Practice of Epidemiology

The Potential Impact of Routine Immunization with Inactivated Poliovirus Vaccine on Wild-type or Vaccine-derived Poliovirus Outbreaks in a Posteradication Setting

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The "endgame" for worldwide poliomyelitis eradication will entail eventual cessation of the use of oral poliovirus vaccine (OPV) in all countries to prevent the reintroduction of vaccine-derived polioviruses—exposing some populations to an unprecedented, albeit low, risk of poliovirus outbreaks. Inactivated poliovirus vaccine (IPV) is likely to play a large part in post-OPV management of poliovirus risks by reducing the consequences of any reintroduction of poliovirus. In this article, we examine the impact IPV would have on an outbreak in a partially susceptible population after OPV cessation, using a mathematical model of poliovirus transmission with a realistic natural history and case reporting. We explore a range of assumptions about the impact of IPV on an individual's infectiousness, given the lack of knowledge about this parameter. We show that routine use of IPV is beneficial under most conditions, increasing the chance of fadeout and reducing the expected prevalence of infection at the time of detection. The duration of "silent" poliovirus circulation prior to detection lengthens with increasing coverage of IPV, although this only increases the expected prevalence of infection at the time of the OPV response if IPV has a very limited impact on infectiousness. Overall, the model predicts that routine use of IPV will be advantageous for the posteradication management of poliovirus.

disease transmission; inactivated poliovirus vaccine; oral poliovirus vaccine; poliovirus eradication; poliomyelitis

Abbreviations: IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; OPV2, serotype 2 oral poliovirus vaccine; VDPV, vaccine-derived poliovirus.

The Global Polio Eradication Initiative has reduced the burden of poliomyelitis by over 99% and the number of endemic countries from 125 in 1988 to just 3 in 2013—Afghanistan, Pakistan, and Nigeria. With renewed commitment to global eradication and the implementation of a strategic plan building on over 20 years of experience, hopes are high for finally interrupting transmission of poliovirus in the few remaining reservoirs of infection. There are currently 5 vaccines in use to control the spread of poliovirus: 4 oral poliovirus vaccines (OPVs) containing varying combinations of the 3 virus serotypes and an intramuscular inactivated poliovirus vaccine (IPV) containing all 3 serotypes.

The live-attenuated OPV has long been the vaccine of choice, being simple to administer, inducing high levels of mucosal immunity, indirectly immunizing secondary contacts of vaccinated persons, and having a lower cost than IPV. The live-attenuated nature of the OPV virus can also result in reversion to a neurovirulent phenotype, causing vaccine-associated paralytic poliomyelitis (approximately 1 in 2.5 million doses of trivalent OPV) [1]. Furthermore, vaccine-derived polioviruses (VDPVs) can revert towards the wild-type phenotype, causing paralysis, and can circulate undetected. VDPVs have caused outbreaks in 17 countries during the last 10 years and have prompted a switch to IPV in countries that have eliminated wild-type poliovirus [2–5].

Routine immunization with IPV successfully eliminated poliomyelitis from Sweden, Finland, the Netherlands, and Iceland. Three doses given at ages 6, 10, and 14 weeks on the

Expanded Programme on Immunization schedule induces serum neutralizing antibodies in over 90% of recipients, but the impact on intestinal mucosal immunity is limited in comparison with OPV (6, 7). Poliovirus shedding in stool occurs at similar frequencies in IPV-vaccinated persons and naive persons following natural exposure to wild-type poliovirus or challenge with OPV, although the quantity and duration of shedding is lower in the former (8–10). For this reason, an IPV-only vaccination schedule is not currently recommended in endemic countries (11, 12).

Recently, a strategy for phased removal of OPV serotypes was endorsed by the World Health Assembly, beginning with serotype 2 because of the global eradication of wild-type 2 poliovirus and the near elimination of circulating serotype 2 VDPVs (13). Following withdrawal of a given OPV serotype, a cohort of children susceptible to that serotype will accumulate. Introduction of VDPV or wild-type poliovirus through accidental contamination or through any individual's excreting virus long-term could cause an outbreak. The Strategic Advisory Group of Experts on Immunization recently recommended introducing at least 1 dose of IPV in OPV-using countries 6 months before cessation of serotype 2 OPV (OPV2) in order to maintain immunity to serotype 2 poliovirus and potentially boost immunity to serotypes 1 and 3 (12). Consequently, it is crucial to understand the impact of using IPV and the implications of OPV cessation.

Here we describe a simple mathematical model of the impact of IPV on wild or vaccine-derived poliovirus transmission in a posteradication setting under different assumptions of vaccine coverage and effectiveness, to examine the benefits and possible risks of its adoption. Specifically, we consider what would be the impact of routine immunization with IPV on the probability of fadeout of poliovirus before detection, the time taken to detect a newly emerging outbreak, and the prevalence of infection at the time the first symptomatic case is detected under different assumptions about the impact of this vaccine on poliovirus transmission. The prevalence of infection by the time a symptomatic case has been detected gives an estimate of the spread of the virus and is important for policy decisions, such as global stockpiling for an OPV response. The scenarios modeled here could represent either a vaccine-derived or a wild-type serotype 2 outbreak in a population following OPV2 cessation or an outbreak of serotype 1 or 3 after cessation of all OPVs. We explore IPV use in 2 settings (high R_0 vs. low R_0) and discuss the model findings in the context of current policy decisions.

MATERIALS AND METHODS

Approach

We used a stochastic, discrete-time susceptible-exposed-infected-recovered model to characterize the spread of wild or vaccine-derived poliovirus of a given serotype from 1 infected person through a partially IPV-vaccinated population following cessation of vaccination with OPV of that serotype (see Web Figure 1, available at http://aje.oxfordjournals.org/). Natural history parameters have been derived from data on previous wild poliovirus outbreaks (Table 1; Web Appendix, section 1, and Web Figure 2). We do not attempt to model age-specific transmission and immune status but instead capture poliovirus spread in a cohort of vaccinated and unvaccinated persons who are assumed to make contact and infect others at random. We assume that persons previously immunized with OPV prior to cessation are fully immune and do not contribute to poliovirus transmission.

Routine IPV vaccination

A fixed proportion of susceptible persons are assumed to be vaccinated with IPV, typifying a posteradication (or post-OPV2) setting where OPV (or trivalent OPV) has ceased to be used and a cohort of children have been immunized only with IPV. We model an IPV schedule that induces an immune response in 98% of recipients, corresponding with a full 3-dose schedule with intramuscular vaccine, or fewer doses if immunological priming is considered protective (6, 14). Therefore, our effective coverage rate will be the stated coverage rate multiplied by 0.98. Similarly, this degree of protection is compatible with observed seroconversion rates following 2–3 fractional doses of intradermally administered IPV (15–17). We consider an all-or-nothing approach here; individuals either receive all doses of IPV necessary to equate with our 98% efficacy assumption or are fully susceptible. If a large subgroup received only 1 dose of IPV, we could assume that approximately 47% of them were protected (derived from the average rates of seroconversion against serotypes 1, 2, and 3: 46.6%, 62.8%, and 32.0%, respectively). Partial immunity effectively reduces our coverage rate. Although they are protected against illness, IPV-vaccinated persons can still become infected and excrete poliovirus, although the degree and duration of an individual's infectiousness is likely to be reduced in comparison with an unvaccinated person (10). We assume that IPV-induced immunity against paralytic poliomyelitis is lifelong, consistent with studies of neutralizing antibodies in Europe and Canada (6, 18–21). We address the uncertainty surrounding IPV by incorporating a range of values for key parameters, including vaccination coverage and the relative duration and degree of infectiousness of IPV-vaccinated persons following infection. We define infectiousness as the rate at which an infected person infects susceptible contacts. This composite measure includes behavioral factors such as contact patterns, along with biological factors such as quantity of viral shedding and probability of transmission upon contact. Limited data are available concerning the impact of IPV on poliovirus transmission; for that reason, we analyze the full range of relative infectiousness of IPV-vaccinated persons in the model (9, 22, 23).

Surveillance

To simulate the appearance of symptomatic cases, we generated a random binomial draw at each time-step of the model from the number of incident infections. The probability of an infected unvaccinated person's developing paralytic disease (case:infection ratio) was 1:200, and the probability of a case's being detected was 1. Each case was subjected to a random gamma-distributed time delay, representing the interval between acquisition of the infection and identification of the infection by routine surveillance, as derived from

Table 1. Key Parameters Used in a Model of the Impact of Inactivated Poliovirus Vaccine on Wild or Vaccine-derived Poliovirus Transmission in a Posteradication Setting Under Different Assumptions of Vaccine Coverage and Effectiveness[a]

Parameter	Value(s) (SD)	Source Reference(s)	Sensitivity Analysis	Comments
Basic reproduction number (R_0)	3 and 10	Patriarca, 1997 (54)		Low R_0 corresponds to an outbreak in a country with good sanitation and mainly oral-oral transmission; high R_0 corresponds to an outbreak in a country with poor sanitation and predominantly fecal-oral transmission
Duration of exposed (latent) period, days (naive and vaccinated)	4 (4)	Grassly, 2006 (56); Krugman, 1961 (57)		Exponentially distributed; based on time from infection to onset of viral shedding
Incubation period, days	16.5 (5.2)	Casey, 1942 (58)		Gamma-distributed; see Web Appendix, section 2, for details
Duration of infectious period (naive), days	43 (43)	Alexander, 1997 (42); Gelfand, 1957 (59); Hatch, 1958 (60)	14	Exponentially distributed; based on shedding of wild-type polioviruses
Duration of infectious period (vaccinated), days	14 (14) and 43 (43)	Hird, 2012 (10); Marine, 1962 (22); Ghendon, 1961 (35); Laassri, 2005 (37)	14 and 4.6	Exponentially distributed; based on relative duration of shedding
Population size	1×10^6			Arbitrarily large
Probability of symptomatic infection	1 case in 200	Sutter, 2008 (61); Nathanson, 1979 (62); Fine, 2001 (63)	1 case in 1,000	Reflects variation in case:infection ratio among different serotypes
Delay in reporting, days	24.6 (11.9)			Gamma-distributed; based on acute flaccid paralysis surveillance data in endemic countries, 2001–2011. See Web Appendix, section 2, for details.
Probability of detecting a symptomatic case	1		0.5	See Web Appendix, section 4, for sensitivity analysis

Abbreviation: SD, standard deviation.

[a] The estimates do not refer to a specific serotype but represent an average across serotypes.

our own unpublished analysis of acute flaccid paralysis surveillance data in endemic countries (Web Appendix, section 2) (24, 25). The simulations stop when the first poliomyelitis case is detected or the infection becomes extinct, at which point we assume that a monovalent OPV response would be implemented using the global stockpile according to current guidelines (26).

Scenario analysis

We present the results of analyses describing the impact of IPV in 2 settings with low and high R_0 values ($R_0 = 3$ and $R_0 = 10$) and changing IPV coverage. We include a range of values for relative infectiousness from 0 to 1 and two estimates for the reduction in the duration of infectiousness (0% and 67%). We focus on 3 outcomes: 1) the proportion of simulated outbreaks which become extinct without further intervention, 2) the time taken to detect an outbreak, and 3) the relative prevalence of infection in the population at the time of detection as compared with an unvaccinated population. We performed 1,000 realizations of each scenario and report the median value for each of the outcomes of interest.

Sensitivity analysis

We performed a sensitivity analysis to explore the robustness of our findings to 3 key assumptions: the proportion of

infections resulting in paralysis, the sensitivity of the surveillance program, and the duration of viral shedding in both vaccinated and unvaccinated persons (Table 1).

RESULTS

Outbreak prevention

On average, the probability of an outbreak's becoming extinct before a paralytic case was detected (a "fadeout") in the absence of vaccination with IPV was 33% when $R_0 = 3$ and 10% when $R_0 = 10$ (i.e., $1/R_0$, as expected; see Web Appendix, section 3) (27). The influence of IPV on the probability of fadeout when R_0 was high was limited and was independent of the duration of infectiousness of infected IPV recipients and, to some extent, of vaccine coverage (Figure 1). If $R_0 = 10$ and IPV reduces infectiousness (i.e., the ability to transmit infection to a susceptible contact) by less than 80%, there is little gain in the likelihood of extinction when coverage is increased from 50% to 80%, because the effective reproduction number (R_v; i.e., R_0 multiplied by the proportion of the population that is susceptible) remains above 1 (estimated R_v values were 6 and 3.6, respectively; see Web Appendix, section 3, and Web Figure 3). With 80% coverage, under the assumptions that IPV reduces the duration of shedding by 67% and infectiousness by 95%, we still see only 40% of outbreaks become extinct before a paralytic case is detected (estimated $R_v = 2.1$). The probability of extinction in this stochastic

model is lower than the expected probability derived using epidemic theory, since a symptomatic case may be reported in the absence of a "major outbreak" in the stochastic model.

In an outbreak with a low R_0, increasing IPV coverage has a greater effect on the probability of fadeout. Coverage of 80% with a vaccine which reduces the duration of infectiousness alone increases the probability of fadeout before a case is detected by approximately 25%. If an epidemic did occur in the model under those conditions which generally favor fadeout, the mean number of infections over the course of the epidemic remained very low because R_e remained close to 1.

Silent transmission

By preventing paralysis due to poliovirus infection, thereby changing the case:infection ratio and reducing the prevalence of symptomatic infection, IPV increases the time taken to detect an outbreak and can allow a poliovirus epidemic to circulate silently (Figure 2). In a setting where we expect R_0 to be high, this delay is substantial only at very high coverage (>90%) and with a vaccine which reduces infectiousness by at least 80%. However, with a low R_0, if IPV reduces the duration of infectiousness, coverage of 60%–80% can result in an outbreak circulating for over a year undetected. The number of undetected cases of poliomyelitis during this period will depend on the effectiveness of surveillance for acute flaccid paralysis (s).

Extent of epidemic at the time of detection

IPV is unlikely to significantly increase the prevalence of infection at the time of detection, despite a potential delay in detecting cases (Figure 3). This result is apparent in both settings, although when $R_0 = 3$ and shedding duration is reduced by 67%, all levels of IPV coverage reduce relative prevalence because R_v is driven below 1. If IPV reduces infectiousness by more than approximately 50%–60%, then the prevalence at the time of detection is nearly always lower than that in an unvaccinated population. If infectiousness is not significantly reduced, high coverage can result in an increased relative prevalence at the time of detection.

Sensitivity analysis

Our findings were generally robust to changes in case:infection ratio, surveillance sensitivity, and the duration of viral shedding (Web Appendix, section 4, and Web Figures 4–6). If the duration of infectiousness is reduced to 14 days in unvaccinated persons, for a given R_0 the time taken to detect a symptomatic case is shorter because the epidemic occurs on a more rapid time scale (due to the shorter generation time). The relative prevalence is mostly unchanged, apart from those instances when a vaccine with a minimal impact on infectiousness is used with high coverage in a setting with a high R_0. In these situations, the relative prevalence is approximately twice that of the baseline prevalence (compared with 8–10 times higher in the original model).

DISCUSSION

Routine immunization with IPV can potentially limit the transmission of emergent poliovirus and protect children against poliomyelitis, but could in some situations allow an outbreak to spread undetected by preventing clinical signs of disease. Here we considered a post-OPV2 or post-OPV setting with a chance importation of poliovirus into a partially vaccinated population to investigate the impact that routine IPV use would have on the transmission and detection of an outbreak.

Our model predicted that to significantly increase the probability of extinction in a high-R_0 setting (e.g., a low-income region with poor sanitation and correspondingly high transmission), IPV coverage of at least 80% must be achieved and the vaccine must reduce infectiousness (as defined in Materials and Methods) by approximately 80% (or 60% if the duration of viral shedding is also reduced). In an outbreak with a lower R_0 (i.e., a high-income setting with lower transmission intensity), a shorter duration of infectiousness significantly increases fadeout probability even with no reduction in the degree of infectiousness. We demonstrate that routine immunization with IPV delays the detection of a poliovirus outbreak (median delays of 15.7 days (95% confidence interval: 1.8, 168.5) for $R_0 = 10$ and 59.1 days (95% confidence interval:
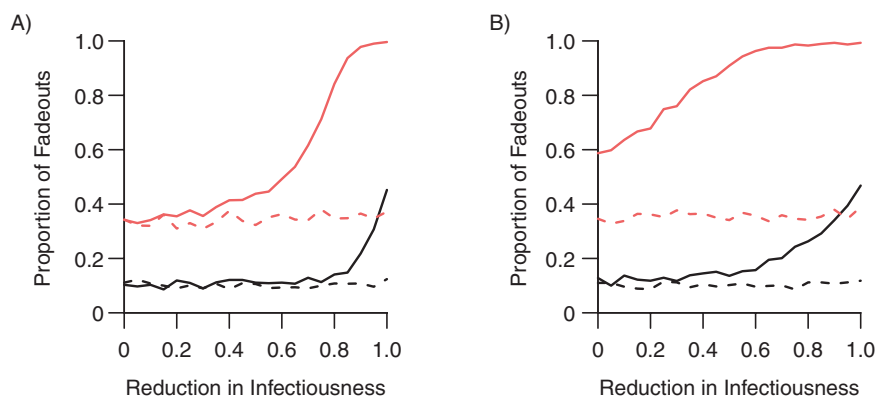

Figure 1. Proportion of stochastic simulations of poliomyelitis eradication resulting in fadeouts (an outbreak's becoming extinct before a paralytic case of poliomyelitis is detected). In part A we assumed no reduction in the duration of infectiousness among persons who received inactivated poliovirus vaccine, while in part B we assumed that the duration of infectiousness in these persons was reduced by 67%. Two coverage levels (50% and 80%) are shown (dashed and solid lines, respectively), with R_0 values of 3 (red lines) and 10 (black lines).
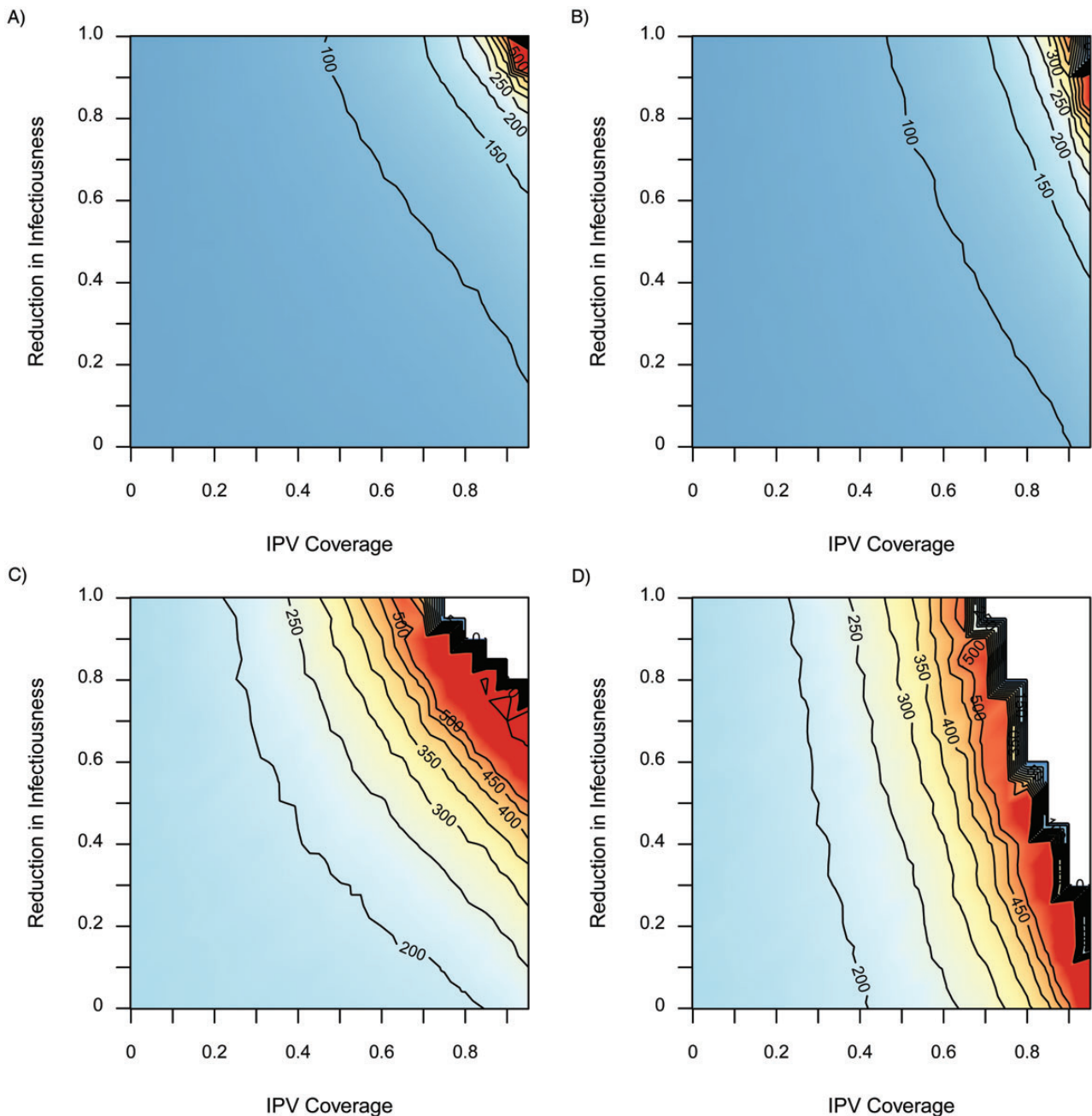
Figure 2. Time taken (days) for a case of paralytic poliomyelitis to be detected from the date of the first infection for an R_0 of 10 (A and B) and an R_0 of 3 (C and D). In parts A and C we assumed no reduction in the duration of infectiousness among persons who received inactivated poliovirus vaccine (IPV), while in parts B and D we assumed that the duration of infectiousness in these persons was reduced by 67%.

0, 526.1) for $R_0 = 3$), but the delay is not substantial unless very high coverage is achieved. During this time, a wild-type virus could increase its geographic range, hindering responsive control efforts. It may also allow VDPVs to revert towards wild-type transmissibility and neurovirulence, although the early evolution process is unclear and loss of key attenuating mutations is known to occur in vaccine recipients (28).

The estimated dates of virus importation in 3 partially vaccinated populations in the Netherlands (serotype 3), the

Dominican Republic (cVDPV1), and Albania (serotype 1) have been previously derived using model-fitting and regression of observed isolates (29). This suggests a delay of 49–64 days before detection in the Dominican Republic and Albania (estimated mean $R_0 = 11$) and a delay of 99 days in the Netherlands (mean $R_0 = 5$) (30–32). The increased time to detection with lower R_0 values is consistent with our findings; our estimates of delay were slightly shorter here, as we assumed a "perfect" surveillance system ($s = 1$) and used
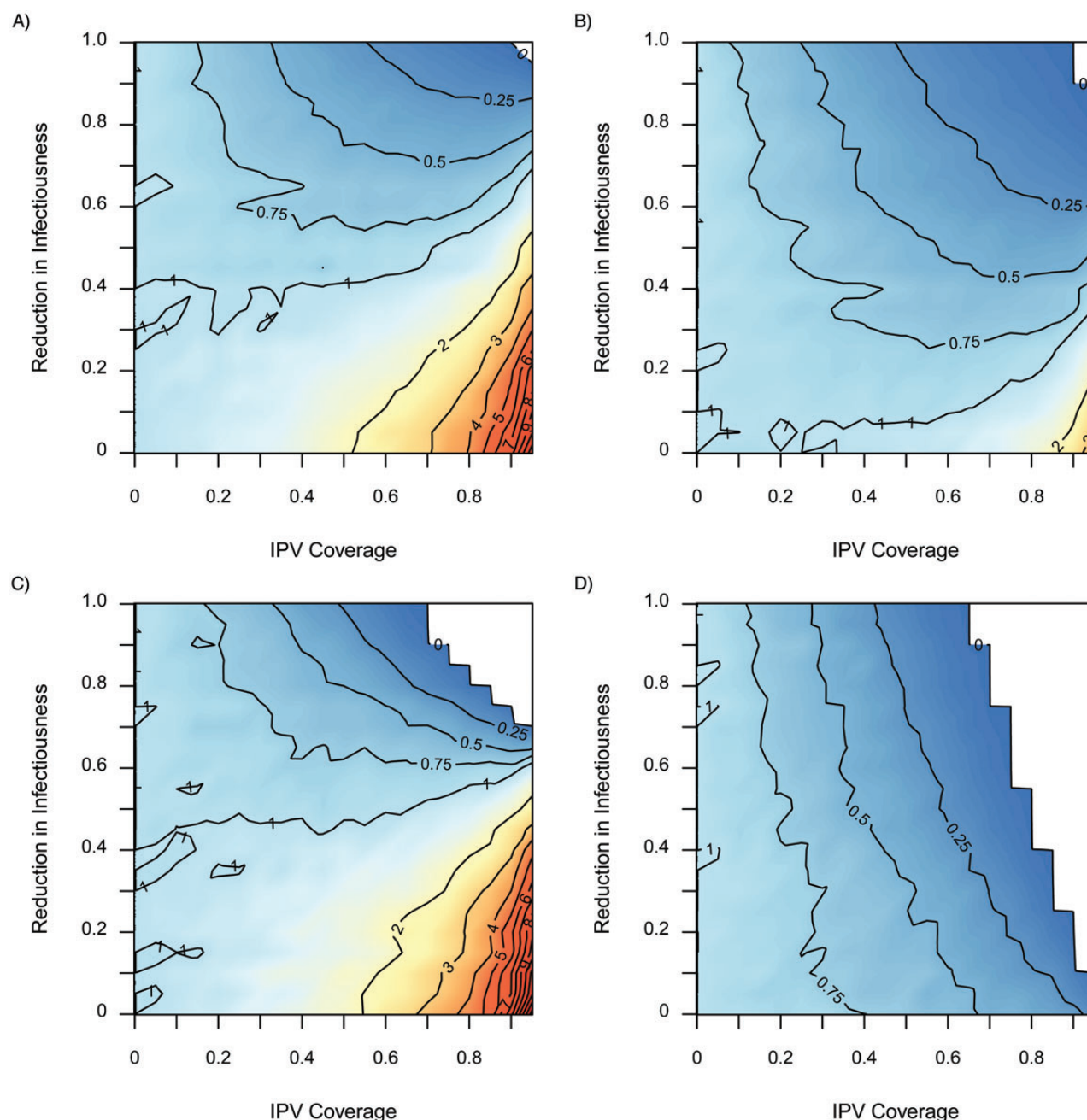
Figure 3. Relative average prevalence of poliovirus at the time the first poliomyelitis case is detected in populations with varying inactivated poliovirus vaccine (IPV) coverage, as compared with a population that did not receive IPV (0% coverage), for an R_0 of 10 (A and B) and an R_0 of 3 (C and D). In parts A and C we assumed no reduction in the duration of infectiousness among persons who received IPV, while in parts B and D we assumed that the duration of infectiousness in these vaccinated persons was reduced by 67%. Prevalence is averaged across all simulations, including those where infection became extinct before any cases were detected (i.e., zero prevalence).

lower estimates of IPV efficacy. Most importantly, we showed that the expected prevalence at the time of detection is not significantly increased unless high coverage is achieved and the vaccine has minimal impact on infectiousness. The absence of poliovirus circulation during the 1992–1993 Netherlands outbreak outside of religious communities refusing vaccination suggests that high coverage (92.2% and 40.4% in sampled

children and adults, respectively) sufficiently maintains herd immunity and prevents transmission in this high-income setting (33). In most scenarios, the use of IPV is beneficial, providing that it reduces infectiousness by at least 50%–60%.

We quantified the impact of IPV in terms of the effect on the duration and degree of infectiousness of IPV-vaccinated persons following infection. In challenge studies, the prevalence

of poliovirus shedding in stools following a dose of OPV is unaffected by IPV, but studies have shown that the amount of poliovirus shed is reduced by 63%–91% (10, 34–39) and that the duration of shedding is approximately halved following 2 doses of IPV (10, 35, 37). If this translated into an approximate 90% reduction in infectiousness, containment of poliovirus outbreaks in most settings should be feasible with 80% coverage, since few infections would occur.

The impact of IPV on poliovirus shedding following challenge with OPV indicates what we may observe in vaccinated children exposed to poliovirus, but we cannot directly relate challenge studies to natural exposure. Vaccine and wild-type poliovirus have differing immune epitopes on their capsids, and shedding following a large challenge dose of vaccine virus may not be exactly comparable with response against a circulating virus (40). In addition, we cannot directly compare reductions in quantity of virus shed with reductions in infectiousness, since they are unlikely to be linearly related. This relationship is governed by a number of other factors, including the transmission route, virus survival in the environment, and individual behavior. Studies of wild-type poliovirus transmission suggest that IPV has a more significant effect on the extent of virus shedding in the nasopharynx (8, 22). Highly industrialized settings with primarily oral-oral transmission may see a greater effect following vaccination, as the reduction in pharyngeal viral shedding would significantly reduce the potential for transmission (41). For that reason, we considered the full range of values for relative infectiousness of IPV recipients and present the results as a sensitivity analysis.

The conclusions drawn in this study are subject to several limitations. First, we assumed that the case:infection ratio was 1:200 and that all paralytic cases were detected by routine surveillance. Second, we did not explicitly differentiate between fecal-oral transmission and oral-oral transmission or incorporate the shorter duration of viral shedding in the nasopharynx compared with the lower intestine. Also, although we assumed that infectiousness was constant over the infectious period, in reality most transmission will probably occur within the first few weeks of infection when the quantity of virus shed is highest (42). The sensitivity analysis explored these assumptions; that is, a case:infection ratio of 1:1,000 may be more realistic for serotype 3 poliovirus or VDPV outbreaks, simulating a surveillance system that detects only half of paralytic cases and reducing the infectious period for unvaccinated persons to 14 days. The results presented here remain broadly the same, with the exception of a shorter infectious period producing a faster generation time. Third, it is uncertain whether the reporting time estimated from surveillance data in endemic countries would be valid for other settings. Fourth, we did not include population structure or age-dependent patterns of vaccination coverage, surveillance performance, and poliovirus transmission. This could lead to changes in the relationship between average vaccination coverage and transmission dynamics. Age-dependent immune responses and variations in vaccine coverage could result in a partially protected population, the net result of which would be a lower effective coverage level. However, our key conclusions are likely to be robust unless IPV coverage and case reporting are perfectly correlated. Our assumptions of random mixing may have overestimated prevalence; more localized transmission

and highly assortative mixing would reduce the expected prevalence (facilitating responsive control efforts). Finally, we ignored any contribution of OPV-vaccinated persons to transmission; these persons are known to shed poliovirus after exposure to children with poliomyelitis, but the quantity of virus shed is likely to be much reduced in comparison with unvaccinated persons (43). In the event that OPV-vaccinated persons do contribute to transmission, this would increase the reproduction number in our model. Additionally, administration of IPV could boost intestinal immunity in OPV-vaccinated persons whose immunity had waned, potentially increasing the benefits of its use (44, 45).

In general, poliomyelitis outbreaks following introduction of wild-type poliovirus into high-income countries (with good sanitation and a low expected R_0) using IPV have been confined to minority groups refusing vaccination (46–48). However, routine immunization with IPV has rarely been implemented in lower-income populations (with poor sanitation), and the impact on poliovirus transmission is not clear (49, 50). It is probable that low-income populations using IPV exclusively may be at greater risk of poliomyelitis in comparison with OPV-using communities due to reduced gut immunity (51). We would expect routine IPV coverage to approach that of the existing 3-dose routine childhood vaccines (75.5% in the African region and 94% in the European region against hepatitis B and diphtheria-tetanus-pertussis in 2011) (52, 53). Heterogeneity in vaccine coverage is likely in certain settings, and pockets of low coverage could sustain an outbreak. In addition, it is probable that higher coverage will be required to prevent outbreaks in settings with poorer sanitation and hygiene, due to increased transmission pressure via the fecal-oral route (54). By improving water treatment and hygiene practices, it is possible to reduce R_0 and potentially prevent outbreaks of poliomyelitis with lower vaccine coverage. This strategy could be highly effective in areas where fecal-oral transmission is predominant and schemes to reduce childhood diarrhea by introducing better sanitation are likely to affect polio outbreaks (55).

Those countries still routinely administering OPV are currently considering the introduction of IPV to minimize the risks associated with OPV withdrawal. Here we have presented the results of a sensitivity analysis predicting that IPV as a first-line defense against polio outbreaks posteradication would be a low-risk strategy under a range of vaccine conditions. Only high coverage with a vaccine incapable of reducing infectiousness would increase prevalence at the time of outbreak detection. To facilitate the use of IPV in routine immunization programs, current research must focus on the development of an affordable product and optimal dosing strategies.

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