Epidemiol. Infect. (2000), **124**, 113–120. Printed in the United Kingdom

The logic of causation and the risk of paralytic poliomyelitis for an American child

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(*Accepted 7 September 1999*)

SUMMARY

Beginning in January 1997, American immunization policy allowed parents and physicians to elect one of three approved infant vaccination strategies for preventing poliomyelitis. Although the three strategies likely have different outcomes with respect to prevention of paralytic poliomyelitis, the extreme rarity of the disease in the USA prevents any controlled comparison. In this paper, a formal inferential logic, originally described by Donald Rubin, is applied to the vaccination problem. Assumptions and indirect evidence are used to overcome the inability to observe the same subjects under varying conditions to allow the inference of causality from non-randomized observations. Using available epidemiologic information and explicit assumptions, it is possible to project the risk of paralytic polio for infants immunized with oral polio vaccine (1·3 cases per million vaccinees), inactivated polio vaccine (0·54 cases per million vaccinees), or a sequential schedule (0·54–0·92 cases per million vaccinees).

INTRODUCTION

For several decades, American physicians relied almost exclusively on live trivalent Sabin-type attenuated oral polio vaccine (OPV) to immunize children against poliomyelitis. This programme was so successful in preventing wild type infection that Sabin viruses became the only source of paralytic polio in the USA, with an incidence of 5–10 cases per year [1]. To reduce the risks of vaccine associated paralytic poliomyelitis (VAPP), alternative vaccination strategies that rely on enhanced inactivated poliomyelitis vaccine (eIPV) exclusively or on sequential use of EIPV and OPV (eIPV–OPV) were proposed [2, 3]. Public debate over optimal polio vaccination strategy, increased lay awareness of the risk of VAPP, and provider anxiety about potential negligence liability if OPV is chosen arbitrarily and VAPP develops, have encouraged providers to include parents in the choice of vaccine plan for a child. In 1997, as part of an evolving vaccine programme, vaccine policy experts on the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) and the Committee on Infectious Diseases of the American Academy of Pediatrics recognized all three plans as acceptable methods of immunization, with preference given to the eIPV–OPV plan for most vaccinees [4, 5]. The committees' recommendations were designed to allow physicians and parents to choose among vaccine strategies by comparing the risk of developing paralytic poliomyelitis with secondary considerations such as cost and availability.

An American infant has a small but non-zero lifelong risk of paralytic poliomyelitis, a risk that varies according to intrinsic immunologic characteristics of the child, the vagaries of chance exposure to neurovirulent virus, and the choice of vaccination strategy. Some children may develop paralytic poliomyelitis no matter which vaccine strategy is chosen. Most will not develop paralytic polio no matter how immunized. A particular child might develop paralytic polio if immunized with one method but not if immunized with another method. A total of eight

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Table 1. *Individual vaccinees may develop paralytic poliomyelitis after all, two, one, or none of the various immunization programmes*

	Hypothetical outcome after immunization with			Immunization received	Observed outcome
	all OPV	all eIPV	eIPV–OPV		
Example patient A					
	−	−	−	All OPV	−
	−	−	−	All eIPV	−
	−	−	−	eIPV–OPV	−
Example patient B					
	+	−	+	All OPV	+
	+	−	+	All eIPV	−
	+	−	+	eIPV–OPV	+

The observed outcome depends on the vaccinee's individual characteristics and the programme assigned. In the table, the observed outcomes for two hypothetical vaccinees are shown. Vaccinee A is immune to paralytic poliomyelitis after any programme and has a favourable outcome no matter how vaccinated. Vaccinee B will develop paralytic poliomyelitis if ever exposed to OPV and has a favourable outcome only when vaccinated with an all-eIPV programme. If a child is immunized with all eIPV and never develops paralytic poliomyelitis, it is not possible to know whether the vaccinee was like Example patient A or example patient B. − indicates no paralytic poliomyelitis; + indicates paralytic poliomyelitis.

combinations of paralysis and non-paralysis associated with the three vaccination strategies are possible. Because a child can only be exposed to one primary immunization strategy, the observed individual outcome narrows the possibilities to four: the child does or does not develop paralytic polio after one form of immunization, while his responses to other strategies remain hidden. Parents and physicians choosing among vaccine strategies, however, want to know the risk of paralytic poliomyelitis for a given strategy among children who would not suffer paralysis under a competing strategy(ies).

Since alternative treatments are never applied to exactly the same subjects, indirect evidence and reasoning must be used to approach the question of whether different treatments will result in different outcomes for a given subject. Rubin and others have described this as the fundamental problem of causal inference [6, 7]. The possible outcomes of a vaccination study can be presented in tabular form with a series of columns describing the subjects' potential outcomes under each treatment strategy, a column designating the treatment received, and a column of observed outcomes. In Table 1, entries for two of the eight theoretical subject types are shown; one child is not at risk for paralysis under any plan and the other would contract VAPP unless vaccinated with IPV exclusively. Such a table gives explicit recognition to the influence of treatment choice on observed outcome and emphasizes the hidden character of important differences between subjects. (In the example table, lines 2 and 5 have the same intervention and the same observed outcome although the subjects are dissimilar.) While a properly randomized, blinded study could answer the question of the parent and clinician at a defined level of confidence, the extreme rarity of VAPP makes prospective controlled comparison of vaccine strategies impractical. Inferences of causation depend, therefore, on methods other than randomization to satisfy the requirement of ignorable treatment allocation [8].

Rubin employs a 2×2 tabular display to examine the simplest case of two alternative treatments and a bivariate outcome [6, 7]. Before proceeding to a more complicated case, it will be useful for the reader to consider a simple 2×2 Rubin model. The development of paralytic poliomyelitis during the early weeks of the 1955 USA poliomyelitis vaccination campaign provides a suitable example with well-documented empirical data, strong indirect evidence in support of the single required assumption, and subject matter related to the primary example of this paper.

The Cutter incident: a model with two alternatives

The Salk inactivated polio vaccine was approved for use in the USA on 12 April 1955, after field trials demonstrated its safety and efficacy. A nationwide programme to vaccinate all first and second graders

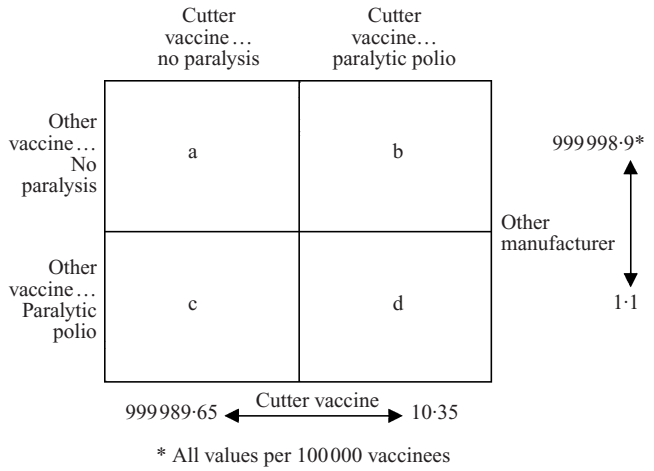

Fig. 1. First and second grade students attending school-based clinics between 13 April 1955 and 26 April 1955 received IPV produced by Cutter or by one of four other manufacturers. Vaccinees who contracted paralytic poliomyelitis before 30 June 1955 were counted for each group. The observed rates per 10^5 recipients are shown as the margin values for Cutter and other vaccines. Indirect evidence suggests that other manufacturers' products did not infect recipients or result directly in paralysis. $c = 0$ implies that $a = 99{,}998{\cdot}9/10^5$, $d = 10{\cdot}35/10^5$ and $b = 9{\cdot}25/10^5$. The Cutter vaccine caused paralytic poliomyelitis in 9·25 children per 100000 vaccinees who would not have contracted paralytic poliomyelitis if vaccinated with a different product.

began on 13 April. Vaccine for administration at school-based clinics was purchased from five manufacturers. On 25 April, a vaccinee in Chicago developed paralytic poliomyelitis. Several cases in California vaccinees were reported on 26 April. On 27 April, the vaccination programme was suspended. During the Spring and Summer of 1955, detailed records of vaccine lots, dates of vaccinations, and incidence of paralytic polio in vaccinees were assembled. Laboratory investigations demonstrated that certain lots of the Cutter vaccine contained live viral particles [9].

Between 13 April and 30 June, 32 cases of paralytic poliomyelitis were observed among 309000 school clinic recipients of the Cutter product (10·35 cases per 10^5 vaccinees), compared to 50 cases of paralytic poliomyelitis among 4550000 school clinic recipients of vaccine produced by other manufacturers (1·10 cases per 10^5 vaccinees) [10]. In the 2×2 table in Figure 1, the bottom row and right hand column represent the unfavourable outcome, paralytic poliomyelitis, for non-Cutter and Cutter recipients respectively. The top row and left column represent the favourable outcome, no paralysis. The observed rates of paralytic poliomyelitis are entered as the margin values of the 2×2 table and the cell values are designated with the letters *a* to *d*.

The question of interest to epidemiologists, pharmaceutical manufacturers (some) and plaintiff's lawyers, was the risk of paralytic poliomyelitis for Cutter recipients who would not have suffered post-vaccine paralysis if they had received an alternative vaccine: cell b. Although margin values do not permit assignment of values to individual cells, relevant indirect evidence is available. The discovery of viable poliovirus in certain lots of the Cutter product but not in vaccine produced by other manufacturers [9], the rate of vaccine failure predicted from the field trial data [11], and differences in the timing, pattern of paralysis, and incidence of contact cases between the Cutter and alternative vaccines [10] support the following claim: no child who suffered paralytic poliomyelitis after vaccination with a non-Cutter product would have been protected by the Cutter vaccine. In other words, $c = 0$. The empirical data, in combination with the inference about cell c, permit assignment of values to the other cells. In particular, from cell b, 9·25 cases of paralysis per 10^5 vaccinees were caused by the Cutter vaccine.

The clear statement of causality depends on a powerful assumption. If $c = 0$ then no other vaccine led directly to paralysis, and each vaccine (including the Cutter vaccine) had the same imperfect ability to protect recipients from community acquired wild type paralytic poliomyelitis. (In fact, the statement $c = 0$ asserts that each vaccine would protect precisely the same recipients. The indirect evidence mentioned above only supports the weaker claim that each vaccine protects the same proportion of recipients. The possibility that the Cutter vaccine might confer

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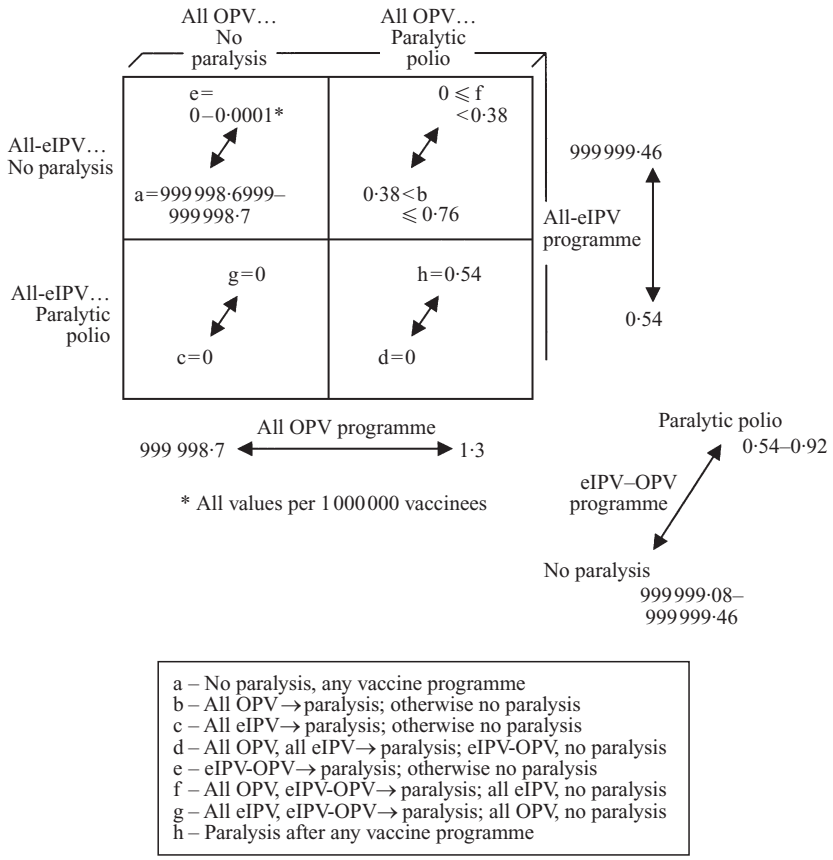

Fig. 2. Parents and physicians of unimmunized infants may elect one of three vaccination schedules to prevent polio infection: all eIPV, all OPV, or sequential eIPV–OPV. The three schedules appear equally likely to induce immunity and the risk of contact with potentially neurovirulent Sabin virus is taken to be independent of the choice of vaccine programme. Thus the risk of contact VAPP is similar for vaccinees on each programme. The risk of paralytic infection resulting directly from vaccination varies from 0 on the all eIPV schedule to $0{\cdot}76 \times 10^{-6}$ on the all OPV schedule. Election of the sequential programme (over all eIPV) increases the risk of paralytic poliomyelitis by an indeterminate amount, ranging from 0 to as much as $0{\cdot}38 \times 10^{-6}$. All values in the figure are per one million vaccine recipients.

protection to a different set of recipients than one or more of the other manufacturers' products is scientifically intriguing, but would not alter the ultimate inference about causality.) While the evidence in support of the assumption is persuasive, it is necessarily indirect. In theoretical terms, such assumptions require that all relevant differences among treatments have been specified, and that the choice of treatment is independent of the outcome, referred to as the 'stable-unit-treatment-value assumption' (SUTVA) or the 'stability assumption' [12, 13]. In this example, a SUTVA violation could be imagined if Cutter recipients had been quarantined following the discovery of the manufacturing error, since isolated vaccinees would have had a decreased risk of community exposure, and thus a stronger protective effect resulting in c not being equal to 0.

For the 1955 vaccination misadventure, the causality claim seems natural. Figure 1 constructs the outcome of an imaginary experiment in which every child is exposed to both conditions: primary vaccination with the Cutter and non-Cutter products. The formalism of the Rubin model serves to expose the assumptions that underlie the inference of causation, and yields a numerical estimate for the excess risk.

Three alternative model

Three treatment options create eight theoretical combinations of outcomes. An untested subject, for example, might have a favourable outcome after treatments 2 and 3, but an unfavourable outcome after treatment 1. The eight combinations can be displayed in a three dimensional $2 \times 2 \times 2$ table (see Fig. 2 which accompanies the discussion below). As before, the margin values, now three pairs, are subject to direct observation but the impossibility of applying

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different treatments to the same subject and the unavailability of randomization force the use of indirect evidence to determine the interior cell values.

Determining the cell values is equivalent to a problem of eight unknowns in four equations (one equation for each observed margin and the equation that sets the sum of all cells equal to one). If the three margin values are known, four additional orthogonal equations are needed to complete the system. For these, the investigator must rely on indirection and assumption.

The choice of vaccine programme for an American infant

Figure 2 is a structure for analysing the choice of vaccine strategy. The lower cells, the right hand cells, and the more distant cells (at the upper end of the diagonal arrows) represent the unfavourable outcome, paralytic poliomyelitis, with eIPV, OPV and eIPV–OPV respectively. The model assumes that the decision maker is primarily motivated by the desire to avoid paralytic poliomyelitis. Of course, secondary motivators are present and may be powerful enough in some cases to overcome an increased risk of paralytic poliomyelitis. The secondary factors all favour the use of OPV. They include: (i) cost (both product and delivery are more expensive for eIPV [14]), (ii) discomfort (since a combined eIPV-DTP injection is not available in the US, use of eIPV necessitates an additional inoculation, often at the same visit with other injections [15–17]), (iii) convenience (additional encounters have been proposed to overcome the problem of multiple inoculations [17]), (iv) availability (some providers may choose to continue the long-established custom of stocking only OPV, forcing parents whose choose an eIPV or eIPV–OPV programme to look elsewhere or pay a premium), (v) fulfilment of an obligation for exemplary conduct (since widespread immunization in underdeveloped countries requires the practicality of OPV, concern has been raised that American abandonment of OPV might degrade the perceived status of the vaccine and endanger the prospects of global eradication of polio [18]), (vi) creation of a halo of polio immunity around the infant (excretion of the Sabin virus by OPV vaccinees exposes and immunizes some vaccinee contacts [19]), and (vii) the altruistic desire to protect the community (prior exposure to OPV may be more effective than exposure to eIPV alone in reducing the amount and duration of viral excretion following subsequent exposure to either wild or Sabin virus [20–22]). Disagreement about the importance of the secondary considerations relative to the risk of paralysis prevented American vaccine experts from endorsing a single uniform policy. It is evident that the secondary factors will have different importance for policy makers than for individual parents and physicians, and will influence different parents in different ways. Quantifying the cells and margin values of Figure 2 allows the decision maker to assess how much risk is attributable to each vaccine choice.

Assignment of values of the $2 \times 2 \times 2$ table

CDC data support a confident estimate of 1·3 cases of paralytic poliomyelitis per 10^6 American OPV recipients, an empirical marginal value for the OPV choice [23]. The rare paralysis victims include recent vaccinees within whom the Sabin virus exhibits neurovirulence, and individuals (with variable immunization histories) who acquire infection through contact with a person shedding vaccine virus. Since large numbers of infants immunized exclusively with eIPV are found only in countries with little or no circulating Sabin virus [24], and since the only countries with historical reliance on sequential schedules are small (Denmark, Egypt, Hungary and Israel) [25], empirical data applicable to an American child vaccinated with eIPV or eIPV–OPV (the other margin values in Fig. 2) do not exist. Reversing the process used in the 2×2 example, indirect evidence and deduction about the cell values can be used to derive the missing margin values.

Persistent third-world reservoirs of wild poliovirus, the ease of international travel, and the presence of inadequately immunized persons in the population imply that no American child is secure from exposure to wild virus [26, 27]. However, wild virus has not caused paralytic poliomyelitis in the USA for nearly two decades and the threat of paralysis for an American vaccinee is effectively limited to vaccine viruses. Contagious cases are therefore simply the VAPP contact cases. For a contact case to occur in a vaccinee, three uncommon events must coincide: the vaccination must have failed to immunize, there must be exposure to a neurovirulent virus, and the infection must progress to involve the central nervous system. Measurements of serum and local antibody levels following immunization with eIPV, OPV and eIPV–OPV schedules suggest similar small rates of immuno-

https://doi.org/10.1017/S0950268899003350 Published online by Cambridge University Press

logic failure [20, 21, 28, 29]. If we assume that exposure rates and the chance of paralysis during the course of infection do not change as a result of the choice of immunization programme, contact case rates will be the same for vaccinees on each schedule. The estimated contact case risk for USA OPV recipients is 0·54 cases per 10^6 vaccinees [23]. Since eIPV does not cause paralytic poliomyelitis (no instances have been recorded since the 1955 accident), $0{\cdot}54/10^6$ becomes the margin value for eIPV. If we accept, as we did for the several products in the 1955 example, that the three schedules provide immunologic protection for the same individuals (the contrary assumption would not alter the choice of programme unless the differences could somehow be predicted), cells c, d and g are 0 and cell $h = 0{\cdot}54/10^6$: a person who suffers paralytic poliomyelitis caused by contact with a circulating Sabin virus would have suffered paralysis regardless of his prior immunization programme.

As in other applications of the Rubin formalism to the epidemiology of infectious diseases, the SUTVA assumption may be violated by the effect on one subject of treatment assignments to other subjects [30]. With respect to polio vaccination, small absolute differences in immunologic failure rates for the three vaccine schedules would likely escape notice in any feasible study, reducing our confidence in applying the contact case rate among OPV recipients to eIPV or eIPV–OPV recipients. Of greater concern, the individual choices of parents and providers may not be independent of the rate of Sabin virus exposure or the risk of neurovirulence. Parents and physicians who elect eIPV or eIPV–OPV for one child may be more likely to make the same choice for siblings, lowering the risk of household exposure VAPP (the source for most cases of contact VAPP). Further, the preferences of a pediatric practice or a managed care administrator might alter the risk of Sabin virus exposure for an entire community [31]. Finally, there is evidence that the viruses excreted by eIPV–OPV recipients may have higher rates of neurovirulence compared to viruses excreted by OPV recipients [31, 32]. These reservations are not reflected in the values shown in Figure 2. Instead, the risk estimates are conditioned on stable exposure rates (to the Sabin viruses), as suggested by Halloran and Struchiner [30].

By using indirect evidence instead of empirical observation to determine the margin value for eIPV, we reversed the process of the first example. Since empirical evidence is unavailable concerning the risk of paralytic poliomyelitis for a US child immunized with a sequential schedule, we must use the same reversed process to estimate the eIPV–OPV margin value. From the reasoning above, $0{\cdot}54/10^6$ is a lower limit. Among children paralysed after immunization with OPV, $0{\cdot}76/10^6$ would have avoided paralytic poliomyelitis if immunized by eIPV. (In the algebra of Fig. 2, $b+d+f+h = 1{\cdot}3/10^6$, $d = 0$, $h = 0{\cdot}54/10^6$, so $b+f = 0{\cdot}76/10^6$.) There is broad expert agreement that at least some OPV victims would not be paralysed by the sequential schedule because it reduces the number of OPV exposures, delays the first OPV exposure, and for most children provides systemic immunity prior to Sabin virus exposure [3, 5, 16, 17, 23, 33] (in Fig. 2, $b > 0$.). In particular, the sequential schedule may permit diagnosis of a larger proportion of congenitally immunodeficient patients before those vulnerable children are fed live virus [33]. Until empirical data become available, the risk of paralytic poliomyelitis caused by the sequential schedule among children paralysed after OPV can only be specified as ranges, as noted for cells b and f in Figure 2.

Various approaches have been taken to estimate the risk of VAPP caused directly by exposure to eIPV followed by OPV. Miller and colleagues used a delphi panel based on 95% protection (against directly caused paralytic polio) for immunocompetent children and no effect for immunodeficient children, concluding that in a programme of uniform sequential immunization, the overall rate of VAPP would be half that of an OPV programme [31]. Other estimates based on overseas experience and statistical modelling have suggested overall reductions of 50–60% [34]. In Figure 2, a reduction of $< 50\%$ for VAPP directly caused by eIPV–OPV, compared to the observed rate for OPV, is postulated. Cell f, representing children protected by eIPV (they do not acquire community VAPP) but who develop paralytic polio after OPV, develop paralytic polio after sequential immunization at a rate less than $0{\cdot}38 \times 10^{-6}$. Cell b, representing children protected by eIPV and eIPV–OPV but paralysed after OPV, ranges from 0·38 to $0{\cdot}76 \times 10^{-6}$.

Is there any child who suffers paralysis following the sequential schedule who would have been spared on the OPV (and eIPV) programme, cell e? Although the circumstance has not been reported, such a child is conceivable. Following early OPV exposure, a child with humoral immunodeficiency might acquire gastrointestinal infection and show prolonged enteroviral excretion, but be protected from systemic infection by maternally derived serum antibody. Modern precise techniques of viral isolation and the widespread

availability of immunoglobulin and IgG subclass measurements could result in the diagnosis of immunodeficiency precisely because of the early OPV exposure, without the risk of paralysis. On a sequential schedule, the child's immunodeficiency might not be discovered. He would not develop immunity as a result of eIPV, and might then be exposed to OPV after maternal antibody protection was lost, risking systemic infection and paralysis. Even if every vulnerable immunodeficient child who currently escapes infantile paralysis were at risk from the sequential schedule, the added risk for an infant with unknown immune status would be very small, as noted on Figure 2, cell e [32]. The value in cell e, far below the accuracy of estimates in other non-zero cells, can be ignored. The margin value for eIPV–OPV ranges from $0{\cdot}54/10^6$ to $0{\cdot}92/10^6$ ($0{\cdot}54+0{\cdot}38$).

DISCUSSION

Figure 2 displays the result of a hypothetical experiment in which the subjects are exposed to each of three conditions: primary immunization with OPV, eIPV and the sequential schedule. The reported risk for OPV and estimates of the cell values were used to derive the as yet unobserved risks of VAPP for eIPV and eIPV–OPV.

The observed lifelong risk of paralytic poliomyelitis for an OPV vaccinee is $1{\cdot}3\times10^{-6}$. Indirect evidence about the immunogenicity of the three vaccination strategies, reasoning about risks for immunodeficient infants, and assumptions about non-vaccination exposures to vaccine virus yield a risk estimate of $0{\cdot}54\times10^{-6}$ for eIPV vaccinees and a $0{\cdot}54$–$0{\cdot}92\times10^{-6}$ range for eIPV–OPV vaccinees. Exchanging an excess risk of 0·76 per million, or an excess risk with a maximum value of 0·38 per million, for advantages in cost, comfort or other considerations may seem reasonable to some parents and physicians but not to others.

Other formal approaches have been proposed to project the risks attributable to polio vaccine strategies. These techniques include standard laundry lists of advantages and disadvantages [2, 3, 18], clinical decision analysis [35, 36], and mathematical modelling [37]. In this paper, the problem has been approached from the perspective of an individual infant's surrogate decision maker, rather than the perspective of public policymaker. The Rubin model of causal inference, although not a standard epidemiologic method, is well adapted to questions for which randomization is foreclosed, because it focuses attention on the known relevant empirical data, accommodates available indirect information, and forces recognition of the underlying assumptions. If American vaccine policy maintains a system of three coexisting regimens, increasing experience will allow revision of the cell estimates through direct observation of the margin values for eIPV or eIPV–OPV schedules.

During the months following the 1997 American policy change, the use of eIPV for the first two infant vaccinations increased dramatically in the USA [38, 39]. During the same period, the percentage of children fully immunized at one year of age was unchanged. These observations suggest that most decision-makers have chosen increased protection from VAPP at the expense of increases in cost, discomfort, and inconvenience.

During 1997 and 1998, four cases of VAPP were reported to the Centers for Disease Control, three in first-time vaccinees immunized with OPV and one in an adult contact of a first-time OPV vaccinee. This crude case rate is less than half the annual case rate of 8–10 associated with the universal all-OPV immunization programme. The favourable reception of the injected vaccine and the diminishing need to protect the community as global eradication efforts go forward will make the all-eIPV schedule more attractive to American vaccine experts.

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