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Modeling poliovirus risks and the legacy of polio eradication

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Abstract

This introduction to the special issue on modeling poliovirus risks provides context about historical efforts to manage polioviruses and reviews the insights from models developed to support risk management and policy development. Following an overview of the contents of the special issue, the introduction explores the road ahead and offers perspective on the legacy of polio eradication.

Keywords

polio; modeling; eradication; prevention

Context

Twenty-five years after the World Health Assembly committed to the eradication of wild polioviruses (WPVs) and the end of poliomyelitis,(1) we find ourselves still managing the complexity of one of the most significant global health projects undertaken to date. Launched in 1988, the Global Polio Eradication Initiative (GPEI) succeeded in eradicating WPV type 2 (WPV2) by the target year of 2000.(2) However, types 1 and 3 (WPV1 and WPV3) continue to circulate, although fortunately in small geographic areas that continue to decrease in size. Is this finally polio's last stand?(3)

The bumpy road toward WPV eradication included many challenges, and the lessons learned along the way should become part of a lasting legacy that continues to improve global health.(3) The papers in this special issue suggest that integrated risk, economic, decision, and dynamic models played an important role in polio eradication and they warrant recognition as part of its legacy as they continue to improve our efforts to manage global health.

Significant events in the early parts of the journey of managing poliovirus risks in the United States included the invention of the iron lung, which provided mechanical respiration for victims paralyzed by polio, and the development of two vaccines: injected inactivated poliovirus vaccine (IPV) and live attenuated oral poliovirus vaccine (OPV).(4) The 1954 clinical trial of IPV(5) represents one of the largest such undertakings. It helped to create

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expectations for the development of rigorous evidence of the efficacy and safety of vaccines and other medical interventions. Largely due to the vision of President Franklin D. Roosevelt, who personally experienced paralysis from polio, and the National Foundation for Infantile Paralysis that he founded to support poliovirus research and vaccine development, mass vaccination efforts in the US started in 1955 following the successful IPV trial.(4) Cutter Laboratories, one of the six licensed IPV producers, tragically failed to adequately inactivate all of its IPV. The resulting Cutter Incident ultimately played a key role in creating the foundations for vaccine safety, regulation, and risk management.(6) The US adoption of IPV in 1955 and OPV in the early 1960s led to a dramatic decline in polio cases.(7) Estimates suggest that the US investments in managing polioviruses between 1955 and 2015 translate into more than $200 billion (US$2010) in net savings for Americans (7).

Not surprisingly, most developed countries rapidly adopted the use of poliovirus vaccines. Like the US, they significantly reduced their burdens of polio and most likely enjoyed proportionately large health and economics benefits as hospitals closed their polio wards and iron lungs became unnecessary. Following the 1974 launch of the Expanded Programme on Immunization (EPI)(8) and successful introduction of poliovirus vaccines throughout the western hemisphere, in 1985 the Pan American Health Organization (PAHO) set a goal to eradicate polio in the Americas by the end of 1990.(9) Progress toward the PAHO goal played an important role in the 1988 global decision to eradicate polio.(1) Despite the global commitment, progress toward the goal depended largely on the timing of national commitments, which varied considerably.(10)

The First Round of Integrated Analyses and 2006 Special Issue

In anticipation of successful eradication of WPVs, the 2006 *Risk Analysis* special issue on poliovirus offered perspective about the role of risk analysis in global infectious disease policy and management (11) while recognizing the importance of managing post WPV-eradication risks (12) and the complexity of the risk management options.(13) Building on a dynamic model that characterized population immunity and the spread of poliovirus infections (12) and quantification of the risks (14) and costs(15,16), Thompson et al.(18) estimated the prospective risks, costs, and benefits of the post-eradication immunization options.(13) The analysis of post-eradication policies used an analytical time horizon that started at the time of eradication of all three WPVs (18) and included full characterization of important uncertainties.(19) The model clearly demonstrated that following successful WPV eradication, stopping OPV vaccination (with or without the use of IPV) represents a better option than continuing OPV, because of the lower risks of vaccine-associated paralytic polio (VAPP) and circulating vaccine-derived polioviruses (cVDPVs).(18) The analysis identified IPV as the most effective option, but not necessarily the most cost-effective option due to the relatively high costs of IPV. Consequently the analysis suggested the need for investments in efforts to reduce IPV costs to make IPV a more affordable post-eradication immunization option.(18) Further game-theoretic analyses demonstrated the critical importance of coordinating OPV cessation internationally in order to minimize the potential for importation of live polioviruses across borders.(20,21) In 2008, the World Health Assembly formally recognized the need for coordinated OPV cessation after WPV eradication.(22)

The 2006 special issue also included discussion of containment (23) and offered perspective about conditions that qualitatively impact the potential severity of post-eradication outbreaks.(24) Given the small, but finite risks of polio outbreaks after WPV eradication, (14) the policy model (18) explicitly included strategies for outbreak response. This led to further analysis of outbreak response strategies that demonstrated “faster is better,” so long as the overall response quality is good and achieves high coverage (i.e., the analysis allowed for some compromise of quality in the first round, but expected high quality in the second and third rounds).(25) This analysis motivated the GPEI to develop field, laboratory, and logistical strategies to speed up outbreak response (pre-eradication)(26, 27) with support of funds mobilized by Rotary International.(28) In addition to significantly reducing the local outbreak size, the rapid control of outbreaks reduces the risks of exportation to other areas. No estimates exist of the cases prevented and costs saved from responding to outbreaks more quickly, but the GPEI saw immediate benefits and continued to seek opportunities to accelerate its case detection and outbreak response efforts.(29) The need to respond quickly to an outbreak motivated analysis of the development of an outbreak response vaccine stockpile,(15,20,30) which helped to support the investment case for the GAVI Alliance International Finance Facility for Immunisation (IFFIm) to provide funding for such a stockpile.(31) Finally, the 2006 special issue offered some reflection on the modeling process and highlights of requirements for successful collaboration.(32)

The integrated models that provided economic estimates of historical American poliovirus investments (7) and the prospective global investments for various global post-WPV eradication immunization options (18) served as the foundation for a model that answered several important questions that arose in late 2006 related to control vs. eradication.(33) Delays in achieving the GPEI objectives led to concerns about the accumulating costs of the effort and questions about whether control might represent a better strategy.(34) Analysis of eradication vs. control options demonstrated that eradication provided more health and financial benefits (i.e., cases prevented and costs saved) than control, assuming the feasibility of eradication.(35) Specifically, the analysis demonstrated that maintaining very high levels of control in perpetuity implied greater health and financial costs than eradication.(34) Given some concerns about the feasibility of eradication, the analysis also demonstrated the need to intensify immunization in northern India to increase population immunity enough to achieve eradication.(34) The analysis showed the trade-offs between immunization intensity and the time required to achieve eradication.(34, see Figure 1) Impressively, following significant intensification of its immunization efforts, the Government of India reported its last case of paralytic polio from endemic transmission of WPVs in early 2011, and it celebrated national elimination of WPVs in early 2012 after its high-quality surveillance system reported no new cases for over a year.(35) Although some chance of undetected circulation of WPV exists, after a year with no detected cases in a very large and dense population with a high birth rate, we should expect a low probability of undetected circulation.(36) The analysis of eradication vs. control also recognized and demonstrated the problems of a wavering commitment,(34) which helped to energize the polio eradication partners to strengthen their resolve.(37) Insights from the analysis led to further consideration of the issues that can arise in the context of shifting priorities(38) and to emphasis of the need for improved management of polio eradication as a major project in

need of stable financing.(39) An analysis of the economics of the GPEI estimated net benefits of $40 billion to $50 billion (US$2010) for polio alone, with an additional $17 billion to $90 billion associated with the delivery of vitamin A as part of Polio Plus campaigns.(40) Combined with the analysis for the US,(7) we can reasonably hypothesize that global net savings from all investments in polio eradication since 1955 probably exceed a trillion dollars, although a thorough economic analysis is needed to fully quantify the benefits and costs.

The Second Round and the 2013 Special Issue Impetus and Contents

Continued delays in achieving eradication (10) combined with several programmatic changes and more complicated policy questions led to the papers in this special issue, which focus on modeling current (i.e., pre-eradication) policies and the road ahead. One significant programmatic change that occurred relates to the development of additional formulations of OPV and IPV. In 2004, the GPEI initiated efforts to accelerate the development of licensed monovalent OPV type 1 (mOPV1) product.(41) Prior to 2006, countries only used trivalent forms of OPV and IPV, and policy analyses (18,19,34) only considered these. However, with some supplemental immunization activities (SIAs) using mOPV1 starting in late 2005, mOPV3 starting in 2007, and bivalent OPV (bOPV) starting in 2010,(42) the options for managing population immunity changed. In addition, experiences with more outbreaks of cVDPVs motivated much more awareness of the evolution of OPV as a dynamic risk. With respect to IPV, manufacturers increasingly moved toward including IPV in combination vaccine formulations. The evolution of IPV-containing combination vaccines continues to complicate the array of products and reduce the relative use of the stand alone formulation in developed countries,(43) while the inclusion of an acellular pertussis component instead of whole-cell pertussis limits the use of IPV-containing combination vaccines by developing countries.

Ongoing research efforts continue to explore options to save costs on IPV, including potential fractional dosing, intradermal delivery mechanisms, adjuvant formulations, etc. All of this complexity led to a much more complicated set of global immunization policy options,(44) and the papers in this special issue enable the development of models to explore the risks, costs, and benefits of these options.

Table 1 provides a list of the abbreviations used throughout the articles in the special issue. Thompson et al. (45) explores the global experience with polio eradication since 2000, the options that countries consider when determining their preferred strategy for managing population immunity, and the current national polio vaccination schedules. Two related papers provide a comprehensive expert review on the vast poliovirus immunity and transmission literature (46) and a synthesis of the information relevant to modeling poliovirus population immunity and transmission.(47) These papers expand the number of immunity states compared to the prior model (14) and they demonstrate that significant uncertainties remain despite a relatively large number of studies performed over several decades. One key theme of the special issue emerges as the need to manage population immunity considering all age groups,(44) defined in a way that considers the entire population ,(14) and supported by modeling.(48) Lowther et al.(49) describe and compare

the current risk assessment tools used by the six WHO regions to qualitatively classify their WPV risks. Updating the earlier assessment of cVDPV risks,(15) Duintjer Tebbens et al.(50) reviews the experience with cVDPV outbreaks and the literature related to understanding and modeling OPV evolution. Finally, the last paper in the special issue puts the pieces together, provides a model of poliovirus transmission and evolution, and offers insights from modeling a diverse set of actual experiences with wild and vaccine-related polioviruses.(51)

The uncertain road ahead

Uncertainty remains about how long it will take to end the circulation of WPV1, WPV3, and ongoing cVDPVs. However, use of the information from national risk assessments (49) and models of poliovirus transmission and evolution (51) offer to help accelerate the process. The regional risk assessment process (49) increased the attention paid to data management, quality, and use, and it led to demands for improved information at a much finer geographical scale, particularly in areas with poor performance. Continued use and further iteration should help countries understand key risk factors and iteratively improve their planning. With support from a population immunity model,(48) the management process should increasingly shift toward using national information to try to protect every individual and to ensure national achievement and maintenance of immunization coverage levels at least high enough to stop and prevent sustained transmission. Managing population immunity and modeling poliovirus transmission requires consideration of all individuals in the population, because vaccinated individuals can potentially get re-infected and participate in the spread of infection, even though they will not show up as symptomatic cases because their prior immunity should protect them from developing paralytic polio disease.(14,46–48,51) By definition, eradication requires ending infections, not just disease, and this means managing effectively to prevent all cases before they occur.(43,48,52,53)

In countries with highly functional health systems, the routine immunization coverage levels obtained may suffice, although pockets of susceptible individuals may exist that could potentially support limited local transmission.(43) In many countries, however, the routine immunization system alone fails to achieve and/or maintain population immunity above the uncertain and variable threshold required to stop sustained transmission, and these countries need to perform SIAs.(45,48) The dynamics matter, because populations and immunity constantly change (i.e., births and immigration in some cases imply inflows of susceptible individuals into the population, deaths imply outflows of immune individuals, and waning makes individuals more able to participate in poliovirus transmission, which reduces their contribution to population immunity).(48,51) As observed early in the fight against polio, SIAs provide a strategy to rapidly increase population immunity to such a high level that transmission stops due to lack of susceptible individuals.(9,54) In the few areas with remaining endemic circulation, immunization efforts will need to focus on increasing the overall population immunity above the threshold as quickly as possible and then maintaining high levels of immunity. Fortunately, models can help us think dynamically and identify the actions required to manage the risks.(52)

The approach of managing population immunity to stop WPVs also represents the best strategy for minimizing the risks of developing cVDPVs – now and through the period of

OPV cessation.(48) Notably, the dynamic model of population immunity helps to demonstrate that all of the investments made to maximize population immunity prior to OPV cessation will pay off significantly in reducing the risks of cVDPVs at the time of and after OPV cessation.(48) In the context of very high population immunity, any circulating live polioviruses die out relatively quickly, but susceptible individuals will begin to accumulate, which means increasing impacts of any reintroduction. Introducing IPV will help to reduce the impacts of a reintroduction by providing protection from paralysis to the individuals who receive it and who would otherwise not be vaccinated. However, if population immunity declines to a level that would allow for sustained transmission, then IPV protection will not prevent these individuals from becoming infected and participating in fecal-oral transmission, although it may reduce their participation to some degree.(14,48,51)

Significant uncertainty remains with respect to the performance of IPV in developing countries and when used in SIAs. Despite its potential role, the future adoption of IPV by countries that do not currently include it in their immunization schedules also remains uncertain. Current global annual IPV production capacity would not support universal global IPV use, and IPV production depends on using virulent wild poliovirus strains, (15) although some newer producers can now successfully make IPV starting with Sabin OPV strains. Current efforts seek to create an affordable IPV option and sufficient supply, but uncertainty remains about which OPV-using countries will want to use IPV following OPV cessation and in what formulations at what price. The current plan (55) focuses on coordinated cessation of type 2 OPV after meeting numerous pre-requisites, including at least one recommended dose of IPV into all routine immunization schedules,(56) but the plans can change and the future remains uncertain.(43) Additional research (see Ref. 47, Table 1 for a list of uncertainties and research possibilities) may provide data that improve the modeling process.

Opportunities to learn with models

Given and despite the uncertainties, we should anticipate the widespread use of models to answer a number of critical questions about the optimal path forward and to help stakeholders manage their expectations of costs and health outcomes. Consumers of the models need to understand the key differences between the various types of models. For example, in contrast to dynamic models that we can use prospectively (14,51) and integrate with economics,(7,18,19,34,40) simple epidemiological models rely on retrospective analyses of surveillance data to test specific hypotheses and identify risk factors.(57–59) In contrast to dynamic viral transmission models,(14,51) the epidemiological models define “population immunity” very narrowly (e.g., as the “fraction of children younger than 5 years of age who were protected by direct vaccination”(57, p. 1669)). This definition focuses on disease instead of infection, and it ignores most of the population and the immunity that individuals may derive from exposure to wild polioviruses, secondary spread of OPV, and cVPDVs.(48) Thus, this definition implicitly misses the potential role that older children and adults may play in viral transmission, which may become increasingly important as immunity wanes and exposures to circulating live polioviruses decreases. In addition, as polio cases disappear, epidemiological models lose their ability to retrospectively infer “vaccine efficacy” by comparing cases observed using one vaccine compared to another.

(60,61) With epidemiological models providing relatively little insight about prospective risks, and increased realization that achieving and maintaining eradication requires risk management and prevention, we should see increased demand for and reliance on dynamic models that focus on infection,(14,51) instead of much simpler epidemiological models that focus on past disease.

Although most of the dynamic modeling for polio to date involves the use of differential equation based models,(14,51) individual-based models may also play an increasing role.(62) These models may offer some advantages, but they do so at the expense of adding significantly more complexity by requiring a very large number of assumptions about the spatial distribution and contact patterns for each individual in the model.(62) The first published individual-based model for polio reported significantly different results by varying assumptions about mixing.(62) Thus, prior to the use of individual-based models for poliovirus transmission for policy analyses, we anticipate the need for thorough review of the assumptions and model performance in the context of replicating a wide range of actual experiences, similar to the process used for the development of the differential-equation based model.(51) The use of preliminary results of insufficiently-reviewed and/or inadequate models could potentially mislead policy makers with respect to important choices and undermine the credibility of models as a tool to support decisions. Thus, consumers of the model insights will also need to make sure that they understand the processes used to develop and test the models prior to using the results, and they should recognize the importance of systematically considering the impacts of key uncertainties.(19,63)

Appreciation of the significance of the ongoing global investment required to achieve and maintain polio eradication continues to motivate more economic analyses, particularly because the challenge of managing insufficient resources remains an ongoing threat to the program that delays its success. As we increasingly coordinate disease management activities globally in the context of scarce resources, stakeholders will increasingly demand better planning and the types of information provided in “investment cases.”(64–66) Some stakeholders will most likely want to see more analysis related to the economics of eradication relative to control,(34) for example starting at the current state of the world instead of at the time of eradication of all wild polioviruses. They may also want to understand the global economic and health benefits of all investments in polio management, which goes beyond the economics of the US investments (7) and the GPEI investments.(40) Based on the existing economic evidence,(7,18,19,34,40) we can reasonably expect that global retrospective investments in polio eradication led to significant net health and financial benefits and that eradication is a much better option than control, as long as it is feasible. However, the path selected with respect to future IPV use and costs will impact the expected overall costs and benefits of national, regional, and global polio management activities going forward,(18,40) and delays in achieving eradication imply increasing costs as well as the tragedy of preventable cases.(34)

The legacy of polio eradication

Like smallpox eradication, which WHO Director-General Halfdan Mahler, described in 1978 as “a triumph of management, not of medicine,”(67, p. 125) polio eradication will

similarly represent a management victory motivated by a clear goal of driving toward “nil incidence.”(68, p. 1354) However, polio eradication will represent a relatively much larger achievement than smallpox eradication due to the significantly different starting point (i.e., less than 1 billion people in 31 countries with endemic smallpox compared to over 4.5 billion people in over 125 countries with polio at the launch of each global eradication effort),(34) the need to eradicate 3 wild poliovirus serotypes, the large proportion of undetected asymptomatic cases, and the use of an attenuated live virus vaccine that can cause paralysis in some relatively rare instances due to VAPP and VDPVs.

Although the current management challenges vary in different countries and regions,(3) including the challenge of sustaining high levels of coverage in countries that no longer observe cases from WPVs, the theme of focusing on and successfully managing population immunity should emerge as one of the most important legacies of polio eradication. In contrast to simply focusing on vaccine coverage levels achieved through routine immunization, understanding and managing population immunity provides a means to prevent viral transmission using all of the tools required. By focusing on the performance-based objective of maintaining population immunity levels (i.e., the “stock” of immunity integrated over the entire population (44,48)) above the threshold required such that sustained transmission cannot occur, we can realize the full benefits of vaccines and achieve the goal of the Global Vaccine Action Plan (GVAP) to create a world “in which all individuals and communities enjoy lives free from vaccine-preventable diseases.”(69)

Highly-functional health systems that provide good routine immunization coverage and sanitation levels can achieve and maintain high levels of population immunity without the need to do more, although even in these populations some individuals will remain at risk.(43) In contrast, in countries with relatively poor systems, with routine immunization alone we see polio outbreaks, which necessitates reactive responses.(3) The GPEI developed a strategy of conducting periodic SIAs to boost population immunity, and these SIAs increasingly and successfully prevent outbreaks before they occur. Thus, while efforts continue to focus on improving the quality and stability of health systems, SIAs can play a major role in disease management efforts and in achieving desired performance levels. Ultimately, preventing cases before they occur requires that we value prevention, invest sufficient resources, and recognize the benefits of effective management.(44,48,52) Although planned SIAs may disrupt health systems to some degree, they may save a greater amount of health and financial costs by preventing an even larger disruption associated with unplanned outbreak response efforts.(48) If experience with polio eradication leads to increased attention to the management of population immunity and expectations for prevention (i.e., performance related to stopping transmission instead of vaccine coverage levels for 0–4 year olds), then this legacy may significantly accelerate achievement of elimination and eradication goals for other vaccine-preventable diseases and realization of the GVAP vision. The shift to managing population immunity should further lead to sustainable financing and improved planning, and it may also lead individuals to change their tolerance and acceptance of cases of vaccine-preventable diseases such that they expect and demand the individual and population protection that vaccines provide. Specifically, by changing the default from accepting cases of vaccine-preventable diseases as normal to not

tolerating a single case as acceptable, polio eradication may play a significant role in the overall paradigm shift that must occur to realize the vision of the GVAP.

Another key legacy of polio eradication relates to thinking dynamically and improving our understanding of the expected requirements for reaching big goals and sustaining these achievements. Integrative models help us appreciate and visualize the trade-offs associated with different paths that we can pursue and "count" the cases prevented and costs saved. With respect to infectious diseases like polio, we must recognize that new susceptible individuals enter the population every day (i.e., births) and individuals with immunity leave (deaths), and this alone creates a dynamic stock that necessitates ongoing management. In addition, due to population growth, the size of the stock continues to increase. Thus, immunization requires a sustained (or increasing) commitment, and wavering on the commitment can lead to a much larger impact than simply failing to protect individuals, because it can potentially put the entire population at risk.(34,48) Unlike many other health interventions that only impact individuals who receive them, vaccines protect the individual and the population to some extent, which means that we must consider the entire population to appreciate the full benefits of vaccines. In the final stages of polio eradication, the GPEI is working very hard to reach every district, community, and child, because eradication depends on preventing transmission in the entire population, including the individuals missed by governments and their health systems. Achieving the goal of polio eradication depends on finding and immunizing the un(der)served, and this should lead to an expectation that countries can and should consider all of the people within their borders when managing population immunity, including non-citizens.

Table 2 summarizes the major contributions of models related to poliovirus management to date. Insights from modeling will continue to provide helpful context to support discussions about national and global policies,(44) but much work remains to achieve eradication and to shift the national, regional, and global focus toward ensuring sustained management of population immunity. The papers in this issue should help with achieving and maintaining polio eradication and with realizing its legacy and the vision of the GVAP.

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Table 1:

List of Abbreviations

Ab = neutralizing antibody (generic term)

AFP = acute flaccid paralysis

aVDPV = ambiguous vaccine-derived poliovirus

bOPV = bivalent oral poliovirus vaccine (types 1 and 3)

cVDPV = circulating vaccine-derived poliovirus (cVDPV1, cVDPV2, and cVDPV3 indicating circulating vaccine-derived poliovirus types 1, 2, and 3, respectively)

CDC = U.S. Centers for Disease Control and Prevention

CID_{50} = cell- or tissue-culture infectious doses

CVID = Common variable immunodeficiency

DTP = Diphtheria and Tetanus toxoids and Pertussis vaccine

DTaP = Diphtheria and Tetanus toxoids and acellular Pertussis vaccine

DTwP = Diphtheria and Tetanus toxoids and whole-cell Pertussis vaccine

eIPV = enhanced-potency inactivated poliovirus vaccine

EIP = effective immune proportion

EIP* = threshold level of EIP below which a population can sustain transmission

ESP = effective susceptible proportion

ESP* = threshold level of ESP above which a population can sustain transmission

FRPV = fully-reverted poliovirus

FS = fully susceptible (immunity state)

GPEI = Global Polio Eradication Initiative

Hep = hepatitis B

Hib = *Haemophilus influenzae* type b conjugate vaccine

GPEI = Global Polio Eradication Initiative

HIGH = high-income country

IgA = immunoglobulin A

IgG = immunoglobulin G

IgM = immunoglobulin M

IPV = inactivated poliovirus vaccine

IPV1 = 1 successful IPV dose (immunity state)

IPV2 = 2 successful IPV doses (immunity state)

IPV3 = 3 or more successful IPV doses (immunity state)

IPVLPV = IPV and LPV (i.e., one or more successful IPV doses and 1 or more LPV infections) (immunity state)

IU = international units

iVDPV = vaccine-derived poliovirus from an immunodeficient individual

LMI = lower-middle-income country

LOW = low-income country

LPV = live poliovirus (WPV, VDPV, and/or OPV)

LPV1 = 1 LPV infection (immunity state)

LPV2 = 2 or more LPV infections (immunity state)

MK = monkey kidney tissue culture

mOPV = monovalent OPV (mOPV1, mOPV2, and mOPV3 indicating monovalent types 1, 2, and 3, respectively)

MPI = maximum population immunity scenario

mOPV = monovalent oral poliovirus vaccine

NA = not applicable

ND = not done

NID = national immunization day

NR = not reported

OPV = oral poliovirus vaccine (generally trivalent unless otherwise specified)

PCR = polymerase chain reaction

pfu = plaque-forming unit

PO = proportion of transmissions via oropharyngeal route

PV = poliovirus (PV1, PV2, and PV3 indicate poliovirus types 1, 2, and 3, respectively

R_0 = basic reproductive number

RCFTI = relative contribution to fecal-oral transmission if infected

RCOTI = relative contribution to oropharyngeal transmission if infected

RT-PCR = reverse transcriptase PCRSIR = susceptible-infected-removed

RPI = realistic population immunity scenario

SES = socio-economic status

SIA = supplemental immunization activity

SNIDs = subnational immunization days

S_r = relative susceptibility

TIAs = targeted immunization activities

tOPV = trivalent oral poliovirus vaccine

UK = United Kingdom

UMI = upper-middle-income country

USA = United States of America

VAPP = vaccine-associated paralytic polio

VDPV = vaccine-derived poliovirus

VP1 = viral protein 1WHA = World Health Assembly

WHO = World Health Organization

WPV - wild poliovirus (WPV1, WPV2, and WPV3 indicate wild poliovirus types 1, 2, and 3, respectively)

Table 2:

Benefits of Using Models to Support and Enhance Polio Eradication Strategies

Model	Key finding(s)	Impact on GPEI and partners
Dynamic disease and economic model of US investments in polio control and elimination (7)	Significant health and financial benefits from US investments in polio management	Recognition of net benefits associated with prevention of polio, promotion of sustained US funding and commitment
Decision trees of national post-eradication management options (13)	Multiple interdependent choices to make after WPV eradication and significant differences between countries of different income levels	Motivation for a systematic and thorough process for managing end-game issues
Dynamic model of polio virus transmission (14)	Complexity due to historical use of OPV and IPV, waning, and potential for re-infection and demonstration of mOPV as a better option for outbreak response than tOPV after WPV eradication	Recognition of the need to develop mOPV stockpiles for post-eradication outbreak response
Outbreak response modeling (25) based on use of dynamic transmission model (14)	Earlier response (with 3 mOPV rounds) better than later, even with some degree of compromise on quality of the first round (second and third rounds of high quality)	Recognition that faster is better and mobilization of funds to reduce the delays in case detection, lab confirmation, and response deployment (26–28)
Quantitative characterization of post-eradication risks (e.g., cVDPVs, iVDPVs)(15)	Non-zero risks of VAPP and re-introduction of live polioviruses due to VDPVs with continued use of OPV	Motivation for improved characterization of iVDPV risks and the development of antiviral compounds to treat iVDPVexcretors
Economic analysis of post-eradication immunization options (18)	OPV use after eradication not optimal, No routine (i.e., OPV cessation) leads to lowest expected costs, IPV leads to lowest expected cases	Resolution to stop OPV use after WPV eradication (22) and program of work to develop and explore lower-cost IPV options
Game theoretic and dynamic disease model for OPV cessation (20)	Need to globally coordinate OPV cessation to prevent the development of cVDPVs due to spread of OPV across international borders and procure and maintain mOPV stockpiles	Resolution to coordinate OPV cessation after WPV eradication (22) and motivation to create a vaccine stockpile for outbreak response (30)
Dynamic disease and economic model of control vs. eradication (34)	Demonstrated eradication better than control, inefficiency of a wavering commitment, and the need to intensify immunization in northern India	Recommitment of partners to complete eradication and intensification in India, which led to last WPV nationally in 2011
Dynamic model of eradication program priority shifting (38) and management (39)	Priority shifting can lead to non-optimal outcomes, eradication programs need sufficient and stable financing as major projects	Motivation for the development of longer-term financial planning and innovative funding mechanisms
Dynamic disease and economic model of investments the GPEI (40)	Significant health and financial benefits from investments in the GPEI	Motivation to organize efforts to support increased funding for the GPEI and complete polio eradication
Dynamic model of current poliovirus vaccination trends in the US (43)	Gaps in population immunity exist even in countries with high quality immunization programs, shift to IPV use changing immunity profile, and IPV combination vaccines impacting availability of standalone IPV for potential outbreak response	Recognition of uncertainty about the impact of a global switch to IPV on population immunity and the need for additional research related to IPV immunogenicity
Decision tree of current global minimum immunization policy options (44)	Complex set of options going forward, coordination essential, role of IPV uncertain, several pre-requisites for OPV cessation	Monitoring of progress related to pre-requisites for OPV cessation, recognition of type 2 cVDPV in Nigeria as a global emergency