Development of a More Thermostable Poliovirus Vaccine

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In 1991, a goal of improved thermostability of oral poliovirus vaccine (OPV) was set, and the Product Development Group was established under the Children's Vaccine Initiative to achieve this goal. Several initial research strategies were unsuccessful. The substitution of deuterium oxide for water in the final blending stage of vaccine production resulted in a significantly more stable product at temperatures of \( \approx 37^\circ\text{C} \). A large body of clinical data shows the safety of deuterium at the dosage in the cold chain, that which extends directly to the point of vaccine administration. Moreover, significant improvements in the thermostability of OPV were identified by EPI advisory groups on the technical aspects of polio eradication in 1990, 1991, and again in 1992 as a critical success factor for the WHO’s initiative for the global eradication of poliomyelitis by the year 2000.

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The strategies for eradication of poliomyelitis are based on immunization with OPV directed to interrupt transmission of the wild poliovirus and surveillance for every possible case of poliomyelitis. Besides a comprehensive system of routine immunization, immunization strategies include mass administration of OPV to all children within the target age range, usually <5 years of age, within a limited time period—national immunization days. Once polio cases have been reduced to a low level, “mopping-up”—house-to-house administration of OPV to those at highest risk—is the strategy to finally eradicate the virus [4].

This strategy has been successful in numerous locations, but nowhere with more dramatic effect than in Latin America, where it has resulted in the recent elimination of endogenously transmitted poliovirus in the Western Hemisphere. The mobility of immunization workers has been a key factor in these supplemental immunization strategies. Mobility could be greatly increased, especially in those hardest-to-reach areas where there has been no history of OPV immunization. Whereas mobility and efficiency have been major factors in eradication programs, it is likely that there will be a need for vaccination in the future.

Cold-chain conditions are defined by the requirements of the vaccine that is least stable, making it clear that efforts to improve the thermostability of vaccines in general must first be focused on OPV. While it is obvious that development of a totally thermostable OPV would not eliminate the need for the cold chain (as other EPI vaccines would continue to require cold storage), the availability of a more thermostable OPV could offer the possibility of modifying the terminal “link” in the cold chain, that which extends directly to the point of vaccine administration. Moreover, significant improvements in the thermostability of OPV were identified by EPI advisory groups on the technical aspects of polio eradication in 1990, 1991, and again in 1992 as a critical success factor for the WHO’s initiative for the global eradication of poliomyelitis by the year 2000.

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Novel drying conditions were also examined, including the use of trehalose (α-D-glucopyranosyl-α-D-glucopyranoside) as an excipient during removal of water [10]. While it was possible to achieve very stable vaccine preparations by several different drying protocols, each protocol resulted in large initial losses in vaccine potency during the drying process. In contrast, the suspension of OPV strains in 87% deuterium oxide was found to result in a substantial improvement in thermostability [11].

Successful Approach: Deuterium Oxide–Stabilized OPV (dOPV)

Studies by Radu Crainic and colleagues at the Institut Pasteur, Paris, demonstrated that suspension of poliovirus in 87% deuterium oxide results in a significant increase in the stability of the virus when subsequently incubated at 37°C, 42°C, or 45°C [11]. For type 3 poliovirus, generally the least stable of all three Sabin serotypes, stabilization in 87% D₂O with 1 M MgCl₂ resulted in a loss of potency of <0.3 log₁₀ over 3 days at 37°C (compared with an ~0.8 log₁₀ loss in 1 M MgCl₂ alone) and a loss of ~0.7 log₁₀ over 3 days at 42°C (compared with a 1.5 log₁₀ loss in 1 M MgCl₂ alone). In general, these findings have been confirmed by similar observations in P. Minor’s laboratory at the National Institute for Biological Standards and Control in London (personal communication, 1994) and in the laboratories of two manufacturers of OPV.

It is likely that the effects of deuterium oxide on poliovirus are very similar for each of the three serotypes after incubation at elevated temperatures for 7 days (figure 1). This appears to be the case for the deuterium stabilization of poliovirus infectivity at 37°C, 42°C, or 45°C [11]. Overall stability for the three types is illustrated in table 1. There is a dramatic increase in the stabilizing effect of deuterium oxide as the temperature increases, especially at temperatures similar to those in the hottest countries of the world.

The stabilizing effect of deuterium oxide on poliovirus is likely to be related to the greater strength of noncovalent oxygen-deuterium or nitrogen-deuterium bonds relative to the corresponding hydrogen bonds. Hydrogen bonds normally determine the base-pairing of double-stranded segments of viral RNA, play an important role in stabilizing the secondary and tertiary structure of poliovirus capsid polypeptides, and are

![Figure 1. Stability of the three types of OPV in heavy water as a function of temperature.](image-url)

**Table 1.** Overall potency loss of stabilized OPV after incubation at indicated temperature for 7 days.

<table>
<thead>
<tr>
<th>Stabilizer</th>
<th>37°C</th>
<th>42°C</th>
<th>45°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₂O/MgCl₂</td>
<td>0.55*</td>
<td>1.52</td>
<td>2.85</td>
</tr>
<tr>
<td>H₂O/MgCl₂</td>
<td>1.32</td>
<td>3.42</td>
<td>5.32</td>
</tr>
<tr>
<td>Fold difference in surviving virus</td>
<td>5.9</td>
<td>79</td>
<td>295</td>
</tr>
</tbody>
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* Log₁₀ drop in virus titer following indicated incubation.
likely to be involved in RNA–capsid protein interactions that are important for virion integrity. When poliovirus is suspended in a high concentration of heavy water, its intra- and intermolecular water molecules are exchanged with heavy water molecules. Moreover, deuterium atoms replace exchangeable hydrogen atoms participating in hydrogen bonds throughout the virion. This results directly in an increase in the stability of the virus particle as demonstrated by microcalorimetry tests (Crainic R, personal communication, 1995). Another possible mechanism might be the slowing of an autocatalytic degradative reaction carried out, for example, by an encapsidated ribonuclease, as suggested recently for poliovirus and for another picornavirus, foot-and-mouth disease virus [12, 13].

Safety, Potency, and Efficacy Considerations Related to the Use of Deuterium as a Stabilizer

Considerations for licensing a deuterium oxide–stabilized polio vaccine relate to the demonstration of the safety, potency, and efficacy of each of the individual components and the exclusion of any untoward interactions between them.

The virus. Live OPV has been used in immunization programs worldwide for >30 years and has an excellent record for safety, potency, and efficacy in actual use conditions. This performance can be assured by maintenance of strict production conditions and by appropriate prerelease testing. These conditions would also be met for an OPV stabilized with deuterium oxide. The virus strains present in dOPV and standard OPV are propagated under identical conditions and are genetically indistinguishable. Thus, the virus-related risks of dOPV (i.e., the risk of paralytic disease due to reversion of the vaccine strains to neurovirulence) should be unchanged from that of OPV. This risk is ~1 case of paralytic disease/530,000 first-time vaccinees or 1 such case/2,000,000 vaccinees overall [14].

Deuterium oxide. Deuterium (H or D) is a stable, nonradioactive natural isotope of hydrogen, which contains one proton and one neutron in its nucleus and has about twice the mass of normal hydrogen. Deuterium is normally present as ~0.014% of the hydrogen atoms in all natural compounds. It enters into all chemical reactions of normal hydrogen, forming equivalent compounds, but generally these reactions proceed more slowly than with normal hydrogen.

Deuterium oxide has not been used as a stabilizer for vaccines intended for human use, but substantial evidence suggests that a standard 0.1-mL dose of OPV containing 87% D<sub>2</sub>O poses a negligible risk to young infants. After a single dose to an infant, the deuterium isotope would constitute ~0.018% of total body water hydrogen. Fractional increases in deuterium loading would be proportionately less in older and thus larger infants receiving the same dose of dOPV. In addition, it should be noted that variations in the natural level of deuterium depend on the water supply. This results in preexisting levels of deuterium that exceed the peak level predicted after a dose of deuterium-stabilized polio vaccine in some locations. In laboratory animals, toxic effects of deuterium oxide have been noted only at much higher total body loading, generally >20% [15].

There are good data supporting the safety of deuterium oxide in the small doses that would be given with this vaccine. Considerable experience has been gained in the use of deuterium oxide as a tracer for studies of nutrition and water exchange rates in human volunteers representing a wide range of ages including the first year of life [16–19]. These studies have demonstrated no adverse effects of deuterium oxide at oral doses ranging from 0.1 to 1.0 g of D<sub>2</sub>O/kg of body weight in small numbers of infants <120 days old [16, 17]. The dose of D<sub>2</sub>O in a 0.1-mL vaccine dose given to a newborn of 3 kg would be 0.032 g/kg of body weight as a single dose. At the older ages of 6, 10, and 14 weeks, the dose would be proportionally less by body weight. Deuterium abundance in urine and saliva may be reliably assessed by infrared absorption or mass spectroscopy [18]. Washout rates are well established. Daily water turnover, including both insensible loss and loss in urine and gastrointestinal secretions, is ~160 mL/kg in 3-month-old infants [19]. Multiple dosing studies in 3-month-old infants have shown no substantial buildup of deuterium when doses of 1 g of D<sub>2</sub>O/kg of body weight were administered by the oral route on a weekly basis over 3 weeks [16]. As noted above, toxic effects of D<sub>2</sub>O have been observed only at much higher doses, 20% of total body water in laboratory animals [15]. Thus, no deuterium-related adverse consequences are expected following administration of dOPV (see [20] for review).

Interactions between deuterium and poliovirus. There is no reason to suspect that stabilization of poliovirus in deuterium oxide will result in an increase in the very low risk of clinically evident vaccine strain reversion (vaccine-associated paralysis). Replacement of deuterium by hydrogen should occur rapidly after exposure to fluids in the oropharynx and stomach. For this reason and because of the small amount of deuterium in an individual dose of dOPV, intracellular deuterium concentrations would be negligibly increased after oral administration of dOPV. There should be no residual effects of deuterium following cellular penetration, uncoating of the virus, and the initial round of viral RNA replication.

It is important to consider whether there are any potential risks of deuterium stabilization that might be related to storage in this compound or to the very earliest steps in viral infection and, specifically, whether there is any potential for selective loss of infectivity of the majority attenuated population of virus present in vaccine (with a resultant positive selection of a normally much smaller, more neurovirulent virus fraction). There is no reason to suspect such a selective effect, however, and substantial data argue strongly against this possibility.

Suspension of poliovirus in 87% deuterium oxide does not reduce the infectious titer of vaccine strains as measured in cell culture (after dilution in deuterium-free medium) [11]. These data indicate that there are no irreversible reductions in poliovirus infectivity due to deuterium oxide per se. Available data appear to exclude significant kinetic differences in uncoat-
ing and initiation of replication. One-step growth analysis of deuterium-stabilized virus in cell culture indicates that virus suspended in deuterium is not measurably delayed in uncoating and initial rounds of RNA replication (Minor, personal communication, 1995). This suggests rapid exchange (washout) of deuterium when stabilized virus is placed in a medium containing normal hydrogen. In addition, there is good evidence that thermal inactivation of deuterium oxide-stabilized poliovirus does not favor selective survival of a neurovirulent virus fraction.

Normally, OPV formulations contain a small fraction of type 3 virus (≈0.75%) with a cytidine residue at nt 472 [21]. This population of 472-C virus has substantially greater neurovirulence than the majority of type 3 virus, which is 472-U. K. Chumakov (personal communication, 1994) of the US Food and Drug Administration (FDA) has used mutant analysis by polymerase chain reaction and restriction enzyme analysis [22, 23] on deuterium-stabilized OPV prepared by Radu Crainic at the Institut Pasteur to determine whether vaccine virus surviving partial thermal inactivation was enriched for a 472-C population. These studies indicated no enrichment following loss of >2 log10 in total virus titer by heat treatment of vaccine. It should be emphasized that no such surrogate tests for neurovirulence are currently applied to standard OPV after partial thermal inactivation. Moreover, it is reasonable to suspect that DOPV may sustain generally lower losses of potency (infectivity) than standard OPV under field conditions, thereby minimizing the potential for selection of thermal-resistant variants compared with the standard vaccine.

Finally, neurovirulence analysis of Sabin vaccine strain type 3 poliovirus in deuterium oxide has been tested by the intraspinal route in Tg21 transgenic mice (Levenbook, US FDA, personal communication, 1995), with no evidence of increased neurovirulence by examination of clinical signs in a test that has been shown to correlate with the predictive behavior of a poliovirus vaccine in the monkey neurovirulence test.

Clinical Trials

Despite the results of these in vitro studies, it would be desirable to demonstrate that deuterium oxide stabilization has no selective effects on poliovirus vaccine infectivity in vivo. Two types of clinical trials could be envisioned. The first would examine patterns of viral shedding and the genetic stability of excreted virus from 60 infants fed either normal OPV or deuterium-stabilized OPV in an industrialized country setting. The study would show that vaccine strain infections are comparable with either vaccine. A second trial would demonstrate clinical efficacy of the deuterium-stabilized vaccine in 200 infants using the standard EPI four-dose schedule in a developing country setting, examining serologic response to the vaccine.

The comparability of poliovirus infection and the rate of uridine-to-cytidine reversion at nt 472 of Sabin type 3 virus would be examined in the first trial. This molecular event occurs regularly over a period of several days following immunization of infants with standard OPV and reflects a selective advantage of the 472-C type 3 virus for replication in the gut. It is anticipated that there would be no difference in the kinetics of this uridine-to-cytidine reversion event following oral administration of DOPV and OPV. However, formal demonstration of the absence of such a difference would provide greater assurance of the comparability of DOPV and OPV and the overall safety of DOPV. Polymerase chain reaction-related technologies would be used to assess the rate of the uridine-to-cytidine reversion in study subjects.

The demonstration of similar effectiveness as measured by seroconversion in the second trial would provide some assurance that there is no loss of infectivity (bioavailability) of vaccine virus suspended in deuterium oxide.

Issues in Introduction of a New Vaccine

Some general issues of vaccine demand, supply, and financing are critical to the effort to introduce a new or improved vaccine. Each national immunization program is developing or has already developed an immunization plan that includes national immunization strategies and their impact on vaccine need. Such plans must consider issues in vaccine handling and delivery and would have to define those training components that would be necessary for introduction of a new vaccine such as this one. They would also consider vaccine source, quality, cost, funding mechanisms, number of doses projected to be needed, and procurement mechanisms. To expedite this, program managers need to be informed about possible changes in vaccine availability and immunization strategy recommendations so they can plan accordingly.

Regulatory and production aspects. Critical supply issues for a new vaccine pertain to the number of manufacturers that have access to the technology, the barriers remaining to license the product in the appropriate countries, and the question of how to make the product available to countries in the developing world. In developing countries where local vaccine production exists, there is the additional question of whether such a country would consider it feasible and desirable to produce the vaccine.

There will be an impact on vaccine supply if the raw materials necessary for production have limited availability. In the case of deuterium oxide, much of the world’s supply is manufactured in Canada. It is estimated that the total amount of deuterium needed to produce sufficient DOPV to complete polio eradication corresponds to only a small percentage of total global stocks of deuterium. However, there are controls on the movements of heavy water, which is an essential component in the production of nuclear weapons. Controls would be exerted on the export of the deuterium oxide to the vaccine manufacturer, but in view of the possible large number of doses involved and the relative ease with which 90% heavy water can be further purified, controls of the movement of the vaccine itself could be significant.
For a new or improved vaccine, licensing issues will have a large impact on supply, and the length of time to product licensure will determine to a large extent when it can be introduced. Clinical trials represent the single largest step to licensure. Sites must be established, ethical issues addressed, investigational lots of vaccine prepared, and the trials conducted.

The European regulatory agencies were approached collectively via the Committee for Proprietary Medicinal Products, which concluded that there was no reason a priori to object to the novel OPV formulation and informally encouraged manufacturers to approach national authorities with a view to conducting trials. Such approaches have been made and persons responsible for review identified. However, batches of deuterium-stabilized OPV to perform such studies would not be available until ~4 months after a decision to proceed.

Informal consultations with regulatory authorities from several countries indicated the need for additional licensing of a novel OPV formulation as a new product requiring controlled clinical trials in areas in which polio is endemic and seroconversion studies, although, in principle, changing to alternative stabilizers for OPV (such as amino acids) would not be problematic. Regulatory approval is generally primarily based on anticipated national usage and risk-benefit analysis for the country in which the vaccine is made. Without such a market, regulatory authorities could hesitate to consider licensing the product.

**Vaccine demand.** The annual demand for a vaccine will depend on the population to be immunized, the immunization strategy taken, and the extent of vaccine wastage (doses that are bought and delivered but not administered).

The wastage factor can be calculated with fair precision for current vaccines using current immunization strategies. However, for new vaccines and where new handling procedures are introduced, wastage may be difficult to calculate. For example, in 1996, suppliers of OPV through UNICEF have introduced individual time and temperature vaccine vial monitors (VVMs) on each vial of OPV. This technology will also be made available to other producers of OPV as soon as possible. These VVMs, which can be tailored to the thermostability of the vaccine produced by each individual manufacturer, along with a relaxation of vaccine vial opening rules announced by EPI in 1995, will allow health centers to use a vial of OPV until it is empty, as long as it does not show signs of contamination by visual inspection and the VVM indicates that it has not been thermally inactivated. Proper use of VVMs is expected to significantly reduce wastage of OPV. Careful monitoring has been initiated to provide quantitative data on the impact of these two new interventions in the next year to confirm anticipated decreases in wastage.

In the final analysis, vaccine demand will depend on how widely the product is used and how much it costs. Current estimates are that the use of D₂O as a stabilizer might result in a US$0.025 increase in the per-dose cost of raw materials used for vaccine production, although there was encouragement for the view that funding could be forthcoming from donors. Thus, there are probably few cost implications.

Use of the product also depends on the perceived benefits relative to the perceived obstacles of its acceptability and its price. Some information on public acceptance of dOPV has been gained through a study funded by the Product Development Group and undertaken in the United Kingdom, using a series of panels of persons representative of the UK population to gauge public reaction to a novel vaccine. The panels were asked to discuss a statement describing the product and its justification. Their reactions indicated that key phrases would have to be developed that would put the product in terms that were widely understood, such as "updated," "long-lived," and "preservative" rather than "improved," "thermostable," and "isotope." The main reaction was surprise that a change was needed in view of the public perception of OPV as one of the safest, most effective, and most acceptable vaccines. The panels interviewed asked if the vaccine had been extensively tested in other populations and if it were safe and effective. Approval by WHO was regarded as a reassuring factor, and there was a need for sufficient clearly expressed information to explain what the material was and why it was needed. The study methodology could be replicated in other settings and could provide useful guidance for vaccine introduction. Nevertheless, the issue of acceptability will be the most difficult one to address for any new vaccine and will vary with the circumstances.

**Lessons Learned from the Product Development Process**

In the years since it was launched, the global initiative for the eradication of poliomyelitis has progressed to a point at which significant areas of the world have succeeded in interrupting transmission of the poliovirus. The success to date has suggested a need to reevaluate the likelihood of successful eradication with the current OPV. In the early days of the eradication initiative, the analogy with smallpox eradication was dominant, and the need for a thermostable smallpox vaccine was considered critical to the success of that initiative. Experience in polio eradication strategies, however, has shown the contribution to protecting vaccine potency made by the infrastructure and cold-chain development that has accompanied the establishment of national immunization programs. Experience has also shown that the differences in the epidemiology of smallpox and polio imply different immunization strategies: Smallpox eradication relied on immunizing around each case (containment), while polio eradication makes use of large national campaigns that can take advantage of the existing infrastructure.

Moreover, it is expected that the VVMs will contribute greatly to the security that OPV potency is protected until its administration. However, the view that a new polio vaccine is not absolutely essential for eradication is not held universally. Elimination of wild poliovirus transmission in areas of the world where it has not yet been interrupted may prove much more difficult than in those regions where it has succeeded.
more thermostable vaccine could provide a decisive advantage in such areas with respect to the eradication of the virus.

In the final analysis, it is public acknowledgment of the need for a new vaccine that will ultimately bring about its incorporation into an immunization program. For dOPV, a case has been made by EPI that the currently available OPV could complete the job of polio eradication and that dOPV might in fact be a hindrance in so far as it could affect public acceptance. In addition, it is estimated that OPV usage will peak in 1996–1997 for a series of national immunization days. The time scale for development of the new formulation is of the order of 2–3 years, so that it would become available too late to play a critical role.

Thus, given the position of EPI that poliomyelitis will be eradicated with existing vaccines, that a more thermostable preparation would not help the eradication process and that dOPV might in fact be a hindrance in so far as it could affect public acceptance. In addition, it is estimated that OPV usage will peak in 1996–1997 for a series of national immunization days. The time scale for development of the new formulation is of the order of 2–3 years, so that it would become available too late to play a critical role.

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The work of the Product Development Group has explored new avenues of constructive collaboration with vaccine manufacturers to influence vaccine development. Issues of public sector access have been negotiated, information exchange has been frequent, and the sharing of views has evolved and improved as a result of CVI activities. Collaboration with manufacturers developed as a necessary and very satisfactory aspect of the work, but the manufacturers' representatives emphasized their desire to be involved at all stages in the decision-making process.

The licensing process and ways in which WHO can influence it have been examined. Whether WHO and CVI can smooth some of the hurdles by developing clinical trial protocols, approaching European licensing authorities, or being prepared to support manufacturers' activities toward product registration remains to be seen. The need for constructive interaction with licensing authorities, while recognized, has been difficult to implement.

A critically important lesson is the realization of the need to assemble unassailable figures on the programmatic impact of a new or improved vaccine. For a new vaccine for which the disease burden is known, this may be a relatively straightforward calculation. In the case of an improved vaccine, the figures may be harder to obtain, but they may be even more important. A change in a vaccine, especially at a higher price, will be difficult to justify unless the benefits are based on verifiable numbers, not on opinions. When there is uncertainty about the impact of or need for the product on the part of the users, manufacturers will not receive the assurance of demand that is necessary for investments into vaccines of public health importance with possibly limited profitability.

A particular area of need outlined by the work of the Product Development Group was an understanding of the need for vaccines of improved thermostability in the light of the potential future changes in the cold chain and the requirements of
other vaccines. The Product Development Group thus recommended that EPI develop an analysis of future needs for heat-stable vaccines in light of the current and future evolution of the cold chain.

Another lesson is that setting an eradication goal depends on having the proper tools to achieve that goal. If a target, such as eradication of polio, is set but its achievement may be contingent on an improved vaccine, that vaccine should be made available before proceeding. Otherwise, the time constraints will defeat the vaccine improvement project or the eradication effort might flounder.

Basic research to develop a new vaccine is relatively easy. Product development and pilot production are more complicated. Introduction is the most complex process. Figure 2 illustrates the different players involved and their respective roles for the thermostable OPV Product Development Group.

A framework for evaluation of new vaccines for use in immunization programs has been developed [24]. The thermostable OPV meets all of the criteria outlined in that analysis: It is of low cost, easy to integrate into existing schedules, and directed against a disease perceived to be important, and it has relatively straightforward licensing and production issues. However, there are substantial challenges to introduction. The key, ultimately, will be strong and well-founded programmatic demand for a new vaccine.

Acknowledgments

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References