POLIO VACCINE --ORAL VS. INJECTABLE *September 12, 1996*

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The ACIP decided in June to recommend changes in the nation's polio vaccination schedule. The new policy calls for inactivated vaccine to be given by inoculation at 2 months and 4 months and for the oral vaccine to be given at 12-18 months with a second dose at school entry. This represents a significant change from the vaccination policy which was adopted more than 30 years ago when OPV was first licensed and which has been reviewed and reaffirmed on several occasions, most recently by an IOM Committee in 1988. Clearly, that policy served this and most other countries well, culminating in 1991 in the eradication of poliomyelitis from the Western Hemisphere. What precipitated the change in policy? Does the rationale make sense?

THE ACIP

The ACIP was created in 1963 and has served to advise the public health community on the best, most appropriate use of vaccines for the population as a whole. For pediatric vaccines, it complements the Red Book Committee. ACIP's members and liaison representatives come from many different constituencies. Its recommendations are customarily developed after careful scientific evaluation and consensus building among the professional community so that the recommendations, when formalized, are seldom questioned. The new recommendations regarding polio vaccine policy represent an unprecedented departure from tradition having been promulgated despite many questions and objections by a number of reputable professional groups. I will endeavor today to summarize briefly for you the background and stated rationale for the change.

RATIONALE FOR CHANGE

The sole rationale for the change proposed by ACIP is to avert cases of VAPP (vaccine-associated paralytic polio). The hope is that by administering first, IPV, followed later by OPV, that some of these rare but important adverse reactions to OPV might be prevented. Vaccine-associated polio cases have been known since 1963 and, through research, efforts have been made to eliminate or at least reduce the risk but without complete success.

How many cases are we talking about? SLIDE 1 Between 1980 and 1984 -- an average of 9.6 cases per year. A new, more stable Type 3 strain replaced the old one in 1985 and the average number of cases fell to an average of 8 cases per year. Finally, in 1990, polio transmission in the Americas effectively ended and with this, a diminished liklihood that imported wild poliovirus cases might occur and be mistaken for vaccine-associated cases. Over the most recent four years, we have had an average of 5.8 cases per year -- a risk of about one case per 4,000,000 doses. Given the now ready availability of compensation through the federal vaccine injury compensation program and the heightened surveillance because of the absence of domestic polio, it is doubtful that there are many, if any, unreported cases.

Of the cases of VAPP, half are in vaccinees and half are in contacts. The CDC believes that the new sequential schedule might prevent a portion of the cases occurring in vaccinees -- based on current data, perhaps 2 or 3 cases and possibly a case among contacts. This is entirely speculative, however, given the fact that there is little experience with an IPV-OPV schedule. Of the very few, small countries which now use an IPV-OPV sequence, none follows a schedule which at all resembles the one being recommended for the U.S.

The recommended change in the schedule has other and adverse implications which counterbalance such benefits as may be offered.

ADVANTAGES OF OPV

When, in the early 1960's, OPV was originally recommended to replace IPV, the risks and benefits had to be carefully weighed. Three particular benefits of OPV were felt to outweigh the small but definite risk of vaccine-associated cases. First and most important is the fact that OPV induces immunity in the child's intestinal tract so that even if a child so protected is exposed to wild poliovirus, that virus will grow poorly or not at all and he is much less likely to transmit infection to others. SLIDE 2 A number of studies have been performed in which a type I vaccine virus has been fed to children with and without natural or vaccine-induced immunity. As is apparent in these studies, children who are naturally immune and those protected by OPV show similar levels of resistance to growth of the challenge virus. In contrast, IPV provides little protection -- in fact, there is little to differentiate children so protected from wholly susceptible controls. Because of this attribute of OPV, public health authorities have strongly favored its use as providing the best possible protection for the community as a whole.

A second advantage of OPV is that the virus can be transmitted to other susceptible persons in the household, especially in lower socio economic areas. SLIDE 3 Thus, others are protected who may not have been vaccinated or whose vaccination might not have been successful

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

INSTITUTE OF MEDICINE REVIEW -- 1988

In 1988, the Public Health Service asked the IOM to review polio vaccination policy, to assess the benefits and risks of each of the vaccines and to recommend as to whether changes in the vaccine policy should be considered. An expert committee was convened and concluded:

1. "No change in the present policy is recommended at this time.

2. "The mixed IPV-OPV program is not recommended if DTP and eIPV 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.

3. "After a combined DTP-eIPV is licensed, consideration should be given to a regimen of two or more doses of eIPV followed by OPV.

CHANGE IN RISK OF IMPORTATIONS

Since the 1988 IOM review what has changed? As noted, the risk of VAPP appears to have diminished and 3 new antigens (8 additional inoculations) have been added to a now even more formidable vaccination schedule. The one change which ACIP identifies as being the deciding one in electing to change vaccination policy is the diminished risk of wild poliovirus being introduced into the U.S. The ACIP draft report states that "in the U.S. the risk of poliomyelitis caused by wild poliovirus is exceedingly remote". It notes that no person infected with wild poliovirus is known to have entered the U.S. since 1986 and that a global eradication program is in progress which is targeted to eradicate polio by the year 2000.

Although there is less risk of an importation now than in 1988, is the risk so "exceedingly remote" that we can abandon our defense against the community spread of wild poliovirus which is provided by OPV? The ACIP draft report notes optimistically that the only case of polio in the U.S. since 1986 was a Nigerian child brought here for treatment. SLIDE 4 For reasons unknown, the report makes no mention of the fact that wild poliovirus was introduced into Canada 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 occurred less than 6 months ago! If the wild virus can and is being repeatedly introduced into Canada, it almost certainly is being introduced into the U.S. In fact, Sutter and his CDC colleagues estimated last year that between 40 and 200 undetected importations of wild poliovirus arre 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. Reality suggests otherwise. The year 2000 date, established nearly 10 years ago, is a goal not a promise or even an expectation. 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. These are the poorest countries, the most crowded and the ones with the least resources. Programs of some sort have begun in most such countries. However, none has yet to develop a functional reporting-surveillance system as is present in the Americas and that alone took four years to achieve. Thus, while the achievements to date are to be commended, the really difficult challenges lie ahead.

A NEW SCHEDULE AND HEIGHTENED SUSCEPTIBILITY TO DISEASE

Special problems are presented by the new schedule. The change will predictably have two serious consequences. First, it will create a rapidly growing pool of children susceptible of acquiring and transmitting wild poliovirus. Second, the additional inoculations, imposed on an already overburdened vaccine inoculation schedule, will require added clinic visits and, predictably, 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 the new schedule, the levels of intestinal immunity before school entry will be very low. SLIDE 5 Depicted here are the results of feeding OPV to children who have been protected by three different schedules -- OPV alone, IPV alone and 2 doses of IPV followed by one of OPV (the recommended new schedule). Of those children who have received 3 doses of OPV and subsequently are fed live vaccine, very few excrete the virus and those who do, for only a short time and in low titer. Such a response is believed to be similar to a child's response when challenged with wild poliovirus. Note the large proportion of children protected by 3 doses of IPV who excrete virus. The new schedule, calling for only one dose of OPV at 12-18 months, provides significant protection against reinfection with type II poliovirus because this is the vaccine strain which grows best in the intestine. However, it offers little protection against poliovaccine types I and III, the two types which account for more than 95% of all paralytic cases. The second dose of OPV at school entry will provide better immunity but, meanwhile, there will be a growing pool of preschool children highly susceptible to the two major types of 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 unnecessarily complicate and compromise the vaccination schedule, only 5 inoculations were then being recommended for children under two years -- 4 DTP and one dose of measles-mumps-rubella vaccine. Since 1988, ACIP has also recommended 4 inoculations of Hemophilus influenzae vaccine, three of Hepatitis B vaccine plus one of varicella vaccine -- bringing the total to 13 in all.

Whereas in 1988, all vaccines could readily be provided during 4 well-child visits, a similar schedule today requires either that 3 or 4 vaccines be inoculated at each visit or that additional visits be scheduled. Manufacturers are now working to combine a number of the vaccines into a single inoculation and there is every reason to believe they will succeed but it will take time. Health staff, meanwhile, are obliged to deal with the problem of too many inoculations for the usual number of well-child visits. Many parents and health personnel object to giving more than 2 inoculations at a single visit and thus added visits have to be scheduled. As has been shown repeatedly, immunization rates fall with each added visit, an effect particularly observed in lower socioeconomic areas. What vaccinations will be given first and which last? The recommendations of ACIP offer no guidance as to how best to address the problem.

Are we to expect a growing pool of children susceptible to measles or pertussis or Hemophilus or all of these, in addition to being more susceptible to wild poliovirus.

SUMMARY

Let me briefly summarize by noting that the ACIP recommendation for a new polio vaccination policy is predicated on the belief that many fewer cases of vaccine-associated paralytic poliomyelitis will occur; that the risk of imported polio is so remote that a substantial decrease in community-wide protection against polio is acceptable; and that a now overburdened vaccination schedule can readily accommodate additional inoculations in some unspecified manner without diminishing overall compliance with recommended vaccination schedules. As I hope is now all too apparent, each of these assumptions is seriously flawed.

So, what should we do? What would I do if I were the Secretary? Would I accept this recommendation which carries a price tag estimated to range from $20 to $75 million -- to perhaps prevent as many as 3 to 4 cases of VAPP at the expense of leaving a growing population of preschoolers susceptible to wild poliovirus infection and compromising overall vaccination coverage, especially among inner-city, minority children?

The real problem is that we need simpler, more comprehensible vaccination schedules and these can only be achieved by new vaccine preparations which combine a number of antigens in a single innoculation. We have used two of these for many years: DTP and MMR. Vaccine manufacturers are working on many other combinations but progress has been slow. I believe the process could be materially speeded by the creation of a Task Force comprised of manufacturers, scientists, public health staff and government vaccine experts to decide on a strategy, timetable and budget to greatly accelerate the effort to bring to market new multi-antigen products which best fit a reasonable schedule of well-child visits. Second, I would ascertain what further assistance the U.S. could provide to further accelerate the global eradication of poliomyelitis. This would represent a far better investment of scarce resources. To borrow from TV -- "It's your money, your choice."

SLIDE 1 VAPP CASES -- BY YEAR

	No. of cases	
1980	6	
1981	10	
1982	11	Average 9.6
1983	13	
1984	8	
1986	7	
1987	8	
1988	9	Average 8.0
1989	9	
1990	6	
1991	9	
1992	6	
1993	3	Average 5.8
1994	5	

SLIDE 2 INTESTINAL IMMUNITY

Children excreting virus after OPV I feeding (%)

	Naturally immune	OPV protected	IPV protected	Non-immune
Ghendon (1961)	34	36	74	80
Henry (1966)		32	86	83
Onorato (1991)		25	63	

SLIDE 3 SPREAD OF OPV IN FAMILIES

	Upper economic		Lower economic	
Virus	No. contacts	Infected	No. contacts	Infected
1	29	2	22	9
2	9	0	36	14
3	25	3	31	22
	63	5 (8%)	89	45 (51%)

Source: Gelfand, et al 1959

SLIDE 4 POLIO IMPORTATIONS INTO NORTH AMERICA

Year	Age	Origin	Country	Vaccine Hx
1980	67	Mexico	U.S.	0
1980	4 mos	Mexico	U.S.	0
1984	25	Zaire	U.S.	5 IPV; 2 OPV
1985*	2	Haiti	U.S.	1 OPV
1986	29	Nepal/Burma	U.S.	3 IPV; 1 OPV
1988	1	India	Canada	3 IPV
1993*	2	Nigeria	U.S.	0
1993	?	Netherlands	Canada	?
1996	15 mos	India	Canada	3 IPV

*Patient brought to U.S. for treatment after onset of disease abroad

SLIDE 5 INTESTINAL IMMUNITY
Children excreting virus after OPV administration (%)

Protected by:	Type I	Type II	Type III
3 OPV	4	3	10
2 IPV/ 1 OPV	27	11	54
3 IPV	18	54	78

Source: Modlin (1991)