Polio Eradicators Use Integrated Analytical Models to Make Better Decisions

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ORGANIZATIONAL OVERVIEW

Dr. Steven G. F. Wassilak
CDC Team Lead for Science, Innovation and Research for the Polio Response, Emergency Operations Center
Poliovirus

- 3 serotypes (types 1, 2, and 3)
- Approximately 1/200 infections lead to paralysis
Polio: A paralyzing disease for life
Rancho Los Amigos Rehabilitation Hospital, California
Iron lungs, 1953 (prior to vaccine introduction)
Vaccines

- Introduction in the 1950s and 1960s
- Opportunity to manage risks
Polio eradication

- Polio transmission in the US stopped in the 1970s
- The last polio case in the American Region occurred in 1991
- 1988 World Health Assembly resolved to eradicate wild polioviruses by 2000
- Global Polio Eradication Initiative (GPEI) launched
Role of CDC in the GPEI

- Primary technical partner
- Funding support
GPEI key operational strategies

1. Routine Immunization

2. Supplemental Immunization Activities (SIAs or mass campaigns)

3. Surveillance
GPEI launch: >125 polio-affected countries

1988
Original target date: 10 polio-affected countries
Estimated polio cases: 1988-2001

1988: Resolution to Eradicate Polio

1999: Type 2 Eradicated

Source: WHO/Polio database, data as of March 2014 for 193 WHO Member States
Collaboration

- CDC and Kid Risk, Inc. collaboration started in late 2001
  - Combine CDC expertise with operations research and management science (OR/MS) tools
  - Model poliovirus transmission and assess the health and economic impacts of policies
- Goal: Improve evidence-based decision making
  - Peer-reviewed technical publications
  - Broad and effective communication with stakeholders
Research on risk management strategies for polioviruses

Even though polio no longer causes widespread fear, take a couple of minutes to learn more about polioviruses and why you should still care about them. In 2001, we launched a collaboration with the U.S. Centers of Disease Control and Prevention (CDC) with support from the CDC-Harvard Joint Initiative in Vaccine Economics (JIVE) to create useful analytical modeling tools to help decision makers consider the implications of the various global immunization and risk management choices after eradicating wild polioviruses. Over a decade later, this research collaboration continues to thrive and expand, and we thank many contributors. In addition to many presentations, our polio research led to peer-reviewed publications related to:

- the decision options that national and international health leaders will face after eradicating wild polioviruses
- dynamically modeling poliovirus transmission and outbreaks
- the health and financial benefits of historical poliovirus vaccination in the United States
- risk management in a polo-free world
- characterization of the risks of future options
- characterization of the costs of future options
- trade-offs associated with outbreak response options
- consideration of the costs and value of global poliovirus surveillance
- lessons learned during this collaborative project (as of December 2006)
- the choice of eradication vs. control (this paper won the 2008 Jay Wright Forrester Award from the System Dynamics Society)
- the risks, costs, and benefits of global policies for managing polo after eradication
- uncertainty and sensitivity analyses of our results related to global post-eradication policies
- the need for global cooperation on a vaccine stockpile and coordinated OPV cessation
- the role of system dynamics in our research
- the consequences of priority shifting when seeking to eradicate multiple diseases
- a framework for optimizing the future use of vaccines from the global polo vaccine stockpile
- building an "individual-based" or "agent-based" model to explore and optimize post wild poliovirus eradication outbreak response strategies
- the economic and health benefits of the Global Polio Eradication Initiative
- trends in the risk of U.S. polo outbreaks and poliovirus vaccine availability for outbreak response
- the role of risk analysis in polo eradication
- the probability of undetected wild poliovirus circulation after apparent global interruption of transmission
- current polo global eradication and control policy options, including perspectives from modeling and policymakers for oral poliovirus vaccine cessation
- prevention as the new paradigm in global health
- modeling poliovirus risks and the legacy of polo eradication
- pre-eradication national vaccine decision options
- expert review of the literature on poliovirus immunity and transmission
- poliovirus and transmission quantitative synthesis of expert assessments of the evidence
- modeling population immunity
- cVDPV risks and characterization of OPV evolution
- characterizing poliovirus transmission and evolution using a model applied to diverse situations
- IPV costs and individual and population immunity considerations for national immunization policy makers evaluating the adoption of IPV
- supplemental immunization activities (SIAs) and the role of expanded age groups
“...This work has been fundamental to so much of what’s happened in the eradication program over the last few years, and it’s helped to support many of our decisions over the last decade and to bring the world much, much closer to one where future generations will never know the terror of this disease.”
PROBLEMS AND CHALLENGES

Dr. Mark A. Pallansch
CDC Director of the Division of Viral Diseases
2001-2013: 50 countries reporting polio cases,

Thompson et al., Risk Analysis, 2013
Poliovirus spread 2013-4
3 polio-endemic countries, 7 countries affected by outbreaks
Difficult to see poliovirus transmission

- Many asymptomatic infections
- The global surveillance system only detects paralytic polio
- Fewer cases to see

The Global Polio Laboratory Network
Managing immunity with poliovirus vaccines

- Countries determine their own immunization strategies as they manage population immunity

- Two poliovirus vaccines with very different costs, risks, and protection from infection
Oral poliovirus vaccine (OPV)

- **Benefits**
  - Relatively cheap and easy to administer
  - Causes infection that can spread to contacts
  - Good protection from re-infection

- **Risks**
  - Very rare cases of vaccine associated paralytic polio (VAPP) in approximately 1 per 1,000,000 infections
  - Can evolve to cause circulating vaccine-derived polioviruses (cVDPVs) in populations with low coverage
Inactivated poliovirus vaccine (IPV)

- **Benefits**
  - No VAPP
  - No cVDPVs

- **Costs**
  - Relatively expensive to make and administer (injection)
  - Essentially no protection from live polio virus infection
  - High coverage required to prevent transmission
Endgame

- Complicated post-eradication choices
- Funding gaps represent a real threat
- High stakes
“... Here in India I am happy to report that these strategies have yielded tremendous “real world” results, and as of today it has been officially certified that another nearly 2 billion people live in a now polio-free region of the world”
APPROACHES AND METHODOLOGY

Dr. Radboud J. Duintjer Tebbens
Kid Risk, Inc., Vice President
**Decision options (post-eradication)**

Major decision options for countries using routine OPV

<table>
<thead>
<tr>
<th>Routine Immunization</th>
<th>Supplemental Immunization</th>
<th>Outbreak Response</th>
<th>Stockpile</th>
<th>Surveillance</th>
<th>Containment</th>
<th>Management of Chronic Excretors</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPERV</td>
<td>None, coordinated cessation</td>
<td>NIDs only</td>
<td>NID with OPERV and restart routine</td>
<td>National &amp; global stockpiles</td>
<td>Passive + environmental</td>
<td>Enforce WHO recommendations</td>
</tr>
<tr>
<td>eIPV</td>
<td>None, not coordinated cessation</td>
<td>NIDs only</td>
<td>NID with eIPV and restart routine</td>
<td>Global stockpile only</td>
<td>Passive only</td>
<td>Screening and education</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NID with OPERV and restart routine</td>
<td>National stockpile only</td>
<td>APP (Dedicated) + environmental</td>
<td>Do not enforce WHO recommendations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NID with eIPV</td>
<td>Local mass immunization with OPERV</td>
<td>Dedicated only</td>
<td>No screening or education</td>
</tr>
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<td>NID with OPERV</td>
<td>Local mass immunization with eIPV</td>
<td>No stockpile</td>
<td></td>
</tr>
</tbody>
</table>

Sangrujee et al., Medscape General Medicine, 2003
**Objective**

- **Overall decision options $i$**
  - Minimize incremental costs per disability-adjusted life year (DALY) saved (Incremental Cost-Effectiveness Ratio)
    \[
    \min_i \frac{C_i - C_{SQ}}{(P_{SQ} - P_i)D}
    \]
  - Maximize difference between economic value of prevented polio cases and incremental costs (Incremental Net Benefits)
    \[
    \max_i (P_{SQ} - P_i)H - (C_i - C_{SQ})
    \]

- $C_i$ = discounted cumulative costs for option $i$
- $C_{SQ}$ = discounted cumulative costs for status quo
- $P_i$ = discounted cumulative paralytic polio cases for option $i$
- $P_{SQ}$ = discounted cumulative paralytic polio cases for status quo
- $D$ = DALY per paralytic polio case
- $H$ = economic value of a prevented paralytic polio case
Integration of OR/MS tools

- **Frame overall problem in decision analytic context**

- **Probabilistic risk analysis modeling**
  - Time-varying risk of virus reintroduction $f$(decision option)
  - Uncertainty in model inputs

- **System dynamics modeling**
  - Population immunity $f$(decision options)
  - Expected polio cases if poliovirus reintroduced
  - Important feedbacks and time delays
Integrated model (high level influence diagram)

**Decision options**
- Routine immunization
- Supplemental immunization activities (SIAs)
- Outbreak response
- Surveillance
- Containment
- Vaccine stockpile

**Conditions**
- Population immunity
  - Immunization and outbreak history
  - Under-vaccinated subpopulations

**& Risks**
- Sustained transmission
- Importations
- (Un)intentional release

**Cases & DALYs**
- Mortality
- Morbidity

**Costs**
- Country-level costs
- Global costs
- Health costs

**Economic estimates**
- Incremental cost-effectiveness ratios (ICERs)
- Incremental net benefits (INBs)

Integrated model (full influence diagram)

- **Fixed global and country-level costs**
  - f(decisions, income level, year, iteration)

- **Population data**
  - f(income level, year)

- **Population immunity**
  - f(decisions, income level, year, iteration)

- **Random outbreak population size, $R_0$, and coverage**
  - f(income level, year, iteration)

- **Risk inputs**
  - f(income level, iteration)

- **Outbreak Poisson rates per 100 million people**
  - f(decisions, income level, year, iteration)

- **Routine VAPP cases**
  - f(decisions, income level, year, iteration)

- **Population data**
  - f(income level, year)

- **Random cVDPV risk**
  - f(income level, iteration)

- **Random number of outbreaks**
  - f(decisions, income level, year, iteration)

- **Cost inputs**
  - f(income level, iteration)

- **Number of OPV doses used in response**
  - f(decisions, income level, outbreak population size, year)

- **Dynamic outbreak sub-model**
  - f(decisions, income level, outbreak population size, $R_0$, coverage, year)

- **VAPP rates per OPV infection**
  - f(iteration)

- **Total response costs**
  - Aggregated over outbreaks, f(decisions, income level, year, iteration)

- **Total outbreak and response VAPP cases**
  - Aggregated over outbreaks, f(decisions, income level, year, iteration)

- **Total cases**
  - Aggregated over all years, f(decisions, income level, iteration)

- **Paralytic cases due to outbreak**
  - f(decisions, income level, outbreak population size, year, iteration)

- **Total costs**
  - Aggregated over all years, f(decisions, income level, iteration)

- **Number of OPV infections**
  - f(decisions, income level, outbreak population size, year)

Duintjer Tebbens et al., Risk Analysis, 2008
Dynamic transmission model

First age group

Births → Fully susceptibles → Regular latents → Regular infecteds → Removeds

Deaths

Aging

Second age group

Deaths

Aging

25th age group

Deaths

Total of 325 stocks to model population immunity and virus behavior

\[ \lambda(t) = (\gamma R_0/N) \sum_{t=0}^{\text{infected}} [R(t) + \sum_{\text{infecteds}} i_{\text{infected}}] \]
Outbreak response

Thompson, Risk Analysis, 2006
Outbreak response

Polio outbreak response: the faster, the better...

In line with the standing recommendations for outbreak response by the Advisory Committee on Polio Eradication (ACPE) (see page 2), mathematical modelling predicts that a rapid, large-scale immunization response is preferable to a delayed response. Exploring the trade-offs between time and coverage, mathematical modelling suggests that an initial quick response with medium coverage (above 70%) is more beneficial in controlling an outbreak than a delayed activity with higher coverage, as long as the initial rapid response is followed by two, large-scale campaigns attaining high coverage (at least >90%).

See figure on right: in a hypothetical outbreak in a low income country of 10 million people, implementing a first round with 75% coverage 15 days after the onset of the first paralytic case leads to 5 cases, compared to 11 cases if the first round occurs 45 days after the onset of the first paralytic case, but attains 90% coverage.

Rapid response translates into a lower number of cases

Main assumptions: 10 million people, low-income country, no SIAs in the previous 5 years, 50% routine OPV3 coverage, R0=10, AFP surveillance, 2nd and 3rd rounds cover 90% of under fives, all rounds use mOPV

Adapted from Kim Thompson and Radboud Duinjir Tebbens
“...This work clearly demonstrated that speed trumps coverage at the beginning of an outbreak response and that was a fundamental shift in the way people were approaching polio outbreak response... most indicative of the depths of impact of this new understanding on our work is that it underpinned a World Health Assembly resolution”
RESULTS, IMPACT, AND CONCLUSIONS

Dr. Kimberly M. Thompson
Kid Risk, Inc., President
Integrated analysis: The US experience

- Reported
- Dynamic model
- No polio vaccination
- Static model

Paralytic cases

Net benefits of $180 billion (US$2002)
Characterization of post-eradication risks

Based on Duintjer Tebbens et al., Risk Analysis, 2006; estimates for realistic population immunity at year 0, cVDPV risks based on confirmed cVDPVs only, and enforced containment

LMI=lower middle-income countries; Low=low-income countries; OPV=oral poliovirus vaccine; SIAs=supplemental immunization activities; UMI=upper-middle income countries
Stochastic simulation showing possible futures

LMI=lower middle-income countries; Low=low-income countries; OPV = oral poliovirus vaccine; SIAs = supplemental immunization activities; UMI = upper-middle income countries

**OPV with low coverage is not a good epidemiological option**
Integrated analysis: Post-eradication vaccination strategy optimization

Continued OPV use after eradication is not a good economic or health option

Impact

- Agreement to coordinate OPV cessation
- 2008 WHA Resolution 61.1 asks the WHO Director-General “to set, if and when appropriate, a date for the eventual cessation of use of oral poliomyelitis vaccine use in routine immunization programmes”
Integrated analysis: Control vs. eradication
Can we stop transmission in Northern India?

India could stop transmission, the time required depends on immunization intensity, and eradication vs. control is a choice.

Thompson and Duintjer Tebbens, Lancet, 2007
Integrated analysis: Control vs. eradication
What are the cost and case trade-offs?

Post-eradication (PE) options offer lower cases and costs than control

Thompson and Duinjter Tebbens, Lancet, 2007
Integrated analysis: Control vs. eradication
What happens with a wavering commitment?

- Incidence
- Immunization rate
- Perceived costs per case
- Gap
- Desired/acceptable costs per case

Wavering
Integrated analysis: Control vs. eradication
What happens with a wavering commitment?

- Vaccinate intensely until eradication (possibly longer)
- Vaccinate intensely until things look good then waver

Wavering is more costly with respect to both costs and cases in the long run

Thompson and Duintjer Tebbens, Lancet, 2007
February 2007 WHO stakeholder consultation

Dr. Margaret Chan, WHO Director-General, told the attendees that their “commitment must not waver” and they would be “seeing today new data that show why, over a 20-year period, every proposed option for controlling polio will cost more, in human suffering and dollars, than finishing eradication. In other words, getting the job done is your best buy.”
Integrated analysis: Impacts of the GPEI

Expected net benefits of the GPEI exceed $40-50 billion (US$2010)

Duintjer Tebbens et al., Vaccine, 2011
Importance to stakeholders

Dr. Carol Pandak, Rotary International, Director of PolioPlus: “We regularly use the $40-50 billion estimate of net benefits of the GPEI as we raise funds to finish polio eradication both within and outside of Rotary. The modeling work made a compelling case for stable and sustained funding, and this helped all of us as we plan ahead.”
Impacts

Integrated analyses used to support the economic case to raise the funds needed to realize net benefits of $40-50 billion of the GPEI
April 2013: Global Vaccine Summit yields US$4 billion in funding commitments to polio endgame plan

“...At a time when most people have forgotten polio, I cannot overstate how critical it was to have these numbers to illustrate the gains of completing polio eradication and the benefits of eradication over control.”
Transportability

- Additional polio complexities
- Other vaccine-preventable diseases
- Complex systems that require consideration of variability, uncertainty, and time
Conclusions

- Insights
- Costs and lives saved
Acknowledgments for this presentation

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  - WHO APW200179134
  - Bill & Melinda Gates Foundation: 4533-17492, 4533-18487, 4533-21031, 4533-23446
“...mathematical modeling can give us an idea of the future and the potential costs and impact of our policy options .... As other teams create analytical models to support decision makers who manage complex systems, I can vouch for how transformational these are for strategic and program planning.”
Thank you

For more information please contact the Centers for Disease Control and Prevention

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Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Trade-offs between objectives

- Trade-offs mainly between human health and money
- Economic results estimated with and without monetization of health outcomes
- Sensitivity analyses explored different values for health outcomes and discount rates
Streams of net benefits

- Ongoing prevention implies ongoing net savings, our work support the efforts to sustain the prevention (outbreak response)

- Economic benefits at any point in time depend on the assumptions made about time horizon, discount rate, and other factors

- Decision makers focused on making the biggest impact on human health as cost-effectively as possible