Invited Commentary: The Scientific Basis for Stopping Polio Immunization

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The global eradication of poliomyelitis is now in sight. Poliomyelitis cases have been reduced by 90 percent since 1988. North and South America, Europe, China, Southeast Asia, the nations of the Pacific, and significant parts of Africa and the Middle East are now polio free. The last case of polio in the world will probably occur by the end of the year 2000 or shortly thereafter.

While stopping transmission of wild polioviruses is the essence of eradication, there are three additional steps that follow: containing laboratory strains in secure facilities, formally certifying eradication, and stopping immunization against polio. The full humanitarian (550,000 cases prevented each year) and financial ($1.5 billion annually) benefits of polio eradication will be realized only when these final steps are complete. An independent global commission has established certification criteria and surveillance standards to provide assurance of eradication. A plan for containment of all polioviruses has been prepared (1). The major remaining question is how polio vaccination can be safely stopped (2, 3).

The World Health Organization convened a meeting of virologists, immunologists, and epidemiologists in March 1998 to address this final and controversial stage of the polio eradication initiative. The objectives of the meeting were to review current knowledge and identify research needs on how and when polio immunization can be stopped. Fine and Carneiro’s literature review and mathematical model (4) was commissioned by the World Health Organization for that meeting. The paper delineated important gaps in the scientific knowledge and helped to define the research agenda for the few years remaining before a decision must be made. Fine and Carneiro concluded that the possibility of continuing circulation of vaccine-derived polioviruses (VDPV) cannot be excluded with absolute certainty. They argue that VDPV may continue to circulate after use of oral polio vaccine stops and that immunodeficient persons may be a potential reservoir from which VDPV could be reintroduced into the general population. The remainder of this article summarizes the meeting and outlines research undertaken to address these important issues.

Circulation of VDPV

The transmission of VDPV from vaccinees to susceptible close contacts was recognized prior to the introduction of oral polio vaccine. VDPV were transmitted from person to person in families, but less readily so than wild strains (5). Although the potential for VDPV to circulate in the community has been less well described, both direct and indirect data are available suggesting that such transmission is limited.

Direct data come from Cuba and Hungary. Since 1962, mass campaigns have been the only method for immunizing children against polio in Cuba. Enterovirus surveillance there recovered polioviruses only for 2 months after campaigns (6, 7). Additional sewage sampling and stool surveys are being conducted to further document the circulation of VDPV. Starting in 1961, Hungary controlled polio with annual mass campaigns administering three doses of monovalent oral polio vaccine spaced 1 month apart. Enterovirus surveillance detected polioviruses only in the 3 months following the campaigns (8). All vaccine-associated paralytic polio cases clustered in the months immediately following the campaigns (9).

Additional indirect evidence comes from the Netherlands where inactivated polio vaccine is used for routine immunization. However, oral polio vaccine was used in 1978 and 1992–1993 to control polio outbreaks occurring in a religious group that refuses immunization. Serologic surveys in the years following each epidemic were consistent with the absence of poliovirus circulation in unvaccinated children from the religious group (10). From 1985 to 1990, Dutch enterovirus surveillance identified only 23 VDPV isolates, all from families with a history of international travel (11). Sewage waters are currently
being sampled from localities where the religious group is concentrated. Any polioviruses isolated will be analyzed for genetic drift indicative of persistent circulation.

Indirect evidence from recent polio outbreaks also suggests limited transmission of VDPV. One example is Chechnya, where polio immunization ceased abruptly with the onset of the secessionist movement in 1992. An outbreak of 143 polio cases occurred in 1995 caused by an imported wild virus. Eighty-four percent of cases were less than 2 years of age (12). Immunity among unvaccinated children was, therefore, at low levels, implying limited circulation of VDPV. Another example comes from the 1996 Albanian polio outbreak. The first case was paralyzed 10 days after a nationwide oral polio vaccine campaign that immunized 98 percent of children aged 2–59 months. Attack rates were highest in infants too young to be vaccinated, followed by young adults and teenagers (13). Since wild poliovirus was apparently introduced concurrently with the campaign and cases were concentrated in populations normally in close contact with children, VDPV must be substantially less transmissible than the outbreak strain.

Fine and Carneiro’s model of transmission and persistence of VDPV predicted that the circulation of VDPV would decline rapidly after oral polio vaccine use ceased (4). However, persistent circulation of VDPV in crowded, urban slums of developing countries remained a theoretical possibility. They suggested that VPDV could then spread to the general population as immunity to polioviruses declined. While this model proved useful for discussion, more advanced models are needed taking into account population heterogeneity (age and social structure), seasonality of transmission, and the relative transmissibility of VDPV compared with wild strains.

Sabin strains differ from their wild-type parents by as few as 10 nucleotides. Mutated VDPV that are neurovirulent in animal models can be isolated from the stools of children within days of vaccination (14). However, neurovirulence in animals does not necessarily predict human neurovirulence or high-level transmissibility. The likelihood, speed, and extent to which VDPV would regain the transmissibility characteristic of wild virus (such as lower infectious dose, longer duration of excretion, higher titer of excreted virus, or prolonged environmental persistence) are not known. Molecular markers of transmissibility are being studied to assess the probability that neurovirulent VDPV might circulate. Available epidemiologic and virologic data are being analyzed to better quantify the differences in transmissibility between wild strains and VDPV.

Molecular methods permit direct measurement of genetic drift in VDPV in the high risk areas of concern to Fine and Carneiro—crowded, poor-hygiene areas of tropical, developing countries where wild polioviruses have been eradicated and population immunity is low. Genomic sequencing was performed on VDPV isolates from Brazilian children with acute flaccid paralysis from localities where immunization coverage had fallen and the potential for VDPV circulation had, presumably, increased. All isolates showed >99 percent similarity to the parent vaccine strains (15). Since poliovirus genomes evolve at a rate of ~1–2 percent per year (16), isolates were of recent origin. This study has now been expanded to include other Latin American countries.

Current surveillance strategies are being reviewed to determine their efficacy in detecting circulating VDPV. The approaches undertaken include the following: studying the usefulness of acute flaccid paralysis surveillance in monitoring circulation of VDPV; reviewing procedures from the World Health Organization’s Global Polio Laboratory Network to determine what additional data can be obtained on VDPV; refining environmental surveillance strategies for the post-vaccination era; and developing simplified laboratory procedures to detect genetically drifted VDPV.

Potential reservoirs of VDPV

Fine and Carneiro are also concerned that, even if circulation did not persist, VDPV could reemerge from reservoirs when population immunity fell to low levels. There are no animal or long-term environmental sources of polioviruses (17). The capacity of polioviruses to recombine with other enteroviruses in nature is unlikely to produce neurovirulent strains that circulate indefinitely (18). However, patients with primary immunodeficiencies, particularly common variable immunodeficiency and X-linked agammaglobulinemia, are potential reservoirs of VDPV. There is no evidence that patients with secondary immunodeficiencies, particularly human immunodeficiency virus infection, excrete polioviruses chronically.

Persistent excretion of VDPV by immunocompromised individuals has been demonstrated. One study in the United Kingdom showed that two of 30 immunodeficient individuals excreted VDPV for more than 6 months (19). A type 1 poliovirus isolated from an immunodeficient man with vaccine-associated paralytic poliomyelitis was recently found to differ at about 10 percent of VP1 nucleotides from the Sabin strain, consistent with infection beginning ~9 years earlier (20). To determine the prevalence of chronic poliovirus infection, stool specimens are being cultured.
from 150 persons with X-linked agammaglobulinemia and common variable immunodeficiency attending a single clinic in the United Kingdom and 500 persons with specific immunodeficiency disorders in the United States. Stool samples are also being cultured from immune-deficient American vaccine-associated paralytic poliomyelitis cases. Polioviruses isolated from these studies plus existing isolates from vaccine-associated paralytic poliomyelitis cases are being sequenced to measure genetic drift. However, genetic drift must be correlated with the duration of infection in immunodeficient persons.

Research is being conducted in Ethiopia, Haiti, and Pakistan to estimate the potential for VDPV to persist among immunodeficient persons in the developing world. These studies will measure the prevalence and duration of chronic poliovirus excretion in children with recurrent infections. Studies have also been proposed to measure the prevalence and duration of poliovirus excretion among human immunodeficiency virus-infected children in developing countries.

While the frequency and duration of chronic excretion of VDPV by immunodeficient persons can be estimated, the risk that such persons pose remains unclear. Quantitative analysis of stool specimens taken from immunodeficient persons excreting VDPV is in progress as one method of estimating the risk of transmission. However, the potential for spread is still unclear since their immunologically normal contacts would quickly become immune. Therapeutic approaches to clear the infection are also being explored. An antiviral drug, Pleconaril (ViroPharma, Inc., Exton, Pennsylvania), has been proposed for treatment of chronic poliovirus infections and will be offered to immunodeficient persons with chronic poliovirus infection identified in the United States and United Kingdom. Similar studies may also be necessary in developing countries.

Possible strategies for stopping immunization

Fine and Carneiro's arguments and current research data will be carefully considered during deliberations on the final recommendation on how (and if) polio immunization can be safely stopped. Several strategies for stopping immunization have been proposed.

If VDPV do not persist, the simplest and least costly strategy would be to stop immunization with oral polio vaccine. Ideally, cessation would be coordinated among countries. Another approach that would permit an assessment of VDPV circulation is stopping administration of the three Sabin types sequentially. Because type 2 wild virus is eradicated quickly, it would probably be removed first. Either a bivalent type 1 and type 3 vaccine or monovalent vaccines could then be used. Safety and efficacy trials would be required to gain regulatory approval.

If vaccine strains do persist, inactivated polio vaccine could be used during an interim period. However, the effectiveness and feasibility of this strategy have not been validated. The immunogenicity of inactivated polio vaccine in developing countries cannot be inferred from studies in industrialized countries. Inactivated polio vaccine administered in the World Health Organization's infant immunization schedule results in a suboptimal serologic response to polioviruses (21). Low immunization coverage in populations at the highest risk for persistent circulation will limit the effectiveness of this approach. Manufacturers indicated that 5–7 years would be required to establish a global inactivated polio vaccine production capacity. These companies would also need to be assured that they would recover their investment before expanding their facilities.

Several genetically engineered polioviruses have been proposed as candidates to replace the current Sabin oral polio vaccine strains or to serve as a nonvirulent seed stock for inactivated polio vaccine. However, significant development work will be necessary before such vaccines would be available. Because a new vaccine would be used only for a limited time, manufacturers are reluctant to be the primary funding source for the necessary research. A series of papers reviewing the relevant issues have been commissioned, and a meeting is planned for late 1999 to reach consensus on the most productive approaches.

Conclusion

With the tremendous progress made toward the global eradication of poliomyelitis, the public health community must now address the issues of the post-eradication era. In the next few years, a recommendation must be made on stopping immunization. A scientifically sound strategy will be the cornerstone of the political process building the consensus necessary to stop immunization worldwide and minimize the threat of polioviruses being inadvertently released into the environment. Fine and Carneiro have made an important contribution in defining research priorities. The situation that will confront the world after eradication has no precedents. The eventual outcome of any course of action, including continuing immunization, cannot be determined with absolute certainty. The meeting concluded that all vaccination against polio can and should stop. Pending the results of current research, simply stopping the use of oral polio vaccine continues to be the most likely strategy. Fine and Carneiro's work also emphasizes that, whatever the strategy, high-level
enterovirus surveillance will be vital in the years after immunization has stopped.

References