. This highlights the importance of using multiple sources of information to accurately assess the incidence of abortion in dairy herds.

5. Different causal patterns of bovine abortion

To test whether cows that are more metabolically demanding could suffer from an imbalance during gestation and whether this could explain abortions that are not attributable to an infectious cause, a prospective observational study was conducted on two farms, one with a history of low (farm A) and another with a history of high lactational incidence of abortions (farm B), both in the southern region of Chile [26]. The gestation of the participating cows and their biochemical parameters were monitored. It was found that farm A had poor adaptation of energy and protein balance and a higher frequency and magnitude in the decrease of body condition score (BCS), while farm B had altered adaptation of protein metabolism. During the first and second third of gestation, cows that aborted had less loss of BCS than those that did not abort ($p < 0.05$), and then they improved their body condition between samplings ($p < 0.05$). A decline in body condition can affect pregnancy outcomes between 40 and 90 days of gestation, as it can reduce the production of progesterone by the corpus luteum; progesterone is essential for maintaining pregnancy and preventing embryonic loss. Therefore, body condition should be monitored and managed carefully during this critical period [34]. It is possible that the loss of body condition in this study did not affect the critical period of the corpus luteum or that the magnitude of the BCS loss was not strong enough to affect it. It is clear that the loss of BCS did not affect the presentation of abortions, since both on farm A and on farm B, cows that were aborted improved their body condition between samplings, which can be explained by the decrease in nutritional requirements when gestation is suspended [35]. There was a relationship between high levels of total protein (Pt), possibly due to plasma globulins (Glob), and the presentation of abortions, in relation to joint cases of mastitis or lameness. Pt is mainly influenced by serum globulins [34]. It has been shown that a case of mastitis or a febrile condition increases the risk of abortion due to an increase in prostaglandin (PGF2), which can cause the loss of gestation by luteolysis and contraction of the myometrium [36, 37]. Due to the seroconversion values for *N. caninum*, it cannot be ruled out that two of the eight abortions may have been favoured by this condition, although in the control group, 21% also had seroconversion without presenting abortion in the studied period and finally gave birth to a live calf.

A cross-sectional study was performed on 40 farms and 400 dairy cows in the central south of Chile to analyse abortigenic diseases in dairy farms [5]. The study used a two-stage sampling method and collected information about the management of the dairy farms using a personal questionnaire. To assess the exposure to four infectious diseases in dairy cattle, blood samples were collected and tested for brucellosis, bovine viral diarrhoea virus (BVD), neosporosis and leptospirosis. The results showed that BVD had the highest farm-level prevalence (97.5%), followed by neosporosis (87.4%) and leptospirosis (52.1%). At the individual level, the same pattern was observed, with BVD having the highest proportion (62.1%), neosporosis (22.4%) and leptospirosis (12.2%). Larger herds had a higher risk of BVD and neosporosis at the farm level. No evidence of brucellosis was detected. The factors associated with each disease were related to biosafety and the intensity of production, despite the control measures implemented [5].

The aim of the study [23] was to investigate the possible associations between bovine abortion syndrome and various factors, such as metabolic disorders and infectious diseases. The study design was a prospective observational cohort, in which cows that experienced abortion were compared with cows that did not. The study measured several parameters, such as blood biochemistry, serology and microbiology, to identify potential causes and risk factors for BAS. We conducted an analysis of how both infectious and non-infectious factors affect the risk of abortion in dairy cows. This study involved selected dairy cows from the Ñuble province of Chile (n = 148) that were 42 days pregnant. The aim was to investigate the effects of different factors on their reproductive performance and health status. Monthly blood samples were taken until abortion or delivery. Biochemical and serological disease indicators were determined. Cows were monitored and sampled monthly during pregnancy by rectal palpation and/or ultrasound. A multivariable logistic regression model and proportional hazard regression were used. In that study, it was found that *Neospora caninum* and *Leptospira interrogans* infections were significantly associated with BAS ($P < 0.05$), with an odds ratio (OR) of 4.27 and a hazard ratio (HR) of 94.35, respectively. We also observed that low cholesterol (Chol) levels ($P < 0.05$) in the fourth month of gestation (OR = 0.61) and a decline in body condition score from month three to four (OR = 0.32) increased the risk of BAS. These results suggest that BAS is related to the negative energy balance shown with beta-hydroxy-butyrate (BHB), the protective role of high cholesterol concentration in the first trimester, and the prevalence of *Neospora caninum*, *Leptospira interrogans* or both.

The results of the analysis for metabolic disorders and infectious diseases [23] indicated different potential aetiologies based on the data collected from the farms under investigation. In farm A, non-infectious factors (energy deficits, protein liver damage, inflammation) were more dominant, except for one abortion case due to neosporosis seropositivity. In farm B, infectious factors associated with leptospirosis (serovars Grippotyphosa and Harjo) and neosporosis were more frequent. These factors are important for the reproductive performance and health of dairy cows. This metabolite, jointly measured with a BCS evaluation, is useful for monitoring energy disorders in dairy herds. The correlation between plasma retinol and BVD titres was negative and moderate ($r = -0.42$, $p < 0.05$).

The study [23] that analysed 18 abortion cases due to different disorders and infections is summarised in **Table 1**. **Table 1** also shows the abortion month for each case. The results indicated that the cows had different metabolic challenges in each trimester of pregnancy. In the first trimester, they had low energy and protein levels, signs of liver damage and increased inflammation markers. In the second trimester, they had low energy and protein levels, increased inflammation markers and positive serology for *Neospora caninum* and *Leptospira interrogans* (serovars Grippotyphosa and Harjo). In the third trimester, they had low energy and protein levels, signs of liver damage, increased inflammation markers and positive serology for *Neospora caninum*.

To reduce reproductive losses in dairy cattle, which are often caused by infectious diseases [38] but not detected by routine tests [39, 40], we need to use epidemiological surveillance tools. These tools can help us improve management practices, disease control and nutritional management, as non-infectious factors may also play a role in the syndrome [22].

These tools can help farmers and veterinarians to identify potential risks and take appropriate actions to prevent or mitigate reproductive losses in their herds. By implementing effective management measures, controlling infectious diseases and

Case	Month	Chol	BHB	Pt	Alb	Glob	Fib	Urea	AST	NEO	Lepto	Possible causal pattern of abortion
1	3	↓	↑				↑					Energy imbalance, inflammation
2	3		↑			↑						Energy imbalance, inflammation
3	3	↓		↓			↑	↑				Protein imbalance, inflammation
4	3				↑				↑			Hepatocellular damage, inflammation
5	3			↓			↑					Inflammation
6	4	↓	↑								Gr	Energy imbalance, leptospirosis
7	4										Ha	Leptospirosis
8	4						↑			+		Inflammation, neosporosis
9	4			↓			↑					Inflammation
10	4						↑					Inflammation
11	4						↑					Inflammation
12	4						↑					Inflammation
13	7		↑						↑	+		Energy imbalance, hepatocellular damage, neosporosis
14	7			↓	↑					+		Inflammation, neosporosis
15	7		↑				↑					Energy imbalance, inflammation
16	8									+		Neosporosis
17	8		↑		↑							Energy imbalance, inflammation
18	8								↑			Hepatocellular damage

↓ = plasmatic concentration under the reference interval (RI) for the species, ↑ = plasmatic concentration over the IR for the species, +: neosporosis positive serology, Gr: L. interrogans Serovar, Grippotyphosa, Ha: L. int. Serovar Hardjo.

Table 1.
Detailed analysis of each abortion case presented in the southern Chile study [23] according to possible causal patterns.

ensuring proper nutritional management, farmers can improve the reproductive performance of their herds and reduce the incidence of bovine abortion syndrome.

6. Possible biomarkers for abortion risk

Acute phase proteins have been analysed and studied in association with infectious and inflammatory diseases in certain livestock populations. These proteins help to restore homeostasis, reduce microbial growth and have been used as biomarkers for inflammation, infection and trauma. Acute phase proteins are a group of proteins that are produced by the liver in response to inflammation, infection or trauma. Some examples of acute phase proteins include C-reactive protein (CRP), serum amyloid A (SAA) and haptoglobin (Hp). These proteins can be measured in blood samples to assess the presence and severity of inflammation, infection or trauma in livestock populations [41, 42].

The authors evaluated how the biochemical profile and acute phase proteins were related in cows that had abortions [40]. That study aimed to identify the multivariate associations of acute phase proteins and biochemical profiles in cows that were aborted. The results suggest that serum amyloid A (SAA) and haptoglobin (Hp), which are acute phase proteins in dairy cows, show different correlations with metabolic indicators of energy, oxidative, protein or organ dysfunction at the time of abortion. These findings indicate that the levels of these proteins and metabolic indicators in the blood could serve as potential biomarkers for assessing the likelihood of abortion in dairy cows. We collected blood samples monthly from 140 dairy cows during their pregnancy and monitored their health status. Out of these, 18 cows were aborted and were classified as 'cases'. We also selected 29 'control' cows that did not abort and matched their samples with the 'cases' by sampling time. We used multivariate analysis to compare the differences between the two groups and to assess the factors associated with abortion. We categorised abortion as either infectious (caused by DVB, leptospirosis or neosporosis) or non-infectious (related to protein or energy imbalances as shown in the metabolic profile). Among the 18 cows that were aborted, six had positive or seroconverted results for the diseases tested, 13 had signs of protein metabolic imbalances, seven had signs of energy imbalances and ten had both situations [40].

The Principal Component Analysis (PCA) showed significant differences ($p < 0.05$) between case and control cows, suggesting that they have distinct multivariate patterns. A cluster of variables related to protein metabolism, such as fibrinogen, serum amyloid A, haptoglobin and antibodies for neosporosis and bovine viral diarrhoea virus, was found in aborted cows. These variables were different from others related to energy and protein imbalance, such as high beta-hydroxy-butyrate, low cholesterol and low total protein.

Serum amyloid A and haptoglobin did not increase in cows that had abortions and were infected with pathogens such as bovine viral diarrhoea virus, leptospirosis or neosporosis. This suggests that these diseases do not cause significant systemic inflammation in aborting cows [40].

Cows that evidenced energy imbalances in their metabolic profiles had higher Hp plasma concentration (0.28 mg/ml) before abortion ($p < 0.05$). Fat mobilisation and negative energetic balance affected liver integrity more in cows that were aborted. Aborted cows also had different multivariate relationships between biochemical variables and serum amyloid A (SAA) and haptoglobin (Hp). We identified a group of variables related to protein metabolism, such as high levels of fibrinogen (Fib), SAA, Hp and antibodies for neosporosis (NEO) and bovine viral diarrhoea virus (BVD). These variables could be biomarkers of infection or inflammation, in addition to the usual indicators of biochemical profiles [40]. Acute phase proteins (APPs) are potential indicators of infection or inflammation in animal health. They are produced by the liver when local defences are overwhelmed by pathogens or tissue damage [41].

Were measured Hp and SAA, two acute phase proteins, in the blood of cows that aborted due to infection or other causes. We found that Hp was higher in cows with infectious abortion and SAA was higher in cows with non-infectious abortion. This means that these proteins can help us to quickly identify the cause of abortion in cows. However, studies also noticed that Hp was higher in cows that had energy imbalances before abortion [40]. These proteins are useful for checking the health and detecting diseases in animals that produce milk or meat [41, 42]. In the study [40], a strong link was found between BVD and NEO, two infectious agents for abortion in cows. The cows that were aborted had lower levels of antibodies for BVD than the cows that did not abort, and some of the cows that were aborted had high levels of antibodies for NEO.

It is important to consider both infectious and non-infectious causes when studying the causality of abortions in a herd. Non-infectious causes can occur in parallel with infectious diseases and can also contribute to the incidence of abortion. Serum amyloid A (SAA) has been suggested as a potential biomarker to differentiate between infectious and non-infectious abortions [40].

7. Economic losses due to bovine abortion syndrome

The losses on production caused by bovine abortion syndrome (BAS) must be comprehensively identified, as they not only correspond to the potential loss of the calf but also to all the actions that had to be carried out to achieve gestation in the cow, such as semen expenses, personnel, feeding, space occupied in infrastructure, etc. In addition, productive losses from the future milk production peak not achieved as a result of the lengthening of the calving interval and sequelae such as infertility or early embryonic losses post-abortion and lengthening of the generational interval must be considered. Bovine abortion problems can be a major cause of cow elimination, reaching 30 or 40% of total replacements [39], being more negative when applied to animals with good genetics and lifespan in the herd [5]. Numerous studies have been carried out using different techniques to estimate the economic losses produced by abortions in dairy production systems. There are reports for dairies in California in the 1980s, where it was estimated that if a cow aborts a 100-day foetus, it means a loss of US$ 640 [1].

The analysis carried out in Chile [38] on the losses caused by bovine abortion syndrome (BAS) according to the conditions of milk production in southern Chile indicates that the economic losses calculated per abortion for the dairy sector studied in one lactation are significant, although they are lower than those reported by studies in other countries [39]. The occurrence of abortion in one lactation was related to longer calving intervals, decreased annual milk production and early elimination of cows, which is consistent with other reports [19]. The main determinants of the cost of abortion were the level of milk production and the age of elimination of cows that had an abortion in their last lactation. Considering the population of cows in the southern zone (Araucanía, Los Ríos, Los Lagos regions), the distribution of the abortion occurrence rate and the distribution of losses due to abortion per year results in an average annual loss of Ch$-8.411 billion (bill), although with a wide variation (p2.5 $-22.247; p97.5 $5.903) and an 87.7% probability that the result of the abortion will be a loss for the producer. Under these conditions, an abortion is more harmful to a producer in a young cow with lower production than in an older cow with better milk production [38].

8. Conclusions

Bovine abortion is an important topic in herd management. Quantifying abortion occurrence using means of observed abortions underestimates the real situation since observed foetal losses are approximately 20% of the total foetal losses. Given the possible lack of a temporal relationship between abortion and the cause that produced it, it is difficult to obtain precise data on the occurrence of abortions to find a causal association. This leads to the need to try to maintain farm records of possible abortion risk factors so that a thorough retrospective farm analysis can be performed when an abortion occurs.

That highlights the importance of using multiple sources of information to accurately assess the incidence of abortion in dairy herds. To prevent the negative impact of reproductive disorders on herd productivity and profitability, it is essential to have epidemiological surveillance tools that enable early detection and intervention of potential problems. These tools include management measures, infectious disease control and proper nutritional management, which can help reduce the risk of reproductive losses and improve herd health and welfare. These tools can help farmers and veterinarians to identify potential risks and take appropriate actions to prevent or mitigate reproductive losses in their herds. By measuring the levels of SAA in blood samples from cows, it may be possible to quickly identify whether an abortion was caused by an infectious or non-infectious factor. By implementing effective management measures, controlling infectious diseases and ensuring proper nutritional management, farmers can improve the reproductive performance of their herds and reduce the incidence of bovine abortion syndrome.

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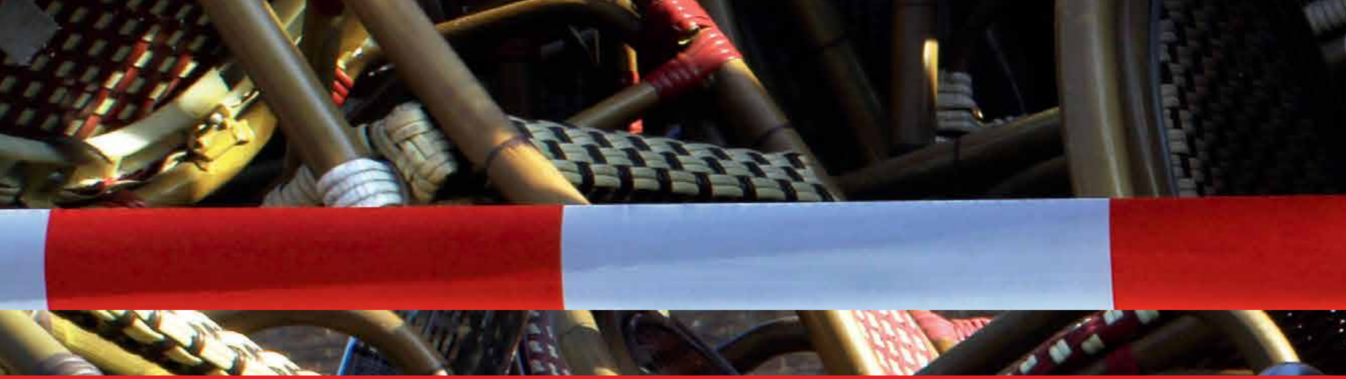

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Epidemics and pandemics caused by infectious diseases, mainly zoonosis, have existed since the beginning of humanity. They affect health, social, economic, and cultural policies around the world. *Epidemic Preparedness and Control* highlights epidemiology as an important scientific matter of research on the prevention and control of infectious diseases. It also examines different aspects of public health after the emergence of SARS-CoV-2, the etiological agent of COVID-19. The book is organized into six sections addressing general aspects of pandemics and epidemics as a result of climate change, environmental degradation, socio-cultural interactions and occurrence of zoonoses, and the experience of SARS-CoV-2 contributing to different tools for use in COVID-19 epidemics and other airborne infectious diseases.

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