THE NEW POLIO VACCINATION SCHEDULES

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Since the early 1960's, oral polio vaccine has been the vaccine of choice for virtually all countries throughout the world. Three particular benefits of OPV have been considered to far outweigh the small but definite risks of vaccine-associated cases (SLIDE 1). First and most important is the fact that OPV induces significant levels of mucosal immunity in the child's intestinal tract so that even if he is infected with wild poliovirus, that virus grows poorly or not at all. Thus, he is most unlikely to transmit infection to others. This has been confirmed in a number of studies. Children who are protected with OPV appear to be essentially as immune to subsequent infection as those with naturally acquired immunity. In contrast, those protected with IPV are only marginally better protected than those with no immunity whatsoever. It is because of the intestinal immunity provided by OPV that public health authorities have so strongly favored its use as providing the best possible protection for the community as a whole. At the same time, it serves to prevent the child from acquiring wild polio virus in such as a day care setting and introducing it into the home to infect siblings or parents.

A second advantage of OPV is that the virus can be transmitted to other susceptible persons in the household, especially in lower socioeconomic areas. SLIDE 2 Note that 50% of susceptible household contacts in lower socioeconomic areas acquired the vaccine virus and so were protected. This is important protection for lower socioeconomic communities.

The third advantage of OPV is that it is given by mouth and so is far easier to administer than IPV. This is an important consideration because of the number of inoculations called for under present vaccination schedules.

For the developing countries in particular, a fourth factor weighs heavily -- and that is cost. The purchase price for OPV for international organizations is now less than 10 cents per dose; IPV costs more than 40 cents per dose, not including the cost of a needle and syringe. Much has been made by some of expected decreases in cost which could be anticipated with greater demands for IPV. However, some 6 years ago, our WHO global advisory committee asked Pasteur-Merieux to quote the expected price for quantities of 200 million doses per year. At first they refused to do so saying that it would depend on many factors. We insisted that as a manufacturer, they must be making estimates such as this quite regularly. Eventually they indicated the price would be about 37 cents per dose -- still a significantly greater price than OPV.

That OPV continues to be the vaccine of choice for all industrialized countries was reaffirmed by a WHO consultative group earlier this year and by the Technical Advisory Group for the Region of the Americas just last week.

Were it not for the occurrence of vaccine-associated paralytic case, a rare adverse event, there would be no debate about which vaccine would be preferred. Vaccine-associated polio cases have been known since 1963. In fact, I was the senior author on the paper describing the first cases. Through research, efforts have been made to eliminate or at least reduce the risk but with limited success. The rationale for adopting the new schedules is the hope that by administering first, IPV, followed later by OPV, some of these very rare complications of OPV might be prevented. Were IPV alone to be used, there would, of course, be no cases of VAPP but this alternative has other significant problems as I will describe.

In the United States, how many cases of VAPP are we talking about? SLIDE 3) Between 1980 and 1984, an average of 9.8 cases per year were recorded. A new, more stable Type 3 strain replaced the old one in 1985 and the average number of cases fell to 8.5 cases per year. During the most recent six years for which data are

Not all of these cases have residual paralysis.

available, there have been an average of about 6 cases per year. These most recent data are probably the most reliable given the now ready availability of compensation through the federal vaccine injury compensation program and because of improved surveillance due to the threat posed by wild poliovirus being imported into a now polio-free hemisphere. For the immunologically normal vaccine recipient, this translates into a risk of less than 1 case per 1.5 million first doses of vaccine given. Taking into account all cases, including those among the immunologically abnormal, the overall risk to the population is one case per 2.4 million vaccinations administered. The risk is real but, however stated, it is extremely small.

Of the cases of VAPP, approximately half occur in vaccinees and half in contacts. CDC believes that the sequential schedule might prevent most of the cases among vaccinees -- in other words, perhaps 2 or 3 cases. They believe that it might even prevent a contact case although this is purely speculative. Whether even this small number would actually be prevented is unknown because of the fact that only a few, small countries have used an IPV-OPV sequence and none has followed a schedule which at all resembles the one being recommended for the U.S. Whatever, the cost of a change is not insubstantial (SLIDE 4).

The new, alternative U.S. schedules, however, have two adverse consequences which counterbalance possible benefits. First, they will create a growing pool of children susceptible of acquiring and transmitting wild poliovirus. Second, the additional inoculations, imposed on an already overburdened vaccination schedule, will require added clinic visits and this, predictably, will result in lower levels of compliance with vaccination recommendations.

The intestinal immunity induced by OPV has played an important role in preventing spread of wild poliovirus but under both of the new schedules, intestinal immunity before school entry will be poor. In a recent study of preschool children

protected with two doses of IPV at 2 and 4 months and one dose of OPV at one year -- the ACIP's favored schedule --SLIDE 5, it was discovered that children were quite well protected against type II virus but had much less protection against types I and III. This is not surprising. It has been known for a very long time that the administration of a single dose of OPV results primarily in growth of the type II vaccine virus. Types I and III grow poorly and so the child given only one dose of OPV remains highly susceptible to infection with types I and III wild poliovirus, the two types which account for more than 95% of all paralytic disease. A second dose of OPV at school entry will provide a better level of intestinal immunity but this is very late, and leaves a growing pool of preschool children highly susceptible to the two major types of wild poliovirus.

The additional inoculations present yet another problem. When, in 1988, the IOM recommended against an IPV-OPV schedule on the grounds that it would complicate and compromise the vaccination program, only 5 inoculations were recommended for children under two years -- 4 DTP and one dose of MMR. Since 1988, the total has grown to 13 inoculations in all.

Whereas in 1988, all vaccines could readily be provided during 4 well-child visits, the revised schedules require either that 3 or 4 vaccines be inoculated at each visit or that additional visits be scheduled. Many parents and health personnel object to giving more than 2 inoculations at a single visit and thus added visits are to be expected. As has been shown repeatedly, immunization rates fall with each added visit, an effect particularly observed in lower socioeconomic areas.

None of this is new information and these were the considerations which caused the IOM in 1988 to recommend <u>against</u> a change in policy. (SLIDE 6) (SLIDE 7) One factor has changed since 1988 and it is identified by ACIP as having been a decisive in their deliberations -- and that is the present risk of importations of poliomyelitis virus into the Americas. Clearly, there is less risk of an importation now than in 1988 but is the risk so

"exceedingly remote", as the ACIP report states, that we can abandon the defense provided by OPV against the community-wide spread of wild poliovirus? SLIDE 6 The report was correct in stating that the last case of polio in the U.S.caused by the wild poliovirus dates back to 1979. Note that there was one case reported in 1993, in a Nigerian child who experienced the onset of polio in Nigeria and was brought here for treatment. I have no idea as to why the CDC even considers this a U.S. case but it does. Curiously, the draft report failed to mention the fact that wild poliovirus had been introduced into Canada on three separate occasions -- in 1988, in 1993 and again in 1996. Two of the importations were in children who had been protected with three doses of IPV and one of these cases occurred just ~~one~~ two years ago not 50 miles from Buffalo, New York! These episodes illustrate clearly the failure of IPV to protect against wild poliovirus infection. If the wild virus can and is being repeatedly introduced into Canada, it almost certainly is being introduced into the U.S and in much larger numbers given the fact that there are many more travelers arriving in the U.S. from endemic areas. In fact, CDC confirmed this belief in a 1995 report to an Institute of Medicine meeting in which Sutter and his colleagues estimated that there were between 40 and 200 undetected importations of wild poliovirus occurring in the U.S. each year.

The fact that there is a goal of global polio eradication by the year 2000 has encouraged some to believe that we need not be concerned about levels of polio immunity for more than a few years. Unfortunately, reality suggests otherwise. The year 2000 date, established ~~nearly~~ 10 years ago, is a goal not a promise nor even an expectation at this time. Although the Western hemisphere and some industrialized countries are polio-free, the disease is still widely endemic throughout the whole of tropical Africa as well as populous areas of South Asia. It is, in fact, endemic over an area roughly comparable to that when the smallpox eradication campaign began. That campaign took ten years. The afflicted areas comprise the poorest and most crowded

countries and the ones with the least resources. Programs of some sort have begun in many of these countries and fewer polio cases are now being reported. These reports, however, must be interpreted with caution. Reports of cases are being received from only a small proportion of the health centers; most such reports are provided after considerable delays and thus are not properly investigated and comparatively few specimens are yet being processed in qualified laboratories. Thus, while the achievements to date are to be commended, it has to be recognized that very difficult challenges lie ahead which make even a target of 2000 anything but a certainty.

Two other arguments regularly surface to argue the case for IPV being the preferred vaccine for use now, if not ultimately. The successful use of IPV by several countries -- notably the Nordic countries, Finland and the Netherlands -- to interrupt polio transmission are cited as evidence that the use of IPV alone is wholly adequate to achieve eradication. To this I would agree but with the caveat "under conditions similar to those prevailing in the cited countries." We know that polio spreads both by droplets and by fecal-oral contact. From studies done beginning in the early 1960's, it is quite clear that droplet spread predominates under better sanitary conditions and fecal-oral spread in lower socioeconomic conditions and in warmer climates. Both IPV and OPV are highly effective in blocking oropharyngeal growth of the virus and so both vaccines would be expected to be successful in interrupting transmission in such as Scandinavia. However, similar results have not been described for IPV application in warmer climate countries and its effect in slum areas must be questioned.

Finally, some have made the assumption that, whatever the case, IPV will be required over the several years after which transmission has been stopped, i.e. during the period of validation of eradication-- during what some now call "the end game". It is suggested that the transition to IPV should begin as soon as possible. Some 5 or 6 years ago, a theoretical argument for this position might have been made. Since then,

we have witnessed, in August 1991, the last know case of polio in the Americas. Three years of surveillance and studies subsequently ensued during which OPV continued to be used. The fact that eradication had been achieved was fully documented to the satisfaction of an independent international commission. There were no difficulties in distinguishing the very rare vaccine-associated cases from cases due to wild virus. Moreover, as has been so frequently demonstrated, vaccine strains do not persist in the environment for more than a few months. Thus, such environmental sampling as one wished to do could be readily undertaken. In brief, there is no need whatsoever for IPV in the concluding stages of polio eradication .

What is the bottom line —

Personally, I believe that for now and for the indefinite future, it would be prudent to assure that all children have adequate intestinal immunity against polio, best conferred by 2 or, better, 3 doses of OPV prior to one year of age. If IPV is to be administered first, it should not be added at the expense of overall vaccine protection. A multivalent product would resolve the problem of logistics if not cost. But it is unclear as to why no multivalent product containing IPV has been submitted for licensure in the United States despite the encouragement of the 1988 IOM Committee for manufacturers to do so. Certainly, such products can be produced. You should know that a DTP-IPV product has been licensed and used in Canada since the late 1960's and a pentavalent product has been available in France since 1993 and in Canada since 1994. One has to wonder why these products are not already available in the United States.

DTaP-IPV-HiB

The product is now widely licensed in many other countries — but wrong have ever applied to the FDA for license.

WHY CONTINUE OPV ?

- Induces intestinal immunity *and* pharyngeal immunity
- Spreads to susceptible household members to produce immunity
- Administered orally

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FAMILY SPREAD OF OPV

	UPPER ECON		LOWER ECON	
Virus	No.contact	Infected	No.contact	Infected
1	29	2	22	9
2	9	0	36	14
3	25	3	31	22
totals	63	5(8%)	89	45(51%)

Source: Gelfand, 1959

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VAPP CASES - BY YEAR

YEAR	CASES	AVERAGE
1980-84	49	9,8
1985-90	51	8.5
1991	9	
1992	6	
1993	3	6.2
1994	8	
1995	6	
1996	5	

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ADDED COSTS OF IPV/OPV

- Assumption:
  42% of children - 1 added visit
  COST $106 000 000
- Prevent 50% of VAPP cases = 3cases
  COST PER CASE
  $35 000 000

Source: Miller, et al. JAMA 276: 967, 1996

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INTESTINAL IMMUNITY

PROTECTED BY	PERCENT EXCRETING VIRUS TYPE I	TYPE II	TYPE III
3 OPV	4 %	3 %	10 %
2 IPV/1OPV	27 %	11 %	54 %
3IPV	54 %	54 %	78 %

SOURCE:MODLIN 1991

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Institute of Medicine

- "After a conbined DTP-IPV is licensed (expected within 2-5 years), consideration should be given to a regimen of two or more doses of IPV followed by OPV".

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INSTITUTE OF MEDICINE

- "The mixed IPV-OPV program is *not* recommended if DTP and IPV must be given separately because of cumbersome administration and greater cost. Simplicity in vaccination schedules is important because of continuing problems with inadequate immunization rates in preschool children."

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POLIO IMPORTATIONS INTO NORTH AMERICA

YEAR	AGE	ORIGIN	COUNTRY	VACCINE
1980	4 mos	Mexico	U.S.	0
1984	25	Zaire	U.S.	5IPV:2OPV
1985	2	Haiti	U.S.	1 OPV
1986	29	Nepal	U.S.	3IPV:1OPV
1988	1	India	Canada	3 IPV
1993	2	Nigeria	U.S.	0
1993	?	Nether.	Canada	?
1996	15 mos	India	Canada	3 IPV

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