

Progress in the Global Framework for Infectious Disease Control in over the Past Thirty Years; What Did We Achieve and Where Are We Going?

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Abstract

In the past 30 years, the accelerating spread of emerging or reemerging infectious diseases resulted in outbreaks in which originating countries could not contain infections within their territory. Given the challenges facing limited number of organizations tasked to handle increased global devastation caused by these numerous infectious diseases, there has been progress during the late 20th century and the early 21st century toward a revised framework for global infectious disease control, including innovative measures to cope with more frequent pandemics. The progress in the framework includes the establishment of UNAIDS, the Global Fund, and new public-private partnerships, such as the STOP Tuberculosis partnership. Although these new entities/organizations had a significant impact on targeted infectious diseases control through the provision of abundant funds and globally unified strategies for developing countries, there were disadvantages to these disease specific (so-called vertical) approaches that led to a shift to horizontal approaches to strengthening health systems. Additionally, there have been innovative changes in programmatic components of infectious disease control, such as the introduction of the concept of “global health security” and the revision of the International Health Regulations. The concept of “global health security” has linked the concept of health security to a global strategy for the prevention of communicable diseases across national borders, though there are persistent discrepancies between developed and developing countries in their understanding of the concept, which hampered international collaboration during the COVID-19 pandemic. Despite this general progress and new initiatives, international aid failed to strengthen health systems in developing countries, which might have subsequently led to limited capacities for infectious disease control as well. These situations collectively resulted in difficulty controlling the Ebola virus outbreak in West African countries in 2014. These tragic experiences led to the proposal of several important initiatives to prevent future pandemics, including reforms of WHO and the preparation of emergency funding mechanisms. The most important points, which strongly relate to the current pandemic of COVID-19, were 1) focusing on resilience to strengthen health system and 2) a better understanding of the significance of community involvement. Conceptual debates on how to develop resilient health systems have continued, with discrepancies between developed and developing countries’ understanding of the concept exacerbated during the COVID-19 pandemic. It is therefore important to focus on developing practical road maps for the establishment of resilient health systems that are applicable to each country based on its context and prioritize “building trust” within countries and among international society.

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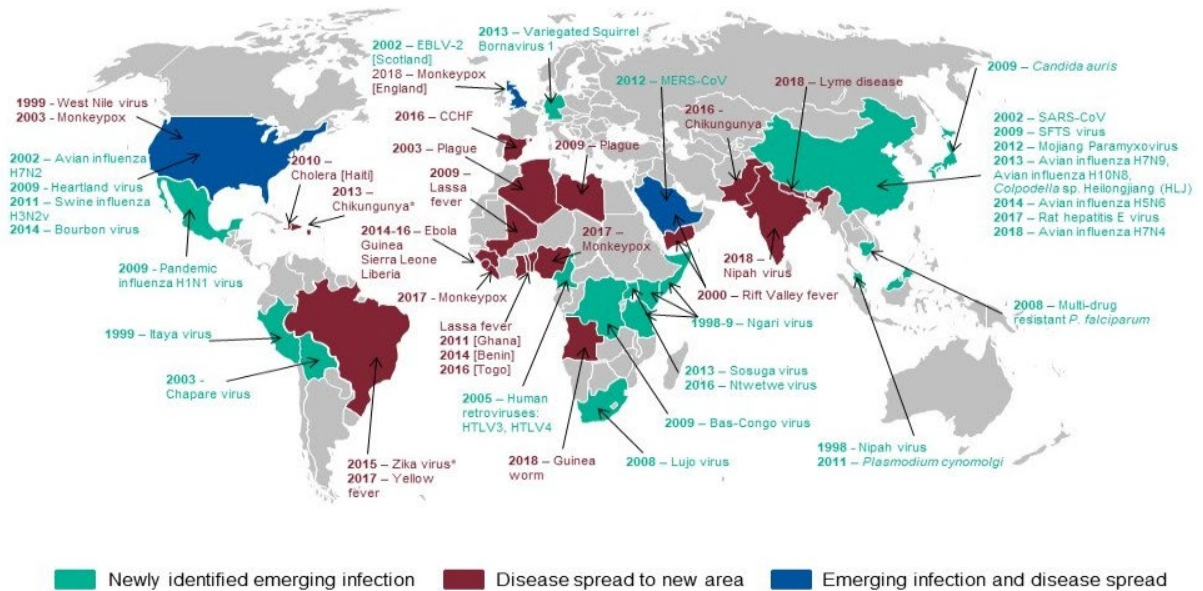
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Introduction

Throughout human history, infectious diseases have emerged as the result of the introduction of new pathogens or reemerged after having been brought under control. Those were then widely spread across borders. The term “emerging infectious disease” is used to define diseases that have newly appeared in the population or have previously existed but are rapidly increasing in incidence or geographic range. The term “reemerging infectious disease” is used to define diseases that reemerge after remaining in environmental reservoirs waiting for an opportunity to prosper. While such outbreaks of infectious diseases have occurred in cycles, in recent decades, the emergence of new infections has accelerated due to several reasons, including: changes in the ecosystem; climate change; increased opportunities for contact with wild animals that carry pathogens; globalization, which allows for the rapid spread of diseases through advanced transportation systems; and urbanization accompanied by poor hygiene systems (Morens et al. 2013; Smith et al. 2014; Fenollar and Mediannikov 2018). Since 1998, there have been many outbreaks of emerging and reemerging infectious diseases (as shown in Figure 1), some of which have caused serious pandemics.

Figure 1: Global map of significant new emerging infections in humans

Global map of significant and new emerging infections in humans: spread to new areas since 1998



*Incursion followed by regional spread

Source: The Government of United Kingdom 2001 - “Emerging infections: how and why they arise”¹

As shown in Figure 1. above, there were many instances where the country of origin was unable to contain an infection within its territory, resulting in the spread of infections to other countries with significant consequences. As the number of these outbreaks has increased, international coordination in response to such outbreaks has become more significant (Bloom and Cadarette 2019; Gersovitz 2014). During the mid-20th century, countries were the key actors in infectious disease control through management of public health in each country. Thereafter, in line with progress in globalization, international governance mechanisms began to play important

¹ <https://www.gov.uk/government/publications/emerging-infections-characteristics-epidemiology-and-global-distribution/emerging-infections-how-and-why-they-arise> (accessed on March 16th, 2022).

roles in infectious disease control. The World Health Organization (WHO) was a core actor in these mechanisms and successfully eradicated smallpox in the late of 20th century (Fidler 2003).

However, at that time, only a few organizations handled the increased global devastation caused by numerous emerging and reemerging infectious diseases and this condition had led to several difficulties. In response to these situations, the framework for global infectious disease control progressed and changed in the late 20th century and the early 21st century, and innovative measures were developed to cope with more frequent pandemics and newly appearing problems (Fidler 2003). Some of these changes and measures related not only to infectious disease control, but also to the development of the entire health system. These changes and newly taken measures eventually brought significant achievements and progress in global infectious disease control; however, important problems and challenges remain unsolved, resulting in subsequent pandemics such as the Ebola virus disease (EVD).

This brief review will outline the progress of the frameworks and measures taken to control global infectious diseases from the late 20th century up to now, with a focus on the following questions: “What problems and challenges triggered the progress and measures?” “What arguments were behind them?” and “What issues remain unsolved even now?” An understanding of the developments in global infectious disease control is critical for developing a response to infectious diseases and determine a path forward in the current situation where pandemics frequently occur.

1. Progress in global frameworks and mechanisms to control infectious diseases up to the early 21st century

Changes in global governance mechanisms in the late 20th and early 21st centuries involved not only countries and international organizations, but also multi-lateral corporations and

nongovernment organizations to cope with the complex situations around the world, which required significant inputs. Although these multilateral corporations were promoted mainly by development banks and UN agencies, such as the WHO or the United Nations Children’s Fund (UNICEF), their role became more critical as globalization progressed. Additionally, new entities were created, such as UNAIDS² in 1994, The Global Fund (GF, originally the Global Fund to Fight against AIDS, Tuberculosis and Malaria)³ in 2002, and the GAVI-Alliance⁴ in 2002, as well as public-private partnerships such as the Roll Back Malaria Partnership to End Malaria⁵ in 1998 and the STOP Tuberculosis (TB) partnership⁶ in 2001. These new entities and organizations brought significant benefits and had a positive impact on targeted infectious disease control through the provision of abundant funds for developing countries, particularly low- and middle-income countries (LMICs). Additionally, they helped develop globally unified strategies with common targets and simple and effective approaches and interventions. As a result, these new entities provide common international regimes for infectious disease control and seek to provide “global public goods” for health, which can be used in developing countries to reduce the prevalence of specific infectious diseases. Although these mechanisms have made tremendous progress in targeting infectious diseases (UNAIDS 2021; WHO 2020A; WHO 2021A; WHO and UNICEF 2020), they have supported only specific disease programs “vertically” – such as the control of the spread of HIV/AIDS or TB control – and were not sufficient to effectively and sustainably create global public goods for common use.

At the same time, with a significant portion of emerging and reemerging diseases being zoonotic, a number of multi-sectoral mechanisms for infectious disease control between animals

² <https://www.unaids.org> (accessed on March 16th, 2022)

³ <https://www.theglobalfund.org/en/> (accessed on March 16th, 2022)

⁴ <https://www.gavi.org> (accessed on March 16th, 2022)

⁵ <https://endmalaria.org> (accessed on March 16th, 2022)

⁶ <https://stoptb.org> (accessed on March 16th, 2022)

and humans were initiated. This streamlined approach was supported by a tripartite of the WHO, the Food and Agricultural Organization of the United Nations (FAO), and the World Organization for Animal Health (OIE), which was established in 2010. The tripartite of organizations concentrated on three main technical topics: antimicrobial resistance, rabies, and zoonotic influenza, and was a representation of the importance of multi-sectoral collaborations (FAO, OIE and WHO 2010). Subsequently, the concept of “One Health” has become an important approach for infectious disease control (FAO, OIE and WHO 2019).

By the early 21st century, several global frameworks and mechanisms for infectious disease control had been developed; these same frameworks have remained generally unchanged up to now and have been complemented by new organizations and initiatives.

2. The concept of global health security

Around the mid-1990s, the concept of “human security” was introduced both in terms of the security of individuals and countries. The term has been widely used as one of the aims of development assistance. Health was listed as one of the seven categories of threats to human security as defined by the United Nations Developmental Program (UNDP 1994). As a result, health concerns have been linked to human security (Aldis 2008). In 2001, the World Health Assembly (WHA) issued Resolution 54.14 ‘Global health security: epidemic alert and response.’ The resolution highlighted the fact that, due to the rapid progress of globalization, any upsurge in cases of infectious diseases in one country could potentially concern the international community as a whole (WHA 2001). It linked the concept of health security to a global strategy for the prevention of communicable diseases across national borders, and asked member states to enhance their capacity and activities in various areas, such as the verification and validation of

surveillance data. Moreover, member states were required to develop and update national preparedness measures, which in turn resulted in support for the acceleration of a revision of the International Health Regulations (IHR), as described in the next section.

In November 2001, the Global Health Security Initiative (GHSI)⁷ was launched by several advanced countries and groups of countries, including the EU. The GHSI, an informal international partnership between developed countries, aimed to confront new threats and risks to global health, including biological, chemical, or radio-nuclear terrorism. The GHSI has facilitated support from developed countries to strengthen the capacity of developing countries to control infectious diseases. Additionally, the initiative intended to "strengthen public health preparedness and response to the threat of international biological, chemical, and radio-nuclear terrorism." (Fidler 2007). As such, it subsequently contributed to the acceleration of health as an important foreign policy issue. However, developing countries have been suspicious of the GHSI as they felt it would work to protect developed countries, especially from bioterrorism. This suspicion resulted in discrepancies in how developed and developing countries understand the concept of "global health security" (Aldis 2008). As the concept of "health security" has remained a prominent rationale for developed countries to invest in global health initiatives, this discrepancy has remained a potentially sensitive issue that may act as a barrier to the development of well-functioning global mechanisms for infectious disease control. While measures had been taken to balance out the health security goals of developed countries and the health equity and development goals of developing countries, these gaps have affected debates in various areas, including on the trade-offs between targeted vertical disease-focused donor aid versus strengthening health systems", as described later (Garrett 2007; Aldis 2008; Bond 2008).

⁷ <http://ghsi.ca/>

3. Revision of the IHR

In parallel to the advancements in the global frameworks and enhancement of recognition of infectious diseases as global threats, several important programmatic components for infectious disease control were renewed or developed. Among them, revision of the IHR was a significant development in the global effort to cope with increasing threats by emerging and reemerging infectious diseases. The IHR, which was renamed from “international sanitary regulations” adopted in 1951, was a legally binding set of regulations and one of the earliest multilateral regulatory mechanisms strictly focusing on global surveillance for communicable diseases (WHA 1995; WHO 1996). There were several major weaknesses in the original version of the IHR, including its focus on only three diseases (cholera, the plague, and yellow fever); a lack of instructions on international measures to cope with outbreaks, such as proper notification measures; and the absence of authority within the WHO to recommend proper guidance on trade and travel restrictions. In 1995, in light of this criticism, the WHO began to revise the IHR; however, after 1998, this procedure slowed down due to conflict over the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and demands for access to anti-retroviral treatment (ART) for African countries. The introduction of the “Global health security: epidemic alert and response” in 2001, described above, and the outbreak of SARS in 2003, again accelerated the revision processes and in 2003, a draft was presented to the WHA (WHA 2003). In 2005, the WHA approved the release of the final draft for governmental and non-governmental review. The final revised version of the IHR went into effect in 2007. The major provisions of the revised version are as follows:

- The purpose of the regulations is to “prevent, protect against, control and provide a public health response to the international spread of disease” in a manner that “avoids unnecessary interference with international traffic and trade.”
- In addition to infectious diseases, the targets covered by the IHR were extended to all events that may potentially threaten human health, including chemical and nuclear contamination.
- All member states are required to develop “core capacity” in areas of prevention, detection, and containment of infectious public health threats including surveillance and laboratory diagnostic capacity. This may indicate increased focus on cross-cutting approaches rather than a disease-specific approach to cope with any infectious diseases, including unknown or emerging diseases.
- All member states are required to report events that may be considered as a Public Health Emergency of International Concern (PHEIC) to the WHO in a timely manner.

Following the introduction of the revised IHR, all member states were asked to develop “core capacity” by 2012. During this time, the world experienced the H1N1 pandemic (2009) and the IHR was reevaluated accordingly. Although there were certain arguments against the revised regulations, especially regarding the determination of health crisis event as a PHEIC, it was generally agreed that the revised IHR could provide a robust framework for responding to public health emergencies through international reporting and communication systems. However, critics (WHO 2011A; Wilson et al. 2010) pointed out the limitations and weaknesses of the revised IHR, particularly on its implementations in each country, and suggestions to address these limitations and weakness were developed as below.

- Accelerate the development of core capacities required by the IHR, especially for surveillance and response.
- Establish a more extensive global public health reserve workforce.
- Create a contingency fund for public health emergencies.
- Agree on a guarantee that allows access to benefits by countries that provide pathogen isolates.
- Issue temporary recommendations concerning the management of a pandemic.
- Monitor responses for unnecessary trade, travel, and human rights restrictions.

However, some issues remained unresolved during subsequent major global threats, such as the EVD outbreaks in West African countries in 2014 or the current global COVID-19 pandemic. Also, up to now, an evaluation of the contents of the IHR themselves have not been thoroughly undertaken and arguments on what is lacking in the contents of the IHR were only presented after the EVD outbreaks in 2014.

4. From vertical to horizontal: health system strengthening (HSS)

The global framework for infectious disease control provided support to developing countries mainly through vertical targeted disease-specific approaches. However, concerns were raised about the disadvantages of these approaches, which affected the entire provision of health services in developing countries. As a result, the concept of health system strengthening (HSS) was introduced as a strategic approach.

In 2001, the WHO issued “The World Health Report 2000 - Health systems: improving performance.” This report attempted to accelerate the development of evidence-based evaluations on the outcomes of health systems and the determinants of these outcomes through an assessment

of the performance of health systems in all member states. Despite its innovative content, the report received significant criticism due to its ranking of the health system performance of all member states by reliability (Navarro 2000; Murray and Frenk 2001). However, the report has greatly contributed to the subsequent development of the HSS strategy, by: 1) placing the assessment of health system performance firmly on the political and research agendas; 2) identifying the elements of a health system; and 3) explaining the concept of resource generation, focusing on non-monetary resources such as human resources and medical products/facilities (McKee 2010). Subsequently, there were concerns about disease-specific vertical approaches, especially for infectious diseases, which included:

- Vertical programs targeting specific diseases with abundant funding, accelerated the shift of human resources to selected areas, which in turn resulted in a lack of human resources in areas for basic primary health care (PHC). (Garrett 2007; WHO 2009A).
- There was a delay in achieving targets in Mother and Child Health (MCH) compared to significant progress in infectious disease control. This was due to weak health systems in developing countries, which hampered the effective utilization of investments (Task Force on Global Action for Health System Strengthening 2009).

In addition to these influential arguments, the global economic crisis of 2008 pushed developed countries to reconsider the use of their limited financial resources. Thus, for effective investment, the significance of “cross cutting approaches” for HSS increased in the global health context. However, despite the comprehensive view of the health system proposed by the WHO and the fact that many aspects of infectious disease control lay the groundwork for HSS, there has been slow progress in HSS in developing countries, due to following factors: (WHO 2007; WHO 2009B; Blanchet 2015).

- As vertical disease-specific approaches remained important for donors, measures and efforts to strengthen health systems with increased external aid mainly focused on a limited number of infectious diseases such as HIV/AIDS, TB, and Malaria, as well as MCH.
- The proposed definition of HSS did not really reflect interactions between actors and dynamic adaptations happening within a system.
- This context of HSS was perceived as being a constraining framework and consequently, HSS interventions resulted in standard practical road maps policies often duplicated from the health systems of western countries without any adjustment to local and contemporary contexts

5. Other important progress in programmatic components of global infectious disease control

In parallel to the progress discussed above, several other important programmatic components of the frameworks for global infectious disease control were introduced in the early 21st century, which significantly affected global strategic directions for infectious disease control.

5.1 The concept of macroeconomics and health

The Commission on Macroeconomics and Health was established by the WHO in January 2000, to assess the place of health in global economic development. The commission's, "Investing in Health for Economic Development", provided a new strategy for investing in health for economic development, especially in the world's poorest countries, based on a new global partnership between developing and developed countries (WHO 2001). Its principal finding was that scaled-up investments in the health sectors of low-income developing countries would bring about economic benefits 6 times larger than those increased investments, which correspond to donors'

contribution of the order of 0.1% of their GDP. The report aimed to focus on primary healthcare, such as infectious disease control and MCH, but detailed analysis in each country related mainly to HIV/AIDS control. This was the first assessment of the investment needed for necessary interventions with clear targets based on the situation in each country. Although this report did not have an instant impact on global health governance, it served as a basis and model for the concept of the subsequent global investment strategies by international societies for infectious disease control.

5.2 Intellectual Property declaration at WTO 4th ministerial conference 2001

After the establishment of the World Trade Organization (WTO) in 1995, the so-called “TRIPS” agreement was seen as the most comprehensive multilateral agreement on disputes regarding intellectual property (IP) rights. As this agreement covered IP for medicine and medical products, access to good quality medicines by developing countries had been restricted, resulting in hampered implementation of necessary interventions for infectious disease control such as ART in African countries. In 2001, the Doha Declaration on Public Health was adopted at the WTO 4th ministerial conference (WTO 2001). This document was a response to the dissatisfaction of developing countries with certain aspects of the TRIPS regime, especially in regard to major infectious diseases such as HIV/AIDS, TB, and malaria. The declaration committed member states to interpret and implement the TRIPS agreement in a way that supported public health and promoted access to medicines. In particular, it directed member states to recognize certain “flexibilities” in the TRIPS agreement to allow each member to grant compulsory licenses for pharmaceuticals. Although this agreement could not clear all barriers to providing necessary high-quality, low-cost medicine to developing countries, it contributed to the acceleration of measures

in this direction and led to the subsequent establishment of UNITAID⁸ in 2007 and the Medicines Patent Pool (MPP)⁹ in 2020.

5.3 The Pandemic Influenza Preparedness framework

Gaps in the understanding of the concept of “Global health security” between developed and developing countries, as described in section 3 above, have affected mechanisms for incentivizing international collaboration in the development of new biomedical countermeasures. At times, manufacturers from high-income countries must rely on low- and middle-income countries (LMICs) to provide the biological samples needed for research and development (R&D); however, LMICs have legitimate concerns that they may not receive an equitable share of any benefits resulting from their contributions, including access to vaccines, drugs, and other products. As a typical example, Indonesia refused to share virus isolates from human cases of H5N1 influenza A infection in 2007 because of the concern that samples provided freely by developing countries will be used by companies in wealthy countries to develop vaccines and other products that are then not affordable in developing countries. Indonesia wanted a guarantee that it would share in the benefits derived from the isolates it provided (Roos 2008).

In light of these debates, the 64th WHA issued the resolution on Pandemic Influenza Preparedness (PIP) Framework for the sharing of influenza viruses and access to vaccines and

⁸ UNITAID was established in collaboration with European countries as a drug purchasing facility to advance international development through supporting the provision of low-cost generic medicines to developing countries with an emphasis on tuberculosis, malaria, and HIV/AIDS and its deadly co-infections. Its financing is unique in that its main income comes from a tax on airline tickets in supporting countries (<https://unitaid.org/#en>, accessed on March 16th, 2022).

⁹ MPP is a United Nations-backed public health organization working to increase access to life-saving medicines for low- and middle-income countries. The Patent Pool employs innovative business models with stakeholders pooling intellectual property for prioritized and license needed medicines by pharmaceutical industries in exchange for financial support. This may eventually encourage the manufacture of generic medicine that can be provided to developing countries. Medicines that are targeted in the MPP are those used for HIV/AIDS, hepatitis C, and TB, but recently COVID-19 related medicines have also been included. (<https://medicinespatentpool.org/who-we-are/about-us>, accessed on March 16th, 2022.)

other benefits. Considering isolates of viruses and the vaccines developed from them to be equally important to collective action for global public health, this resolution urges member states to commit to sharing these equally in cases of H5N1 and other influenza viruses with the potential to cause a human pandemic. It also urges all stakeholders to recognize that the benefits arising from the arrangement described above, including access to and distribution of affordable vaccines, diagnostics and treatments to those in need in a timely manner, should be shared with all member states on the basis of public health risk and need (WHO 2011B).

5.4 Nagoya Protocol

The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity was adopted in October 2009. Its objective was the fair and equitable sharing of benefits arising from the use of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity (Convention on Biological Diversity United Nations Environmental Program 2011). Although this protocol was intended to preserve biological diversity, it eventually covered the utilization of pathogens for infectious diseases. Practically, companies that want to obtain pathogens to develop medicines, vaccines, or diagnostic kits for commercial use are obliged to obtain approval from the relevant governments and develop contracts with suppliers (such as research institutes) that may include benefit sharing. For infectious disease control, implementation of the Nagoya Protocol, along with PIP, which is considered to be a special international agreement under the Nagoya Protocol, can support rapid and systematic access to pathogens that affect human health, through clear and harmonized rules. At the same time, it ensures fair and equitable sharing of benefits arising from the utilization of those pathogens. Rapid access to pathogens would facilitate and speed up risk assessment as well as the development of vaccines and medicines, while fair

and equitable benefit sharing can improve access to affordable treatments even in developing countries. The protocol was also expected to enhance joint ownership of intellectual property rights and the transfer of technology.

However, there has been disagreement about whether the Nagoya Protocol should be applied to infectious diseases. The WHO reported that access and benefit-sharing arrangements have become common, especially between collaborating laboratories that cover patents, technology transfers, shared publication authorship and ownership, for example, although there are variations in these arrangements among pathogens. At the same time, the report indicated concerns regarding the slowdown of sample sharing due to lengthy bilateral negotiations for material transfer agreements and procedures, which jeopardize prompt measures against endemics/pandemics, such as risk assessment or vaccine virus selection processes (WHO 2021B; Cressey 2014). In reality, under the Nagoya Protocol and PIP framework, most pathogen sharing has been done bilaterally between countries and on an ad hoc basis, which has been slow and leaves some countries without access to the benefits and tools. Contrary to this, however, on January 10, 2020, in the very early phase of the COVID-19 pandemic, Chinese scientists shared the full SARS-CoV-2 sequence; this sharing of information resulted in the development of multiple vaccines created in record time. In this case, China did not consider any negotiations to develop contracts or obtain rewards, as indicated in the Nagoya Protocol. This fed into the debate around whether it is appropriate to include pathogens under the Nagoya Protocol from the point of view that immediate access to data about a pathogen can be lifesaving (Cueni 2020, 2021).

6. EVD outbreaks and the aftermath

Despite the above-mentioned general progress and new initiatives that arose from the late-1990s up to the early 21st century as result of increased external aid, in most developing countries, only a small portion of external aid was directly invested to support the overall development of health systems and enhance capacities for infectious disease control. This lack of aid resulted in inadequate health systems in developing countries. Moreover, while there were always numerous activities and reports following an outbreak of infectious diseases, political interest quickly waned and important measures that were recommended by international groups of experts or research institutes for infectious disease control remained unachieved. The same occurred with numerous valuable recommendations after the H1N1 pandemic in 2009 described above. These situations collectively resulted in difficult challenges for controlling the EVD outbreaks in West African countries (Liberia, Sierra Leone, and Guinea) in 2014, which led to tragic humanitarian disasters. Consequently, outbreaks in these countries exposed significant weakness and problems not only in infectious disease control, but also in the entire health system; the international community was unprepared for a large-scale pandemic.

6.1 Lessons learned from the EVD outbreaks

The EVD outbreaks in West Africa revealed weaknesses in the essential health system functions and the management capacity within governments. There were many reports from governmental and international organizations and from academia that assessed the backgrounds and situation during the outbreaks, including evaluating the implementation of the IHR. Although those reports provided various conclusions and recommendations for ways forward, the essence of them was summarized by the IHR Review Committee High-Level Conference on Global Public Health

Security conducted by EC as follows (IHR Review Committee High-Level Conference on Global Public Health Security 2016):

- Failure of Member States to fully implement the IHR core capacity requirements was a significant cause of the Ebola escalation.
- Failure of Member States to fully implement the IHR core capacity requirements was strongly related to weak health systems.
- Failure of Member States to fully implement the IHR core capacity requirements was the result of limited assistance and collaboration between State Parties.
- Despite their pertinence, recommendations from the 2010 IHR Review Committee were only partially implemented, which had a major impact on the implementation of the IHR core capacity and was a cause of the Ebola escalation.

In addition to the above points, the haphazard and slow reactions of the international community were also criticized (Commission on a Global Health Risk Framework for the Future 2016).

The weaknesses in health systems were discussed in a number of reports (Kruk 2015; Commission on a Global Health Risk Framework for the Future 2016; Moon 2015; United Nations High-Level Panel on the Global Response to Health Crises 2016). The most important points raised in these reports can be summarized as: shortages of qualified health workers, inappropriate infrastructure, weak surveillance capacity and health information systems, weak capacity for risk assessment and management, and weak logistics systems, including drug supply systems.

In addition, the significance of community involvement was proposed:

- Communities need to be recognized as a central actor in health systems and not simply a recipient of healthcare.

- Engaging and communicating with communities is critical for obtaining the trust and cooperation of local populations who are fundamental to any prevention and response strategies.

In relation to the limited international assistance and collaboration, a number of criticisms were given, including a lack of proper collaboration mechanisms among the international community, a lack of emergency funding mechanisms, weak capacity and leadership within the WHO, and weak international collaborations for R&D on new medicine and vaccine development.

6.2 Measures and initiatives taken after the EVD outbreaks

Considering a summary of lessons learned from the EVD outbreaks, the following issues have become major concerns for international infectious disease control: 1) enhancing international collaboration mechanisms to enhance capacity in each country for proper implementation of the IHR; 2) developing new mechanisms for emergency funding; and 3) enhancing the capacity and leadership of the WHO to cope with emergency health threats.

6.2.1 The Global Health Security Agenda

The EVD outbreaks showed the international community that infectious disease outbreaks would be significant threats not only to health security, but also to global socioeconomics. These concerns led to the establishment of the Global Health Security Agenda (GHSA) in 2014, an international effort for the prevention and control of infections. The Agenda was an initiative of the USA along with 44 countries and organizations including the WHO, OIE and FAO. It was launched as a five-year multilateral effort aimed at accelerating the implementation of the IHR and promoting the concept of “One Health”, particularly in developing countries. Eleven

objective areas were defined under three pillars (Prevent, Detect, and Respond) to enhance capacity for the IHR implementation. Each participant country shared all areas of responsibility. Additionally, the GHSA assessed baseline situations in each country through self-assessments and the “Joint External Evaluation (JEE)” and developed action plans to fully implement the IHR. Although implementation of JEE was integrated into the WHO Strategic Partnership for Health Security and Emergency Preparedness¹⁰ and evaluations were completed in more than 100 countries,¹¹ the initiatives of the GHSA in this area were key to gaining momentum in global health security. Subsequently, the GHSA has worked on collaborative assistance to develop the IHR capacities in developing countries through multi-sectoral engagement and to increase high-level commitments to global health security. In 2017, GHSA was expanded to include non-state actors. It has now been extended to the end of 2024 with the release of the Global Health Security Agenda (GHSA) 2024 Framework (Global Health Security Agenda 2018).

6.2.2 Pandemic Emergency Financing Facility (PEF)

The Pandemic Emergency Financing Facility or “PEF” was developed by the World Bank as a new emergency financing mechanism for outbreaks of designated infectious diseases. The purpose of PEF was to provide financing to developing countries to respond to cross-border, large-scale outbreaks. The PEF’s design was unique in that payments went directly to governments and pre-approved frontline responder organizations (such as the WHO and UNICEF). There were two channels of financing with defined triggers or conditions: insurance (a form of CAT bond) and cash windows. However, after funding was released to help countries

¹⁰ <https://extranet.who.int/sph/> (accessed on March 16th, 2022).

¹¹ <https://extranet.who.int/sph/jee> (accessed on March 16th, 2022).

cope with the outbreak of EVD in the Democratic Republic of Congo, and the COVID-19 pandemic, the facility was officially closed at the end of April 2021 (World Bank 2021).

6.2.3 Reform of the WHO

Although the WHO tried to advance the reform of its programs, the EVD outbreaks exposed the dysfunctionality inherent in its structure and its weak governance, including a lack of capable human resources needed to respond to health emergencies (Clift 2014; Commission on a Global Health Risk Framework for the Future 2016; Moon 2015; United Nations High-level Panel on the Global Response to Health Crises 2016). These criticisms prompted the WHO to make fundamental reforms based on the lessons learned from the EVD outbreaks. The reforms fell under the areas of programs, governance, and management; two notable reforms were quickly implemented, namely the development of one integrated health emergency program and the establishment of the Contingency Fund for Emergencies (CFE).

The WHO health emergency program: The program was developed in 2016 to integrate previously separate programs on outbreaks and humanitarian crises. The program aimed to streamline the WHO emergency response efforts via the formation of a single-incident management system, with one workforce, one budget, one line of accountability, one set of processes and systems, and one set of benchmarks. The program works on an all-hazards approach to cope with any kind of crisis, whether caused by conflict, disease outbreaks, or disasters. Additionally, the program has a common structure across the organization (in-country offices, regional offices, and headquarters) (WHO 2021C).

The Contingency Fund for Emergencies: The CFE was established in 2016 to avail flexible funding for health emergencies totaling approximately 100 million USD. This fund aims to support initial responses by the WHO to cope with health emergencies for a maximum period of 3 months. This fund was utilized during the cholera outbreak in the Democratic Republic of Congo and the yellow fever outbreak in the central African countries (WHO 2021D).

6.3 From HSS to Resilient Health System Strengthening

In addition to changes in the system and the framework to cope with global infectious diseases, arguments were made in favor of the concept of Resilient Health System Strengthening (RHSS) as a way of developing stronger health systems in developing countries. Initially, the term “resilient” was introduced as an adjective for health system strengthening at the time of the global financial crisis caused by the Lehman shock in 2008. This crisis badly affected health systems in European countries, resulting in the reorganization, or actual downsizing, of systems, due to cutbacks in health budgets. After the EVD outbreaks, the idea of RHSS swiftly gained popularity as a concept within global health contexts and there has been wide consensus that the global community must help build more resilient health systems.

Generally, resilience can be understood as the capacity of a system to absorb change but continue to retain essentially the same identity and function. While there have been various discussions about the definition of a “resilient health system” and its contents and components, as yet, no consensus has been reached (Topp 2020). There are many discussions on how to make health systems resilient in relation to broader issues including the effect of climate change, increasing threats by antimicrobial resistance, and shifting disease burdens. Putting opinions and discussions together, the definition of a “resilient health system” may be summarized as a “health system which has the capacity to absorb, adapt, and transform when exposed to a shock and still

retain control over its structure and functions.” Thus, health systems are resilient if they exhibit absorptive, adaptive, or transformational capacity in the face of shocks of different intensity. It is also important that resilient health systems can deliver everyday benefits and positive health outcomes in both good times and bad times; this can be described as the resilience dividend. In addition to solid ordinary health systems with the capacity required for infectious disease control as defined by the IHR, components of resilient health systems could include (see Thomas et al. 2013; Kieny et al. 2014; Kruk et al. 2015; Commission on a Global Health Risk Framework for the Future 2016; Blanchet et al. 2017; Kruk et al. 2017; Hanefield et al. 2018; Fridell et al. 2020; Durski et al. 2020; Biddle et al. 2020; Jit et al. 2021.)

- Legal preparations to address challenges that may emerge during a crisis.
- Adaptable response plans coupled with the required capacity for actors in a system to manage resilience.
- Emergency funds.
- The reserve capacity of a system, especially for human resources and infrastructure.
- Trust by communities for robust community engagement.
- Broader connections and collaborations (global and regional).

In the wake of a number of major international health crises, including the Zika virus outbreaks in 2016 and the EVD outbreaks, conceptual debates on how to develop resilient health systems have intensified with the inclusion of questions around “fragmented health systems.” These debates indicated that the IHR does not clearly include implementation of curative services or clinical surge capacities, including primary healthcare, and focuses on public health areas, resulting in the creation of gaps between the concept of global health security and the concept of

HSS, which could lead to universal health coverage. The imperative of embedding the IHR core capacities for global health security into the main health system functions, has been the subject of discussions on RHSS (Erondu et al., Kluge et al. 2018). These conceptual debates continue today, in the era of COVID-19 pandemic. However, unfortunately they have not yet provided any practical guidance on how to develop resilient health systems that can be adapted to the contexts of developing countries where equal investment to all necessary components of a health system are constrained by limited resources.

7. R&D

Along with progress and changes in the framework and programmatic components of global infectious disease control, there have been important advancements in R&D for infectious disease control particularly in the development of a global framework to accelerate R&D and of international mechanisms for clinical trials.

The frequent emergence and reemergence of infectious disease outbreaks has made R&D for infectious diseases a necessity. It is critical to accelerate R&D in a coordinated manner across the whole range of medical sciences, especially in relation to the development of new medicines, vaccines, and diagnostic reagents (Commission on a Global Health Risk Framework for the Future 2016). However, low returns on investments have discouraged pharmaceutical companies from developing new medicines, vaccines, and diagnostic agencies for infectious disease control (Pedrique et al. 2013). This lack of development has increased the inaccessibility of appropriate diagnosis and treatment for certain infectious diseases in developing countries. Thus, it is essential to develop international mechanisms for securing funds for R&D for infectious disease control and mitigating risks for pharmaceutical companies and academic

institutes to develop new medicines, vaccines, and diagnostic agencies. For this purpose, in addition to independent funding mechanisms provided by international organizations, new funding mechanisms have been developed, including the Drugs for Neglected Disease initiative (DNDi),¹² the Global Health Innovative Technology (GHIT) Fund,¹³ and the Coalition for Epidemic Preparedness Innovations (CEPI).¹⁴ As a result of these new funds, a significant number of new medicines, vaccines, and diagnostic agencies have been developed.

The EVD outbreaks in West African countries revealed difficulties in conducting effective clinical trials for new medicines during a pandemic (Sissoko et al. 2016). This was because there were limitations not only in the design of trials with a large sample size, but also difficulties in implementing randomized control trials properly due to several reasons, including ethics. This strongly indicated the need for large-scale, internationally coordinated clinical trials and integrated clinical research into care standards. In 2017, the Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)¹⁵ was initiated as a platform for a large-scale clinical trial to develop new treatments for community-acquired pneumonia. REMAP-CAP is the first large-scale platform with an adaptive trial design to evaluate a number of treatment options simultaneously. The design of REMAP-

¹² DNDi was established in 2003 as an international non-profit organization initiated by *Médecins sans Frontières* in collaboration with the WHO and five international research institutions such as the Pasteur Institute to develop new medicines and new treatments for neglected tropical diseases. Also, it works to support capacity development and enhance advocacy in related areas. It has already developed 9 new medicines such as fexinidazole and treatment regimens. (<https://dndi.org>) (accessed on March 16, 2022).

¹³ The GHIT Fund was established in 2012 as an international non-profit organization by initiatives of Government of Japan in innovative collaboration with international organizations and pharmaceutical companies. The purpose of the GHIT Fund is to fund the development of medicines, vaccines, and diagnostic agencies for infectious diseases intended for use in developing countries. It has supported to develop more than 40 medicines, vaccines, and diagnostic agencies. (<https://www.ghitfund.org>) (accessed on March 16th, 2022).

¹⁴ CEPI was established in 2017 as an innovative global public private partnership to develop affordable vaccines for developing countries for infectious diseases that could trigger serious outbreaks. For COVID-19, CEPI funded several pharmaceutical companies to develop vaccines. (<https://cepi.net>, accessed on March 16, 2022).

¹⁵ <https://www.remapcap.org> (accessed on March 16, 2022.).

CAP is such that it can adapt to events during a pandemic, ensuring an increased likelihood that patients will receive the treatment that is most likely to be effective for them.

During the COVID-19 pandemic, new large-scale platforms were established, such as the WHO COVID-19 Solidarity Therapeutic Trials¹⁶ and the RECOVERY Trial; Randomized Evaluation of COVID-19 Therapy¹⁷. Although there were several small trials for individual medicines or regimes, which often led to the duplication of efforts and insufficient results, these platforms, as international research collaborations, helped with the quick evaluation of new medicines or the repurposing of old medicines for use against COVID-19 (Jit et al. 2021).

8. The COVID-19 pandemic

The current COVID-19 pandemic has influenced the creation of new international entities to help cope with the pandemic through global collaborations, including the Access to COVID-19 Tools Accelerator (ACT-T),¹⁸ COVAX (COVID-19 Vaccines Global Access) Facility,¹⁹ and the BioHub.²⁰ However, many important points raised after the EVD outbreaks in West Africa in 2014, such as the need for enhanced infectious disease controls, remain unresolved. The current pandemic is still ongoing and there are several important assessments or reports that evaluate the

¹⁶ <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments> (accessed on March 16, 2022).

¹⁷ <https://www.recoverytrial.net> (accessed on March 16, 2022).

¹⁸ The ACT-T was established in 2021 by the WHO as a global collaboration mechanism to speed up an end to the pandemic by supporting the development and equitable distribution of the tests, treatments, and vaccines the world needs to reduce mortality and severe disease. (<https://www.who.int/initiatives/act-accelerator/about> accessed on March 16, 2022)

¹⁹ The COVAX was established in 2020, and co-led by GAVI, CEPI, and the WHO to accelerate the development and manufacture of COVID-19 vaccines and to guarantee fair and equitable access for all countries through innovative mechanisms. (<https://www.who.int/initiatives/act-accelerator/covax>, accessed on March 16, 2022)

²⁰ Established in 2021, the BioHub serves as a center for the safe receipt, sequencing, storage, and preparation of biological materials for distribution to other laboratories, in order to inform risk assessments, and sustain global preparedness against these pathogens. This BioHub will be expected to ensure timeliness and predictability in response to activities. (<https://www.who.int/news/item/24-05-2021-who-and-switzerland-launch-global-biohub-for-pathogen-storage-sharing-and-analysis>, accessed on March 16, 2022.)

current situation, including the implementation of the IHR, and provide recommendations on ways to prevent future pandemics (Independent Panel for Pandemic Preparedness and Response 2021; Sirleaf and Clark 20121; WHO 2021E; Singh et al. 2021). This review does not go into details about these evaluations or recommendations, but addresses some important issues related to the streamlining described above:

- Within the framework of global infectious disease control, the pandemic illustrated the tension between short-term national incentives and long-term imperatives for international cooperation towards achieving global public good. This may lead to an increased necessity for multi-lateral cooperation and additional mechanisms, such as regional frameworks in collaboration for infectious disease control (Jit et al. 2021; Kliem 2021).
- The pandemic tested the resilience of health systems in each country and their ability to withstand shocks while maintaining routine functions, accelerating discussions around what resilient health systems entail. These discussions repeat those that took place after the EVD outbreaks, although current discussions put more emphasis on models/theories for pandemic preparedness defined in the IHR to account for complex effects by COVID-19 pandemic (Lal et al. 2021).
- The pandemic also exposed the importance of community engagement and obtaining trust from communities for effective infection control measures including non-pharmaceutical interventions, as previously suggested (Commission on a Global Health Risk Framework for the Future 2016). In this regard, meaningful community engagement through effective communication of risk is critical – a point that is lacking in current frameworks for health emergencies, such as the IHR (Lal et al. 2021; WHO 2020B).
- Incompatible understandings of “global health security” have frequently surfaced and have again become a central point for debate as significant inequities in vaccine distribution to

developing countries, especially in Africa, remain (Trozenburg 2021; Usher 2021). The situation also accelerated arguments around IP for vaccine production, and debates on whether the Nagoya Protocol should cover infectious diseases (as discussed above) (Zarocostas 2021).

Conclusion

After the establishment of a fundamental framework for global infectious disease control in the early 21st century, the international society continuously added necessary entities and mechanisms for collaboration based on needs and lessons learned from previous outbreaks or pandemics. Along with these developments, programmatic components, such as IP or concepts of global health security, have been introduced or revised. Despite these efforts and advances in medical science, infectious diseases continue to be one of the biggest risks for humankind; the need for enhancement of the current framework for infectious disease control remains critical. This review explored the idea that building “resilient health systems” in each country is a global common target for strengthening mechanisms for global infectious disease control. As discussed in this review, despite the numerous recommendations and proposals in this area, international efforts to build resilient health systems have thus far been insufficient.

Two important points are worth noting: first, efforts should be focused on developing practical road maps for establishing resilient health systems that can be applied to each country based on its context, rather than repeating conceptual discussions, which have thus far failed to strengthen health systems. Second, it is essential that trust is built both within countries and within the international community. While the former indicates gaining the trust and cooperation of local populations, the latter requires drastic changes whereby developed countries as donors need to

obtain the trust of developing countries. The lack of a shared understanding or recognition of the concept of “global health security” between developed and developing countries remains a barrier to global infectious disease control, which has been exacerbated during the COVID-19 pandemic. Filling these gaps is essential to the establishment of well-functioning and coordinated global mechanisms for infectious disease control. The following meaningful suggestion should be borne in mind:

“The response to COVID-19 must target two objectives: to stop the loss of life; and to ensure this doesn’t happen again. We must seize the opportunity to break out of the cycle of panic and neglect that has characterized our approach to infectious disease outbreaks. But a new approach to global health security must embrace a much broader notion of health security than we’ve typically used. To start with, it won’t work if it is only focused on pandemics, since every pandemic starts as a small outbreak. Unless you’re looking at the small sparks, you’ll miss the potential inferno. Even more importantly, it also won’t work if the definition of health security only encompasses infectious diseases that threaten the lives of people in rich countries. Quite apart from the dubious morality of such a distinction, you’ll never succeed in getting countries and communities to care more about diseases that might kill them than those that are killing them... We should not be thinking of people in other countries as disease vectors, but as people.”

Peter Sands, Executive director, the Global Fund (Sands 2021)

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