Polio: Measuring the Protection That Matters Most

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This issue of the Journal contains an important contribution to the effort to rid the world of polio—an article that measures the effectiveness of oral polio vaccine (OPV) in reducing poliovirus excretion in northern India [1]. Its importance lies in its shifting of attention from measures of protection against disease to measures of protection against infection transmission in the field, a shift that is essential if the eradication program is to succeed.

The Global Polio Eradication Initiative faces major challenges. Now 9 years beyond its original target date (the year 2000, set by the World Health Assembly in 1988), the initiative has been unable to stop wild-virus transmission in 4 countries (Afghanistan, Pakistan, Nigeria, and India), and these countries continue to export wild virus to other regions of the world. The problems are clear: in Afghanistan, Pakistan, and Nigeria, it is largely failure to vaccinate; in India, it appears to be vaccine failure. The failure to vaccinate in Afghanistan and Pakistan is largely a consequence of political instability and security difficulties that hamper program activities, adding another misfortune to the many serious problems in that troubled region. In Nigeria, the low coverage is due to program failure, aggravated by low public confidence and insufficient political will in the face of unfounded rumors that polio vaccine is unsafe. Resolution of these problems is proving difficult, but at least they do not challenge the technical feasibility of the eradication goal. The situation in India is different and more serious—wild virus has continued to circulate despite the most intensive vaccination program ever conducted.

The problem is not present throughout India but primarily exists in 2 northern states, Uttar Pradesh (UP) and Bihar, that have a long history as entrenched foci of major infectious diseases. Supplementary immunization activities (SIAs) have been performed in these states since the mid-1990s, first as additional house-to-house rounds of trivalent OPV (tOPV) administered to all children <5 years of age and later (since 2005) up to 10 house-to-house rounds per annum with either tOPV, type 3 monovalent OPV (mOPV), or, in particular, type 1 mOPV. As a consequence of these efforts, many children received >20 doses of OPV. The strategy appeared to be working—no disease attributable to type 1 virus was seen in western UP from September 2006 through May 2008, but then cases reappeared. Transmission continues.

The analyses reported in this issue take advantage of data collected in the course of acute flaccid paralysis (AFP) surveillance, which gathered detailed data on vaccination histories, along with stool specimens, of >100,000 individuals with AFP across India between 2005 and 2007. By concentrating on individuals whose paralysis was not attributed to poliomyelitis but who had received OPV ≤4 weeks before clinical onset, the authors have been able to explore the extent of virus excretion after the most recent (“challenge”) vaccination as a function of the individual’s prior vaccination status. They show that fecal virus excretion is reduced as a function of the number of previous vaccinations, that the decline is greater elsewhere in India than in the states of UP and Bihar, and that the decline is greater after mOPV than after tOPV administration. They show, for example, that excretion of type 1 virus after a challenge dose is reduced by 40% and 70% among individuals in UP and Bihar who had received ≥5 previous doses of tOPV or mOPV, respectively, compared with individuals who had received 0 previous doses. Elsewhere in India, ≥5 doses of OPV reduce excretion by some 75%. These decline-in-excretion statistics are analogous, but not identical, to traditional vaccine efficacy measures, having been derived through logistic regression of excretion probabilities at different times after the challenge dose.

This approach is similar to a study design that has been used for small numbers
of individuals by several investigators—comparisons of virus excretion after a challenge dose of OPV as a function of prior vaccination status [2–4]. These small studies have generally shown that individuals with a history of infection with wild or OPV virus excrete lower titers of challenge OPV virus for shorter durations than do individuals who have no experience with polio antigens or who have received only inactivated vaccine. Such results, which indicate that oral vaccines provide greater protection against infection and infectiousness than do inactivated vaccines, were among the reasons why OPVs were long favored in most countries of the world and why they were favored by the Global Polio Eradication Initiative.

The new observations are consistent with much other information that has been obtained to date, in particular the findings of a study by the same investigators demonstrating that oral vaccines provide less protection against disease in UP and Bihar than elsewhere in India and that mOPV imparts greater protection against disease than does tOPV [5]. The authors are suitably cautious as to potential confounders, but the broad results are credible. Their importance is in shifting attention from measures of protection against disease to protection against infection or infectiousness at the population level.

Polio is one of those diseases for which the distinction between infection and disease is crucial. The distinction is of particular importance in the context of an eradication initiative, whose ultimate goal must be to stop all transmission of infection. Because <1% of wild-virus infections are manifested as recognizable clinical disease, reported disease statistics reveal only a small proportion of the extent of infection in a population. Furthermore, it has long been evident that the mechanism of protection against infection is not identical to that for protection against disease. For example, most reports on immune responses to polio vaccines emphasize assays of immunoglobulin G (IgG) neutralization antibodies, for which a titer of 1:8 is considered protective—against clinical disease. Several studies have shown that inactivated polio vaccine (IPV) regimens can in general produce higher titers of such antibody than OPV regimens, but they are less effective in protecting against infection, as demonstrated in OPV challenge studies [2–4]. If the goal of a control program were only to reduce the incidence of disease, then such serum antibody data would be relevant. Insofar as the task of an eradication program is to stop transmission, the relevance of such antibodies is less clear. Identification of an immunological marker of mucosal protection that correlates with protection against infection or infectiousness has thus far proven to be elusive [3, 6]. These recent results should stimulate more studies in this direction.

The poor performance of OPV in the UP and Bihar populations is likely attributable to their poverty, crowded living conditions, and high prevalence of enteric infections. That OPV functions less well in tropical than in temperate environments has long been recognized, and previous studies have shown that IgG seroconversion rates are low among children of low socioeconomic background and among children with diarrhea [7, 8]. It is thought that this reflects an inability of oral vaccine viruses to establish themselves in a gut inflamed by other pathogens. Whether there are other reasons for the extreme conditions in Uttar Pradesh and Bihar is unknown.

The unique nature of the intervention in UP and Bihar deserves attention. Never before has a population received so many doses of any vaccine. Researchers with interests in mucosal immunity may find these unusual circumstances a fertile field for investigation.

The programmatic implications of these observations are under discussion. Because the repeated mOPV SIAs have thus far failed to stop transmission, options include further enhancement of the potency of mOPVs, extension of the target for mOPV to older age groups, and/or introduction of 1 or 2 rounds of IPV to young children in addition to the massive use of OPV. Studies are now being planned to evaluate whether age groups contribute sufficiently to transmission to warrant their being included in OPV SIAs. A proposed mass supplemental use of IPV would be even more radical. Such an intervention has never been attempted in such circumstances, let alone evaluated. Although IPV alone induced sufficient enteric immunity to stop transmission of polioviruses in the Netherlands and Scandinavia [6], there is little evidence that such an intervention would have a substantial effect on transmission in a tropical setting with heavy fecal exposure, as in the state of UP. A World Health Organization–sponsored introduction project in Yokjakarta Province of Indonesia found that, beginning 3 weeks after the switch from OPV to IPV, no Sabin vaccine viruses were detected in environmental samples for >5 months, and only 2 samples have tested positive since then (which are thought to represent excretion by an IPV-vaccinated child). These preliminary results suggest that IPV-induced immunity may be able to prevent circulation of Sabin-derived viruses in some tropical settings, although one cannot with confidence generalize these findings from Yokjakarta to northern India. Most authorities would argue that inactivated vaccines alone are unlikely to be sufficient in such circumstances, but it is possible that they could induce a marginal supplement to protection (on top of that induced by repeated administration of oral vaccines) sufficient to stop transmission. And some authorities have noted that inactivated vaccines might reduce transmission by affecting the oropharyngeal route [6]. Such an option would present immense logistic difficulties, because of the need for injections, as well as a formidable public relations challenge. But it
could have extremely important implications, not only for success in UP and Bihar but also for other contingencies that may arise during the final stages of the eradication effort. Unless this approach is tried—and tried on a massive scale—it utility will remain conjectural. If the government of India does opt for such an approach, there is an overwhelming argument that it should be monitored closely for both immunological and epidemiological effect—against infection, not just disease.

References