Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby gran to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Brittany Gentry Date

Global Collaboration Needed to Prevent Pandemics

By

Brittany Gentry
Master of Public Health

Hubert Department of Global Health

_____

Scott JN McNabb, PhD, MS
Thesis Committee Chair

Global Collaboration Needed to Prevent Pandemics

By

Brittany Gentry

Bachelor of Science
University of California, Irvine 2017

Thesis Committee Chair: Scott JN McNabb, PhD, MS

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2021

Abstract

Global Collaboration Needed to Prevent Pandemics

By: Brittany Gentry

Introduction: Global collaboration is the backbone for effective public health responses to threats of pandemic potential. Pandemic threats have grown more immediate in recent years with the expansion of globalization, climate change, and human encroachment on animal habitats. Over the course of the past two decades, the world experienced intimately the importance of global collaboration by the 2003 SARS, 2009 H1N1, 2012 MERS-CoV, 2014 Ebola, and now the COVID-19 pandemics. This review synthesizes existing global mechanisms of collaboration to prevent and mitigate pandemics to better understand the perceived gaps.

Methods: Using PubMed, a systematic literature search was performed for studies that discussed mechanisms of global collaboration to prevent pandemics. Articles discussing global-level efforts were included with a focus to understand the gaps in global collaboration to prevent pandemics.

Results: Among 39 eligible articles, most focused on research, development, distribution, public health surveillance, information sharing, and funding. Existing gaps in funding, enforcement mechanisms, national-level public health capacity, and the rise of hyper-nationalism were identified.

Conclusion: It is important to recognize and address gaps in global collaboration to prepare our nations and global organizations to prevent, detect, and control the next pandemic threat.

Global Collaboration Needed to Prevent Pandemics

By

Brittany Gentry

Bachelor of Science
University of California, Irvine 2017

Thesis Committee Chair: Scott JN McNabb, PhD, MS

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2021

Acknowledgements

First, I would like to express my thanks and appreciation to my thesis advisor, Dr. Scott McNabb, for his support throughout the writing process.

Second, I would also like to thank Mrs. Shenita Peterson for her support in the planning of systematic literature review and her helpful advice along during the writing process.

Finally, my big thanks to my family for their support and love. This accomplishment would not have been possible without them.

Table of Contents

Introductory Pages

Appendix

Introduction

Pandemics are part of human history and the evolution of public health. From the earliest recorded pandemic during the Peloponnesian war (430 B.C.) to the COVID-19 pandemic, policies (or lack thereof) have spurred public health innovation, sparked unrest, and even led to the rise and fall of empires [1].

Now – more than ever – societies are interconnected. Relying on international trade and travel, this interconnectedness contributes to the movement of disease that once would be isolated to regions of origin. The collaboration and cooperation of member states (MS) has long been recognized as the main guard against pandemics. Unfortunately, while touted as the best mechanism to prevent and mitigate pandemics, collaboration and cooperation is extremely difficult to execute.

Specifically, the COVID-19 pandemic shows both the importance and the shortcomings of global collaboration to prevent pandemics in ways that previous outbreaks (e.g., SARS, H1N1, Ebola, MERS-CoV) only hinted. The lack of global collaboration has led to strained economies, millions of excess deaths, and the erosion of the social fabric.

To discuss better collaboration and cooperation among nations we first introduce the institutions that govern global collaboration. WHO was established in1948 [2]. The main legal framework that WHO uses to govern pandemic threats is the International Health Regulations (IHR). The first official framework under the name IHR was created in 1969, though some aspects of the IHR can be traced back to the 1850s Sanitary Conferences [2]. Revisions to IHR have occurred since inception with the most recent changes coming in 2005 after worries over the global response to SARS. Newer revisions

included obligating nations to notify WHO within 24 hours of detected events within their territory which may constitute a Public Health Emergency of International concern (PHEIC). This gave the WHO's director general the ability to declare a PHEIC and added clauses that require MS improve their domestic capacities to prevent and respond to infectious diseases [3].

Under WHO authority are mechanisms (formal and informal) that assist nations collaborate during outbreaks and pandemics. Two are public health surveillance (PHS) and data sharing. Globally there are multiple networks focused on collecting and sharing infectious diseases data (e.g., FluNet, Global Public Health Intelligence Network [GPHIN], Global Initiative on Sharing All Influenza Data [GISAID]). These networks serve as early warning systems. Others include partnerships in research and development for vaccine candidates and therapeutics as well as funding networks to help countries in need. Due to these expansive mechanisms, the collection and synthesis of global information is essential for public health to improve.

This systematic review aims to investigate global mechanisms of collaboration to prevent and mitigate pandemics by summarizing existing literature and understanding the gaps and strengths of the systems in place. We compiled different multi-lateral and bilateral collaborations used during outbreaks and the COVID-19 pandemic and included both peer-reviewed articles, and the grey literature.

Methods

The goal of this systematic literature review is to synthesize existing literature on the efforts and gaps in international cooperation to prevent pandemics. The search strategy, which combined Medical Subject Headings (MESH) and text-based terms related to international stakeholders and methods of collaboration was developed with the help of a reference librarian at Emory University (Table 1). A search for peer-reviewed literature was performed using the database PubMed. Searches were not limited by publication type or geography and included published literature from Jan 1, 2010 to Feb 22, 2021. The date January 1 was not a predetermined cutoff date; rather, it was what was pulled from the results of the specific search string.

After the search strategy was applied to the database, all citations were exported to EndNote (N=379). All references were moved to the online systematic review program Covidence, where a title and abstract screen was conducted. All titles and abstracts went through an initial screening. There were no additional articles added to the systematic review after the initial screening was done. A total of 137 articles were chosen for full text review. The reviewer read each full text to ensure all inclusion/ exclusion criteria were met. Inclusion and exclusion criteria are listed below.

Inclusion:

1. Discussed multilateral or bilateral cooperation between nations, governmental organizations, NGOs, researchers, public health specialists, or other relevant entities that focused on mechanisms to prevent or mitigate pandemics.

2. Discussed informal and formal mechanisms by which collaboration has occurred in previous pandemics or during the current COVID-19 pandemic and the importance or shortcomings of these mechanisms.

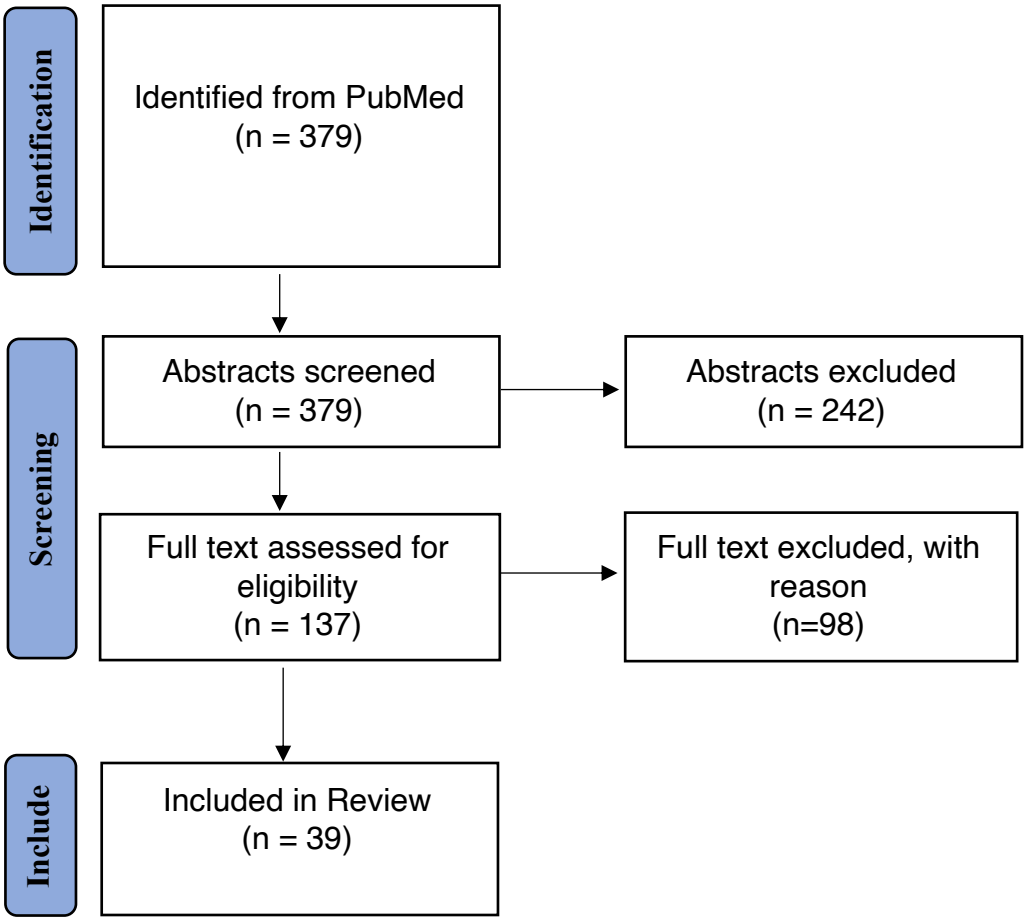
Exclusion:

1. Full text articles that were not in English were excluded due to a lack of ability to translate them.
2. Multi-national collaboration in clinical settings for specific treatments or adaptations to service used during pandemics were not included on the basis that this form of collaboration, though extremely necessary, is specifically focused on the outcomes of individuals.

A total of 137 articles were chosen for full text review. Of those included in the full text review, 43 articles were included in the data extraction phase. A PRISMA flow diagram that depicts the different phases of the search and article inclusion process of a systematic review is shown below (Figure 1).

Relevant data were extracted with the help of Covidence extraction template. Data extracted included: outcome measures; perceived gaps; and recommendations if provided. The data were then grouped into categories using similar discussion points from the articles and summarized. This study did not require review by the Institutional Review Board (IRB) because it consisted of synthesizing existing published data.

Figure 1. PRISMA Flow Diagram of Search and Article Inclusion Process 2021



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Results

We describe the main mechanisms of collaboration and key findings of the 39 articles chosen after the full text review. The information is presented as a systematic narrative synthesis, instead of a quantitative meta-analysis due to the broad and sometimes subjective nature of the articles. The types of global collaboration mechanisms this systematic review identified are presented as the following main categories: research and development, finance, and information systems (Table 2). The gaps and obstacles to these mechanisms will also be presented through a similar grouping strategy (Table 3).

The earliest article reviewed was published in 2010 [4] and the most recent articles were published in 2020. Twenty-three of the 39 (59%) articles reviewed were published after Jan 1, 2020. All articles included in the final synthesis are English articles. Sixteen articles discussed mechanisms of information networks, such as public health surveillance (PHS) and data-sharing networks, nine articles discussed the financial mechanisms that global collaboration to function properly, nine articles mentioned the global mechanisms of research, development, and distribution. The gaps of global collaboration were heavily discussed throughout the articles. Ten articles discussed the gaps and obstacles to proper funding of collaboration efforts, eight discussed the shortfalls of a nation's individual public health and healthcare capacity as a major gap to global collaboration, 13 articles mentioned the lack of legal or other enforcement mechanisms as an obstacle to collaboration efforts, and five discussed that rising

problem of nationalism/competition of nations during outbreaks as a major obstacle to collaboration.

The articles included a diverse set of primary, secondary and grey literature sources. Commentary articles and policy papers where the two most common types of articles included. Perspectives and editorials made up the second largest group of articles, while the smallest group of articles was primary research papers.

Mechanisms of Global Collaboration

Research, Development, and Distribution

Research, development, and distribution mechanisms were recognized as an important aspect of preventing pandemics through global collaboration in nine articles (23%). Three aspects that were discussed as requirements for effective R&D were sustainable investment, access to intellectual property, and data/sample sharing [5]. At least one of the three aspects is mentioned in all the articles that discuss research, development, and distribution.

Partnerships have been crucial to development within R&D and will spur growth in the field [6]. For instance, the public-private partnership Coalition for Epidemic Preparedness Innovations (CEPI) with $630 million committed funding undertook the development of vaccines for priority diseases set by WHO [7]. Another example of global collaboration through R&D is the partnership between countries, pharmaceutical companies and WHO towards the creation of live attenuated influenza vaccines with the purpose of combating pandemic influenza viruses of different serotypes [8]. Recently, the role of philanthropic foundations has started to play a larger role in R&D with

organizations like the Bill & Melinda Gates Foundation, funding new mechanisms for vaccine and drug development [9].

During the COVID-19 pandemic, the need for medical supplies and therapeutics became ever more apparent. One mechanism that appeared in response to the global community needing a more equitable way to distribute vaccines was COVAX, which was created through the collaboration of CEPI, GAVI, and the WHO [7]. The COVAX group announced it intended to distribute 2 billion doses to member countries which include 64 industrialized and 92 lower GDP nations, regardless of their ability to pay [10]. An important note is that even though this collaboration is a much welcomed one, it does only translate to 3% for the population of its member countries [10]. Global collaboration through the Access to COVID-19 Tools (ACT) Accelerator, lead to the development and access to diagnostic tests, treatments, and vaccines [11].

R&D involves a high level of global collaboration, but as described in the Mallapaty (2020) article, it is noted that during times of outbreaks and specifically during the COVID-19 pandemic there was a tendency for collaborators to shrink participation on research papers to their most comfortable groups. There was also an important discussion on how research and development as well as distribution of therapeutics and vaccines is focused in the Global North, leaving the Global South out of research trials and other aspects of R&D which could lead to gaps in global collaboration [12].

Financial Mechanisms

Funding is one of the most important mechanisms for preventing and mitigating pandemics through global collaboration. Since WHO is one of the main coordinating

bodies in global health, many of the articles discussed the financial channels for WHO. Three articles described pandemic prevention funding as being allocated through emergency response avenues as opposed to a steady funding stream [13-15]. An example of this type of funding can be seen in the current COVID-19 response, with low and middle income countries (LMIC) as well as WHO having to rely on funding assistance from the World Bank Pandemic Emergency Financing Facility and other such mechanisms [16]. WHO has to rely on funding mechanisms like the World Bank, due to its sometimes-inconsistent revenue streams. Its two primary sources of funding are through expected contributions from MS and voluntary contributions from outside actors and MS [17, 18]. As Birn & Nervi (2020) discussed, WHO's budget is only $2.4 billion per year which is less than one third of New York Presbyterian Hospital's budget. This lack of necessary funds to perform its mandate leaves the WHO beholden to the interests of those that fund it. The fragmentation of resources due to donors earmarking funds to specific diseases or particular activities was discussed by three articles [13, 19, 20]. Earmarking of funds has been a steadily growing trend for decades, as shown in the article Bogich et al., (2012).

According to the Organization for Economic Co-operation and Development (OECD), infectious disease control aid commitments have increased from 8% between 1990 and 1998 to 16% between 2005 and 2008, while basic health infrastructure aid commitments have declined from 11% to 5% during this period.

WHO is also not immune to the trend of earmarking funds, due to the United States and aligned countries disrupting its independence by beginning to interfere with WHO's

budget in 1981 [11, 21]. Multiple articles described the funding landscape as fragmented due the large array of global health actors, such as international, non-governmental, governmental, public/private partnerships, and philanthropies [13, 14, 19, 22].

Information Networks and Public Health Surveillance

A crucial aspect in preventing and mitigating pandemics is the ability to share information in a timely and effective manner. This is why the most highlighted mechanism of global collaboration in this review is information networks and public health surveillance (PHS) that streamline sharing of information. Virtually all articles mentioned the importance of data sharing and PHS, though 16 of the articles highlighted both different information networks and systems as well as the importance of this mechanism in a more substantial way.

Many of the information systems reviewed are in some way related to WHO. One mechanism discussed in the literature was the Pandemic Influenza Preparedness (PIP) Framework. The framework helps govern the sharing of influenza viruses that have human pandemic potential and the sharing of benefits through the use of WHO CC's or WHO H5 Reference Laboratory [21, 23-25]. As explained in M. Rourke et al. (2020), this framework is the only pathogen-specific international access and benefit-sharing (ABS) instrument and also safeguards access to virus samples. The materials provided under the PIP framework can be transferred through the Global Influenza Surveillance and Response System (GISRS) [26].

Three information networks were discussed including GHPIN, Global Outbreak and Alert Response Network (GOARN), and Virus Outbreak Data Network (VODAN). GPHIN was developed by Canadas public health agency and collaborates with WHO through GOARN, to act as an early warning system. GPHIN continuously scans global media sources such as web pages of major newspapers, biomedical journals and electronic-mail-based discussion groups looking for signs of unusual disease events, if an event is found they are then verified with countries [27]. GOARN is a network of public health institutions, laboratories and NGO's that observe and respond to outbreaks [11, 28]. VODAN, unlike the other two networks, is new with its creation being spurred by the COVID-19 pandemic. It aims to be used on projects that are in line with FAIR data practices and services relevant to COVID-19 [29]. Formal mechanisms were highlighted in the literature, but informal mechanism and networks have been shown to be just as useful and sometimes even more immediate than established networks [27].

Three PHS systems were discussed: Global Influenza surveillance network (GISN); GISRS; and FluNet. GISN has 131 national influenza centers (NICs) in 105 countries, five highly specialized collaborating centers (WHO CCs), three national licensing agencies or essential regulatory laboratories [30]. GISRS is a global network of laboratories that aim to provide the WHO with information regarding the spread of influenza [24]. Another aspect of PHS discussed was the importance of PHS capacities of individual nations and the need to be constantly improving current systems [20, 31]. During the 2009 H1N1 pandemic, some MS did not have high quality PHS which hindered the response to the outbreak [4]. Though it is important to note that PHS

capabilities during the H1N1 outbreak were improved from the H5N1 outbreak in 2004, which led to an overall better response in 2009 [31].

There are also regional PHS that help make up the entire global landscape of PHS, such as Eastern Mediterranean Acute Respiratory Infection Surveillance (EMARIS) [24]. It has also been noted that the absences of a global PHS mechanism, like FluNet, for epidemiologic data has contributed to sporadic collection of global level data during past outbreaks [30].

The collection and dissemination of data is a crucial step in the global response to a disease of pandemic potential, but it is only as useful as the response to that information [32]. Early alert systems relay information to WHO which allow it to declare a Public Health Emergency of International Concern (PHEIC) if necessary. Unfortunately, during the current COVID-19 pandemic, the PHEIC declaration was largely ignored for six to eight weeks [32].

Impediments and Gaps in Global Collaboration

Funding Mechanisms

Public health programs tend toward vertical, disease-specific global health programs. Due to the specificity of disease-focused work and increase in organizations and programs in public health there has been a troubling fragmentation of funds [13, 19, 20, 22]. According to Markel (2014) fragmentation also creates an environment of competition between organizations and government as well as competition with local programs. Funding for basic health infrastructure and development has also been

forgotten affecting the capacity of countries and systems too function over the long term [14].

There is a clear need to invest in R&D with multiple articles addressing this gap in global preparedness. According to one article, an extra $1 billion per year for 15 years, above the amount currently being spent on R&D is needed to better prepare for infectious diseases with pandemic potential [9]. Yamada, Ogawa & Freire (2016) described this amount as equivalent to the R&D budget of a medium-sized pharmaceutical company and argues this a manageable goal for global security. Funding for antiviral drugs and antibody therapies that can be stockpiled and rapidly manufactured to stop the potential spread of disease of pandemic potential has also been highlighted as a gap to the prevention of pandemics through collaboration [7]. These funding mechanisms and partnerships in manufacturing must be set up long before they are needed in preventing pandemics [7, 9]

WHO's current funding model has also created larger gaps and impediments to a fully functioning global response and governance of potential pandemic threats. Earmarking of funds has become a trend within WHO leaving them with inconsistent revenue streams [13, 19, 20]. At the start of the COVID-19 pandemic, the Director-General of the WHO warned that WHO was facing an immediate $20 million funding gap; this hinders global response and collaboration efforts [15]. Voluntary earmarked funds being allowed by nations and organizations, has given the perception that national interests may conflict with WHO's mandate to equitably protect the health of everybody [18]. Rather than focusing on large social, political, and commercial determinants of health or

broader public health capacities which include PHS, preparedness, and other areas needed for pandemic prevention and management; WHO is being forced to work on more specific diseases [11]. This allows high-income countries the power to control the direction of public health work globally [11].

Capacity of Nations

Global collaboration is dependent on individual capacities of nations to prevent pandemics or outbreaks through preparation and capacity building of healthcare and public health infrastructure. There is currently a 70-fold difference between average *per capita* spending in low versus high income countries [14]. This is evident in the inadequate funding of national public health systems despite a core component of the IHR 2005 that mandates the maintaining and strengthening of these health systems [5, 14, 33]. Nations are allowed by WHO to do self-assessments of the core components of their health systems. Even with the ability to complete the assessment themselves only 64 member states have affirmed meeting the core capacities [5]. As shown in the article Neogi & Preetha (2020) current WHO metrics for preparedness did not necessarily match with the best response by a country during the COVID-19 pandemic. Collaboration within the nation as well as external global collaboration is critical to the response [34]

Another aspect of a nation's capacity that is vital to global collaboration is its ability to monitor and collect PHS data on diseases of pandemic potential. Currently, there are too many nations that simply do not have the resources to perform PHS in a quick and accurate way [5, 17, 27, 28, 30]. The lack of effective monitoring systems on the

national level has been highlighted by the COVID-19 pandemic with calls for the IHR 2005 to be updated again with provisions on monitoring and PHS [33].

Enforcement and Legal Mechanisms

One of the most discussed gaps to global collaboration to prevent and mitigate pandemics was the lack of clear enforcement mechanisms both through legal means and non-legal consequences. WHO's constitution endows normative powers over creating governmental obligations to report actions of their recommendations and conventions, but international health law remains lacking [21].

Over the course of the past two decades there has been multiple outbreaks of diseases such as H1N1, SARS, Ebola, and COVID-19. A common denominator between these outbreaks was the use of restriction on trade and travel that went directly against both the IHR 2005 article 43 and the recommendations of WHO [4, 27, 30]. The IHR (2005) provided the WHO with a legal basis for requesting the withdrawal of measures implemented by MS with due rational [27]. Even with the legal basis there was still a lack of consequences or attempt to enforce the IHR 2005 mandates by WHO in regard to trade and travel which has weakened the ability of WHO to properly coordinate responses during outbreaks [4, 33, 35, 36]. During the 2009 H1N1 outbreak, there were controversies regarding isolation or quarantine of individuals and groups from affected countries which were also not in line with WHO recommendations, subsequently only one country had their rationale for their restrictions questioned [4].

The need to strengthen WHO has become even more apparent during the course of the COVID-19 pandemic with multiple articles calling for enhanced authority in enforcing

norms [18, 32, 37, 38]. As mentioned in the WHO bulletin (2020) the travel restrictions are not only harmful in weakening the stance of WHO but also detrimental to the flow of goods and services making collaboration even more difficult during the COVID-19 pandemic [37, 38]. A second troubling occurrence during the COVID-19 pandemic was that MS did not report additional health measures to WHO, in direct violation of the IHR 2005 [37].

Another important aspect of global collaboration discussed was the continual flow of information from nations to WHO and between partnerships. The IHR 2005 does not mandate continual reporting of epidemiologic and clinical data during an ongoing crisis which limited the ability of WHO to consistently provide information to MS [30]. The lack of mandate played a role in the inconsistent nature of the sharing of information and biological samples during the COVID-19.

Competition and Hyper-nationalism

The most alarming impediment to global collaboration to prevent and mitigate pandemics is the role of competition among nations and the role of hyper-nationalism during the COVID-19 pandemic. Five articles mentioning the rise of competition and hyper-nationalism were all written in 2020. The competition among countries for public health commodities such as vaccines, therapeutics, and personal protective equipment have been well documented over the course of the pandemic and was described as a moral failure [39]. This competition effectively excluded LMICs from being able to protect their citizens therefore hindering the global response.

According to Eyawo and Vines (2020), Africa was unable to purchase needed diagnostics during the COVID-19 pandemic due to global protectionism, with 70 countries imposing restrictions on export of diagnostic supplies. The purchasing of vaccines during COVID-19 showed the worst of this competition with high income countries out purchasing LMIC even after stark warnings of “vaccine nationalism” from the head of WHO Tedros Adhanom Ghebreyesus [10, 11].

Hyper-nationalism has also shown to be a concerning obstacle to global collaboration with nations disregarding the IHR 2005 and WHO’s recommendations as they fit under the guise of “protecting” their nations [37, 38]. Leaders of these nations have been described as weakening WHO’s authority, blocking a coordinated response, and dividing the world [38].

Discussion

Summary of Evidence

The goal of the systematic review is to synthesize literature on global collaboration to prevent and mitigate pandemics as well as the gaps and impediments faced. The main categories found in the literature included: research, development, distribution of financial or funding mechanisms, information networks, PHS, and data-sharing. A key aspect of research, development, and distribution were the siloed, multitude of partnerships from different types of sectors such as public, private, philanthropic, and governmental. Gaps in research, development, and distribution mostly deal with the lack of proper funding. WHO is funded through expected contributions from MS and voluntary contributions from donors. Public health organizations, NGOs, and governmental programs secure funding through philanthropic, governmental, and international mechanism.

There has been a trend towards funding disease-specific programs and activities hindering broader public health capacities. Information networks, PHS, and data-sharing were the most discussed mechanism of global collaboration to prevent and mitigate potential pandemic threats. The individual capacity of nations to perform PHS is a gap in the overall fabric of information sharing on the global stage. Funding was the cause of gaps and obstacles for every mechanism addressed. One of the more concerning obstacles to global collaboration was the noted rise of competition by nations and hyper-nationalistic policies during COVID-19 pandemic responses.

The ability of nations and global actors to quickly develop and manufacture therapeutics and vaccines is crucial in response to diseases of pandemic potential. These partnerships must be established long before they are needed to be effective in preventing a pandemic. In recent years, partnerships and investments have come from philanthropic organizations, with many of these organizations focusing on vaccine development. One of the interesting partnerships that developed from the COVID-19 pandemic, was that of CEPI, GAVI, and WHO. The intent of the COVAX initiative is to allocate vaccines to countries who might be unable to obtain them through the global market [10]. The partnership behind this initiative could be a great example of how to distribute vaccines more equitably in the future and potentially become a more permanent system that focuses on making vaccines more accessible for LMICs.

PHS and information systems that allow for early detection of diseases of pandemic potential are one of the clearest examples of the importance of global collaboration. Both informal and formal information networks play a major role in the dissemination of information. This review found that even though global PHS mechanisms are in place and widely used globally the gaps in PHS on the national level greatly hinders response to outbreaks. There is also an issue of countries not acting on information from PHS, as was seen with the COVID-19 pandemic and nations initial disregard for the PHEIC declaration [32].

In the review of funding mechanisms, we found that pandemic prevention funding has largely been allocated through emergency response avenues as opposed to a steady funding stream [13-15]. Emergency response avenues simply do not provide the

necessary amount of funds to properly maintain and strengthen broad public health capacities that are at the center of preventing diseases of pandemic potential through global collaboration. There is a dire need to shift pandemic prevention funding from the emergency response model to a steadier stream of funds. The fragmentation of funds towards specific diseases has also been shown to be a problem for pandemic prevention and planning [13, 19, 20, 22]. The two most concerning issues of the fragmentation of funds is the competition it creates on a national, and sometimes even local level, as well as the power it gives private funding organizations. In order to be better prepared for future pandemics and set up public health systems to be ready to collaborate on a global scale the different public health programs need to find a way to work in their spaces without competing our hurting national or local level interests. Philanthropic organizations have also seen a sharp increase in power and leverage over public health decisions in recent years. Allowing these organizations to have almost full dictation over what programs are being funded gives a lot of power to high-income countries to control public health choices for the world. The public health needs of LMIC are often much different from those in high income countries, which is another reason why broad public health funding is needed going forward.

This systematic review also identified the worrying rise of hyper-nationalistic policies during the response to the COVID-19 pandemic. Over the course of the pandemic high-income countries have virtually monopolized global markets purchasing excess amounts of vaccines, and snatching up therapeutics and PPE [39]. The monopolization of vaccines has even been dubbed as vaccine nationalism. Nationalistic policies has

weakened the WHO's ability to coordinate the COVID-19 response and turned the response into survival of the wealthiest [38]. Moving forward the legal mechanisms of enforcement need to be strengthened through the IHR and the WHO should be willing and able to enforce public health mandates on countries. Without the ability to enforce the IHR countries will continue to enact the policies they see fit, whether or not they are backed by science, under the guise of protecting their nations.

Limitations

Due the broad nature of this topic and the subjective nature of the inclusion and exclusion criteria, there are limitations in this systematic review. There are many ways to study global collaboration. It could be researched from a wide-view lens or by focusing on a narrow aspect of collaboration. This review was limited to wider, more-formal avenues of global collaboration tied to WHO, whether formally or informally. Informal actors or private non-governmental organizations and their partnerships might be found in search databases, even if those partnerships were vital to the fabric of global collaboration to prevent pandemics. Since, grey literature is also used in this review, individual biases towards systems or international actors could cloud assessment of the global mechanisms usefulness or gaps assessed.

Another limitation was the inability to translate articles from other languages. To get a full scope of how global collaboration mechanisms are both perceived and used around the world, it would be vital to gain viewpoints of those who are not writing their articles in English. Only including articles that are written in English could inherently discount and remove the input of countries whose input is sorely needed. Unfortunately, there is

already a bias in public health and on the global stage to focus mainly on the countries of higher economic status from the global north, being unable to gather views from countries or authors who do not speak English perpetuates this trend.

The third limitation of this review is there was only one reviewer and one search engine used. With only one reviewer there could be a perceived lack of rigor. When a review has multiple reviewers independently review articles and then try to come to a consensus on the different points of view there allow for more deep thought and checks of individual biases. Also, only PubMed was used as a search engine for this systematic review. Using multiple search engines helps improve precision, recall, and reproducibility of systematic reviews.

Conclusions

This systematic review provided a search of the literature about mechanisms of global collaboration that are in place to prevent and mitigate pandemics. It provided evidence on the prevalence of research and identified different types of mechanisms as well as their importance and gaps. More research should be conducted to quantify and describe the types of global collaboration. Though this review was conducted using rigorous methods, there are clearly gaps on the topic, especially because it was written during the COVID-19 pandemic.

We expect that a wide variety of research will be coming out in the near future discussing global collaboration because of the huge role it played in the COVID-19 pandemic. Global mechanisms of collaboration clearly have many strengths, but there

are also clear areas that need strengthening such as global health governance and enforcement mechanisms as well as steadier funding streams for pandemic preparation and broader public health systems. Looking forward it is important to keep an eye on the rise of hyper-nationalism across the globe and its effects on public health and try to shift focus to the richness that is gained by relying on the strengths of global collaboration.

References

1. Huremović, D., *Brief History of Pandemics (Pandemics Throughout History)*. 2019, Springer International Publishing. p. 7-35.
2. Gostin, L.O. and R. Katz, *The International Health Regulations: The Governing Framework for Global Health Security.* The Milbank Quarterly, 2016. **94**(2): p. 264-313.
3. Gostin, L.O., R. Habibi, and B.M. Meier, *Has Global Health Law Risen to Meet the COVID-19 Challenge? Revisiting the International Health Regulations to Prepare for Future Threats.* Journal of Law, Medicine & Ethics, 2020. **48**(2): p. 376-381.
4. Wilson, K., J.S. Brownstein, and D.P. Fidler, *Strengthening the International Health Regulations: lessons from the H1N1 pandemic.* Health Policy Plan, 2010. **25**(6): p. 505-9.
5. Gostin, L.O., C.C. Mundaca-Shah, and P.W. Kelley, *Neglected Dimensions of Global Security: The Global Health Risk Framework Commission.* Jama, 2016. **315**(14): p. 1451-2.
6. Burley, S.K., *How to help the free market fight coronavirus.* Nature, 2020. **580**(7802): p. 167.
7. Gates, B., *Innovation for Pandemics.* N Engl J Med, 2018. **378**(22): p. 2057-2060.
8. Rudenko, L., et al., *Development and approval of live attenuated influenza vaccines based on Russian master donor viruses: Process challenges and success stories.* Vaccine, 2016. **34**(45): p. 5436-5441.
9. Yamada, T., V.A. Ogawa, and M. Freire, *Policy: Security spending must cover disease outbreaks.* Nature, 2016. **533**(7601): p. 29-31.
10. Garfinkel, M., P.J. Sansonetti, and B. Pulverer, *Survival of the Wealthiest?* Embo j, 2020. **39**(23): p. e107227.

11. Bump, J.B., P. Friberg, and D.R. Harper, *International collaboration and covid-19: what are we doing and where are we going?* Bmj, 2021. **372**: p. n180.

12. Johnson, S.B., *Advancing Global Health Equity in the COVID-19 Response: Beyond Solidarity.* J Bioeth Inq, 2020. **17**(4): p. 703-707.

13. Bogich, T.L., et al., *Preventing pandemics via international development: a systems approach.* PLoS Med, 2012. **9**(12): p. e1001354.

14. Casale, M., *COVID-19: Can this crisis be transformative for global health?* Glob Public Health, 2020. **15**(11): p. 1740-1752.

15. Usher, A.D., *WHO launches crowdfund for COVID-19 response.* Lancet, 2020. **395**(10229): p. 1024.

16. Bedford, J., et al., *COVID-19: towards controlling of a pandemic.* Lancet, 2020. **395**(10229): p. 1015-1018.

17. Burkle, F.M., *Political Intrusions into the International Health Regulations Treaty and Its Impact on Management of Rapidly Emerging Zoonotic Pandemics: What History Tells Us.* Prehosp Disaster Med, 2020. **35**(4): p. 426-430.

18. Nay, O., et al., *The WHO we want.* Lancet, 2020. **395**(10240): p. 1818-1820.

19. Birn, A.E. and L. Nervi, *(Re-)Making a People's WHO.* Am J Public Health, 2020. **110**(9): p. 1352-1353.

20. Fineberg, H.V., *Pandemic preparedness and response--lessons from the H1N1 influenza of 2009.* N Engl J Med, 2014. **370**(14): p. 1335-42.

21. Gostin, L.O. and D. Sridhar, *Global health and the law.* N Engl J Med, 2014. **370**(18): p. 1732-40.

22. Markel, H., *Worldly approaches to global health: 1851 to the present.* Public Health, 2014. **128**(2): p. 124-8.

23. Fidler, D.P. and L.O. Gostin, *The WHO pandemic influenza preparedness framework: a milestone in global governance for health.* Jama, 2011. **306**(2): p. 200-1.

24. Abubakar, A., et al., *Fourth meeting of the Eastern Mediterranean Acute Respiratory Infection Surveillance (EMARIS) network and first scientific conference on acute respiratory infections in the Eastern Mediterranean Region, 11-14 December, 2017, Amman, Jordan.* J Infect Public Health, 2019. **12**(4): p. 534-539.

25. Rourke, M., et al., *Policy opportunities to enhance sharing for pandemic research.* Science, 2020. **368**(6492): p. 716-718.

26. Rourke, M.F., *Access by Design, Benefits if Convenient: A Closer Look at the Pandemic Influenza Preparedness Framework's Standard Material Transfer Agreements.* Milbank Q, 2019. **97**(1): p. 91-112.

27. Bell, M., A. Warren, and L. Budd, *Scales of governance: the role of surveillance in facilitating new diplomacy during the 2009-2010 H1N1 pandemic.* Health Place, 2012. **18**(6): p. 1404-11.

28. Pang, T., *Is the global health community prepared for future pandemics? A need for solidarity, resources and strong governance.* EMBO Mol Med, 2016. **8**(6): p. 587-8.

29. Mons, B., *The VODAN IN: support of a FAIR-based infrastructure for COVID-19.* Eur J Hum Genet, 2020. **28**(6): p. 724-727.

30. Briand, S., A. Mounts, and M. Chamberland, *Challenges of global surveillance during an influenza pandemic.* Public Health, 2011. **125**(5): p. 247-56.

31. Bresee, J., et al., *Progress and Remaining Gaps in Estimating the Global Disease Burden of Influenza.* Emerg Infect Dis, 2018. **24**(7): p. 1173-1177.

32. Maxmen, A., *Why did the world's pandemic warning system fail when COVID hit?* Nature, 2021. **589**(7843): p. 499-500.

33. Taylor, A.L., et al., *Solidarity in the wake of COVID-19: reimagining the International Health Regulations.* Lancet, 2020. **396**(10244): p. 82-83.

34. Neogi, S.B. and G.S. Preetha, *Assessing health systems' responsiveness in tackling COVID-19 pandemic.* Indian J Public Health, 2020. **64**(Supplement): p. S211-s216.

35. Gostin, L.O., R. Habibi, and B.M. Meier, *Has Global Health Law Risen to Meet the COVID-19 Challenge? Revisiting the International Health Regulations to Prepare for Future Threats.* J Law Med Ethics, 2020. **48**(2): p. 376-381.

36. Zarocostas, J., *What next for the coronavirus response?* Lancet, 2020. **395**(10222): p. 401.

37. Habibi, R., et al., *Do not violate the International Health Regulations during the COVID-19 outbreak.* Lancet, 2020. **395**(10225): p. 664-666.

38. Gostin, L.O., S. Moon, and B.M. Meier, *Reimagining Global Health Governance in the Age of COVID-19.* Am J Public Health, 2020. **110**(11): p. 1615-1619.

39. Eyawo, O. and A.M. Viens, *Rethinking the Central Role of Equity in the Global Governance of Pandemic Response.* J Bioeth Inq, 2020. **17**(4): p. 549-553.

40. Mallapaty, S., *Scientists' worlds will shrink in the wake of the pandemic.* Nature, 2020. **582**(7811): p. 169-170.

41. Bassat, Q., et al., *The first Global Pneumonia Forum: recommendations in the time of coronavirus.* Lancet Glob Health, 2020. **8**(6): p. e762-e763.

42. *The need for a coordinated international pandemic response.* Bull World Health Organ, 2020. **98**(6): p. 378-379.

Appendix

Table 1: Global Collaboration Search Strategy Conducted on PubMed 2021

Concept Terms	#	Search Terms	Results
International Stakeholders	1	Federal Government[Mesh] OR Government Agencies[Mesh] OR Organizations[Mesh] OR World Health Organization[Mesh]OR International Agencies[Mesh]	463,045
Collaboration	2	International Cooperation[Mesh] OR Public-Private Sector Partnerships[Mesh] OR Intersectoral Collaboration[Mesh] OR Global Health[Mesh] OR Public Health Surveillance[Mesh] OR International Health Regulation*[Mesh]	198,458
Pandemic	3	Pandemic*[Mesh] OR COVID-19[Mesh]	70,661
	4	#1 AND #2 AND #3	379

Table 2: Mechanisms of Global Collaboration to Prevent Pandemics

Mechanisms of Global Collaboration to Prevent Pandemics

Intervention	Key Findings	Articles Reviewed
Research & Development & Distribution	Research and Development(R&D) of therapeutics and vaccine candidates is key to prevent pandemics • Key aspects of R&D are sustainable investments, access to intellectual property, data, and biological samples as needed. • Research collaboration on scientific papers have been shown to shrink during outbreaks, as scientists fall back on known collaborators. • There is a focus on R&D in the Global North, with the Global South being left out of advancements, therapeutic trials, etc. New mechanisms of vaccine allotment and distribution have appeared during the COVID-19 pandemic • COVAX group (CEPI, GAVI and WHO) has announced it intends to distribute 2 billion doses to its member countries.	[5] [8] [9] [7] [6] [10] [12] [40] [11]
Financial Mechanisms	The WHO has two primary sources of revenue: assessed contributions expected to be paid by member state governments and voluntary contributions provided by member states, private organizations, and individuals. Bilateral and international development aid agencies, such as United States Agency for International Development (USAID) and World Bank, address pandemic prevention as a development issue, typically providing funding through emergency response avenues. There has been a change in funding streams and allocation of funds from more broad systems to specific diseases in funding agencies. This trend has also been occurring among donors who are specifying their funds for specific disease rather than infrastructure or development. • "According to the Organization for Economic Co-operation and Development (OECD), infectious disease control aid commitments have increased from 8% between 1990 and 1998 to 16% between 2005 and 2008, while basic health infrastructure aid commitments have declined from 11% to 5% during this period." [13]	[13] [22] [41] [16] [17] [14] [18] [15] [11]

Information Networks/ Surveillance/ Data-sharing	Global Influenza surveillance network (GISN) is a major global partnership: • 131 national influenza centers (NICs) in 105 countries • 5 highly specialized collaborating centers (WHO CCs) • 3 national licensing agencies or essential regulatory laboratories Global Public Health Information Network (GHPIN) is an internet based early warning system • continuously scans global media sources such as the web pages of major newspapers, biomedical journals and electronic-mail-based discussion groups • unusual disease events are verified with countries Global Influenza Surveillance and Response System (GISRS) • global network of laboratories that aim to provide the WHO with information regarding the spread of influenza Pandemic Influenza Preparedness (PIP) Framework • governs sharing of influenza viruses with human pandemic potential and the sharing of benefits • encourages member states to share PIP biological material with a WHO CC on Influenza or WHO H5 Reference Laboratory • providing materials equates to consenting to the transfer and use of these materials within and outside GISRS Global Outbreak and Alert Response Network (GOARN) • network of a multitude of different public health institutions, laboratories and NGO's that observe and respond to outbreaks FluNet • global web-based tool used for influenza surveillance Virus Outbreak Data Network (VODAN) • is a newly created data network infrastructure that supports evidence-based responses, it focuses on FAIR data: findable, accessible, interoperable, and reusable	[4] [30] [23] [27] [20] [21] [28] [31] [24] [26] [16] [12] [29] [25] [11] [32]

Table 3: Gaps and Obstacle to Global Collaboration

Gaps and Obstacles to Global Collaboration		
Gap	**Key Findings**	**Articles Reviewed**
Funding Mechanisms	Public health programs are trending toward establishing vertical, disease-specific global health programs. • Funding for basic health infrastructure and development may be forgotten affecting the capacity of countries and systems too function over the long term. • Due to this specificity, there are also a proliferation of programs and organizations in the public health world creating a fragmentation of funds. • There is a clear need to invest in research and development. WHO Financing • National interests may conflict with a mandate to equitably protect the health of everybody as the nations they are trying to regulate are the same nations that fund them. • More than 80% of funds are earmarked by donors for particular activities which gives control to certain high-income countries.	[13] [20] [22] [9] [7] [19] [17] [14] [18] [15] [11]
Capacity of Nations	Global collaboration is dependent on the individual capacities of nations in preventing and responding to pandemics or outbreaks. The gaps and impediments in a country's ability to respond hinders the global response to an outbreak. WHO pandemic preparedness guidance grants member states the right to develop their own national plan. Current WHO metrics for preparedness do not necessarily match with the best response by a country. WHO metrics might need to be revised to better capture the preparedness of a country. Collaboration within the nation is critical to the response.	[30] [27] [5] [28] [17] [14] [34] [33]

Enforcement/ Legal Mechanisms	A key factor in the COVID-19 pandemic has been the inability of the WHO to enforce its guideline, recommendations or the IHR mandates. Recommendations have fallen on deaf ears across the world which has the public health world discussing how this can be adjusted for future pandemics. Though it has been evident during COVID-19, other past outbreaks such as SARS and H1N1 have shown the same gaps. **IHR(2005)** • does not contain a mandatory dispute settlement process or enforcement mechanism • continual reporting of epidemiological and clinical data is not mandated • provided the WHO with a legal basis for requesting the withdrawal of unilateral measures by countries though the so far measures by countries have come with little to no consequences **WHO** • has Treaty-making powers, but needs two thirds of the assembly to vote in a conventions favor • soft law mechanisms such as the creation of norms or formal recommendations have been used, though some nations have disregarded them during pandemics and outbreaks • WHO and IHR do not hold power over nonstate actors which are increasingly playing a major role in Public Health	[4] [30] [27] [21] [42] [35] [38] [37] [18] [25] [33] [36] [32]
Competition/ Hyper-Nationalism by Nations	During the COVID-19 pandemic one of concerning obstacles to global collaboration was the competition between nations for public health commodities such as personal protective equipment (PPE) as well as therapeutics and vaccines. • High income countries (HIC) have outbid low- and middle-income countries (LMIC) for supplies which hindered the global response to COVID-19 Another concerning obstacle to global collaboration is hyper-nationalism, with nations disregarding the IHR and WHO's recommendations as they see fit under the guise of "protecting" their nations.	[39] [10] [38] [37] [11]