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# BMJ Open

## **Certification of global poliovirus eradication: The role of hard-to-reach subpopulations and confidence about the absence of transmission**

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3 1 **Certification of global poliovirus eradication: The role of hard-to-reach subpopulations**  
4 **and confidence about the absence of transmission**  
5 2  
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8 4 Radboud J. Duintjer Tebbens,<sup>1</sup> Dominika A. Kalkowska,<sup>1</sup> Kimberly M. Thompson<sup>1</sup>  
9 5

11 6 1. Kid Risk, Inc., Columbus, OH, USA  
12 7

15 8 Running title: **Poliovirus certification confidence**  
16 9

18 10 Correspondence to: Kimberly M. Thompson, Kid Risk, Inc., 605 N High St, #253, Columbus,  
19 11 OH 43215, USA, Email: kimt@kidrisk.org  
20 12  
21 13

24 13 **Abstract:**

25 14 **Objective:** To explore the extent to which under-vaccinated subpopulations may influence the  
26 15 confidence about no circulation of wild poliovirus (WPV) after the last detected case.  
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29 16 **Design and participants:** We used a hypothetical model to examine the extent to which the  
30 17 existence of an under-vaccinated subpopulation influences the confidence about no WPV  
31 18 circulation after the last detected case as a function of different characteristics of the  
32 19 subpopulation (e.g., size, extent of isolation). We also used the hypothetical population model to  
33 20 inform the bounds on the maximum possible time required to reach high confidence about no  
34 21 circulation in a completely-isolated and unvaccinated subpopulation starting either at the  
35 22 endemic equilibrium or with a single infection in an entirely susceptible population.  
36 23

41 23 **Results:** It may take over three years to reach 95% confidence about no circulation for this  
42 24 hypothetical population despite high surveillance sensitivity and high vaccination coverage in the  
43 25 surrounding general population if: (1) ability to detect cases in the under-vaccinated  
44 26 subpopulation remains exceedingly small, (2) the under-vaccinated subpopulation remains small  
45 27 and highly isolated from the general population, and (3) the coverage in the under-vaccinated  
46 28 subpopulation remains very close to the minimum needed to eradicate. Fully-isolated  
47 29 hypothetical populations of 4,000 people or less cannot sustain endemic transmission for more  
48 30 than 5 years, with at least 20,000 people required for a 50% chance of at least 5 years of  
49 31 sustained transmission in a population without seasonality that starts at the endemic equilibrium.  
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3 32 Notably, however, the population size required for persistent transmission increases significantly  
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5 33 for realistic populations that include some vaccination and seasonality and/or that do not begin at  
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7 34 the endemic equilibrium.

8 35 **Conclusions:** Significant trade-offs remain inherent in global polio certification decisions,  
9  
10 36 which underscore the need for making and valuing investments to maximize population  
11  
12 37 immunity and surveillance quality in all remaining possible WPV reservoirs.  
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14 38

15 39 **Strengths and limitations of this study:**

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17 40 • Demonstrates the somewhat limited but important role of under-vaccinated  
18  
19 41 subpopulations in the time required to achieve high confidence about no WPV  
20  
21 42 transmission after the last reported case.  
22  
23 43 • Highlights competing trends as time increases such that for smaller population sizes  
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25 44 continued transmission becomes exceedingly unlikely, while for larger population sizes  
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27 45 undetected circulation becomes less likely due to the higher frequency of cases and  
28  
29 46 greater chances of detection.  
30  
31 47 • Results underscore the importance of continued investments to maximize population  
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33 48 immunity and surveillance quality.  
34  
35 49 • Analyses remain limited by model assumptions, but in abstract provide insights relevant  
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37 50 to likely last poliovirus reservoirs.  
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38 52 **Keywords:** polio, eradication, certification, modeling  
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## 56 Background

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58 Achieving the 1988 World Health Assembly polio eradication goal of ending all cases of  
59 poliomyelitis<sup>1</sup> requires a successful transition from the interruption of the current low level of  
60 wild poliovirus (WPV) transmission through coordinated cessation of all use of live attenuated  
61 oral poliovirus vaccine (OPV) to effective long-term risk management. The Global Polio  
62 Laboratory Network supports the Global Polio Eradication Initiative (GPEI) by testing stool  
63 samples from acute flaccid paralysis (AFP) cases and sewage samples for polioviruses. As the  
64 GPEI approaches success, the transition to the polio endgame has begun. The endgame involves  
65 significant complexity, because all countries must achieve and maintain sufficient population  
66 immunity<sup>2-4</sup> to stop and prevent the transmission of three separate poliovirus serotypes (i.e., 1, 2,  
67 and 3) and globally coordinate cessation of each OPV serotype.<sup>5-7</sup> In September 2015, the  
68 Global Certification Commission declared successful eradication of serotype 2 WPV (WPV2),<sup>8</sup>  
69 which represented a prerequisite to the globally-coordinated cessation of all serotype 2-  
70 containing OPV use. Global cessation of serotype 2-containing OPV occurred in late April and  
71 early May 2016, during which time over 150 countries stopped using trivalent OPV (tOPV,  
72 which contains all three serotypes) and switched to bivalent OPV (bOPV, which contains only  
73 serotypes 1 and 3 OPV).<sup>9</sup>

74  
75 The Global Polio Laboratory Network reported the lowest number of annual paralytic serotype 1  
76 WPV (WPV1) cases in 2017,<sup>10</sup> and no serotype 3 WPV (WPV3) cases since November 2012.<sup>11</sup>  
77 Successful WPV eradication requires stopping all transmission, which manifests as an absence of  
78 detected WPVs despite actively looking. With increasing time of not seeing cases (while  
79 actively looking), confidence increases about WPV die-out. However, the absence of evidence is  
80 not evidence of absence. Extended silent transmission can occur, because most poliovirus  
81 infections do not lead to symptoms and surveillance gaps can exist. For example, a WPV3  
82 resurfaced in Sudan/Chad in 2004 after no reported cases during 1997-2003<sup>12</sup> and a WPV1  
83 resurfaced in Borno, Nigeria in 2016 after nearly 3 years with no reported cases<sup>13</sup>. The average  
84 paralysis-to-infection ratio (PIR), defined as the fraction of infections in fully susceptible  
85 individuals that leads to paralytic poliomyelitis (polio) symptoms, equals approximately 1/200,  
86 1/2000, and 1/1000, for serotype 1, 2, and 3 WPV, respectively.<sup>14</sup> The last reported naturally-

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3 87 occurring WPV2 case occurred in India in 1999,<sup>15</sup> and since then, only two episodes of WPV2  
4 88 infections occurred that traced back to laboratory strains.<sup>16 17</sup> Despite the possibility of silent  
5 89 circulation, the absence of any naturally-occurring WPV2 cases for over 15 years (and in many  
6 90 countries for many decades) led to very high confidence about the die-out of WPV2  
7 91 transmission.  
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12 92  
13 93 Multiple prior mathematical modeling studies explored the probability of undetected circulation  
14 94 of WPVs in the absence of reported cases or other poliovirus detections. Polio eradication  
15 95 efforts in the Americas, which reported the last indigenous WPV case of any serotype in Peru in  
16 96 1991,<sup>18</sup> motivated the first analysis and discussion of certification requirements. A statistical  
17 97 analysis of Pan American Health Organization epidemiological data reported less than a 5%  
18 98 chance of undetected indigenous WPV circulation after 4 years since the last reported confirmed  
19 99 case.<sup>19</sup> A simple, stochastic model of poliovirus transmission and die-out characterized the  
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21  
22 100 probability of undetected poliovirus circulation in a hypothetical, homogeneously mixed  
23 101 population of 200,000 people in a relatively low-income country, and estimated that not  
24 102 observing a case for 3 years provided 95% confidence about local extinction of WPV  
25 103 infections.<sup>20</sup> This seminal paper provided the foundation for appropriate characterization of the  
26 104 probability of undetected circulation as a function of the time since the last detected case.<sup>20</sup>  
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28  
29 105 Related modeling also explored theoretical thresholds to stop transmission<sup>21</sup> and estimated a  
30 106 minimum population size for persistent transmission of 50,000-100,000 in developing countries  
31 107 and over 200,000 in developed countries required to achieve at least 95% probability of  
32 108 poliovirus persistence for 5 years or more in the absence of vaccination.<sup>22</sup> These studies  
33 109 supported the 2004-8 GPEI Strategic Plan requirement of at least 3 years of no polio cases  
34 110 detected by AFP surveillance for certification,<sup>23</sup> which remains the current minimum  
35 111 requirement.<sup>24</sup> A 2012 study<sup>25</sup> relaxed some of the assumptions of the prior theoretical model<sup>20</sup>  
36 112 and highlighted that the probability of undetected circulation varied for different poliovirus  
37 113 serotypes, places, and conditions, which suggested the need to focus on appropriate  
38 114 characterization of conditions in the last likely WPV reservoirs.<sup>25</sup> A 2015 study<sup>26</sup> also used the  
39 115 prior model<sup>20</sup> to show that in the context of an instantaneous introduction of vaccination, the  
40 116 time of the last case relative to vaccine introduction further informs the confidence about the  
41 117 absence of circulation.  
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5 119 Subsequent analyses focused on modeling the conditions in specific and more realistic  
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7 120 populations. A 2015 study<sup>27</sup> used a previously-developed poliovirus dynamic transmission  
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9 121 model<sup>2</sup> applied to: recently-endemic transmission in two states in northern India,<sup>28</sup> endemic  
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11 122 transmission in northwest Nigeria,<sup>29</sup> a 2010 outbreak in Tajikistan,<sup>30</sup> and transmission following  
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13 123 a 2013 WPV1 introduction into Israel detected by environmental surveillance.<sup>31</sup> The study  
14  
15 124 characterized the confidence about no undetected poliovirus circulation by serotype as a function  
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17 125 of time without reported polio cases or environmental detections considering realistic  
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19 126 assumptions for surveillance, immunization, and other national inputs.<sup>27</sup> The results suggested  
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21 127 that time periods of 0.5 to 3 years without detected polio cases provided 95% confidence about  
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23 128 the interruption of transmission in the context of perfect AFP surveillance depending on  
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25 129 situation-specific characteristics (e.g., the overall population immunity, endemic versus outbreak  
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27 130 conditions, and virus serotype).<sup>27</sup> This model also suggested longer times required for less-than-  
28  
29 131 perfect AFP surveillance and potentially shorter times using highly-sensitive environmental  
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31 132 surveillance based on the experience in Israel.<sup>27</sup> A recent statistical analysis of the 2013 WPV1  
32  
33 133 outbreak in Israel demonstrated a rapid increase in confidence about no undetected local  
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35 134 transmission following outbreak response immunization after repeated negative environmental  
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37 135 surveillance samples in a city.<sup>32</sup> A non-dynamic, statistical model<sup>33</sup> estimated a shorter time  
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39 136 (compared to<sup>27</sup>) of 14 months required to reach high confidence about no undetected circulation.  
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41 137 For its most conservative assumptions about surveillance and force-of-infection, the study  
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43 138 estimated a probability of 93% of a WPV-free Africa in the absence of any new WPV cases  
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45 139 reported by the end of 2015,<sup>33</sup> shortly before the WPV reemerged.<sup>13</sup> Contrasting with all other  
46  
47 140 modeling studies, a recent study<sup>34</sup> suggested a relatively high probability of undetected  
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49 141 circulation after more than 3 years without any polio cases in small populations, although a  
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51 142 correction to that analysis emphasized the unrealistic nature of one of the assumptions.<sup>35</sup>  
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53 143 Remarkably, the analysis reported that closed populations of 10,000 people or fewer could  
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55 144 support many years of transmission in the absence of vaccination, and experience gaps between  
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57 145 polio cases of over 5 years.<sup>34</sup> A reanalysis of this hypothetical model identified issues with the  
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59 146 analysis and its framing, and reported results consistent with the prior literature after correcting  
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147 for some errors.<sup>36</sup>  
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3 149 Although the modeling results demonstrated the critical importance of sustaining high population  
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5 150 immunity through immunization programs and high-quality surveillance to obtain high  
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7 151 confidence about no undetected circulation, the current GPEI strategic plan only covers 2013-  
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9 152 2018,<sup>6</sup> which leads to uncertainty about the ability to sustain high program performance after  
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11 153 2018. As of mid-2018, questions continue to arise about when the GPEI will cease to exist and  
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13 154 what resources will be available to support the polio endgame, including the certification of  
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15 155 eradication of WPV1 and WPV3 with high confidence. The GPEI partners already began  
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17 156 transition planning, and this process already led to some downsizing of national poliovirus  
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19 157 programs, including the reduction of some AFP surveillance activities.<sup>37</sup> Thus, while the prior  
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21 158 modeling assumed strong GPEI and national polio program performance up through the end of  
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23 159 the polio endgame, this assumption now appears optimistic, and further analyses that explore the  
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25 160 impact of lower quality surveillance may prove useful in the context of global certification  
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27 161 decisions for WPV1 and WPV3 eradication. Further motivation for developing models to  
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29 162 support certification decisions comes from the re-appearance of WPV1 in security-compromised  
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31 163 areas in Borno, Nigeria after apparent interruption, which raised questions about the ability of  
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33 164 poliovirus circulation without detection in communities not (or poorly) accessed by  
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35 165 immunization and surveillance efforts within larger populations with high immunity and good  
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37 166 surveillance.

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41 168 This study aims to support future decisions about WPV certification by: (1) informing  
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43 169 confidence about the absence of circulation by modeling the role of hard-to-reach populations,  
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45 170 (2) examining the minimum population size required to sustain poliovirus transmission, and (3)  
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47 171 developing a conceptual framework to provide some structure for future certification decisions.

## 172 173 **Methods**

174  
175 To inform confidence about the absence of circulation by modeling the role of hard-to-reach  
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177 populations, we explored the impact of key assumptions using an existing model of a  
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179 hypothetical population comprised of a well-vaccinated general population and an under-  
vaccinated subpopulation.<sup>38</sup> Table 1 lists the model inputs used to characterize this hypothetical  
population and explore the role of key assumptions (see appendix for model details). To explore



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3 180 different population characteristics, we varied the total population size, the size of the under-  
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5 181 vaccinated subpopulation, and the degree of mixing between the under-vaccinated and general  
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7 182 population around a base case indicated by the bold values in Table 1. In addition, for each  
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9 183 variation around the base case, we simultaneously varied the routine immunization coverage and  
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11 184 detection probability per polio case in the under-vaccinated subpopulation. We interpret the total  
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13 185 hypothetical population as one epidemiological block (e.g., a country) and therefore compute the  
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15 186 confidence about no circulation based on all detections that occur in the general population and  
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17 187 under-vaccinated subpopulation combined. However, we fix the detection probability in the  
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19 188 general population at 95% to characterize high-quality national surveillance while considering  
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21 189 lower detection probabilities only in the under-vaccinated subpopulation (Table 1).<sup>38</sup> To  
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23 190 estimate the confidence about no circulation in this conceptual model, we use a simplified  
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25 191 version (see appendix) of the stochastic approach developed by Eichner and Dietz (1996)<sup>20</sup> and  
26  
27 192 adopted by others.<sup>25-27</sup> We define the probability of undetected circulation after a given period of  
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29 193  $t$  months without a detection as the number of times in multiple stochastic simulations that  $t$   
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31 194 months went by without a detection despite continued circulation, divided by the total number of  
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33 195 times that  $t$  months went by without a detection (i.e., with or without continued circulation).  
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35 196 Intuitively, the fraction of all time periods of  $t$  months without a detection but with transmission  
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37 197 still ongoing should decrease as  $t$  increases, corresponding to an increasing probability of no  
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39 198 circulation. Confidence about no circulation equals one minus the probability of undetected  
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41 199 circulation. To visualize the impact of varying the model inputs, we focus on the time without a  
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43 200 detection until the confidence about no circulation first exceeds 95% (CNC95%).

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45 201  
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47 202 We revisit the question of silent transmission in small populations<sup>22 34 36</sup> using the hypothetical  
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49 203 population model<sup>38</sup> in an attempt to inform the bounds on the maximum possible CNC95%. To  
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51 204 do so, we ignore the general population and effectively assume a completely-isolated and  
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53 205 unvaccinated subpopulation and otherwise adopt the hypothetical population assumptions from  
54  
55 206 Table 1. We transform the DEB model to a stochastic form using the Gillespie algorithm,<sup>39</sup> as  
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57 207 described elsewhere,<sup>27</sup> and start either at the endemic equilibrium<sup>34</sup> or with a single infection in  
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59 208 an entirely susceptible population. Instead of modeling die-out using the transmission  
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61 209 threshold,<sup>27</sup> we allow transmission to continue until the infection prevalence becomes 0. This  
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63 210 complements the existing work<sup>22 34 36</sup> by providing a comparison to the same situation with a

211 more comprehensive model for poliovirus transmission,<sup>2</sup> adding consideration of the impact of  
212 the initial conditions, and adding the impact on confidence about no circulation.

213  
214 Finally, recognizing the complexity and inter-related nature of certification decisions, we  
215 developed an influence diagram to relate certification timing decisions to outcomes. The  
216 diagram provides a conceptual framework to support certification decisions and formulate  
217 decisions about the timing of certification as an optimization problem. The diagram uses  
218 conventions from causal loop diagrams<sup>40</sup> and specifies the directionality of relationships  
219 between variables using unidirectional arrows. The polarity or sign at the arrow head indicates  
220 whether increasing the variable at the base of the arrow increases (+) or decreases (-) the variable  
221 that the arrow points to with all else being equal.

### 223 *Patient and Public Involvement*

225 This survey did not involve patients or public opportunities for engagement.

## 227 **Results**

229 Figure 1 illustrates how the confidence about no circulation increases with time after the last  
230 detection as a function of the surveillance quality in the under-vaccinated subpopulation (i.e., the  
231 detection probability). Clearly, higher confidence implies the need to wait longer after the last  
232 detected case, and lower detection probabilities further increase the time required to reach a  
233 certain level of confidence (e.g., the 95% line). Figure 1 shows a relatively modest effect of the  
234 detection probability in the under-vaccinated subpopulation for this hypothetical model due to  
235 continued occurrence of cases in the general population for the assumed degree of mixing (see  
236 appendix).

238 Figure 2 shows the CNC95% values as a function of coverage and detection probability for the  
239 under-vaccinated subpopulation. The figure shows longer times required to reach CNC95%  
240 values with increasingly more isolated under-vaccinated subpopulations (left column, top to  
241 bottom), with decreasing relative sizes of the under-vaccinated subpopulation (middle column,

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3 242 top to bottom), and decreasing absolute sizes of a fully-isolated under-vaccinated subpopulation  
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5 243 (right column, top to bottom, note increased y-axis ranges). The panels in Figure 2 omit curves  
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7 244 for coverage values that do not result in eradication, because they do not allow for calculation of  
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9 245 any confidence about eradication. The panels also omit the data point for 0 detection probability  
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11 246 in the event of a fully-isolated under-vaccinated subpopulation, because that would imply no  
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13 247 ability to detect the virus. Consistent with previous findings,<sup>27</sup> all panels in Figure 2 show  
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15 248 higher CNC95% values with higher coverage in the under-vaccinated subpopulation. In each  
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17 249 panel, the lowest shown coverage value may result in the longest period of undetected circulation  
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19 250 before interruption and therefore result in the longest time to achieve high confidence about no  
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21 251 circulation.

22 252  
23 253 Looking more closely at the differences between the columns, the left column of Figure 2 shows  
24  
25 254 a very strong influence of the degree of isolation on the CNC95%. With little isolation and no  
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27 255 surveillance in the under-vaccinated subpopulation, the general population with high surveillance  
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29 256 quality can still detect transmission because of relatively frequent spillover of polio cases (see  
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31 257 appendix). Thus, the results do not depend much on the detection probability in the under-  
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33 258 vaccinated subpopulation for  $p_{\text{within}}=0.8$ . In contrast, for a fully isolated under-vaccinated  
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35 259 subpopulation ( $p_{\text{within}}=1$ ), the detection probability in this population becomes a more important  
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37 260 driver of the CNC95% than the coverage (i.e., for detection probability of 0.1 or very poor  
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39 261 surveillance and all other inputs at the base case, the CNC95% equals almost 6 years regardless  
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41 262 of coverage). The middle column of Figure 2 shows CNC95% values of approximately 5 years  
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43 263 with no surveillance in a relatively small under-vaccinated subpopulation. Although the relative  
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45 264 size of the under-vaccinated subpopulation affects the mixing dynamics and incidence of cases in  
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47 265 both populations, much of the observed effect comes from the implied change in the absolute  
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49 266 size of the under-vaccinated subpopulation, which directly affects the typical time between cases.  
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51 267 As shown in the right column of Figure 2, changing the absolute size of the under-vaccinated  
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53 268 subpopulation in the event of full isolation from the general population and a detection  
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55 269 probability of 0.1 dramatically affects the CNC95%, which ranges from slightly over 2 years for  
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57 270 500,000 people to approximately 9 years for 50,000 people (i.e., a 4-fold increase in CNC95%  
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59 271 for a 10-fold increase in population size).

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3 273 Considering the relatively high CNC95% observed for small, isolated populations in Figure 2,  
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5 274 Figure 3a uses a stochastic model to show the distribution of the duration of circulation in a  
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7 275 single population not reached by vaccination at all. Figure 3a shows the results as a function of  
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9 276 population size for a model initialized at the endemic equilibrium. For very small population  
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11 277 sizes (e.g., hundreds), not surprisingly poliovirus infections typically die-out within a year, with  
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13 278 a maximum duration of circulation of one year and 4 months for a closed population of 1,000  
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15 279 people (based on 10,000 iterations). The maximum duration of circulation increases rapidly for  
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17 280 larger populations. For a population of 5,000 people, circulation continues for 3 or more years in  
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19 281 50 of 10,000 (0.5%) iterations. With population sizes of 10,000, 20,000, 30,000, 40,000 and  
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21 282 50,000, circulation continues for at least 10 years for 3%, 34%, 63%, 79%, and 88% of  
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23 283 iterations, respectively.

24 285 Figure 3b shows the same analysis as Figure 3a except that it changes the initial conditions by  
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26 286 assuming a population with no prior exposure to any polioviruses. In this context, a single  
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28 287 introduction rapidly burns through the entire susceptible population and quickly exhausts  
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30 288 susceptible individuals, leading to die-out and a maximum duration of circulation of less than 2  
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32 289 years for all population sizes considered in Figure 3b. Together, Figures 3a-b encompass the  
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34 290 bounds on the possible duration of circulation for different initial conditions. In reality, small,  
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36 291 completely isolated populations are unlikely to remain at the endemic equilibrium because of  
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38 292 random fluctuations in the incidence, seasonality, and die-out, and no completely naïve  
39  
40 293 populations likely exist. In a separate analysis using the same model, we verified that the  
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42 294 addition of seasonality decreases the typical duration of circulation and increases the probability  
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44 295 of eradication within 5 years. For example, for a population size of 20,000 people, the  
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46 296 probability of eradication within 5 years increased from approximately 64% without seasonality  
47  
48 297 to 78%-92% with a seasonal amplitude of 10% (applied to the basic reproduction number of 10),  
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50 298 depending on the timing of the seasonal peak.

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52 300 While Figure 3 implies that increasing the population size results in an increasing probability of  
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54 301 persistent circulation (i.e., a greater probability of sustained undetected transmission), Figure 2  
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56 302 implies that increasing population size decreases the typical time interval between cases (i.e.,  
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58 303 lower probabilities of sustained undetected circulation). Figure 4 shows the net effect of these

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3 304 two opposing trends and suggests that an optimal population size exists around 20,000 people.  
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5 305 For smaller population sizes, continued transmission becomes exceedingly unlikely (Figure 3),  
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7 306 while for larger population sizes, undetected circulation becomes less likely due to the higher  
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9 307 frequency of cases. This non-linear behavior suggests a maximum CNC95% of approximately  
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11 308 2.5 years for a detection probability of 1, although the maximum increases to up to 9 years for a  
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13 309 very low detection probability of 0.1 and a population size of 20,000 to 30,000 people.  
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15 310  
16 311 Figure 5 shows how the desired confidence about no circulation may influence certification  
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18 312 timing and key health economic outcomes (see appendix for details). Earlier certification and  
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20 313 OPV cessation may increase the risk of undetected circulation after OPV cessation (and therefore  
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22 314 the possibility of needing to restart OPV use) but may decrease the costs until OPV cessation  
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24 315 (and therefore the overall global costs for planned polio immunization). Therefore, the  
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26 316 fundamental optimization problem consists of finding the desired confidence about no WPV  
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28 317 circulation at OPV cessation that minimizes the resulting total financial and societal costs.  
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30 318 Figure 5 also shows that the costs and risks both depend on the GPEI budget until and after OPV  
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32 319 cessation, with a lower budget saving costs in the short term but increasing the time of OPV  
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34 320 cessation at a given confidence level and the risks of OPV restarts, which may ultimately result  
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36 321 in greater overall costs. Optimization of the desired confidence about no WPV circulation  
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38 322 depends critically on how the confidence about no circulation increases with time after the last  
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40 323 detected event from the surveillance system.  
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42 324

## 43 325 **Discussion**

44 326  
45 327 Hard-to-reach subpopulations may play a key role in deliberations about WPV circulation and  
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47 328 decisions about WPV certification. The timing of WPV certification and subsequent OPV  
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49 329 cessation involves high stakes and largely depends on the desired confidence about the absence  
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51 330 of circulation. Surveillance quality emerges as a key factor that affects both the confidence  
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53 331 about the absence of circulation and the ability to detect and control any outbreaks after OPV  
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55 332 cessation. However, national surveillance indicators may not suffice to measure the overall  
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57 333 surveillance system quality because gaps in surveillance at the level of tens of thousands of  
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59 334 people may influence confidence. Our modeling suggests that high quality surveillance suffices

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3 335 to detect transmission in the context of a relatively well-mixed under-vaccinated subpopulation  
4 (e.g., in Pakistan and Afghanistan),<sup>41</sup> while local gaps may miss transmission for several years in  
5 336 the context of highly-isolated under-vaccinated subpopulations. With respect to global  
6 337 certification of WPV eradication, this implies a need to address any such gaps in isolated  
7 338 populations that experienced WPV transmission during the last decade. The recent experience in  
8 339 Borno and previously in Chad and Sudan demonstrated the ability of WPVs to circulate  
9 340 undetected for many years in sub-populations missed by both surveillance and immunization  
10 341 efforts.<sup>12 13</sup> However, one of the main contributions of this work is that it shows that very small,  
11 342 isolated subpopulations cannot sustain transmission indigenously, while in the context of even  
12 343 very limited surveillance, persistent undetected transmission becomes increasingly unlikely for  
13 344 increasing population sizes. To our knowledge, the existence of a worst-case population size for  
14 345 undetected circulation has not yet been demonstrated for polioviruses. Our analysis confirms  
15 346 that with high-quality surveillance, 3 years without a detected WPV case suffices to attain high  
16 347 confidence about no circulation for serotype 1, even considering possible persistence in very  
17 348 small population sizes.  
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19 350  
20 351 Explicit consideration of the decision to certify WPV eradication (Figure 5) suggests that if we  
21 352 remain confident that we can prevent the need to restart OPV due to uncontrolled outbreaks  
22 353 resulting from a possible WPV reemergence, then we should accept a lower confidence about the  
23 354 absence of circulation to certify sooner, because the costs of delaying OPV cessation would  
24 355 outweigh the risk of premature certification. Earlier OPV cessation particularly represents the  
25 356 best option if diminishing GPEI financial and/or global OPV supply resources limit our ability to  
26 357 maintain population immunity and/or respond effectively to post-cessation outbreaks. However,  
27 358 this choice depends on a willingness to accept the reputational risk of finding out that WPV still  
28 359 circulates despite its certification. With WPV3 not detected anywhere since 2012<sup>11</sup> and in many  
29 360 places for decades, the confidence about no WPV3 circulation continues to grow. Although  
30 361 confidence about no circulation increases more slowly for WPV3 than WPV1 due to the lower  
31 362 PIR,<sup>25 27</sup> assuming 1-2 years to prepare for coordinated global OPV cessation, starting the  
32 363 process of removing serotype 3 OPV now would imply at least 7 years of no detection since the  
33 364 last WPV3 case and synchronized cessation of serotype 3 OPV use (i.e., 2012 to 2019-2020).  
34 365 The transition of GPEI resources already occurring leads to expected decreases in population



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3 366 immunity for serotype 3 in some areas. Combined with on-going serotype 3 vaccine-associated  
4 367 paralytic poliomyelitis, this should motivate careful consideration of the costs, benefits, and risks  
5 368 of globally certifying WPV3 eradication and synchronizing serotype 3 OPV cessation before  
6 369 completing WPV1 eradication and serotype 1 OPV cessation, which now appears at least 4 years  
7 370 away.  
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12 372 Our results related to minimum population sizes appear consistent with a prior study<sup>22</sup> that  
13 373 found an average of approximately 5 years of circulation for a population of 20,000 people in a  
14 374 high- $R_0$  setting and an exponential increase in the average duration of circulation with increasing  
15 375 population size. The prior study also reported a higher probability of virus persistence as the  
16 376 degree of mixing between subpopulations increases.<sup>22</sup> Our study suggests that more mixing  
17 377 between subpopulations may not lead to a higher probability of undetected circulation because  
18 378 surveillance can more easily detect persistent viruses for higher degrees of mixing. Using a more  
19 379 realistic model than another prior analysis,<sup>36</sup> we similarly do not find a high probability of  
20 380 persistent transmission for populations of 10,000 people or less.  
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30 382 Like all models, our model makes simplifying assumptions that affect its behavior.<sup>2</sup> Specifically,  
31 383 we characterized a stylized, hypothetical population to systematically explore key assumptions,  
32 384 used a simplified semi-stochastic approach to compute CNC95% that does not fully account for  
33 385 all stochastic variability, and deterministically characterized die-out. However, for the analysis  
34 386 of small population sizes that depend most on stochastic variability, we accounted for stochastic  
35 387 variability and die-out at the individual level.  
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42 389 While this study highlights the importance of ensuring high surveillance quality in all  
43 390 subpopulations, it also reiterates the role of immunization in accelerating confidence about no  
44 391 circulation after the last detection.<sup>27</sup> Achieving and maintaining high population immunity to  
45 392 transmission represents a mission critical component of the GPEI. Populations with immunity  
46 393 near the threshold experience increased risk of prolonged undetected transmission. Thus, if  
47 394 ensuring high-quality surveillance in all subpopulations remains an elusive goal, then achieving  
48 395 better coverage in those subpopulations would still result in higher confidence about no  
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396 circulation. In contrast, high quality surveillance in the context of poor immunization still leaves  
397 the population and the world at risk.

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399 Poliovirus environmental surveillance can detect polioviruses even in the absence of  
400 symptomatic polio cases<sup>42 43</sup> and offers the potential to fill some local gaps in symptomatic  
401 poliovirus surveillance. However, despite the potential for high sensitivity of environmental  
402 surveillance to detect infected individuals excreting into the catchment area, its sensitivity  
403 remains zero outside of the catchment area and depends on sampling frequency (e.g., one sample  
404 every year provides little increase in confidence over AFP alone).<sup>44</sup> Environmental surveillance  
405 system designs generally depend on access to a centralized sewage network,<sup>43</sup> which hard-to-  
406 reach subpopulations (i.e., those most likely to sustain undetected poliovirus transmission) may  
407 not possess. Further research should help to explore the ability of environmental surveillance to  
408 increase confidence about no circulation in specific areas, and the value of the information  
409 obtained from environmental surveillance relative to its costs requires evaluation.

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411 **List of abbreviations:** AFP, acute flaccid paralysis; CNC95%, Time until the confidence about  
412 no circulation reaches 95%; cVDPV, circulating VDPV DEB, differential-equation based; GPEI,  
413 Global Polio Eradication Initiative; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus  
414 vaccine; PIR, paralysis-to-infection ratio; VDPV, vaccine-derived poliovirus; WPV(1,2,3), wild  
415 poliovirus (of serotype 1, 2, 3, respectively)

416  
417 **DECLARATIONS**

418  
419 **Authors' contributions**

420 All authors (RDT, DAK, KMT) contributed to the study design, model development,  
421 interpretation of results, manuscript writing, and revisions. The first and second authors (RDT,  
422 DAK) performed the modeling and analyses, and the last author (KMT) secured the funding for  
423 the study.

424  
425 **Ethics approval and consent to participate**

426 Not applicable



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5 428 **Consent to publish**

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7 429 Not applicable

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10 431 **Competing interests**

11  
12 432 None

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24 439 [OPP1129391].  
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27 441 **Data sharing statement**

28  
29 442 Technical appendix available on request from the authors.  
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31 443

32 444 **References**

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**Table 1: Model inputs to characterize a hypothetical population that contains an under-vaccinated subpopulation.**

Model input	Value(s) <sup>a</sup>	Source/notes
Total population size	500,000; <b>1 million</b> ;5 million	No effect on DEB model behavior, but required for stochastic analysis of detections
Time until vaccination starts, years		Assumption to characterize hard-to-reach subpopulation within well-vaccinated general population
General population	30	
Under-vaccinated subpopulation	40	
Initial age distribution		Equilibrium age distribution <sup>38</sup>
0-2 months	0.01	
3-59 months	0.15	
5-14 years	<b>0.25</b>	
≥ 15 years	<b>0.59</b>	
Birth rate, births/person/year	0.02	<sup>38</sup>
Death rate, deaths/person/year	0.02	<sup>38</sup>
Basic reproduction number ( $R_0$ )	10	<sup>38</sup>
Proportion of transmissions via oropharyngeal route	0.3	<sup>38</sup>
Proportion of contacts reserved for individuals within the same mixing age group	0.4	Same value as used in <sup>38</sup> (not explicitly listed)
Average per-dose take rate for serotype 1 OPV	0.6	Increased from 0.5 to maintain similar coverage thresholds with different run-up <sup>38</sup>
Routine immunization coverage		Represents coverage with exactly 3 OPV doses; general population based on <sup>38</sup> , under-vaccinated varied around threshold to eradicate, which equals 0.82 for the bolded values in the middle column
General population	0.95	
Under-vaccinated subpopulation	0.75; <b>0.82</b> ;0.85; <b>0.90</b> ;0.95 <sup>b</sup>	
Proportion of contacts with under-vaccinated subpopulation ( $p_{\text{within}}$ )	0.8; <b>0.95</b> ;1.00	Selected values from <sup>38</sup>
Size of under-vaccinated subpopulation compared to total population	1/20; <b>1/10</b> ;1/5	Selected values from <sup>38</sup>
Paralysis-to-infection ratio (PIR)	1/200	Average for serotype 1 wild poliovirus <sup>2 14</sup>
Detection probability per polio case		Assumption to characterize hard-to-reach subpopulation within general population with high acute flaccid paralysis surveillance quality
General population	0.95	
Under-vaccinated subpopulations	0;0.1;0.2;0.3;0.4;0.5;0.6;0.7;0.8;0.9;0.95 <sup>b</sup>	

Abbreviations: DEB, differential-equation based; OPV, oral poliovirus vaccine

<sup>a</sup> Values shown in bold represent values that we held fixed when varying other values in sensitivity analyses

<sup>b</sup> All values considered jointly in all sensitivity analysis (hence no single value bolded)

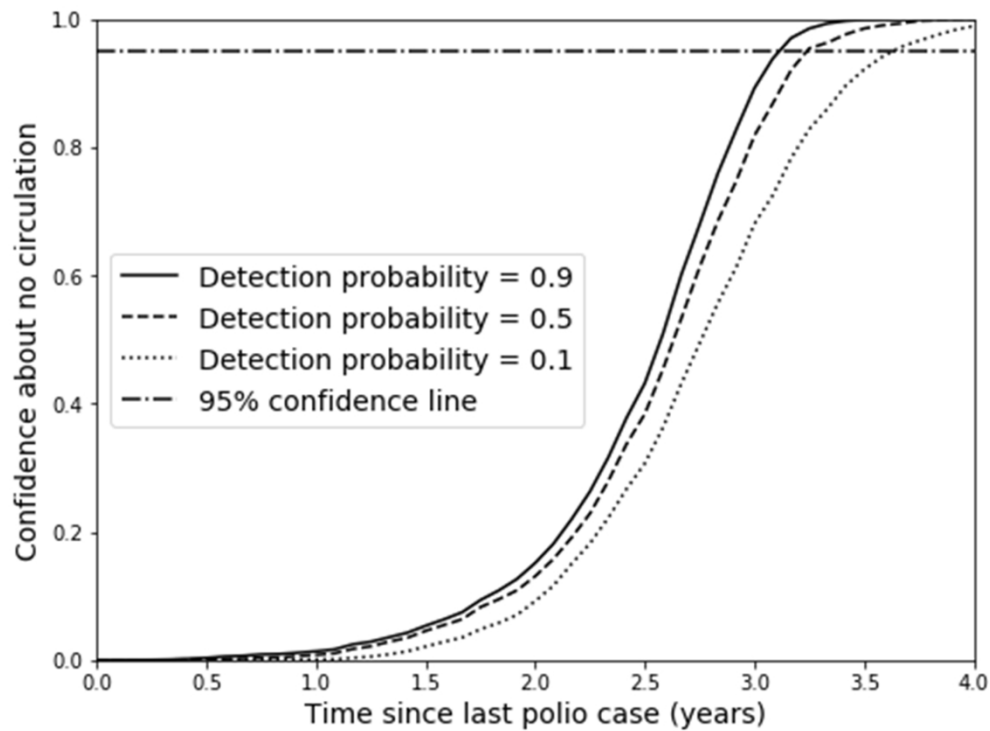


Figure 1: Confidence about no circulation as a function of time since the last detection for different detection probability values for the hypothetical model base case, with coverage at the corresponding minimum to eliminate WPV (i.e., 0.82).

179x133mm (300 x 300 DPI)

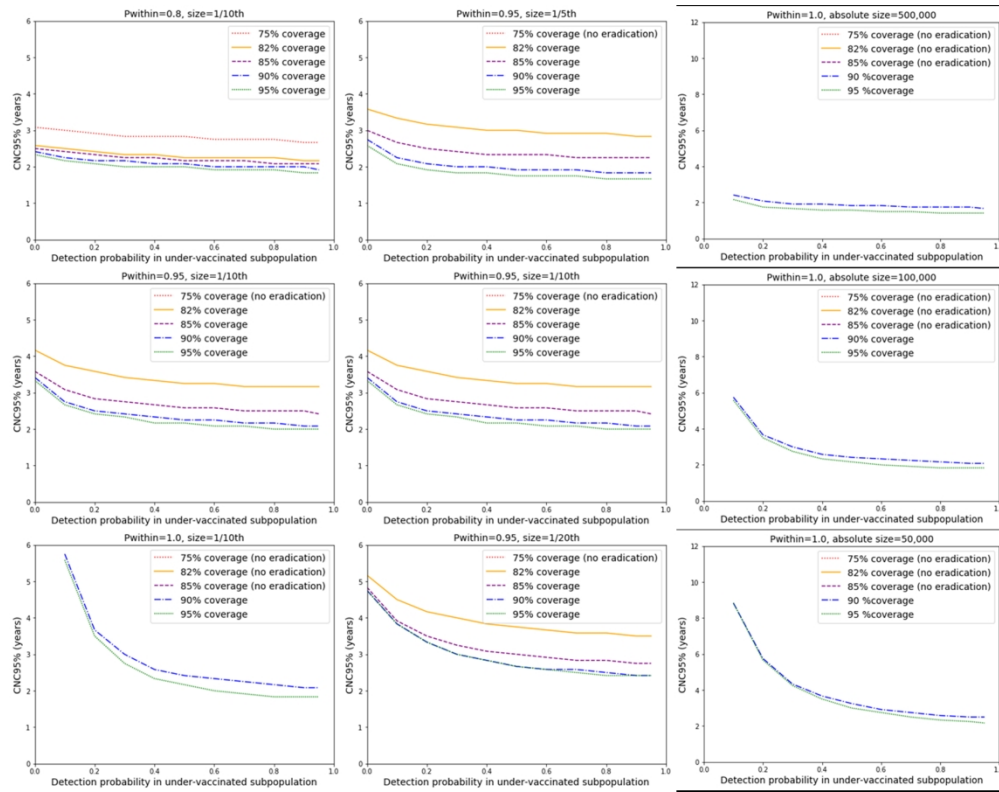
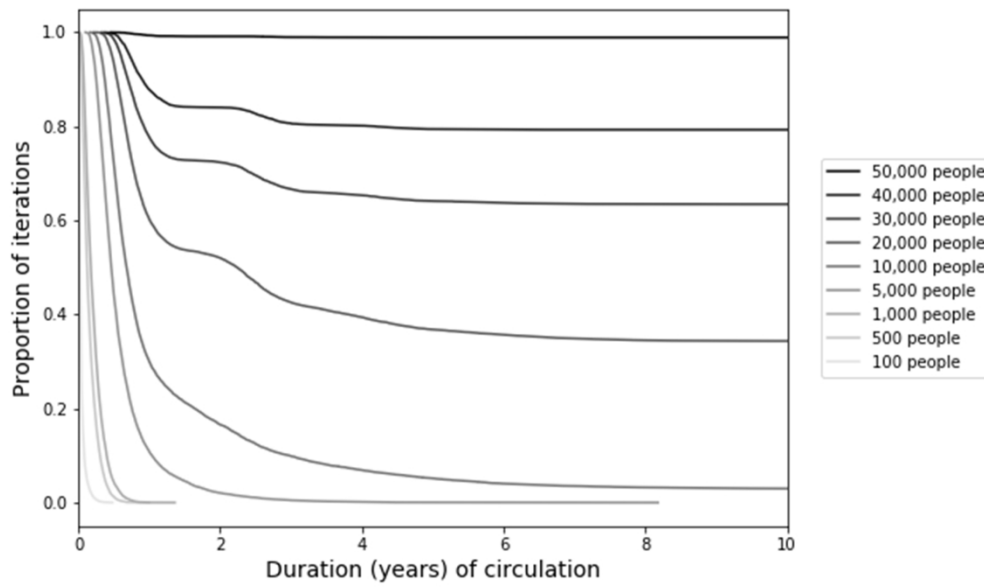


Figure 2: Time until the confidence about no circulation reaches 95% (CNC95%) from the stochastic analysis for different degrees of isolation of the under-vaccinated subpopulation (left column), relative sizes of the under-vaccinated subpopulation (middle column), and absolute sizes of a fully-isolated under-vaccinated subpopulation (right column, note doubled y-axis ranges).

250x196mm (300 x 300 DPI)





Results from the analysis of the relationship between population size and persistence of circulation of serotype 1 wild poliovirus transmission in the fully stochastic model (a) Model starts at the endemic equilibrium

222x133mm (300 x 300 DPI)

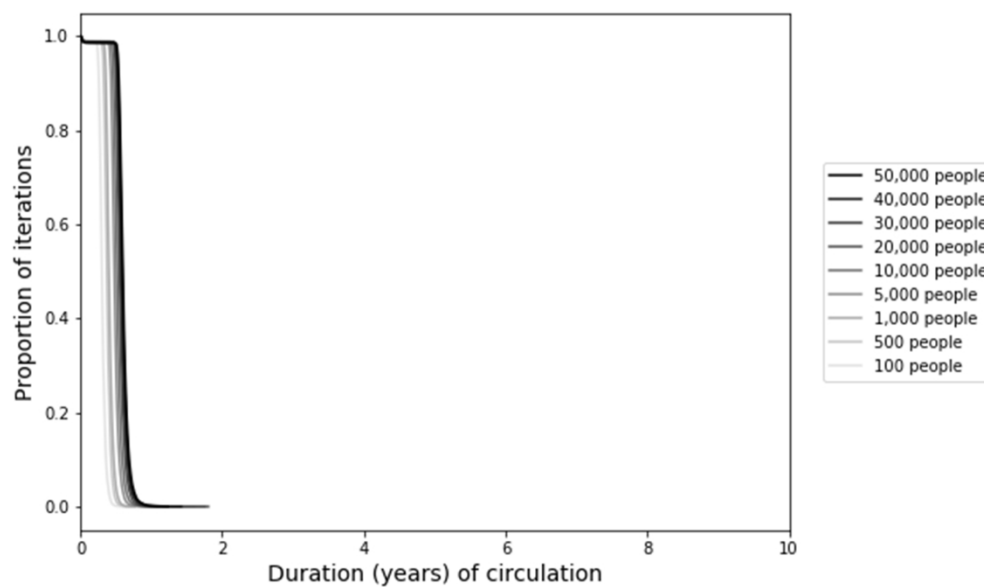


Figure 3: Results from the analysis of the relationship between population size and persistence of circulation of serotype 1 wild poliovirus transmission in the fully stochastic model (b) Model starts with a single infection in a fully susceptible population

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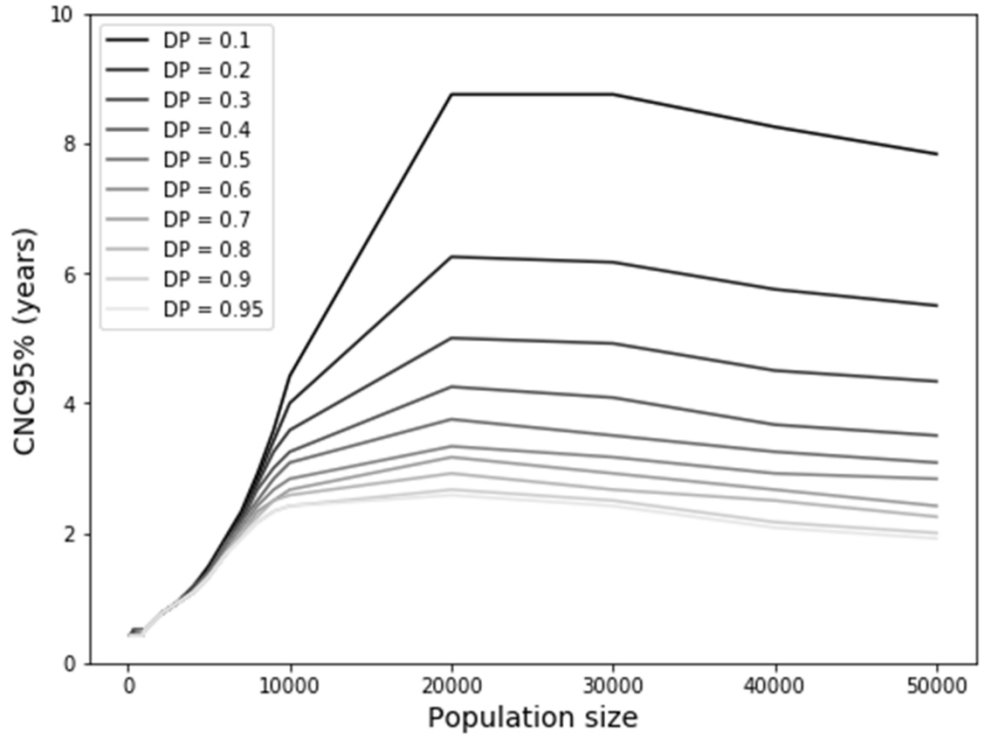


Figure 4: Time until the confidence about no circulation reaches 95% (CNC95%) for small population sizes in the fully stochastic model that starts at the endemic equilibrium, by detection probability (DP)

177x133mm (300 x 300 DPI)

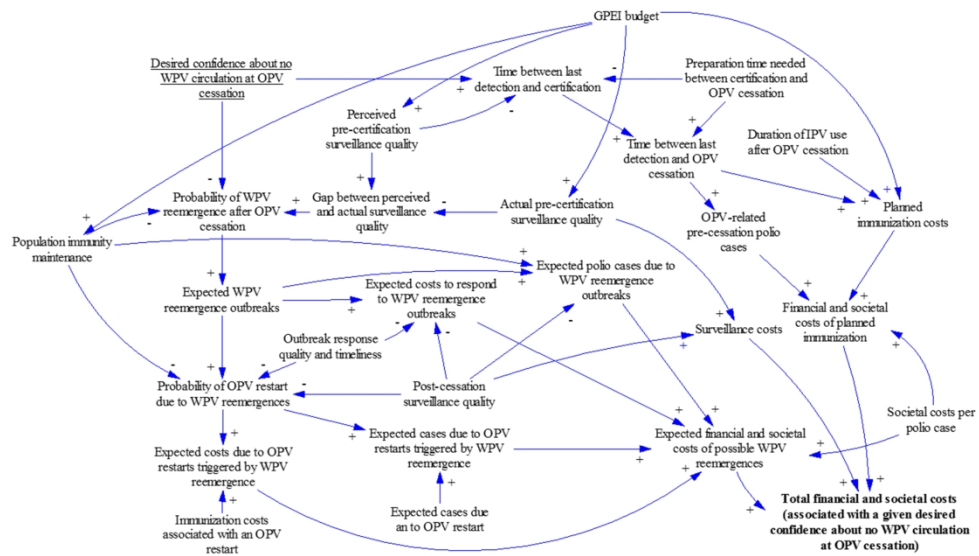


Figure 5: Conceptual diagram for the implications of choices about the timing of certification of eradication of a wild poliovirus serotype on total financial and societal costs

228x135mm (300 x 300 DPI)

## APPENDIX for “Certification of global eradication: The role of hard-to-reach subpopulations and confidence about the absence of transmission”

Radboud J. Duintjer Tebbens,<sup>1</sup> Dominika A. Kalkowska,<sup>1</sup> Kimberly M. Thompson<sup>1</sup>

### *Differential-equation based model and results*

The DEB model we use to examine the role of subpopulations<sup>38</sup> made simplifying assumptions about what a high-risk population might look like and otherwise adopted the comprehensive structure and setting-invariant model inputs of a previously developed and calibrated differential-equation based poliovirus transmission and OPV evolution model.<sup>2,30</sup> The following text from the appendix of a prior publication<sup>45</sup> (with references renumbered) briefly describes the model and Figures A1-2 and Table A1 cited in the text provide the model structure and generic inputs (i.e., model inputs that remain the same for all populations).

“The differential equation-based poliovirus transmission and OPV evolution model (DEB model)<sup>2</sup> tracks the movement of people between demographic age groups (grouped into mixing age groups that mix preferentially amongst themselves), and for each serotype between oropharyngeal and intestinal infection stages (resulting in potential oropharyngeal and fecal-oral transmission, respectively), immunity states, and waning stages. Figure A1 provides an overview of the model structure based on prior work.<sup>2</sup> Figure A1a depicts the immunity states with the flows that move individuals in and out of them and Figure A1b details how effectively vaccinated or infected individuals progress through different stages of infection and, in the event of infection with OPV, through OPV evolution stages. The model assumes that active immunity from prior vaccination or infection results in permanent protection from polio (disease), but only partial protection from subsequent infection and participation in transmission, depending on the nature of immunity (IPV-induced vs. LPV-induced or both) and time since the last exposure (i.e. waning stage). The model includes 5 waning stages, 6 fecal-oral and 6 oropharyngeal infection stages (2 latent and 4 infectious, with varying degrees of infectiousness), and also accounts for a delay between IPV receipt and development of the immune response that moves individuals to the next IPV immunity state. In Figure A1a, we note that the model assumes identical properties for “IPV and LPV” and “ $\geq 2$  LPV infections” and that the recent waning stages of these immunity states represent the highest degree of immunity to transmission in the model. The model further tracks OPV evolution by moving individuals infected with the OPV parent strain (stage 0) through 20 successive reversion stages that can each transmit and that come with increasing paralysis-to-infection ratios and relative basic reproduction numbers ( $R_0$  values) compared to homotypic WPVs. The last reversion stage (stage 19) represents fully-reverted VDPVs with assumed paralysis-to-infection ratio and  $R_0$  equivalent to homotypic WPVs. For WPVs or any OPV reversion stage, the DEB model mimics die-out by setting the force-of-infection for the given strain to 0 whenever its effective prevalence of infections resides below a calibrated threshold of 5 per million people. Consequently, OPV-related viruses can only continue to transmit and thus evolve to cVDPVs through successive infections when low enough population immunity to transmission permits circulation of the OPV viruses introduced in the population through vaccination. We fixed the die-out process, model structure, and numerical

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3 model inputs that characterize them across all populations we modeled and Table A1 includes  
4 the corresponding generic model inputs. [...]

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7 “Figure A2 summarizes the results of the model calibration process, based on prior work.<sup>2</sup> With  
8 the generic model inputs from Table A1 fixed, we compared our model behavior against i) data  
9 on children with non-polio acute flaccid paralysis who reported no receipt of OPV for northern  
10 India (modeled separately for Western Uttar Pradesh (WUP) and Bihar) and northwest (NW)  
11 Nigeria; ii) data on polio incidence and die-out of endemic WPV transmission for all situations  
12 and serotypes (shown in Figure A2 for WPV1 and WPV3 in northern India and northwest  
13 Nigeria and for all 3 WPV serotypes in the USA); iii) data from WPV importation outbreak  
14 behavior in the Netherlands, Tajikistan, and Albania; iv) data on age distributions of cases for all  
15 situations in which meaningful data was available (shown in Figure A2 for the Netherlands,  
16 Tajikistan, and Albania); v) available serological data on the effect of secondary OPV immunity in  
17 the USA and Cuba (not shown); vi) indigenous emergence of cVDPVs (shown in Figure A2 for  
18 northern India, NW Nigeria (both serotype 2), Haiti, and Madura in Indonesia (both serotype 1);  
19 and vii) no indigenous emergence of cVDPVs in all other situations and serotypes (die-out of  
20 serotype 1 OPV-related viruses shows in Figure A2 for Cuba and Haiti). We subsequently  
21 applied the model to successfully reproduce the asymptomatic transmission of an imported  
22 WPV1 in Israel in 2013.<sup>31, 45, online supplement pp. 1-2</sup>

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26 Most critically in the context of certification questions, the DEB model approximates  
27 interruption of live poliovirus transmission (i.e., of an OPV, WPV, vaccine-derived poliovirus  
28 (VDPV), or OPV-related strain) in a population to occur when the effective infectiousness-  
29 weighted proportion of the population infectious with that poliovirus drops below 5 per million  
30 people (i.e., the transmission threshold  $EPI^*$ ).<sup>2</sup> While this simplifies the true die-out behavior,  
31 which depends on local heterogeneity and chance, it appears capable of generating WPV die-out  
32 times consistent with observations in a broad range of settings.<sup>2, 30, 31, 41</sup> Moreover, when applied  
33 to the persistence of OPV-related viruses that evolve to fully transmissible and neurovirulent  
34 circulating VDPVs (cVDPVs), the approximation produces cVDPV outbreaks for conditions in  
35 which they occurred (e.g., in Hispaniola<sup>46</sup> and Nigeria<sup>47</sup>) and no cVDPV outbreaks for conditions  
36 in which they did not occur despite OPV use and cessation (e.g., in Cuba<sup>48</sup> and the USA<sup>49</sup>).<sup>2</sup>

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40 Use of the hypothetical model clarified that under-vaccinated subpopulations can sustain  
41 poliovirus transmission independently despite high coverage in the surrounding general  
42 population and showed how the minimum coverage needed to interrupt transmission depends on  
43 the degree of isolation and the relative size of the under-vaccinated subpopulation.<sup>38</sup> To explore  
44 the role of hard-to-reach under-vaccinated subpopulations for certification questions, we  
45 modified the hypothetical model in two ways and added a stochastic layer on top of the DEB  
46 model to simulate polio case detections. The first modification consisted of desynchronizing the  
47 time when vaccination starts in the general and under-vaccinated subpopulations to simulate the  
48 concept of a population that remains inaccessible for an extended period of time. Specifically,  
49 we run the model, which assumes equal birth and death rates and thus no population growth  
50 (Table 1), without vaccination for 30 years to settle into the endemic equilibrium, and then  
51 instantly change the routine immunization coverage in the general population with three OPV  
52 doses to 0.95, which lies well above the threshold of 0.92 needed to interrupt transmission in a  
53 closed population with similar characteristics.<sup>38</sup> However, we assume that the under-vaccinated  
54 subpopulation initially remains completely unreached by vaccination, with vaccine introduction  
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3 in the under-vaccinated subpopulation occurring 10 years after vaccine introduction in the  
4 general population. Desynchronizing the introduction of vaccination affects the dynamics and  
5 effectively makes it more difficult to interrupt transmission after introducing vaccination in the  
6 last subpopulation. To offset this effect, we consider a different hypothetical population with a  
7 slightly higher average per-dose take rate for OPV of 0.6 instead of 0.5 in the original analysis<sup>38</sup>  
8 (e.g., due to lower exposure to enteric viruses that interfere with vaccine take<sup>50</sup>). As in the  
9 original analysis,<sup>38</sup> we vary the coverage in the under-vaccinated subpopulation, the relative size  
10 of the under-vaccinated subpopulation compared to the total population, and the degree of  
11 preferential mixing, characterized by the proportion of potentially infectious contacts of  
12 individuals in the under-vaccinated subpopulations with other individuals in the same  
13 subpopulation ( $p_{\text{within}}$ ).  
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17 Figure A3 shows the behavior of the incidence of infections in fully susceptible individuals and  
18 infants born with maternal immunity as a function of the varied DEB model inputs. Generally,  
19 the model yields incidence proportional to population size before vaccination starts. After the  
20 introduction of vaccination with high coverage in the general population, the initially still  
21 unvaccinated subpopulation becomes the main contributor to the total incidence. However, with  
22 less than 100% coverage in the general population and some interaction between the two  
23 populations (i.e.,  $p_{\text{within}} < 1$ ), some incidence continues to occur in the general population as  
24 exported viruses find unvaccinated individuals. Lower values of  $p_{\text{within}}$  imply more interaction  
25 between the two populations and result in more incidence in the general population before  
26 vaccination in the under-vaccinated subpopulation begins (middle column of Figure A3). The  
27 relative size of the under-vaccinated subpopulation also affects the extent to which the under-  
28 vaccinated subpopulation affects the general population (right column of Figure A3). With base  
29 case model inputs, the minimum coverage in the under-vaccinated subpopulation to interrupt  
30 transmission equals 0.82. Higher coverage values mean interruption occurs sooner after the  
31 introduction of vaccination in the under-vaccinated subpopulation, while lower coverage values  
32 mean that transmission continues and can eventually rebound and settle into a new equilibrium  
33 (left column in Figure A1).  
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38 While the prior approach used fully stochastic transmission models to randomly generate  
39 infections, die-out, and polio cases and detections,[19-22] for efficiency we use post-hoc  
40 processing of DEB model results to randomly generate only the times when polio cases and  
41 detections stochastically occur. Specifically, for each setting of the DEB model, we record the  
42 deterministic realization of the daily incidence of infections in fully susceptible individuals of  
43 any age and 50% of infants less than 3 months of age born with maternal immunity, which  
44 represent the only individuals at risk of becoming a polio case in the DEB model.[2] We then  
45 randomly determine the number of polio cases resulting from the infection incidence on each day  
46 using a Poisson draw with a rate equal to the infection incidence multiplied by the PIR. For each  
47 generated case, we use a separate uniform random draw to determine whether it results in a  
48 detection based on each of the detection probabilities in Table 1 (e.g., a random uniform draw of  
49 0.45 would mean that the case results in a detection only for detection probabilities of more than  
50 0.45). For each DEB model setting, we repeat the post-hoc stochastic process 10,000 times and  
51 we start generating cases 10 years before vaccination starts in the general population, which we  
52 assume starts vaccination 10 years earlier than the under-vaccinated subpopulation (see  
53 appendix). The precise choice of when to start randomly generating cases exerts negligible  
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3 influence on the results as long as it occurs before cases become rare (i.e., before the interval  
4 between cases becomes longer). For simplicity, although prior work showed the significant role  
5 of serotype differences and seasonality,[20, 22] the hypothetical model inputs reflect WPV1 and  
6 assumes no seasonality. A limitation arises from the direct scaling of the DEB model with  
7 absolute population size, such that die-out depends on the effective proportion of infectious  
8 individuals rather than the absolute number. Using the post-hoc stochastic analysis, the absolute  
9 population size affects the number of infections, which affects the typical interval between  
10 detected cases. We show that CNC95% increases substantially for smaller absolute population  
11 sizes.  
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15 Our initial findings motivated analysis of the minimum population size that can sustain WPV  
16 circulation on its own to determine whether the upper bound on the CNC95% of 9 years could  
17 occur in real populations. However, for population sizes far below 100,000, the DEB model  
18 becomes inadequate because it allows prevalence to remain above the die-out threshold even  
19 with only fractional numbers of infections (i.e., less than one infected person). Therefore, we  
20 used a fully stochastic model to explore questions of minimum population size. We run the  
21 model 10,000 times for different population sizes and initial conditions and report the  
22 distribution of the duration of circulation and the CNC95%.  
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### 25 **Exploration of the causal interactions relevant to global WPV certification decisions with** 26 **an influence diagram (Figure 5)** 27

28 Table A2 provides indicative estimates of the key quantities in Figure 5, based on the literature.  
29 Figure 5 assumes that policy makers explicitly or implicitly set a *desired confidence about no*  
30 *WPV circulation at OPV cessation*. In reality, they may focus on the confidence at certification,  
31 but given that it takes some fixed *preparation time needed between certification and OPV*  
32 *cessation*, any set confidence at the time of certification corresponds to some *desired confidence*  
33 *about no WPV circulation at OPV cessation*. A higher desired confidence level implies a longer  
34 *time between last detection and certification*. This time decreases with increasing investments in  
35 immunization and surveillance from the *GPEI budget through population immunity maintenance*  
36 and the *perceived pre-certification surveillance quality*, respectively. The main drawback of a  
37 longer *time between last detection and OPV cessation* comes in the form of longer OPV use in  
38 most countries, which results in *planned immunization costs* and *OPV-related pre-cessation*  
39 *polio cases* (i.e., vaccine-associated paralytic polio and VDPVs). In addition, with some  
40 globally-recommended or nationally-preferred *duration of IPV after OPV cessation*, later OPV  
41 cessation would imply greater overall IPV costs, because global IPV use already started (i.e.,  
42 only the end, and not the beginning of IPV use depends on the timing of cessation of the last  
43 OPV serotypes). These drawbacks together lead to *financial and societal costs of planned*  
44 *immunization*. This includes the monetary equivalent of the *OPV-related polio cases*, which  
45 depends on the country income-level-dependent *societal costs per polio case*.  
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50 On the left side of Figure 5, we see the benefits of setting a higher *desired confidence about no*  
51 *WPV circulation at OPV cessation*. A higher confidence implies a lower *probability of a WPV*  
52 *reemergence after OPV cessation* (all else being equal). However, this probability does not  
53 directly equal the reciprocal of the confidence in the event of a *gap between perceived and actual*  
54 *surveillance quality*. Specifically, if the *perceived pre-certification surveillance quality* exceeds  
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3 the *actual pre-certification surveillance quality*, then the true *probability of WPV reemergence*  
4 *after OPV cessation* equals more than 1 minus the *desired confidence about no WPV circulation*  
5 *at OPV cessation*, and vice versa. This potential discrepancy highlights the importance of  
6 continued assessment of surveillance quality and assurance of high surveillance quality. A lower  
7 *GPEI budget* also decreases *population immunity maintenance* and thus increases the *probability*  
8 *of WPV reemergence after OPV cessation*, which implies an increase in *expected WPV*  
9 *reemergence outbreaks*. Unlike other possible types of post-cessation outbreaks, a WPV  
10 reemergence would almost certainly occur in the most challenging populations. Any such  
11 reemergences would lead to *expected polio cases due to WPV reemergence outbreaks* and  
12 *expected costs to respond to WPV emergence outbreaks*. The expected costs and cases decrease  
13 with higher *post-cessation surveillance quality*, which affects the extent of viral spread at the  
14 time of outbreak detection (and beyond), and with a better *outbreak response quality and*  
15 *timeliness*, which both increase the probability of effective outbreak control.<sup>51</sup> However, the  
16 occurrence of any outbreaks comes with some probability of uncontrolled outbreaks, either by  
17 failing to control the original outbreak virus, or by creating new cVDPV outbreaks with the OPV  
18 vaccine used in the response. This implies some *probability of OPV restart due to WPV*  
19 *reemergences*, which would carry very significant *expected costs due to an OPV restart*  
20 *triggered by WPV reemergence* and *expected cases due to an OPV restart triggered by WPV*  
21 *emergence* (Table A2). For moderate or high *probability of OPV restart due to WPV*  
22 *reemergences*, the resulting *expected costs due to OPV restarts triggered by WPV reemergence*  
23 and *expected cases due to OPV restarts triggered by WPV reemergence* would likely dwarf the  
24 costs and cases associated with any controlled outbreaks due to WPV reemergences and would  
25 therefore drive the *expected financial and societal costs of possible WPV reemergences*.  
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31 Together with the *surveillance costs*, which act to moderate the costs of delayed OPV cessation  
32 or premature OPV cessation, the *expected financial and societal costs of possible WPV*  
33 *reemergences* and the *financial and societal costs of planned immunization* together make up the  
34 *total financial and societal costs (associated with any given desired confidence about no WPV*  
35 *circulation at OPV cessation)*. The costs of possible WPV emergences and the costs of planned  
36 immunization move in opposite directions as a function of the *desired confidence about no*  
37 *circulation at OPV cessation*.  
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40 Figure 5 also highlights the consequences of the GPEI already scaling down some of its  
41 supplemental immunization and surveillance activities. While scaling down saves costs in the  
42 short term, doing so could lead to larger long-term costs by delaying certification and OPV  
43 cessation (i.e., requiring higher confidence about no circulation), which would imply that OPV  
44 cessation could occur in the context of lower global population immunity to transmission and  
45 lower ability to rapidly detect outbreaks. This ultimately implies an increase in the expected  
46 *total financial and societal costs (associated with any given desired confidence about no WPV*  
47 *circulation at OPV cessation)*. For visual simplicity, Figure 5 omitted some additional  
48 complexity involved in this decision. Furthermore, given that the confidence about no  
49 circulation increases with time after the last detection, we could have equivalently centered  
50 Figure 5 around finding the optimal time between the last detection and certification or OPV  
51 cessation. The amounts in Table A2 highlight the significant financial and humanitarian stakes  
52 involved in finding the optimal *desired confidence about no WPV circulation at OPV cessation*.  
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**Table A1: Generic inputs of the DEB model<sup>2 30</sup> (adopted from the online supplement of Duintjer Tebbens et al., 2017<sup>45</sup>)**

Model input (symbol)	Best estimate	Source
Relative susceptibility ( $\sigma$ ) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.78;0.79;0.77 0.91;0.92;0.90 0.80;0.80;0.79 0.72;0.72;0.71 0.42;0.43;0.41 0.21;0.22;0.20 0.21;0.22;0.20	52 53
Duration of latent period ( $\xi^{fec}$ or $\xi^{oro}$ , in days)	$\sim 3^a$	52 53
Duration of fecal infectiousness ( $\gamma^{fec}$ , in days) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Fully susceptible</li> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	28.0;27.8;28.3 24.6;24.6;24.6 24.5;24.4;24.7 21.1;20.8;21.3 18.0;17.7;18.2 11.6;10.5;10.5 10.1;8.9;8.9 10.1;8.9;8.9	52 53
Duration of oropharyngeal infectiousness ( $\gamma^{oro}$ , in days) of recent immunity states (no serotype differences) <ul style="list-style-type: none"> <li>- Fully susceptible</li> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	13.4 11.9 9.9 6.6 6.1 5.0 3.7 3.7	52 53
Relative fecal infectiousness ( $\pi^{fec}$ ) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.96;0.96;0.95 0.92;0.92;0.91 0.70;0.69;0.68 0.61;0.59;0.59 0.39;0.43;0.43 0.20;0.23;0.23 0.20;0.23;0.23	52 53
Relative oropharyngeal infectiousness ( $\pi^{oro}$ ) of recent immunity states (no serotype differences) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.68 0.30 0.17 0.12 0.33 0.21 0.21	52 53
Number of infection stages <ul style="list-style-type: none"> <li>- Latent period (<math>r</math>)</li> <li>- Infectious period (<math>s</math>)</li> </ul>	2 4	
Relative weight of infection stages, compared to average weight over the infectious period ( $\theta_j, j=0, \dots, r+s-1$ )		52 53

- Infection stage 0 and 1 (latent stages)	0	
- Infectious stage 2	12/17	
- Infectious stage 3	40/17	
- Infectious stage 4	12/17	
- Infectious stage 5	4/17	
IPV immunity delay ( $\phi$ , in days)	7	54
Number of waning stages ( $nw$ )	5	
Shape of waning function ( $z_w$ )	5	52 53
Average time to reach last waning stage ( $\rho$ , in days)		52 53
- Type 1&2	4×365	
- Type 3	3×365	
Average time for maternal immunes to wane to fully susceptible ( $\rho_{MI}$ , in days)	0.25×365	52 53
Relative susceptibility ( $\sigma$ ) for last waning stage (no serotype differences)		52 53
- 1 successful IPV	1.0	
- 2 successful IPV	1.0	
- $\geq 3$ successful IPV	1.0	
- 1 LPV infection	0.8	
- $\geq 2$ LPV infections	0.7	
- IPV and LPV	0.7	
Duration of fecal infectiousness ( $\gamma^{fec}$ , in days) of last waning stage (for PV1;PV2;PV3)		52 53
- 1 successful IPV	26.6;26.4;26.9	
- 2 successful IPV	25.2;25.0;25.5	
- $\geq 3$ successful IPV	23.8;23.6;24.1	
- 1 LPV infection	14.0;13.9;14.1	
- $\geq 2$ LPV infections	11.4;11.4;11.6	
- IPV and LPV	11.4;11.4;11.6	
Duration of oropharyngeal infectiousness ( $\gamma^{oro}$ , in days) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	11.4	
- 2 successful IPV	6.7	
- $\geq 3$ successful IPV	6.6	
- 1 LPV infection	6.7	
- $\geq 2$ LPV infections	4.0	
- IPV and LPV	4.0	
Relative fecal infectiousness ( $\pi^{fec}$ ) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	0.95	
- 2 successful IPV	0.9	
- $\geq 3$ successful IPV	0.85	
- 1 LPV infection	0.5	
- $\geq 2$ LPV infections	0.3	
- IPV and LPV	0.3	
Relative oropharyngeal infectiousness ( $\pi^{oro}$ ) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	0.43	
- 2 successful IPV	0.25	
- $\geq 3$ successful IPV	0.13	
- 1 LPV infection	0.5	
- $\geq 2$ LPV infections	0.3	
- IPV and LPV	0.3	
Number of reversion stages ( $h$ )	20	
Shape of reversion function with respect to:		
- $R_0(z_r)$	1	
- $\ln(\text{PIR})(z_p)$	2.5	

Average time to reach last reversion stage ( $\varepsilon$ , in days) (for PV1;PV2;PV3)	620.5; 408; 620.5	<sup>30</sup>
Paralysis-to-infection ratio for fully susceptible individuals infected with OPV ( $PIR_0$ ) (for PV1; PV2;PV3)	$0.26 \times 10^{-6}$ ; $1.2 \times 10^{-6}$ ; $1.8 \times 10^{-6}$	
Paralysis-to-infection ratio for fully susceptible individuals infected with FRPV ( $PIR_{h-1}$ ) (for PV1; PV2;PV3)	0.005; 0.0005; 0.001	<sup>2 14 54</sup>
Relative $R_0$ of OPV vs. FRPV ( $\tau_0$ ) (for PV1; PV2; PV3)	0.37;0.55;0.25	<sup>2 52 53</sup>
Effective infectious proportion below which we assume 0 force-of-infection (transmission threshold $EPI^*$ )	5/1,000,000	
Relative PIR for maternally immunes compared to fully susceptible individuals ( $RPIR_{M1}$ )	0.5	
Ratio of $R_0$ by serotype in the same setting (PV1:PV2:PV3)	1:0.9:0.75	<sup>30</sup>
Average incubation period ( $\delta$ , in days)	10	<sup>54 55</sup>
Demographics for all situations	Time series 1950-2100	<sup>56</sup>

**Acronyms:** CDC = (U.S.) Centers for Disease Control and prevention; cVDPV = circulating vaccine-derived poliovirus; DEB = differential equation-based FRPV = fully-reverted poliovirus; GPLN = Global Polio Laboratory Network; IPV = inactivated poliovirus vaccine; LPV = live poliovirus; OPV = oral poliovirus vaccine; PIR = paralysis-to-infection ratio; PV(1,2,3) = poliovirus (type 1, 2, or 3, respectively);  $R_0$  = basic reproductive number; UN = United Nations; USA = United States of America; VAPP = vaccine-associated paralytic poliomyelitis; VP1 = viral protein 1; WPV(1,2,3) = wild poliovirus (type 1, 2, or 3, respectively)

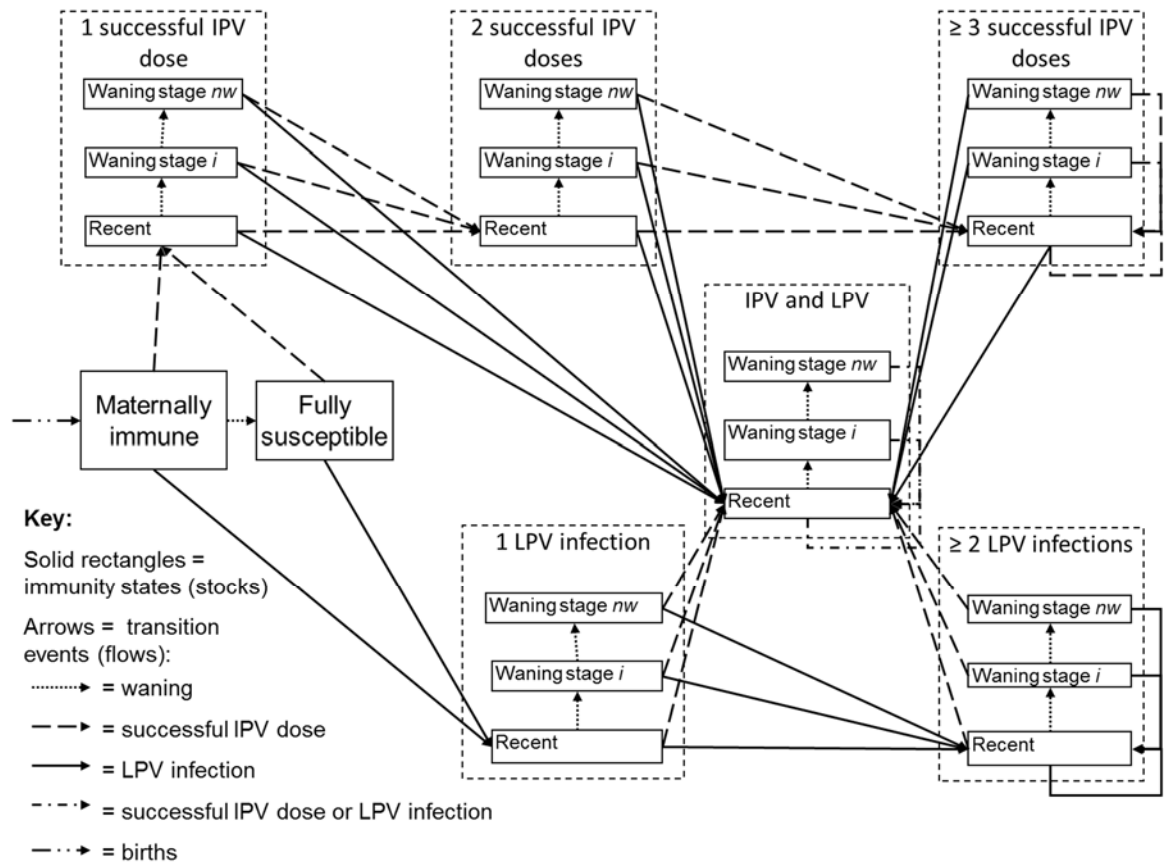
**Notes:** <sup>a</sup> Mean estimates obtained from experts and used in the model for the different immunity states, serotypes, and excretion modes vary between 2.85 and 3.37 days

**Table A2: Indicative estimates of key variables from Figure 5**

Variable	Estimate	Notes and sources
Preparation time needed between certification and OPV cessation	Approximately 1 year	Depends on when setting of the OPV cessation date occurs relative to certification <sup>57</sup>
Planned immunization costs	\$1 billion in external GPEI funds per year, plus internal contributions	Most of the \$1.1 billion GPEI budget for 2016 was for immunization and coordination of activities; <sup>58</sup> Countries may internally contribute at a similar rate as the external contributions; <sup>59</sup> The current GPEI budget projects a decrease from 2018 forward, which would imply some offset of costs for maintenance of activities, or alternatively the activities previously supported by external contributions may end, which would imply declines in programmatic activities and quality
OPV-related polio cases	Hundreds per year	Vaccine-associated paralytic polio cases, <sup>60</sup> which depends on timing of IPV doses, <sup>61</sup> and presumably local cVDPV outbreaks <sup>62</sup>
Surveillance costs	Around \$100 million per year	The 2016 GPEI budget included \$67 million in external support for surveillance and laboratories, <sup>58</sup> with additional significant internal contributions by countries <sup>59 63</sup>
Probability of OPV restart due to WPV reemergence	Unknown	Prior studies estimated an approximately 5% chance of an OPV restart due primarily to OPV-associated risks, although the actual implementation of risk management policies was not as good as suggested by these models. <sup>59 64</sup>
Immunization costs associated with an OPV restart	\$ billions (hundreds of millions per year)	An OPV restart would involve reintroduction of OPV vaccination in most countries in perpetuity, with supplemental immunization activities needed in countries with insufficient routine immunization coverage. <sup>59</sup> Significant uncertainty exists about what an OPV restart would look like in practice.
Expected cases due to an OPV restart	Up to thousands per year	Reintroduction of OPV in most countries would result in hundreds of vaccine-associated paralytic polio cases per year and could result in continued cVDPV outbreaks in countries with insufficient routine immunization coverage that do not conduct regular preventive supplemental immunization activities. <sup>59 64</sup>

**Figure A1: Schematic of the DEB model structure, adopted from Duintjer Tebbens et al. (2013)<sup>2</sup>, p. 706**

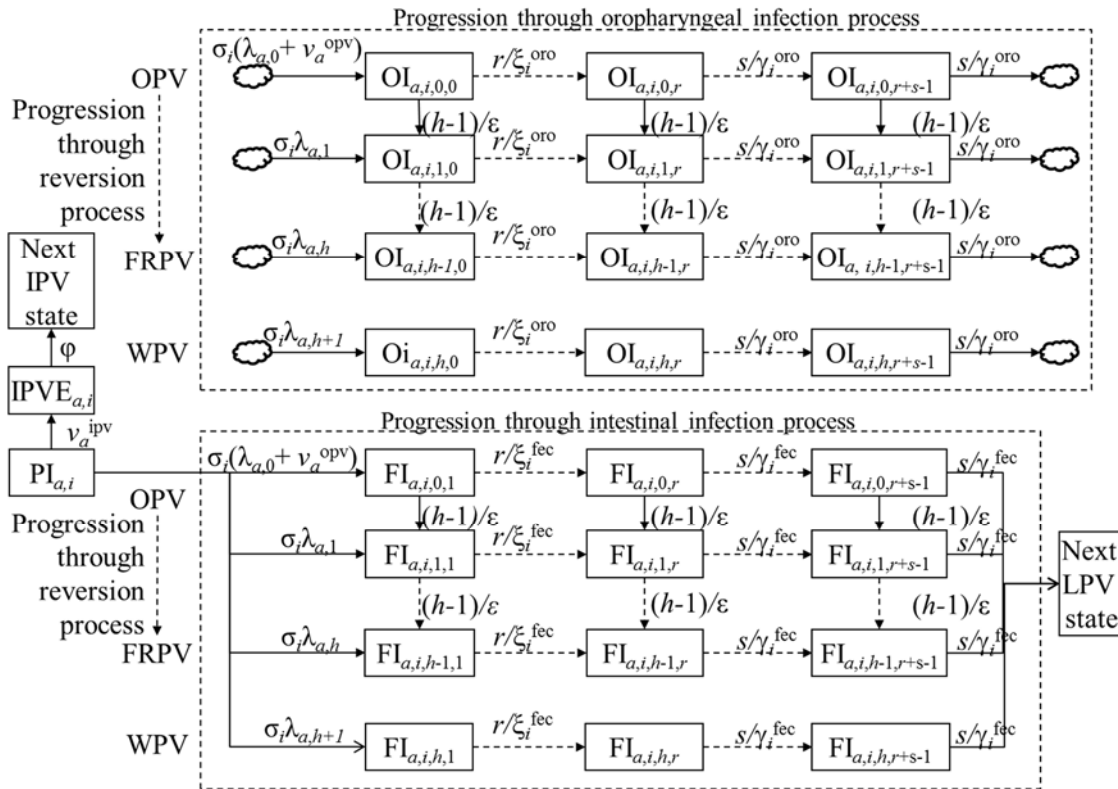
**(a) Immunity states and flows between them due to epidemiological events**



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## (b) Progression through infection and reversion stages



“**Acronyms:** FRPV = fully-reverted poliovirus; IPV = inactivated poliovirus vaccine; OPV = oral poliovirus vaccine; WPV = wild poliovirus; **Symbols:**  $PI_{a,i}$  = partially infectible in age group  $a$  and immunity state  $i$ ;  $IPVE_{a,i}$  = IPV-exposed individual from immunity state  $i$  and age group  $a$ ;  $FI_{a,i,j,k}$  ( $OI_{a,i,j,k}$ ) = individual in age group  $a$  from immunity state  $i$ , infected with virus strain  $j$  and in fecal (oropharyngeal) infection stage  $k$ ;  $\lambda_{a,j}$  = force-of-infection to age group  $a$  for virus strain  $j$ ;  $v_a^{ipv}$  ( $v_a^{opv}$ ) = force-of-IPV(OPV)-vaccination to age group  $a$  as a result of routine and supplementary immunization;  $\sigma_i$  = relative susceptibility for immunity state  $i$ ;  $\xi_i^{fec}$  ( $\xi_i^{oro}$ ) = average duration of the fecal (oropharyngeal) latent period for immunity state  $i$ ;  $\gamma_i^{fec}$  ( $\gamma_i^{oro}$ ) = average duration of the fecal (oropharyngeal) infectious period for immunity state  $i$ ;  $\varphi$  = IPV immunity delay;  $h$  = number of reversion stages;  $r$  = number of latent stages;  $s$  = number of infectious stages”<sup>2</sup>, p. 706

Figure A2: Summary results from the model calibration process, adapted from Duintjer Tebbens et al. (2013)<sup>2</sup>

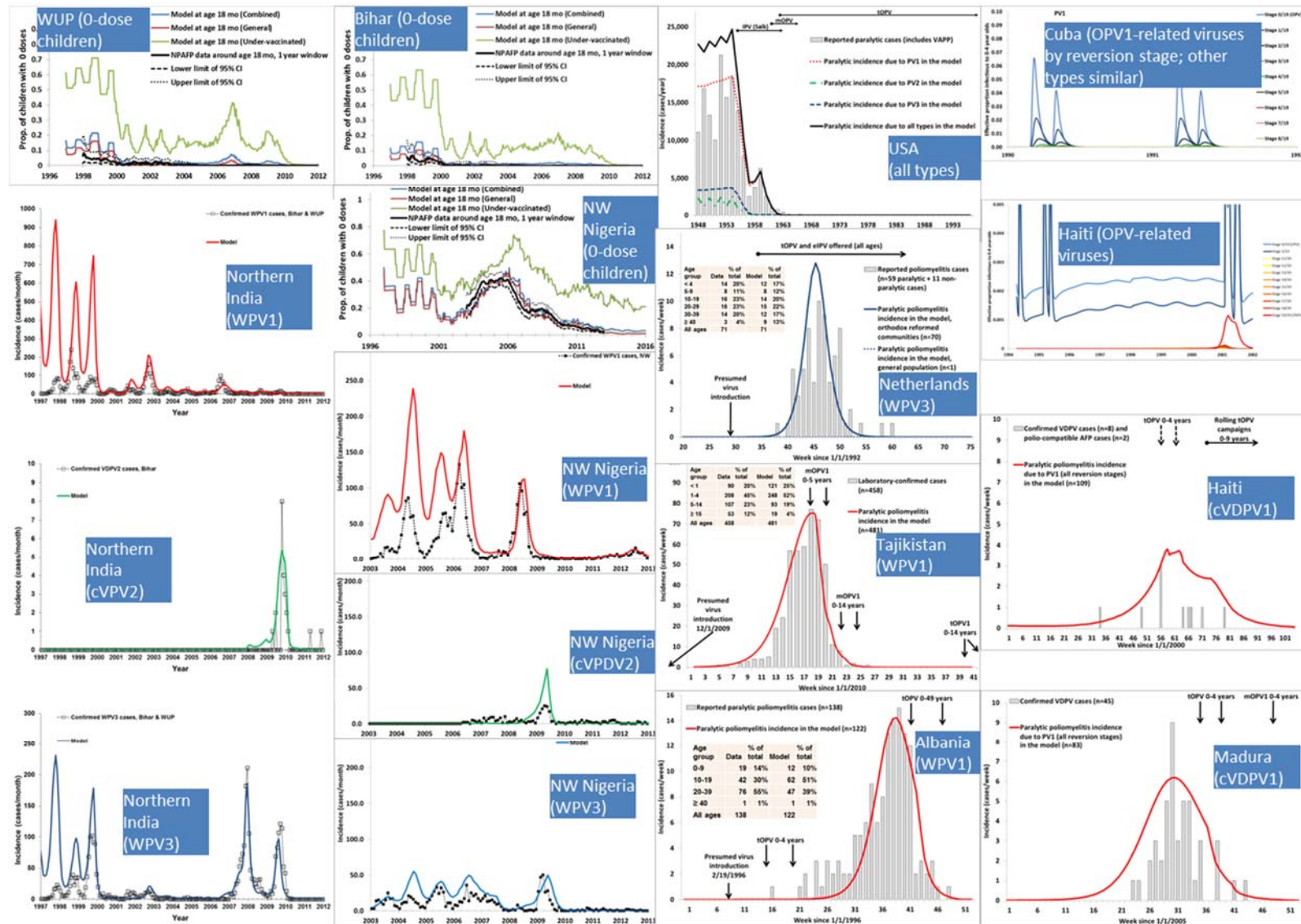
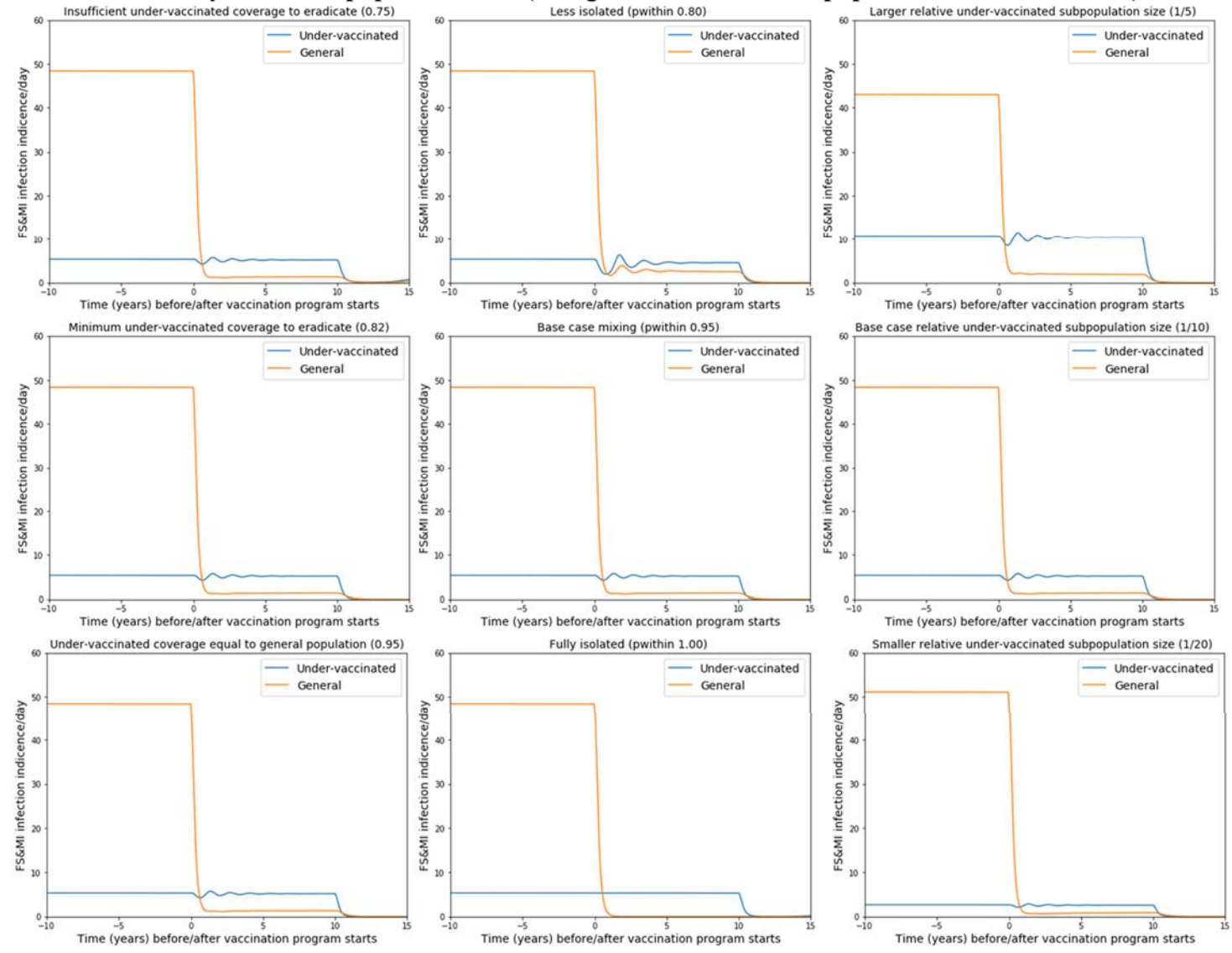




Figure A3: Differential-equation based model results for base case model inputs and varied coverage (left column), varied degree of isolation with coverage 0.82 (middle column), and varied relative size with coverage of 0.82 (right column). The y-axis scales linearly with total population size (all figures assume a total population size of 1 million).



# BMJ Open

## Global certification of wild poliovirus eradication: Insights from modeling hard-to-reach subpopulations and confidence about the absence of transmission

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Manuscripts

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3 1 **Global certification of wild poliovirus eradication: Insights from modeling hard-to-reach**  
4 **subpopulations and confidence about the absence of transmission**  
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8 4 Radboud J. Duintjer Tebbens,<sup>1</sup> Dominika A. Kalkowska,<sup>1</sup> Kimberly M. Thompson<sup>1</sup>  
9 5

10 6 1. Kid Risk, Inc., Columbus, OH, USA  
11 7  
12 7

13 8 Running title: **Poliovirus certification confidence**  
14 9

15 10 Correspondence to: Kimberly M. Thompson, Kid Risk, Inc., 605 N High St, #253, Columbus,  
16 11 OH 43215, USA, Email: kimt@kidrisk.org  
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19 13 **Abstract:**

20 14 **Objective:** To explore the extent to which under-vaccinated subpopulations may influence the  
21 15 confidence about no circulation of wild poliovirus (WPV) after the last detected case.  
22 16

23 17 **Design and participants:** We used a hypothetical model to examine the extent to which the  
24 18 existence of an under-vaccinated subpopulation influences the confidence about no WPV  
25 19 circulation after the last detected case as a function of different characteristics of the  
26 20 subpopulation (e.g., size, extent of isolation). We also used the hypothetical population model to  
27 21 inform the bounds on the maximum possible time required to reach high confidence about no  
28 22 circulation in a completely-isolated and unvaccinated subpopulation starting either at the  
29 23 endemic equilibrium or with a single infection in an entirely susceptible population.  
30 24

31 25 **Results:** It may take over three years to reach 95% confidence about no circulation for this  
32 26 hypothetical population despite high surveillance sensitivity and high vaccination coverage in the  
33 27 surrounding general population if: (1) ability to detect cases in the under-vaccinated  
34 28 subpopulation remains exceedingly small, (2) the under-vaccinated subpopulation remains small  
35 29 and highly isolated from the general population, and (3) the coverage in the under-vaccinated  
36 30 subpopulation remains very close to the minimum needed to eradicate. Fully-isolated  
37 31 hypothetical populations of 4,000 people or less cannot sustain endemic transmission for more  
38 32 than 5 years, with at least 20,000 people required for a 50% chance of at least 5 years of  
39 33 sustained transmission in a population without seasonality that starts at the endemic equilibrium.  
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3 32 Notably, however, the population size required for persistent transmission increases significantly  
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5 33 for realistic populations that include some vaccination and seasonality and/or that do not begin at  
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7 34 the endemic equilibrium.

8 35 **Conclusions:** Significant trade-offs remain inherent in global polio certification decisions,  
9  
10 36 which underscore the need for making and valuing investments to maximize population  
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12 37 immunity and surveillance quality in all remaining possible WPV reservoirs.  
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15 39 **Strengths and limitations of this study:**

- 16  
17 40 • Demonstrates the somewhat limited but important role of under-vaccinated  
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19 41 subpopulations in the time required to achieve high confidence about no WPV  
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21 42 transmission after the last reported case.  
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23 43 • Highlights competing trends as time increases such that for smaller population sizes  
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25 44 continued transmission becomes exceedingly unlikely, while for larger population sizes  
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27 45 undetected circulation becomes less likely due to the higher frequency of cases and  
28  
29 46 greater chances of detection.  
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31 47 • Results underscore the importance of continued investments to maximize population  
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33 48 immunity and surveillance quality.  
34  
35 49 • Analyses remain limited by model assumptions, but in abstract provide insights relevant  
36  
37 50 to likely last poliovirus reservoirs.  
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39 51

38 52 **Keywords:** polio, eradication, certification, modeling  
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## 56 Background

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58 Achieving the 1988 World Health Assembly polio eradication goal of ending all cases of  
59 poliomyelitis<sup>1</sup> requires a successful transition from the interruption of the current low level of  
60 wild poliovirus (WPV) transmission through coordinated cessation of all use of live attenuated  
61 oral poliovirus vaccine (OPV) to effective long-term risk management. The Global Polio  
62 Laboratory Network supports the Global Polio Eradication Initiative (GPEI) by testing stool  
63 samples from acute flaccid paralysis (AFP) cases and sewage samples for polioviruses. As the  
64 GPEI approaches success, the transition to the polio endgame has begun. The endgame involves  
65 significant complexity, because all countries must achieve and maintain sufficient population  
66 immunity<sup>2-4</sup> to stop and prevent the transmission of three separate poliovirus serotypes (i.e., 1, 2,  
67 and 3) and globally coordinate cessation of each OPV serotype.<sup>5-7</sup> In September 2015, the  
68 Global Certification Commission declared successful eradication of serotype 2 WPV (WPV2),<sup>8</sup>  
69 which represented a prerequisite to the globally-coordinated cessation of all serotype 2-  
70 containing OPV use. Global cessation of serotype 2-containing OPV occurred in late April and  
71 early May 2016, during which time over 150 countries stopped using trivalent OPV (tOPV,  
72 which contains all three serotypes) and switched to bivalent OPV (bOPV, which contains only  
73 serotypes 1 and 3 OPV).<sup>9</sup>

74  
75 The Global Polio Laboratory Network reported the lowest number of annual paralytic serotype 1  
76 WPV (WPV1) cases in 2017,<sup>10</sup> and no serotype 3 WPV (WPV3) cases since November 2012.<sup>11</sup>  
77 Successful WPV eradication requires stopping all transmission, which manifests as an absence of  
78 detected WPVs despite actively looking. With increasing time of not seeing cases (while  
79 actively looking), confidence increases about WPV die-out. However, the absence of evidence is  
80 not evidence of absence. Extended silent transmission can occur, because most poliovirus  
81 infections do not lead to symptoms and surveillance gaps can exist. For example, a WPV3  
82 resurfaced in Sudan/Chad in 2004 after no reported cases during 1997-2003<sup>12</sup> and a WPV1  
83 resurfaced in Borno, Nigeria in 2016 after nearly 3 years with no reported cases<sup>13</sup>. The average  
84 paralysis-to-infection ratio (PIR), defined as the fraction of infections in fully susceptible  
85 individuals that leads to paralytic poliomyelitis (polio) symptoms, equals approximately 1/200,  
86 1/2000, and 1/1000, for serotype 1, 2, and 3 WPV, respectively.<sup>14</sup> The last reported naturally-

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3 87 occurring WPV2 case occurred in India in 1999,<sup>15</sup> and since then, only two episodes of WPV2  
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5 88 infections occurred that traced back to laboratory strains.<sup>16 17</sup> Despite the possibility of silent  
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7 89 circulation, the absence of any naturally-occurring WPV2 cases for over 15 years (and in many  
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9 90 countries for many decades) led to very high confidence about the die-out of WPV2  
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11 91 transmission.  
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13 92  
14 93 Multiple prior mathematical modeling studies explored the probability of undetected circulation  
15 94 of WPVs in the absence of reported cases or other poliovirus detections. Polio eradication  
16 95 efforts in the Americas, which reported the last indigenous WPV case of any serotype in Peru in  
17 96 1991,<sup>18</sup> motivated the first analysis and discussion of certification requirements. A statistical  
18 97 analysis of Pan American Health Organization epidemiological data reported less than a 5%  
19 98 chance of undetected indigenous WPV circulation after 4 years since the last reported confirmed  
20 99 case.<sup>19</sup> A simple, stochastic model of poliovirus transmission and die-out characterized the  
21 100 probability of undetected poliovirus circulation in a hypothetical, homogeneously mixed  
22 101 population of 200,000 people in a relatively low-income country, and estimated that not  
23 102 observing a case for 3 years provided 95% confidence about local extinction of WPV  
24 103 infections.<sup>20</sup> This seminal paper provided the foundation for appropriate characterization of the  
25 104 probability of undetected circulation as a function of the time since the last detected case.<sup>20</sup>  
26 105 Related modeling also explored theoretical thresholds to stop transmission<sup>21</sup> and estimated a  
27 106 minimum population size for persistent transmission of 50,000-100,000 in developing countries  
28 107 and over 200,000 in developed countries required to achieve at least 95% probability of  
29 108 poliovirus persistence for 5 years or more in the absence of vaccination.<sup>22</sup> These studies  
30 109 supported the 2004-8 GPEI Strategic Plan requirement of at least 3 years of no polio cases  
31 110 detected by AFP surveillance for certification,<sup>23</sup> which remains the current minimum  
32 111 requirement.<sup>24</sup> A 2012 study<sup>25</sup> relaxed some of the assumptions of the prior theoretical model<sup>20</sup>  
33 112 and highlighted that the probability of undetected circulation varied for different poliovirus  
34 113 serotypes, places, and conditions, which suggested the need to focus on appropriate  
35 114 characterization of conditions in the last likely WPV reservoirs.<sup>25</sup> A 2015 study<sup>26</sup> also used the  
36 115 prior model<sup>20</sup> to show that in the context of an instantaneous introduction of vaccination, the  
37 116 time of the last case relative to vaccine introduction further informs the confidence about the  
38 117 absence of circulation.  
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5 119 Subsequent analyses focused on modeling the conditions in specific and more realistic  
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7 120 populations. A 2015 study<sup>27</sup> used a previously-developed poliovirus dynamic transmission  
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9 121 model<sup>2</sup> applied to: recently-endemic transmission in two states in northern India,<sup>28</sup> endemic  
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11 122 transmission in northwest Nigeria,<sup>29</sup> a 2010 outbreak in Tajikistan,<sup>30</sup> and transmission following  
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13 123 a 2013 WPV1 introduction into Israel detected by environmental surveillance.<sup>31</sup> The study  
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15 124 characterized the confidence about no undetected poliovirus circulation by serotype as a function  
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17 125 of time without reported polio cases or environmental detections considering realistic  
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19 126 assumptions for surveillance, immunization, and other national inputs.<sup>27</sup> The results suggested  
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21 127 that time periods of 0.5 to 3 years without detected polio cases provided 95% confidence about  
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23 128 the interruption of transmission in the context of perfect AFP surveillance depending on  
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25 129 situation-specific characteristics (e.g., the overall population immunity, endemic versus outbreak  
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27 130 conditions, and virus serotype).<sup>27</sup> This model also suggested longer times required for less-than-  
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29 131 perfect AFP surveillance and potentially shorter times using highly-sensitive environmental  
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31 132 surveillance based on the experience in Israel.<sup>27</sup> A recent statistical analysis of the 2013 WPV1  
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33 133 outbreak in Israel demonstrated a rapid increase in confidence about no undetected local  
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35 134 transmission following outbreak response immunization after repeated negative environmental  
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37 135 surveillance samples in a city.<sup>32</sup> A non-dynamic, statistical model<sup>33</sup> estimated a shorter time  
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39 136 (compared to<sup>27</sup>) of 14 months required to reach high confidence about no undetected circulation.  
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41 137 For its most conservative assumptions about surveillance and force-of-infection, the study  
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43 138 estimated a probability of 93% of a WPV-free Africa in the absence of any new WPV cases  
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45 139 reported by the end of 2015,<sup>33</sup> shortly before the WPV reemerged.<sup>13</sup> Contrasting with all other  
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47 140 modeling studies, a recent study<sup>34</sup> suggested a relatively high probability of undetected  
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49 141 circulation after more than 3 years without any polio cases in small populations, although a  
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51 142 correction to that analysis emphasized the unrealistic nature of one of the assumptions.<sup>35</sup>  
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53 143 Remarkably, the analysis reported that closed populations of 10,000 people or fewer could  
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55 144 support many years of transmission in the absence of vaccination, and experience gaps between  
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57 145 polio cases of over 5 years.<sup>34</sup> A reanalysis of this hypothetical model identified issues with the  
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59 146 analysis and its framing, and reported results consistent with the prior literature after correcting  
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147 for some errors.<sup>36</sup>  
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3 149 Although the modeling results demonstrated the critical importance of sustaining high population  
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5 150 immunity through immunization programs and high-quality surveillance to obtain high  
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7 151 confidence about no undetected circulation, the current GPEI strategic plan only covers 2013-  
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9 152 2018,<sup>6</sup> which leads to uncertainty about the ability to sustain high program performance after  
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11 153 2018. As of mid-2018, questions continue to arise about when the GPEI will cease to exist and  
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13 154 what resources will be available to support the polio endgame, including the certification of  
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15 155 eradication of WPV1 and WPV3 with high confidence. The GPEI partners already began  
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17 156 transition planning, and this process already led to some downsizing of national poliovirus  
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19 157 programs, including the reduction of some AFP surveillance activities.<sup>37</sup> Thus, while the prior  
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21 158 modeling assumed strong GPEI and national polio program performance up through the end of  
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23 159 the polio endgame, this assumption now appears optimistic, and further analyses that explore the  
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25 160 impact of lower quality surveillance may prove useful in the context of global certification  
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27 161 decisions for WPV1 and WPV3 eradication. Further motivation for developing models to  
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29 162 support certification decisions comes from the re-appearance of WPV1 in security-compromised  
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31 163 areas in Borno, Nigeria after apparent interruption, which raised questions about the ability of  
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33 164 poliovirus circulation without detection in communities not (or poorly) accessed by  
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35 165 immunization and surveillance efforts within larger populations with high immunity and good  
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37 166 surveillance.

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39 167  
40 168 This study aims to support future decisions about WPV certification by: (1) informing  
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42 169 confidence about the absence of circulation by modeling the role of hard-to-reach populations,  
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44 170 (2) examining the minimum population size required to sustain poliovirus transmission, and (3)  
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46 171 developing a conceptual framework to provide some structure for future certification decisions.  
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## 49 173 **Methods**

50 174  
51 175 To inform confidence about the absence of circulation by modeling the role of hard-to-reach  
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53 176 populations, we explored the impact of key assumptions using an existing model of a  
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55 177 hypothetical population comprised of a well-vaccinated general population and an under-  
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57 178 vaccinated subpopulation.<sup>38</sup> Table 1 lists the model inputs used to characterize this hypothetical  
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59 179 population and explore the role of key assumptions (see appendix for model details). To explore

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3 180 different population characteristics, we varied the total population size, the size of the under-  
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5 181 vaccinated subpopulation, and the degree of mixing between the under-vaccinated and general  
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7 182 population around a base case indicated by the bold values in Table 1. In addition, for each  
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9 183 variation around the base case, we simultaneously varied the routine immunization coverage and  
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11 184 detection probability per polio case in the under-vaccinated subpopulation. We interpret the total  
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13 185 hypothetical population as one epidemiological block (e.g., a country) and therefore compute the  
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15 186 confidence about no circulation based on all detections that occur in the general population and  
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17 187 under-vaccinated subpopulation combined. However, we fix the detection probability in the  
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19 188 general population at 95% to characterize high-quality national surveillance while considering  
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21 189 lower detection probabilities only in the under-vaccinated subpopulation (Table 1).<sup>38</sup> To  
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23 190 estimate the confidence about no circulation in this conceptual model, we use a simplified  
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25 191 version (see appendix) of the stochastic approach developed by Eichner and Dietz (1996)<sup>20</sup> and  
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27 192 adopted by others.<sup>25-27</sup> We define the probability of undetected circulation after a given period of  
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29 193  $t$  months without a detection as the number of times in multiple stochastic simulations that  $t$   
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31 194 months went by without a detection despite continued circulation, divided by the total number of  
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33 195 times that  $t$  months went by without a detection (i.e., with or without continued circulation).  
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35 196 Intuitively, the fraction of all time periods of  $t$  months without a detection but with transmission  
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37 197 still ongoing should decrease as  $t$  increases, corresponding to an increasing probability of no  
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39 198 circulation. Confidence about no circulation equals one minus the probability of undetected  
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41 199 circulation. To visualize the impact of varying the model inputs, we focus on the time without a  
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43 200 detection until the confidence about no circulation first exceeds 95% (CNC95%).

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47 202 We revisit the question of silent transmission in small populations<sup>22 34 36</sup> using the hypothetical  
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49 203 population model<sup>38</sup> in an attempt to inform the bounds on the maximum possible CNC95%. To  
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51 204 do so, we ignore the general population and effectively assume a completely-isolated and  
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53 205 unvaccinated subpopulation and otherwise adopt the hypothetical population assumptions from  
54  
55 206 Table 1. We transform the DEB model to a stochastic form using the Gillespie algorithm,<sup>39</sup> as  
56  
57 207 described elsewhere,<sup>27</sup> and start either at the endemic equilibrium<sup>34</sup> or with a single infection in  
58  
59 208 an entirely susceptible population. Instead of modeling die-out using the transmission  
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61 209 threshold,<sup>27</sup> we allow transmission to continue until the infection prevalence becomes 0. This  
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63 210 complements the existing work<sup>22 34 36</sup> by providing a comparison to the same situation with a

211 more comprehensive model for poliovirus transmission,<sup>2</sup> adding consideration of the impact of  
212 the initial conditions, and adding the impact on confidence about no circulation.

213  
214 Finally, recognizing the complexity and inter-related nature of certification decisions, we  
215 developed an influence diagram to relate certification timing decisions to outcomes. The  
216 diagram provides a conceptual framework to support certification decisions and formulate  
217 decisions about the timing of certification as an optimization problem. The diagram uses  
218 conventions from causal loop diagrams<sup>40</sup> and specifies the directionality of relationships  
219 between variables using unidirectional arrows. The polarity or sign at the arrow head indicates  
220 whether increasing the variable at the base of the arrow increases (+) or decreases (-) the variable  
221 that the arrow points to with all else being equal.

222

### 223 *Patient and Public Involvement*

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225 This survey did not involve patients or public opportunities for engagement.

226

## 227 **Results**

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229 Figure 1 illustrates how the confidence about no circulation increases with time after the last  
230 detection as a function of the surveillance quality in the under-vaccinated subpopulation (i.e., the  
231 detection probability). Clearly, higher confidence implies the need to wait longer after the last  
232 detected case, and lower detection probabilities further increase the time required to reach a  
233 certain level of confidence (e.g., the 95% line). Figure 1 shows a relatively modest effect of the  
234 detection probability in the under-vaccinated subpopulation for this hypothetical model due to  
235 continued occurrence of cases in the general population for the assumed degree of mixing (see  
236 appendix).

237

238 Figure 2 shows the CNC95% values as a function of coverage and detection probability for the  
239 under-vaccinated subpopulation. The figure shows longer times required to reach CNC95%  
240 values with increasingly more isolated under-vaccinated subpopulations (left column, top to  
241 bottom), with decreasing relative sizes of the under-vaccinated subpopulation (middle column,

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3 242 top to bottom), and decreasing absolute sizes of a fully-isolated under-vaccinated subpopulation  
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5 243 (right column, top to bottom, note increased y-axis ranges). The panels in Figure 2 omit curves  
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7 244 for coverage values that do not result in eradication, because they do not allow for calculation of  
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9 245 any confidence about eradication. The panels also omit the data point for 0 detection probability  
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11 246 in the event of a fully-isolated under-vaccinated subpopulation, because that would imply no  
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13 247 ability to detect the virus. Consistent with previous findings,<sup>27</sup> all panels in Figure 2 show  
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15 248 higher CNC95% values with higher coverage in the under-vaccinated subpopulation. In each  
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17 249 panel, the lowest shown coverage value may result in the longest period of undetected circulation  
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19 250 before interruption and therefore result in the longest time to achieve high confidence about no  
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21 251 circulation.

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23 253 Looking more closely at the differences between the columns, the left column of Figure 2 shows  
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25 254 a very strong influence of the degree of isolation on the CNC95%. With little isolation and no  
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27 255 surveillance in the under-vaccinated subpopulation, the general population with high surveillance  
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29 256 quality can still detect transmission because of relatively frequent spillover of polio cases (see  
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31 257 appendix). Thus, the results do not depend much on the detection probability in the under-  
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33 258 vaccinated subpopulation for  $p_{\text{within}}=0.8$ . In contrast, for a fully isolated under-vaccinated  
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35 259 subpopulation ( $p_{\text{within}}=1$ ), the detection probability in this population becomes a more important  
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37 260 driver of the CNC95% than the coverage (i.e., for detection probability of 0.1 or very poor  
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39 261 surveillance and all other inputs at the base case, the CNC95% equals almost 6 years regardless  
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41 262 of coverage). The middle column of Figure 2 shows CNC95% values of approximately 5 years  
42  
43 263 with no surveillance in a relatively small under-vaccinated subpopulation. Although the relative  
44  
45 264 size of the under-vaccinated subpopulation affects the mixing dynamics and incidence of cases in  
46  
47 265 both populations, much of the observed effect comes from the implied change in the absolute  
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49 266 size of the under-vaccinated subpopulation, which directly affects the typical time between cases.  
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51 267 As shown in the right column of Figure 2, changing the absolute size of the under-vaccinated  
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53 268 subpopulation in the event of full isolation from the general population and a detection  
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55 269 probability of 0.1 dramatically affects the CNC95%, which ranges from slightly over 2 years for  
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57 270 500,000 people to approximately 9 years for 50,000 people (i.e., a 4-fold increase in CNC95%  
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59 271 for a 10-fold increase in population size).

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3 273 Considering the relatively high CNC95% observed for small, isolated populations in Figure 2,  
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5 274 Figure 3a uses a stochastic model to show the distribution of the duration of circulation in a  
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7 275 single population not reached by vaccination at all. Figure 3a shows the results as a function of  
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9 276 population size for a model initialized at the endemic equilibrium. For very small population  
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11 277 sizes (e.g., hundreds), not surprisingly poliovirus infections typically die-out within a year, with  
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13 278 a maximum duration of circulation of one year and 4 months for a closed population of 1,000  
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15 279 people (based on 10,000 iterations). The maximum duration of circulation increases rapidly for  
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17 280 larger populations. For a population of 5,000 people, circulation continues for 3 or more years in  
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19 281 50 of 10,000 (0.5%) iterations. With population sizes of 10,000, 20,000, 30,000, 40,000 and  
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21 282 50,000, circulation continues for at least 10 years for 3%, 34%, 63%, 79%, and 88% of  
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23 283 iterations, respectively.

24 285 Figure 3b shows the same analysis as Figure 3a except that it changes the initial conditions by  
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26 286 assuming a population with no prior exposure to any polioviruses. In this context, a single  
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28 287 introduction rapidly burns through the entire susceptible population and quickly exhausts  
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30 288 susceptible individuals, leading to die-out and a maximum duration of circulation of less than 2  
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32 289 years for all population sizes considered in Figure 3b. Together, Figures 3a-b encompass the  
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34 290 bounds on the possible duration of circulation for different initial conditions. In reality, small,  
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36 291 completely isolated populations are unlikely to remain at the endemic equilibrium because of  
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38 292 random fluctuations in the incidence, seasonality, and die-out, and no completely naïve  
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40 293 populations likely exist. In a separate analysis using the same model, we verified that the  
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42 294 addition of seasonality decreases the typical duration of circulation and increases the probability  
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44 295 of eradication within 5 years. For example, for a population size of 20,000 people, the  
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46 296 probability of eradication within 5 years increased from approximately 64% without seasonality  
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48 297 to 78%-92% with a seasonal amplitude of 10% (applied to the basic reproduction number of 10),  
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50 298 depending on the timing of the seasonal peak.

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52 300 While Figure 3 implies that increasing the population size results in an increasing probability of  
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54 301 persistent circulation (i.e., a greater probability of sustained undetected transmission), Figure 2  
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56 302 implies that increasing population size decreases the typical time interval between cases (i.e.,  
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58 303 lower probabilities of sustained undetected circulation). Figure 4 shows the net effect of these

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3 304 two opposing trends and suggests that an optimal population size exists around 20,000 people.  
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5 305 For smaller population sizes, continued transmission becomes exceedingly unlikely (Figure 3),  
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7 306 while for larger population sizes, undetected circulation becomes less likely due to the higher  
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9 307 frequency of cases. This non-linear behavior suggests a maximum CNC95% of approximately  
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11 308 2.5 years for a detection probability of 1, although the maximum increases to up to 9 years for a  
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13 309 very low detection probability of 0.1 and a population size of 20,000 to 30,000 people.  
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15 310  
16 311 Figure 5 shows how the desired confidence about no circulation may influence certification  
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18 312 timing and key health economic outcomes (see appendix for details). Earlier certification and  
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20 313 OPV cessation may increase the risk of undetected circulation after OPV cessation (and therefore  
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22 314 the possibility of needing to restart OPV use) but may decrease the costs until OPV cessation  
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24 315 (and therefore the overall global costs for planned polio immunization). Therefore, the  
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26 316 fundamental optimization problem consists of finding the desired confidence about no WPV  
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28 317 circulation at OPV cessation that minimizes the resulting total financial and societal costs.  
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30 318 Figure 5 also shows that the costs and risks both depend on the GPEI budget until and after OPV  
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32 319 cessation, with a lower budget saving costs in the short term but increasing the time of OPV  
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34 320 cessation at a given confidence level and the risks of OPV restarts, which may ultimately result  
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36 321 in greater overall costs. Optimization of the desired confidence about no WPV circulation  
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38 322 depends critically on how the confidence about no circulation increases with time after the last  
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40 323 detected event from the surveillance system.  
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## 43 325 **Discussion**

44 326  
45 327 Hard-to-reach subpopulations may play a key role in deliberations about WPV circulation and  
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47 328 decisions about WPV certification. The timing of WPV certification and subsequent OPV  
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49 329 cessation involves high stakes and largely depends on the desired confidence about the absence  
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51 330 of circulation. Surveillance quality emerges as a key factor that affects both the confidence  
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53 331 about the absence of circulation and the ability to detect and control any outbreaks after OPV  
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55 332 cessation. However, national surveillance indicators may not suffice to measure the overall  
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57 333 surveillance system quality because gaps in surveillance at the level of tens of thousands of  
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59 334 people may influence confidence. Our modeling suggests that high quality surveillance suffices



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3 335 to detect transmission in the context of a relatively well-mixed under-vaccinated subpopulation  
4 (e.g., in Pakistan and Afghanistan),<sup>41</sup> while local gaps may miss transmission for several years in  
5 336 the context of highly-isolated under-vaccinated subpopulations. With respect to global  
6 337 certification of WPV eradication, this implies a need to address any such gaps in isolated  
7 338 populations that experienced WPV transmission during the last decade. The recent experience in  
8 339 Borno and previously in Chad and Sudan demonstrated the ability of WPVs to circulate  
9 340 undetected for many years in sub-populations missed by both surveillance and immunization  
10 341 efforts.<sup>12 13</sup> However, one of the main contributions of this work is that it shows that very small,  
11 342 isolated subpopulations cannot sustain transmission indigenously, while in the context of even  
12 343 very limited surveillance, persistent undetected transmission becomes increasingly unlikely for  
13 344 increasing population sizes. To our knowledge, the existence of a worst-case population size for  
14 345 undetected circulation has not yet been demonstrated for polioviruses. Our analysis confirms  
15 346 that with high-quality surveillance, 3 years without a detected WPV case suffices to attain high  
16 347 confidence about no circulation for serotype 1, even considering possible persistence in very  
17 348 small population sizes.  
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19 350  
20 351 Explicit consideration of the decision to certify WPV eradication (Figure 5) suggests that if we  
21 352 remain confident that we can prevent the need to restart OPV due to uncontrolled outbreaks  
22 353 resulting from a possible WPV reemergence, then we should accept a lower confidence about the  
23 354 absence of circulation to certify sooner, because the costs of delaying OPV cessation would  
24 355 outweigh the risk of premature certification. Earlier OPV cessation particularly represents the  
25 356 best option if diminishing GPEI financial and/or global OPV supply resources limit our ability to  
26 357 maintain population immunity and/or respond effectively to post-cessation outbreaks. However,  
27 358 this choice depends on a willingness to accept the reputational risk of finding out that WPV still  
28 359 circulates despite its certification. With WPV3 not detected anywhere since 2012<sup>11</sup> and in many  
29 360 places for decades, the confidence about no WPV3 circulation continues to grow. Although  
30 361 confidence about no circulation increases more slowly for WPV3 than WPV1 due to the lower  
31 362 PIR,<sup>25 27</sup> assuming 1-2 years to prepare for coordinated global OPV cessation, starting the  
32 363 process of removing serotype 3 OPV now would imply at least 7 years of no detection since the  
33 364 last WPV3 case and synchronized cessation of serotype 3 OPV use (i.e., 2012 to 2019-2020).  
34 365 The transition of GPEI resources already occurring leads to expected decreases in population



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3 366 immunity for serotype 3 in some areas. Combined with on-going serotype 3 vaccine-associated  
4 367 paralytic poliomyelitis, this should motivate careful consideration of the costs, benefits, risks,  
5 368 and logistical challenges of globally certifying WPV3 eradication and synchronizing serotype 3  
6 369 OPV cessation before completing WPV1 eradication and serotype 1 OPV cessation, which now  
7 370 appears at least 4 years away.

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12 372 Our results related to minimum population sizes appear consistent with a prior study<sup>22</sup> that  
13 373 found an average of approximately 5 years of circulation for a population of 20,000 people in a  
14 374 high- $R_0$  setting and an exponential increase in the average duration of circulation with increasing  
15 375 population size. The prior study also reported a higher probability of virus persistence as the  
16 376 degree of mixing between subpopulations increases.<sup>22</sup> Our study suggests that more mixing  
17 377 between subpopulations may not lead to a higher probability of undetected circulation because  
18 378 surveillance can more easily detect persistent viruses for higher degrees of mixing. Using a more  
19 379 realistic model than another prior analysis,<sup>36</sup> we similarly do not find a high probability of  
20 380 persistent transmission for populations of 10,000 people or less.

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22 381  
23 382 Like all models, our model makes simplifying assumptions that affect its behavior.<sup>2</sup> Specifically,  
24 383 we characterized a stylized, hypothetical population to systematically explore key assumptions,  
25 384 used a simplified semi-stochastic approach to compute CNC95% that does not fully account for  
26 385 all stochastic variability, and deterministically characterized die-out. However, for the analysis  
27 386 of small population sizes that depend most on stochastic variability, we accounted for stochastic  
28 387 variability and die-out at the individual level.

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31 389 While this study highlights the importance of ensuring high surveillance quality in all  
32 390 subpopulations, it also reiterates the role of immunization in accelerating confidence about no  
33 391 circulation after the last detection.<sup>27</sup> Achieving and maintaining high population immunity to  
34 392 transmission represents a mission critical component of the GPEI.<sup>4</sup> Populations with immunity  
35 393 near the threshold experience increased risk of prolonged undetected transmission. Failing to  
36 394 invest relatively small amounts of resources to maintain high population immunity can lead to  
37 395 much more costly outbreaks, as occurred for example in Tajikistan.<sup>3</sup> Thus, if ensuring high-  
38 396 quality surveillance in all subpopulations remains an elusive goal, then achieving better coverage

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3 397 in those subpopulations would still result in higher confidence about no circulation. In contrast,  
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5 398 high quality surveillance in the context of poor immunization still leaves the population and the  
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7 399 world at risk.

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10 401 Poliovirus environmental surveillance can detect polioviruses even in the absence of  
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12 402 symptomatic polio cases<sup>42 43</sup> and offers the potential to fill some local gaps in symptomatic  
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14 403 poliovirus surveillance. For example, the extensive environmental surveillance system in Israel  
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16 404 effectively detected transmission of circulating WPV1 in the absence of any cases and despite  
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18 405 very high coverage with inactivated poliovirus vaccine (IPV).<sup>31 44</sup> However, despite the potential  
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20 406 for high sensitivity of environmental surveillance to detect infected individuals excreting into the  
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22 407 catchment area, its sensitivity remains zero outside of the catchment area and depends on  
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24 408 sampling frequency (e.g., one sample every year provides little increase in confidence over AFP  
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26 409 alone).<sup>45</sup> Environmental surveillance system designs generally depend on access to a centralized  
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28 410 sewage network,<sup>43</sup> which hard-to-reach subpopulations (i.e., those most likely to sustain  
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30 411 undetected poliovirus transmission) may not possess. Further research should help to explore the  
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32 412 ability of environmental surveillance to increase confidence about no circulation in specific  
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34 413 areas, and the value of the information obtained from environmental surveillance relative to its  
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36 414 costs requires evaluation.

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40 416 Overall, IPV plays a relatively limited role with respect to the CNC. While IPV protects  
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42 417 otherwise susceptible individuals from paralysis if they become subsequently infected with a live  
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44 418 poliovirus and may reduce the participation of these individuals in transmission to some degree,  
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46 419 the decreased frequency of paralysis may delay the detection of any circulating live poliovirus in  
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48 420 countries with surveillance systems that rely on AFP surveillance (i.e., the detection of cases).

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50 421 Overall, immunization with IPV helps to maintain population immunity to transmission  
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52 422 somewhat, but given births of immunologically naïve, deaths of immune individuals, waning  
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54 423 immunity, and the absence of circulating live polioviruses, population immunity to transmission  
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56 424 declines following WPV eradication and homotypic OPV cessation, even with very high IPV  
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58 425 coverage.<sup>46</sup> The extent of transmission possible following reintroduction of a live poliovirus into  
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60 426 a country with high IPV coverage will depend on the relative contributions of fecal-oral and  
427 oropharyngeal routes to overall transmission.<sup>4</sup> In countries dominated by fecal-oral

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3 428 transmission, the use of IPV will not prevent or stop transmission, and reintroduced live  
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5 429 polioviruses that restart transmission may lead to the need to restart the use of OPV.<sup>47</sup>  
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8 431 **List of abbreviations:** AFP, acute flaccid paralysis; CNC95%, Time until the confidence about  
9 432 no circulation reaches 95%; cVDPV, circulating VDPV DEB, differential-equation based; GPEI,  
10 433 Global Polio Eradication Initiative; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus  
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12 434 vaccine; PIR, paralysis-to-infection ratio; VDPV, vaccine-derived poliovirus; WPV(1,2,3), wild  
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14 435 poliovirus (of serotype 1, 2, 3, respectively)  
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## 17 437 **DECLARATIONS**

18  
19 438

### 20 439 **Authors' contributions**

21  
22 440 All authors (RDT, DAK, KMT) contributed to the study design, model development,  
23  
24 441 interpretation of results, manuscript writing, and revisions. The first and second authors (RDT,  
25  
26 442 DAK) performed the modeling and analyses, and the last author (KMT) secured the funding for  
27  
28 443 the study.  
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30 444

### 31 445 **Ethics approval and consent to participate**

32 446 Not applicable  
33  
34 447

### 35 448 **Consent to publish**

36 449 Not applicable  
37  
38 450

### 39 451 **Competing interests**

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41  
42 453

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8 461 **Data sharing statement**  
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10 462 Technical appendix available on request from the authors.  
11  
12 463

13 464 **References**  
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**Table 1: Model inputs to characterize a hypothetical population that contains an under-vaccinated subpopulation.**

Model input	Value(s) <sup>a</sup>	Source/notes
Total population size	500,000; <b>1 million</b> ;5 million	No effect on DEB model behavior, but required for stochastic analysis of detections
Time until vaccination starts, years		Assumption to characterize hard-to-reach subpopulation within well-vaccinated general population
General population	30	
Under-vaccinated subpopulation	40	
Initial age distribution		Equilibrium age distribution <sup>38</sup>
0-2 months	0.01	
3-59 months	0.15	
5-14 years	0.25	
≥ 15 years	0.59	
Birth rate, births/person/year	0.02	38
Death rate, deaths/person/year	0.02	38
Basic reproduction number ( $R_0$ )	10	38
Proportion of transmissions via oropharyngeal route	0.3	38
Proportion of contacts reserved for individuals within the same mixing age group	0.4	Same value as used in <sup>38</sup> (not explicitly listed)
Average per-dose take rate for serotype 1 OPV	0.6	Increased from 0.5 to maintain similar coverage thresholds with different run-up <sup>38</sup>
Routine immunization coverage		Represents coverage with exactly 3 OPV doses; general population based on <sup>38</sup> , under-vaccinated varied around threshold to eradicate, which equals 0.82 for the bolded values in the middle column
General population	0.95	
Under-vaccinated subpopulation	0.75; <b>0.82</b> ;0.85;0.90;0.95 <sup>b</sup>	
Proportion of contacts with under-vaccinated subpopulation ( $p_{within}$ )	0.8; <b>0.95</b> ;1.00	Selected values from <sup>38</sup>
Size of under-vaccinated subpopulation compared to total population	1/20; <b>1/10</b> ;1/5	Selected values from <sup>38</sup>
Paralysis-to-infection ratio (PIR)	1/200	Average for serotype 1 wild poliovirus <sup>2 14</sup>
Detection probability per polio case		Assumption to characterize hard-to-reach subpopulation within general population with high acute flaccid paralysis surveillance quality
General population	0.95	
Under-vaccinated subpopulations	0;0.1;0.2;0.3;0.4;0.5;0.6;0.7;0.8;0.9;0.95 <sup>b</sup>	

Abbreviations: DEB, differential-equation based; OPV, oral poliovirus vaccine

<sup>a</sup> Values shown in bold represent values that we held fixed when varying other values in sensitivity analyses

<sup>b</sup> All values considered jointly in all sensitivity analysis (hence no single value bolded)

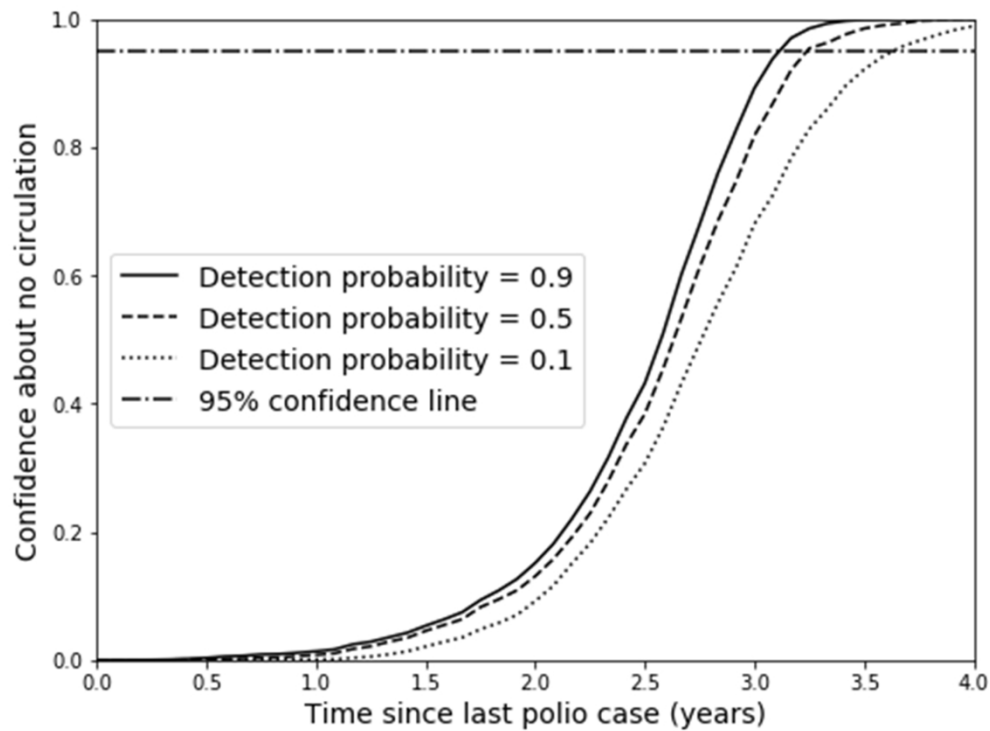


Figure 1: Confidence about no circulation as a function of time since the last detection for different detection probability values for the hypothetical model base case, with coverage at the corresponding minimum to eliminate WPV (i.e., 0.82).

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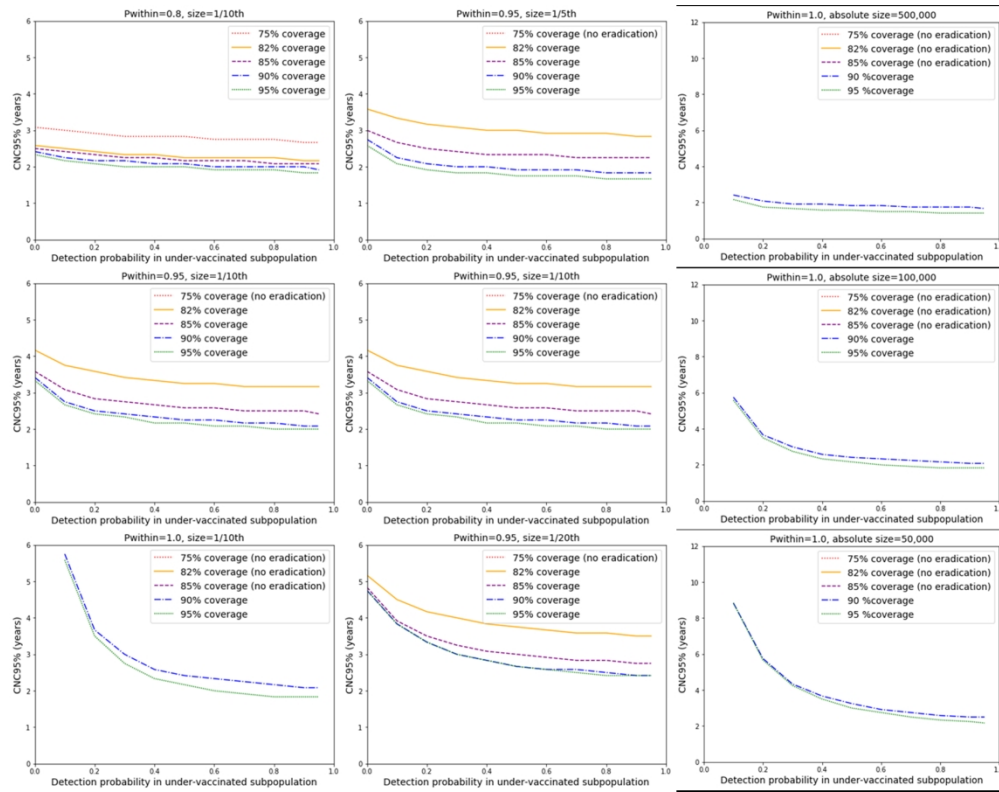
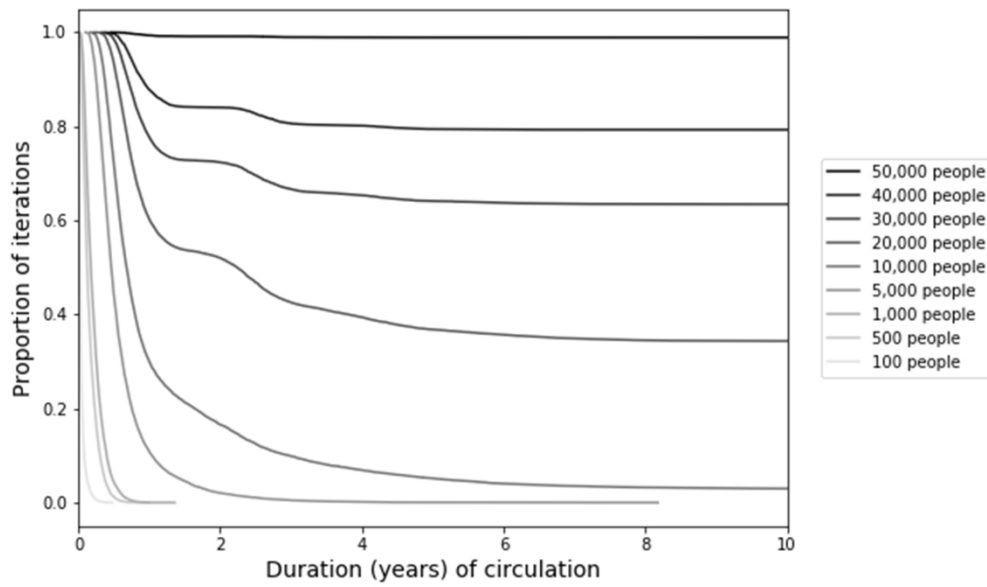


Figure 2: Time until the confidence about no circulation reaches 95% (CNC95%) from the stochastic analysis for different degrees of isolation of the under-vaccinated subpopulation (left column), relative sizes of the under-vaccinated subpopulation (middle column), and absolute sizes of a fully-isolated under-vaccinated subpopulation (right column, note doubled y-axis ranges).

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Results from the analysis of the relationship between population size and persistence of circulation of serotype 1 wild poliovirus transmission in the fully stochastic model (a) Model starts at the endemic equilibrium

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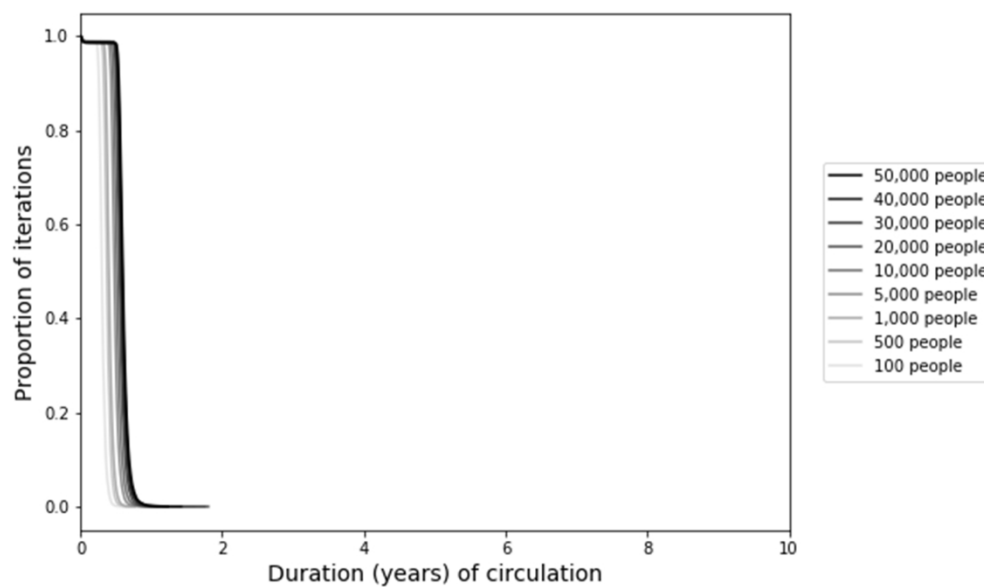


Figure 3: Results from the analysis of the relationship between population size and persistence of circulation of serotype 1 wild poliovirus transmission in the fully stochastic model (b) Model starts with a single infection in a fully susceptible population

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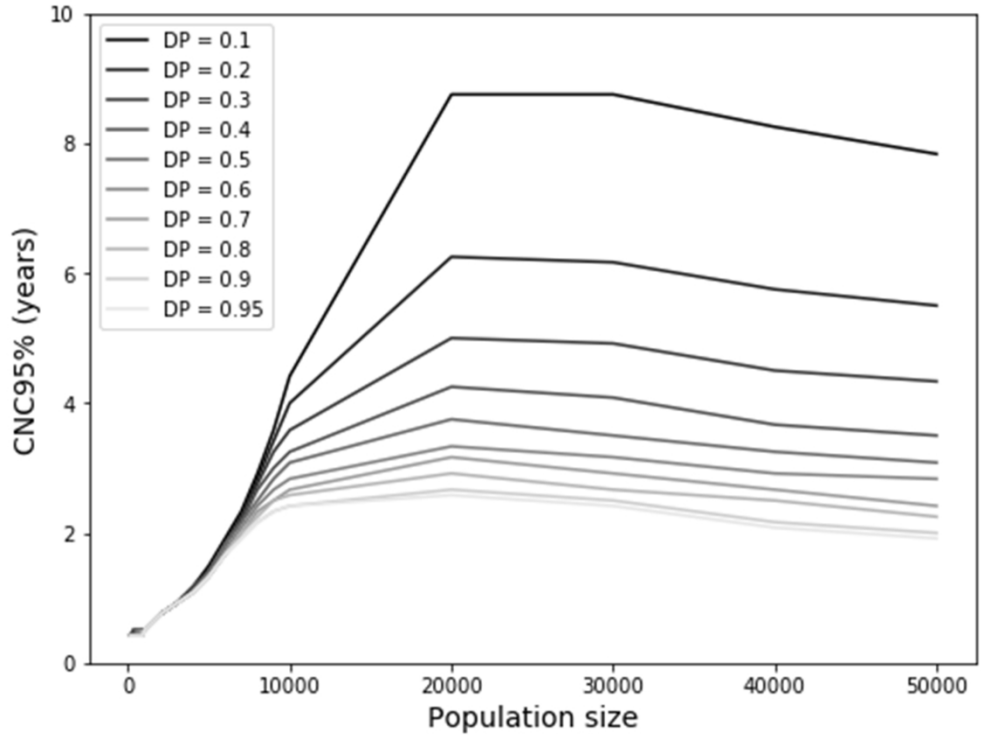


Figure 4: Time until the confidence about no circulation reaches 95% (CNC95%) for small population sizes in the fully stochastic model that starts at the endemic equilibrium, by detection probability (DP)

177x133mm (300 x 300 DPI)

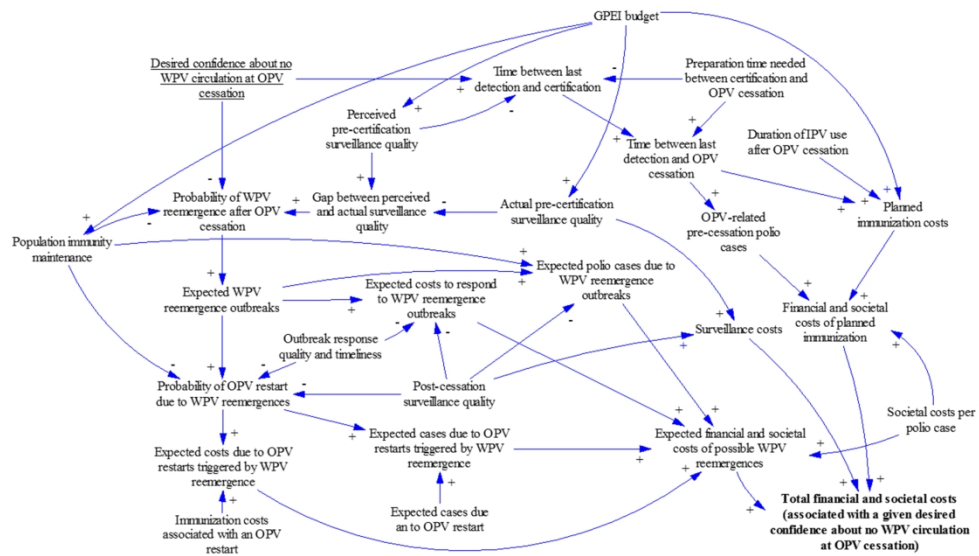


Figure 5: Conceptual diagram for the implications of choices about the timing of certification of eradication of a wild poliovirus serotype on total financial and societal costs

228x135mm (300 x 300 DPI)



## APPENDIX for “Certification of global eradication: The role of hard-to-reach subpopulations and confidence about the absence of transmission”

Radboud J. Duintjer Tebbens,<sup>1</sup> Dominika A. Kalkowska,<sup>1</sup> Kimberly M. Thompson<sup>1</sup>

### *Differential-equation based model and results*

The DEB model we use to examine the role of subpopulations<sup>38</sup> made simplifying assumptions about what a high-risk population might look like and otherwise adopted the comprehensive structure and setting-invariant model inputs of a previously developed and calibrated differential-equation based poliovirus transmission and OPV evolution model.<sup>2,30</sup> The following text from the appendix of a prior publication<sup>45</sup> (with references renumbered) briefly describes the model and Figures A1-2 and Table A1 cited in the text provide the model structure and generic inputs (i.e., model inputs that remain the same for all populations).

“The differential equation-based poliovirus transmission and OPV evolution model (DEB model)<sup>2</sup> tracks the movement of people between demographic age groups (grouped into mixing age groups that mix preferentially amongst themselves), and for each serotype between oropharyngeal and intestinal infection stages (resulting in potential oropharyngeal and fecal-oral transmission, respectively), immunity states, and waning stages. Figure A1 provides an overview of the model structure based on prior work.<sup>2</sup> Figure A1a depicts the immunity states with the flows that move individuals in and out of them and Figure A1b details how effectively vaccinated or infected individuals progress through different stages of infection and, in the event of infection with OPV, through OPV evolution stages. The model assumes that active immunity from prior vaccination or infection results in permanent protection from polio (disease), but only partial protection from subsequent infection and participation in transmission, depending on the nature of immunity (IPV-induced vs. LPV-induced or both) and time since the last exposure (i.e. waning stage). The model includes 5 waning stages, 6 fecal-oral and 6 oropharyngeal infection stages (2 latent and 4 infectious, with varying degrees of infectiousness), and also accounts for a delay between IPV receipt and development of the immune response that moves individuals to the next IPV immunity state. In Figure A1a, we note that the model assumes identical properties for “IPV and LPV” and “ $\geq 2$  LPV infections” and that the recent waning stages of these immunity states represent the highest degree of immunity to transmission in the model. The model further tracks OPV evolution by moving individuals infected with the OPV parent strain (stage 0) through 20 successive reversion stages that can each transmit and that come with increasing paralysis-to-infection ratios and relative basic reproduction numbers ( $R_0$  values) compared to homotypic WPVs. The last reversion stage (stage 19) represents fully-reverted VDPVs with assumed paralysis-to-infection ratio and  $R_0$  equivalent to homotypic WPVs. For WPVs or any OPV reversion stage, the DEB model mimics die-out by setting the force-of-infection for the given strain to 0 whenever its effective prevalence of infections resides below a calibrated threshold of 5 per million people. Consequently, OPV-related viruses can only continue to transmit and thus evolve to cVDPVs through successive infections when low enough population immunity to transmission permits circulation of the OPV viruses introduced in the population through vaccination. We fixed the die-out process, model structure, and numerical

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3 model inputs that characterize them across all populations we modeled and Table A1 includes  
4 the corresponding generic model inputs. [...]

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7 “Figure A2 summarizes the results of the model calibration process, based on prior work.<sup>2</sup> With  
8 the generic model inputs from Table A1 fixed, we compared our model behavior against i) data  
9 on children with non-polio acute flaccid paralysis who reported no receipt of OPV for northern  
10 India (modeled separately for Western Uttar Pradesh (WUP) and Bihar) and northwest (NW)  
11 Nigeria; ii) data on polio incidence and die-out of endemic WPV transmission for all situations  
12 and serotypes (shown in Figure A2 for WPV1 and WPV3 in northern India and northwest  
13 Nigeria and for all 3 WPV serotypes in the USA); iii) data from WPV importation outbreak  
14 behavior in the Netherlands, Tajikistan, and Albania; iv) data on age distributions of cases for all  
15 situations in which meaningful data was available (shown in Figure A2 for the Netherlands,  
16 Tajikistan, and Albania); v) available serological data on the effect of secondary OPV immunity in  
17 the USA and Cuba (not shown); vi) indigenous emergence of cVDPVs (shown in Figure A2 for  
18 northern India, NW Nigeria (both serotype 2), Haiti, and Madura in Indonesia (both serotype 1);  
19 and vii) no indigenous emergence of cVDPVs in all other situations and serotypes (die-out of  
20 serotype 1 OPV-related viruses shows in Figure A2 for Cuba and Haiti). We subsequently  
21 applied the model to successfully reproduce the asymptomatic transmission of an imported  
22 WPV1 in Israel in 2013.<sup>31, 45, online supplement pp. 1-2</sup>

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26 Most critically in the context of certification questions, the DEB model approximates  
27 interruption of live poliovirus transmission (i.e., of an OPV, WPV, vaccine-derived poliovirus  
28 (VDPV), or OPV-related strain) in a population to occur when the effective infectiousness-  
29 weighted proportion of the population infectious with that poliovirus drops below 5 per million  
30 people (i.e., the transmission threshold  $EPI^*$ ).<sup>2</sup> While this simplifies the true die-out behavior,  
31 which depends on local heterogeneity and chance, it appears capable of generating WPV die-out  
32 times consistent with observations in a broad range of settings.<sup>2, 30, 31, 41</sup> Moreover, when applied  
33 to the persistence of OPV-related viruses that evolve to fully transmissible and neurovirulent  
34 circulating VDPVs (cVDPVs), the approximation produces cVDPV outbreaks for conditions in  
35 which they occurred (e.g., in Hispaniola<sup>46</sup> and Nigeria<sup>47</sup>) and no cVDPV outbreaks for conditions  
36 in which they did not occur despite OPV use and cessation (e.g., in Cuba<sup>48</sup> and the USA<sup>49</sup>).<sup>2</sup>

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40 Use of the hypothetical model clarified that under-vaccinated subpopulations can sustain  
41 poliovirus transmission independently despite high coverage in the surrounding general  
42 population and showed how the minimum coverage needed to interrupt transmission depends on  
43 the degree of isolation and the relative size of the under-vaccinated subpopulation.<sup>38</sup> To explore  
44 the role of hard-to-reach under-vaccinated subpopulations for certification questions, we  
45 modified the hypothetical model in two ways and added a stochastic layer on top of the DEB  
46 model to simulate polio case detections. The first modification consisted of desynchronizing the  
47 time when vaccination starts in the general and under-vaccinated subpopulations to simulate the  
48 concept of a population that remains inaccessible for an extended period of time. Specifically,  
49 we run the model, which assumes equal birth and death rates and thus no population growth  
50 (Table 1), without vaccination for 30 years to settle into the endemic equilibrium, and then  
51 instantly change the routine immunization coverage in the general population with three OPV  
52 doses to 0.95, which lies well above the threshold of 0.92 needed to interrupt transmission in a  
53 closed population with similar characteristics.<sup>38</sup> However, we assume that the under-vaccinated  
54 subpopulation initially remains completely unreached by vaccination, with vaccine introduction  
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3 in the under-vaccinated subpopulation occurring 10 years after vaccine introduction in the  
4 general population. Desynchronizing the introduction of vaccination affects the dynamics and  
5 effectively makes it more difficult to interrupt transmission after introducing vaccination in the  
6 last subpopulation. To offset this effect, we consider a different hypothetical population with a  
7 slightly higher average per-dose take rate for OPV of 0.6 instead of 0.5 in the original analysis<sup>38</sup>  
8 (e.g., due to lower exposure to enteric viruses that interfere with vaccine take<sup>50</sup>). As in the  
9 original analysis,<sup>38</sup> we vary the coverage in the under-vaccinated subpopulation, the relative size  
10 of the under-vaccinated subpopulation compared to the total population, and the degree of  
11 preferential mixing, characterized by the proportion of potentially infectious contacts of  
12 individuals in the under-vaccinated subpopulations with other individuals in the same  
13 subpopulation ( $p_{\text{within}}$ ).  
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17 Figure A3 shows the behavior of the incidence of infections in fully susceptible individuals and  
18 infants born with maternal immunity as a function of the varied DEB model inputs. Generally,  
19 the model yields incidence proportional to population size before vaccination starts. After the  
20 introduction of vaccination with high coverage in the general population, the initially still  
21 unvaccinated subpopulation becomes the main contributor to the total incidence. However, with  
22 less than 100% coverage in the general population and some interaction between the two  
23 populations (i.e.,  $p_{\text{within}} < 1$ ), some incidence continues to occur in the general population as  
24 exported viruses find unvaccinated individuals. Lower values of  $p_{\text{within}}$  imply more interaction  
25 between the two populations and result in more incidence in the general population before  
26 vaccination in the under-vaccinated subpopulation begins (middle column of Figure A3). The  
27 relative size of the under-vaccinated subpopulation also affects the extent to which the under-  
28 vaccinated subpopulation affects the general population (right column of Figure A3). With base  
29 case model inputs, the minimum coverage in the under-vaccinated subpopulation to interrupt  
30 transmission equals 0.82. Higher coverage values mean interruption occurs sooner after the  
31 introduction of vaccination in the under-vaccinated subpopulation, while lower coverage values  
32 mean that transmission continues and can eventually rebound and settle into a new equilibrium  
33 (left column in Figure A1).  
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38 While the prior approach used fully stochastic transmission models to randomly generate  
39 infections, die-out, and polio cases and detections,[19-22] for efficiency we use post-hoc  
40 processing of DEB model results to randomly generate only the times when polio cases and  
41 detections stochastically occur. Specifically, for each setting of the DEB model, we record the  
42 deterministic realization of the daily incidence of infections in fully susceptible individuals of  
43 any age and 50% of infants less than 3 months of age born with maternal immunity, which  
44 represent the only individuals at risk of becoming a polio case in the DEB model.[2] We then  
45 randomly determine the number of polio cases resulting from the infection incidence on each day  
46 using a Poisson draw with a rate equal to the infection incidence multiplied by the PIR. For each  
47 generated case, we use a separate uniform random draw to determine whether it results in a  
48 detection based on each of the detection probabilities in Table 1 (e.g., a random uniform draw of  
49 0.45 would mean that the case results in a detection only for detection probabilities of more than  
50 0.45). For each DEB model setting, we repeat the post-hoc stochastic process 10,000 times and  
51 we start generating cases 10 years before vaccination starts in the general population, which we  
52 assume starts vaccination 10 years earlier than the under-vaccinated subpopulation (see  
53 appendix). The precise choice of when to start randomly generating cases exerts negligible  
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3 influence on the results as long as it occurs before cases become rare (i.e., before the interval  
4 between cases becomes longer). For simplicity, although prior work showed the significant role  
5 of serotype differences and seasonality,[20, 22] the hypothetical model inputs reflect WPV1 and  
6 assumes no seasonality. A limitation arises from the direct scaling of the DEB model with  
7 absolute population size, such that die-out depends on the effective proportion of infectious  
8 individuals rather than the absolute number. Using the post-hoc stochastic analysis, the absolute  
9 population size affects the number of infections, which affects the typical interval between  
10 detected cases. We show that CNC95% increases substantially for smaller absolute population  
11 sizes.  
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15 Our initial findings motivated analysis of the minimum population size that can sustain WPV  
16 circulation on its own to determine whether the upper bound on the CNC95% of 9 years could  
17 occur in real populations. However, for population sizes far below 100,000, the DEB model  
18 becomes inadequate because it allows prevalence to remain above the die-out threshold even  
19 with only fractional numbers of infections (i.e., less than one infected person). Therefore, we  
20 used a fully stochastic model to explore questions of minimum population size. We run the  
21 model 10,000 times for different population sizes and initial conditions and report the  
22 distribution of the duration of circulation and the CNC95%.  
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### 25 **Exploration of the causal interactions relevant to global WPV certification decisions with** 26 **an influence diagram (Figure 5)** 27

28 Table A2 provides indicative estimates of the key quantities in Figure 5, based on the literature.  
29 Figure 5 assumes that policy makers explicitly or implicitly set a *desired confidence about no*  
30 *WPV circulation at OPV cessation*. In reality, they may focus on the confidence at certification,  
31 but given that it takes some fixed *preparation time needed between certification and OPV*  
32 *cessation*, any set confidence at the time of certification corresponds to some *desired confidence*  
33 *about no WPV circulation at OPV cessation*. A higher desired confidence level implies a longer  
34 *time between last detection and certification*. This time decreases with increasing investments in  
35 immunization and surveillance from the *GPEI budget through population immunity maintenance*  
36 and the *perceived pre-certification surveillance quality*, respectively. The main drawback of a  
37 longer *time between last detection and OPV cessation* comes in the form of longer OPV use in  
38 most countries, which results in *planned immunization costs* and *OPV-related pre-cessation*  
39 *polio cases* (i.e., vaccine-associated paralytic polio and VDPVs). In addition, with some  
40 globally-recommended or nationally-preferred *duration of IPV after OPV cessation*, later OPV  
41 cessation would imply greater overall IPV costs, because global IPV use already started (i.e.,  
42 only the end, and not the beginning of IPV use depends on the timing of cessation of the last  
43 OPV serotypes). These drawbacks together lead to *financial and societal costs of planned*  
44 *immunization*. This includes the monetary equivalent of the *OPV-related polio cases*, which  
45 depends on the country income-level-dependent *societal costs per polio case*.  
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50 On the left side of Figure 5, we see the benefits of setting a higher *desired confidence about no*  
51 *WPV circulation at OPV cessation*. A higher confidence implies a lower *probability of a WPV*  
52 *reemergence after OPV cessation* (all else being equal). However, this probability does not  
53 directly equal the reciprocal of the confidence in the event of a *gap between perceived and actual*  
54 *surveillance quality*. Specifically, if the *perceived pre-certification surveillance quality* exceeds  
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3 the *actual pre-certification surveillance quality*, then the true *probability of WPV reemergence*  
4 *after OPV cessation* equals more than 1 minus the *desired confidence about no WPV circulation*  
5 *at OPV cessation*, and vice versa. This potential discrepancy highlights the importance of  
6 continued assessment of surveillance quality and assurance of high surveillance quality. A lower  
7 *GPEI budget* also decreases *population immunity maintenance* and thus increases the *probability*  
8 *of WPV reemergence after OPV cessation*, which implies an increase in *expected WPV*  
9 *reemergence outbreaks*. Unlike other possible types of post-cessation outbreaks, a WPV  
10 reemergence would almost certainly occur in the most challenging populations. Any such  
11 reemergences would lead to *expected polio cases due to WPV reemergence outbreaks* and  
12 *expected costs to respond to WPV emergence outbreaks*. The expected costs and cases decrease  
13 with higher *post-cessation surveillance quality*, which affects the extent of viral spread at the  
14 time of outbreak detection (and beyond), and with a better *outbreak response quality and*  
15 *timeliness*, which both increase the probability of effective outbreak control.<sup>51</sup> However, the  
16 occurrence of any outbreaks comes with some probability of uncontrolled outbreaks, either by  
17 failing to control the original outbreak virus, or by creating new cVDPV outbreaks with the OPV  
18 vaccine used in the response. This implies some *probability of OPV restart due to WPV*  
19 *reemergences*, which would carry very significant *expected costs due to an OPV restart*  
20 *triggered by WPV reemergence* and *expected cases due to an OPV restart triggered by WPV*  
21 *emergence* (Table A2). For moderate or high *probability of OPV restart due to WPV*  
22 *reemergences*, the resulting *expected costs due to OPV restarts triggered by WPV reemergence*  
23 and *expected cases due to OPV restarts triggered by WPV reemergence* would likely dwarf the  
24 costs and cases associated with any controlled outbreaks due to WPV reemergences and would  
25 therefore drive the *expected financial and societal costs of possible WPV reemergences*.  
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31 Together with the *surveillance costs*, which act to moderate the costs of delayed OPV cessation  
32 or premature OPV cessation, the *expected financial and societal costs of possible WPV*  
33 *reemergences* and the *financial and societal costs of planned immunization* together make up the  
34 *total financial and societal costs (associated with any given desired confidence about no WPV*  
35 *circulation at OPV cessation)*. The costs of possible WPV emergences and the costs of planned  
36 immunization move in opposite directions as a function of the *desired confidence about no*  
37 *circulation at OPV cessation*.  
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40 Figure 5 also highlights the consequences of the GPEI already scaling down some of its  
41 supplemental immunization and surveillance activities. While scaling down saves costs in the  
42 short term, doing so could lead to larger long-term costs by delaying certification and OPV  
43 cessation (i.e., requiring higher confidence about no circulation), which would imply that OPV  
44 cessation could occur in the context of lower global population immunity to transmission and  
45 lower ability to rapidly detect outbreaks. This ultimately implies an increase in the expected  
46 *total financial and societal costs (associated with any given desired confidence about no WPV*  
47 *circulation at OPV cessation)*. For visual simplicity, Figure 5 omitted some additional  
48 complexity involved in this decision. Furthermore, given that the confidence about no  
49 circulation increases with time after the last detection, we could have equivalently centered  
50 Figure 5 around finding the optimal time between the last detection and certification or OPV  
51 cessation. The amounts in Table A2 highlight the significant financial and humanitarian stakes  
52 involved in finding the optimal *desired confidence about no WPV circulation at OPV cessation*.  
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**Table A1: Generic inputs of the DEB model<sup>2 30</sup> (adopted from the online supplement of Duintjer Tebbens et al., 2017<sup>45</sup>)**

Model input (symbol)	Best estimate	Source
Relative susceptibility ( $\sigma$ ) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.78;0.79;0.77 0.91;0.92;0.90 0.80;0.80;0.79 0.72;0.72;0.71 0.42;0.43;0.41 0.21;0.22;0.20 0.21;0.22;0.20	52 53
Duration of latent period ( $\xi^{fec}$ or $\xi^{oro}$ , in days)	$\sim 3^a$	52 53
Duration of fecal infectiousness ( $\gamma^{fec}$ , in days) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Fully susceptible</li> <li>- Maternally immune</li> <li>- 1 successful IPV,</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	28.0;27.8;28.3 24.6;24.6;24.6 24.5;24.4;24.7 21.1;20.8;21.3 18.0;17.7;18.2 11.6;10.5;10.5 10.1;8.9;8.9 10.1;8.9;8.9	52 53
Duration of oropharyngeal infectiousness ( $\gamma^{oro}$ , in days) of recent immunity states (no serotype differences) <ul style="list-style-type: none"> <li>- Fully susceptible</li> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	13.4 11.9 9.9 6.6 6.1 5.0 3.7 3.7	52 53
Relative fecal infectiousness ( $\pi^{fec}$ ) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.96;0.96;0.95 0.92;0.92;0.91 0.70;0.69;0.68 0.61;0.59;0.59 0.39;0.43;0.43 0.20;0.23;0.23 0.20;0.23;0.23	52 53
Relative oropharyngeal infectiousness ( $\pi^{oro}$ ) of recent immunity states (no serotype differences) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.68 0.30 0.17 0.12 0.33 0.21 0.21	52 53
Number of infection stages <ul style="list-style-type: none"> <li>- Latent period (<math>r</math>)</li> <li>- Infectious period (<math>s</math>)</li> </ul>	2 4	
Relative weight of infection stages, compared to average weight over the infectious period ( $\theta_j, j=0, \dots, r+s-1$ )		52 53

- Infection stage 0 and 1 (latent stages)	0	
- Infectious stage 2	12/17	
- Infectious stage 3	40/17	
- Infectious stage 4	12/17	
- Infectious stage 5	4/17	
IPV immunity delay ( $\phi$ , in days)	7	54
Number of waning stages ( $n_w$ )	5	
Shape of waning function ( $z_w$ )	5	52 53
Average time to reach last waning stage ( $\rho$ , in days)		52 53
- Type 1&2	4×365	
- Type 3	3×365	
Average time for maternal immunes to wane to fully susceptible ( $\rho_{MI}$ , in days)	0.25×365	52 53
Relative susceptibility ( $\sigma$ ) for last waning stage (no serotype differences)		52 53
- 1 successful IPV	1.0	
- 2 successful IPV	1.0	
- $\geq 3$ successful IPV	1.0	
- 1 LPV infection	0.8	
- $\geq 2$ LPV infections	0.7	
- IPV and LPV	0.7	
Duration of fecal infectiousness ( $\gamma^{fec}$ , in days) of last waning stage (for PV1;PV2;PV3)		52 53
- 1 successful IPV	26.6;26.4;26.9	
- 2 successful IPV	25.2;25.0;25.5	
- $\geq 3$ successful IPV	23.8;23.6;24.1	
- 1 LPV infection	14.0;13.9;14.1	
- $\geq 2$ LPV infections	11.4;11.4;11.6	
- IPV and LPV	11.4;11.4;11.6	
Duration of oropharyngeal infectiousness ( $\gamma^{oro}$ , in days) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	11.4	
- 2 successful IPV	6.7	
- $\geq 3$ successful IPV	6.6	
- 1 LPV infection	6.7	
- $\geq 2$ LPV infections	4.0	
- IPV and LPV	4.0	
Relative fecal infectiousness ( $\pi^{fec}$ ) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	0.95	
- 2 successful IPV	0.9	
- $\geq 3$ successful IPV	0.85	
- 1 LPV infection	0.5	
- $\geq 2$ LPV infections	0.3	
- IPV and LPV	0.3	
Relative oropharyngeal infectiousness ( $\pi^{oro}$ ) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	0.43	
- 2 successful IPV	0.25	
- $\geq 3$ successful IPV	0.13	
- 1 LPV infection	0.5	
- $\geq 2$ LPV infections	0.3	
- IPV and LPV	0.3	
Number of reversion stages ( $h$ )	20	
Shape of reversion function with respect to:		
- $R_0(z_r)$	1	
- $\ln(\text{PIR})(z_p)$	2.5	



Average time to reach last reversion stage ( $\varepsilon$ , in days) (for PV1;PV2;PV3)	620.5; 408; 620.5	<sup>30</sup>
Paralysis-to-infection ratio for fully susceptible individuals infected with OPV ( $PIR_0$ ) (for PV1; PV2;PV3)	$0.26 \times 10^{-6}$ ; $1.2 \times 10^{-6}$ ; $1.8 \times 10^{-6}$	
Paralysis-to-infection ratio for fully susceptible individuals infected with FRPV ( $PIR_{h-1}$ ) (for PV1; PV2;PV3)	0.005; 0.0005; 0.001	<sup>2 14 54</sup>
Relative $R_0$ of OPV vs. FRPV ( $\tau_0$ ) (for PV1; PV2; PV3)	0.37;0.55;0.25	<sup>2 52 53</sup>
Effective infectious proportion below which we assume 0 force-of-infection (transmission threshold $EPI^*$ )	5/1,000,000	
Relative PIR for maternally immunes compared to fully susceptible individuals ( $RPIR_{M1}$ )	0.5	
Ratio of $R_0$ by serotype in the same setting (PV1:PV2:PV3)	1:0.9:0.75	<sup>30</sup>
Average incubation period ( $\delta$ , in days)	10	<sup>54 55</sup>
Demographics for all situations	Time series 1950-2100	<sup>56</sup>

**Acronyms:** CDC = (U.S.) Centers for Disease Control and prevention; cVDPV = circulating vaccine-derived poliovirus; DEB = differential equation-based FRPV = fully-reverted poliovirus; GPLN = Global Polio Laboratory Network; IPV = inactivated poliovirus vaccine; LPV = live poliovirus; OPV = oral poliovirus vaccine; PIR = paralysis-to-infection ratio; PV(1,2,3) = poliovirus (type 1, 2, or 3, respectively);  $R_0$  = basic reproductive number; UN = United Nations; USA = United States of America; VAPP = vaccine-associated paralytic poliomyelitis; VP1 = viral protein 1; WPV(1,2,3) = wild poliovirus (type 1, 2, or 3, respectively)

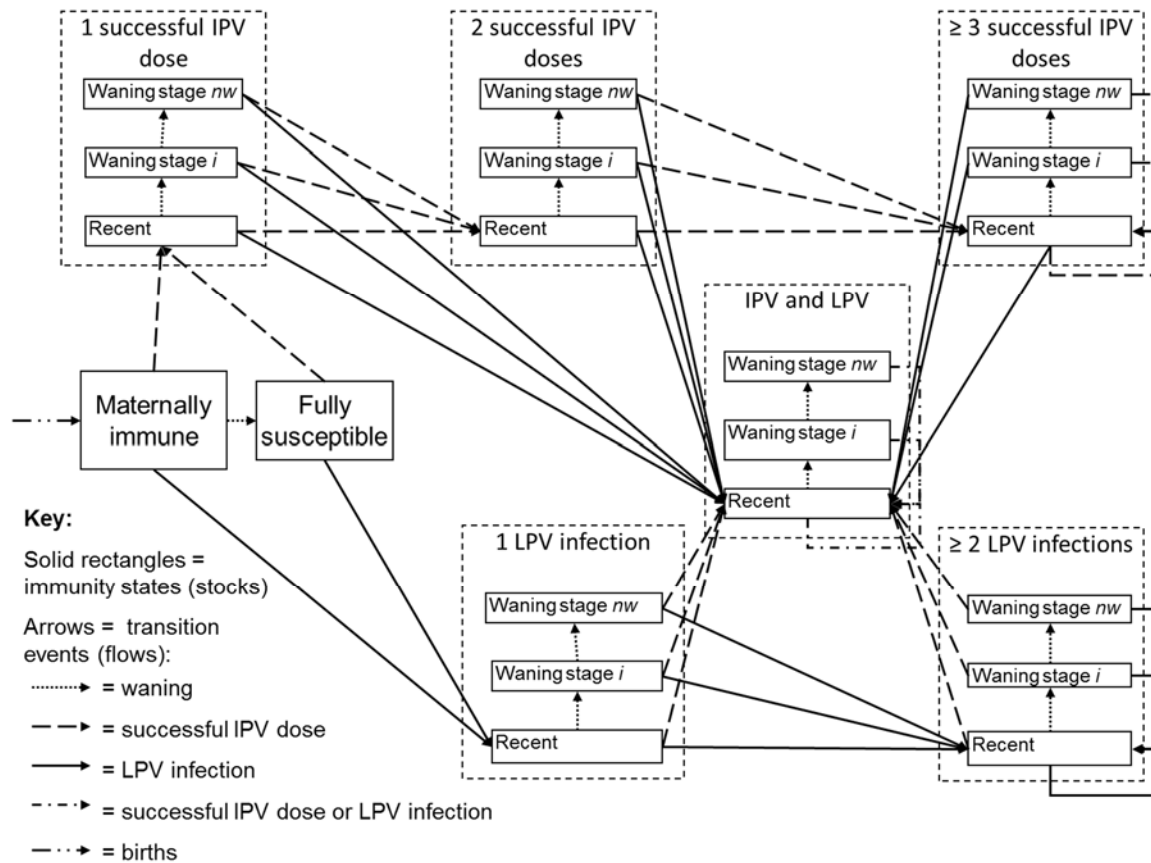
**Notes:** <sup>a</sup> Mean estimates obtained from experts and used in the model for the different immunity states, serotypes, and excretion modes vary between 2.85 and 3.37 days

**Table A2: Indicative estimates of key variables from Figure 5**

Variable	Estimate	Notes and sources
Preparation time needed between certification and OPV cessation	Approximately 1 year	Depends on when setting of the OPV cessation date occurs relative to certification <sup>57</sup>
Planned immunization costs	\$1 billion in external GPEI funds per year, plus internal contributions	Most of the \$1.1 billion GPEI budget for 2016 was for immunization and coordination of activities; <sup>58</sup> Countries may internally contribute at a similar rate as the external contributions; <sup>59</sup> The current GPEI budget projects a decrease from 2018 forward, which would imply some offset of costs for maintenance of activities, or alternatively the activities previously supported by external contributions may end, which would imply declines in programmatic activities and quality
OPV-related polio cases	Hundreds per year	Vaccine-associated paralytic polio cases, <sup>60</sup> which depends on timing of IPV doses, <sup>61</sup> and presumably local cVDPV outbreaks <sup>62</sup>
Surveillance costs	Around \$100 million per year	The 2016 GPEI budget included \$67 million in external support for surveillance and laboratories, <sup>58</sup> with additional significant internal contributions by countries <sup>59 63</sup>
Probability of OPV restart due to WPV reemergence	Unknown	Prior studies estimated an approximately 5% chance of an OPV restart due primarily to OPV-associated risks, although the actual implementation of risk management policies was not as good as suggested by these models. <sup>59 64</sup>
Immunization costs associated with an OPV restart	\$ billions (hundreds of millions per year)	An OPV restart would involve reintroduction of OPV vaccination in most countries in perpetuity, with supplemental immunization activities needed in countries with insufficient routine immunization coverage. <sup>59</sup> Significant uncertainty exists about what an OPV restart would look like in practice.
Expected cases due to an OPV restart	Up to thousands per year	Reintroduction of OPV in most countries would result in hundreds of vaccine-associated paralytic polio cases per year and could result in continued cVDPV outbreaks in countries with insufficient routine immunization coverage that do not conduct regular preventive supplemental immunization activities. <sup>59 64</sup>

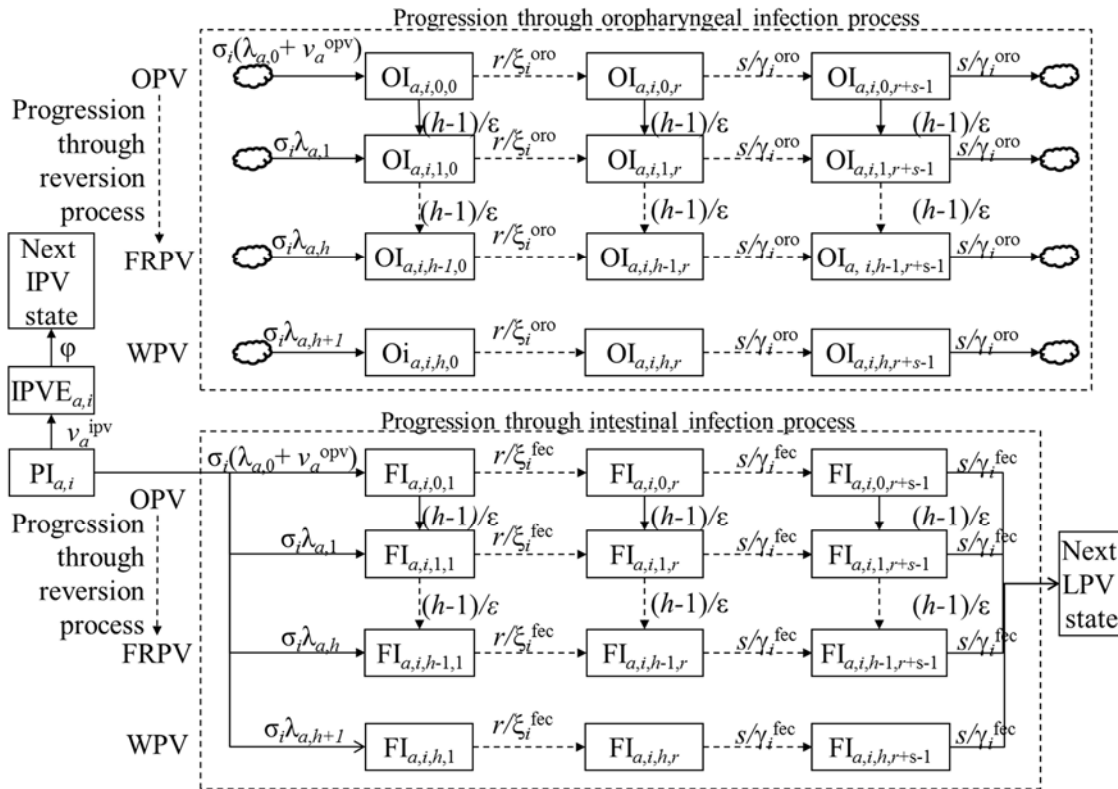
**Figure A1: Schematic of the DEB model structure, adopted from Duintjer Tebbens et al. (2013)<sup>2</sup>, p. 706**

**(a) Immunity states and flows between them due to epidemiological events**



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## (b) Progression through infection and reversion stages



“**Acronyms:** FRPV = fully-reverted poliovirus; IPV = inactivated poliovirus vaccine; OPV = oral poliovirus vaccine; WPV = wild poliovirus; **Symbols:**  $PI_{a,i}$  = partially infectible in age group  $a$  and immunity state  $i$ ;  $IPVE_{a,i}$  = IPV-exposed individual from immunity state  $i$  and age group  $a$ ;  $FI_{a,i,j,k}$  ( $OI_{a,i,j,k}$ ) = individual in age group  $a$  from immunity state  $i$ , infected with virus strain  $j$  and in fecal (oropharyngeal) infection stage  $k$ ;  $\lambda_{a,j}$  = force-of-infection to age group  $a$  for virus strain  $j$ ;  $v_a^{ipv}$  ( $v_a^{opv}$ ) = force-of-IPV(OPV)-vaccination to age group  $a$  as a result of routine and supplementary immunization;  $\sigma_i$  = relative susceptibility for immunity state  $i$ ;  $\xi_i^{fec}$  ( $\xi_i^{oro}$ ) = average duration of the fecal (oropharyngeal) latent period for immunity state  $i$ ;  $\gamma_i^{fec}$  ( $\gamma_i^{oro}$ ) = average duration of the fecal (oropharyngeal) infectious period for immunity state  $i$ ;  $\varphi$  = IPV immunity delay;  $h$  = number of reversion stages;  $r$  = number of latent stages;  $s$  = number of infectious stages”<sup>2</sup>, p. 706

Figure A2: Summary results from the model calibration process, adapted from Duintjer Tebbens et al. (2013)<sup>2</sup>

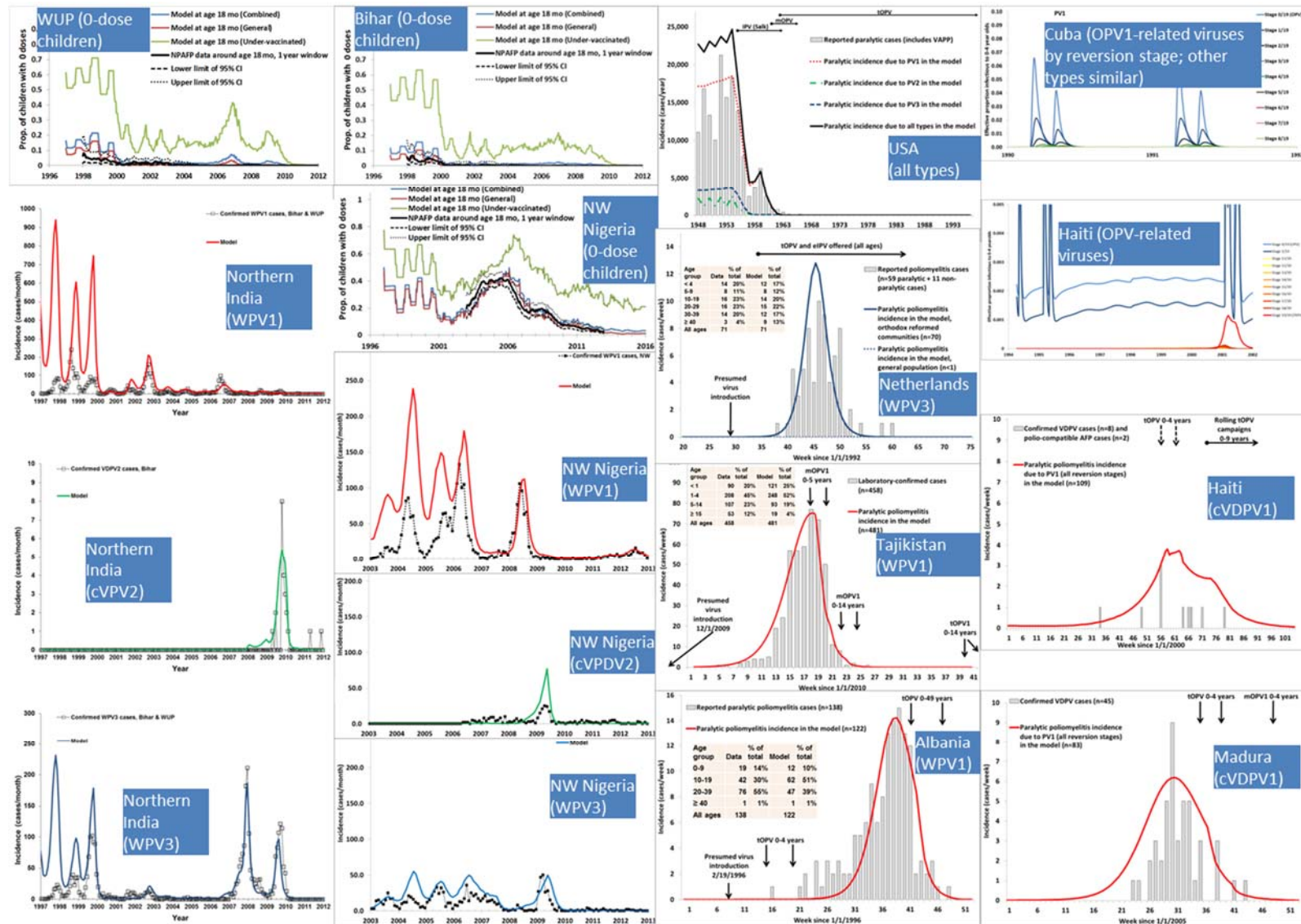
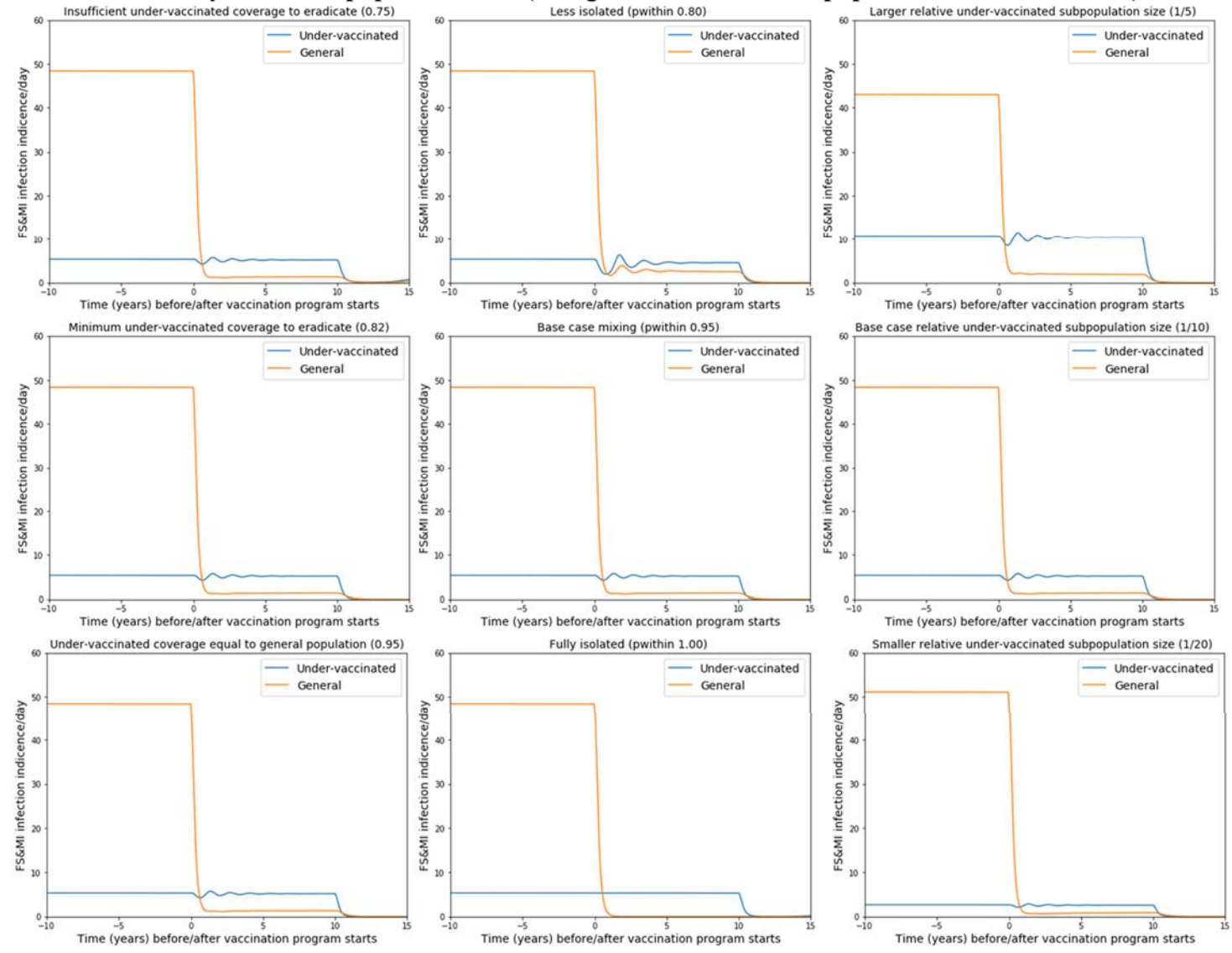




Figure A3: Differential-equation based model results for base case model inputs and varied coverage (left column), varied degree of isolation with coverage 0.82 (middle column), and varied relative size with coverage of 0.82 (right column). The y-axis scales linearly with total population size (all figures assume a total population size of 1 million).



# BMJ Open

## Global certification of wild poliovirus eradication: Insights from modeling hard-to-reach subpopulations and confidence about the absence of transmission

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Keywords:	polio, eradication, certification, modeling

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3 1 **Global certification of wild poliovirus eradication: Insights from modeling hard-to-reach**  
4 **subpopulations and confidence about the absence of transmission**  
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8 4 Radboud J. Duintjer Tebbens,<sup>1</sup> Dominika A. Kalkowska,<sup>1</sup> Kimberly M. Thompson<sup>1</sup>  
9 5

10 6 1. Kid Risk, Inc., Columbus, OH, USA  
11 7  
12 7

13 8 Running title: **Poliovirus certification confidence**  
14 9

15 10 Correspondence to: Kimberly M. Thompson, Kid Risk, Inc., 605 N High St, #253, Columbus,  
16 11 OH 43215, USA, Email: kimt@kidrisk.org  
17 12  
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19 13 **Abstract:**

20 14 **Objective:** To explore the extent to which under-vaccinated subpopulations may influence the  
21 15 confidence about no circulation of wild poliovirus (WPV) after the last detected case.  
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23 17 **Design and participants:** We used a hypothetical model to examine the extent to which the  
24 18 existence of an under-vaccinated subpopulation influences the confidence about no WPV  
25 19 circulation after the last detected case as a function of different characteristics of the  
26 20 subpopulation (e.g., size, extent of isolation). We also used the hypothetical population model to  
27 21 inform the bounds on the maximum possible time required to reach high confidence about no  
28 22 circulation in a completely-isolated and unvaccinated subpopulation starting either at the  
29 23 endemic equilibrium or with a single infection in an entirely susceptible population.  
30 24

31 25 **Results:** It may take over three years to reach 95% confidence about no circulation for this  
32 26 hypothetical population despite high surveillance sensitivity and high vaccination coverage in the  
33 27 surrounding general population if: (1) ability to detect cases in the under-vaccinated  
34 28 subpopulation remains exceedingly small, (2) the under-vaccinated subpopulation remains small  
35 29 and highly isolated from the general population, and (3) the coverage in the under-vaccinated  
36 30 subpopulation remains very close to the minimum needed to eradicate. Fully-isolated  
37 31 hypothetical populations of 4,000 people or less cannot sustain endemic transmission for more  
38 32 than 5 years, with at least 20,000 people required for a 50% chance of at least 5 years of  
39 33 sustained transmission in a population without seasonality that starts at the endemic equilibrium.  
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3 32 Notably, however, the population size required for persistent transmission increases significantly  
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5 33 for realistic populations that include some vaccination and seasonality and/or that do not begin at  
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7 34 the endemic equilibrium.

8 35 **Conclusions:** Significant trade-offs remain inherent in global polio certification decisions,  
9  
10 36 which underscore the need for making and valuing investments to maximize population  
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12 37 immunity and surveillance quality in all remaining possible WPV reservoirs.  
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15 39 **Strengths and limitations of this study:**

- 16  
17 40 • Models the limited but important role of under-vaccinated subpopulations in achieving  
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19 41 confidence about no WPV transmission after the last reported case.  
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21 42 • Explores trends in transmission and detection for different population sizes as time  
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23 43 increases since the last reported case.  
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25 44 • Examines the importance of maximizing population immunity and surveillance quality.  
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27 45 • Provides critical information to support decisions related to the ultimate certification of  
28  
29 46 wild poliovirus elimination.  
30  
31 47 • Analyses remain limited by model assumptions, but in abstract provide insights relevant  
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33 48 to likely last poliovirus reservoirs.  
34

35 50 **Keywords:** polio, eradication, certification, modeling  
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## 54 **Background**

55  
56 Achieving the 1988 World Health Assembly polio eradication goal of ending all cases of  
57 poliomyelitis<sup>1</sup> requires a successful transition from the interruption of the current low level of  
58 wild poliovirus (WPV) transmission through coordinated cessation of all use of live attenuated  
59 oral poliovirus vaccine (OPV) to effective long-term risk management. The Global Polio  
60 Laboratory Network supports the Global Polio Eradication Initiative (GPEI) by testing stool  
61 samples from acute flaccid paralysis (AFP) cases and sewage samples for polioviruses. As the  
62 GPEI approaches success, the transition to the polio endgame has begun. The endgame involves  
63 significant complexity, because all countries must achieve and maintain sufficient population  
64 immunity<sup>2-4</sup> to stop and prevent the transmission of three separate poliovirus serotypes (i.e., 1, 2,  
65 and 3) and globally coordinate cessation of each OPV serotype.<sup>5-7</sup> In September 2015, the  
66 Global Certification Commission declared successful eradication of serotype 2 WPV (WPV2),<sup>8</sup>  
67 which represented a prerequisite to the globally-coordinated cessation of all serotype 2-  
68 containing OPV use. Global cessation of serotype 2-containing OPV occurred in late April and  
69 early May 2016, during which time over 150 countries stopped using trivalent OPV (tOPV,  
70 which contains all three serotypes) and switched to bivalent OPV (bOPV, which contains only  
71 serotypes 1 and 3 OPV).<sup>9</sup>

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73 The Global Polio Laboratory Network reported the lowest number of annual paralytic serotype 1  
74 WPV (WPV1) cases in 2017,<sup>10</sup> and no serotype 3 WPV (WPV3) cases since November 2012.<sup>11</sup>  
75 Successful WPV eradication requires stopping all transmission, which manifests as an absence of  
76 detected WPVs despite actively looking. With increasing time of not seeing cases (while  
77 actively looking), confidence increases about WPV die-out. However, the absence of evidence is  
78 not evidence of absence. Extended silent transmission can occur, because most poliovirus  
79 infections do not lead to symptoms and surveillance gaps can exist. For example, a WPV3  
80 resurfaced in Sudan/Chad in 2004 after no reported cases during 1997-2003<sup>12</sup> and a WPV1  
81 resurfaced in Borno, Nigeria in 2016 after nearly 3 years with no reported cases<sup>13</sup>. The average  
82 paralysis-to-infection ratio (PIR), defined as the fraction of infections in fully susceptible  
83 individuals that leads to paralytic poliomyelitis (polio) symptoms, equals approximately 1/200,  
84 1/2000, and 1/1000, for serotype 1, 2, and 3 WPV, respectively.<sup>14</sup> The last reported naturally-

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3 85 occurring WPV2 case occurred in India in 1999,<sup>15</sup> and since then, only two episodes of WPV2  
4 86 infections occurred that traced back to laboratory strains.<sup>16 17</sup> Despite the possibility of silent  
5 87 circulation, the absence of any naturally-occurring WPV2 cases for over 15 years (and in many  
6 88 countries for many decades) led to very high confidence about the die-out of WPV2  
7 89 transmission.  
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12 91 Multiple prior mathematical modeling studies explored the probability of undetected circulation  
13 92 of WPVs in the absence of reported cases or other poliovirus detections. Polio eradication  
14 93 efforts in the Americas, which reported the last indigenous WPV case of any serotype in Peru in  
15 94 1991,<sup>18</sup> motivated the first analysis and discussion of certification requirements. A statistical  
16 95 analysis of Pan American Health Organization epidemiological data reported less than a 5%  
17 96 chance of undetected indigenous WPV circulation after 4 years since the last reported confirmed  
18 97 case.<sup>19</sup> A simple, stochastic model of poliovirus transmission and die-out characterized the  
19 98 probability of undetected poliovirus circulation in a hypothetical, homogeneously mixed  
20 99 population of 200,000 people in a relatively low-income country, and estimated that not  
21 100 observing a case for 3 years provided 95% confidence about local extinction of WPV  
22 101 infections.<sup>20</sup> This seminal paper provided the foundation for appropriate characterization of the  
23 102 probability of undetected circulation as a function of the time since the last detected case.<sup>20</sup>  
24 103 Related modeling also explored theoretical thresholds to stop transmission<sup>21</sup> and estimated a  
25 104 minimum population size for persistent transmission of 50,000-100,000 in developing countries  
26 105 and over 200,000 in developed countries required to achieve at least 95% probability of  
27 106 poliovirus persistence for 5 years or more in the absence of vaccination.<sup>22</sup> These studies  
28 107 supported the 2004-8 GPEI Strategic Plan requirement of at least 3 years of no polio cases  
29 108 detected by AFP surveillance for certification,<sup>23</sup> which remains the current minimum  
30 109 requirement.<sup>24</sup> A 2012 study<sup>25</sup> relaxed some of the assumptions of the prior theoretical model<sup>20</sup>  
31 110 and highlighted that the probability of undetected circulation varied for different poliovirus  
32 111 serotypes, places, and conditions, which suggested the need to focus on appropriate  
33 112 characterization of conditions in the last likely WPV reservoirs.<sup>25</sup> A 2015 study<sup>26</sup> also used the  
34 113 prior model<sup>20</sup> to show that in the context of an instantaneous introduction of vaccination, the  
35 114 time of the last case relative to vaccine introduction further informs the confidence about the  
36 115 absence of circulation.  
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5 117 Subsequent analyses focused on modeling the conditions in specific and more realistic  
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7 118 populations. A 2015 study<sup>27</sup> used a previously-developed poliovirus dynamic transmission  
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9 119 model<sup>2</sup> applied to: recently-endemic transmission in two states in northern India,<sup>28</sup> endemic  
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11 120 transmission in northwest Nigeria,<sup>29</sup> a 2010 outbreak in Tajikistan,<sup>30</sup> and transmission following  
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13 121 a 2013 WPV1 introduction into Israel detected by environmental surveillance.<sup>31</sup> The study  
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15 122 characterized the confidence about no undetected poliovirus circulation by serotype as a function  
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17 123 of time without reported polio cases or environmental detections considering realistic  
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19 124 assumptions for surveillance, immunization, and other national inputs.<sup>27</sup> The results suggested  
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21 125 that time periods of 0.5 to 3 years without detected polio cases provided 95% confidence about  
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23 126 the interruption of transmission in the context of perfect AFP surveillance depending on  
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25 127 situation-specific characteristics (e.g., the overall population immunity, endemic versus outbreak  
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27 128 conditions, and virus serotype).<sup>27</sup> This model also suggested longer times required for less-than-  
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29 129 perfect AFP surveillance and potentially shorter times using highly-sensitive environmental  
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31 130 surveillance based on the experience in Israel.<sup>27</sup> A recent statistical analysis of the 2013 WPV1  
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33 131 outbreak in Israel demonstrated a rapid increase in confidence about no undetected local  
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35 132 transmission following outbreak response immunization after repeated negative environmental  
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37 133 surveillance samples in a city.<sup>32</sup> A non-dynamic, statistical model<sup>33</sup> estimated a shorter time  
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39 134 (compared to the 2015 study<sup>27</sup>) of 14 months required to reach high confidence about no  
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41 135 undetected circulation. For its most conservative assumptions about surveillance and force-of-  
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43 136 infection, the study estimated a probability of 93% of a WPV-free Africa in the absence of any  
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45 137 new WPV cases reported by the end of 2015,<sup>33</sup> shortly before the WPV reemerged.<sup>13</sup>  
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47 138 Contrasting with all other modeling studies, a recent study<sup>34</sup> suggested a relatively high  
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49 139 probability of undetected circulation after more than 3 years without any polio cases in small  
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51 140 populations, although a correction to that analysis emphasized the unrealistic nature of one of the  
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53 141 assumptions.<sup>35</sup> Remarkably, the analysis reported that closed populations of 10,000 people or  
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55 142 fewer could support many years of transmission in the absence of vaccination, and experience  
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57 143 gaps between polio cases of over 5 years.<sup>34</sup> A reanalysis of this hypothetical model identified  
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59 144 issues with the analysis and its framing, and reported results consistent with the prior literature  
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145 after correcting for some errors.<sup>36</sup>  
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3 147 Although the modeling results demonstrated the critical importance of sustaining high population  
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5 148 immunity through immunization programs and high-quality surveillance to obtain high  
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7 149 confidence about no undetected circulation, the current GPEI strategic plan only covers 2013-  
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9 150 2018,<sup>6</sup> which leads to uncertainty about the ability to sustain high program performance after  
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11 151 2018. As of mid-2018, questions continue to arise about when the GPEI will cease to exist and  
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13 152 what resources will be available to support the polio endgame, including the certification of  
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15 153 eradication of WPV1 and WPV3 with high confidence. The GPEI partners already began  
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17 154 transition planning, and this process already led to some downsizing of national poliovirus  
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19 155 programs, including the reduction of some AFP surveillance activities.<sup>37</sup> Thus, while the prior  
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21 156 modeling assumed strong GPEI and national polio program performance up through the end of  
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23 157 the polio endgame, this assumption now appears optimistic, and further analyses that explore the  
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25 158 impact of lower quality surveillance may prove useful in the context of global certification  
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27 159 decisions for WPV1 and WPV3 eradication. Further motivation for developing models to  
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29 160 support certification decisions comes from the re-appearance of WPV1 in security-compromised  
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31 161 areas in Borno, Nigeria after apparent interruption, which raised questions about the ability of  
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33 162 poliovirus circulation without detection in communities not (or poorly) accessed by  
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35 163 immunization and surveillance efforts within larger populations with high immunity and good  
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37 164 surveillance.

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41 166 This study aims to support future decisions about WPV certification by: (1) informing  
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43 167 confidence about the absence of circulation by modeling the role of hard-to-reach populations,  
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45 168 (2) examining the minimum population size required to sustain poliovirus transmission, and (3)  
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47 169 developing a conceptual framework to provide some structure for future certification decisions.  
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## 171 **Methods**

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173 To inform confidence about the absence of circulation by modeling the role of hard-to-reach  
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175 populations, we explored the impact of key assumptions using an existing model of a  
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177 hypothetical population comprised of a well-vaccinated general population and an under-  
vaccinated subpopulation.<sup>38</sup> Table 1 lists the model inputs used to characterize this hypothetical  
population and explore the role of key assumptions (see appendix text, Table A1, and Figures

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3 178 A1, A2, and A3 for model details). To explore different population characteristics, we varied the  
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5 179 total population size, the size of the under-vaccinated subpopulation, and the degree of mixing  
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7 180 between the under-vaccinated and general population around a base case indicated by the bold  
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9 181 values in Table 1. In addition, for each variation around the base case, we simultaneously varied  
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11 182 the routine immunization coverage and detection probability per polio case in the under-  
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13 183 vaccinated subpopulation. We interpret the total hypothetical population as one epidemiological  
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15 184 block (e.g., a country) and therefore compute the confidence about no circulation based on all  
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17 185 detections that occur in the general population and under-vaccinated subpopulation combined.  
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19 186 However, we fix the detection probability in the general population at 95% to characterize high-  
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21 187 quality national surveillance while considering lower detection probabilities only in the under-  
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23 188 vaccinated subpopulation (Table 1).<sup>38</sup> To estimate the confidence about no circulation in this  
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25 189 conceptual model, we use a simplified version (see appendix) of the stochastic approach  
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27 190 developed by Eichner and Dietz (1996)<sup>20</sup> and adopted by others.<sup>25-27</sup> We define the probability  
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29 191 of undetected circulation after a given period of  $t$  months without a detection as the number of  
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31 192 times in multiple stochastic simulations that  $t$  months went by without a detection despite  
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33 193 continued circulation, divided by the total number of times that  $t$  months went by without a  
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35 194 detection (i.e., with or without continued circulation). Intuitively, the fraction of all time periods  
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37 195 of  $t$  months without a detection but with transmission still ongoing should decrease as  $t$  increases,  
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39 196 corresponding to an increasing probability of no circulation. Confidence about no circulation  
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41 197 equals one minus the probability of undetected circulation. To visualize the impact of varying  
42  
43 198 the model inputs, we focus on the time without a detection until the confidence about no  
44  
45 199 circulation first exceeds 95% (CNC95%).

46  
47 200  
48 201 We revisit the question of silent transmission in small populations<sup>22 34 36</sup> using the hypothetical  
49  
50 202 population model<sup>38</sup> in an attempt to inform the bounds on the maximum possible CNC95%. To  
51  
52 203 do so, we ignore the general population and effectively assume a completely-isolated and  
53  
54 204 unvaccinated subpopulation and otherwise adopt the hypothetical population assumptions from  
55  
56 205 Table 1. We transform the DEB model to a stochastic form using the Gillespie algorithm,<sup>39</sup> as  
57  
58 206 described elsewhere,<sup>27</sup> and start either at the endemic equilibrium<sup>34</sup> or with a single infection in  
59  
60 207 an entirely susceptible population. Instead of modeling die-out using the transmission  
61  
62 208 threshold,<sup>27</sup> we allow transmission to continue until the infection prevalence becomes 0. This



209 complements the existing work<sup>22 34 36</sup> by providing a comparison to the same situation with a  
210 more comprehensive model for poliovirus transmission,<sup>2</sup> adding consideration of the impact of  
211 the initial conditions, and adding the impact on confidence about no circulation.

212  
213 Finally, recognizing the complexity and inter-related nature of certification decisions, we  
214 developed an influence diagram to relate certification timing decisions to outcomes. The  
215 diagram provides a conceptual framework to support certification decisions and formulate  
216 decisions about the timing of certification as an optimization problem. The diagram uses  
217 conventions from causal loop diagrams<sup>40</sup> and specifies the directionality of relationships  
218 between variables using unidirectional arrows. The polarity or sign at the arrow head indicates  
219 whether increasing the variable at the base of the arrow increases (+) or decreases (-) the variable  
220 that the arrow points to with all else being equal.

#### 222 *Patient and Public Involvement*

224 This study did not involve patients or public opportunities for engagement.

## 226 **Results**

228 Figure 1 illustrates how the confidence about no circulation increases with time after the last  
229 detection as a function of the surveillance quality in the under-vaccinated subpopulation (i.e., the  
230 detection probability). Clearly, higher confidence implies the need to wait longer after the last  
231 detected case, and lower detection probabilities further increase the time required to reach a  
232 certain level of confidence (e.g., the 95% line). Figure 1 shows a relatively modest effect of the  
233 detection probability in the under-vaccinated subpopulation for this hypothetical model due to  
234 continued occurrence of cases in the general population for the assumed degree of mixing (see  
235 appendix).

237 Figure 2 shows the CNC95% values as a function of coverage and detection probability for the  
238 under-vaccinated subpopulation. The figure shows longer times required to reach CNC95%  
239 values with increasingly more isolated under-vaccinated subpopulations (left column, top to

1  
2  
3 240 bottom), with decreasing relative sizes of the under-vaccinated subpopulation (middle column,  
4  
5 241 top to bottom), and decreasing absolute sizes of a fully-isolated under-vaccinated subpopulation  
6  
7 242 (right column, top to bottom, note increased y-axis ranges). The panels in Figure 2 omit curves  
8  
9 243 for coverage values that do not result in eradication, because they do not allow for calculation of  
10  
11 244 any confidence about eradication. The panels also omit the data point for 0 detection probability  
12  
13 245 in the event of a fully-isolated under-vaccinated subpopulation, because that would imply no  
14  
15 246 ability to detect the virus. Consistent with previous findings,<sup>27</sup> all panels in Figure 2 show  
16  
17 247 higher CNC95% values with higher coverage in the under-vaccinated subpopulation. In each  
18  
19 248 panel, the lowest shown coverage value may result in the longest period of undetected circulation  
20  
21 249 before interruption and therefore result in the longest time to achieve high confidence about no  
22  
23 250 circulation.

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25 251  
26  
27 252 Looking more closely at the differences between the columns, the left column of Figure 2 shows  
28  
29 253 a very strong influence of the degree of isolation on the CNC95%. With little isolation and no  
30  
31 254 surveillance in the under-vaccinated subpopulation, the general population with high surveillance  
32  
33 255 quality can still detect transmission because of relatively frequent spillover of polio cases (see  
34  
35 256 appendix). Thus, the results do not depend much on the detection probability in the under-  
36  
37 257 vaccinated subpopulation for  $p_{\text{within}}=0.8$ . In contrast, for a fully isolated under-vaccinated  
38  
39 258 subpopulation ( $p_{\text{within}}=1$ ), the detection probability in this population becomes a more important  
40  
41 259 driver of the CNC95% than the coverage (i.e., for detection probability of 0.1 or very poor  
42  
43 260 surveillance and all other inputs at the base case, the CNC95% equals almost 6 years regardless  
44  
45 261 of coverage). The middle column of Figure 2 shows CNC95% values of approximately 5 years  
46  
47 262 with no surveillance in a relatively small under-vaccinated subpopulation. Although the relative  
48  
49 263 size of the under-vaccinated subpopulation affects the mixing dynamics and incidence of cases in  
50  
51 264 both populations, much of the observed effect comes from the implied change in the absolute  
52  
53 265 size of the under-vaccinated subpopulation, which directly affects the typical time between cases.  
54  
55 266 As shown in the right column of Figure 2, changing the absolute size of the under-vaccinated  
56  
57 267 subpopulation in the event of full isolation from the general population and a detection  
58  
59 268 probability of 0.1 dramatically affects the CNC95%, which ranges from slightly over 2 years for  
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269 500,000 people to approximately 9 years for 50,000 people (i.e., a 4-fold increase in CNC95%  
270 for a 10-fold increase in population size).

1  
2  
3 271  
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5 272 Considering the relatively high CNC95% observed for small, isolated populations in Figure 2,  
6  
7 273 Figure 3A uses a stochastic model to show the distribution of the duration of circulation in a  
8  
9 274 single population not reached by vaccination at all. Figure 3A shows the results as a function of  
10  
11 275 population size for a model initialized at the endemic equilibrium. For very small population  
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13 276 sizes (e.g., hundreds), not surprisingly poliovirus infections typically die-out within a year, with  
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15 277 a maximum duration of circulation of one year and 4 months for a closed population of 1,000  
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17 278 people (based on 10,000 iterations). The maximum duration of circulation increases rapidly for  
18  
19 279 larger populations. For a population of 5,000 people, circulation continues for 3 or more years in  
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21 280 50 of 10,000 (0.5%) iterations. With population sizes of 10,000, 20,000, 30,000, 40,000 and  
22  
23 281 50,000, circulation continues for at least 10 years for 3%, 34%, 63%, 79%, and 88% of  
24  
25 282 iterations, respectively.

26 283  
27 284 Figure 3B shows the same analysis as Figure 3A except that it changes the initial conditions by  
28  
29 285 assuming a population with no prior exposure to any polioviruses. In this context, a single  
30  
31 286 introduction rapidly burns through the entire susceptible population and quickly exhausts  
32  
33 287 susceptible individuals, leading to die-out and a maximum duration of circulation of less than 2  
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35 288 years for all population sizes considered in Figure 3b. Together, Figures 3A and 3B encompass  
36  
37 289 the bounds on the possible duration of circulation for different initial conditions. In reality,  
38  
39 290 small, completely isolated populations are unlikely to remain at the endemic equilibrium because  
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41 291 of random fluctuations in the incidence, seasonality, and die-out, and no completely naïve  
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43 292 populations likely exist. In a separate analysis using the same model, we verified that the  
44  
45 293 addition of seasonality decreases the typical duration of circulation and increases the probability  
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47 294 of eradication within 5 years. For example, for a population size of 20,000 people, the  
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49 295 probability of eradication within 5 years increased from approximately 64% without seasonality  
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51 296 to 78%-92% with a seasonal amplitude of 10% (applied to the basic reproduction number of 10),  
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53 297 depending on the timing of the seasonal peak.

54 298  
55 299 While Figure 3 implies that increasing the population size results in an increasing probability of  
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57 300 persistent circulation (i.e., a greater probability of sustained undetected transmission), Figure 2  
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59 301 implies that increasing population size decreases the typical time interval between cases (i.e.,  
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3 302 lower probabilities of sustained undetected circulation). Figure 4 shows the net effect of these  
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5 303 two opposing trends and suggests that an optimal population size exists around 20,000 people.  
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7 304 For smaller population sizes, continued transmission becomes exceedingly unlikely (Figure 3),  
8  
9 305 while for larger population sizes, undetected circulation becomes less likely due to the higher  
10  
11 306 frequency of cases. This non-linear behavior suggests a maximum CNC95% of approximately  
12  
13 307 2.5 years for a detection probability of 1, although the maximum increases to up to 9 years for a  
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15 308 very low detection probability of 0.1 and a population size of 20,000 to 30,000 people.

16 309  
17 310 Figure 5 shows how the desired confidence about no circulation may influence certification  
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19 311 timing and key health economic outcomes (see appendix text and Table A2 for details). Earlier  
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21 312 certification and OPV cessation may increase the risk of undetected circulation after OPV  
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23 313 cessation (and therefore the possibility of needing to restart OPV use) but may decrease the costs  
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25 314 until OPV cessation (and therefore the overall global costs for planned polio immunization).  
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27 315 Therefore, the fundamental optimization problem consists of finding the desired confidence  
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29 316 about no WPV circulation at OPV cessation that minimizes the resulting total financial and  
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31 317 societal costs. Figure 5 also shows that the costs and risks both depend on the GPEI budget until  
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33 318 and after OPV cessation, with a lower budget saving costs in the short term but increasing the  
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35 319 time of OPV cessation at a given confidence level and the risks of OPV restarts, which may  
36  
37 320 ultimately result in greater overall costs. Optimization of the desired confidence about no WPV  
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39 321 circulation depends critically on how the confidence about no circulation increases with time  
40  
41 322 after the last detected event from the surveillance system.

## 42 323 43 324 **Discussion**

44 325  
45 326 Hard-to-reach subpopulations may play a key role in deliberations about WPV circulation and  
46  
47 327 decisions about WPV certification. The timing of WPV certification and subsequent OPV  
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49 328 cessation involves high stakes and largely depends on the desired confidence about the absence  
50  
51 329 of circulation. Surveillance quality emerges as a key factor that affects both the confidence  
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53 330 about the absence of circulation and the ability to detect and control any outbreaks after OPV  
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55 331 cessation. However, national surveillance indicators may not suffice to measure the overall  
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57 332 surveillance system quality because gaps in surveillance at the level of tens of thousands of

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3 333 people may influence confidence. Our modeling suggests that high quality surveillance suffices  
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5 334 to detect transmission in the context of a relatively well-mixed under-vaccinated subpopulation  
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7 335 (e.g., in Pakistan and Afghanistan),<sup>41</sup> while local gaps may miss transmission for several years in  
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9 336 the context of highly-isolated under-vaccinated subpopulations. With respect to global  
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11 337 certification of WPV eradication, this implies a need to address any such gaps in isolated  
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13 338 populations that experienced WPV transmission during the last decade. The recent experience in  
14  
15 339 Borno and previously in Chad and Sudan demonstrated the ability of WPVs to circulate  
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17 340 undetected for many years in sub-populations missed by both surveillance and immunization  
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19 341 efforts.<sup>12 13</sup> However, one of the main contributions of this work is that it shows that very small,  
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21 342 isolated subpopulations cannot sustain transmission indigenously, while in the context of even  
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23 343 very limited surveillance, persistent undetected transmission becomes increasingly unlikely for  
24  
25 344 increasing population sizes. To our knowledge, the existence of a worst-case population size for  
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27 345 undetected circulation has not yet been demonstrated for polioviruses. Our analysis confirms  
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29 346 that with high-quality surveillance, 3 years without a detected WPV case suffices to attain high  
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31 347 confidence about no circulation for serotype 1, even considering possible persistence in very  
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33 348 small population sizes.

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35 349  
36 350 Explicit consideration of the decision to certify WPV eradication (Figure 5) suggests that if we  
37  
38 351 remain confident that we can prevent the need to restart OPV due to uncontrolled outbreaks  
39  
40 352 resulting from a possible WPV reemergence, then we should accept a lower confidence about the  
41  
42 353 absence of circulation to certify sooner, because the costs of delaying OPV cessation would  
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44 354 outweigh the risk of premature certification. Earlier OPV cessation particularly represents the  
45  
46 355 best option if diminishing GPEI financial and/or global OPV supply resources limit our ability to  
47  
48 356 maintain population immunity and/or respond effectively to post-cessation outbreaks. However,  
49  
50 357 this choice depends on a willingness to accept the reputational risk of finding out that WPV still  
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52 358 circulates despite its certification. With WPV3 not detected anywhere since 2012<sup>11</sup> and in many  
53  
54 359 places for decades, the confidence about no WPV3 circulation continues to grow. Although  
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56 360 confidence about no circulation increases more slowly for WPV3 than WPV1 due to the lower  
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58 361 PIR,<sup>25 27</sup> assuming 1-2 years to prepare for coordinated global OPV cessation, starting the  
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60 362 process of removing serotype 3 OPV now would imply at least 7 years of no detection since the  
363 last WPV3 case and synchronized cessation of serotype 3 OPV use (i.e., 2012 to 2019-2020).

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3 364 The transition of GPEI resources already occurring leads to expected decreases in population  
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5 365 immunity for serotype 3 in some areas. Combined with on-going serotype 3 vaccine-associated  
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7 366 paralytic poliomyelitis, this should motivate careful consideration of the costs, benefits, risks,  
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9 367 and logistical challenges of globally certifying WPV3 eradication and synchronizing serotype 3  
10  
11 368 OPV cessation before completing WPV1 eradication and serotype 1 OPV cessation, which now  
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13 369 appears at least 4 years away.

14 370  
15 371 Our results related to minimum population sizes appear consistent with a prior study<sup>22</sup> that  
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17 372 found an average of approximately 5 years of circulation for a population of 20,000 people in a  
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19 373 high- $R_0$  setting and an exponential increase in the average duration of circulation with increasing  
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21 374 population size. The prior study also reported a higher probability of virus persistence as the  
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23 375 degree of mixing between subpopulations increases.<sup>22</sup> Our study suggests that more mixing  
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25 376 between subpopulations may not lead to a higher probability of undetected circulation because  
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27 377 surveillance can more easily detect persistent viruses for higher degrees of mixing. Using a more  
28  
29 378 realistic model than another prior analysis,<sup>36</sup> we similarly do not find a high probability of  
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31 379 persistent transmission for populations of 10,000 people or less.

32 380  
33 381 Like all models, our model makes simplifying assumptions that affect its behavior.<sup>2</sup> Specifically,  
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35 382 we characterized a stylized, hypothetical population to systematically explore key assumptions,  
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37 383 used a simplified semi-stochastic approach to compute CNC95% that does not fully account for  
38  
39 384 all stochastic variability, and deterministically characterized die-out. However, for the analysis  
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41 385 of small population sizes that depend most on stochastic variability, we accounted for stochastic  
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43 386 variability and die-out at the individual level.

44 387  
45 388 While this study highlights the importance of ensuring high surveillance quality in all  
46  
47 389 subpopulations, it also reiterates the role of immunization in accelerating confidence about no  
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49 390 circulation after the last detection.<sup>27</sup> Achieving and maintaining high population immunity to  
50  
51 391 transmission represents a mission critical component of the GPEI.<sup>4</sup> Populations with immunity  
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53 392 near the threshold experience increased risk of prolonged undetected transmission. Failing to  
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55 393 invest relatively small amounts of resources to maintain high population immunity can lead to  
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57 394 much more costly outbreaks, as occurred for example in Tajikistan.<sup>3</sup> Thus, if ensuring high-



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3 395 quality surveillance in all subpopulations remains an elusive goal, then achieving better coverage  
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5 396 in those subpopulations would still result in higher confidence about no circulation. In contrast,  
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7 397 high quality surveillance in the context of poor immunization still leaves the population and the  
8  
9 398 world at risk.

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11  
12 400 Poliovirus environmental surveillance can detect polioviruses even in the absence of  
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14 401 symptomatic polio cases<sup>42 43</sup> and offers the potential to fill some local gaps in symptomatic  
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16 402 poliovirus surveillance. For example, the extensive environmental surveillance system in Israel  
17  
18 403 effectively detected transmission of circulating WPV1 in the absence of any cases and despite  
19  
20 404 very high coverage with inactivated poliovirus vaccine (IPV).<sup>31 44</sup> However, despite the potential  
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22 405 for high sensitivity of environmental surveillance to detect infected individuals excreting into the  
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24 406 catchment area, its sensitivity remains zero outside of the catchment area and depends on  
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26 407 sampling frequency (e.g., one sample every year provides little increase in confidence over AFP  
27  
28 408 alone and the quality matters).<sup>45</sup> Environmental surveillance system designs generally depend on  
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30 409 access to a centralized sewage network,<sup>43</sup> which hard-to-reach subpopulations (i.e., those most  
31  
32 410 likely to sustain undetected poliovirus transmission) may not possess. Further research should  
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34 411 help to explore the ability of environmental surveillance to increase confidence about no  
35  
36 412 circulation in specific areas, and the value of the information obtained from environmental  
37  
38 413 surveillance relative to its costs requires evaluation.

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41 415 IPV plays a relatively limited role with respect to the CNC. While IPV protects otherwise  
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43 416 susceptible individuals from paralysis if they become subsequently infected with a live  
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45 417 poliovirus and may reduce the participation of these individuals in transmission to some degree,  
46  
47 418 the decreased frequency of paralysis in live poliovirus-infected individuals in the population may  
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49 419 delay the detection of any circulating live poliovirus in countries by AFP surveillance (i.e., less  
50  
51 420 frequent detection of polio AFP cases depending on IPV coverage) We note the polio AFP  
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53 421 detection rate depends on the exposure of fully-susceptible individuals to live poliovirus and it  
54  
55 422 differs from the non-polio AFP detection rate, with the Global Polio Laboratory Network uses to  
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57 423 monitor performance of the AFP surveillance system and is not affected by IPV use). Overall,  
58  
59 424 immunization with IPV helps to maintain population immunity to transmission somewhat, but  
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425 given births of immunologically naïve, deaths of immune individuals, waning immunity, and the



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3 426 absence of circulating live polioviruses, population immunity to transmission declines following  
4 427 WPV eradication and homotypic OPV cessation, even with very high IPV coverage.<sup>46</sup> The  
5 428 extent of transmission possible following reintroduction of a live poliovirus into a country with  
6 429 high IPV coverage will depend on the relative contributions of fecal-oral and oropharyngeal  
7 430 routes to overall transmission.<sup>4</sup> In countries dominated by fecal-oral transmission, the use of IPV  
8 431 will not prevent or stop transmission, and reintroduced live polioviruses that restart transmission  
9 432 may lead to the need to restart the use of OPV.<sup>47</sup>  
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15 433  
16  
17 434 **List of abbreviations:** AFP, acute flaccid paralysis; CNC95%, Time until the confidence about  
18 435 no circulation reaches 95%; cVDPV, circulating VDPV DEB, differential-equation based; GPEI,  
19 436 Global Polio Eradication Initiative; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus  
20 437 vaccine; PIR, paralysis-to-infection ratio; VDPV, vaccine-derived poliovirus; WPV(1,2,3), wild  
21 438 poliovirus (of serotype 1, 2, 3, respectively)  
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26 439

## 27 440 **DECLARATIONS**

28 441

### 29 442 **Authors' contributions**

30 443 All authors (RDT, DAK, KMT) contributed to the study design, model development,  
31 444 interpretation of results, manuscript writing, and revisions. The first and second authors (RDT,  
32 445 DAK) performed the modeling and analyses, and the last author (KMT) secured the funding for  
33 446 the study.  
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### 40 448 **Ethics approval and consent to participate**

41 449 Not applicable  
42  
43  
44

45 450

### 46 451 **Consent to publish**

47 452 Not applicable  
48  
49

50 453

### 51 454 **Competing interests**

52 455 None  
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## 464 **Data sharing statement**

465 Technical appendix available on request from the authors.

466

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**Table 1: Model inputs to characterize a hypothetical population that contains an under-vaccinated subpopulation.**

Model input	Value(s) <sup>a</sup>	Source/notes
Total population size	500,000; <b>1 million</b> ;5 million	No effect on DEB model behavior, but required for stochastic analysis of detections
Time until vaccination starts, years		Assumption to characterize hard-to-reach subpopulation within well-vaccinated general population
General population	30	
Under-vaccinated subpopulation	40	
Initial age distribution		Equilibrium age distribution <sup>38</sup>
0-2 months	0.01	
3-59 months	0.15	
5-14 years	0.25	
≥ 15 years	0.59	
Birth rate, births/person/year	0.02	38
Death rate, deaths/person/year	0.02	38
Basic reproduction number ( $R_0$ )	10	38
Proportion of transmissions via oropharyngeal route	0.3	38
Proportion of contacts reserved for individuals within the same mixing age group	0.4	Same value as used in <sup>38</sup> (not explicitly listed)
Average per-dose take rate for serotype 1 OPV	0.6	Increased from 0.5 to maintain similar coverage thresholds with different run-up <sup>38</sup>
Routine immunization coverage		Represents coverage with exactly 3 OPV doses; general population based on <sup>38</sup> , under-vaccinated varied around threshold to eradicate, which equals 0.82 for the bolded values in the middle column
General population	0.95	
Under-vaccinated subpopulation	0.75; <b>0.82</b> ;0.85;0.90;0.95 <sup>b</sup>	
Proportion of contacts with under-vaccinated subpopulation ( $p_{within}$ )	0.8; <b>0.95</b> ;1.00	Selected values from <sup>38</sup>
Size of under-vaccinated subpopulation compared to total population	1/20; <b>1/10</b> ;1/5	Selected values from <sup>38</sup>
Paralysis-to-infection ratio (PIR)	1/200	Average for serotype 1 wild poliovirus <sup>2 14</sup>
Detection probability per polio case		Assumption to characterize hard-to-reach subpopulation within general population with high acute flaccid paralysis surveillance quality
General population	0.95	
Under-vaccinated subpopulations	0;0.1;0.2;0.3;0.4;0.5;0.6;0.7;0.8;0.9;0.95 <sup>b</sup>	

Abbreviations: DEB, differential-equation based; OPV, oral poliovirus vaccine

<sup>a</sup> Values shown in bold represent values that we held fixed when varying other values in sensitivity analyses

<sup>b</sup> All values considered jointly in all sensitivity analysis (hence no single value bolded)



## Figure Captions

Figure 1: Confidence about no circulation as a function of time since the last detection for different detection probability values for the hypothetical model base case, with coverage at the corresponding minimum to eliminate WPV (i.e., 0.82).

Figure 2: Time until the confidence about no circulation reaches 95% (CNC95%) from the stochastic analysis for different degrees of isolation of the under-vaccinated subpopulation (left column), relative sizes of the under-vaccinated subpopulation (middle column), and absolute sizes of a fully-isolated under-vaccinated subpopulation (right column, note doubled y-axis ranges).

Figure 3: Results from the analysis of the relationship between population size and persistence of circulation of serotype 1 wild poliovirus transmission in the fully stochastic model when (A) the model starts at the endemic equilibrium and (B) the model starts with a single infection in a fully susceptible population

Figure 4: Time until the confidence about no circulation reaches 95% (CNC95%) for small population sizes in the fully stochastic model that starts at the endemic equilibrium, as a function of detection probability (DP)

Figure 5: Conceptual diagram for the implications of choices about the timing of certification of eradication of a wild poliovirus serotype on total financial and societal costs



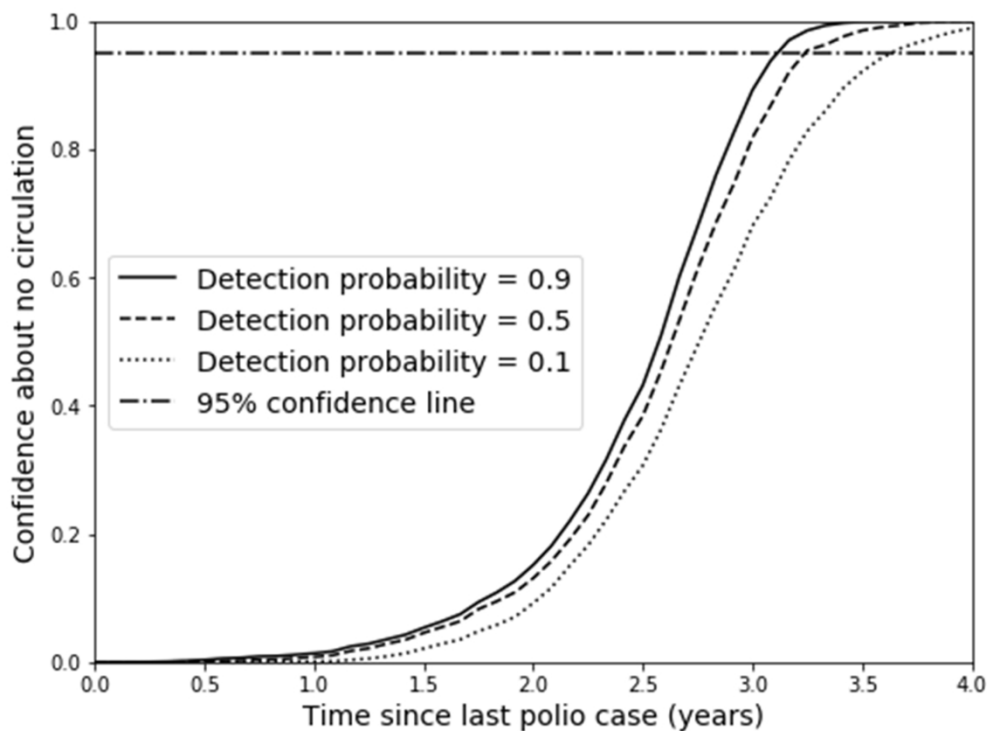


Figure 1: Confidence about no circulation as a function of time since the last detection for different detection probability values for the hypothetical model base case, with coverage at the corresponding minimum to eliminate WPV (i.e., 0.82).

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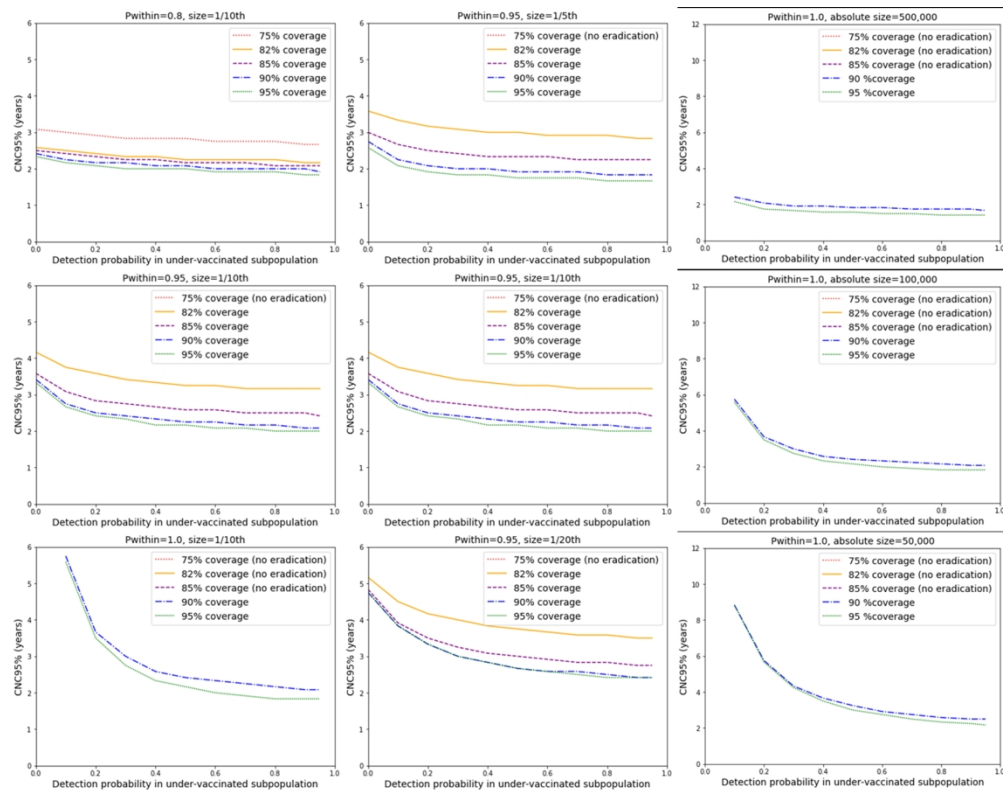


Figure 2: Time until the confidence about no circulation reaches 95% (CNC95%) from the stochastic analysis for different degrees of isolation of the under-vaccinated subpopulation (left column), relative sizes of the under-vaccinated subpopulation (middle column), and absolute sizes of a fully-isolated under-vaccinated subpopulation (right column, note doubled y-axis ranges).

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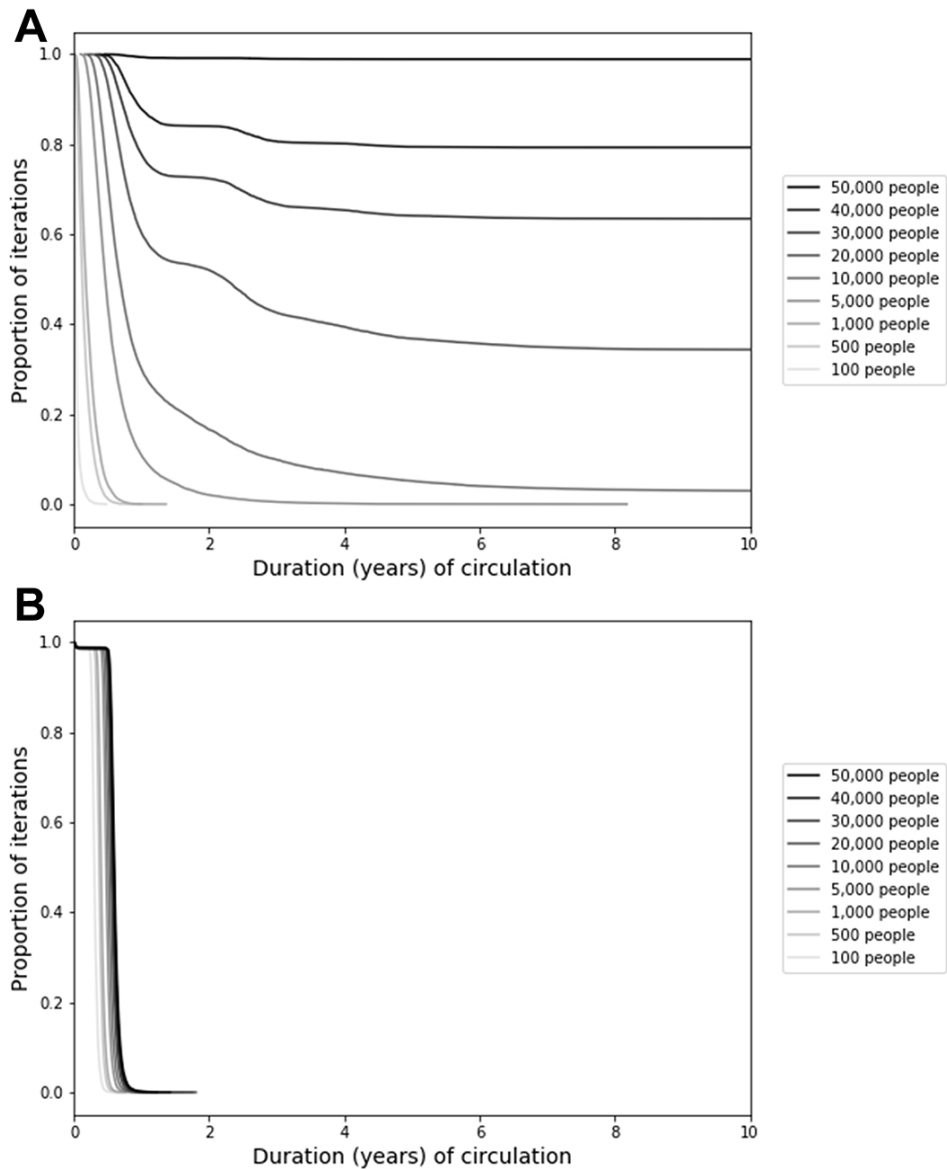


Figure 3: Results from the analysis of the relationship between population size and persistence of circulation of serotype 1 wild poliovirus transmission in the fully stochastic model when (A) the model starts at the endemic equilibrium and (B) the model starts with a single infection in a fully susceptible population

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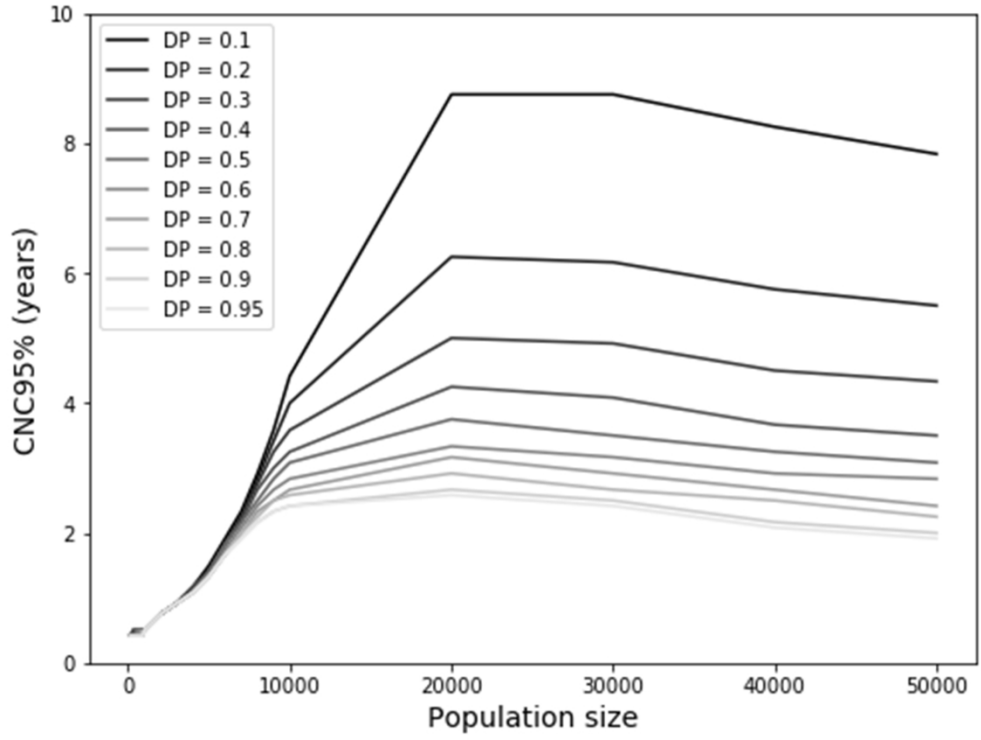


Figure 4: Time until the confidence about no circulation reaches 95% (CNC95%) for small population sizes in the fully stochastic model that starts at the endemic equilibrium, by detection probability (DP)

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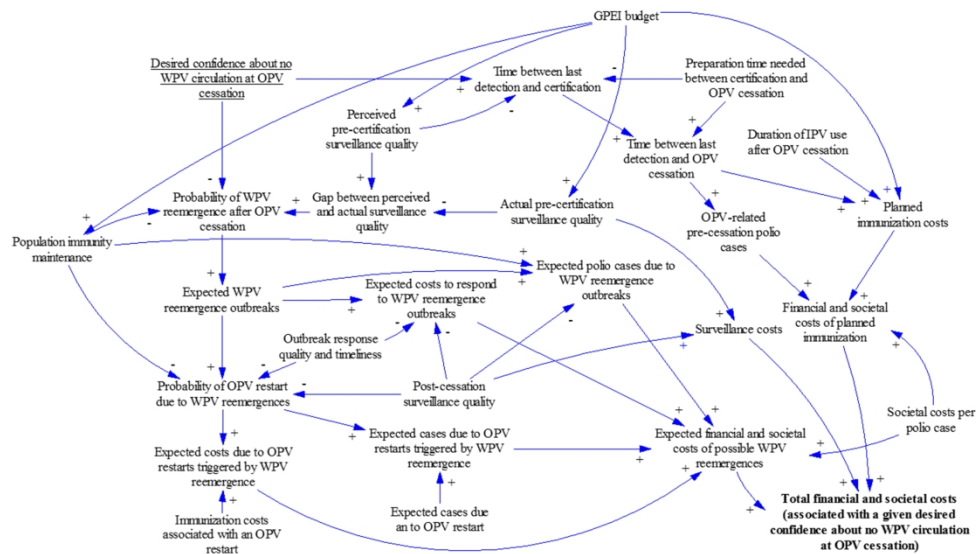


Figure 5: Conceptual diagram for the implications of choices about the timing of certification of eradication of a wild poliovirus serotype on total financial and societal costs

228x135mm (300 x 300 DPI)

## APPENDIX for “Certification of global eradication: The role of hard-to-reach subpopulations and confidence about the absence of transmission”

Radboud J. Duintjer Tebbens,<sup>1</sup> Dominika A. Kalkowska,<sup>1</sup> Kimberly M. Thompson<sup>1</sup>

### *Differential-equation based model and results*

The DEB model we use to examine the role of subpopulations<sup>38</sup> made simplifying assumptions about what a high-risk population might look like and otherwise adopted the comprehensive structure and setting-invariant model inputs of a previously developed and calibrated differential-equation based poliovirus transmission and OPV evolution model.<sup>2,30</sup> The following text from the appendix of a prior publication<sup>45</sup> (with references renumbered) briefly describes the model and Figures A1-2 and Table A1 cited in the text provide the model structure and generic inputs (i.e., model inputs that remain the same for all populations).

“The differential equation-based poliovirus transmission and OPV evolution model (DEB model)<sup>2</sup> tracks the movement of people between demographic age groups (grouped into mixing age groups that mix preferentially amongst themselves), and for each serotype between oropharyngeal and intestinal infection stages (resulting in potential oropharyngeal and fecal-oral transmission, respectively), immunity states, and waning stages. Figure A1 provides an overview of the model structure based on prior work.<sup>2</sup> Figure A1a depicts the immunity states with the flows that move individuals in and out of them and Figure A1b details how effectively vaccinated or infected individuals progress through different stages of infection and, in the event of infection with OPV, through OPV evolution stages. The model assumes that active immunity from prior vaccination or infection results in permanent protection from polio (disease), but only partial protection from subsequent infection and participation in transmission, depending on the nature of immunity (IPV-induced vs. LPV-induced or both) and time since the last exposure (i.e. waning stage). The model includes 5 waning stages, 6 fecal-oral and 6 oropharyngeal infection stages (2 latent and 4 infectious, with varying degrees of infectiousness), and also accounts for a delay between IPV receipt and development of the immune response that moves individuals to the next IPV immunity state. In Figure A1a, we note that the model assumes identical properties for “IPV and LPV” and “ $\geq 2$  LPV infections” and that the recent waning stages of these immunity states represent the highest degree of immunity to transmission in the model. The model further tracks OPV evolution by moving individuals infected with the OPV parent strain (stage 0) through 20 successive reversion stages that can each transmit and that come with increasing paralysis-to-infection ratios and relative basic reproduction numbers ( $R_0$  values) compared to homotypic WPVs. The last reversion stage (stage 19) represents fully-reverted VDPVs with assumed paralysis-to-infection ratio and  $R_0$  equivalent to homotypic WPVs. For WPVs or any OPV reversion stage, the DEB model mimics die-out by setting the force-of-infection for the given strain to 0 whenever its effective prevalence of infections resides below a calibrated threshold of 5 per million people. Consequently, OPV-related viruses can only continue to transmit and thus evolve to cVDPVs through successive infections when low enough population immunity to transmission permits circulation of the OPV viruses introduced in the population through vaccination. We fixed the die-out process, model structure, and numerical

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3 model inputs that characterize them across all populations we modeled and Table A1 includes  
4 the corresponding generic model inputs. [...]

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7 “Figure A2 summarizes the results of the model calibration process, based on prior work.<sup>2</sup> With  
8 the generic model inputs from Table A1 fixed, we compared our model behavior against i) data  
9 on children with non-polio acute flaccid paralysis who reported no receipt of OPV for northern  
10 India (modeled separately for Western Uttar Pradesh (WUP) and Bihar) and northwest (NW)  
11 Nigeria; ii) data on polio incidence and die-out of endemic WPV transmission for all situations  
12 and serotypes (shown in Figure A2 for WPV1 and WPV3 in northern India and northwest  
13 Nigeria and for all 3 WPV serotypes in the USA); iii) data from WPV importation outbreak  
14 behavior in the Netherlands, Tajikistan, and Albania; iv) data on age distributions of cases for all  
15 situations in which meaningful data was available (shown in Figure A2 for the Netherlands,  
16 Tajikistan, and Albania); v) available serological data on the effect of secondary OPV immunity in  
17 the USA and Cuba (not shown); vi) indigenous emergence of cVDPVs (shown in Figure A2 for  
18 northern India, NW Nigeria (both serotype 2), Haiti, and Madura in Indonesia (both serotype 1);  
19 and vii) no indigenous emergence of cVDPVs in all other situations and serotypes (die-out of  
20 serotype 1 OPV-related viruses shows in Figure A2 for Cuba and Haiti). We subsequently  
21 applied the model to successfully reproduce the asymptomatic transmission of an imported  
22 WPV1 in Israel in 2013.<sup>31, 45, online supplement pp. 1-2</sup>

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26 Most critically in the context of certification questions, the DEB model approximates  
27 interruption of live poliovirus transmission (i.e., of an OPV, WPV, vaccine-derived poliovirus  
28 (VDPV), or OPV-related strain) in a population to occur when the effective infectiousness-  
29 weighted proportion of the population infectious with that poliovirus drops below 5 per million  
30 people (i.e., the transmission threshold  $EPI^*$ ).<sup>2</sup> While this simplifies the true die-out behavior,  
31 which depends on local heterogeneity and chance, it appears capable of generating WPV die-out  
32 times consistent with observations in a broad range of settings.<sup>2, 30, 31, 41</sup> Moreover, when applied  
33 to the persistence of OPV-related viruses that evolve to fully transmissible and neurovirulent  
34 circulating VDPVs (cVDPVs), the approximation produces cVDPV outbreaks for conditions in  
35 which they occurred (e.g., in Hispaniola<sup>46</sup> and Nigeria<sup>47</sup>) and no cVDPV outbreaks for conditions  
36 in which they did not occur despite OPV use and cessation (e.g., in Cuba<sup>48</sup> and the USA<sup>49</sup>).<sup>2</sup>

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40 Use of the hypothetical model clarified that under-vaccinated subpopulations can sustain  
41 poliovirus transmission independently despite high coverage in the surrounding general  
42 population and showed how the minimum coverage needed to interrupt transmission depends on  
43 the degree of isolation and the relative size of the under-vaccinated subpopulation.<sup>38</sup> To explore  
44 the role of hard-to-reach under-vaccinated subpopulations for certification questions, we  
45 modified the hypothetical model in two ways and added a stochastic layer on top of the DEB  
46 model to simulate polio case detections. The first modification consisted of desynchronizing the  
47 time when vaccination starts in the general and under-vaccinated subpopulations to simulate the  
48 concept of a population that remains inaccessible for an extended period of time. Specifically,  
49 we run the model, which assumes equal birth and death rates and thus no population growth  
50 (Table 1), without vaccination for 30 years to settle into the endemic equilibrium, and then  
51 instantly change the routine immunization coverage in the general population with three OPV  
52 doses to 0.95, which lies well above the threshold of 0.92 needed to interrupt transmission in a  
53 closed population with similar characteristics.<sup>38</sup> However, we assume that the under-vaccinated  
54 subpopulation initially remains completely unreached by vaccination, with vaccine introduction  
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3 in the under-vaccinated subpopulation occurring 10 years after vaccine introduction in the  
4 general population. Desynchronizing the introduction of vaccination affects the dynamics and  
5 effectively makes it more difficult to interrupt transmission after introducing vaccination in the  
6 last subpopulation. To offset this effect, we consider a different hypothetical population with a  
7 slightly higher average per-dose take rate for OPV of 0.6 instead of 0.5 in the original analysis<sup>38</sup>  
8 (e.g., due to lower exposure to enteric viruses that interfere with vaccine take<sup>50</sup>). As in the  
9 original analysis,<sup>38</sup> we vary the coverage in the under-vaccinated subpopulation, the relative size  
10 of the under-vaccinated subpopulation compared to the total population, and the degree of  
11 preferential mixing, characterized by the proportion of potentially infectious contacts of  
12 individuals in the under-vaccinated subpopulations with other individuals in the same  
13 subpopulation ( $p_{\text{within}}$ ).  
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17 Figure A3 shows the behavior of the incidence of infections in fully susceptible individuals and  
18 infants born with maternal immunity as a function of the varied DEB model inputs. Generally,  
19 the model yields incidence proportional to population size before vaccination starts. After the  
20 introduction of vaccination with high coverage in the general population, the initially still  
21 unvaccinated subpopulation becomes the main contributor to the total incidence. However, with  
22 less than 100% coverage in the general population and some interaction between the two  
23 populations (i.e.,  $p_{\text{within}} < 1$ ), some incidence continues to occur in the general population as  
24 exported viruses find unvaccinated individuals. Lower values of  $p_{\text{within}}$  imply more interaction  
25 between the two populations and result in more incidence in the general population before  
26 vaccination in the under-vaccinated subpopulation begins (middle column of Figure A3). The  
27 relative size of the under-vaccinated subpopulation also affects the extent to which the under-  
28 vaccinated subpopulation affects the general population (right column of Figure A3). With base  
29 case model inputs, the minimum coverage in the under-vaccinated subpopulation to interrupt  
30 transmission equals 0.82. Higher coverage values mean interruption occurs sooner after the  
31 introduction of vaccination in the under-vaccinated subpopulation, while lower coverage values  
32 mean that transmission continues and can eventually rebound and settle into a new equilibrium  
33 (left column in Figure A1).  
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38 While the prior approach used fully stochastic transmission models to randomly generate  
39 infections, die-out, and polio cases and detections,[19-22] for efficiency we use post-hoc  
40 processing of DEB model results to randomly generate only the times when polio cases and  
41 detections stochastically occur. Specifically, for each setting of the DEB model, we record the  
42 deterministic realization of the daily incidence of infections in fully susceptible individuals of  
43 any age and 50% of infants less than 3 months of age born with maternal immunity, which  
44 represent the only individuals at risk of becoming a polio case in the DEB model.[2] We then  
45 randomly determine the number of polio cases resulting from the infection incidence on each day  
46 using a Poisson draw with a rate equal to the infection incidence multiplied by the PIR. For each  
47 generated case, we use a separate uniform random draw to determine whether it results in a  
48 detection based on each of the detection probabilities in Table 1 (e.g., a random uniform draw of  
49 0.45 would mean that the case results in a detection only for detection probabilities of more than  
50 0.45). For each DEB model setting, we repeat the post-hoc stochastic process 10,000 times and  
51 we start generating cases 10 years before vaccination starts in the general population, which we  
52 assume starts vaccination 10 years earlier than the under-vaccinated subpopulation (see  
53 appendix). The precise choice of when to start randomly generating cases exerts negligible  
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3 influence on the results as long as it occurs before cases become rare (i.e., before the interval  
4 between cases becomes longer). For simplicity, although prior work showed the significant role  
5 of serotype differences and seasonality,[20, 22] the hypothetical model inputs reflect WPV1 and  
6 assumes no seasonality. A limitation arises from the direct scaling of the DEB model with  
7 absolute population size, such that die-out depends on the effective proportion of infectious  
8 individuals rather than the absolute number. Using the post-hoc stochastic analysis, the absolute  
9 population size affects the number of infections, which affects the typical interval between  
10 detected cases. We show that CNC95% increases substantially for smaller absolute population  
11 sizes.  
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15 Our initial findings motivated analysis of the minimum population size that can sustain WPV  
16 circulation on its own to determine whether the upper bound on the CNC95% of 9 years could  
17 occur in real populations. However, for population sizes far below 100,000, the DEB model  
18 becomes inadequate because it allows prevalence to remain above the die-out threshold even  
19 with only fractional numbers of infections (i.e., less than one infected person). Therefore, we  
20 used a fully stochastic model to explore questions of minimum population size. We run the  
21 model 10,000 times for different population sizes and initial conditions and report the  
22 distribution of the duration of circulation and the CNC95%.  
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### 25 **Exploration of the causal interactions relevant to global WPV certification decisions with** 26 **an influence diagram (Figure 5)** 27

28 Table A2 provides indicative estimates of the key quantities in Figure 5, based on the literature.  
29 Figure 5 assumes that policy makers explicitly or implicitly set a *desired confidence about no*  
30 *WPV circulation at OPV cessation*. In reality, they may focus on the confidence at certification,  
31 but given that it takes some fixed *preparation time needed between certification and OPV*  
32 *cessation*, any set confidence at the time of certification corresponds to some *desired confidence*  
33 *about no WPV circulation at OPV cessation*. A higher desired confidence level implies a longer  
34 *time between last detection and certification*. This time decreases with increasing investments in  
35 immunization and surveillance from the *GPEI budget through population immunity maintenance*  
36 and the *perceived pre-certification surveillance quality*, respectively. The main drawback of a  
37 longer *time between last detection and OPV cessation* comes in the form of longer OPV use in  
38 most countries, which results in *planned immunization costs* and *OPV-related pre-cessation*  
39 *polio cases* (i.e., vaccine-associated paralytic polio and VDPVs). In addition, with some  
40 globally-recommended or nationally-preferred *duration of IPV after OPV cessation*, later OPV  
41 cessation would imply greater overall IPV costs, because global IPV use already started (i.e.,  
42 only the end, and not the beginning of IPV use depends on the timing of cessation of the last  
43 OPV serotypes). These drawbacks together lead to *financial and societal costs of planned*  
44 *immunization*. This includes the monetary equivalent of the *OPV-related polio cases*, which  
45 depends on the country income-level-dependent *societal costs per polio case*.  
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50 On the left side of Figure 5, we see the benefits of setting a higher *desired confidence about no*  
51 *WPV circulation at OPV cessation*. A higher confidence implies a lower *probability of a WPV*  
52 *reemergence after OPV cessation* (all else being equal). However, this probability does not  
53 directly equal the reciprocal of the confidence in the event of a *gap between perceived and actual*  
54 *surveillance quality*. Specifically, if the *perceived pre-certification surveillance quality* exceeds  
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3 the *actual pre-certification surveillance quality*, then the true *probability of WPV reemergence*  
4 *after OPV cessation* equals more than 1 minus the *desired confidence about no WPV circulation*  
5 *at OPV cessation*, and vice versa. This potential discrepancy highlights the importance of  
6 continued assessment of surveillance quality and assurance of high surveillance quality. A lower  
7 *GPEI budget* also decreases *population immunity maintenance* and thus increases the *probability*  
8 *of WPV reemergence after OPV cessation*, which implies an increase in *expected WPV*  
9 *reemergence outbreaks*. Unlike other possible types of post-cessation outbreaks, a WPV  
10 reemergence would almost certainly occur in the most challenging populations. Any such  
11 reemergences would lead to *expected polio cases due to WPV reemergence outbreaks* and  
12 *expected costs to respond to WPV emergence outbreaks*. The expected costs and cases decrease  
13 with higher *post-cessation surveillance quality*, which affects the extent of viral spread at the  
14 time of outbreak detection (and beyond), and with a better *outbreak response quality and*  
15 *timeliness*, which both increase the probability of effective outbreak control.<sup>51</sup> However, the  
16 occurrence of any outbreaks comes with some probability of uncontrolled outbreaks, either by  
17 failing to control the original outbreak virus, or by creating new cVDPV outbreaks with the OPV  
18 vaccine used in the response. This implies some *probability of OPV restart due to WPV*  
19 *reemergences*, which would carry very significant *expected costs due to an OPV restart*  
20 *triggered by WPV reemergence* and *expected cases due to an OPV restart triggered by WPV*  
21 *emergence* (Table A2). For moderate or high *probability of OPV restart due to WPV*  
22 *reemergences*, the resulting *expected costs due to OPV restarts triggered by WPV reemergence*  
23 and *expected cases due to OPV restarts triggered by WPV reemergence* would likely dwarf the  
24 costs and cases associated with any controlled outbreaks due to WPV reemergences and would  
25 therefore drive the *expected financial and societal costs of possible WPV reemergences*.  
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31 Together with the *surveillance costs*, which act to moderate the costs of delayed OPV cessation  
32 or premature OPV cessation, the *expected financial and societal costs of possible WPV*  
33 *reemergences* and the *financial and societal costs of planned immunization* together make up the  
34 *total financial and societal costs (associated with any given desired confidence about no WPV*  
35 *circulation at OPV cessation)*. The costs of possible WPV emergences and the costs of planned  
36 immunization move in opposite directions as a function of the *desired confidence about no*  
37 *circulation at OPV cessation*.  
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40 Figure 5 also highlights the consequences of the GPEI already scaling down some of its  
41 supplemental immunization and surveillance activities. While scaling down saves costs in the  
42 short term, doing so could lead to larger long-term costs by delaying certification and OPV  
43 cessation (i.e., requiring higher confidence about no circulation), which would imply that OPV  
44 cessation could occur in the context of lower global population immunity to transmission and  
45 lower ability to rapidly detect outbreaks. This ultimately implies an increase in the expected  
46 *total financial and societal costs (associated with any given desired confidence about no WPV*  
47 *circulation at OPV cessation)*. For visual simplicity, Figure 5 omitted some additional  
48 complexity involved in this decision. Furthermore, given that the confidence about no  
49 circulation increases with time after the last detection, we could have equivalently centered  
50 Figure 5 around finding the optimal time between the last detection and certification or OPV  
51 cessation. The amounts in Table A2 highlight the significant financial and humanitarian stakes  
52 involved in finding the optimal *desired confidence about no WPV circulation at OPV cessation*.  
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**Table A1: Generic inputs of the DEB model<sup>2 30</sup> (adopted from the online supplement of Duintjer Tebbens et al., 2017<sup>45</sup>)**

Model input (symbol)	Best estimate	Source
Relative susceptibility ( $\sigma$ ) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.78;0.79;0.77 0.91;0.92;0.90 0.80;0.80;0.79 0.72;0.72;0.71 0.42;0.43;0.41 0.21;0.22;0.20 0.21;0.22;0.20	52 53
Duration of latent period ( $\xi^{fec}$ or $\xi^{oro}$ , in days)	$\sim 3^a$	52 53
Duration of fecal infectiousness ( $\gamma^{fec}$ , in days) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Fully susceptible</li> <li>- Maternally immune</li> <li>- 1 successful IPV,</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	28.0;27.8;28.3 24.6;24.6;24.6 24.5;24.4;24.7 21.1;20.8;21.3 18.0;17.7;18.2 11.6;10.5;10.5 10.1;8.9;8.9 10.1;8.9;8.9	52 53
Duration of oropharyngeal infectiousness ( $\gamma^{oro}$ , in days) of recent immunity states (no serotype differences) <ul style="list-style-type: none"> <li>- Fully susceptible</li> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	13.4 11.9 9.9 6.6 6.1 5.0 3.7 3.7	52 53
Relative fecal infectiousness ( $\pi^{fec}$ ) of recent immunity states (for PV1;PV2;PV3) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.96;0.96;0.95 0.92;0.92;0.91 0.70;0.69;0.68 0.61;0.59;0.59 0.39;0.43;0.43 0.20;0.23;0.23 0.20;0.23;0.23	52 53
Relative oropharyngeal infectiousness ( $\pi^{oro}$ ) of recent immunity states (no serotype differences) <ul style="list-style-type: none"> <li>- Maternally immune</li> <li>- 1 successful IPV</li> <li>- 2 successful IPV</li> <li>- <math>\geq 3</math> successful IPV</li> <li>- 1 LPV infection</li> <li>- <math>\geq 2</math> LPV infections</li> <li>- IPV and LPV</li> </ul>	0.68 0.30 0.17 0.12 0.33 0.21 0.21	52 53
Number of infection stages <ul style="list-style-type: none"> <li>- Latent period (<math>r</math>)</li> <li>- Infectious period (<math>s</math>)</li> </ul>	2 4	
Relative weight of infection stages, compared to average weight over the infectious period ( $\theta_j, j=0, \dots, r+s-1$ )		52 53

- Infection stage 0 and 1 (latent stages)	0	
- Infectious stage 2	12/17	
- Infectious stage 3	40/17	
- Infectious stage 4	12/17	
- Infectious stage 5	4/17	
IPV immunity delay ( $\phi$ , in days)	7	54
Number of waning stages ( $nw$ )	5	
Shape of waning function ( $z_w$ )	5	52 53
Average time to reach last waning stage ( $\rho$ , in days)		52 53
- Type 1&2	4×365	
- Type 3	3×365	
Average time for maternal immunes to wane to fully susceptible ( $\rho_{MI}$ , in days)	0.25×365	52 53
Relative susceptibility ( $\sigma$ ) for last waning stage (no serotype differences)		52 53
- 1 successful IPV	1.0	
- 2 successful IPV	1.0	
- $\geq 3$ successful IPV	1.0	
- 1 LPV infection	0.8	
- $\geq 2$ LPV infections	0.7	
- IPV and LPV	0.7	
Duration of fecal infectiousness ( $\gamma^{fec}$ , in days) of last waning stage (for PV1;PV2;PV3)		52 53
- 1 successful IPV	26.6;26.4;26.9	
- 2 successful IPV	25.2;25.0;25.5	
- $\geq 3$ successful IPV	23.8;23.6;24.1	
- 1 LPV infection	14.0;13.9;14.1	
- $\geq 2$ LPV infections	11.4;11.4;11.6	
- IPV and LPV	11.4;11.4;11.6	
Duration of oropharyngeal infectiousness ( $\gamma^{oro}$ , in days) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	11.4	
- 2 successful IPV	6.7	
- $\geq 3$ successful IPV	6.6	
- 1 LPV infection	6.7	
- $\geq 2$ LPV infections	4.0	
- IPV and LPV	4.0	
Relative fecal infectiousness ( $\pi^{fec}$ ) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	0.95	
- 2 successful IPV	0.9	
- $\geq 3$ successful IPV	0.85	
- 1 LPV infection	0.5	
- $\geq 2$ LPV infections	0.3	
- IPV and LPV	0.3	
Relative oropharyngeal infectiousness ( $\pi^{oro}$ ) of last waning stage (no serotype differences)		52 53
- 1 successful IPV	0.43	
- 2 successful IPV	0.25	
- $\geq 3$ successful IPV	0.13	
- 1 LPV infection	0.5	
- $\geq 2$ LPV infections	0.3	
- IPV and LPV	0.3	
Number of reversion stages ( $h$ )	20	
Shape of reversion function with respect to:		
- $R_0(z_r)$	1	
- $\ln(\text{PIR})(z_p)$	2.5	



Average time to reach last reversion stage ( $\varepsilon$ , in days) (for PV1;PV2;PV3)	620.5; 408; 620.5	<sup>30</sup>
Paralysis-to-infection ratio for fully susceptible individuals infected with OPV ( $PIR_0$ ) (for PV1; PV2;PV3)	$0.26 \times 10^{-6}$ ; $1.2 \times 10^{-6}$ ; $1.8 \times 10^{-6}$	
Paralysis-to-infection ratio for fully susceptible individuals infected with FRPV ( $PIR_{h-1}$ ) (for PV1; PV2;PV3)	0.005; 0.0005; 0.001	<sup>2 14 54</sup>
Relative $R_0$ of OPV vs. FRPV ( $\tau_0$ ) (for PV1; PV2; PV3)	0.37;0.55;0.25	<sup>2 52 53</sup>
Effective infectious proportion below which we assume 0 force-of-infection (transmission threshold $EPI^*$ )	5/1,000,000	
Relative PIR for maternally immunes compared to fully susceptible individuals ( $RPIR_{M1}$ )	0.5	
Ratio of $R_0$ by serotype in the same setting (PV1:PV2:PV3)	1:0.9:0.75	<sup>30</sup>
Average incubation period ( $\delta$ , in days)	10	<sup>54 55</sup>
Demographics for all situations	Time series 1950-2100	<sup>56</sup>

**Acronyms:** CDC = (U.S.) Centers for Disease Control and prevention; cVDPV = circulating vaccine-derived poliovirus; DEB = differential equation-based FRPV = fully-reverted poliovirus; GPLN = Global Polio Laboratory Network; IPV = inactivated poliovirus vaccine; LPV = live poliovirus; OPV = oral poliovirus vaccine; PIR = paralysis-to-infection ratio; PV(1,2,3) = poliovirus (type 1, 2, or 3, respectively);  $R_0$  = basic reproductive number; UN = United Nations; USA = United States of America; VAPP = vaccine-associated paralytic poliomyelitis; VP1 = viral protein 1; WPV(1,2,3) = wild poliovirus (type 1, 2, or 3, respectively)

**Notes:** <sup>a</sup> Mean estimates obtained from experts and used in the model for the different immunity states, serotypes, and excretion modes vary between 2.85 and 3.37 days

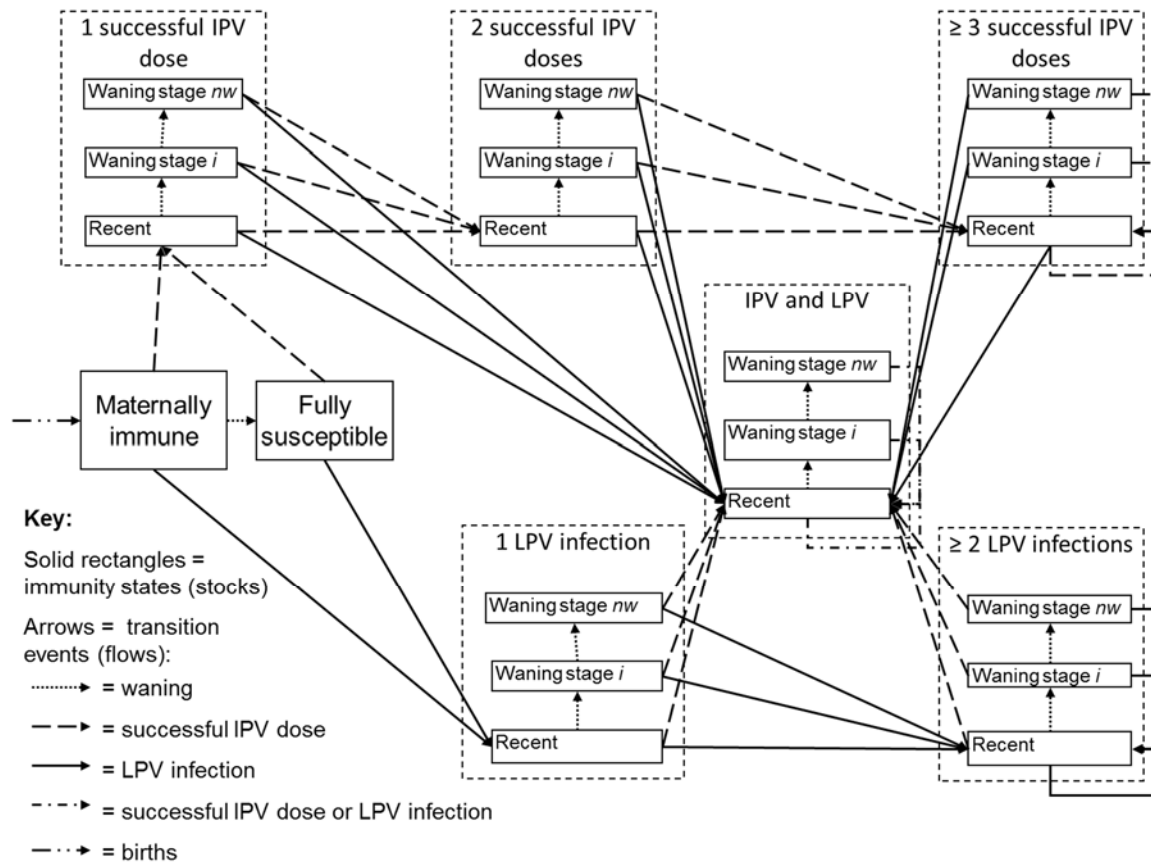
**Table A2: Indicative estimates of key variables from Figure 5**

Variable	Estimate	Notes and sources
Preparation time needed between certification and OPV cessation	Approximately 1 year	Depends on when setting of the OPV cessation date occurs relative to certification <sup>57</sup>
Planned immunization costs	\$1 billion in external GPEI funds per year, plus internal contributions	Most of the \$1.1 billion GPEI budget for 2016 was for immunization and coordination of activities; <sup>58</sup> Countries may internally contribute at a similar rate as the external contributions; <sup>59</sup> The current GPEI budget projects a decrease from 2018 forward, which would imply some offset of costs for maintenance of activities, or alternatively the activities previously supported by external contributions may end, which would imply declines in programmatic activities and quality
OPV-related polio cases	Hundreds per year	Vaccine-associated paralytic polio cases, <sup>60</sup> which depends on timing of IPV doses, <sup>61</sup> and presumably local cVDPV outbreaks <sup>62</sup>
Surveillance costs	Around \$100 million per year	The 2016 GPEI budget included \$67 million in external support for surveillance and laboratories, <sup>58</sup> with additional significant internal contributions by countries <sup>59 63</sup>
Probability of OPV restart due to WPV reemergence	Unknown	Prior studies estimated an approximately 5% chance of an OPV restart due primarily to OPV-associated risks, although the actual implementation of risk management policies was not as good as suggested by these models. <sup>59 64</sup>
Immunization costs associated with an OPV restart	\$ billions (hundreds of millions per year)	An OPV restart would involve reintroduction of OPV vaccination in most countries in perpetuity, with supplemental immunization activities needed in countries with insufficient routine immunization coverage. <sup>59</sup> Significant uncertainty exists about what an OPV restart would look like in practice.
Expected cases due to an OPV restart	Up to thousands per year	Reintroduction of OPV in most countries would result in hundreds of vaccine-associated paralytic polio cases per year and could result in continued cVDPV outbreaks in countries with insufficient routine immunization coverage that do not conduct regular preventive supplemental immunization activities. <sup>59 64</sup>



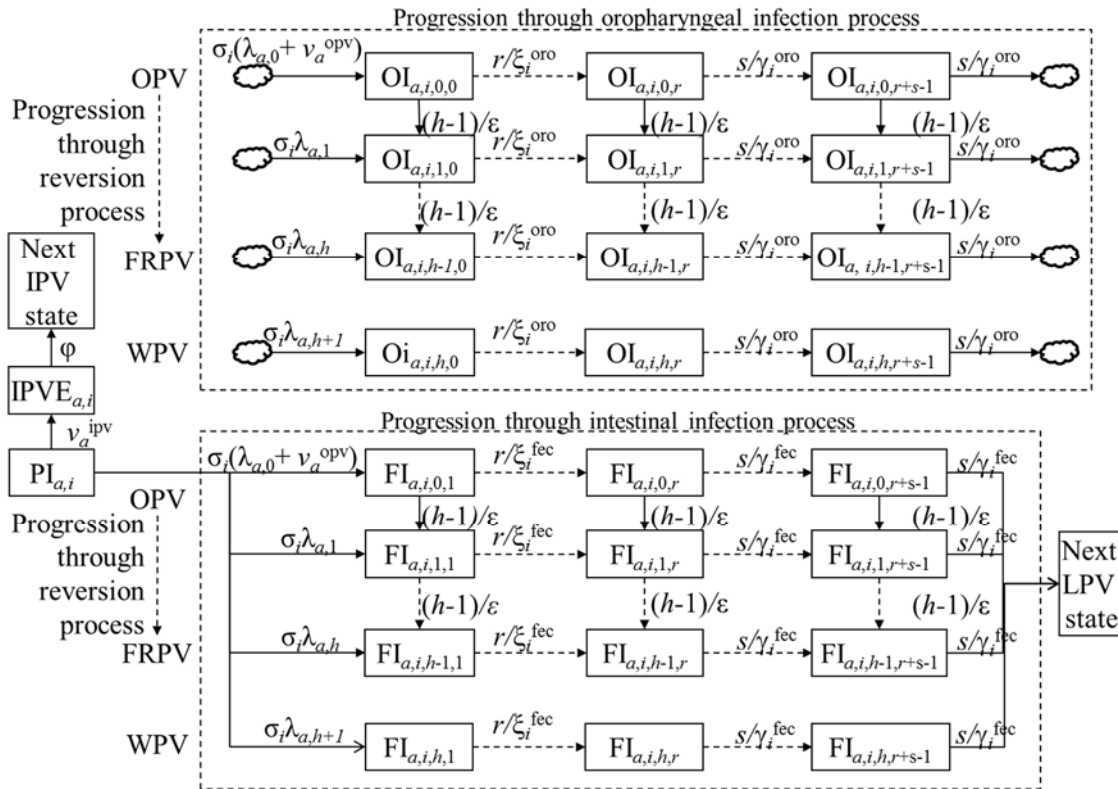
**Figure A1: Schematic of the DEB model structure, adopted from Duintjer Tebbens et al. (2013)<sup>2</sup>, p. 706**

**(a) Immunity states and flows between them due to epidemiological events**



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## (b) Progression through infection and reversion stages



“**Acronyms:** FRPV = fully-reverted poliovirus; IPV = inactivated poliovirus vaccine; OPV = oral poliovirus vaccine; WPV = wild poliovirus; **Symbols:**  $PI_{a,i}$  = partially infectible in age group  $a$  and immunity state  $i$ ;  $IPVE_{a,i}$  = IPV-exposed individual from immunity state  $i$  and age group  $a$ ;  $FI_{a,i,j,k}$  ( $OI_{a,i,j,k}$ ) = individual in age group  $a$  from immunity state  $i$ , infected with virus strain  $j$  and in fecal (oropharyngeal) infection stage  $k$ ;  $\lambda_{a,j}$  = force-of-infection to age group  $a$  for virus strain  $j$ ;  $v_a^{ipv}$  ( $v_a^{opv}$ ) = force-of-IPV(OPV)-vaccination to age group  $a$  as a result of routine and supplementary immunization;  $\sigma_i$  = relative susceptibility for immunity state  $i$ ;  $\xi_i^{fec}$  ( $\xi_i^{oro}$ ) = average duration of the fecal (oropharyngeal) latent period for immunity state  $i$ ;  $\gamma_i^{fec}$  ( $\gamma_i^{oro}$ ) = average duration of the fecal (oropharyngeal) infectious period for immunity state  $i$ ;  $\varphi$  = IPV immunity delay;  $h$  = number of reversion stages;  $r$  = number of latent stages;  $s$  = number of infectious stages”<sup>2</sup>, p. 706

Figure A2: Summary results from the model calibration process, adapted from Duintjer Tebbens et al. (2013)<sup>2</sup>

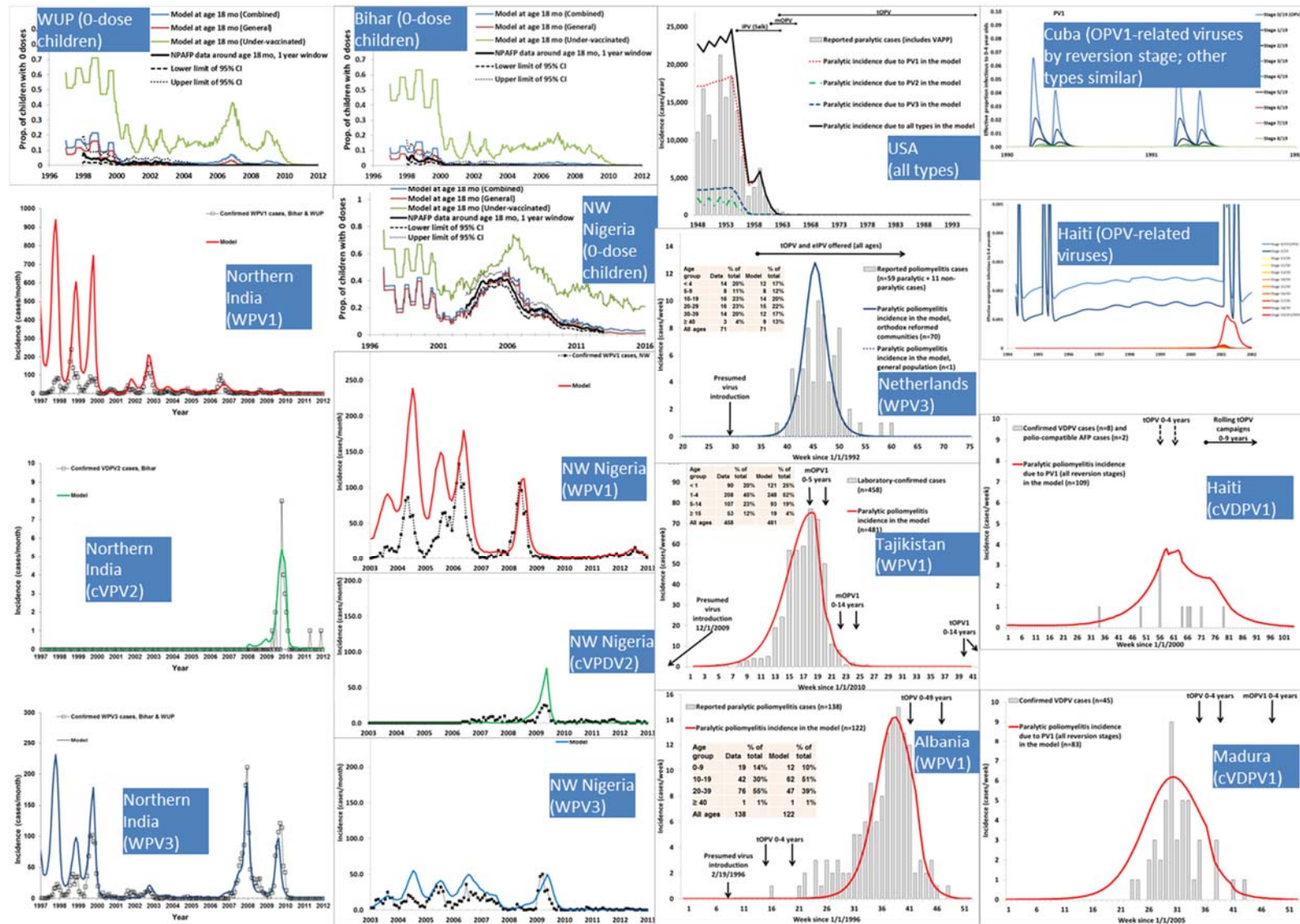


Figure A3: Differential-equation based model results for base case model inputs and varied coverage (left column), varied degree of isolation with coverage 0.82 (middle column), and varied relative size with coverage of 0.82 (right column). The y-axis scales linearly with total population size (all figures assume a total population size of 1 million).

