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Review

Review

Public health emergencies of international concern: a historic overview

Annelies Wilder-Smith, MD[1,2,*] and Sarah Osman, MPH[1]

[1]Global Health and Epidemiology, University of Umea, 901 87 Umea, Sweden and [2]Heidelberg Institute of Global Health, University of Heidelberg, Im Neuenheimer Feld 365, 6900 Heidelberg, Germany

*To whom correspondence should be addressed. Email: anneliesws@gmail.com

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Abstract

Rationale: The International Health Regulations (IHR) have been the governing framework for global health security since 2007. Declaring public health emergencies of international concern (PHEIC) is a cornerstone of the IHR. Here we review how PHEIC are formally declared, the diseases for which such declarations have been made from 2007 to 2020 and justifications for such declarations.

Key findings: Six events were declared PHEIC between 2007 and 2020: the 2009 H1N1 influenza pandemic, Ebola (West African outbreak 2013–2015, outbreak in Democratic Republic of Congo 2018–2020), poliomyelitis (2014 to present), Zika (2016) and COVID-19 (2020 to present). Poliomyelitis is the longest PHEIC. Zika was the first PHEIC for an arboviral disease. For several other emerging diseases a PHEIC was not declared despite the fact that the public health impact of the event was considered serious and associated with potential for international spread.

Recommendations: The binary nature of a PHEIC declaration is often not helpful for events where a tiered or graded approach is needed. The strength of PHEIC declarations is the ability to rapidly mobilize international coordination, streamline funding and accelerate the advancement of the development of vaccines, therapeutics and diagnostics under emergency use authorization. The ultimate purpose of such declaration is to catalyse timely evidence-based action, to limit the public health and societal impacts of emerging and re-emerging disease risks while preventing unwarranted travel and trade restrictions.

Key words: COVID-19, Zika, H1N1, influenza, poliomyelitis, Hajj, measles

Introduction

The International Health Regulations (IHR) have been the governing framework for global health security for the past decade and are a nearly universally recognized World Health Organization (WHO) treaty, with 196 States Parties.[1] The IHR is one of the six leadership priorities of the WHO programme of work, the purpose of which is to promote health and well-being. Declaring public health emergencies of international concern (PHEIC) is a cornerstone of the IHR.[2] The IHR provide an overarching legal framework that defines countries' rights and obligations in handling public health events and emergencies that have the potential to cross borders. The IHR are an instrument of international law that is legally binding on 196 countries, including the 194 WHO Member States. Through IHR, countries have agreed to build their capacities to detect, assess and report public health events. IHR includes specific measures at ports, airports and ground crossings to limit the spread of health risks to neighbouring countries, and to prevent unwarranted travel and trade restrictions so that traffic and trade disruption is kept to a minimum. Here we review how PHEIC are formally declared, the diseases for which such declarations have been made from 2007 to 2020 and justifications for such declarations. Information on PHEIC was manly obtained from WHO sources.

Public health emergency of international concern (PHEIC)

A PHEIC is a formal declaration by WHO of 'an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response', formulated when a situation arises that is 'serious, sudden, unusual or

unexpected', which 'carries implications for public health beyond the affected state's national border' and 'may require immediate international action' (Box 1).[2] States have a legal duty to respond promptly to a PHEIC.

Box 1

The IHR decision algorithm assists WHO Member States in deciding whether a potential PHEIC exists and the WHO should be notified. The WHO should be notified if any two of the four following questions are affirmed:

- Is the public health impact of the event serious?
- Is the event unusual or unexpected?
- Is there a significant risk for international spread?
- Is there a significant risk for international travel or trade restrictions?

The responsibility of determining whether an event is within this category lies with the WHO Director General and requires the convening of a committee of experts—the IHR Emergency Committee. Committee members are selected based on expertise, geographic and gender diversity. This committee advises the Director General on the recommended measures to be promulgated on an emergency basis, known as temporary recommendations. Temporary recommendations include health measures to be implemented by the State Party experiencing the PHEIC, or by other States Parties, to prevent or reduce the international spread of disease and avoid unnecessary interference with international traffic.[3] The recommendations require reviews every 3 months.

WHO Member States have 24 hours within which to report potential PHEIC events to the WHO. It does not have to be a member State that reports a potential outbreak; reports to the WHO can also be received informally.[4] Under the IHR (2005), ways to detect, evaluate, notify and report events are being ascertained by all countries in order to avoid PHEICs. The PHEIC criteria include a list of diseases that are always notifiable, such as SARS, smallpox, wild type poliomyelitis and any new subtype of human influenza are always a PHEIC and do not require an IHR decision to declare them as such.

PHEIC are not confined to only infectious diseases and may cover events caused by chemical agents or radioactive materials. However, to date, all PHEIC declarations have been for viral emerging infectious diseases, not for bacterial diseases, nor for chemical or radioactive materials. The IHR (2005) were endorsed in 2005 and cane into legal force in 2007. Since 2007, there have been six PHEIC declarations,[5] starting with the H1N1 pandemic in 2009. Table 1 summarizes the dates and the recommendations of those six PHEIC.

The Influenza A (H1N1) pandemic 2009

In March 2009, human cases of infection with a novel strain of influenza A virus (H1N1) emerged in Mexico, and Northern America. By 26 May 2009, this virus had spread to 46 countries, accounting for ≈13 000 cases.[6] The IHR (2005) enabled an unprecedented level of timely cooperation and communication for assessing and responding to the novel influenza A virus (H1N1). On 25 April, the Director General of WHO, after convening a meeting of the Emergency Committee, determined that the outbreak of novel influenza A (H1N1) constituted a PHEIC. This was the first declaration of a PHEIC after the entry into force of the IHR (2005). At the initial meeting of the Emergency Committee on April 25, members decided to maintain the current WHO-designated pandemic phase at a level 3 (no sustained human-to-human transmission sufficient to sustain community-level outbreaks). The Emergency Committee met again on 27 April, and on the basis of the developing epidemic, recommended changing from pandemic phase 3 to pandemic phase 4 (human-to-human transmission is verified). Following this recommendation, the Director General upgraded the classification to pandemic phase 4. The epidemic continued to expand globally, and the Emergency Committee met again and determined that the pandemic classification should be changed from phase 4 to phase 5 (the same identified virus is causing sustained community-level outbreaks in multiple countries). The Director General announced on 29 April, 2009 that the world was at phase 5 on the WHO pandemic scale.[6]

Caused by a new strain of influenza type A H1N1 virus which is a re-assortment of several strains of influenza viruses commonly infecting human, avian and swine population, it originated in Mexico and rapidly spread around the world via air travel.[7] WHO reported 18 631 laboratory-confirmed pandemic deaths in 2009, but the total pandemic mortality burden was substantially higher. Modelling estimated the 2009 pandemic mortality to be between 123 000 and 203 000 in 2009, 10 times higher than that reported to WHO.[8] The majority were attributed to persons under 65 years of age.[8] There was a striking regional heterogeneity, with almost 20-fold higher mortality in some countries in the Americas than in Europe. In the USA, 14 800 excess respiratory and cardiac deaths to pandemic influenza activity during April 2009–April 2010, 79% of which occurred in people under 65 years.[9]

Critical to preparedness has been the development pandemic preparedness plans for developing monovalent pandemic vaccines. These plans were effective in responding to the H1N1 pandemic in 2009, and although vaccine was delivered relatively late, it was demonstrated to be effective.[10] Combination strategies delayed spread, reduced overall number of cases, and delayed and reduced peak attack rate.[11] The 2009 pandemic was also the first time where hydroxychloroquine was assessed for the prophylactic use to prevent influenza, but the trial did not find hydroxychloroquine to be efficacious.[12]

The 2014 PHEIC declaration for poliomyelitis

On 5 May 2014 the WHO Director General declared the international spread of poliovirus in 2014 a PHEIC under IHR (2005), issued Temporary Recommendations to reduce the international spread of poliovirus, and requested a reassessment of this situation by the Emergency Committee every 3 months. Indeed, 26 meetings have been held since, and polio remains a PHEIC. The 26th meeting of the Emergency Committee was held in October 2020.[13]

It may be perceived as odd that polio was declared a PHEIC at a time when there were only 68 recorded cases of wild poliovirus in 2014, compared to the previous year when there were 417 cases. The reason for the WHO declaration was the risk that the

Table 1. The rationale for declaring a PHEIC, and the IHR emergency Committee's recommendations (1) (Source: World Health Organization)

PHEIC	Date of declaration	Date of undeclaration	Countries affected at the time of the PHEIC declaration	Number of cases at the time of the declaration	Rationale	Recommendations
H1N1	25 April 2009	10 August 2010	Mexico and the USA	Forty-two confirmed cases (20 in USA and 22 in Mexico), 3 death confirmed in Mexico. None in USA	1. The widespread presence of the virus. 2. Virus containment unfeasibility at that stage.	1. All countries intensify surveillance for unusual outbreaks of influenza-like illness and severe pneumonia 2. Personal protection recommendations 3. In healthcare settings PAHO/WHO recommends enhanced infection control and surveillance and personal protection. 4. It is not recommended to close to border nor restrict international travels. However, it is recommended that travel is postponed if the person is sick, and medical advice should be sought if the person becomes sick after travel.
Poliovirus	5 May 2014	Remains to be a PHEIC (as decided on the 23rd IHR Emergency Committee meeting held in January 2020) (2)	Afghanistan, Cameroon, Equatorial Guinea, Ethiopia, Israel, Nigeria, Pakistan, Somalia, and the Syrian Arab Republic.	Seventy-four cases (59 of those cases have been reported from Pakistan and within Pakistan).	1. The risk of international spread of wild virus and the increasing evidence that adult travellers were contributing to the spread. 2. During the low season in 2014, there were 10 countries that are considered to have active transmission of wild poliovirus and in contrast with previous years, there has already been a spread from three of these countries internationally. 3. Considering the large number of polio free but conflict torn and fragile states which have severely compromised routine immunization services and are particularly at high risk of infection.	Temporary recommendations for States currently exporting wild poliovirus (Pakistan, Cameroon and the Syrian Arab Republic): 1. Officially declare, that the interruption of poliovirus transmission is a national public health emergency. 2. Ensure that all residents and long-term receive a dose of OPV or inactivated poliovirus vaccine prior to international travel. 3. Ensure that such travellers are provided with an International Certificate of Vaccination or to record their polio vaccination and serve as proof of vaccination. 4. Maintain these measures until meeting the criteria made by the IHR. Temporary recommendations for States infected with wild poliovirus but not currently exporting (Afghanistan, Equatorial Guinea, Ethiopia, Iraq, Israel, Somalia and particularly Nigeria): 1. Officially declare, that the interruption of poliovirus transmission is a national public health emergency. 2. Encourage residents and long-term visitors to receive a dose of OPV or IPV 4 weeks to 12 months prior to international travel; those undertaking urgent travel (i.e. within 4 weeks) should be encouraged to receive a dose at least by the time of departure. 3. Ensure that travellers who receive such vaccination have access to an appropriate document to record their polio vaccination status. 4. Maintain these measures until meeting the criteria made by the IHR. Any polio-free State which becomes infected with wild poliovirus should immediately implement the advice for 'States infected with wild poliovirus but not currently exporting'.

(Continued)

Table 1. Continued

PHEIC	Date of declaration	Date of undeclaration	Countries affected at the time of the PHEIC declaration	Number of cases at the time of the declaration	Rationale	Recommendations
Ebola (West Africa)	8 August 2014	29 March 2016	Guinea, Liberia, Nigeria and Sierra Leone.	1711 cases (1070 confirmed, 436 probables, 205 suspect), including 932 deaths.	1. The Ebola outbreak in West Africa constitutes an 'extraordinary event' and a public health risk to other States. 2. The possible consequences of further international spread are particularly serious in view of the virulence of the virus, the intensive community and health facility transmission patterns and the weak health systems in the currently affected and most at-risk countries. 3. A coordinated international response is deemed essential to stop and reverse the international spread of Ebola.	To the States with Ebola transmission: 1. The Head of State should declare a national emergency. 2. Health Ministers and other health leaders should assume a prominent leadership role in coordinating and implementing emergency Ebola response measures. 3. States should activate their national disaster/emergency management mechanisms and establish an emergency operation center. 4. States should ensure that there is a large-scale and sustained effort to fully engage the community. 5. It is essential that a strong supply pipeline be established to ensure that sufficient medical commodities. 6. In areas of intense transmission, the provision of quality clinical care, and material and psychosocial support for the affected populations should be used as the primary basis for reducing the movement of people. 7. States should ensure health care workers receive adequate security measures for their safety and protection. 8. States should ensure that: treatment centers and reliable diagnostic laboratories are situated as closely as possible to areas of transmission. 9. States should conduct exit screening of all persons at international airports, seaports and major land crossings, for unexplained febrile illness consistent with potential Ebola infection. 10. There should be no international travel of Ebola contacts or cases unless the travel is part of an appropriate medical evacuation. To minimize the risk of international spread of EVD: 11. States should ensure funerals and burials are conducted by well-trained personnel, with provision made for the presence of the family and cultural practices, and in accordance with national health regulations 12. States should ensure that appropriate medical care is available for the crews and staff of airlines operating in the country 13. States with EVD transmission should consider postponing mass gatherings until EVD transmission is interrupted. To the States with a potential or confirmed Ebola Case, and unaffected States with land borders with affected States: 1. Unaffected States with land borders adjoining States with Ebola transmission should urgently establish surveillance for clusters of unexplained fever or deaths due to febrile illness. 2. Any State newly detecting a suspect or confirmed Ebola case or contact, or clusters of unexplained deaths due to febrile illness, should treat this as a health emergency. 3. If Ebola transmission is confirmed to be occurring in the State, the full recommendations for States with Ebola Transmission should be implemented. To all states: 1. There should be no general ban on international travel or trade; restrictions outlined in these recommendations regarding the travel of EVD cases and contacts should be implemented. 2. States should provide travellers to Ebola affected and at-risk areas with relevant information on risks. 3. States should be prepared to detect, investigate, and manage Ebola cases. 4. The general public should be provided with accurate and relevant information on the Ebola outbreak and measures to reduce the risk of exposure. 5. States should be prepared to facilitate the evacuation and repatriation of nationals (e.g. health workers) who have been exposed to Ebola.

(Continued)

Table 1. Continued

PHEIC	Date of declaration	Date of undeclaration	Countries affected at the time of the PHEIC declaration	Number of cases at the time of the declaration	Rationale	Recommendations
Zika	1 February 2016	18 November 2016	Brazil, France, United States of America, and El Salvador	594 reported microcephaly cases potentially related to a Zika virus infection, 39 cases were confirmed (30 from Brazil, nine from French Polynesia)	1. The rising international concerns about Zika infections in South America, especially in Brazil. 2. The postulated link to rising numbers of babies born with the congenital abnormality known as microcephaly.	Regarding Zika virus transmission: 1. Surveillance for Zika virus infection should be enhanced, with the dissemination of standard case definitions and diagnostics to at-risk areas. 2. The development of new diagnostics for Zika virus infection should be prioritized to facilitate surveillance and control measures. 3. Risk communications should be enhanced in countries with Zika virus transmission. 4. Vector control measures and appropriate personal protective measures should be aggressively promoted. 5. Attention should be given to ensuring women of childbearing age and particularly pregnant women have the necessary information and materials to reduce risk of exposure. 6. Pregnant women who have been exposed to Zika virus should be counselled and followed for birth outcomes. Regarding longer term measures: 1. Appropriate research and development efforts should be intensified for Zika virus vaccines, therapeutics, and diagnostics. 2. In areas of known Zika virus transmission health services should be prepared for potential increases in neurological syndromes and/or congenital malformations. Regarding travel measures: 1. There should be no restrictions on travel or trade with countries, areas and/or territories with Zika virus transmission. 2. Travellers to areas with Zika virus transmission should be provided with up to date advice on potential risks and appropriate measures to reduce the possibility of exposure to mosquito bites. 3. Standard WHO recommendations regarding disinfection of aircraft and airports should be implemented. Regarding data sharing: 1. National authorities should ensure the rapid and timely reporting and sharing of information of public health importance relevant to this PHEIC. 2. Clinical, virologic and epidemiologic data related to the increased rates of microcephaly and/or GBS, and Zika virus transmission, should be rapidly shared with WHO to facilitate international understanding of these events.

(Continued)

Table 1. Continued

PHEIC	Date of declaration	Date of undeclaration	Countries affected at the time of the PHEIC declaration	Number of cases at the time of the declaration	Rationale	Recommendations
Ebola (DRC)	17 July 2019	26 June 2020 (3)	DRC (in the northeast, specifically in North Kivu and Ituri, Goma), Uganda (Kasese)	2522 confirmed cases, 1698 deaths were reported (overall case-fatality ratio 67%)	1. The concern about potential spread from Goma (as the city is a provincial capital with an airport with international flights.) 2. The concern of the reinfection and ongoing transmission in Beni, which has been previously associated with seeding of virus into multiple other locations. 3. The murder of two HCWs demonstrates continued risk for responders owing to the security situation. 4. The lack of the global community contribution to sustainable and adequate technical assistance, human or financial resources for outbreak response, despite the previous recommendations for increased resources.	For affected countries: 1. Sustain the political commitment and multisectoral coordination approach to the response and expand this commitment to local areas and hot spots of the outbreak. 2. Further enhance the acceptance, access and security situation to provide an enabling environment for all response partners to support public health operations as an essential platform for accelerating disease-control efforts. 3. Continue to strengthen strategy, capacity, implementation, and coordination for community awareness and engagement. 4. Continue cross-border screening and screening at main internal roads, with a particular focus on routes connected to areas with current transmission. 5. Accelerate comprehensive action for active surveillance for cases and unexplained deaths in all areas. 6. Continue to implement optimal vaccine strategies that have proven maximum impact on curtailing the outbreak. 7. Strengthen measures to prevent nosocomial infections, including systematic mapping of health facilities. 8. Strengthen preparedness in non-affected provinces of DRC, and more generally strengthen health system across the country to respond to concurrent health emergencies. For countries at-risk: 1. At-risk countries should work urgently with partners to improve their preparedness for detecting and managing imported or locally acquired cases. 2. Countries should continue to map population movements and sociological patterns that can predict risk of disease spread. 3. Risk communications and community engagement, especially at points of entry, should be increased. 4. At-risk countries should continue to put in place approvals for investigational medicines and vaccines as an immediate priority for preparedness. For all States: 1. No country should close its borders or place any restrictions on travel and trade. 2. National authorities should work with airlines and other transport and tourism industries to ensure that they do not exceed WHO's advice on international traffic. 3. The Committee does not consider entry screening at airports or other ports of entry outside the region to be necessary.

(Continued)

Table 1. Continued

PHEIC	Date of declaration	Date of undeclaration	Countries affected at the time of the PHEIC declaration	Number of cases at the time of the declaration	Rationale	Recommendations
COVID-19	30 January 2020	-	China, Japan, Korea, Viet Nam, Singapore, Australia, Malaysia, Cambodia, Philippines, Thailand, Nepal, Sri Lanka, India, USA, Canada, France, Finland, Germany and United Arab Emirates.	Total of 7794 confirmed cases. 7711 confirmed cases in China (170 deaths of them died), 83 confirmed cases in 18 countries (Of these, only seven had no history of travel in China)	The Committee acknowledged the significant increases in numbers of cases and additional countries reporting confirmed cases and that there are still many unknowns, and human-to-human transmission has occurred outside Wuhan and outside China. The Committee believes that it is still possible to interrupt virus spread, provided that countries put in place strong measures to detect disease early, isolate and treat cases, trace contacts, and promote social distancing measures commensurate with the risk.	To WHO: 1. Coordination, planning, and monitoring 2. One health (collaboration) 3. Preparedness to support countries to access and manage all essential health services 4. Risk communication and community engagement 5. Travel and trade (development of a strategic guidance and update recommendations on appropriate travel measures) 6. Surveillance To all states parties: 1. Coordination and Collaboration 2. Preparedness 3. Surveillance 4. Health workers protection prioritization 5. Food security 6. Risk communications and community engagement 7. Research and development 8. Maintenance essential health services.

1. Organization WH. IHR Emergency Committees Reports 2020 [Available from: http://www.euro.who.int/en/health-topics/emergencies/international-health-regulations/reporting-events/ihr-committees/ihr-emergency-committee.
2. Organization WH. Statement of the 23rd IHR Emergency Committee Regarding the International Spread of Poliovirus. 2020.
3. Final statement on the eighth meeting of the International Health Regulations (2005) [press release]. 2020.

goal of polio eradication may be not be achieved, unless more international coordinated efforts occur. Although polio at the time was limited to a handful of countries, there were more than 26 exportation events, and spread through international spread was considered the main threat to eradicating polio. Indeed, spread of polio is driven by land border crossings and by air travel.[14,15] Air travel has increased significantly in past decades.[16] Wild poliovirus has been eradicated in all continents except Asia, and as of 2020, Afghanistan and Pakistan are the only two countries where the disease is still classified as endemic.

Recent polio cases arise from two sources, the original 'wild' poliovirus (WPV), and mutated oral vaccine strains, so-called circulating vaccine-derived poliovirus (cVDPV). Of the three strains of WPV, the last recorded wild case caused by type 2 (WPV2) was in 1999, and WPV2 was declared eradicated in 2015. All wild-virus cases since that date have been due to type 1 (WPV1). Vaccines against each of the three types have given rise to emergent strains of cVDPV, with cVDPV2 being most prominent.

The 2014 outbreak of Ebola in Western Africa

The Western African Ebola virus epidemic from end 2013 to 2016 was the most widespread outbreak of Ebola virus disease in history—causing major loss of life and socioeconomic disruption in the region. Starting in Guinea with rapid spread to Libera and Sierra Leone, it was associated with a high case-fatality rate. The final numbers of infected persons was 28 616 including 11 310 deaths, resulting in a case-fatality rate of 40%. The death toll on health care and aid workers was high. The 4-month delay by WHO after the international spread of Ebola in West Africa before declaring a PHEIC has drawn much criticism.[17] With public health measures in particular personal protective equipment and community engagement, the Ebola outbreak came to an end. A ring fencing efficacy trial was conducted in West Africa towards the end of the outbreak by vaccinating contacts of Ebola cases and contacts of contacts.[18,19] The estimated vaccine efficacy was close to 100%.[18]

The 2018–2020 Ebola epidemic in the Democratic Republic of Congo

The Democratic Republic of the Congo notified WHO of four cases of Ebola in the eastern region of Kivu on 1 August 2018, but WHO required four Emergency Committee meetings, including on 17 October 2018 (216 confirmed cases, 139 deaths and 64% case-fatality ratio), and 12 April and 14 June 2019 (four confirmed cases in Uganda). Due to the location and lack of high travel volumes, with a very low risk of international spread[20] this epidemic was not declared a PHEIC until the first long-haul exportation to Goma in June 2019, and on 17 July 2019, WHO announced the PHEIC. By November 2018, the outbreak became the biggest Ebola outbreak in the DRC's history; and by November, it had become the second-largest Ebola outbreak

in recorded history. Armed conflict in the Ebola affected zones made the response challenging. Rapid deployment of the Ebola vaccine that had undergone the ring fencing trial in West Africa with a focus on vaccinating contacts as well as contacts of contacts kept the outbreak under control.[21] On 25 June 2020, the outbreak was declared ended. In total, 3470 cases and 2280 deaths were reported.

The 2015–2016 Zika virus epidemic

On 1 February 2016, the reported clusters of microcephaly and other neurological disorders in Brazil were declared a PHEIC. The rationale for the declaration was not driven by what is known about Zika virus infection at the time of the declaration, but by the unusual clusters of hitherto unknown complications that required immediate international coordinated effort.[22] During the discussions of the IHR emergency committee it became clear that infection with the Zika virus only causes a fairly mild disease with fever, malaise, and at times a maculopapular rash, conjunctivitis, or both, with very low mortality and a high rate of asymptomatic infections. The mild nature of Zika was noted in contrast to other Aedes-transmitted viral infections such as dengue which can cause severe complications such as haemorrhagic shock and death,[23] or chikungunya associated with prolonged often severe arthralgias and arthritis[24,25] or Japanese encephalitis associated with high case-fatality rates and frequent neurological disabilities in survivors.[26–28] The advice to declare a PHEIC was rather made on the basis of what is not known about the clusters of microcephaly,[29] Guillain-Barré syndrome,[30] and possibly other neurological defects reported by country representatives from Brazil and retrospectively from French Polynesia[31] that were associated in time and place with outbreaks of Zika infection. Although dengue and chikungunya rarely lead to maternal complications or birth defects, Zika virus' propensity to lead to congenital Zika syndrome is concerningly high.[32,33] Zika was rapidly introduced into more than 100 countries around the world via travellers.[34–37] The concern was that sexual transmission of Zika could lead to introduction and establishment of Zika also in countries where the vector does not exist, and WHO and CDC advised for measures to avoid pregnancy for certain months after return from travelling from a Zika endemic country.[38] A number of countries issued travel warnings, and the outbreak reduced tourism significantly, including calls to cancel the Olympics in Rio de Janeiro.[39,40] Several countries took the unusual step of advising their citizens to delay pregnancy until more was known about the virus and its impact on foetal development. The incidence of Zika was very high in the Americas resulting in high seroprevalence rates and therefore a high degree of herd immunity, and the outbreak was effectively over within a year.[41] Although the vector exists in Asia, only sporadic cases, clusters or small outbreaks of Zika virus infections were reported in Asia.[42–45] Why Zika did not cause more havoc in Asia remains unknown, although phylogenetic studies speculate that Culex-borne flaviviruses, including West Nile virus[46,47] and Japanese encephalitis virus,[27] might induce cross-protective T-cell responses against Zika virus This would explain why explosive Zika epidemics occurred in DENV-endemic regions of Micronesia, Polynesia and the Americas where Culex-borne flavivirus outbreaks are infrequent and why Zika virus did not cause major epidemics in Asia where Culex-borne flaviviruses are widespread.[48] The impact of a Zika virus infection that precedes dengue infection is currently under investigation, but initial findings suggest that there may be some initial cross-protection followed by potential enhancement of dengue after 2 years.[49,50] Although Zika virus has disappeared as a public health problem, sporadic cases still occur in the Americas and in travellers.[51,52]

The 2020 COVID-19 pandemic

The ongoing global pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in December 2019 in Wuhan, China, is the worst pandemic of this century in terms of incidence and number of deaths, if not the worst pandemic of the past 100 years. Only the 'Spanish flu' slightly more than 100 years ago, in 1918–1919, had much higher case-fatality rates and far higher absolute number of deaths, also in younger persons.[53] Although the virus shares about 86% homology with the SARS virus from the SARS outbreak in 2003, and the clinical and radiological manifestations of SARS and COVID-19 are very similar, COVID-19 is much worse than SARS because of its higher reproductive number,[54] and high proportion of asymptomatic infections that amplify the outbreak through silent spread. Therefore, although the infection fatality rate is lower than for SARS, the overall number of deaths is exponentially higher than SARS.[55] SARS was effectively eradicated in 2003 as a result of rigorous top–down pandemic responses, with in total about 8000 cases and 800 deaths.[55]

At the first Emergency Committee meeting on 22 January 2020 (at a time when 309 COVID-19 cases and six deaths had been reported in mainland China; five confirmed cases in four countries or territories), the Emergency Committee said it did not have key facts from China, and extended the meeting to the next day, when cases had risen to 571, with 17 deaths and 10 cases in seven other countries or territories. Yet, the Emergency Committee could not achieve consensus, and the Director General concluded that the outbreak was 'an emergency in China, but it had not yet become a global health emergency'.[56] By the time the Emergency Committee declared a PHEIC for COVID-19 on 30 January 2020, 7736 cases and 179 deaths had been confirmed in mainland China, with 107 cases confirmed in 21 other countries.

WHO declared COVID-19 a pandemic in March 2020. By 25 November 2020, global daily/cumulative cases were standing at 591 000/60.5 Million with 1.42 million deaths attributed to COVID-19, with high excess mortality, overwhelming of health care systems, and a high death toll among health care workers. Most governments have responded with public health measures such as isolation, contact tracing, quarantining of contacts, community quarantine including social distancing[57] and varying degrees of lockdowns.[58] The responses have caused global social and economic disruption,[59] economic losses, downturn of the tourism industry and a global recession. Many educational institutions have been partially or fully closed. Misinformation has circulated with an unprecedented infodemic associated with conspiracy theories and contributed to xenophobia and discrimination against Chinese people.[60] Mass gatherings and mobility

of social networks played a major role in the rapid global spread.[61,62] The annual Hajj pilgrimage to the Kingdom of Saudi Arabia attracts more than 2 million pilgrims from all over the world for an extended period of at least 2 weeks, and hence can lead to massive amplification and also worldwide spread of various diseases.[63–66] calling for improved global health security measures.[67] The Hajj pilgrimage was the first major religious mass gathering to be temporarily suspended.[68] There was also a call to act to mitigate potentially serious consequences of the Hindu pilgrimage in India.[69]

At the time of writing, cases are still increasing exponentially. Since April 2020, the Access to COVID-19 tools Accelerator (ACT-Accelerator) partnership, launched by WHO and partners, has supported the fastest, most coordinated and successful global effort in history to develop tools to fight COVID-19. With significant advances in research and development by academia, private sector and government initiatives, 'the ACT-Accelerator is on the cusp of securing a way to end the acute phase of the pandemic by deploying the tests, treatments and vaccines the world needs.'[70] This pandemic requires an all-society, all-government approach and we can only beat it with global coordination.[71,72]

Diseases or health threats that were not declared PHEIC

Despite the multiple disease threats in the world since the IHR were endorsed in 2005 and fully active since 2007, only six diseases were declared a PHEIC between 2007 and 2020. Importantly, this was not only because of the clear ability of these six diseases to cause widespread human suffering, but also their ability to disrupt international trade. Large-scale health emergencies which attract public attention do not necessarily fulfil the criteria to be a PHEIC. For example, IHR emergency committees were not convened for the cholera outbreak in Haiti, chemical weapons use in Syria or the Fukushima nuclear disaster in Japan. Also the outbreak of pneumonic plague in Madagascar did not lead to a PHEIC because the risk of international spread was considered to be low.[73] However, often disproportionate to a declaration and in contrast to the intention and spirit of IHR, outbreaks lead to travel warnings, and loss in tourism and air travel.[74]

PHEIC was not invoked with the Middle Eastern Respiratory Syndrome (MERS) outbreak in 2013. Originating in Saudi Arabia, MERS reached more than 24 countries and resulted in more than 580 deaths by 2015, although most cases were in hospital settings rather than sustained community spread. As of May 2020, there have been 876 deaths. The virus is similar to the coronaviruses that caused SARS and COVID-19, is associated with a much higher case-fatality rate than SARS or COVID-19, but fortunately has a much lower reproduction number. Nevertheless, a call for action is needed to ensure that MERS does not spread further, and is swiftly contained as soon as a case or a cluster is detected.[75]

The resurgence of measles in the Americas after the Americas had been declared measles-free, mainly due to low vaccine coverage rates in Venezuela and subsequent exportation to neighbouring countries as a result of the migration crisis,[76,77] was a set-back to the measles eradication efforts. Record high numbers of measles were also reported in Europe in 2018,[78,79] with rising numbers of measles also seen in travellers reported to GeoSentinel,[80] a network of global travel medicine providers that see ill-returned travellers.[81] Therefore, the question was asked whether measles should be declared a PHEIC.[82] Should 'extraordinary resources' be mobilized by the international community to respond to this public health risk that has the potential to cross borders and threaten people worldwide? The answer should be affirmative, however, PHEIC was not declared because one key element was missing, e.g. the threat to travel and trade for measles resurgence, and the fact that interventions are available in the form of a highly effective vaccine.

The yellow fever outbreak in Angola in 2016 was unusual as it was the first largely urban outbreak in Africa for decades, resulted in rapid spread via population movements[83] and also resulted in exportation of the virus to China via 11 travellers in 2016.[84] At WHO, there were discussion at the time to declare the yellow fever outbreak a PHEIC because it clustered around urban areas with easy access to airports and potential for rapid spread. Indeed, yellow fever carries a high case-fatality rate,[85] and introduction into Asia where the necessary vectors exist could become a disaster to more than 2 billion persons residing in Asia. Fortunately, swift action with fractional yellow fever vaccination ended the outbreak in Angola and neighbouring DRC.[86,87] Yellow fever is currently the only disease specified in *IHR* (2005) for which countries may require proof of vaccination, and many lessons can be learned from yellow fever now for COVID-19.[88] Immunity passports for COVID-19 are not the way forward, at least not for the time being.[89]

Some have argued that antimicrobial resistance (AMR) should be considered a PHEIC.[90] Indeed, AMR is a threat to global health and hospitalized medicine, and international travel including play a key role in the spread of highly resistant strains.[91–93] The COVID-19 pandemic may even exacerbate AMR.[94] Surveillance across all countries is needed to monitor and respond to this emerging threat. Such surveillance for AMR is also needed for migrants.[93,95–97] Medical tourism also contributes to AMR.[98,99] Enhanced surveillance and research to provide improved evidence-based strategies and policies should harness the One Health approach, inter-country collaborations, and new emerging technologies.[100] A case has been made to utilize the revised IHR 2005 to encourage Member States to report all cases of AMR as they fulfil 'at least two' of the criteria for a PHEIC.[90] However, AMR would not best harness a declaration of PHEIC. Although AMR crosses borders, and is serious, it does not affect trade and travel and does not present a PHEIC. The IHR would also not offer the right instruments to tackle AMR. A regionally and globally coordinated effort that is target-driven, sustainable and builds on a framework facilitating communication and governance will strengthen the fight against AMR, but not the declaration of a PHEIC.[101] Obviously, a newly emerging multi-drug resistant bacterium that is rapidly spreading requiring international coordinated efforts may call for a PHEIC.

What about the HIV pandemic? The HIV pandemic started before IHR (2005). On 5 June 1981, when the Centers for Disease Control reported five cases of *Pneumocystis carinii* pneumonia in young homosexual men in Los Angeles, few suspected it heralded a pandemic of AIDS.[102] In the first 25 years since the first report, more than 65 million persons have been infected with HIV, and more than 25 million have died of AIDS. Worldwide,

more than 40% of new infections among adults are in young people 15–24 years of age.[102] The vast majority of these infections and deaths have occurred in developing countries. AIDS incidence increased rapidly through the 1980s, peaked in the early 1990s, and then declined due to the advent of highly active retroviral therapy. In the USA, as of 31 December 2000, e.g. in the first 19 years after its emergence in 1981, 774 467 persons had been reported with AIDS, since its emergence in 1981; 448 060 of these had died.[103] In contrast, COVID-19 affected more than 12 million and killed more than 250 000 persons in the USA within the first 9 months of its emergence. Would the HIV pandemic have been declared a PHEIC if it had occurred after 2007? Probably yes, although the long latency from infection to death, and the spread almost exclusively via sexual transmission and blood products, would have blunted the initial assessment of the potential for rapid international spread. Travel restrictions however did occur for HIV.[104]

Concluding remarks

Six diseases have been declared PHEIC since 2007, of which Ebola was declared a PHEIC twice. The purpose of declaring a PHEIC is to focus attention on those acute public health risks that have the potential to cross borders and threaten people worldwide, and 'require coordinated mobilisation of extraordinary resources by the international community' for prevention and response.[82] A declaration of a PHEIC may appear as an economic burden to the country facing the epidemic. Incentives to declare an epidemic are lacking and the PHEIC declaration can be seen as placing limitations on trade in countries that are already struggling economically. Indeed, the biggest challenge in declaring a PHEIC is to mobilize international efforts while minimizing trade and travel restrictions. The disproportionate decline in travel and trade was particularly obvious during the Ebola outbreak.[74] The reasons for interruption of travel during the 2014–2016 Ebola outbreak were complex, with decisions by States only partly contributing to the cessation. Decisions by non-state actors, particularly the travel industry itself, contributed significantly and were based on a variety of factors. However, the scale of travel restrictions in 2020 due to the COVID-19 pandemic far exceeded those from the Ebola outbreak.

IHR has several limitations. IHR do not provide surveillance infrastructure; they are merely a set of recommendations that rely on goodwill to steer inter-state behaviour. Although the IHR draw on several existing surveillance networks to accomplish their mission, there is no dedicated infrastructure, and only limited IHR-dedicated staff at WHO. Therefore, the IHR is not an implementation tool. However, a declaration of a PHEIC does facilitate and streamline funding, in particular it facilitates development of therapeutics, vaccines and/or diagnostics under emergency use authorization.

Numerous travel stakeholders are affected by, and affect, large-scale infectious disease outbreaks. Peer pressure plays an important role for both governments and the travel sector, and the reactions of the media and public influence and are influenced by these stakeholders.[74] A PHEIC declaration invariably increases media attention and may lead to disproportionate travel warnings. Although various data sources on travel are available, and WHO is mandated to work with States, there is no recognized coordinating body to disseminate timely, consistent, reliable and authoritative information and best practices to all travel stakeholders.[74] The binary nature of a declaration (yes/no) is often not helpful where a tiered, staggered or graded approach is needed.[1] A multilevel PHEIC process with each level defined by objective epidemiological criteria and paired with specific readiness actions has been proposed.[56] The authors suggest three levels: 'Level 1 PHEIC alert should indicate a high risk outbreak in a single country, with the potential for international spread requiring concerted public health efforts to contain and manage it locally. Level 2 PHEIC should imply that multiple countries have had importations and that limited spread has occurred in those countries. Level 3 PHEIC would indicate large clusters in multiple countries, with evidence of ongoing local transmission.'

Several proposals have been made for change. These recommendations focus mainly on the development and strengthening of IHR core capacities but also on new financing mechanisms; harmonization with the Global Health Security Agenda and One Health strategies; public health and clinical workforce development; Emergency Committee transparency and governance; tiered processes; enhanced compliance mechanisms; and an enhanced role for civil society.[1] A tiered approach would provide less ambiguous risk signalling, while also encouraging earlier, public health measures.[56] Further research, analysis and policy development are required to mitigate the health and economic consequences of infectious disease outbreaks.

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Conflict of interest

None declared.

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