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REVIEW

Transmissibility and Persistence of Oral Polio Vaccine Viruses: Implications for the Global Poliomyelitis Eradication Initiative

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The global poliomyelitis eradication initiative has been a tremendous success, with current evidence suggesting that wild poliovirus will cease to circulate anywhere in the world soon after the year 2000. As the goal of wild poliovirus eradication is approached, concern has been raised about the potential for persistent transmission of oral polio vaccine (OPV) viruses, as these viruses are known to revert toward wild-type neurovirulence. This paper has been extracted from a document prepared for the World Health Organization on the implications of OPV transmissibility for the strategy of stopping OPV vaccination after global eradication of wild polioviruses. The authors review the empirical evidence on OPV transmissibility available from household and community transmission studies and from mass-vaccination experiences. They then consider theoretical measures of transmissibility and persistence for wild and OPV viruses (secondary attack rate, basic reproduction number, and critical populations' size), to assess whether transmissibility of OPV viruses is sufficient to allow persistence of these viruses after cessation of vaccination. The findings indicate that OPV viruses could persist under various plausible circumstances, and that this potential should be a major consideration when planning the cessation of OPV vaccination. *Am J Epidemiol* 1999;150:1001–21.

enterovirus; immunization programs; poliomyelitis; poliovirus vaccine, oral; vaccines

Vaccination against polio has provided one of the triumphs of public health in the 20th century. After their introduction in 1955, these vaccines (first formalin-inactivated polio vaccine (IPV) and later live oral polio vaccine (OPV)) led to immense reductions in the burden of poliomyelitis disease in country after country. These successes led to a 1988 resolution by the World Health Assembly, committing the World Health Organization to "global eradication of poliomyelitis by the year 2000" (1, p. 2). Progress toward this goal has been impressive, and there is increasing confidence that wild-type polio viruses will cease to circulate in human populations, anywhere in the world, soon after the year 2000.

The global eradication program has emphasized the use of OPV. Among the reasons for this choice are the low cost and the relative logistic ease of administering OPV, as compared with IPV. The mode of action is rapid, through immediate competition with wild viruses in the intestines, in addition to the induction of local (gut) immunity. Furthermore, OPV viruses can be transmitted from vaccinees to their contacts, which results in immunization of some individuals who may be missed by a vaccination program. Although some countries now use IPV or combined IPV-OPV schedules, the vast majority of polio vaccine currently in use is OPV. The problem facing the Polio Eradication Initiative is whether OPV viruses could persist as naturally acquired and transmitted infections in human populations, after cessation of vaccination. While advantageous for vaccination programs, the property of transmissibility, coupled with the fact that OPV

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Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IPV, formalin-inactivated polio vaccine; OPV, oral polio vaccine; R_0, basic reproduction number; R_n, actual (= effective = net) reproduction number; $TCID_{50}$, tissue culture infective dose; VAPP, vaccine-associated paralytic poliomyelitis.

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viruses can, on rare occasions, cause disease, becomes a potential *dis*advantage as we near the global eradication of wild polio. The potential for OPV viruses to persist could threaten the eradication program, given that the overall goal implies the need to rid the world of polioviruses altogether. This concern forms the background to this paper.

Polioviruses. The three serotypes of wild polioviruses differ in the amount of disease for which they are responsible. This has varied among places and over time, reflecting complex epidemiologic dynamics. The relative virulence of the wild viruses (defined as the proportion of paralytic cases among infected individuals) is generally considered to be greatest for type 1 and least for type 2 (2), while their relative transmissibility, measured in various ways discussed below, is thought to be roughly equal. The OPV viruses were derived by serial tissue culture passage attenuation of the wild viruses, which resulted in reduced virulence. Several research groups succeeded in producing strains sufficiently attenuated for vaccine use, but Sabin's strains were the least neurovirulent and are incorporated in all OPV vaccines in use today.

An important feature of polioviruses, and OPV viruses in particular, is their continued genetic variation through mutation and recombination. Molecular studies have identified that attenuation of the Sabin strains is based on just a few base differences for types 2 and 3, with many more for type 1 (3). The attenuating mutations are unstable and, under selection pressures of the human gut, tend to "revert" toward the wild-type sequence within 2–5 weeks of vaccination in 50–100 percent of vaccinees who excrete (4, 5). The issue of reversion is complicated, and the term is used loosely to describe a variety of genetic changes "from" a classic OPV genome "toward" a wild-type genome. Reversions are probably responsible for most of the rare cases of vaccine-associated paralytic poliomyelitis (VAPP), although some cases have been associated with intertypic recombinants (6–8). The full implications of such genetic changes are unclear, but it is not unreasonable to assume that selection pressures under conditions of human-to-human transmission might favor wild-type rather than vaccine-type characteristics. The magnitude and speed of such selection are unknown.

Sources of infection. Polioviruses are enteroviruses, transmitted mainly through the intestinal-fecal-oral route. The viruses are also found in oral secretions (though in lower concentrations) and are thought to be transmitted to some degree via the respiratory-oral route. The relative importance of these routes must depend upon levels of fecal and respiratory hygiene in the population. Overall, wealthier societies have higher levels of fecal hygiene than do poorer societies, as reflected by the relative prevalence of many enteric pathogens. Respiratory hygiene may also be correlated with socioeconomic factors. For example, coughing, sneezing, and spitting behavior probably differ among social groups as do crowding within the home and recirculation of air through ventilation systems. The relation is complex, but it is likely that the *relative* contribution of pharyngeal to fecal-oral transmission of polioviruses differs among societies, and that the *ratio* of pharyngeal as opposed to fecal transmission is positively correlated with socio-economic "development" among societies and with socioeconomic "status" within societies.

As polioviruses generally depend on human (fecal-oral) transmission for their persistence in nature, human feces is currently the most important natural source of polioviruses. Once vaccination ceases, the residual vaccine stocks, as well as the feces of vaccinees and of their direct and indirect contacts, will be the most obvious and important sources of OPV viruses, at least in the short term. In the long term, other potential sources must be considered.

Residual vaccine stocks. An obvious potential source of OPV viruses after the cessation of vaccination will be the remaining vaccine vials contained in refrigerators and freezers of health centers, pharmacies, hospitals, and physicians' offices, as well as district, regional, and national vaccine stores throughout the world. Inventory and recovery of these residual stocks will pose a major challenge. This consideration implies that it may be important to stop vaccination everywhere, simultaneously, rather than to allow vaccination to persist in some areas while populations of susceptible individuals accumulate in others.

Persistently infected humans. There is no long-term carrier state for poliovirus in immunocompetent individuals, with the duration of excretion ranging from 1 day to about 4 months (2). However, it has recently been recognized that individuals with various immunologic deficiencies may maintain and excrete polioviruses for many months, even years, providing a potential source for the reintroduction of poliovirus in the future. Immunodeficient individuals most at risk of prolonged enteroviral excretion are those with predominantly antibody defects (e.g., X-linked agammaglobulinemia, immunoglobulin A deficiency, and common variable deficiency), who may shed virus for years in the absence of treatment (9). While cases of VAPP have been reported in individuals with combined immunodeficiencies of B- and T-cell production (10, 11), prolonged excretion has only been documented for those with predominantly antibody defects (12–15).

MacCallum (12) reported excretion of OPV-related viruses for up to 32 months by hypogammaglobulinemic individuals, while Hara et al. (13) detected excretion of vaccine-like viruses for at least 34 months by an agammaglobulinemic VAPP case. Recent molecular analyses of poliovirus isolates from a VAPP patient (with common variable immunodeficiency) suggest that OPV viruses may have persisted in the patient for 7 years (15). The pattern of excretion in another 28 hypogammaglobulinemic individuals fed monovalent OPV was the same as that expected for immunocompetent individuals (12), suggesting that chronic infections are rare. Persons with selective immunoglobulin A deficiencies have been shown to have an impaired ability to clear poliovirus infections, although none were observed to excrete OPV viruses after 6 months (14).

Registry data indicate that antibody defects are the most common primary immunodeficiencies. Common variable immunodeficiency prevalence has been estimated at 0.77:100,000 and X-linked agammaglobulinemia at 0.23:100,000 in Australia (16), while immunoglobulin A deficiencies are consistently the most frequent with an estimate of 2:100,000 in Sweden (17). Though the overall incidence of primary immunodeficiencies may not have changed in the last two decades, it is likely that their prevalence in industrialized countries is increasing because of greater recognition and better treatment, enabling increased survival of persons with these conditions. In industrialized countries, the average survival of people treated for antibody defects is greater than 5 years (16) and in some cases can extend beyond 30 years (18). Few data are available on the prevalence and life expectancy associated with primary immunodeficiencies in developing countries. In Sao Paulo, Brazil, individuals with severe combined immunodeficiency had 100 percent mortality over a 15-year period, while those with humoral defects had a mortality rate of just 3 percent, with intravenous immunoglobulin therapy or antibiotic treatment of infections (19). In areas where access to medical care is poor and treatment options are limited, survival rates are likely to be low.

One of the most common immunodeficiencies in developing countries is acquired immunodeficiency syndrome (AIDS), caused by infection with the human immunodeficiency virus (HIV) and primarily affecting T-cells. The implications of HIV infection for the duration of poliovirus or other enterovirus excretion are unknown. To date, only one case of VAPP in an HIV-infected infant has been reported, although no causal relation was established between the HIV infection and VAPP (20). A study of children born to HIV-negative and -positive mothers, in Zaire, found that OPV vaccination induced protective antibody titers in 95 percent of HIV-infected children with no excess risk of vaccine-associated adverse events (21). Although OPV-related adverse events are extremely rare, these data provide no evidence that HIV infection increases the risk of VAPP. If AIDS results in prolonged excretion of poliovirus, these patients may be important sources of OPV in the short term, as AIDS patients survive for a median of 1–2 years with antiretroviral therapy in industrialized countries and for a median of 7–9 months without such treatment in developing country situations (22–24). It is important that more information is obtained regarding this possible long-term source of polioviruses (25).

Nonhuman animal reservoirs. No polioviruses have been isolated from nonprimates in nature, and the success of wild poliovirus eradication in the Americas indicates no previously unsuspected source of wild poliovirus in wild or domestic animals. Nonhuman primates were used extensively in early studies on polio infection and revealed that chimpanzees and some monkeys are susceptible to oral poliovirus infection, but to a lesser degree than humans (26). The low densities of such higher primate populations in the wild, their lower susceptibility to poliovirus infections, and the lack of evidence for a persistent carrier state suggest that these animals are unlikely to sustain continued transmission (27).

Environmental persistence. Fecal contamination is ubiquitous. Wild polioviruses and OPV viruses have been isolated from floors and furniture in households and daycare centers containing infected individuals (28, 29). The viruses can remain viable in contaminated soil, sewage, or water for some time, and even sewage treatment does not inactivate the full virus content (30). The half-life for survival of polioviruses, as measured by many studies on attenuated strains, depends on environmental conditions and is adversely affected by low relative humidity (31), low moisture content, high temperature, low pH, low organic content, and high bacterial growth (32). Differential environmental survival associated with seasonal changes in temperature and humidity may explain the seasonality associated with the prevalence of natural enterovirus infections (2, 33, 34).

Temperature is the most important determining factor for poliovirus survival, with 90 percent inactivation in a variety of surface waters seen only after 133–259 days at –20°C, 17.7–24.7 days at 1°C, and 3.8–6.7 days at 22°C, under laboratory conditions (32). Irrigation of crops with treated sewage effluent is practiced increasingly in industrialized countries. The high organic content favors poliovirus survival, and viable virus has been recovered from crops 23 days after treatment by sludge or effluent irrigation (35). Land surface appli-

cation of sewage effluent creates the potential for poliovirus to overwinter in ice resulting from the process (32). Viruses can migrate to potable groundwaters, where survival is greater (29 days for 90 percent inactivation at 12°C) than in surface waters (30). The use of "nightsoil" for fertilization is practiced in many developing countries, and the survival of polioviruses in untreated sewage is likely to be longer than in the treated sewage measured in many studies. These reports suggest that poliovirus would be rapidly inactivated under tropical conditions, but temperate environments with high levels of environmental contamination (perhaps in the Andes or in the Himalayas) could favor soil- and waterborne poliovirus as a source of infection for some months. The probability of poliovirus survival for as long as a year appears to be remote except under unusual conditions, for example, involving subfreezing temperatures.

Laboratories. Many laboratories maintain living polioviruses of wild or OPV origin, either as part of ongoing research activities, or unknowingly in stored clinical or environmental samples. It will be a major task for the Global Poliomyelitis Eradication Initiative to ensure that such sources are contained, or preferably removed entirely, by destruction of all polioviruses except reserve stocks required for vaccine production. These must be kept under the tightest security conditions, and this will be a difficult task. There will also be a need to maintain large stocks of vaccine as a contingency after the eradication of poliovirus. Because of the high levels of control and containment required for OPV, stockpiling of IPV may be considered preferable under some circumstances, despite its being less efficient than OPV in outbreak control. There will be the associated issue of vaccinating laboratory workers involved in the production and maintenance of vaccine strains. It has been suggested that IPV may be used for this purpose (36), but this will need to be considered carefully, as wild prototype IPV viruses have already been isolated from clinical samples in the Netherlands and France (37). Alternatively, if OPV is used there may be a need to enforce postvaccination quarantine of staff until they are no longer potential sources of infection to contacts. The absolute necessity for this measure will depend on the potential for such viruses to spread and persist in susceptible human populations, the issue addressed in this report.

The practical difficulties associated with identification and destruction of laboratory virus stocks must be appreciated. Too few people today know that the last case of smallpox occurred in England in September 1978 as the result of a laboratory "accident." The potential for one or another poliovirus to be released inadvertently from a laboratory at some time in the future is substantial. This subject has been discussed at length, and a plan of action has been written for implementation in 1998 (36). This describes procedures for laboratory containment of wild polioviruses, which will be extended to OPV viruses after the cessation of OPV vaccination. In addition, it has been recommended that the World Health Organization seek agreement ultimately to destroy all poliovirus strains and potential infectious materials. Consideration may need to be given in the recommendations to materials that potentially harbor OPV viruses.

Transmissibility of polioviruses—empirical evidence

The ability of OPV viruses to persist within semi-immune populations has been assessed by population/environmental surveillance following large-scale immunization of whole populations or targeted groups. Such studies form the basis of our current knowledge regarding the transmissibility of OPV viruses and are discussed briefly here. Few studies were carried out on the transmissibility of wild virus strains, and those available were considered for comparative purposes. It should be noted that, while these studies were carried out under both good and poor hygiene conditions, many are from communities in the United States and Russia and may not be wholly representative of the situation in developing countries.

Transmission to contacts. When OPV was introduced in the late 1950s, there were several investigations of the spread of OPV virus strains to direct and indirect contacts. Vaccinees were fed either monovalent, bivalent, or trivalent OPV and monitored for duration of fecal, and sometimes pharyngeal, excretion and virus titer (28, 38–54). In addition, unvaccinated siblings and other contacts were monitored for evidence of infection (fecal excretion or seroconversion) with the virus type fed. These studies varied in design, using Sabin, Cox, and/or Koprowski strains, employing different administration regimens and dosages, and recruiting individuals with different immune backgrounds. We have reviewed much of the published literature on such studies, using manual searching of a poliomyelitis abstracting journal (1951–1962), reference lists of publications, and computer-based searches of the MEDLINE reference database (1966–1998). The review may have missed a few non-English language publications but should not be otherwise biased. OPV now contains Sabin strains exclusively, so we excluded studies on Cox and Koprowski strains when estimating parameters. As IPV was available prior to the use of OPV, many investigations of the spread of OPV viruses were carried out in populations with prior IPV exposure. Though the effect of

IPV on subsequent excretion was a point of contention at the time many of these studies were carried out, some studies still did not stratify their data according to prior IPV exposure. The main findings of the studies on Sabin-type OPV virus transmission and the few studies on spread of wild poliovirus (2, 34, 55–62) are summarized in table 1 (complete tabulation is in the original report and is available on request from the authors). It is clear that many properties of wild and OPV viruses that affect transmission are similar.

Reversion to neurovirulence. To assess whether the live attenuated viruses might exhibit increasing neurovirulence upon replication in the human gut, several investigators have assessed the virulence of excreted OPV viruses. This was done with monkey neurovirulence tests or in vitro tissue culture markers correlated with neurovirulence, such as temperature and pH sensitivity. Wild viruses are more robust than are OPV viruses, surviving at higher temperatures and lower pH levels in culture (26). There have been reports of reversion of OPV viruses toward wild-type phenotypes and increased monkey neurovirulence of vaccine progeny (63–67). More recent studies at a molecular level have shown clearly that OPV viruses undergo extensive mutation, including reversion back toward wild-type genotypes (4).

An important consideration of this reversion is whether neurovirulence increases with passage through the human gut. Dane et al. (68) showed a progressive increase in monkey neurovirulence over time, after multiplication in the human gut, although Sabin (69) had found no evidence for this. Increased neurovirulence of OPV viruses excreted by a contact, compared with that excreted by the initial vaccinee, was reported from one study (63), while another found no evidence for this in contacts (70). A comparison of consecutive (second- and third-degree) contacts of vaccinees (siblings and contacts of siblings) found similar phenotypic reversion frequencies in viruses excreted by vaccinees and contacts (41). To account for dosage effects during contact infections, Dane et al. (68) purified OPV type 2 viruses excreted by a vaccinee and fed different doses (1–3 log tissue culture infective dose ($TCID_{50}$)) to homotypic seronegative children. This study showed an increase in neurovirulence after a second passage but a similar degree of

TABLE 1. Summary of findings from WT* and OPV* virus transmission studies, under various conditions

Wild polioviruses	OPV viruses
• Most susceptible contacts were infected	• Not much transmission under conditions of high preexisting immunity, considerable spread under conditions of low population immunity
• Risk of transmission is associated with duration and intimacy of contact	
• Young children are responsible for most transmission	• Young children are responsible for most transmission
• Differential transmission associated with SES*	• Greater effect of SES on differential transmission than with wild poliovirus
• Previously "immune" contacts can be reinfected	• Previously "immune" contacts can be reinfected, but replication is reduced (shorter, intermittent duration)
	• Reinfection is dose dependent
• Seasonal transmission	• Contacts often showed abortive excretion
	• Contacts more susceptible to reinfection than vaccinees
• Equal transmission of all three serotypes over time	• NPEV* interference effects (OPV dominant at high doses)
	• Type 2 (generally) most transmissible
• Heterotypic antibodies do not protect against infection	• Intertypic interference effects (excretion of individual types was less with TOPV* than with Mono)
	• (Transient) heterotypic rise in antibodies
• Probability of fecal excretion unaffected by IPV* (but could only measure infection by excretion, because of high antibody levels)	• IPV not fully protective against reinfection (but duration of excretion reduced)
• Pharyngeal excretion reduced by IPV	• Pharyngeal excretion reduced by IPV at high antibody levels
	• Probability of pharyngeal excretion after IPV, proportional to dose
• Some herd immunity provided by IPV	

* WT, wild type; OPV, oral polio vaccine; SES, socioeconomic status; NPEV, non-polio enteroviruses; TOPV, trivalent oral polio vaccine (all three serotypes); IPV, formalin-inactivated polio vaccine.

neurovirulence after a third passage through the human gut (contacts of "secondary vaccinees"). Studies have suggested that the rate of mutation of polioviruses within the gut of one immunodeficient individual (15) is similar to that observed during circulation of wild poliovirus through the population over a 10-year period (71). This might enhance the probability of reversion to neurovirulence in immunodeficient OPV recipients.

Reversion to wild-type transmissibility. No evidence is available on whether OPV viruses "revert" toward the level of transmissibility of wild polioviruses during serial human-to-human transmission. This is a difficult issue to investigate, as the molecular and genetic basis of poliovirus transmissibility is not understood. A small number of such serial transmission studies were carried out in Russia during the late 1950s, designed to identify progressive trends in neurovirulence. The limited published data on fecal excretion titers show no evidence of consistent or significant change in transmissibility, as assessed from the viral titers excreted, over nine serial transfers of type 1, 2, or 3 OPV viruses (72).

Transmission within the community. Several studies have detected secondary spread of OPV viruses by serologic monitoring of unvaccinated individuals in areas known to be free of wild-type viruses. A seroprevalence study among preschool children with no record of prior vaccination in Houston, Texas, and Detroit, Michigan, showed convincing evidence of secondary spread of OPV viruses (42 percent type 2 seroprevalence in unvaccinated children) (73). Another study among Italian gypsy populations with very low vaccine coverage revealed greater than 90 percent seropositivity to type 2 poliovirus, which has been virtually eradicated from Europe, irrespective of vaccination status (74). Evidence for secondary spread of OPV viruses was also shown in a study in Oman, where infants given only IPV showed double the seroconversion rate to type 2 (82 percent) after potential exposure to targeted OPV campaigns, compared with those studied before the campaigns (41 percent) (75). These studies do not reveal the full potential of transmission of OPV viruses, as the extent of exposure to OPV viruses in these OPV-unvaccinated individuals is not known. In addition, high levels of natural or vaccine-attributable herd immunity in these populations may have limited the ability of OPV viruses to circulate.

Poliovirus persistence was monitored by population fecal surveys and sewage sampling following vaccination trials and campaigns when OPV was first made available. Studies in Czechoslovakia (76) and Hungary (77) showed that OPV viruses did not circulate at detectable levels after 5 months. Interpretation of these data is made difficult by the fact that both the Czechoslovakian and Hungarian populations vaccinated with OPV had received IPV during the previous 2 years. A trial in Mexico also showed little persistence of OPV viruses (78), but the preexisting high levels of natural immunity and the consequent lack of susceptible individuals must have limited the ability of OPV viruses to persist.

Many of these earlier studies did not distinguish between wild and attenuated polioviruses, making the data difficult to interpret. Fortunately, data on circulation of OPV viruses, in the absence of wild poliovirus, are available because of the unique poliovirus vaccination schedule in Cuba. All OPV is administered during two annual vaccination campaigns with no other routine poliovirus vaccination, providing an opportunity to study the persistence of OPV viruses in the environment and in the population during the rest of the year. Monthly cross-sectional stool surveys were carried out on children less than 2 years old and detected polioviruses only during and immediately after the vaccination campaigns (79, 80). A subsequent serologic survey, carried out on unvaccinated infants born 1–9 months after the last annual national immunization day, confirmed a lack of exposure to poliovirus in those born 3 months after the national immunization day (81). Because of the interfering effect of maternal antibodies in the children below 6 months, it is unclear whether OPV (especially type 2) continued to circulate for more than 2 months, and more intensive fecal surveillance will be necessary to answer this question.

Administration of trivalent oral polio vaccine (all three serotypes) to more than 90 percent of the Finnish population in 1984 to control a type 3 wild poliovirus epidemic (82) gave an opportunity to study the persistence of OPV viruses under conditions of intense and sensitive environmental surveillance. Countrywide sewage sampling detected OPV viruses for up to 6 months after the vaccination campaign (82, 83). However, while wild poliovirus type 3 was able to spread because of insufficient type-specific immunity (because of a poorly immunogenic type 3 IPV), it is likely that high levels of immunity (induced by IPV against types 1 and 2 and induced by the wild virus against type 3) limited the subsequent spread of the OPV viruses. Trivalent oral polio vaccine was also used to control an epidemic of type 3 wild poliovirus in the Netherlands in 1992–1993 (84), but sewage sampling was not carried out intensely enough to allow conclusions on the *duration* of OPV virus circulation in this population.

These results indicate that OPV viruses persisted within these populations for a very few months, but they provide no evidence that OPV viruses can persist

indefinitely. However, all of these study populations had high proportions of immune individuals among those not targeted for vaccination. It is clear that levels of immunity sufficient to stop wild poliovirus circulation in outbreak control campaigns must also block OPV virus circulation. We also note that national immunization days have been found to produce higher seroconversion rates than are achieved by routine vaccination (85). This is likely to be due in part to the intensive effort and better cold-chain facilities but also to increased exposure to OPV viruses. For unvaccinated individuals, both the probability of exposure to virus and the average dose encountered will increase with the intensity of the campaign effort. Thus, effective transmissions are likely to occur rapidly, reducing the proportion of susceptible individuals available for continued transmission. These implications of massive simultaneous use of OPV should be considered if and when OPV vaccination is stopped.

Also relevant are those communities where OPV is not accepted, where there is no endemic transmission of wild poliovirus, and where there is potential for exposure to OPV viruses. Such communities have little natural protection, the susceptible proportion will have increased since the local eradication of wild poliovirus, and any introduced OPV viruses would have an opportunity to invade the population. This is analogous to the situation that will arise some years after the cessation of vaccination and may provide us with important insights. A seroprevalence study of the conservative Amish communities in the United States revealed that 89 percent of unvaccinated children, born since eradication of wild poliovirus in the United States, had antibodies to type 2 poliovirus (Roland Sutter, Centers for Disease Control and Prevention, Atlanta, personal communication, 1997). A similar survey among unvaccinated communities in Canada detected that approximately 70 percent had antibodies to types 1 and/or 2 (Philippe Duclos, Laboratory Center for Disease Control, Ottawa, personal communication, 1998). It is important to note that, in many of the communities that reject vaccination in the Netherlands, Canada, and the United States, some members may accept vaccination, thus introducing OPV viruses directly into the community via multiple sources. However, it is clear that, once introduced, OPV viruses can spread in poorly vaccinated communities with good standards of hygiene, as seen in the Netherlands in 1992 (86).

The absence of VAPP "epidemics" (87) might suggest that, if OPV viruses do persist within unvaccinated communities, they rarely show increasing neurovirulence as they are transmitted between individuals. However, with the high levels of OPV coverage currently being attained in much of the world, it is unlikely that there are many susceptible communities large enough to enable continued spread of OPV viruses among susceptible individuals. Such a situation could have arisen in Albania, where suboptimal seroconversion due to poor cold-chain conditions led to a situation of low population immunity in the 18- to 35-year age group (88). Mass OPV campaigns targeted at children less than 5 years old were undertaken in 1996 and could have resulted in spread of OPV viruses to the remainder of the poorly vaccinated population. However, a simultaneous epidemic of wild type 1 occurred among the susceptible (mainly young adult) population (88), and this may have inhibited transmission of the OPV viruses. There is much anecdotal "evidence" about the absence of OPV virus spread in communities with low vaccine coverage, but the lack of seroprevalence data, the low case-to-infection ratio expected, and the absence of fecal sampling in these populations make it difficult to interpret such information.

More intensive surveillance for VAPP in countries with poor vaccination coverage could be helpful to supplement data on its frequency among populations with low levels of immunity. However, VAPP is difficult to define under conditions of endemic or recent endemic wild-type transmission, as discussed by Andrus et al. (87). VAPP is defined by exclusion of paralytic cases with wild-type virus isolation or any epidemiologic connection with wild-type cases or outbreaks. This is a necessity, under the impetus of eradication, to prevent any possible wild-type cases from being overlooked as VAPP cases. Nevertheless, this definition of VAPP, and the exclusion of paralytic cases with OPV virus isolation but no known OPV exposure history, could lead to VAPP cases being missed. These cases are important for the issue of OPV spread, and such "noncontact" VAPP cases need to be monitored closely to clarify their origin (87).

Such evidence reveals that OPV viruses, especially type 2, are transmitted frequently to susceptible individuals in direct contact with vaccinees and possibly also via infected nonvaccinees. While population and environmental sampling show limited persistence of OPV viruses after large, targeted campaigns, this has been influenced by high existing levels of immunity, high vaccine coverage, and concurrent infection of contacts, reducing the potential for continued transmission of OPV viruses. These studies do not show whether OPV viruses might persist in the very different circumstances that would prevail in a post-polio vaccination world. It is therefore important to estimate, as far as possible, the potential for OPV viruses to persist within largely susceptible populations. For this we turn to theoretical measures of transmissibility such as

the secondary attack rate, basic reproduction number (R_0), and critical population size.

Transmissibility of polio viruses—theoretical approach

Several tools have been developed to measure the transmissibility and the persistence potential of infectious agents. The most useful of these are the *("secondary") attack rate*, the *(basic) reproduction number*, and the concept of *critical population size*. The *secondary attack rate* is typically defined as the proportion of individuals exposed to a "primary" case who go on to develop disease because of that exposure. A very different measure of transmissibility is provided by the *reproduction number* of an infection. This concept describes transmission not as a risk, or probability, but as an average *number* of transmissions per case. As this will depend upon the prevalence of immunity in the population, the reference statistic, called the *basic reproduction number* (R_0), is defined in theoretical terms as the average number of (successful) transmissions of infection (secondary "cases") that would occur if a single infected individual were introduced into a totally susceptible population. Finally, the long-term persistence of an infectious agent in a population is not just a function of its R_0, but it will also depend upon the proportion of susceptibles available for infection (determined by the nature of the immune response and the dynamics of the host population). This leads us to consider the concept of a *critical population size*, defined as the minimum *total* (human) population size required for maintenance, in perpetuity, of an infectious agent (89).

In order to assess the transmissibility of OPV viruses, we have emphasized comparisons between estimates for wild poliovirus and OPV viruses. This is because of the nature of the available data and the fact that the demonstrable ability of wild viruses to spread and persist provides a baseline against which to compare the estimated transmissibility of OPV viruses. Of course, OPV viruses must be less transmissible than wild polioviruses, or they would have driven out the wild viruses. The problem is to evaluate *how much* less transmissible they are.

Secondary attack rate. Estimates of the risk of transmission of polioviruses require close serologic and virologic surveillance of infected individuals and their contacts. While few studies were carried out on the risk of wild poliovirus infection among defined susceptible contact groups exposed to known "primary" cases, several investigators have provided estimates of transmission of OPV viruses among contacts of vaccine recipients. Although some of these measures are similar to the classical secondary attack rate, in many studies the exposed contacts were not confirmed as susceptible at the time the source was vaccinated. If some contacts had some prior immunity, the secondary attack rate estimates will be too low. Another problem is the inability to distinguish between secondary and tertiary, etc., transmissions, as the classical secondary attack rate should include only secondary cases in the numerator. This is difficult to ensure in studies of polioviruses, as the serial intervals for secondary and tertiary transmissions overlap (58, 90), with infected individuals being able to excrete viruses within 24 hours of infection and to be infectious for several weeks. If the numerator includes individuals infected as the result of a third generation or extrafamilial transmission, the secondary attack rate estimates will be too high. Finally, numerical estimates for secondary attack rates will depend upon the context in which they are measured. The degree of intimacy varies between a household, institution, or community, and even between households, and the secondary attack rate estimate will vary accordingly.

Published infection risk (secondary attack rate-like) estimates for wild and OPV viruses on naive and IPV-immune backgrounds range from below 10 percent to over 90 percent (tables available in full report). The range reflects many study design, behavioral, and environmental factors. The accumulated data gave the impression that the transmissibility of OPV viruses is less than that of wild polioviruses, although the wide confidence intervals around the attack rate estimates, and the different social contexts used (households, closed institutions, schools, communities), make it difficult to interpret these results reliably. However, many of these studies reported a limitation in the transmission of OPV viruses, in particular Fox (39, p. 24), who concluded that "the most notable feature ... was the rapid decline in momentum of vaccine virus spread and its essential termination while a *high* [our italics] proportion of susceptibles were still available." We note below that this residual susceptible proportion is in fact a key (inverse) correlate of transmissibility.

Basic reproduction number (R_0). To measure the reproductive capacity of wild poliovirus and OPV viruses, we must consider several factors. 1) We are interested in the transmission of infection, not incidence of disease, and thus the statistic counts *infected* individuals. 2) As with the secondary attack rates, the basic reproduction number for any infection will obviously vary according to circumstances (crowding, hygiene behavior, and so on). Despite the problems inherent in its definition, the measure is used widely in theoretical epidemiologic work. This wide use was encouraged when Dietz pointed out that the R_0 for an infection may be estimated as the reciprocal of the pro-

portion susceptible to infection, *for a population in which the infection is at some stable endemic state* (91). From its definition, we appreciate that, if the R_0 for an infection is below unity, then the infection cannot persist in a totally susceptible population. On the other hand, if the R_0 exceeds unity, then some transmission of the infection is expected.

Though R_0 provides one of the most elegant concepts in infectious disease epidemiology, it should not be overinterpreted. It reflects an average and carries an underlying assumption of homogeneity and random mixing, which does not reflect the real world. Given the global scope of the question before us and the tremendous variety of epidemiologic contexts in the real world, we will need to consider carefully the effect of this heterogeneity on estimates of transmissibility.

The basic reproduction number (R_0) for OPV viruses cannot be measured directly from the proportion susceptible in a situation of "endemic stability," as no population exists in which the immune proportion has been determined solely by *natural* spread of OPV viruses. However, stability did exist for wild poliovirus in many populations prior to the introduction of routine vaccination in the 1950s. Many studies of age- and type-specific poliovirus antibody prevalence were carried out prior to the introduction of vaccination in communities around the world (57, 92–104). By estimating the values of R_0 for wild polioviruses and comparing the parameters of wild and OPV viruses that influence transmissibility, it may be possible to provide a rough relative estimate of the R_0 for OPV viruses and therefore to assess their potential for spread in susceptible populations.

If an infection is endemic (and the population is demographically stable) then, on average, each infection leads to one subsequent infection. This implies that the "average" proportion immune = $(R_0 - 1) / R_0 = 1 - (1 / R_0)$, and thus the susceptible proportion (S) = $1 / R_0$ (105, 106). It may be noted that several authors have used the equation $R_0 = L / A$ or $R_0 = (1 + L / A)$ to derive estimates of R_0, where A is the average age at infection and L is the average life expectancy (reviewed by Dietz (107)). These formulas are shortcut approximations to estimate the proportion susceptible under assumptions of rectangular or exponential population structures, respectively (91, 105, 106), and they may not always be appropriate. Using published data on age-specific seroprevalence and available demographic data on the structure of the study populations (108, 109), we have estimated the proportions of each study population with and without type-specific antibodies against poliovirus and, hence, the R_0 values for wild polioviruses under those conditions. The results show a reassuring consistency and are similar to those derived by Eichner et al. (110, 111). We plot the maximum of the serotype-specific R_0 values for each population in figure 1, excluding data for serotypes responsible for recent epidemics. One publication has derived estimates of the R_0 of wild polioviruses higher than those presented here (for some of the same populations) (112), but these were based on the shortcut formula, $R_0 = 1 + L / A$.

Figure 1 shows that type-specific values of R_0 ranged from 2 to 4 in areas of good hygiene and from 8 to 14 in areas of poor hygiene. This relation between transmission efficiency and standards of hygiene and sanitation is intuitively reasonable and has been noted by many authors (39, 57, 73, 99, 113). A high prevalence of diarrheal illness, reduced environmental survival in the dry season, and competitive interference by other enteroviruses may act to reduce the transmissibility of wild polioviruses in developing countries. It is important to note that the incidence of polio was not entirely "stable" in the populations in which these studies were carried out. Some had experienced recent epidemics, the studies were undertaken during different seasons, and the serotype distribution varied between years (59). Consequently, the differences in serotype-specific values of R_0 may reflect in part the time since last introduction of particular serotypes rather than true differences in transmissibility. The estimates from areas of poor hygiene suggest that the three serotypes were transmitted to a roughly equal degree, and all three serotypes persisted within the same populations.

An important assumption of this method is that individuals with detectable antibodies (i.e., "humoral immunity") are immune to subsequent homotypic infection. However, many studies have shown that individuals with naturally induced immunity (defined by homotypic neutralizing serum antibodies at a dilution ≥1:8) can in fact be reinfected and excrete wild or attenuated poliovirus, especially after high challenge doses (2, 39, 59, 114, 115). If humoral immunity is not completely equivalent to gut immunity, it is important to assess to what extent an individual with humoral antibodies may still be "susceptible" to homologous reinfection and able to transmit the poliovirus.

A comparison of the total viral output from individuals with and without naturally and vaccine-acquired homotypic antibodies was carried out by challenging individuals with different prior exposures to poliovirus, with Sabin type 1 poliovirus (116). The study enables us to compare the *relative* potential of each group of individuals for further transmission. From table 2, we see that the proportion excreting, the duration of fecal excretion, and amount of virus excreted were all greater in the nonimmunes than in

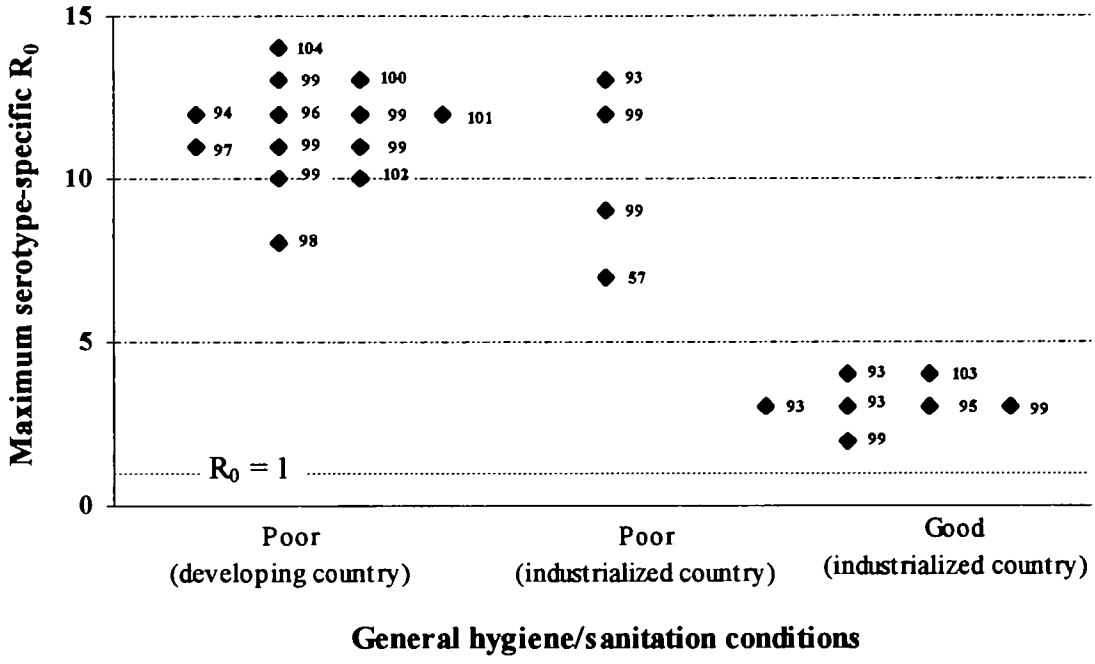

FIGURE 1. Comparison of estimated R_0 values for wild-type polioviruses from different studies (reference numbers given) in populations living under different sanitation and hygiene conditions. The highest serotype-specific R_0 value has been used under the assumption that all serotypes have roughly the same potential for transmission in a given population, and any differences observed are due to epidemic patterns and the sequential transmission of serotypes through the population.

TABLE 2. Fecal virus excretion by groups with different previous exposure to wild or OPV* viruses, after challenge with 6 logs of Sabin type 1†

Immunologic status	Sample size	Proportion excreting Sabin 1	Mean excretion duration (days)	Mean $\log_{10}$ virus titer ($TCID_{50}$)/g of feces	Total viral output per person‡	Reduction in fecal virus excretion (%)
"Nonimmunes"	30	0.80	20.4	5.2	3.9×10^6	
Prior IPV*,§	31	0.74	12.3	4.1	1.7×10^7	96.00
Prior OPV§	33	0.37	4.6	2.2	4.1×10^4	99.99
Prior wild type 1 infection§	19	0.37	5.0	2.2	4.4×10^4	99.99
Immune to three types§	32	0.34	5.4	2.0	2.7×10^4	99.99
Prior paralytic polio§	18	0.00				100

* OPV, oral polio vaccine; IPV, formalin-inactivated polio vaccine.
† Y. Z. Ghendon and I. I. Sanakoyeva. Acta Virol 1961;5:265–73.
‡ Assuming 150 g of feces per day.
§ All with high serum antibody titers against type 1 (1:64–1:256).

those with evidence of previous homotypic intestinal infection with wild or OPV viruses, or with prior IPV.

These data imply that a prior wild or OPV homotypic infection results in a reduction in excretion potential of approximately 99.99 percent. This reduction in virus output is considerable and provides support for the assumption that humoral antibody attributable to past *infection* is a reasonable surrogate for gut immunity with respect to reducing transmission. Consequently, we do not believe that our equation of humoral and intestinal immunity, implied in the method of deriving estimates of R_0, has led to serious error. If some seropositive individuals can be infected and significantly contribute to further transmission, the assumption will lead to an overestimation of R_0, that is, a conservative estimate for our purposes (discussed in original report).

These estimates of R_0 for wild polioviruses are based on data collected several decades ago, and it is likely that hygienic conditions have improved in most industrialized countries since then. However, the documented spread of wild viruses in the Finnish outbreak of 1984 (82) and the outbreaks in unvaccinated groups in the Netherlands in 1978 and 1992 (86, 117), the

United States in 1979 (118), and Canada in 1993 (119) show that the R_0 of wild polioviruses is still greater than unity even in wealthier, industrialized countries.

Because of similarities in the epidemiology of hepatitis A and poliovirus prior to the introduction of poliomyelitis vaccination (103), current patterns of hepatitis A transmission (in the absence of vaccination) may provide an indication of the potential epidemiology of natural poliovirus infection under current conditions. Studies have revealed a marked reduction in the prevalence of hepatitis A antibodies in recent years, for example, in urban Hong Kong and Taiwan, where the socioeconomic status and conditions of sanitation have improved (120, 121). In contrast, studies in rural communities with poor hygiene have shown that extremely high exposure to hepatitis A still occurs (121, 122), indicating that, in these situations, hygiene and environmental sanitation conditions may be as favorable for the spread of poliovirus now as they were 40 years ago.

The greatest potential for persistence of OPV viruses is likely to occur in the poorer, "developing" country populations of the world. Our estimates show that R_0 values of 10–15 prevailed in such countries for wild polioviruses, at the times these studies were carried out. We suspect that the hygienic conditions in many poor populations have not improved greatly in recent decades, in particular considering the growth of urban slums. It is possible that, in some populations of the world, perhaps urban shanty towns in Latin America, Africa, or Asia, the R_0 for wild poliovirus is now greater than 15. However, in the absence of evidence to the contrary, we conclude, on the basis of this literature review and analyses, that the R_0 of wild poliovirus is unlikely to exceed 20 for any populations of appreciable size today.

Several studies have shown that, under conditions of poor hygiene, seroconversion responses after OPV vaccination are generally lower in the tropics than seen in temperate countries (75, 123–126). This has been attributed to various factors, including high levels of maternal antibodies from boosted natural immunity in endemic situations (127), interference by concurrent enteroviral infections, diarrhea, poor nutritional status, and so on (123, 125, 126). Interference between OPV viruses and other enteroviral infections has been reported by many studies (28, 39, 40, 52, 53, 128–131), though others have reported no apparent interference in OPV "take" by preexisting enteroviral infections (42, 49, 124, 132). The higher seroconversion after IPV versus OPV vaccination in tropical situations (133) favors interference as an important influence. Our R_0 estimates already take into consideration these various factors, including any interference that was occurring in the populations where these seroprevalence studies were carried out. Such interfering mechanisms are likely to affect transmission of wild as well as OPV viruses.

Extrapolation of R_0 from wild to OPV viruses. To estimate how much lower the R_0 is for OPV than for wild polioviruses, we examined in turn the several components of poliovirus transmissibility that are likely to affect R_0: infectious dose, duration of fecal (or pharyngeal) virus excretion, amount of virus passed in fecal excretion or pharyngeal secretions, and virus stability under various environmental conditions. The relative transmissibility of individual serotypes may not be identical for wild and OPV viruses. We have noted above that the transmissibility of types 1, 2, and 3 *wild* polioviruses appears to be similar, based on seroprevalence data, whereas studies of OPV viruses suggest that type 2 is more transmissible than the other serotypes.

It is not possible to determine the infectious dose of wild viruses for humans, but studies have been carried out on the minimum infectious dose of attenuated strains in humans. Early studies on Koprowski and Cox strains indicated that some, but not all, naive individuals could be infected with doses of just 1–2 $TCID_{50}$ (!) (134). The Sabin type 2 virus was shown to be infective in some individuals at doses of 2 log $TCID_{50}$/g but was not infective to others at 3 logs. The latter finding may have been complicated by an effect of heterotypic priming at low doses (26). If we assume that the more neurovirulent, non-Sabin strains were less attenuated, these results suggest that larger infective doses are required for the more attenuated strains. There is evidence that hygiene conditions have a greater effect upon the dissemination of OPV viruses than on wild polioviruses (38, 39, 45) (although this may have been confounded by effects of IPV-induced immunity on pharyngeal excretion). If so, this may reflect at least in part that a higher dose of OPV virus than of wild poliovirus is required to initiate human infection.

Analyses of data on the duration of excretion (2, 48, 50, 53, 62, 135–137) indicate that this may be marginally less for OPV than for wild polioviruses (details in main report) (138).

The limited data available on fecal and pharyngeal viral titers indicate that these were roughly comparable for wild and OPV virus infections. This was the conclusion of a review by Melnick and Rennick (139), though Sabin (26) had reported that attenuated strains generally yielded 6 $\log_{10}$ $TCID_{50}$ of virus per gram of feces, but that the current Sabin type 1 regularly yielded 100-fold lower peak titers. In addition, an association between neurovirulence and tissue culture

plaque size has been shown, with more attenuated strains producing smaller plaques (26, 65), suggestive of reduced multiplication by OPV viruses.

There are few comparative data on the environmental stability of wild and OPV viruses. Although temperature and pH sensitivity markers of neurovirulence suggest that wild polioviruses are more robust than the OPV viruses, the only comparative study reported that attenuated strains were more resistant to the effects of chlorination and adsorbed better to different soils than virulent strains (140). As reversion toward wild-type phenotypes on passage through the human gut may reduce any differences in survival capacity, there is a need for studies on the environmental survival of vaccine virus progeny.

Finally, we need to consider the effect of competition or interference by other enteroviruses that may obstruct transmission of OPV viruses. If OPV viruses are less able than wild-type viruses to resist such competition, this will introduce a differential infectiousness/transmissibility between OPV and wild-type viruses. Evidence of OPV competitive advantage against wild-type virus comes from studies where OPV was used to stop epidemics and was seen to replace the wild-type virus when wild-type titers were low, but not when wild-type titers were high (129, 131). A review by Reichler and Patriarca (141) describes situations in which outbreak control with OPV was not successful. All these failures were related to late initiation of vaccination (sometimes in association with low coverage), and they are therefore consistent with the already established virus being the more successful competitor. Competition studies in tissue culture have confirmed that the outcome of interference is dependent on the relative amounts of each virus type present (142). This suggests that competition can work both ways, depending on the growth phase of the established infection when a second infection is encountered, and provides no supporting evidence for OPV viruses being less competitive than wild poliovirus.

Interference among serotypes of OPV viruses has been observed (47, 53, 78, 143, 144), with type 2 generally producing higher seroconversion rates, despite being less immunogenic than type 1 (40, 47). This is clearest during the peak enterovirus transmission season, when seroconversion to types 1 and 3, but not type 2, tends to decline (123, 126). In vitro competition studies have reported a delay in multiplication of types 1 and 3 in the presence of type 2 (142). The relative amounts of types 1, 2, and 3 in trivalent oral polio vaccine have been adjusted to account for this, with ratios of 10:1:3 recommended (10:1:6 in developing countries (145)). There is evidence that the type 2 Sabin strain is more robust than the other serotypes, and this may be because it was a primary isolate, unlike types 1 and 3, which were products of laboratory selection from "wild" strains (26). On administration of trivalent OPV, type 2 is excreted most (48, 51), appears to be most transmissible to contacts (41, 47, 73, 74, 146), and is most prevalent in environmental surveys (83, 147). This heterogeneity in transmissibility of OPV serotypes will be an important consideration when assessing the probability of persistence of any single OPV strain.

In summary, these data indicate that OPV viruses are no fitter than wild-type strains of poliovirus in any single characteristic (except perhaps environmental stability?). This is of course to be expected, as wild poliovirus strains are ipso facto the result of selection under human transmission conditions. The crucial issue of the magnitude of the overall "fitness" difference between OPV and wild strains is very difficult to assess. It may be twofold, tenfold, or even greater. Though a precise relative estimate is not accessible, an important point for this discussion is that the difference in transmissibility may in fact be only twofold or fivefold. The only estimate we have noted for this differential is in a paper by Eichner and Dietz (111), who assume the R_0 of OPV viruses to be 25 percent that of wild viruses (using estimates from 15 to 35 percent). However, even if the transmissibility of OPV viruses were 10–15 times less than that of wild polioviruses, it is likely that the R_0 of some OPV viruses, in particular type 2, would be greater than unity in some circumstances. *Thus, in theory, OPV viruses could persist indefinitely by person-to-person transmission if introduced into a totally susceptible population under poor hygiene conditions.*

Accumulation of susceptibles. While the R_0 measure provides an appropriate baseline measure of "absolute" transmissibility, it does not reflect actual (average) numbers of transmissions that occur in populations with some immunity. In theory, and assuming random mixing, the effective number of transmissions of an infection should be measured by R_0 multiplied by the proportion susceptible in the population ($R_0 \times S$). This actual number, R_n ($= R_0 \times S$), is sometimes called the *effective* or *net reproduction number* (148).

In considering whether OPV viruses will persist in a community after cessation of vaccination, it is important to appreciate that the proportion susceptible in most of the world's populations is now very low. This is a function of high vaccine coverage in recent years (a *global* average of 82 percent for third doses of trivalent oral polio vaccine among infants in 1996 (149), in addition to widespread campaigns among children in many countries) and some "natural" immunity (attributable to

wild poliovirus) among older individuals. It is therefore likely that the *average* number of successful transmissions (R_n) of OPV viruses per OPV-infected individual is currently appreciably less than unity in virtually all populations of the world. It is for this reason that transmission of OPV viruses appears to be time limited in all circumstances where it has been measured. This will be the situation if and when routine polio vaccination ceases. R_n will then begin to increase, as the proportion of susceptible individuals begins to rise immediately upon cessation of vaccination.

To evaluate the implications of this change, we have estimated the increase in the proportion susceptible in human populations. The method assumes that individuals are born with a prevalence of maternally derived antibodies equivalent to the prevalence of immunity in the adult population, and that this maternal immunity has a half-life of 1 month (136, 150) (it thus has little effect on the results). Two scenarios were modeled, that of lifelong mucosal immunity (figure 2) and that of mucosal immunity lost at a rate of 1 percent per annum. Using population-specific birth, death, and infant mortality rates, and starting with different susceptible proportions, one can estimate the time until the (potential) net reproductive number ($R_0 \times S$) should reach unity, for a range of OPV serotype-specific R_0 values. Once R_n exceeds unity, we expect any individual infected with OPV viruses to transmit the infection, on average, to at least one other individual. The figure thus illustrates the window of time, after cessation of vaccination, before conditions appropriate for endemic persistence of OPV viruses would be reached given a variety of assumptions.

These analyses suggest that, for example in Africa, if the R_0 for OPV viruses were 3 and immunity did not wane, it would take approximately 11, 10, 8, or 5 years for the potential R_n to exceed unity, if 1 percent, 5 percent, 10 percent, or 20 percent of the population were susceptible at the time vaccination ceased. These intervals would be shortened to 8.5, 8, 7.5, or 4 years, respectively, if immunity waned at 1 percent per annum (see original report for details). The "window" period would be appreciably shorter if the true R_0 for OPV virus were as high as 5 or 10.

Such estimates should not be overinterpreted. They represent averages and imply isolated populations in which people mix at random. In particular, these analyses do not include age differences in contact patterns. *This may be important, as young children are generally found to have the highest secondary attack rate values* (2, 34, 43, 55, 57, 61), *and the increased susceptible proportion after cessation of vaccination will be precisely in these high-risk age groups.* Despite the several assumptions on which they are based, these results provide not unreasonable descriptions of possible scenarios.

An important consideration when predicting the rate of accumulation of susceptibles is the persistence of mucosal immunity. This is difficult to measure under current conditions of intensive vaccination, because of the potential for repeated infection by circulating OPV virus. A study by Nishio et al. (151) reported an increase in antibody levels over a period of years among Japanese vaccinees, suggestive of boosting by natural infection with OPV viruses. Although there are data on the persistence of humoral immunity in the absence of boosting (natural or vaccine related), there are no data on the persistence of mucosal immunity under these circumstances. Levels of mucosal immunity can be measured by challenge with OPV viruses (116, 144, 151, 152), and such studies have shown an inverse relation between levels of serum antibodies and viral excretion. This is clearly dependent on the mode of antibody induction, as antibodies attributable to prior intestinal infection by wild or OPV viruses are associated with much greater levels of intestinal immunity than are IPV-induced antibodies of the same level (see table 2).

Studies suggest that IPV-induced antibody levels are associated with reduced fecal excretion rates only at high antibody levels (≥1:128) (34, 62), while infection-induced antibodies are associated with reduced fecal excretion rates at lower levels (≥1:8) (151). There is an inverse association between antibody level and excretion rate (34, 54, 153, 154), even for maternally derived antibodies (136, 155). On the basis of such data, we can infer the persistence of intestinal immunity from information on the duration of detectable serum antibodies. The most appropriate data come from a serologic survey of Eskimo populations (92). There was evidence that polioviruses had not been maintained in this population, with a lack of antibodies to type 2 in individuals below 19 years old and a lack of antibodies to types 1 and 3 in individuals below 30 and 40 years old, respectively. Despite this lack of exposure for 20 years, serum antibody to type 2 persisted at a titer ≥1:100 in individuals aged 20–40 years old, after which antibody levels declined with age (92). Assuming that high levels of antibodies equate to gut protection, this suggests that intestinal immunity was maintained for at least 20 years in the absence of boosting, in younger adults, and this is supported by other such studies (99, 102, 156).

Critical population size. Even if an OPV strain were introduced into a population in which infection incidence increased (i.e., in which $R_n = S \times R_0 > 1$), it does not necessarily follow that transmission would persist indefinitely. Persistence implies a sufficient

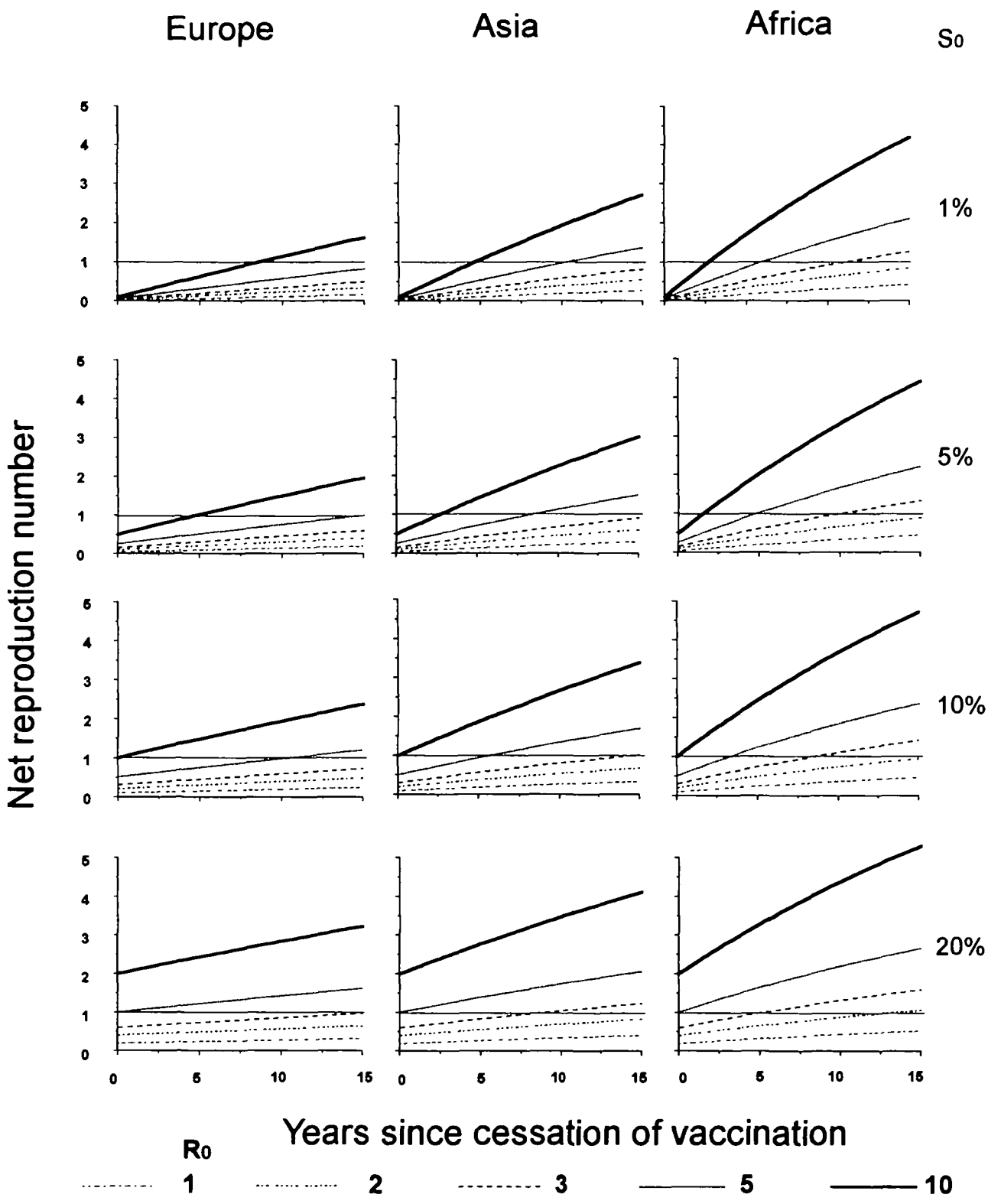

FIGURE 2. Estimates of the (potential) net reproduction number for oral polio vaccine (OPV) strains in relation to the time since cessation of vaccination in different populations, assuming different proportions susceptible (S_0) when vaccination is stopped. The model uses population-specific birth, mortality, and infant mortality rates (see text) and explores different estimates of the basic reproduction number (R_0) for OPV strains. Maternal immunity is assumed to last, on average, for 1 month, while naturally or vaccine-acquired immunity is lifelong.

supply of susceptibles and therefore depends on birth rates and total population size. The difficulty in estimating a critical population size for polio arises from the fact that it is a complex function of epidemiology, behavior, hygiene, and demography, each of which varies greatly among different "populations." We know from serologic studies that isolated populations of a few hundred individuals cannot maintain wild polioviruses permanently, as evidenced by the seronegativity of individuals born after periodic epidemics (70, 92, 157) due to introduced virus.

There are no seroprevalence data from large island populations, which might allow us to estimate how large an isolated population must be to support persistence of (wild) polioviruses, but it is likely to be on the order of several hundred thousand. Eichner et al. (110) used a simple simulation model to estimate the critical population size for wild poliovirus. They noted its dependence upon virus transmissibility (R_0) and even more on population turnover (e.g., birth rate) and estimated that wild poliovirus could persist in *unvaccinated* populations of 500,000 under conditions of good hygiene ($R_0 = 5$) and low birth rate (i.e., industrialized countries). With higher levels of population growth (i.e., developing countries) and conditions of poor hygiene ($R_0 = 12$), a virus could persist in populations as low as 100,000. Their basic model assumed homogeneous mixing and no seasonality, and the inclusion of heterogeneous contact patterns improved persistence of the virus, thus reducing the critical population size.

Whether the critical population size for OPV viruses would be much greater than this is an even more complicated issue, as the efficiency of transmission is not a simple determinant of critical population size. Infections that spread very efficiently may exhaust susceptibles rapidly and may therefore need large population sizes or geographic heterogeneity for maintenance. Alternatively, poorly transmissible infections may only be able to persist in a large and dense population. We are thus unable to provide a convincing estimate of the theoretical minimum human population size necessary for persistent transmission of OPV viruses. On the other hand, while an interesting concept, the critical population size is of questionable relevance for the immediate practice of poliovirus eradication, for the simple fact that most human populations are heavily vaccinated (whereas the critical population size refers by definition to unvaccinated populations) and are not isolated. We consider the heterogeneity and interaction of contemporary human populations to be more important for the ultimate persistence of OPV viruses than the possibility that some isolated population will independently maintain these viruses for a long time.

Predicting the future

We must do our best to anticipate what will/might happen if the current use of OPV succeeds in global eradication of wild polioviruses, and this is followed by cessation of polio vaccination. Precisely what happens will depend upon the strategy used for the discontinuation of vaccination, in particular, whether it is geographically phased out or simultaneous, whether it involves discontinuation of all OPV or sequential stopping (i.e., dropping one serotype from the vaccine first), and whether special end-stage vaccination strategies are used (e.g., global OPV or IPV national immunization days, or wide-scale use of IPV). We consider here the simplest scenario, that wild polioviruses are in fact eradicated (at least from human populations, if not laboratories) and that wide-scale use of OPV continues at essentially current levels until some date, for example, December 31, 2005, when it is stopped simultaneously throughout the world. All available evidence suggests that OPV viruses would continue to circulate and to be detectable in the environment of most populations (especially in sewage) for several months after cessation of vaccination. This duration will vary among populations but, given the variety of epidemiologic contexts, some viable virus may persist within certain closed communities and/or environments for at least a year after cessation of vaccination.

What happens next will depend on several factors: the initial proportion and distribution of susceptibles, the rate of increase of susceptibles (a function of birth rates and possibly loss of immunity), opportunities for transmission within the population (a function of hygiene, behavior, season, age distribution, social structure...), and opportunities for transmission among populations (a function of travel, proximity, migration, and population upheaval). Our analyses of R_n indicated that in any single population it is unlikely that transmission of OPV viruses would increase (R_n exceed unity) for at least 3 years after cessation of vaccination. These analyses assume a very high prevalence of immunity at the time of cessation of vaccination, and they do not include either the age heterogeneity within populations, the variance expected among populations, or the opportunities for transmission among them. Real world population heterogeneity provides a network of "high-risk" populations (generally associated with poor hygiene conditions and low vaccine coverage), such as the networks that enabled spread of wild poliovirus to Amish communities of the United States in the 1970s. Considering the immense heterogeneity of populations and transmission patterns, as well as the low detectability of infections with OPV viruses (a func-

tion of the extremely low case:infection ratio), there will be considerable opportunity for undetected transmission of OPV viruses, particularly in large, urban populations of Latin America, Asia, and Africa. On the basis of current knowledge, we cannot be certain that OPV would not continue to circulate somewhere or in some complex of populations for the 2–3 years prior to the virus being able to persist in a single population.

OPV virus may disappear from circulation within a year or two of cessation of vaccination. Another question arises when considering the situation several years after vaccination ceases, when the world will contain an appreciable proportion of poliovirus-susceptible individuals, as a consequence of births and possibly also a decline in immunity. As the prevalence of susceptible individuals increases toward unity, the effective (at least potential) net reproductive number approaches R_0. The available data suggest that the R_0 for OPV viruses is likely to be greater than unity in some poorer populations, though perhaps not in the industrialized countries. There is therefore the possibility that, were OPV viruses to be successfully eradicated but then reintroduced into a poor, developing country many years later, they would persist there. This might be associated with very little paralytic ("VAPP") disease, perhaps with a morbidity incidence as low as one case per million. On the other hand, continued person-to-person transmission could lead to selection of the viruses toward wild-type properties associated with increased transmissibility and virulence. Such selection is likely to occur, though its rate and force cannot reliably be forecast.

Potential scenarios come to mind. An old vial of OPV is discovered in a refrigerator somewhere and is administered by someone not understanding the potential implications. Or an immunocompromised child in a developed country continues to excrete OPV viruses for several years after cessation of global vaccination. S/he then infects a friend, who travels to Rio de Janeiro (Bombay, Nairobi ...) while excreting poliovirus. Or, in the year 2010, a professor of parasitology in a school of public health examines stool specimens collected some years before and stored at –20°C. The laboratory does not use high containment for such procedures .... Such scenarios are not implausible. The probability of any one's occurring may be small, but the probability of something like them happening is not negligible. The plan of action for containment of polioviruses will need to encompass such eventualities (36).

Summary

The question of whether OPV viruses will (could, might ...) persist after cessation of vaccination does not admit a simple answer. Experience to date shows that live OPV viruses will persist in most populations for at least several months after cessation of OPV vaccination, by a combination of environmental persistence and direct person-to-person transmission. Given the high levels of immunity that prevail in most populations because of extensive immunization coverage in recent years, the incidence and prevalence of OPV infections will decline rapidly and would probably not persist in any "single" population. However, given the variety, heterogeneity, interconnectedness, and sheer number of human populations, the possibility cannot be excluded that OPV viruses could succeed in persisting for several years, somewhere, in one or another population network. This may be associated with very little characteristic disease and may be exceedingly difficult to detect. The speculative nature of such predictions should be emphasized. The attempt to predict highlights important gaps in our knowledge.

A different situation will arise several years after cessation of vaccination, as the susceptible proportion increases through births, possibly enhanced by the waning of immunity in older individuals no longer exposed to poliovirus. Available information indicates that OPV viruses, in particular the Sabin type 2, would be able to persist indefinitely if introduced into a totally susceptible population living under conditions of poor hygiene. Transmission has generally been found to be most efficient among young children, and the accumulation of large numbers of susceptibles in this age group, soon after cessation of vaccination, will favor conditions for continued transmission. Thus, a crucial question is whether OPV viruses can persist "by luck" for a few years before conditions arise that would effectively ensure their persistence. The probability of this occurring is extremely difficult to assess a priori, but logic may point toward the wisdom of introducing a "2-less" OPV vaccine and monitoring closely what happens to the type 2 strain, before cessation of vaccination altogether (158, 159).

Another factor that is difficult to predict is the likelihood that OPV strains would revert to wild-type transmissibility, once "left" to themselves in a world with an increasing density of susceptibles and in the absence of competition from large numbers of recently administered vaccine viruses. Given that the wild- and vaccine-type viruses differ by only a few point mutations, such reversion is possible, but our ignorance of the molecular and genetic determinants of transmissibility does not allow us to quantify a priori the likelihood or extent to which it may occur.

Even if continued transmission of OPV strains is broken entirely, a danger exists for reintroduction of one or another poliovirus, most probably OPV, mediated through long-term excretion of viruses by some

immunocompromised individual, or through accidental contamination or infection from stored vaccine or clinical or fecal material. The likelihood of such introductions will decrease with time, but the potential consequences increase with time, because of increasing numbers and proportions of susceptible individuals and therefore increased probability that any introduced virus would persist.

We conclude that there is a risk that OPV viruses will persist and that such persistence could occur in a variety of ways. Important questions remain unanswered, and research is needed to assess the implications for OPV virus persistence. Issues requiring the most immediate attention are those of long-term excretion by immunodeficient individuals, especially those with HIV and AIDS; the ability for OPV viruses to spread and persist in communities with low seroprevalence; the risk of reversion to wild-type transmissibility; environmental survival and potential reservoirs of OPV virus; duration of mucosal immunity; and the prevalence of viable poliovirus in stored samples. Careful consideration must be given to the implications of various options for phasing out vaccination and to implementing a research agenda that will provide appropriate information to guide policy, to ensure a successful end to this important public health endeavor.

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