Hypothetical emergence of poliovirus in 2020: part 1. Consequences of policy decisions to respond using nonpharmaceutical interventions

Kimberly M. Thompson, Dominika A. Kalkowska and Kamran Badizadegan

Kid Risk, Inc., Orlando, FL, USA

ABSTRACT

Objectives: As efforts to control COVID-19 continue, we simulate hypothetical emergence of wild poliovirus assuming an immunologically naive population. This differs from the current global experience with polio and serves as a model for responding to future pandemics.

Methods: Applying an established global model, we assume a fully susceptible global population to polioviruses, independently introduce a virus with properties of each of the three stable wild poliovirus serotypes, and explore the impact of strategies that range from doing nothing to seeking global containment and eradication.

Results: We show the dynamics of paralytic cases as the virus spreads globally. We demonstrate the difficulty of eradication unless aggressive efforts begin soon after initial disease detection. Different poliovirus serotypes lead to different trajectories and burdens of disease. In the absence of aggressive measures, the virus would become globally endemic in 2–10 years, and cumulative paralytic cases would exceed 4–40 million depending on serotype, with the burden of disease shifting to younger ages.

Conclusions: The opportunity to eradicate emerging infections represents an important public policy choice. If the world first observed the emergence of wild poliovirus in 2020, adopting aggressive control strategies would have been required to prevent a devastating global pandemic.

1. Introduction

The global experience of an emerging infectious disease depends on multiple factors, including microbial transmission dynamics, pathogen characteristics, population demographics, contact patterns (population mixing characteristics), and the societal actions taken to contain or prevent transmission. Although individual and public health perceptions and fears about new infectious diseases differ from perceptions and fears about known and established ones, the psychosocial familiarity with known disease does not make them less devastating to human health and welfare. For example, measles continues to cause costly and devastating outbreaks every year [1] with an estimated 142,300 deaths in 2018 [2]. This happens despite elimination of indigenous transmission in the western hemisphere and many countries [2], and a sufficient global supply of a highly effective and safe vaccine that used effectively could potentially eradicate measles [3]. New infectious diseases emerge periodically (e.g. HIV, Severe Acute Respiratory Syndrome (SARS), Zika) and pose substantial threats to human health. Most recently, the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in late 2019 resulted in the Coronavirus Disease 2019 (COVID-19) pandemic with catastrophic health and welfare consequences. COVID-19 is perceived as a unique and challenging threat to human health, but this perception lacks context. Is COVID-19 truly unique, or would other potential emerging infections pose equally significant global threats?

Transmission modeling can provide useful insights to support the selection of policies by characterizing the potential risks, costs, and benefits of investments in different nonpharmaceutical interventions (NPIs). The emergence of SARS motivated modeling to explore the pandemic potential of emerging diseases [4,5], which later shifted to a focus on pandemic influenza [6]. Seminal studies in the literature identified hospitals as critical in controlling transmission [7,8], no response to a pandemic threat like SARS as catastrophic [9], and factors that affect the ability to control the transmission of an emerging infectious disease [10,11]. Modeling the response to SARS in China [12], Taiwan [13], Singapore [7], Hong Kong [9], and Toronto [14] demonstrated the importance of health systems in isolating infected individuals as soon as they became infectious and in the prevention of nosocomial infections, which motivated substantial responses by the national health systems to shut down SARS transmission. Discussions of strategies to mitigate the impacts of pandemic influenza identified the opportunity to use models ‘as a tool to aid in open discussion for making explicit alternative strategies, assumptions, data, and gaps’ while cautioning that ‘it would be a mistake for policymakers to assume that any of these models can provide an exact roadmap of actions to take during the next influenza pandemic’ [15]. This review concluded that
models of NPIs generally show that the interventions can: 'flatten the epidemic peak, but the evidence is less convincing that they can reduce the overall size of the epidemic. Delay of the epidemic peak is critically important because it allows additional time for vaccine development and antiviral production. Lowering the peak of the epidemic is crucial also because it can reduce the burden on healthcare infrastructure by avoiding an extremely large influx of patients. Another important finding is that interventions will likely be most effective if they are initiated early in the epidemic and sustained until the threat of reintroduction of the virus has been eliminated' [15]. The concept of ‘flattening the curve’ broadly recognized that the health system can play two key roles in controlling transmission: (1) treating the symptoms of infection to improve health outcomes (i.e. quality and length of life) and (2) preventing transmission by isolating highly infectious individuals. The latter depends to a large extent on effective control of nosocomial infections. US pandemic influenza planning focused on flattening the epidemic peak to save lives by reducing transmission and isolation at home (i.e. outside of the health system), and emphasized the importance of rapid vaccine development [16]. Current experience with SARS-CoV-2 transmission reveals varying levels of success associated with the range of NPIs used.

1.1. Emergence and detection of SARS-CoV-2

transmission

How fast can we detect the emergence of a novel pathogen and what can we learn from the recent experience with SARS-CoV-2? The identification of clinically significant infectious diseases typically reflects the recognition of multiple individuals presenting with similar clinical signs and symptoms of sufficient morbidity or mortality to attract attention (i.e. a disease cluster). Detecting clusters remains challenging due to the wide spectrum of clinical presentations for most emerging and established diseases. For instance, an outbreak of a novel respiratory infection would be extremely difficult to identify based on clinical presentation alone in the background of numerous other existing respiratory infections. Although historically clinical signs and symptoms provided the only means for case identification in the context of an emerging infectious disease, diagnostic technology, if utilized effectively, can now rapidly characterize microbial pathogens using molecular signatures of the disease such as unique nucleotide sequences within the infectious agent. As of 2020, highly specialized diagnostic tools could perform rapid genomic sequencing and phylogenetic analyses that support prompt case identification and real-time tracking of transmission for an emerging pathogen. The nature and timeline of international response to SARS-CoV-2 characterization serves a model for (or an approximation to) future emerging pathogens.

In the winter of 2019, residents of Wuhan, China began to present with a severe respiratory illness reminiscent of SARS [17]. China notified the World Health Organization (WHO) of ‘pneumonia of unknown etiology’ on 31 December 2019 [18]. On 3 January 2020, the Chinese Center for Disease Control (China-CDC) reported whole-genome sequencing of the causative agent [19], and the first sequence released in GenBank on January 5 [20]. The results of these and multiple subsequent studies led to rapid development of primers for molecular diagnostics [21], shortly followed by virus identification as a novel human betacoronavirus [22–24]. Figure 1 shows key milestones of SARS-CoV-2 emergence until declaration of

| Days since the first symptomatic case |
|---|
| Nov 16: First symptomatic patient (Guangdong, China) |
| Dec 1: First symptomatic patient (Wuhan, China) |
| SARS (2002-03) |
| Dec 31: WHO notified of disease cluster |
| Jan 1: Huanan Wet Market shuts down |
| Jan 3: Sequencing reveals novel virus |
| Jan 5: WHO disease outbreak report |
| (i.e. Hong Kong fever) |
| Jan 10: CDC-China releases primers for PCR testing |
| Jan 13: First known case outside China (Thailand) |
| Jan 30: WHO issues PHIEC |
| COVID-19 (2019-20) |
| Feb 10: WHO notified of disease cluster |
| Feb 11: WHO disease outbreak report |
| Feb 26: First known case outside China (Viet Nam) |
| Mar 12: WHO issues global alert |
| Mar 15: WHO issues travel advisory |
| Mar 24: Quarantine in Singapore |
| Mar 27: Hong Kong schools close |
| Mar 27: WHO strict air travel protocols |
| Apr 16: Sequencing reveals novel virus |

Figure 1. Key milestones for COVID-19 from emergence of the first case to declaration of a global pandemic. Compared with SARS that emerged less than two decades ago, significant differences in global reaction and pathogen identification can be observed. Similar events between COVID-19 and SARS are highlighted by the use of similar font colors. Gray bar near the center of the timeline highlights day 75, which is used as a key date in modeling.

Abbreviations: CDC, Center for Disease Control and Prevention; COVID-19, Coronavirus Disease 2019; PCR, polymerase chain reaction; PHIEC, Public Health Emergency of International Concern; SARS, Severe Acute Respiratory Syndrome; WHO, World Health Organization
global pandemic [17–19,25–29], and contrasts the early response timeline with that of SARS less than two decades ago [30].

1.2. Historical emergence and detection of poliovirus transmission

How does diagnostic technology today compare with the historical experience with polio? Polioviruses likely infected human populations for centuries [31], but the recognition of poliomyelitis as a distinct disease traces back to 1840 when Joseph Heine synthesized various clinical accounts of this paralytic disease as manifestations of one and the same disease [32]. Anecdotal evidence of other disease clusters soon followed, and in 1890 Medin presented the first known ‘epidemic’ of 44 cases of infantile paralysis, including various forms of poliomyelitis [33]. Medin characterized polio as an acute infection, although he found no evidence of ‘contagion’ in families of affected patients. These and subsequent studies culminated in the seminal work of Wickman who provided an analysis of >1,000 cases of acute poliomyelitis based on a 1905 Scandinavian epidemic [34]. Wickman’s studies led to demonstration of person-to-person transmission of the disease, and to recognition of ‘abortive’ (mild or asymptomatic) infections without paralysis. Definitive evidence for transmissibility came from studies that demonstrated transmission from humans to monkeys by injection of spinal cord material from a patient with severe poliomyelitis into the inantriperitoneal space of two old-world monkeys, one of whom developed flaccid paralysis [35]. This work and multiple additional lines of evidence (reviewed in [36]), identified the etiological agent as a ‘filterable’ virus and named the poliovirus.

Progress toward understanding the pathophysiology of poliomyelitis slowed until the mid-twentieth century when Bodian and colleagues showed the ability to isolate poliovirus from untreated stools of patients with poliomyelitis [37] and to detect poliovirus in the blood of infected patients before the onset of symptoms [38]. Additional studies showed the existence of three distinct serotypes of polioviruses [39] among multiple other contributions (reviewed in [40]). These studies paved the way for vaccine development and provided a diagnostic paradigm for poliomyelitis through serological assays.

Historical experience with polio demonstrates that an emerging pathogen or an unnamed novel pathogen can transmit without clinical detection or public health action for extended periods of time. Although our collective ability to identify human pathogens continues to increase, diagnostic testing is often limited to a fraction of viruses, bacteria, and fungi that are known to cause the majority of human infections, and novel, rare or esoteric infections can go undetected. In the US, cases and clusters of acute flaccid myelitis reported since 2014 provide an example of polio-like illnesses caused by non-polio and yet unidentified pathogens [41–43]. The contrasting examples of rapid detection of SARS-CoV-2 compared to historical experience with polio provide an indication of the substantial advancement of technology. However, the experience with emerging nonpolio neurotropic enteroviruses (e.g. EV-68, EV-71) demonstrates that rapid detection will not always occur despite the availability of technology. Escalation to a critical status is required to drive global action, such as declaration of a Public Health Emergency of International Concern by the World Health Organization.

1.3. Polio transmission modeling

A recent review provides details about all existing poliovirus transmission models [44]. This body of work includes studies that explored the historical US experience with polioviruses and characterized the health and economic benefits of their control and national elimination [45]. With ongoing active efforts to eradicate polio globally, a 2011 study estimated the potential health and economic benefits of the Global Poliovirus Eradication Initiative (GPEI) assuming its success by 2012 (or as late as 2015) [46]. A separate 2011 discussion of the economics of disease eradication included recognition of the different stages of human experience with infectious diseases, and emphasized the opportunity to stop transmission and prevent the establishment of emerging infectious diseases before they became endemic [47]. Notably, that discussion highlighted the 2003 experience with SARS (or SARS-CoV-1) as a successful example of eradication of an emerging infectious disease prior to its global establishment [47]. Updated global poliovirus modeling accounts for epidemiological experiences through 2020 [48,49], and provides an updated economic analysis of the economics of the GPEI [50]. Not surprisingly, given the delay in achieving polio eradication, the updated analysis [50] shows a decline in the expected incremental net benefits of the GPEI compared to the prior analysis [46].

Given our extensive experience modeling polio and in the context of global emergence of SARS-CoV-2, we explore the dynamics of a familiar disease (i.e. polio) as if it newly emerged in 2020 (instead of SARS-CoV-2), to provide context about the evolution of human experiences with infectious diseases. We emphasize that this hypothetical situation represents a completely different situation than what actually exists with polio, which emerged centuries ago, established endemic transmission, and for which existing vaccines enable the efforts of the GPEI. Instead, we explore the hypothetical simulation of polio as an emerging disease in 2020 using a well-established, integrated global model to inform our understanding of global COVID-19 emergence and evolution, as well as future potential pandemics.

2. Methods

We use our exiting global poliovirus transmission model [48], but initialize the population in 2020 assuming no prior immunity or exposure to polioviruses (i.e. a completely naïve population with no immunologically cross-reactive species). This represents a completely different situation than what actually exists, because historical endemic transmission and widespread use of polio vaccines currently imply very high levels of individual and population immunity. We ignore any cross-protection that may exist from prior exposure of some individuals in the population to any related enteroviruses. Since three independent stable serotypes of wild polioviruses (WPVs) exist (WPV1, WPV2, and WPV3) with different properties [48], we model each
Table 1. Summary of inputs for restrictions applied for the different modeled scenarios.

| Input                                           | FTC1 | FTC2 | C&E |
|-------------------------------------------------|------|------|-----|
| Delay in triggering restrictions after subsequent detections [days] | 30   | 15   | 15  |
| Delay in triggering restrictions after declaration of pandemic [days] | NA   | NA   | 7   |
| Duration of restrictions                        | 3 months | 6 months | Until global eradication |
| E* during restrictions                          | - Li and LMI | 250,000 | 250,000 |
| - UMI and HI                                   | 50,000 | 250,000 | 250,000 |
| Reduction in R0 during restrictions             | 1    | 3    | 3   |
| Subpopulation affected by restrictions          | Only subpopulations with detection | Only subpopulations with detection | Before pandemic declaration: only subpopulations with detection |
| Quarantine of all travelers to ensure no effective importations during restrictions | NA   | NA   | After pandemic declared: all subpopulations |

Abbreviations: C&E, contain and eradicate; E*, exportation threshold; FTC, flatten the curve; HI, high-income; LI, low-income; LMI, lower middle-income; NA, not applicable; R0, basic reproduction number; UMI, upper middle-income

Independently to show the different behaviors with respect to transmission dynamics and expected disease burden. We refer to these generally as novel WPV (nWPV) and specifically as nWPV1, nWPV2, and nWPV3 to indicate properties like the existing WPV serotypes.

Most poliovirus infections occur asymptomatically, and the infections can spread prior to disease detection. Moreover, poliovirus infections exhibit different clinical presentations due to differences in serotype properties. Notably, paralytic disease occurs in approximately 1 out of 200 WPV1, 1 out of 2,000 WPV2, and 1 out of 1,000 WPV3 infectious, ranging from stereotypical limb paralysis to fatal bulbar disease [48,51]. We assume introduction of each serotype on 1 November 2019 into a subpopulation in the global polio model that represents conditions similar to a province in China. November 1 represents the approximate time of emergence of SARS-CoV-2 in the human population based on modeling [17] and is consistent with clinical identification of the first hospitalized patient nearly a month later [52]. For this analysis, we assume delays in detection and intervention consistent with modern technology and the experience with SARS-CoV-2.

2.1. Model specification

The technical appendix provides details about the model with Table A1 highlighting the key generic inputs. The actual properties of any newly emerged novel neurotropic enterovirus will determine its behavior in the population following the establishment of endemic transmission (see [53] for an insightful analysis related to the expected endemic phase of SARS-CoV-2). The population structure in the updated global model [48] subdivides the word into 72 blocks of 10 subpopulations each representing approximately 10.7 million people per subpopulation in 2019 [54]. Appendix Figure A1 provides context related to the reported first case of SARS-CoV-2 distributed over the blocks in our model structure. Blocks are grouped into preferentially mixing areas (PMA), and we assume people mix homogenously in space and heterogeneously by age. We characterize the blocks by World Bank income levels as low-income (LI), lower middle-income (LMI), upper middle-income (UMI), and high-income (HI) [55], which allows us to capture some of the global variability in conditions, costs, values, and preferences.

2.2. Detection assumptions and intervention scenarios

We use the model to demonstrate how the transmission dynamics play out at the global level over a time horizon of 1 January 2020 to 1 January 2025 for several different scenarios. Table 1 summarizes the specific input assumptions for each scenario. Consistent with the potential experience of no coordinated efforts to control unidentified pathogens, we model the worst-case scenario in which the nWPV remains unidentified, no response occurs, and mixing remains unchanged (scenario label ‘NR’). Although normal human tendencies to seek self-preservation may make no response unrealistic in the face of a significant disease such as polio, in the absence of identification of the pathogen, the ability to control it would remain limited and the pathogen can essentially burn through the population until it dies out or establishes endemicity. We also assume that if the nWPV emerged in a subpopulation with characteristics like China in 2020, the clinical realization of its severity and suspicion of a novel pathogen of concern would quickly lead to molecular identification and the development of rapid molecular diagnostic methods. This assumption is consistent with the state of molecular diagnostics in China and other technologically advanced countries in 2020, as demonstrated in the rapid identification, sequencing and classification of SARS-CoV-2 [19] followed by the rapid transition to real-time RT-PCR for routine diagnostics. Specifically, we assume that the timeline of nWPV identification and development of primers for RT-PCR assays would closely follow the timing of similar activities recently observed for SARS-CoV-2.

Although the current diagnostic paradigm for polioviruses includes a complex mix of viral cultures, intratypic differentiation (ITD) by ELISA, real-time PCR and/or sequencing [56–59], we assume that a 2020 de novo poliovirus diagnostic approach would rapidly evolve from viral culture and sequencing to real-time RT-PCR or a comparable nucleic acid amplification technology as occurred with SARS-CoV-2. While the diagnostic yields may initially vary, polioviruses grow well in a variety of
viral culture substrates used in clinical laboratories for pan-
viral cultures and for the identification of enteroviruses \cite{60,61}. Recent experience with poliovirus diagnostic advances further supports the feasibility of such a sequence of events (e.g. detection of emerging vaccine-related polioviruses by deep sequencing \cite{62}, numerous algorithms for detection and ITD of polioviruses by various RT-PCR approaches \cite{63–66}).

We assume that upon detection of a nWPV paralytic disease cluster and initial signals from molecular testing of a common genetic signature, China would enact a containment strategy characterized by testing, contact tracing, ramping up treatment capacity, and social distancing measures in the affected block upon recognition of the infectious disease, similar to what occurred for SARS-CoV-2. We further assume that China similarly would share information about nWPV that would enable its clinical recognition, preparation for clinical management, and laboratory diagnostic testing for other countries able to develop, license, and support such ventures.

In the absence of vaccines, clinical treatment for polio would involve support of severe cases using respirators, and hospitals would likely establish polio wards with ventilators, as they once did in the 1940s with less sophisticated technologies such as the iron lungs to treat patients with bulbar polio \cite{67,68}. We assume that the acquisition of sufficient ventilators would take time, and that those needing respirators but unable to access them due to insufficient supply would die, consistent with the pathophysiology of polio. For this analysis, we assume that 10% of paralytic cases lead to mortality, although the case fatality ratios vary by age and treatment \cite{68}. We highlight that treatment capacity would require time and resources to develop, and as such the mortality associated with the rapid spread of the nWPV could lead to substantially higher initial mortality rates. At the same time, the ability to rapidly ramp up production capacity for necessary medical devices could lead to much greater availability of treatment, which could lead to lower mortality rates.

We explore the demand for treatment and assume that respirator support would last for a period of 90 days on average, although we emphasize that the actual clinical experience with polio included individuals who only needed respiratory support for short periods of time (i.e. weeks), while others depended on an iron lung for life-long support. Importantly, this differs from the experience with SARS-CoV-2, in which ventilation days during early phases of pandemic averaged approximately 2 weeks and carried a relatively high mortality risk \cite{69}. We implicitly assume that the COVID-19 pandemic did not occur in 2020. We run the model with NR scenario showing the impact emergence of the nWPV in three different subpopulations with properties in the model like China, Indonesia, or India. We also run the model for scenarios that assume either significant decreases in mixing that aim to ‘flatten the curve’ (labeled as ‘FTC’) or global efforts to contain and eradicate the nWPV (labeled as ‘C&E’), as occurred in effect following the emergence of SARS in 2003 \cite{47}.

We operationalize these scenarios by reducing exports out of the affected subpopulations to other subpopulations by increasing the exportation threshold (E*) and reducing the subpopulation-specific basic reproduction number (R0), both of which would represent the net effect of NPIs. E* represents the cumulative number of infections within a subpopulation required to export into another subpopulation (see \cite{48} and appendix). We assume a value of E* of 125,000 for LI and MLI based on fitting to type 2 poliovirus transmission, which currently occurs in countries in these World Bank income levels. Data on international travel categorized by LMI, UMI, and HI show substantially more potential for exportation from UMI and HI countries, which led us to assume an E* of 25,000 (i.e. 5 times lower) for UMI and HI \cite{70,71}. For all scenarios, we increase E* and reduce the R0 after observation of the first clinical case of paralysis in a subpopulation in HI and UMI countries, or after the fifth clinical case in LMI and LI. We assume a delay of 75 days after disease emergence (i.e. identification of the first symptomatic patient) before effective NPIs would start the FTC or C&E efforts in the subpopulation of the first global detection, which roughly corresponds to the time delay for major global policy decisions on SARS-CoV-2 containment (Figure 1).

We model two different FTC strategies. For the first FTC strategy (FTC1), we assume a delay of 30 days for policy decisions following any subsequent disease detection in other subpopulations. For this reactive strategy, we assume a short-term and one-time restriction in mixing lasting for a period of 3 months in the subpopulation. The restriction involves a temporary reduction of R0 for each subpopulation by 1 and increase in E* by factor of 2. We also consider a second reactive strategy (FTC2) that involves a more aggressive policy approach by imposing restrictions 15 days after each subsequent disease detection that would increase E* to 250,000, decreases R0 for each subpopulation by 3, and lasts for a period of 6 months. For the C&E strategy, initially we assume the same delay in triggering the restrictions, E* increase and R0 decrease as in FTC2, but with extended duration of restrictions until global eradication of all nWPV. However, for the C&E strategy, we further extended these restrictions in all subpopulations with transmission until the model reaches 100,000 paralytic cases, at which point the model assumes the ‘declaration’ of a global pandemic (regardless of the precise geographic distribution of the cases). The declaration of a global pandemic then triggers NPIs that start 7 days later in all remaining subpopulations, including those yet to impose any restrictions and without any transmission. These strict pandemic restrictions increase E* to 250,000, effectively stop all importations by quarantining all travelers coming into any country, decrease R0 by 3 in all subpopulations to simulate substantial contract reduction measures (e.g. lockdowns, masks, hand washing, cleaning, school and workplace closures, etc.), and the model sustains all of these restrictions until the global die out of all nWPV transmission.

Recognizing the importance of different aspects of potential C&E strategies, we explored other variations of this strategy based on global declaration of a pandemic using different criteria and assuming a global commitment to eradication for which we used a longer time horizon out through 2029. We consider 2 different actions with respect to quarantining all travelers: (A) strict quarantine, such that no effective
importations occur, or (B) less strict quarantine (i.e. importations can still occur but at a much lower rate due to the higher exportation threshold, $E^*$). We consider both actions using 6 different criteria to trigger the declaration of a global pandemic based on the detection of: (1) 100,000 cases, (2) 1,000,000 cases, (3) cases in at least 2 blocks outside of the blocks that represent China, (4) cases in at least 13 blocks outside of the blocks that represent China, (5) at least 1 case in 2 PMAs, and (6) at least one case in each of the PMAs. These correspond to scenarios C&E1-6 for the assumptions of aggressive quarantine and C&E7-12 for no quarantine.

We coded the model in the general-purpose programming language JAVA™ in the integrated development environment Eclipse™. For each scenario, we perform 100 stochastic iterations using conserved seed values to facilitate comparisons across scenarios using the Amazon Elastic Compute Cloud (Amazon EC2). For each scenario, we show the probability of eradication, the number of subpopulations with one or more cases to demonstrate the speed of geographic spread and the incidence of cases over time. We report the expected values (medians and ranges in the appendix) of cases for the time horizon.

3. Results

3.1. Variability in the model results by scenario

As with any stochastic model, the results from individual iterations of the model can vary considerably due to the different timing of introductions into different countries. Figure 2 shows the variability in the modeled incidence over the time horizon for the 100 stochastic iterations of (a) NR, (b) C&E, (c) FTC1, and (d) FTC2 for nWPV1 paralytic cases. Each trajectory in Figure 2 represents a potential path for a given scenario, and for the various scenarios, the global experience would likely include times with more and less cases (e.g. waves) in the context of progression along any single path. No prospective analysis can predict which of the individual modeled curves would represent the actual path (if any), because the actual path would depend on stochastic events and actions taken (or not taken). Figure 2 also shows the striking differences between taking no action in response to the emerging infection (NR), which burns through the population relatively rapidly and results in endemic transmission (discussed below) compared to C&E, which affects a smaller number of individuals overall and leads to die out in the time horizon.

![Figure 2](image.png)

**Figure 2.** Global nWPV1 incidence of modeled paralytic polio cases shows the variability in the modeled incidence over the time horizon for 100 iterations. Similar variability results for the other modeled serotypes not shown.

Abbreviations: C&E, contain and eradicate; FTC, flatten the curve; NR, no response; nWPV1, novel wild poliovirus serotype 1
3.2. Role of the location of emergence
An equally important observation is the potential impact of the geographic location of the disease emergence, because of the association between economic level and international travel, and consequentially mixing across population blocks. These effects are obviously best demonstrated for the NR scenario, which represents the natural influence of location not confounded by any societal action in response to the disease. Figure 3 shows the expected values of the cumulative geographic spread through the 720 subpopulations (panels on the left side) and the cumulative incidence of paralytic disease (panels on the right side) for the 100 stochastic iterations considering the NR scenario for: (a) nWPV1, (b) nWPV2, and (c) nWPV3 assuming disease emergence in China, India, or Indonesia. In addition, comparison of Figure 2a to Figure 3a for China shows how the results track between the incidence of paralytic disease as a function of time (Figure 2a) and the cumulative incidence of the disease as a function of time (Figure 3a, right panel). Since there is no probability of disease eradication for the NR scenario when the nWPV emerges in China (detailed below), every individual run in Figure 2a will eventually reach all 720 global population subpopulations,

![Figure 3](image-url)

Figure 3. The average expected speed of virus spread through 720 subpopulations (left) and growth of expected cumulative global incidence of paralytic polio (right, using different y-axis scales) over time as a function with emergence in different modeled locations.

Abbreviations: nWPV(1,2,3), novel wild poliovirus (serotypes 1, 2, 3, respectively)
Table 2. Probability of eradication, expected total incidence in millions, and expected subpopulation spread by serotype of nWPV for modeled scenarios for 1 January 2020–1 January 2025.

| Scenario | Probability of eradication | Expected total incidence of paralytic cases in millions | Expected subpopulation spread |
|----------|----------------------------|---------------------------------------------------------|-------------------------------|
|          | nWPV1 | nWPV2 | nWPV3 | nWPV1 | nWPV2 | nWPV3 | nWPV1 | nWPV2 | nWPV3 |
| NR       | 0%    | 0%    | 0%    | 40.4  | 4.0   | 7.9   | 720   | 720   | 720   |
| FTC1     | 2%    | 0%    | 0%    | 39.6  | 4.0   | 7.9   | 705   | 720   | 719   |
| FTC2     | 14%   | 13%   | 17%   | 28.4  | 3.1   | 5.6   | 527   | 569   | 540   |
| C&E      | 100%  | 96%   | 87%   | 0.3   | 0.2   | 0.1   | 20    | 51    | 27    |

Abbreviations: C&E, contain and eradicate; FTC, flatten the curve; NR, no response; nWPV(1,2,3), novel wild poliovirus (serotypes 1, 2, 3, respectively)

albeit at different rates and with different burdens of paralytic disease as a function of time.

Figure 3 demonstrates that the emergence in different locations (China, India, or Indonesia) changes the expected average speed of viral spread through the 720 model subpopulations (left panels) and growth of the expected cumulative global incidence of paralytic polio cases (right panels). As anticipated, Figure 3 shows that the location of disease emergence impacts the speed of global spread, with more rapid spread following emergence in a subpopulation characterized by high population density and high R0 (like India). Comparison of the cumulative number of subpopulations (Figure 3, left panels) for the serotypes shows relatively faster global spread of nWPV1 than nWPV2 and nWPV3, consistent with the known biological behavior of the different serotypes. As shown in the cumulative paralytic case results (Figure 3, right panels), the location of emergence does not change the expected total cumulative incidence over the time horizon. This reflects the situation that in the absence of actions taken to stop or slow transmission, the nWPV continues global transmission until it establishes endemic transmission. Importantly, the expected cumulative paralytic cases also vary for the three serotypes consistent with the different paralysis-to-infection ratios (PIRs) (i.e. PIR(WPV1) > PIR(WPV3) > PIR(WPV2)), with the most expected cases (approximately 40 million) for nWPV1 and the least (approximately 4 million) for nWPV2. This clinical variability suggests that an emerging infectious disease with low morbidity and mortality to infection ratios could burn through the global population without significant socioeconomic impact or even clinical detection. For context, we can compare paralytic polio to a hospitalized and/or intubated COVID-19 case, in contrast with mild or subclinical SARS-CoV-2 infection, which is fundamentally similar to mild or subclinical infection with a poliovirus. Finally, for the cumulative incidence estimates in Figure 3 (right panels), if we assume a case-fatality rate of approximately 10% for paralytic polio [68], this would imply on the order of 400,000 (nWPV2) to 4 million (nWPV1) deaths depending on the serotype during the modeled time horizon.

3.3. Impacts of NPIs

Focusing next on the potential effects of societal action in response to an emerging disease, Figure 4 shows the expected values of the 100 stochastic iterations of the modeled scenarios of NR, C&E, FTC1, and FTC2, for: (a) nWPV1, (b) nWPV2, and (c) nWPV3 assuming disease emergence in China. As before, panels on the left show the expected speed of transmission through population blocks, while panels on the right show the expected cumulative incidence of paralytic disease. Additional model results are shown in Table 2, which reports the probability of eradication (stochastic die out of transmission), as well as the expected incidence of paralytic cases (and by extension the number of fatalities) and the number affected subpopulations for each scenario. Note that an ideal intervention would maximize the probability of die-out and minimize the disease burden (incidence and spread).

Given the structure of the global model, Figure 4 reports the average spread of the nWPVs from the subpopulation of emergence (see legend) to the other 720 subpopulations in the model, with the NR curves for emergence in China corresponding to the same serotype-specific curves in Figure 3. Again, in a manner consistent with biological differences between polioviruses, the extent of the spread depends on the serotype, with the lowest average spread of nWPV3, while nWPV1 and nWPV2 spread faster. On average, the FTC1 scenario (Table 1) somewhat slows the spread down in the first year after the nWPV emergence, but it does little over the long run compared to NR. In other words, the probability of die-out for FTC1 is still essentially zero (Table 2), suggesting that FTC1 will buy the global population time to ramp up treatment capacity, but global transmission will continue and establish endemicity.

In contrast, the FTC2 scenario (Table 1), which implements restrictions faster, longer, and more stringently than FTC1, reduces the spread through subpopulations by 21–27% (Figure 4 and Table 2), and increases the probability of die-out to somewhere between 10 and 20% (Table 2). As such, FTC2 represents a marginally effective and incomplete response to disease emergence. For comparison, the C&E scenario reduces spread by 93–97% over the time horizon and increases the probability of die-out to 100%, 96% and 87% for serotypes 1, 2 and 3, respectively, over the time horizon.

As shown in Figure 4 and indicated in Table 2, with a long enough time horizon, all subpopulations will experience transmission of the nWPVs in the absence of an effective containment and eradication strategy. If global policy makers do nothing in response to an emerging infection or engage in a process of slow and/or short-term flattening the curve strategy (e.g. FTC1 in this simulation), the emerging nWPVs will burn through the population relatively quickly and lead to a situation of global endemic transmission fueled by the susceptibility of new birth cohorts. Furthermore, in the absence of
preventive interventions (e.g. vaccines), transmission leads to the establishment of endemic equilibrium, with some countries experiencing episodic outbreaks followed by die out and then subsequent outbreaks after reimportation. Figure 5 demonstrates this periodic behavior of disease incidence over an extended time horizon after the emergence of the disease.

In Figure 5, the initial rise of the disease in 2020 shown in Figure 2 has been intentionally truncated by limiting the vertical axis to 100,000 cases per year to demonstrate dynamics beginning 1 year after the emergence. In addition, Figure 5 includes an expected incidence line (bold black line) superimposed on the individual runs to show the expected level and periodicity of endemic disease in the absence of eradication. Importantly, while the initial emergence affects individuals of all ages (because no one has immunity), after the initial burn through the population, most of the disease incidence would appear in children who have no immunity. (This is essentially...
Table 3. Probability of declaration of a global pandemic and probability of eradication for each serotype of nWPV for C&E scenarios modeled for 1 January 2020–1 January 2030 with emergence modeled in China.

| Scenario                        | Probability of declaration of a pandemic (cases) | Probability of eradication |
|--------------------------------|-----------------------------------------------|----------------------------|
|                                | nWPV1 | nWPV2 | nWPV3 | nWPV1 | nWPV2 | nWPV3 |
| A: Strict quarantine of all travelers in all countries after pandemic declared (no effective importations) |
| C&E*                           | 100,000 global                          | 85% | 47% | 28% | 100% | 99% | 100% |
| C&E                            | 1,000,000 global                        | 51% | 50% | 27% | 92%  | 98% | 100% |
| C&E                            | In China + 2 blocks                     | 52% | 49% | 26% | 98%  | 100%| 100% |
| C&E                            | In China + 13 blocks                    | 50% | 49% | 28% | 88%  | 99% | 100% |
| C&E                            | In 2 PMAs                              | 51% | 51% | 28% | 100% | 100%| 100% |
| C&E                            | In all PMAs                            | 46% | 46% | 25% | 68%  | 93% | 97%  |
| B: Less strict quarantine of all travelers in all countries after pandemic declared (some effective importations) |
| C&E                            | 100,000 global                         | 85% | 50% | 25% | 59%  | 60% | 77%  |
| C&E                            | 1,000,000 global                       | 51% | 52% | 25% | 49%  | 69% | 85%  |
| C&E                            | In China + 2 blocks                    | 53% | 51% | 26% | 48%  | 59% | 78%  |
| C&E                            | In China + 13 blocks                   | 51% | 51% | 29% | 51%  | 62% | 78%  |
| C&E                            | In 2 PMAs                             | 52% | 55% | 31% | 52%  | 62% | 79%  |
| C&E                            | In all PMAs                           | 48% | 46% | 22% | 51%  | 71% | 79%  |

Note: *C&E the same as C&E in Table 2 except simulated for a longer time horizon

Abbreviations: C&E, contain and eradicate; FTC, flatten the curve; nWPV(1,2,3), novel wild poliovirus (serotypes 1, 2, 3, respectively); PMAs, preferentially mixing areas

why and how an established infectious disease such as polio comes to be known as a ‘childhood disease’). Flattening the curve shows a slower accumulation of cases over time and thus a less rapid decline of the average age of infection. The endemic equilibrium in 2030 for the expected birth cohort of approximately 136 million surviving infants [54] would lead to 680,000, 68,000, or 136,000 expected paralytic polio cases in 2030 for nWPV1, nWPV2, or nWPV3, respectively.

3.4. Effect of an early global commitment to eradication and the probability of success

Tables 3 and 4 report results of different assumptions for the C&E scenarios that demonstrate how the extent of quarantine actions and criterion used to define and declare a pandemic changes the model outcomes for each serotype. The results in Tables 3 and 4 use a longer time horizon than those reported in Table 2, and the simulations are grouped into two overarching policy measures. The top part of Table 3 shows the results assuming strict quarantine (A), such that after a pandemic is declared, all travelers entering all countries are quarantined to ensure no effective importations. The bottom part of Table 3 shows the results assuming less strict quarantine (B), such that after a pandemic is declared, importations can still occur when an infected traveler moves to a different subpopulation, albeit at a lower frequency. As shown in Tables 3 and 4, both the assumptions about quarantine (A or B) and the criterion used to define and declare a pandemic affect the results. The results implicitly assume actions consistent with FTC2 prior to the declaration of global pandemic that leads to globally applied and sustained contact and travel restrictions. The C&E1 scenario under strict quarantine (A) in Tables 3 and 4 corresponds to the assumptions underlying Table 2 data, except for the longer time horizon.

Table 3 shows the probability of declaration of a pandemic (left) and the probability of achieving eradication (right) during the time horizon for each scenario. The probability of declaring a pandemic does not depend on the strictness of

Table 4. Expected time (days) to eradication (for iterations that eradicate) and expected total incidence in millions for iterations that eradicate for each serotype of nWPV for C&E scenarios modeled for 1 January 2020–1 January 2030 with emergence modeled in China.

| Scenario                        | Expected time (days) to eradication** | Expected total incidence of paralytic cases in millions** |
|--------------------------------|--------------------------------------|----------------------------------------------------------|
|                                | nWPV1 | nWPV2 | nWPV3 | nWPV1 | nWPV2 | nWPV3 |
| A: Strict quarantine of all travelers in all countries after pandemic declared (no effective importations) |
| C&E*                           | 100,000 global                       | 489 | 886 | 1083 | 0.3  | 0.2 | 0.1  |
| C&E                            | 1,000,000 global                     | 796 | 1099 | 1165 | 1.5  | 0.8 | 0.5  |
| C&E                            | In China + 2 blocks                  | 725 | 811 | 1071 | 0.6  | 0.1 | 0.1  |
| C&E                            | In China + 13 blocks                 | 891 | 994 | 1143 | 2.5  | 0.3 | 0.3  |
| C&E                            | In 2 PMAs                           | 654 | 751 | 1019 | 0.2  | 0.0 | 0.0  |
| C&E                            | In all PMAs                          | 1080 | 1214 | 1301 | 6.6  | 1.2 | 1.1  |
| B: Less strict quarantine of all travelers in all countries after pandemic declared (some effective importations) |
| C&E                            | 100,000 global                       | 859 | 1131 | 1121 | 0.8  | 0.5 | 0.1  |
| C&E                            | 1,000,000 global                     | 740 | 1301 | 1285 | 0.2  | 1.0 | 0.7  |
| C&E                            | In China + 2 blocks                  | 747 | 1158 | 1120 | 0.9  | 0.5 | 0.2  |
| C&E                            | In China + 13 blocks                 | 783 | 1201 | 1172 | 1.5  | 0.7 | 0.5  |
| C&E                            | In 2 PMAs                           | 787 | 1154 | 1146 | 0.9  | 0.4 | 0.3  |
| C&E                            | In all PMAs                          | 786 | 1294 | 1285 | 2.4  | 1.1 | 0.8  |

Note: *C&E the same as C&E in Table 2, except simulated for a longer time horizon; **See Table 3 for the probability of eradication for each scenario (results shown here only consider iterations that eradicated by the end 2029)

Abbreviations: C&E, contain and eradicate; FTC, flatten the curve; nWPV(1,2,3), novel wild poliovirus (serotypes 1, 2, 3, respectively); PMAs, preferentially mixing areas
quarantine (A or B) and only varies by the pandemic declaration criterion and serotype. As shown Table 2, the transmission in some iterations following FTC2 died out relatively early in the time horizon and led to eradication. Comparison of the probability of eradication results for C&E in Table 2 to the C&E1 results in Table 3 show how censoring (or shortening) the time horizon may reduce the probability of eradication (e.g. 87% for nWPV3 in Table 2, increases to 100% with a longer time horizon in Table 3). The time horizon matters less for nWPV1, which spreads more quickly and causes more paralytic cases per infection. The results in Table 3 also show that not all of the iterations with the C&E strategies officially declare a pandemic. While potentially counterintuitive, considering that the C&E scenarios in Table 3 assume restrictions similar to FTC2 prior to the declaration of a pandemic and some non-zero probability occurs with FTC2 in Table 2, some iterations in Table 3 eradicate prior to the declaration of a pandemic. Comparison of the overall results in Table 3 shows that applying effective and stringent quarantine (A, scenarios C&E1 to C&E6) leads to much higher probabilities of eradication than no or ineffective quarantine (B, scenarios C&E7 to C&E12).

For the fraction of iterations in Table 3 that eradicated by the end of 2029, Table 4 summarizes the expected time (days) required to achieve eradication and the expected total incidence of paralytic cases in millions (see Table A3 for medians and ranges). The different criteria explored for the C&E scenarios in Table 3 provide an indication of the impact of moving to aggressive global control and eradication earlier. For example, acting at the time of 100,000 global paralytic cases (independent of where they appear) substantially reduces the expected time required to achieve eradication and decreases the expected cumulative paralytic cases compared to waiting until 1,000,000 cases. Similarly, acting at the time of detection of cases in 2 population blocks outside of China leads to better outcomes than waiting to detect more geographic spread. For the structure of our model, which uses preferential mixing areas (PMAs) to simulate a large country like China or continents, if we apply strict contain and eradicate efforts after detection in 2 PMAs, then this also shuts down transmission much more rapidly with strict quarantine. With the declaration of a pandemic based on the fastest reached triggers modeled (i.e. 100,000 cases or cases in 2 PMAs) and strict quarantine, eradication occurs in 100% of iterations within an expected 1.5–2 years for nWPV1, 2–2.5 years for nWPV2, and 3 years for nWPV3. In the absence of strict quarantine, the probability of eradication decreases substantially (Table 3), and the results in Table 4 suggest that if eradication occurs, it takes longer. These results underscore the importance of preventing effective importations through travel restrictions and/or quarantine.
4. Discussion

The global response to the emergence and global spread of COVID-19 provided a stark reminder that world leaders tend to act in a surprised and uncoordinated fashion in response to emerging pathogens that should arguably be predictable based on existing knowledge [47]. We take advantage of a well-known and established global model to simulate the hypothetical emergence of polio as a novel disease in the same time frame as COVID-19. Our simulation reiterates and reaffirms the fundamental lessons learned in the global experience with SARS and COVID-19. Specifically, in the absence of decisive and coordinated global action, emerging infectious diseases will spread rapidly through the global community and become endemic with substantial costs to human health. Our analysis informs global policy makers about the consequences of choices and action (or inaction) by highlighting the effect of non-intuitive policy decisions such as the effect of the speed and scope of action on the spread of an emerging disease. As an added benefit, since the global polio model includes the behavior of three clinically different polioviruses, our modeling efforts represent three different pathogens with different behaviors and health outcomes.

COVID-19 has been a disruptive global pandemic, in spite of an unprecedented flow of information, and characterized by difficulties in separating policy from politics and rational decisions from emotional reactions. Importantly, for the public health community that witnessed the successful control and eradication of SARS less than two decades ago followed by the establishment of multiple global programs to enable the same outcome in the next pandemic, lingering questions remain about the sources of policy failure with COVID-19. This is particularly puzzling given that, unlike SARS, identification of a novel pathogen with COVID-19 happened with weeks of the disease emergence (Figure 1). We show that the global population and its mixing characteristics in 2020 would most likely result in devastating global polio pandemic with the strategies deployed globally to control COVID-19 for all three poliovirus serotypes, albeit with different magnitudes and dynamics. With the global community at risk of novel emerging pathogens almost constantly, we hope that this analysis informs the need for strict control and eradication policies above and beyond what the world was prepared for with the emergence of COVID-19. In retrospect, SARS emerged at a time that global population was 25% smaller and international travel was an order of magnitude less. Thus, the policies that led to success eradication of SARS-CoV-1 in 2003 might not have been as successful in 2020, although several countries such as China, Taiwan, and Singapore managed to control national transmission of SARS-CoV-2 much more successfully to date using the strategies that they learned from SARS-CoV-1.

Although no quantification exists of the economics of the actual strategies used to prevent the establishment of SARS-CoV-1, commenting on its global die out, a discussion of the economics of eradication of emerging diseases suggested that ‘global health authorities should seek to ensure that proper incentives exist to motivate early detection, reporting, coordination, and action related to the management of emerging diseases’ [47]. The costs of failing to prevent a global pandemic like COVID-19 include substantial declines in wealth [71]. While acknowledging biological differences between SARS-CoV-1 and SARS-CoV-2, the COVID-19 pandemic in 2020 shows the consequences of failing to act rapidly and decisively. Although prior literature suggests the need for early introduction of interventions [10], global declaration of the COVID-19 pandemic occurred relatively late [29]. Notably, the delay in global action occurred despite rapid identification of the causative agent of COVID-19 as a novel pathogen within weeks of the emergence of the disease (Figure 1).
We believe that the semantics and the definition of a ‘pandemic’ represent key factors in the delay of a global response to COVID-19, which served as an important triggering event for global action. Surprisingly, WHO does not include the word ‘pandemic’ in the glossary of WHO humanitarian health emergencies [72], and the US CDC vaguely defines pandemic as ‘a worldwide epidemic’ and epidemic as the ‘occurrence of disease within a specific geographical area or population that is in excess of what is normally expected’ [73]. WHO did not declare COVID-19 as a pandemic prior to 114 countries reporting over 118,000 cases globally [29], which contrasts with declaration of an H1N1 influenza pandemic in 2011 with 74 countries reporting nearly 30,000 cases. We show (Table 3 and Figure 3) that the spread of an emerging infectious disease has less to do with arbitrary geopolitical definitions of countries and continents, and more to do with the size and scope of infected populations and the nature of the population mixing behaviors. We suspect that one key difference between the global spread of SARS-CoV-1 and SARS-CoV-2 is the significant change in the mixing behavior of the Chinese population between 2002 and 2019 when the viruses emerged, respectively. Based on the World Development Indicators published by the World Bank, international travel out of China increased by an order of magnitude between 2002 and 2019 (Figure 6), corresponding substantially higher chances for global spread. As shown in Figure 3, in addition to biological and clinical characteristics of the pathogen, the geographic location of disease emergence is a key indicator of the speed of global spread.

Perhaps our results for scenarios other than C&E provide one of our most important insights, because our analyses show that an emerging disease will burn through the susceptible global population quite effectively, and efforts to flatten the curve only extend the time required to reach endemic transmission (Figures 2 and 4). We find little difference between a policy of global inaction (scenario NR) and our FTC1 scenario (Table 1), which is characterized by relatively slow response (30 days) to disease detection in a subpopulation, short duration of restrictions (3 months) and spotty restrictions resulting in a small and/or variable reduction in $R_0$. In contrast, more aggressive and repeated efforts (FTC2) result in a slower spread of the disease, but the disease will still spread throughout the population. Flattening-the-curve strategies that essentially became the global policy action against COVID-19 do not represent eradication strategies and will only slow the disease progression. The FTC scenarios may represent acceptable strategies for managing healthcare capacity and buying time for the development and deployment of vaccines and therapeutics, but a natural outcome of these strategies is progression to an endemic state (Figure 5), which will lead to a substantial expected health and economic costs.

Importantly, these conclusions occur independent of the clinical behavior of the nWPV serotype. Figure 4 (panels on the right) showed the consequences of the different reproduction numbers ($R_0$) and different disease severity (paralysis-to-infection ratios or PIRs) for nWPV serotypes 1, 2, and 3. However, all three serotypes spread through the global population at an approximately comparable time scale (Figure 4, panels on the left). The actual observed experience for a newly emerged neurotropic enterovirus would depend on its properties. Thus, if a virus emerged with the same transmission routes and types of immunological responses as we assumed for nWPV but with a much smaller PIR (e.g. on the order of 1 per million instead of 1 per thousand), then the burden of disease could remain very low and difficult to detect as clinically significant. This explains why some emerging viruses may potentially spread through the global population as an undetected novel/emerging disease or a subclinical infection altogether (e.g. mysterious cases of acute flaccid myelitis (AFM) for a neurotropic enterovirus, or undetected pneumonias masked or appearing as a ‘bad flu season’ for a respiratory virus).

We recognize clinical identification of an emerging infectious disease as a difficult task. Relatively rapid identification of COVID-19 as a novel disease arguably represents a notable exception, because of the recent memory of SARS and the widespread availability of advanced molecular diagnostics in China. For an emerging neurotropic enterovirus, we might assume that identification of an acute paralytic disease (acute flaccid paralysis or AFP) cluster would occur relatively easily, because these would appear as clusters with noticeably higher rates of AFP than occurs at the background rate in populations. The broad clinical differential diagnosis of AFP includes a wide array of diverse neuromuscular diseases [74]. In the context of such diversity, identification of a novel disease cluster characterized by a heterogeneous clinical spectrum and linked only through the presence of a novel pathogen represents a difficult task. Consistent with the above observations, another study [75] estimates an average prevalence of 98.7 (adults) and 75.9 (children) for all neuromuscular disorders per 100,000 individuals in the year 2014 in Canada, many of which may include AFP as a clinical presentation. Further confounding the identification of an emerging neurotropic enterovirus, for example, in cases of AFM, laboratory testing reveals a wide range of non-polio enteroviruses isolated from clinical samples for up to 30% of AFM cases depending on age and other demographics [76,77]. Thus, even with relatively advanced clinical and laboratory tools, a clinically significant novel pathogen may not be characterized as such for multiple weeks, or months, if at all. These issues become even more confounded by increasingly limited and managed healthcare resources that typically aim to identify and classify known etiologies (such as the commonly used viral PCR panels) rather than approaching diagnosis with the type of genome sequencing that led to the rapid identification of SARS-CoV-2.

As with any modeling work, the results presented here are limited by all of the structural and input assumptions (as detailed previously [48]). Specifically, we model the hypothetical spread of an nWPV between subpopulations using thresholds to trigger potentially effective exportations. Since real exportations represent stochastic events, with chance determining the actual path of viral transmission, the value of $E^*$ remains uncertain, and any actual path of emergence would reflect the stochastic nature of human interactions. While we modeled a couple of different strategies for slowing
transmission (FTC1 and FTC2), the actual restrictions that would occur (i.e. delays, duration, and strength) remain both uncertain and variable. For purposes of this hypothetical analysis, specific characterization of the NPIs does not matter, because we focus on the effect of the interventions at a high level. We note, however, that the actual interventions applied could come with widely different costs and levels of effectiveness and would matter in modeling efforts that aim to characterize an actual situation. The length of the time horizon modeled also plays an important role, most notably while determining the probability of eradication under C&E scenarios, with shorter time horizon artificially lowering the probability of eradication.

As emphasized in the introduction, this hypothetical simulation is not relevant to the current situation that exists for the established polioviruses, which emerged centuries ago and that remain the focus of current global eradication efforts. The dynamics of introducing an infection into a population differ substantially for a completely immunologically naive population (as we simulated in this hypothetical analysis) compared to a population with transmission at the endemic equilibrium (see Figure 3 of [78] for discussion of this concept). Current modeling for polio and performance of the GPEI to date provide relevant context about the actual situation [50,79]. In addition, for this hypothetical analysis, we implicitly assumed no availability of vaccines at the time of emergence, and we refer to a separate analysis that explores the potential impact of vaccines [80].

With respect to the COVID-19 pandemic, we emphasize that this analysis did not model the emergence of a virus with the specific properties of SARS-CoV-2 and that both similarities (e.g. asymptomatic transmission and the potential for reinfection) and differences (e.g. routes and receptors, viral transmissibility characteristics) exist between polioviruses and SARS-CoV-2. In addition, while this analysis does not relate to the current situation with polio or efforts of the GPEI, the emergence of SARS-CoV-2 and declaration of the COVID-19 pandemic led to the disruption of national immunization activities, including routine immunization for polio in some areas, and disrupted GPEI-supported supplemental immunization activities. Notably, unlike prior threats to GPEI activities, for which the GPEI historically provided global surge capacity (i.e. human, financial, and technical resources) to rapidly respond to emerging infectious diseases with a goal of preventing them from becoming pandemic (e.g. SARS, Ebola), the GPEI only committed resources to combat COVID-19 after global declaration of the pandemic resulted in disruption of GPEI operations. As discussed above, the declaration of the pandemic occurred 100 days after the emergence of the first symptomatic patient and more than one month after declaration of Public Health Emergency of International Concern (PHEIC) (Figure 1), which experience shows occurred too late to prevent the establishment of widespread transmission. Consistent with transition plans that assumed success [81], the GPEI substantially reduced its human resources [82] despite ongoing challenges with polio eradication.

Exploration of the dynamics of emergence of familiar diseases with existing models can provide helpful context about the types of dynamic behavior that we might expect following the emergence of novel viruses. Future health economic studies should quantify the health and economic impacts of the emergence of SARS-CoV-2 and the subsequent global policy decisions and actions. Our work with an integrated global polio model provides a framework for such future studies.

5. Conclusion
The opportunity to eradicate emerging infectious diseases before they become established represents an important choice that we should recognize as likely to impact health and financial outcomes for multiple generations. If wild poliovirus or a pathogen of similar characteristics first emerged in 2020, then the size of the global population and human mixing characteristics would most likely result in devastating global polio pandemic assuming adoption of the strategies that were deployed globally to control COVID-19.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Author contributions
KMT, DAK, and KB conceived the study and contributed to the writing of the first draft and all subsequent revisions. KMT and DAK developed the model used. DAK performed all of the modeling. KB designed the figures. KMT acquired the funding for the study. All authors read and approved the final manuscript.

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ORCID
Kimberly M. Thompson http://orcid.org/0000-0002-0849-9147
Kamran Badizadegan http://orcid.org/0000-0003-4900-9455

References
Papers of special note have been highlighted as either of interest (+) or of considerable interest (+) to readers.
1. Thompson KM, Badizadegan ND. Modeling the transmission of measles and rubella to support global management policy analyses and eradication investment cases. Risk Anal. 2017;37(6):1109–1131.
2. Patel MK, Dumolard L, Nedelec Y, et al. Progress toward regional measles elimination - worldwide, 2000-2018. MMWR Morb Mortal Wkly Rep. 2019 Dec 6;68(48):1105–1111.
3. Smith G, Michelson J, Singh R, et al. Is there enough vaccine to eradicate measles? An integrated analysis of measles-containing vaccine supply and demand. J Infect Dis. 2011 Jul;204(Suppl 1): S62–70.
4. Donnelly CA, Fisher MC, Fraser C, et al. Epidemiological and genetic analysis of severe acute respiratory syndrome. Lancet Infect Dis. 2004 Nov;4(11):672–683.

5. Kwon KO, Tang A, Wei VWI, et al. Epidemic models of contact tracing: systematic review of transmission studies of Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome. Comput Struct Biotechnol J. 2019;17:186–194.

---Systematically reviews models of SARS

6. Coburn BJ, Wagner BG, Blower S. Modeling influenza epidemics and pandemics: insights into the future of swine flu (H1N1). BMC Med. 2009;7(1): 30. 2009/06/22

7. Lipstich M, Cohen T, Cooper B, et al. Transmission dynamics and control of severe acute respiratory syndrome. Science. 2003;300(5627):1966–1970.

8. Lloyd-Smith JO, Galvani AP, Getz WM. Curtailing transmission of severe acute respiratory syndrome within a community and its hospital. Proc Biol Sci. 2003 Oct;270(1258):1979–1989.

---Demonstrates the importance of early implementation of non-pharmaceutical interventions in response to SARS

9. Riley S, Fraser C, Donnelly CA, et al. Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science. 2003 Jun 20;300(5627):1961–1966.

10. Fraser C, Riley S, Anderson RM, et al. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci USA. 2004 Apr 20;101(16):6146–6151.

---Provides perspective the characteristics of emerging infectious diseases that make them show different transmission dynamics.

11. Longini IM Jr., Nizam A, Xu S, et al. Containing pandemic influenza at the source. Science. 2005 Aug 12;309(5737):1083–1087.

12. Zhang J, Lou J, Ma Z, et al. A compartmental model for the analysis of SARS transmission patterns and outbreak control measures in China. Appl Math Comput. 2005 Mar 15;162(2):909–924.

13. Hsu S-B, Hsieh Y-H. Modeling intervention measures and severity-dependent public response during severe acute respiratory syndrome outbreak. SIAM J Appl Math. 2005;66(2):627–647.

14. Webb GF, Blaser MJ, Zhu H, et al. Critical role of nosocomial transmission in the toronto sars outbreak. Math Biosci Eng. 2004 Jun;1(1):1–13.

15. Institute of Medicine. Modeling community containment for pandemic influenza: A letter report Washington, DC: National Academies Press; 2006 [cited 2020 Nov 1]. Available from: https://www.nap.edu/catalog/11800/modeling-community-containment-for-pandemic-influenza-a-letter-report

16. Centers for Disease Control and Prevention. Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States: early, targeted, layered use of nonpharmaceutical interventions 2007 [cited 2020 Nov 1]. Available from: https://stacks. cdc.gov/view/cdc/11425

17. Li X, Wang W, Zhao X, et al. Transmission dynamics and evolutionary history of 2019-nCoV. J Med Virol. 2020 May;92(5):501–511.

18. World Health Organization, Poliomyelitis: WHO information for health professionals. [updated 2020 Jan 5]. Available from: https://www.who.int/csr/don/05-january-2020-poliomyelitis-who-information-for-health-professionals

19. Tan W, Zhao X, Ma X, et al. A novel coronavirus genome identified in a cluster of pneumonia cases - Wuhan, China 2019-2020. China CDC Weekly. 2020;2(4):61–62.

20. Zhang Y-Z, Wu F, Chen Y-M, et al. Wuhan seafood market pneumonia virus isolate Wuhan-Hu-1, complete genome. 2020 5 Jan. Document No.: GenBank: MN908947.1. Available from: https://www.ncbi.nlm.nih.gov/nuccore/MN908947.1

21. Anon. Specific primers and probes for detection 2019 novel coronavirus 2020 [Cited 2020 Apr 7]. Available from: http://ivdch.inacdc.cn/kjyz/202001/t20200121_111337.html

22. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565–574.

23. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China. 2019. N Engl J Med. 2020 Feb 20;382(8):727–733.

24. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020. DOI:10.1038/s41586-020

25. Juan D Wuhan wet market closes amid pneumonia outbreak: China daily global edition; 2020 [updated 1 Jan 2020; cited 2020 Apr 8]. Available from: https://www.chinadaily.com.cn/a/202001/01/WS5e694a9363f3e354a1e30.html

26. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(11):1199–1207.

27. GISAID. Genomic epidemiology of hCoV-19: global initiative on sharing all influenza data (GISAID); 2020 [updated 8 Apr 2020; cited 2020 Apr 12]. Available from: https://www.gisaid.org/epiflu-applications/next-hcov-19-app/

28. World Health Organization. Statement on the second meeting of the international health regulations (2005) emergency committee regarding the outbreak of novel coronavirus (2019-nCoV) 2020 [cited 2020 Aug 20]. Available from: https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

29. World Health Organization, WHO director-general’s opening remarks at the media briefing on COVID-19-11 March 2020: world health organization; 2020 [updated 11 Mar 2020; 2020Mar1]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020

30. World Health Organization. Update 95 - SARS: chronology of a serial killer 2003 [cited 2020 Nov 1]. Available from: https://www.who.int/csr/don/2003_07_04/en/

31. Horstmann DM. The poliomyelitis story: A scientific hegira. Yale J Biol Med. 1985;58:79–90.

32. Heine J. Beobachtungen über Lähmungszustände der unteren Extremitäten und deren Behandlung. Stuttgart, Germany: Franz Heinrich Köhler; 1840.

33. Medin O. En epidemi af infantil paralysis. Hygieia. 1890;52:657–668.

34. Wickman I. Die akute Poliomyelitis bzw.: Heine Medinsche Krankheit. Berlin: Springer; 1911. p. 108.

35. Landsteiner K, Popper E. Uebertragung der Poliomyelitis acuta auf Affen. Z Imunitatstforsch 1909;2:377–390.

36. Eggers HJ. Milestones in early poliomyelitis research (1840 to 1949). J Virol. 1999;73(6):4533–4535.

37. Howe HA, Bodian D. Untreated human stools as a source of polio- myelitis virus. J Infect Dis. 1940;66(3):198–201.

38. Howe HA, Bodian D. Second attacks of poliomyelitis: an experimental study. J Exp Med. 1941 Jul 31;74(2):145–166.

39. Bodian D. Neutralization of three immunological types of polio- myelitis virus by human gamma globulin. Proc Soc Exp Biol Med. 1949 Oct;72(1):259–261.

40. Molliver ME, Bodian D 1910-1992: A biographical memoir. national academy of sciences; 2012. [Cited 2020 Nov 15]. Available from: http://www.nasonline.org/member-directory/deceased-members /57585.html

41. McKay SL, Lee AD, Lopez AS, et al. Increase in acute flaccid myelitis - United States, 2018. MMWR Morb Mortal Wkly Rep. 2018;67 (45):1273–1275.

42. Morens DM, Folkers GK, Fauci AS. Acute flaccid myelitis: something old and something new. mBio. 2019;10(2):e00521–19.

43. Kidd S, Lopez A, Nix WA, et al. Vital signs: clinical characteristics of patients with confirmed acute flaccid myelitis, United States, 2018. MMWR Morb Mortal Wkly Rep. 2020 August 4;69(31):1031–1038.

44. Thompson KM, Kalkowska DA. Review of poliovirus modeling performed from 2000-2019 to support global polio eradication. Expert Rev Vaccines. 2020;19(7):661–686.

---Systematically reviews the poliovirus modeling papers published 2000-2019
45. Thompson KM, Duintjer Tebbens RJ. Retrospective cost-effectiveness analyses for polio vaccination in the United States. Risk Anal. 2006;26(6):1423–1440.

46. Duintjer Tebbens RJ, Pallansch MA, Cochi SL, et al. Economic analysis of the global polio eradication initiative. Vaccine. 2011 December;29(23):334–343.

47. Thompson KM, Duintjer Tebbens RJ. Economic evaluation of the benefits and costs of disease elimination and eradication initiatives. In: Cech SL, Dowdle WR, editors. Disease eradication in the 21st century: implications for global health. Cambridge, MA: MIT Press; 2011. p. 115–130.

48. Kalkowska DA, Wassilak SGF, Cochi SL, et al. Global transmission of live polioviruses: updated integrated dynamic modeling of the polio endgame. Risk Anal. 2021;41(2):248–265.

49. Kalkowska DA, Pallansch MA, Cochi SL, et al. Updated characterization of post-OPV cessation risks: lessons from 2019 serotype 2 outbreaks and implications for the probability of OPV restart. Risk Anal. 2021;41(3):320–328.

50. Thompson KM, Kalkowska DA. An updated economic analysis of the global polio eradication initiative. Risk Anal. 2021;41(2):393–406.

51. Nathanson N, Kew OM. From emergence to eradication: the epide- miology of poliomyelitis deconstructed. Am J Epidemiol. 2010 Dec 1;172(11):1213–1229.

52. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497–506.

53. Lavine JS, Bjornstad ON, Antia R. Immunological characteristics govern the transition of COVID-19 to endemicity. Science. 2021 Jan 12;371(6530):741–745.

54. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. World population prospects. The 2019 revision [cited 2019 Jul 17]. Available from: https://unpopulation.un.org/wpp/

55. World Bank. World Bank list of economies (June 2019) [cited 2019 Jul 17]. Available from: http://databank.worldbank.org/data/download/site/CLASS.xls

56. World Health Organization. Polio laboratory manual - 4th edition. global polio laboratory network: 2004. [Cited 2020 Nov 15]. Available from: http://polioreadication.org/wp-content/uploads/2017/05/Polio_Lab_Manual04.pdf

57. World Health Organization. Polio laboratory manual - 4th edition - supplement S1. global polio laboratory network: 2004. [Cited 2020 Nov 15]. Available from: http://polioreadication.org/wp-content/uploads/2017/05/NewAlgorithmForPoliopolioIsolationSupplement1.pdf

58. World Health Organization. Updates on ITD molecular assays and testing algorithm (including 6 appendices) guidance paper 2: global polio laboratory network: 2016 [cited 2020 Nov 1]. Available from: http://polioreadication.org/wp-content/uploads/2020/01/GP2-Updates-on-ITD-molecular-testing.pdf

59. World Health Organization. Reporting vaccine derived polioviruses (VDPVs) guidance paper 5: global polio laboratory network: 2019 [cited 2020 Nov 1]. Available from: http://polioreadication.org/wp-content/uploads/2020/01/GP5-VDPV-Reporting-for-SEQ-Lab-Vs1.pdf

60. Chonnaintre T, Ford C, Sanders C, et al. Comparison of cell cultures for rapid isolation of enteroviruses. J Clin Microbiol. 1988 Dec;26(12):2576–2580.

61. Smith CD, Craft DW, Shiromoto RS, et al. Alternative cell line for virus isolation. J Clin Microbiol. 1986 Aug;24(2):265–268.

62. Sahoo MK, Holubar M, Huang C, et al. Detection of emerging vaccine-related polioviruses by deep sequencing. J Clin Microbiol. 2017 Jul;55(7):2162–2171.

63. van Hoorebeke C, Huang C, Leary S, et al. Lab protocol paper: use of a high-throughput, multiplex reverse-transcription quantitative polymerase chain reaction assay for detection of Sabin oral polio vaccine in fecal samples. Clin Infect Dis. 2018 Oct 30;67(suppl_1):S121–S126.

64. Altamirano J, Leary S, van Hoorebeke C, et al. Validation of a high-throughput, multiplex, real-time qualitative polymerase chain reaction assay for the detection of Sabin oral polio vaccine in environmental samples. Clin Infect Dis. 2018 Oct 30;67(suppl_1):S98–S102.

65. Manukyan H, Rodionova E, Zagorodnyaya T, et al. Multiplex PCR-based titration assay for determination of infectious titers of the three Sabin strains of live poliovirus vaccine. Virol J. 2019 Oct 28;16(1):122.

66. Manukyan H, Zagorodnyaya T, Ruttimann R, et al. Quantitative multiplex one-step RT-PCR assay for identification and quantitation of Sabin strains of poliovirus in clinical and environmental specimens. J Virol Methods. 2018;259:74–80.

67. Oshinsky DM. Polio: an American Story. New York: Oxford University Press; 2005.

68. Sutter RW, Kew OM, Cochi SL, et al. Poliovirus vaccine – live. In: Plotkin SA, Orenstein WA, Offit PA, et al., editors. Plotkin’s vaccines. Sixth ed Philadelphia: Saunders Elsevier. 2017. p. 866–917.

69. Karagianidis C, Mostert C, Hentschker C, et al. Case characteristics, resource use, and outcomes of 10021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med. 2020 Jul 28;8(9):853–862.

70. World Bank. International tourism number of departures 2020 [cited 2020 Oct 5]. Available from: https://data.worldbank.org/indicator/ST.INT.DPRT

71. World Bank. Poverty and shared prosperity 2020 reversals of fortune 2020 [cited 2020 Nov 1]. Available from: https://openknowledge.worldbank.org/bitstream/handle/10986/34496/9781464816024.pdf

72. World Health Organization. Humanitarian health action: definitions, emergencies 2020 [cited 2020 Oct 13]. Available from: https://www.who.int/hac/about/definitions/en/

73. Centers for Disease Control and Prevention. Vaccines and immunizations: glossary 2020 [cited 2020 Aug 20]. Available from: https://www.cdc.gov/vaccines/terms/glossary.html

74. Marx A, Glass JD, Sutter RW. Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance. Epidemiol Rev. 2000;22(2):298–316.

75. Rose L, McKim D, Leasa D, et al. Trends in incidence, prevalence, and mortality of neuromuscular disease in Ontario, Canada: A population-based retrospective cohort study (2003-2014). PLoS One. 2019;14(3):e0210574.

76. Dietz V, Andrus J, Oliveira J, et al. Epidemiology and clinical characteristics of acute flaccid paralysis associated with non-polio enterovirus isolation: the experience in the Americas. Bull World Health Organ. 1995;73(5):597–603.

77. Lakshminandana R, Yergolkar P, Gopalkrishna V, et al. Characterization of the non-polio enterovirus infections associated with acute flaccid paralysis in South-Western India. PLoS One. 2013;8(4):e61650.

78. Duintjer Tebbens RJ, Kalkowska DA, Thompson KM. Global certification of wild poliovirus eradication: insights from modelling hard-to-reach subpopulations and confidence about the absence of transmission. BMJ Open. 2019;9(1):e023938.

79. Kalkowska DA, Wassilak SGF, Cochi SL, et al. Global transmission of live polioviruses: updated integrated dynamic modeling of the polio endgame. Risk Anal. 2020 Jan 20; online January 22 DOI:10.1111.risa.13447.

80. Thompson KM, Kalkowska DA, Badizadegan K. Hypothetical emergence of poliovirus in 2020. 2. Exploration of the potential role of vaccines in control and eradication. Expert Rev Vaccines. 2021 Feb 18. DOI: 10.1080/14760584.2021.1891889.

81. World Health Organization. Report on polio transition planning - advance draft as of 18 April, 2017 2017 [cited 2018 Mar 12]. Available from: http://www.who.int/mediacentre/events/2017/advance-report-polio-transition.pdf?ua=1

82. Provides perspective on the potential impact of introducing vac- cines following the application of NPIs in response to an emerg- ing pathogen.

83. World Health Organization. Poliomyelitis: polio transition planning and polio post-certification 2021 [cited 2021 Jan 25]. Available from: https://apps.who.int/gb/ebwha/pdf_files/EB148/B148_23-en.pdf
83. Johns Hopkins University Center for Systems Science and Engineering. CSSEGIS and Data/COVID-19 2020 [cited 2020 May 18]. Available from: https://github.com/CSSEGISandData/COVID-19
84. Anon. Public announcements (Translated from Chinese): Wuhan municipal health commission; 2020 [updated 5 Feb 2020; cited 2020 Apr 14]. Available from: http://wjw.wuhan.gov.cn/front/web/list2nd/no/710
85. Ai J-W, Zhang Y, Zhang H-C, et al. Era of molecular diagnosis for pathogen identification of unexplained pneumonia, lessons to be learned. Emerg Microbes Infect. 2020;9(1):597–600.
86. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3).
87. Corman V, Bleicker T, Brünink S, et al. Diagnostic detection of 2019-nCoV by real-time RT-PCR - Protocol and preliminary evaluation. Charité Virology, Berlin, Germany, Tib-Molbiol, Berlin, Germany, Erasmus MC, Rotterdam, The Netherlands, and Public Health England, London, UK; 2020 17 Jan, 2020. [Cited 2020 Oct 5]. Available from: https://www.who.int/docs/default-source/coronaviruse(protocol-v2-1.pdf);sfvrsn=a9ef618c_2
88. Centers for Disease Control and Prevention. CDC 2019-novel coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel - Revision 01. United States centers for disease control and prevention; 2020 2/4/2020. Document No.: CDC-006-00019, Revision: 01.
89. Centers for Disease Control and Prevention. Real-time RT-PCR panel for detection 2019-novel coronavirus (2020Jan24). United States Centers for Disease Control and Prevention; 2020 1/24/ 2020. Document No.: 2019-nCoV RT-PCR Panel Instruction for Use.
90. Centers for Disease Control and Prevention. 2019-novel coronavirus (2019-nCoV) real-time rRT-PCR panel primers and probes: United States centers for disease control and prevention; 2020 [updated 24 Jan 2020; cited 2020 Jan 24]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/rt-pcr-panel-primer-probes.html
91. Centers for Disease Control and Prevention. CDC 2019-novel coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel - Revision 02. United States centers for disease control and prevention; 2020 3/15/2020. Document No.: CDC-006-00019, Revision: 02.
92. Centers for Disease Control and Prevention. CDC 2019-novel coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel - Revision 03. United States centers for disease control and prevention; 2020 3/30/2020. Document No.: CDC-006-00019, Revision: 03.
93. Food and Drug Administration. Emergency use authorizations - COVID-19 in vitro diagnostic EUAs: food and drug administration; 2020 [updated 14 Apr 2020; cited 2020 Apr 14]. Available from: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#cov19ivd
94. World Health Organization. Coronavirus disease (COVID-19) Pandemic – emergency use listing procedure (EUL) open for in vitro diagnostics 2020 [cited 2020 Aug 4]. Available from: https://www.who.int/diagnostics_laboratory/EUL/en/
95. Egbertson SH, Mayo DR. A microneutralization test for the identification of enterovirus isolates. J Virol Methods. 1986 Nov;14(3–4):305–307.
96. Lim KA, Benyesh-Melnick M. Typing of viruses by combinations of antiserum pools. application to typing of enteroviruses (Coxsackie and ECHO). J Immunol. 1960 Mar;84:309–317.
97. World Health Organization. Manual for the virological investigation of poliomyelitis - 1st edition. World health organization expanded program on immunization and division of communicable diseases; 1990. Document No.: WHO/EPI/CDS/POLIO/90.1. [Cited 2020 Nov 5]. Available from: https://apps.who.int/iris/bitstream/handle/10665/62186/WHO_EPI_CDS_POLIO_90.1.pdf?sequence=1&isAllowed=y
98. Hull BP, Dowdle WR. Poliovirus surveillance: building the global polio laboratory network. J Infect Dis. 1997 February;175(Suppl 1): S113–6.
99. Racaniello VR, Baltimore D. Molecular cloning of poliovirus cDNA and determination of the complete nucleotide sequence of the viral genome. Proc Natl Acad Sci USA. 1981 Aug;78(8):4887–4891.
100. van derWerf S, Bregegere F, Kopecka H, et al. Molecular cloning of the genome of poliovirus type 1. Proc Natl Acad Sci USA. 1981 Oct;78(10):5983–5987.
101. Nomoto A, Kitamura N, Lee JJ, et al. Identification of point mutations in the genome of the poliovirus Sabin vaccine LSc 2ab, and catalogue of RNase T1- and RNase A-resistant oligonucleotides of poliovirus type 1 (Mahoney) RNA. Virol. 1981 Jul 15;112(1):217–227.
102. Manzara S, Muscillo M, La Rosa G, et al. Molecular identification and typing of enteroviruses isolated from clinical specimens. J Clin Microbiol. 2002 Dec;40(12):4554–4560.