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Managing population immunity to reduce or eliminate the risks of circulation following the importation of polioviruses

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ABSTRACT

Poliovirus importations into polio-free countries represent a major concern during the final phases of global eradication of wild polioviruses (WPVs). We extend dynamic transmission models to demonstrate the dynamics of population immunity out through 2020 for three countries that only used inactivated poliovirus vaccine (IPV) for routine immunization: the US, Israel, and The Netherlands. For each country, we explore the vulnerability to re-established transmission following an importation for each poliovirus serotype, including the impact of immunization choices following the serotype 1 WPV importation that occurred in 2013 in Israel. As population immunity declines below the threshold required to prevent transmission, countries become at risk for re-established transmission. Although importations represent stochastic events that countries cannot fully control because people cross borders and polioviruses mainly cause asymptomatic infections, countries can ensure that any importations die out. Our results suggest that the general US population will remain above the threshold for transmission through 2020. In contrast, Israel became vulnerable to re-established transmission of importations of live polioviruses by the late 2000s. In Israel, the recent WPV importation and outbreak response use of bivalent oral poliovirus vaccine (bOPV) eliminated the vulnerability to an importation of poliovirus serotypes 1 and 3 for several years, but not serotype 2. The Netherlands experienced a serotype 1 WPV outbreak in 1992–1993 and became vulnerable to re-established transmission in religious communities with low vaccine acceptance around the year 2000, although the general population remains well-protected from widespread transmission. All countries should invest in active management of population immunity to avoid the potential circulation of imported live polioviruses. IPV-using countries may wish to consider prevention opportunities and/or ensure preparedness for response. Countries currently using a sequential IPV/OPV schedule should continue to use all licensed OPV serotypes until global OPV cessation to minimize vulnerability to circulation of imported polioviruses.

1. Introduction

The risk of infectious agents crossing international borders motivates global disease coordination and management efforts, including the Global Polio Eradication Initiative [1]. As long as wild polioviruses (WPVs) circulate anywhere, they pose some risk of importation (i.e., crossing the border) into all countries. Not surprisingly, once countries succeed in stopping endemic (i.e., indigenous) WPV transmission (i.e., national elimination) and become "polio free," their concerns about WPVs primarily turn to potential importations. Detection of an importation typically depends on the Global Polio Laboratory Network finding paralytic cases, and consequently WPV importations that do not result in identified paralytic cases go unnoticed. Notable exceptions occurred with the detection of asymptomatic WPV serotype 1 (WPV1) transmission in 2013 by the extensive Israeli environmental surveillance system, which allowed Israel to respond to the circulation and successfully prevent cases [2–4], and similar detection and response to the same WPV1 in Egypt [5].

Recently, the World Health Organization focused on importations as a primary concern for the polio endgame and established temporary recommendations for international travel immunization to reduce the international spread of poliovirus [6]. While efforts to increase the immunity of individual international travelers may reduce the number of importation events, this approach

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does not eliminate the risk altogether and focuses only on the nationally less-controllable part of the risk of re-established transmission. In addition to the importation event (e.g., WPV entering the population), the risk of re-established transmission of an imported WPV depends on the vulnerability of the population receiving the imported virus to sustain transmission, which depends on its population immunity to poliovirus transmission [7]. Thus, while countries cannot easily control all of the border crossings that may lead to importation events [8,9], particularly for a disease that primarily spreads asymptomatically, national immunization decisions determine population immunity to transmission and thus the overall national risk of re-established transmission of imported polioviruses [7].

Population immunity to transmission represents the aggregation of the immunity of all individuals within a population, and it changes over time with demographic changes (i.e., births of immunologically-naïve individuals, deaths of immune individuals, and immigration) and factors that impact individual immunity (i.e., immunization, infection, and waning of antibodies) [7]. Models of population immunity must consider all dynamic inputs, and also account for the different types of immunological protection provided by oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV) [7]. As a live, attenuated virus, OPV causes infections in vaccine recipients who can spread their infections to effectively immunize contacts or boost their immunity, providing benefits beyond the vaccine recipient. However, OPV comes with a small risk of vaccine-associated paralytic polio (VAPP) [10], and OPV-using populations with low immunity levels can support sustained transmission of OPV-related viruses that evolve to become circulating vaccine-derived polioviruses (cVDPVs), which behave like WPVs [10,11]. For serotype 2, cVDPVs now represent the primary importation risk given the absence of any serotype 2 WPV since 2000 [8]. In contrast to OPV, IPV provides protection only to vaccine recipients and it does not come with VAPP or cVDPV risks. However, IPV does not protect as well as OPV against asymptomatic intestinal infections or fecal-oral transmission [12,13]. After successful immunization with IPV or recovery from an infection with a live poliovirus (LPV, i.e., WPV, cVPDV, OPV, or OPV-related virus) of a specific serotype, individuals benefit from permanent homotypic protection from paralysis, but they can get re-infected and participate asymptomatically in homotypic transmission to some degree [12–15].

Fig. 1 summarizes the number of calendar years that countries reported one or more WPV or cVDPV cases during 2000–2014 and demonstrates ongoing national challenges associated with maintaining high population immunity. Social disruptions appear to represent a significant risk factor (e.g., Syria, Iraq), which suggests that areas with social unrest (e.g., Somalia, Pakistan, and more recently, Ukraine, Guinea, Liberia, Sierra Leone) may warrant particular attention. Full protection from paralytic polio requires immunity for all three poliovirus serotypes. Both IPV and trivalent OPV (tOPV) currently used for routine immunization (RI) contain all three serotypes, but countries can use bivalent OPV (bOPV, containing serotypes 1 and 3) and monovalent OPV (mOPV) formulations for supplemental immunization activities (SIAs) [8,16]. Immunization choices imply trade-offs [16], and current discussions about the polio endgame lead to questions about the dynamics of coordinated global OPV cessation and the role of IPV with respect to managing population immunity [17–20]. Current plans include globally-coordinated cessation of serotype-2 containing OPV (i.e., OPV2 cessation) first, followed by globally-coordinated OPV cessation of serotypes 1 and 3 (i.e., OPV1&3 cessation) [21]. The GPEI identified 6 criteria as prerequisites to OPV2 cessation [21], and we highlighted the importance of assuring high enough population immunity at the time of OPV2 using sufficient tOPV SIAs as an additional prerequisite to the safe withdrawal of OPV2 [16].

Models characterizing the dynamics of poliovirus transmission and population immunity demonstrate the importance of maintaining high population immunity to achieve WPV eradication and successfully stop OPV use [15,17–20,22,23]. Prior modeling emphasizes that OPV-using countries must keep their population immunity sufficiently above the threshold required to prevent transmission in order to prevent cVDPV emergences prior to and after OPV cessation [17–20]. Thus, OPV-using countries should use tOPV with sufficiently high coverage (i.e., RI with SIAs as needed) up until the point of OPV2 cessation, at which point they should switch to bOPV and again maintain high coverage to ensure high population immunity until OPV1&3 cessation [16–20]. Countries should recognize that their vaccine choices will also affect their probabilities of undetected LPV circulation after apparent interruption of transmission [24]. The prior models focused on OPV-using countries [16–20]. However, with all countries at risk for importations from any circulating WPVs or cVDPVs [8], we recognize the importance of considering national vulnerability to re-established transmission following a LPV importation into IPV-only using countries.

2. Methods

We extend our prior modeling [4,15,17–20,22–24] to characterize vulnerability to re-established transmission and options that IPV-only using countries may consider to reduce or eliminate their vulnerability (see Appendix A). Briefly, the model tracks the population in different immunity states as a result of births, deaths, immigration, immunization, infection, and waning. We developed generic model inputs for human immunological responses to polioviruses and poliovirus transmission characteristics by serotype that remain constant across all modeled situations (i.e., immunity state inputs for susceptibility, infectiousness, and duration of the latent and infectious periods, kinetics of waning immunity and OPV virus evolution (i.e., to become cVDPVs following sufficient sustained transmission), and relative poliovirus transmissibility and paralysis-to-infection ratios by serotype) based on an extensive expert review and elicitation process [12,13,15]. We calibrated the model inputs across ten diverse epidemiological situations (i.e., geographic areas with different conditions and experiences with WPVs and cVDPVs), which used situation-specific appropriate inputs for population, historical RI and SIA vaccination, basic reproductive number (R_0), seasonality, and relative proportion of overall (i.e., fecal-oral and oropharyngeal) transmissions that occur via the oropharyngeal route (p^{oro}). The calibration process focused on ensuring that the model inputs yielded behavior and estimates consistent with the actual reported WPV and/or cVDPV incidence by age, the actual apparent timing of WPV die-out (where appropriate), the absence or emergence of cVDPVs, and available data on secondary OPV transmission and children missed by SIAs [4,15,17–20,22–24]. The model tracks viral transmission, including asymptomatic infections in individuals with prior immunity, and explicitly recognizes that relative susceptibility to infection and relative infectiousness over time determine the relative potential contribution to transmission for individuals in each immunity state [7,15]. Aggregating the proportions of individuals in each immunity state, their potential contribution to transmission, and considering the mixing properties for different age groups and subpopulations in the model, we characterize population immunity to poliovirus transmission by computing the age-and-subpopulation-mixing-adjusted effective immune proportion (EIPM) [20]. We also characterize the seasonally-varying immunity threshold $EIP^* = (1 - 1/R_0)$ above which infections eventually die out [20].