Different Views

Live or Inactivated Poliomyelitis Vaccine: An Analysis of Benefits and Risks

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Abstract: Using decision analysis we evaluated the benefits and risks of continued primary reliance on oral poliomyelitis vaccine (OPV) compared to use of inactivated poliovirus vaccine (IPV). We followed a hypothetical cohort of 3.5 million children from birth to age 30 assuming 95 per cent coverage with 98 per cent effective vaccine. Primary reliance on IPV would result in more cases of paralytic poliomyelitis as well as more susceptibles remaining in the population than would be expected with continuing OPV use (74.1 vs 10.0 cases and 5.9 per cent vs 1.1 per cent susceptibles, respectively). However, with OPV use, most cases of paralysis seen would be associated with the vaccine. Our analysis supports a continuation of current US policy placing primary reliance on OPV but the conclusion is heavily dependent on assumptions of risk of exposure to wild virus in the United States. Major declines in risk of exposure to wild virus could alter the balance significantly. (*Am J Public Health* 1988; 78:291–295.)

Introduction

In the United States, poliomyelitis (polio) occurred in epidemic waves of increasing magnitude, reaching a peak in 1952, when more than 20,000 cases of paralytic disease were reported. Within the first four years after introduction of inactivated poliovirus vaccine (IPV) in 1955, nearly 300 million doses of IPV were distributed and there was a dramatic decline in the reported incidence of polio. However, there was a resurgence of cases in 1959–60 and this, coupled with the fact that cases of disease were reported in fully vaccinated individuals, led to concerns that IPV might not be fully effective.[1] Live attenuated (oral) polio vaccine (OPV) was introduced in 1961 and OPV quickly supplanted IPV as the vaccine of choice in the United States (and in most of the rest of the world). Since 1968, IPV has accounted for less than 0.5 per cent of the polio vaccine distributed in the United States.

Continued widespread use of OPV has essentially eliminated poliomyelitis in the United States. Only three outbreaks have occurred in the past 15 years and these have totaled only 40 cases. The most recent outbreak (in 1979) involved 10 cases in members of a religious sect who had refused vaccination.[2] The number of sporadic cases due to wild virus has been small (less than one case per year for the past 10 years) and the last case of indigenously acquired wild poliovirus disease was reported in 1979.[3] Nonetheless, an average of eight cases of paralytic polio continue to be reported each year in association with the administration of OPV. Paralysis associated with the use of OPV has been recognized for approximately 20 years[4] and its infrequent occurrence (overall one case per 2.6 million doses of OPV distributed) has been tolerated in view of the extraordinary benefits of the vaccine. However, the continued occurrence of vaccine-associated cases, coupled with the absence of disease due to wild poliovirus has led to renewed debate as to whether OPV or IPV is the more appropriate formulation for routine use in the United States.

Since the Cutter incident of 1955,[5] in which 60 IPV recipients and 89 of their contacts were paralyzed as a result of incomplete inactivation of poliovirus in the vaccine, there have been no serious untoward adverse effects reported in association with use of IPV. Furthermore, improvements in its potency have apparently eliminated the vaccine failures associated with earlier IPV.[6] Consequently the claim is now made that it is an equally effective but "totally safe" alternative to OPV.[7,8]

A review of available information by the Institute of Medicine-National Academy of Sciences in 1977 concluded that the OPV characteristic of spread to others, thereby immunizing them, was important since immunization levels in the US at that time were estimated to be only 75–80 per cent.[9] However, the study concluded that if immunization levels of 95 per cent could be achieved and maintained in the US this benefit might no longer be important. A major effort to improve immunization levels has since raised coverage in school children to 97 per cent, although levels in preschool children are lower, with only an estimated 80–85 per cent of 2-year-old children having received a complete series of three doses, according to data submitted by states to the Centers for Disease Control (CDC). The situation has thus changed substantially over the course of the past 10 years and continuing questions are being raised about the most appropriate vaccine policy for the United States. Answers to these questions are not all readily found in existing data but depend on certain assumptions.

In the past several years, the techniques of decision analysis have been applied increasingly in the health sciences to assist decision makers in areas of uncertainty where knowledge may not be complete and probabilities (sometimes selective) must be used to predict outcomes. The approach has the advantage of requiring explicit accounting of variables and assumptions.[10,11] Accordingly, we have used decision analysis to evaluate the alternative policies of relying on IPV or OPV for routine immunization in the United States.

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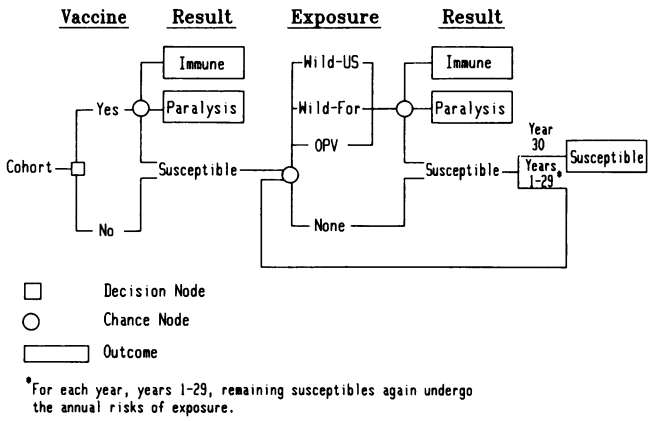

FIGURE 1—Polio Vaccine Decision Tree

Methods

A decision tree was constructed to identify important outcomes regarding polio (Figure 1). The model follows a hypothetical cohort of 3.5 million persons (the approximate number of US births in recent years) from birth to age 30 years. All polio-related activity is considered to occur within this period. For purposes of simplification, it was assumed that all polio vaccination would be accomplished in early infancy, all vaccine-related risks to the recipient would occur in early infancy, and that the vaccine recipient would not be exposed to wild polio virus before vaccination. Vaccine-induced protection was assumed to be lifelong. Three mutually exclusive outcomes were considered possible following exposure to any poliovirus, whether wild or vaccine-derived: immunity (I), paralysis (P), or continued susceptibility (S). The first two outcomes were considered permanent and to remove an individual from further polio risk. Immunity and susceptibility were assumed to be to all three types of polio virus.

After initial vaccination (or non-vaccination) an individual was considered to be at annual risk of possible exposure to polioviruses (either wild viruses in the US or abroad or vaccine viruses) with each exposure having the same three possible outcomes. In each year, remaining susceptibles would be exposed to the annual risks of exposure. For both OPV and IPV, vaccine coverage was assumed to be 95 per cent and vaccine efficacy to be 98 per cent. Estimates of the ratio of cases of paralysis to infection with wild polio virus have ranged from 1:100 – 1:1,000. Assuming that infection in developing countries is universal and knowing that poliomyelitis-associated lameness rates in these countries are typically on the order of 5/1,000, we assumed a paralysis:infection ratio of 1:200.[12] Additionally, since serosurveys rarely demonstrate 100 per cent seropositivity, we assumed that some individuals infected with wild poliovirus would fail to develop immunity. The outcome of exposure to wild poliovirus was thus assumed to be: immunity - 0.98, paralysis - 0.005, and susceptibility - 0.015. Estimation of the probability of other events is described below. Most estimates regarding the OPV use model were based on recent experience in the US, where OPV is used almost exclusively and immunization levels have risen to 97 per cent by the age of school entry. For purposes of estimating risks, the current level of susceptibility in the total United States population was estimated to be 2 per cent (4.6 million susceptibles total).

Risk of Exposure to Wild Poliovirus in the US

During the period 1973–84, 10 epidemic cases, 13 imported cases, and eight cases of endemic non-vaccine associated polio in which wild poliovirus was isolated were reported in the United States, an annual average of 2.58 cases.[13]

Assuming that reporting efficiency is 100 per cent and that each case represents 200 infections in susceptibles, it can be estimated that each year 516 susceptibles were infected with wild virus; 516 infections/year in the estimated 4.6 million susceptibles indicate an annual risk of exposure to wild virus of 1/8,915 susceptibles (0.0001121).

The risk of exposure to wild poliovirus if IPV is used is more difficult to estimate. It is almost certainly greater than the risk if OPV is used, because OPV is more effective in limiting wild virus transmission by vaccinees and because there is not the same direct competition for circulation between wild and vaccine virus as exists with OPV. For the base case it was estimated that the annual risk of exposure to wild poliovirus among susceptibles if IPV was used would be similar to recent experience in The Netherlands, where IPV is used exclusively and where there have been repeated introductions of wild poliovirus. In the 11-year period 1974–84, 114 cases were reported.[14] The average incidence of polio was thus 10.4 cases/year in a population of approximately 14 million. Vaccine coverage was 95 per cent. Assuming vaccine efficacy of 98 per cent, 10.4 cases occurred each year in a population of approximately 966,000 susceptibles. If each case represents 200 infections, the annual risk of infection in susceptibles can be estimated to be approximately 0.00215.

Risk of Exposure to Wild Poliovirus in Foreign Countries

The risk of exposure to wild poliovirus in foreign countries represents a combination of the likelihood of travel to a foreign country and the risk of exposure given such travel. In 1983 there were approximately five million US travelers to less developed countries (approximately 2 per cent of the US population). In the 12-year period 1973–84, an annual average of one case of polio has occurred in US travelers to foreign countries (mostly Mexico).[13] Consequently, it can be assumed that 200 infections occur each year in susceptible travelers abroad. If 2 per cent of the five million travelers are susceptible (100,000), the current risk of exposure to wild poliovirus for a susceptible traveler to a developing country can be estimated to be 0.002 (200/100,000), assuming that susceptible travelers have the same risk of exposure as all travelers. Since the annual probability of travel to a developing country is approximately 2 per cent, the overall annual population risk of exposure abroad is estimated to be 0.2×0.002, or 0.00004.

Risk of Paralysis Associated with Vaccine

The risk of paralysis associated with vaccine was derived using the reported occurrence of vaccine-associated paralysis and estimates of susceptible vaccine recipients and contacts. All vaccine-associated cases were included in the analysis. In the United States, during the period 1973–84, 85 cases of paralysis occurred in immunocompetent individuals in association with OPV administration: 35 in vaccine recipients and 50 in contacts of vaccinees.[13] In addition, 14 cases of vaccine-associated paralysis occurred in individuals with compromised immune mechanisms, 11 of them in OPV recipients, and three in contacts of vaccinees. None of these individuals had been known previously to be immunodeficient. Six cases of paralysis occurred in individuals with no known exposure to OPV but from whom vaccine-like virus

TABLE 1—Base Case Conditions

	OPV Used	IPV Used
Vaccine Coverage	0.95	0.95
Vaccine Efficacy	0.98	0.98
Outcome of Exposure		
Wild virus		
immunity	0.98	0.98
paralysis	0.005	0.005
susceptibility	0.015	0.015
Vaccine virus-recipient		
immunity	0.98	—
paralysis	0.00000112	—
susceptibility	0.01999	—
Vaccine virus-contact		
immunity	0.98	0.98
paralysis	0.0000179	0.0000179
susceptibility	0.0199	0.0199
Annual Risk of Exposure		
wild virus USA	0.000112	0.00215
wild virus foreign	0.00004	0.00004
vaccine virus	0.0596	0.0030

TABLE 2—Estimates from Delphi Survey

Issue	Response	
	Median	Interquartile Range*
% Efficacy of OPV	95	95–95
% Probability OPV immunity is lifelong	90	90–95
% Efficacy of IPV	95	95–98
% Probability IPV immunity is lifelong	85	60–90
% Proportion of US population which is currently susceptible	10	10–15
Number of effective contacts per vaccinee	3.5	3–4
If OPV is used (current situation), number of persons exposed each year**		
to wild virus	5,000	1,000–10,000
to OPV virus	11 million	7.2 million–13 million
If IPV is used, number of persons exposed each year**		
to wild virus	100,000	10,000–100,000
to OPV virus	1,000	1,000–10,000

*Obtained by discarding the highest two estimates and lowest two estimates of the nine panel members.

**Assumes total population of U.S. approximately 230 million

was isolated. There were 41.1 million births during this period. Assuming that all US children received at least one dose of OPV, the overall risk of paralysis in vaccinees can thus be calculated to be 46/41.1 million or 1/893,000 persons vaccinated (0.00000112). For contacts, the overall risk is 59/41.1 million or 1/697,000 vaccinees (0.00000144). To estimate the risk in susceptible contacts, we assumed that each vaccinee had, on average, four contacts of sufficient closeness to permit transmission of vaccine virus ("effective" contacts) and that 2 per cent of the contacts are susceptible. Using these assumptions, the risk of paralysis in a susceptible contact can be estimated. One contact case has been reported for every 697,000 vaccinees. If there are four contacts for every vaccinee and 2 per cent of the contacts are susceptible, for every contact case reported there have been 697,000 × 4 × 0.02 susceptibles exposed or one contact case per 55,760 susceptible contacts exposed (0.0000179), based on recent US experience.

The risk of paralysis associated with IPV was assumed to be zero. Since the Cutter incident of 1955 no cases of vaccine-associated polio have been reported and a query of officials in countries that have used IPV widely (Canada, Denmark, Finland, Netherlands, Sweden) did not indicate any adverse effects of severity comparable to paralysis.

Risk of Exposure to OPV Virus

Virtually all OPV recipients excrete vaccine virus. However, not everyone will necessarily come in effective contact (as defined above) with a vaccinee at the time the vaccinee is excreting the virus. The current annual risk of exposure to vaccine virus in the United States can be estimated as follows: there were 59 cases of contact vaccine-associated paralysis in the United States in the 12-year period 1973–84, an annual average of 4.92 cases.[13] If each of these cases represents 55,760 infected susceptible contacts, it can be projected that there are 274,153 contact OPV infections in susceptibles in the country each year. This indicates an annual risk of exposure to OPV in the 4,600,000 susceptibles in the United States of 1/16.78 (.0596). Assuming that susceptibles have the same likelihood of exposure as the rest of the population, this figure can be used as an estimate of the annual risk of exposure to OPV in the United States given OPV use. If IPV was used, it was assumed that the risk of exposure to vaccine virus would be much lower but would not be zero, as there would be importations of vaccine virus from other countries. It was assumed that the annual risk of exposure to OPV virus if IPV was used would be 5 per cent of that if OPV was used, 0.0030 (.0596 × .05). Table 1 summarizes the conditions of the base case analysis.

Sensitivity Analysis

Sensitivity analysis was performed to determine the outcomes given varying vaccine coverages and varying vaccine efficacies. Further sensitivity analysis involved, in the OPV alternative, doubling and halving the annual risk of exposure to OPV virus from the base case level at varying levels of vaccine coverage. In both alternatives, the effects of doubling and halving the risks of exposure to wild virus in the United States were studied. In addition, each alternative was studied using the risk of exposure estimated for the base case of the other alternative. In the IPV alternative, the estimated risk of exposure to wild virus in Finland and Sweden was also used in the sensitivity analysis.[14] During the period 1974–84, three cases of polio were reported from Finland, a country with a population of 4.8 million. Six cases were reported from Sweden (population 8.3 million) during that same period. Using the same assumptions for coverage and efficacy as for The Netherlands, annual risks of exposure to wild virus can be estimated at 0.000163 and 0.000190, respectively. Finally, the impact on risk of paralysis following contact with OPV was studied by varying the numbers of effective contacts for each vaccinee and varying levels of susceptibility.

Delphi Survey Analysis

Since many of the values used in the analysis required estimates and assumptions, we also obtained informed opinion from experts in poliomyelitis. Consequently, a Delphi survey[15] of nine experts produced the following estimates: efficacy of IPV and OPV, duration of immunity, proportion of the US population currently susceptible to polio, number of effective contacts a vaccinee has, and probability of exposure to wild or OPV virus under conditions of exclusive OPV or IPV use (Table 2). To facilitate response, the question on duration of immunity was posed as the probability that immunity would be lifelong and the questions on exposure to wild or OPV virus were posed as the number of

TABLE 3—Expected Outcomes in Base Case

	Strategy	
	OPV	IPV
Total Cases	10.0	74.1
Wild Virus	2.6	73.7
Vaccine Recipient	3.7	0
Vaccine Contact	3.7	0.4
Susceptibles	39,510	207,175
% Susceptible	1.1	5.9

individuals in the entire US population who would be exposed in the course of a year under different conditions.

Results

The results of the base case analysis are shown in Table 3. If OPV is used, the model projects that 10.0 cases of paralysis would be expected in the cohort, with wild poliovirus causing 2.6 of the cases. Other cases would be divided equally between vaccine recipients and their contacts. If IPV is used, the model projects a total of 74.1 cases, with wild poliovirus causing virtually all of the disease. Because of the spread effect of OPV, OPV use would result in only 1.1 per cent of the population remaining susceptible even though only 95 per cent of the cohort directly received vaccine. By contrast, if IPV is used, it is projected that 5.9 per cent of the population would remain susceptible.

In the sensitivity analysis, for any given level of vaccine efficacy, the number of cases of polio projected is greater and the number of susceptibles remaining in the population is greater if IPV is used. For example, if vaccine efficacy was 95 per cent instead of 98 per cent, we project a total of 12.6 cases of paralysis if OPV is used but 104.7 cases if IPV was used. Similarly, if vaccine coverage was 90 per cent rather than 95 per cent (with vaccine efficacy of 98 per cent), we project 14.3 cases of polio if OPV is used and 126.7 cases if IPV is used. Variations in the risk of exposure to OPV create minor variations in the numbers of susceptibles remaining in the population if OPV is used. Variations in the risk of exposure to wild virus could result in substantial changes in the number of disease expected, however (Table 4).

TABLE 4—Expected Outcomes Given Vaccine Efficacy of 98 Per Cent, Vaccine Coverage of 95 Per Cent, and Specified Levels of Risk of Exposure to Wild Virus in the US

		Cases			
				Vaccine	
Risk of Exposure	Comment	Total	Wild Virus	Recipient	Contacts
OPV Used					
0.000112	Base	10.0	2.6	3.7	3.7
0.000224	2 × Base	12.0	4.5	3.7	3.7
0.0000556	1/2 Base	9.1	1.6	3.7	3.7
0.00215	IPV Base	44.3	37.0	3.7	3.6
IPV Used					
0.00215	Base	74.1	73.7	0	0.4
0.0043	2 × Base	142.2	141.8	0	0.4
0.00108	1/2 Base	38.6	38.3	0	0.4
0.000112	OPV Base	5.6	5.3	0	0.4
0.000163	Finland	7.4	7.0	0	0.4
0.000190	Sweden	8.3	8.0	0	0.4

TABLE 5—Expected Outcomes under Conditions of Delphi Estimates

	Strategy	
Median Estimates	OPV	IPV
Total Cases	6.5	24.1
Wild Virus	1.7	24.1
Vaccine Recipient	3.7	0
Vaccine Contact	1.1	0.002
Susceptibles	80,687	336,452
% Susceptible	2.3	9.6
"Best Case" Estimates		
Total Cases	5.1	3.0
Wild Virus	1.1	3.0
Vaccine Recipient	3.7	0
Vaccine Contact	0.3	0.0003
Susceptibles	61,663	240,597
% Susceptible	1.8	6.9
"Worst Case" Estimates		
Total Cases	7.6	24.1
Wild Virus	2.8	24.1
Vaccine Recipient	3.7	0
Vaccine Contact	1.0	0.0002
Susceptibles	133,659	336,452
% Susceptible	3.8	9.6

The Delphi survey suggests (Table 5) that fewer cases would be expected with either vaccine than are projected in the base case model but more cases would be expected if the IPV was used than if OPV was used. The "best case" variation of IPV use yields fewer cases than the OPV "best case" but the "worst case" variation of OPV yields fewer cases than the IPV median or "worst case" estimates.

Discussion

Given the high efficacy of both IPV and OPV, an immunization program with either vaccine would result in very few polio cases compared to the pre-vaccination situation in the US. Under the conditions of the base case model, the total number of expected cases is greater if IPV is used. With the OPV alternative, most cases would be associated with vaccine, whereas under the IPV model virtually all cases would be due to wild virus. This model has considered all cases of polio as equivalent with no difference in social or financial costs of vaccine-associated versus wild cases, although society tends to consider the former more unacceptable than the latter. Under all conditions considered, the number of susceptibles remaining in the population is substantially greater if IPV is used rather than OPV.

Major questions relate to the firmness of the estimates of risk of exposure to wild virus and the risks of contact-associated disease if OPV is used. If the risk of exposure to wild virus given IPV use is significantly greater than that expected with OPV use, use of IPV would result in a greater incidence of disease in the US than if OPV was used. It is anticipated that the risk of exposure to wild poliovirus will decrease substantially over the next few years as a result of implementation of the Expanded Program on Immunization of the World Health Organization. Perhaps more directly relevant, the Pan American Health Organization has announced a hemispheric target of eradication of wild poliovirus transmission by 1990.[16] Since Mexico has been the predominant source of polio importations into the US, achievement of this target will have major impact on the risk of exposure to wild poliovirus within the US and consequently could affect the relative benefits of OPV versus IPV. When eradication is achieved in the Americas, the risk of introduction of wild poliovirus will become so low that this model would

predict more cases of paralysis if OPV is used (all vaccine-associated) than if IPV is used. Nonetheless, it seems unlikely that the risk of exposure to wild poliovirus in the United States would be as low if IPV is used as if OPV is used.

We have used the experience in The Netherlands in the base case to estimate the risk of exposure to wild virus if IPV is used. At least two other countries—Sweden and Finland—have relied exclusively on IPV and have had lower rates of polio than The Netherlands.[14] If their experience is translatable to the United Staes, the numbers of cases of paralysis due to wild virus given IPV use might be considerably lower than projected in the base case and the total number of cases projected might actually be lower if IPV was used than if OPV was used. However, each of these countries has a relatively homogeneous population with a more limited pattern of immigration and travel to polio endemic areas. We believe The Netherlands experience of repeated introductions of poliovirus is more applicable for the United States, but it is clear that the risk of exposure to wild virus is the major factor influencing the numbers of cases expected under the IPV alternative.

The model has assumed lifelong protection from both vaccines. If IPV-induced immunity is of shorter duration than OPV (as suggested by the Delphi panel), there might be some increase in the numbers of cases expected if IPV was used or a need to provide booster doses in order to maintain immunity.

Obviously, discovery of a severe adverse event associated with the use of IPV at any appreciable frequency (e.g., 1/500,000 or more frequent) would have a further influence on the outcome of this analysis. Although no such event has been reported from the countries relying on the use of IPV, it should be noted that these countries have relatively small populations and are using less than 500,000 doses of IPV per year. Consequently, infrequent adverse events might not be detected.

Finally, this analysis suggests a major difference in the number of susceptibles remaining in the population with IPV use rather than OPV use. The model assumes an essentially linear relationship between number of susceptibles and likelihood of sustained transmission. However, most epidemic models suggest that when a high enough proportion of immunes is reached, herd immunity will protect the remaining susceptibles whereas, above a given level of susceptibility, transmission in a population might be sustained or amplified. Although the exact level of susceptibility at which this might occur is not known, it is clear that the greater the level of susceptibility, the more likely that epidemic (or endemic) transmission might be established. Consequently, the number (or proportion) of susceptibles remaining in the population could be of great importance.

This model has assumed uniform vaccine coverage as well as uniform risk of exposure to wild poliovirus. It is likely, in reality, that there may be areas of lower coverage (e.g., in inner cities or in preschool populations) as well as areas of higher risk of exposure to wild poliovirus (e.g, along the US-Mexico border). If these areas coincide, it is likely there would be greater spread of wild poliovirus and more cases of poliomyelitis than predicted in this model. It also seems likely the effect would be greater if IPV is used because of the greater numbers of susceptibles remaining in any population group if IPV is used.

A combined vaccine approach, in which IPV was administered initially and OPV was given later, should reduce the number of vaccine-associated cases in vaccine recipients. However, since the impact of IPV vaccination on spread of poliovirus is not well quantified, it is not clear to what extent this would decrease the number of contact vaccine-associated cases. Additionally, it is not clear how such a strategy would affect the number of susceptibles remaining in the population. If it is assumed that a combined strategy would abolish vaccine-associated polio in recipients and reduce the likelihood of exposure to vaccine virus by 50 per cent (while maintaining risk of exposure to wild virus at OPV base-conditions), this model projects a total of 6.3 cases of polio (3.7 wild virus and 2.6 in vaccine contacts) and a remaining susceptible population of 98,796 (2.8 per cent). It is not clear, however, that this model can adequately assess the outcomes of a combined vaccine strategy.

In summary, this decision analysis model suggests that under base case assumptions more cases of polio would occur if IPV is used, although the few cases seen if OPV is used will almost all be due to vaccine virus. Additionally, more susceptibles would be present if IPV was used. The impact of a combined IPV-OPV strategy is difficult to assess with confidence. It must be kept in mind that models are simply that and should not be used as the sole basis for making decisions. Nonetheless, they are useful in highlighting the relative importance of different variables. This analysis supports a continuation of current US policy placing primary reliance on OPV[17] but this conclusion is heavily dependent on assumptions of risk of exposure to wild virus in the United States. Major declines in risk of exposure to wild virus could alter the balance significantly.

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