What laboratory studies will reduce the risk of wild poliovirus reservoirs being missed?

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Round Table Discussion

Gaps in our knowledge about transmission of vaccine-derived polioviruses

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It has long been known that oral poliovirus vaccine (OPV) viruses are transmissible "to some degree" between vaccinated individuals and their contacts. This property has generally been considered an advantage of these vaccines, since it can spread immunity, despite the fact that the viruses sometimes (albeit rarely) revert to virulence and hence can also cause vaccine-attributable paralytic poliomyelitis in vaccinees and their contacts. This transmissibility emerges as a considerable disadvantage of OPV when we consider the process and implications of the ultimate discontinuation of polio vaccination after the eradication of wild polioviruses.

The biggest outstanding question about the transmissibility of these viruses is simply: "Could they *persist* indefinitely if introduced into any human population after cessation of all polio vaccination?" If the answer to this question is "no", we don't have a problem, and we can just stop vaccination in any convenient way and watch the OPV viruses disappear. Unfortunately, however, as the main article by Wood et al. (*1*) shows, current evidence does not provide the grounds for a confident negative answer to the question. It appears unlikely that such viruses could survive where there are high standards of hygiene, but these do not prevail everywhere, and there are countries in which large numbers of children live in conditions of poor hygiene (*2*). Furthermore, we cannot answer the question definitively without carrying out a potentially unethical experiment, such as stopping vaccination in a large population living in poor hygienic conditions and then exposing it to OPV, for instance from neighbouring countries.

In the absence of a convincing "no" to the question of potential persistence, we must take three courses of action: first, gather as much relevant information as we can about the transmissibility of these viruses under various conditions, in order to inform our decisions; second, organize the cessation of vaccination in such a way as to minimize the probability of continued transmission; and third, take stringent measures to prevent the future reintroduction of these viruses.

Among the priority research questions relevant to this question of transmission are the following:

- What is the transmissibility (as reflected in some measure such as the household secondary attack rate) of OPV viruses between humans, in particular children, living in very poor hygienic conditions? This might be measured by careful virological monitoring under special circumstances, perhaps in Cuba, between their immunization days, or in some religious group which refuses vaccination.
- What is the correlation between humoral and intestinal immunity, and how rapidly does OPV-induced immunity decay in the absence of boosting exposure? This might be studied, for example, using an OPV challenge in populations where OPV has been discontinued in favour of IPV, and thus where OPV-vaccinated individuals are no longer exposed to a booster challenge
- What are the rates of (back) selection of OPV viruses to wild-type transmissibility and neurovirulence, under conditions of serial passage *in vitro* and in humans? This requires further work on the genetic bases of transmissibility and of neurovirulence, and examination of forward and backward mutation frequency at these loci.
- What is the prevalence of OPV viruses in stored clinical samples? This can be estimated by examining, for example, faecal samples stored for parasitological research, and such studies are currently planned.
- How long can OPV viruses remain viable outside the human host under "ideal" environmental conditions? The literature on this subject is small, but the experiments (e.g. to evaluate survival curves of OPV virus populations in conditions that vary with regard to temperature, humidity, alkalinity, organic matrix and other such factors) are relatively simple to carry out.
- What is the prevalence and survival duration of immunodeficiency conditions favouring long-term carriage of OPV virus infections, and how long can these infections last? Such studies are currently under way.
- What is the sensitivity of environmental sampling for OPV viruses, and how can this be optimized?

Each of these questions represents a particular and worthwhile research challenge.

Even with much more information than is now available on each of these questions, we are unlikely to be fully confident that OPV viruses cannot persist where there are high numbers of susceptibles (particulary children because their habits predispose them to high infection risks), living in poor hygienic conditions. It is not yet clear how optimally to discontinue OPV vaccination so as to minimize the chance of continued OPV virus transmission. Various crude scenarios have been suggested, as summarized by Wood, Sutter and Dowdle (cf. Table 1) (*1*), but these raise questions themselves, and deserve considerable refinement. For example if it appears too "difficult" to prepare a bivalent type 1–3 OPV vaccine, it might be argued that IPV vaccine should

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be used selectively in high risk populations such as those in poor urban areas for a few years after cessation of OPV, to increase the likelihood of OPV virus disappearance from such settings. Beyond this, much thought will be needed on how best to monitor disappearance of OPV virus, and how to respond if OPV virus should be found to persist somewhere, or to be introduced. The cessation of OPV vaccination will introduce an epidemiological situation which has never before been experienced, and will require intense and imaginative implementation and monitoring to ensure its success. ■

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2. **Fine PEM, Carneiro IAM.** Transmissibility and persistence of oral polio vaccine viruses: implications for the global poliomyelitis eradication initiative. *American Journal of Epidemiology*, 1999, **150** (10): 1001–1021.

It is too early to stop polio vaccination

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The paper by Wood, Sutter and Dowdle presents a balanced discussion of the hurdles facing the eradication effort (*1*). However, there are significant omissions, and many questions remain unanswered.

The WHO Global Plan of Action for Laboratory Containment of Wild Polioviruses (*2*) calls for cessation of vaccination at some point after eradication and containment. An important question is whether vaccine virus excreted from vaccinees will persist and constitute a threat to unimmunized infants. There are some data from a few countries on the extent of poliovirus vaccine persistence in the population. Some have concluded from these data that persistence is of limited duration, but in this writer's opinion the data are far too limited to justify this conclusion. For example, there is a report of 'silent' circulation of poliovirus type 2 in Israel (*3*), and this phenomenon might be more widespread. An even greater problem is prolonged shedding of poliovirus by immunocompromised vaccinees. It is already known that they may harbour poliovirus for up to 10 years. It seems unlikely that all such persons can be identified. Certainly, no provision for doing so is included in the Global Plan of Action. It can only be concluded that immunocompromised vaccinees will be a continuing threat in the post-immunization era.

Wood et al. describe a number of ongoing studies designed to characterize the transmission of poliovirus vaccine strains (*1*). It is hard to imagine how such data could ever rule out the possibility that a shed vaccine virus might constitute a threat to unimmunized individuals. For example, mutations might arise during circulation of poliovirus that enhance endemic transmission. Unfortunately, there are no animal models with which to study poliovirus transmission. Transgenic mice that express the poliovirus receptor are not susceptible to infection by the oral route. It might be feasible to engineer transgenic mice that are orally susceptible but such a result is likely to be several years away, and it is not guaranteed that such animals would be suitable for studying the molecular basis of poliovirus transmission.

An important component of the eradication effort is the identification and destruction of poliovirus stocks, to prevent reintroduction of the virus in the post-vaccination era. Not enough attention has been paid to the lessons and revelations that have come out in the past few years about smallpox eradication. In that case, a virus that had been very tightly controlled in a small number of laboratories is now perceived as the number one bioterrorism threat in the world (*4*). Wood et al. do not indicate why poliovirus would be easier to contain or restrict than smallpox virus. There is no discussion of the mind-boggling scale of tracking down all poliovirus stocks, particularly in light of the absence of an enforcement authority. Wood et al. state that laboratories with known poliovirus stocks can be 'relatively simply identified through surveys'. This opinion is disconcerting: one could easily imagine, for example, that certain countries would prefer to keep their poliovirus stocks for biological warfare. The problem of identifying laboratories that harbour poliovirus without knowing it is an even greater challenge, and seems unsolvable. And how do we deal with the situation in which a tube labelled 'Coxsackievirus B3' actually contains poliovirus type 2? Since such a situation has actually occurred (*5*), it is not a hypothetical threat, but a real possibility. The suggestion by Wood et al. that 'goodwill' and the 'thoroughness with which ... nations exercise their responsibilities' will make the effort succeed is simplistic. A more detailed plan should be produced.

One possible reservoir for the poliovirus genome is through recombination with other enteroviruses. Wood et al. conclude that 'recombinants are unlikely to pose a threat to the eradication programme'. One basis for this statement is that 'only recombinants carrying the wild-type poliovirus capsid' would be virulent. The assumption is that the poliovirus receptor is the principal determinant of tissue tropism, but this is incorrect (*6*). It is possible that capsids from other enteroviruses, or even hybrid capsids of poliovirus and other viruses, might result in delivery of the virus to motor neurons, where replication would produce poliomyelitis. Furthermore, although not all enterovirus non-coding elements function well in cells of neuronal origin, one cannot predict how recombinant elements with selected mutations will behave. Thus, it seems naive to assume that recombination will not be a threat to the eradication effort.

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Wood et al. suggest that it is debatable whether polioviruses are effective weapons for biological warfare. In this writer's opinion, there is no question that the virus would be an effective item in a bioterrorist's toolbox. Perhaps it would be useful to recall the pre-vaccine era, when poliomyelitis was a constant threat to the unimmunized population and caused hundreds of thousands of cases of paralysis annually. Even if we could destroy all known poliovirus stocks, it would be relatively easy to synthesize infectious poliovirus DNA in the laboratory. By this author's estimate (*5*), a single release of virus into the water supply could lead to 7000 cases of paralytic poliomyelitis in a city of 10 million unvaccinated individuals. One must not underestimate the power of poliovirus as a weapon for biological warfare.

A paradox arises from poliovirus vaccine production in the post-oral polio vaccine (OPV) era. It will be critically important to continue producing vaccine stocks for use in the event of an outbreak of the disease. A poliovirus vaccine production facility will become a hazard equivalent to a bioweapons plant when the population has lost immunity to the virus. This problem was avoided with smallpox because of the strain differences between the vaccine and wild viruses, but poliovirus vaccines do not offer such an easy solution. Which poliovirus vaccine will be made in the post-OPV era? The inactivated polio vaccine (IPV) is produced from wild-type strains of poliovirus; its production would probably require a high containment facility. Alternatively, IPV might be produced from the Sabin poliovirus strains, although some research would be required to demonstrate the feasibility of this approach. However, immunization with IPV would not prevent intestinal carriage of the virus, increasing the likelihood of spread of the virus in the population. Vaccination with OPV would probably be more effective in curtailing epidemics of poliomyelitis, but excretion of virus in the faeces would be problematic for reasons discussed above. There are no easy answers to these questions, but it is disturbing that a detailed plan for poliovirus vaccine production in the post-OPV era has not been formulated. Until we know how we will produce vaccine stocks in the post-vaccination world, it will not be prudent to stop vaccinating.

I applaud the polio eradication effort, and I truly hope it can succeed. However, I question whether it is scientifically wise to propose cessation of polio immunization while there are many unanswered questions. In my opinion, the Global Plan of Action needs full step-by-step details. Given our current understanding of poliovirus epidemiology, biology and pathogenesis, despite the arguments made by Wood et al., it seems likely that poliomyelitis would re-emerge in the post-OPV era. This conclusion is based on the numerous uncertainties associated with each phase of the eradication initiative. Are we willing to take the chance that infants and children will once again be paralysed and sent to iron lungs by a disease that can be prevented by vaccination? Even if some people are, who is willing to take responsibility for taking that chance by deciding to stop vaccinating?

Although Wood et al. conclude that the 'most plausible' course of action is simultaneous worldwide cessation of vaccination, I do not agree that this is the wisest one. We should shift to using IPV wherever it is practical to do so, and continue using OPV where IPV distribution is not feasible. Research on poliovirus transmission, vaccines, and antiviral compounds should continue until such time as it makes sense scientifically to cease vaccination. ■

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The risks of stopping vaccination: perspectives from the developing world

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The ultimate indirect benefit from the eradication of a vaccine-preventable disease is the ability to make the decision to stop vaccinating and reap the resultant cost and safety gains. However, the spectre of a vulnerable population, progressively increasing in its vulnerability with each new generation of people who have not been exposed to either wild-type or vaccine virus, makes the decision to stop vaccinating a particularly awesome one. Wood, Sutter and Dowdle have reviewed the current status of knowledge of the potential risks in stopping vaccinating against polio (*1*). They also discuss the ongoing research which we hope will provide some of the answers to the disquieting questions such a decision raises. In the main, these investigations have been carried out in, or been oriented towards, the industrialized world. While much of the reassuring data discussed in the review is generalizable to all parts of the world, there are important issues which pertain more specifically to the developing world, and they merit serious consideration.

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For example, the proposed option for a complete or partial inactivated poliovirus vaccine (IPV) strategy to precede the termination of vaccination is one which is, in practice, unaffordable in most developing countries and ought not to feature in the global plan. Secondly, studies to assess the transmissibility of Sabin-like viruses, which have been carried out in industrialized countries in populations with high immunity, may not provide enough valid data for the circumstances which prevail in a developing country where there is lower vaccine coverage, lower population immunity, poor sanitation and an inadequate clean water supply, all of which facilitate the spread of a large burden of virus. Thirdly, the potential of chronic carriers to act as reservoirs to re-seed virus into a susceptible population would need especially urgent attention in the developing world.

The incidence of primary immunodeficiency is largely unknown in much of the developing world. In deprived areas with poor medical facilities the majority of the more profoundly immunosuppressed infants would probably not survive long enough to be a potential epidemiological threat. However, children with less severe immunodeficiencies, such as immunoglobulin A (IgA) deficiency, which in themselves would not result in chronic excretion in developed countries, may, in combination with secondary causes of immunodeficiency such as HIV, malnutrition or chronic tropical diseases, become a source of long-term excretion of poliovirus.

However, of far greater importance in the developing world is the potential of HIV to be a risk factor for long-term excretion of poliovirus. It has been estimated that more than one in 20 of the children born at the Chris Hani Baragwanath Maternity Hospital in South Africa, the largest hospital in the world, are HIV-positive. There is a vast population of infants and children on the African continent with subnormal immunity due to HIV infection, and they are being regularly infected with Sabin-like poliovirus and, in some instances, wild-type poliovirus. Wood et al. mention the very limited studies which have been carried out to determine the potential of HIV infection as a risk factor for chronic excretion of poliovirus, and refer to ongoing studies in Kenya and Guatemala. Data to date suggest that HIV infection is not a risk factor, and this would be consistent with the characteristics of HIV immunodeficiency, which is predominantly cell-mediated. However, there is a progressive drop-off in humoral immune function with advancing HIV disease and a falling CD4+ lymphocyte count. Given the enormous number of HIV-infected infants on the continent, there are clearly numerous encounters of Sabin-like virus with hosts in the latter stages of HIV disease who have significant humoral immunodeficiency. Although children with AIDS in developing countries are unlikely to survive for any significant length of time, the population of infected children is so large that it could conceivably sustain the transmission cycle if these children became chronic excretors of the virus because of humoral immunodeficiency. The magnitude of the HIV problem and the implications of re-seeding the population with virus from chronic carriers after cessation of vaccination make it indispensable for the relation between HIV-mediated immunodeficiency and chronic excretion of poliovirus to be investigated in greater depth, both immunologically and virologically. It is really insufficient to rely solely on observations of post-vaccination virus excretion in a limited population of HIV-infected children.

There are additional issues related to stopping vaccination in the developing world, such as the deficiencies in surveillance capacity in many of these countries. Cessation of vaccination would demand a particularly efficient and reliable surveillance mechanism to detect any possible introduction and silent transmission of the virus. In particular, monitoring would need a relatively sensitive environmental surveillance capacity. Unfortunately environmental surveillance would be especially difficult in many developing countries where there is frequently no reticulated sewage system from which to do systematic sampling and, in the more arid developing countries, it may well be difficult to access natural sampling points such as surface water.

Implications for the termination of vaccination are of considerable public health concern and a great deal more research will still need to be done before there is enough reassuring information to take the critical decision to stop vaccinating with confidence. Many of the questions which still need to be answered pertain to developing countries where most of the relevant issues are compounded by poverty and deprivation. The eradication of polio in all its phases is a global effort and its success is dependent on the assurance that the virus has been permanently extinguished and will not reappear in any part of the globe. Much work still needs to be done in the developing world to define and quantify these additional risk factors. This will require significant research investment by the industrialized economies, in addition to a commitment to build up the surveillance capacities in the developing world. ■

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What laboratory studies will reduce the risk of wild poliovirus reservoirs being missed?

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Humans are the only natural host for polioviruses. During the acute non-persistent infection, the virus is

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transmitted by the host or in the excretions of the host to other persons. The persistence of the virus in the environment is limited in time, and no animal populations have been found to sustain wild poliovirus circulation. Together with the two excellent polio vaccines, these are the biological principles on which the objective of polio eradication is based (*1, 2*). It is conceivable that these principles will be challenged in the later phases of the eradication programme, when the present scientific evidence might not be sufficiently convincing to satisfy the public and political perception of risk. Then, earlier studies demonstrating the absence of animal reservoirs and the finitude of environmental survival, may have to be extended.

For the purpose of polio eradication, WHO has developed a surveillance system based on the detection, reporting and clinical and virological examination of all patients less than 15 years of age with acute flaccid paralysis (AFP) (*3*). A small number of cases will remain 'compatible', requiring further investigation. Laboratory studies must be started to evaluate supplemental methods for resolution of these cases, for example by using IgM serology or nucleic acid amplification methods.

Although AFP surveillance may not detect every case of polio and certainly less than 1% of poliovirus infections, experience has shown that it does allow detection of sustained wild poliovirus transmission in a community. Nevertheless, when complete interruption of wild poliovirus transmission is approaching, even high quality AFP surveillance becomes an insensitive method for detecting the virus (*4*). Therefore, the need for more convincing evidence of the disappearance of polioviruses will increase with further progress of eradication. This means we must start now to explore the potential that alternative methods may have.

A number of industrialized countries that have been free of cases of poliomyelitis for many years are not able to carry out AFP surveillance of acceptable quality. They too will have to document the absence of wild poliovirus transmission. Therefore, some have proposed alternative surveillance strategies, including enterovirus surveillance and environmental surveillance. The concept and technical basis of both surveillance systems are now by and large accepted, but additional work is required to determine their population sensitivity and to establish scientifically based performance criteria. Environmental surveillance, in particular, could become a very important tool to document the absence of wild poliovirus circulation, especially when the technology can be further developed. Environmental surveillance has been used to detect poliovirus circulation well before and after cases occurred and even in the absence of cases (*5–8*). The potential that new (molecular) technology is offering, however, has been insufficiently applied to improve the sensitivity, applicability and rapidity of environmental surveillance for wild polioviruses in sewage or surface waters. Therefore, there is an urgent need for a more aggressive approach to apply new technology for environmental polio surveillance. The new methodology could for example include immunological or molecular capture technology, nucleic acid amplification and the use of 'flow' sampling instead of 'grab' sampling, as has been shown to be effective for detection of hepatitis A and E viruses (*9–12*). Of course, the excess of OPV-derived viruses may present considerable problems for the detection of wild viruses and may necessitate, for the time being, further development of the potential that conventional cell culture-based methods still have (*8*, *13*). In addition, environmental surveillance should be evaluated more extensively in the various parts of the world where wild poliovirus is still endemic.

After eradication, AFP surveillance needs to be continued in most countries before certification may be achieved. It will probably need to be supplemented with environmental surveillance studies or targeted stool surveys in selected samples of the population in countries with relatively low routine immunization coverage and lesser levels of hygiene. More developed countries should continue to collect data from various sources that support the absence of wild poliovirus circulation within their borders. For this purpose, enterovirus surveillance data may be useful, provided that the effects of the increasing use of nucleic acid amplification methods for diagnosis of virus infections are dealt with. However, environmental surveillance, particularly after improvements in sensitivity and efficiency, may be a more attractive surveillance option in these countries.

Laboratory investigations are of paramount importance in the eradication process; their significance will only increase. Investments in laboratory studies are urgently needed and will have to include new technology development in addition to the more regular epidemiological, virological and serological studies. Such investments, however, should be considered as good value for money since, ultimately, laboratory-based investigations will have to provide the confidence that polioviruses have been eradicated and immunization can be stopped. ■

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