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Vaccine Control of Poliomyelitis in the 1980s

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The main challenge of vaccine control of poliomyelitis in the 1980s is in the subtropical and tropical regions of the world where "lameness" surveys in recent years have shown how very high the average annual incidence of paralytic poliomyelitis can be in both rural and urban areas in the absence of epidemics. The procedures by which oral polio vaccine (OPV) *rapidly* eliminated all or almost all paralytic disease caused by polioviruses from the economically developed temperate climate countries have been inadequate in tropical and subtropical countries, except in some small countries with good health services, largely because there is much more year-round circulation of "wild" polioviruses which continue to produce the disease in the unvaccinated and incompletely vaccinated children. Not even a cheap, hypothetically 100 percent effective, one-dose vaccine could eliminate poliomyelitis in the tropics if, for a variety of reasons, it would reach only a portion of the infant population. Paralytic disease caused by polioviruses has been quickly eliminated from both small and large tropical countries by OPV in *well-organized* programs of *annual mass vaccinations* of almost all children under a certain age.

FOREWORD

In 1961, Dorothy Horstmann was the guest editor of a Festschrift for John R. Paul on the occasion of his retirement as chairman of the Department of Preventive Medicine of the Yale University School of Medicine. It was in this department, which Dr. Horstmann joined 40 years ago, that she has been making her outstanding contributions to our understanding of poliomyelitis and other human viral diseases. And now it is her turn for a Festschrift, in which I am happy to be one of the contributors and also to wish her many more years of happiness in her work and personal life.

The Yale Poliomyelitis Unit, with John R. Paul and James D. Trask, was founded in 1931, the year of severe poliomyelitis epidemics in New York City and New Haven, the year I graduated from the New York University College of Medicine, the year I began to work on poliomyelitis, the year I first met Paul and Trask, the year in which my own highly rewarding close relationship with these two outstanding investigators began. Shortly after Jim Trask's tragic premature death in May 1942, Dorothy Horstmann joined the Yale Poliomyelitis Unit—and we have shared common interests and a warm personal relationship ever since then. For some reason, I cannot forget one episode in 1943 when as a major in the U.S. Army, just returned from Egypt, I participated along with John Paul, Dorothy Horstmann, and other members of the club in a meeting of the Virus Commission of the Army Epidemiological Board. After the meeting we all went to dinner and enjoyed among other things dancing to good music. While Dorothy Horstmann and I were having fun on the dance floor, I was tapped on the shoulder by one of her young associates, a recently commissioned lieutenant, who said to me: "Major, take it easy." It has taken me a long time to heed his warning, but I am ready to do it now, and before I retire at the end of June 1982, I will speak my mind on "Vaccine Control of Poliomyelitis in the 1980s," the topic assigned to me by the Festschrift Committee.

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The issues and challenges in the prevention of persisting paralytic disease caused by polioviruses are different in the temperate climate countries with limited seasonal dissemination of polioviruses and in the subtropical and tropical countries with extensive year-round dissemination of polioviruses.

ISSUES AND CHALLENGES IN TEMPERATE CLIMATE COUNTRIES

Countries Using Exclusively Oral Polio Vaccine (OPV)

OPV has been used exclusively in temperate climate countries with a combined total population of almost 2,000 million people, including China, the USSR, the U.S.A., Japan, and many smaller countries in Europe, the Americas, and Oceania. The vaccination programs in these countries have varied considerably in the extent of vaccine coverage in initial national or regional mass campaigns for rapidly breaking the chain of transmission of "wild" polioviruses as well as in subsequent vaccination of the oncoming generations of children; the continuous importation of "wild" polioviruses from adjacent regions or countries has also varied. Accordingly, it is not surprising that the extent to which paralytic poliomyelitis caused by polioviruses has been controlled in these countries has also varied from complete since 1960 (e.g., Czechoslovakia, East Germany) and almost complete in recent years (e.g., U.S.A., Japan, most of the USSR, most European countries, Australia, New Zealand, etc.) to extensive reduction in much of China.

In the U.S.A., the average estimated number of nonpersisting and persisting cases of paralytic poliomyelitis was 135 per million total population per year during the pre-vaccine period of 1951–1955, an average of 26 mostly persisting paralytic cases per million total population per year during the five years of 1956–1960 when only inactivated polio vaccine (IPV) was used, and only an average of 4 per 100 million total population per year during the six years of 1973–1978, when only OPV was used [1]. The very small number of reported cases in 1973–1978 included imported cases as well as cases whose poliovirus etiology is, in my judgment, in doubt. My analysis of previously published data [2–4] indicated the dubious etiology of the rare "vaccine-associated," "family contact," "community contact," or "immunodeficient" cases. Recently I also reported the isolation of polioviruses from a variety of paralytic cases in Brazil, initially reported as poliomyelitis, and subsequently found not to be poliomyelitis, and indicated the clinical and clinical laboratory findings that are not compatible with a definite diagnosis of a paralytic disease as poliomyelitis [1]. The total number of *reported* cases for a total population of about 230 million was six in 1980 and six in 1981, i.e., an average of 2.6/100 million/year in the U.S.A.

It is noteworthy that this extraordinary elimination of paralytic poliomyelitis from the U.S.A. has been achieved despite (a) the large number of economically deprived one- to four-year-old children who have had no vaccine at all and the still larger number who had less than three doses [1] and (b) the continuous annual importation of "wild" polioviruses by thousands of Mexican families with small children.

If currently available more potent IPV would replace OPV in the U.S.A. as some are proposing [5], the benefits derived from the current break in the chain of transmission of imported "wild" polioviruses and from the contact immunization of unvaccinated children [1] would disappear in due time, and the unvaccinated and those who lost their IPV-acquired immunity would again face the danger of paralytic disease caused by polioviruses.

Countries Using Exclusively IPV

There is no question that more potent IPV, especially as used in multiple doses, in almost 100 percent of children in Sweden [6], Finland [7], and Holland [8] can protect against paralytic poliomyelitis caused by polioviruses. As I have previously pointed out [1] paralytic poliomyelitis did not disappear quickly in these countries as it did in many countries after the initial mass campaign with OPV, and the reason for the marked reduction or suggested complete elimination of circulating polioviruses is not entirely clear.

Thus, in Finland (population, 4–5 million) with extensive use of IPV since 1957, there were 302 paralytic cases reported in 1959, and 273 cases in 1960. And then, remarkably, no cases have been reported since 1964, despite the fact that an antibody survey in 1964–1966 showed that about 60 percent of children under three years of age, i.e., those born after the 1959 and 1960 epidemics, had no demonstrable antibodies to types 1 and 3 polioviruses [9]. According to Lapinleimu and Stenvik [7] although "97% of children have received complete primary vaccination" (vaccine used and potency not mentioned), a serological survey of preschool children in 1972–1974 showed that antibodies were not demonstrable for type 1 in 30–40 percent, for type 3 in 50 percent, and for type 2 in 10–20 percent. Moreover, the antibody titers before the booster dose at school entry were very low—"about 1:4 to type 3 and 1:8 to type 1." And yet an intensified search for polioviruses in 1972–1974 in 309 cases of aseptic meningitis, encephalitis, and transient paralysis, in fecal samples from 4,878 healthy preschool children, and in weekly samples of sewage from Helsinki yielded not a single poliovirus but many other enteroviruses. Lapinleimu and Stenvik [7] concluded: "Experiences in Finland show that low and even undetectable antibodies protect people from poliomyelitis and even eliminate polio viruses from the country, provided that nearly all children have been vaccinated." This conclusion on transmission of polioviruses and protection of children who lost IPV-induced antibody is not in accord with a great deal of data on the multiplication of OPV strains and naturally occurring polioviruses in persons with only IPV-acquired antibody or the occurrence of paralytic poliomyelitis in persons with four or more doses of killed vaccine (177 cases in 1959 in the U.S.A.). There must be some other explanations for these findings in Finland, among them that extensive rapid mass vaccinations with OPV in most of Europe by 1964 greatly reduced the introduction of "wild" polioviruses in neighboring countries.

The control of paralytic poliomyelitis in Sweden is unquestionably due to the extensive vaccination of nearly 100 percent of the susceptible age groups with many doses of potent IPV [6]. Although the antibody status of preschool children in Sweden is much better than in Finland, the remarkable disappearance of detectable polioviruses may have the same explanation as in Finland, and cannot be attributed to the IPV-induced antibodies [1].

In Holland, where nearly 100 percent of children (excepting certain religious groups) have for many years received many doses of more potent IPV [8], the average annual incidence of about 11 paralytic cases per 100 million during the ten-year period of 1966–1975 is about three times more than was reported in the U.S.A. during the six-year period of 1973–1978 [1]. Recent reports by Bijkerk et al. [10] and by Kapsenberg et al. [11] indicated that during the 1978 "wild" type 1 poliovirus epidemic in unvaccinated persons, fully vaccinated healthy schoolchildren also excreted the type 1 epidemic strain, and that type 3 and type 2 polioviruses were also being disseminated in Holland, as indicated by the finding of type 3 and type 2 an-

tibodies in 22 percent and 5 percent, respectively, of unvaccinated children of the religious groups opposed to vaccination. Yet, examination of 19,416 fecal samples from 0–4-year-old children *entering* kindergartens and day nurseries in Amsterdam over a period of 15 consecutive years (1963–1977), yielded 613 other enteroviruses but no polioviruses [11].

Since there are practically no unvaccinated children in Sweden and Finland, the more sensitive serologic survey test for dissemination of polioviruses cannot be used there. As part of a more detailed discussion of "herd immunity" in Sweden and Finland, I previously pointed out [1] that in the prevaccine era in Sweden, even a serologic survey of 200 children failed to detect dissemination of polioviruses for as long as five years after an epidemic.

ISSUES AND CHALLENGES IN SUBTROPICAL AND TROPICAL COUNTRIES

New Perspectives on Incidence of Poliomyelitis in the Tropics

Although it had long been suspected that the number of officially reported cases of paralytic poliomyelitis in the tropics was an inadequate measure of the real incidence of the disease, it was the "lameness surveys" in Ghana in 1974 [12,13] that first indicated the real magnitude of the problem of persisting paralytic poliomyelitis in rural and urban areas in the absence of epidemics. The *minimal* average, annual incidence of 235–280 cases of *persisting* paralytic poliomyelitis per million total population, which could be estimated from the prevalence of residual paralytic poliomyelitis in Ghana, was much higher than the average annual rate of 135 reported cases of persisting and nonpersisting cases per million in the last five years (1951–1955) of the prevaccine era in the U.S.A. [1] and of 170 per million in Sweden [6]. Subsequent surveys for residual paralytic poliomyelitis in Burma, Egypt, Philippines, Thailand, Indonesia, Malawi, Ivory Coast, and Brazil (summarized in [1]) and also in India, Yemen, United Republic of Cameroon, and Niger, reported in the World Health Organization *Weekly Epidemiological Record* of 1981 (56:131, 297, 397) and 1982 (57:4), have yielded varying but similar results. These accumulated data have demolished the old dogma about poliomyelitis in the tropics (still being repeated by experts), i.e., that while the infection rate with polioviruses was high the paralytic rate was low, and that an increased incidence of the paralytic disease was related to emerging epidemics and an improvement in the standard of living reflected in diminishing infant mortality rates.

These new data have shown us in a most vivid manner that the main challenge to the vaccine control of paralytic poliomyelitis caused by polioviruses in the 1980s is in the subtropical and tropical regions of the world, where the major part of the world population lives in poverty, and where shortage of food, inadequate housing, water supplies, sanitary facilities, and sewage disposal are the main causes of poor health and debility; i.e., the part of the world that presents the greatest challenge to advance public health by the simplest possible procedures before economic development makes it possible to copy the procedures of the economically developed countries in the temperate climate zones.

Vaccine Control of Poliomyelitis in the Tropics and Subtropics

In some small subtropical and tropical countries, e.g., Puerto Rico, Panama, Singapore, and Hong Kong, with good health services, good control of poliomyelitis has been achieved by extensive routine vaccination of almost all children with OPV.

In 1979, I analyzed the problem of elimination of paralytic poliomyelitis caused by polioviruses from econmically underdeveloped countries with inadequate health services and concluded that the problem was administrative and not immunological or epidemiological [14]. It was evident that the problem was not with the immunogenicity of OPV in these countries, as was assumed by the investigators who were selected to participate in the 1980 International Symposium on Reassessment of Inactivated Poliomyelitis Vaccine in Bilthoven, Holland [15], but rather that the procedures of using OPV that were so highly effective in the temperate climate countries had to be modified in parts of the world where paralytic polioviruses are propagating throughout the year in a very large proportion of the infant population, even as early as the first month of life. It became evident to me almost 20 years ago that initial mass vaccination programs with OPV followed by routine vaccination concurrently with other vaccines routinely administered as part of regular health care during the first year of life which brought about such dramatically rapid elimination of the disease in many large and small temperate climate countries, had only a temporary impact in tropical countries, largely because a *single* mass campaign reaching even 90 percent or more of susceptible children only temporarily suppresses the circulation of "wild" polioviruses and also because subsequent routine vaccination programs at best reached only 20–40 percent of the total infant population. Under such conditions, even a hypothetical vaccine that would provide lifelong immunity in a single dose to 100 percent of children receiving it early in life could at best only reduce the incidence of the disease.

Twenty years ago, Cuba was the first country to introduce the procedure of national, annual mass vaccination campaigns with OPV on two Sundays of the year of all children under five years of age, regardless of how many doses they may have had before, with a rapid and lasting elimination of the disease [16]. In 1968, Dorothy Horstmann and I, as consultants to the Pan American Health Organization, recommended a similar program for other Latin American countries, but despite my repeated recommendations [3,14] Brazil and Mexico have only recently adopted this procedure. The particular point in such *annual* national mass vaccinations with OPV is not only that the special organization of large numbers of nonprofessional personnel makes it possible to reach an extraordinarily high proportion of all children even in remote areas of large countries, but that most of the vaccination is carried out in one or two days which rapidly establishes a dominant circulation of the attenuated vaccine strains in the community [17]. When vaccination of children is spread out over a long period of time, as each one reaches the age of routine vaccination, the "wild" polioviruses and other enteroviruses that are so extensively disseminated in subtropical and tropical regions remain the dominant viruses in the community. This is another reason why the World Health Organization Expanded Immunization Programme, which is patterned after polio immunization programs of the temperate climate, developed countries will remain only partly effective in the undeveloped, tropical countries, even after the goal of routine vaccinations of a larger proportion of the children has been achieved.

In 1980 and 1981, Brazil has shown how a geographically huge country can successfully organize a huge, standing army of nonprofessional volunteers to bring OPV to almost all children under five years of age (over 18 million) in annual, national mass campaigns carried out almost entirely on a single day twice a year, with an interval of two months. The 1980 program was carried out in June and August, and the 1981 program in August and October. There was a precipitous drop in reported cases [18]. A personal analysis of the small number of cases reported in five

months after the 1980 campaign showed that 76 percent were not compatible with a clinical diagnosis of paralytic poliomyelitis by strict criteria, and that many paralytic cases which clinically were not poliomyelitis excreted polioviruses in their feces and had evidence of concurrent infection with polioviruses [1]. In August 1981, I analyzed the 35 cases that had been reported since the beginning of the year in the states of São Paulo, Minas Gerais, and the Distrito Federal before the second national campaign, and found that, with the possible exception of one case of transitory paralysis, the other paralytic cases did not fulfill the strict criteria for a clinical diagnosis of poliomyelitis (unpublished observations). In Mexico, there were five-day national mass vaccination campaigns in 1981 and 1982 which reached about 80 percent of children under five years of age (personal communication from Dr. Jorge Fernandez de Castro, Director General of Epidemiology, Ministry of Health, Mexico). In June and August 1982, Brazil again vaccinated most of the children under five years of age.

In subtropical and tropical countries there are many more paralytic conditions that clinically closely resemble poliomyelitis but which pathologically are not and which exhibit certain clinical and clinical laboratory findings that can distinguish them from paralytic poliomyelitis caused by enteroviruses [1]. In 1969, my associates and I [19] reported that in Mexico 45 percent of 57 fatal cases of paralytic disease, clinically diagnosed as paralytic poliomyelitis, were found not to be poliomyelitis but three varieties of noninflammatory pathological neuronal syndromes—Guillain-Barré infectious polyneuritis (10 cases), cytoplasmic neuronopathy (8 cases), and nuclear neuronopathy (7 cases) with type 1 poliovirus in the feces and intestinal tract of one of the latter. In 1971, Valenciano et al. [20] described an outbreak of 25 cases of lower motoneuron paralytic illness *without fever, pleocytosis, or increased CSF protein* in Albacete, Spain. Postmortem findings in three of the five fatal cases also showed no inflammatory reaction in the nervous system, with changes comparable to cytoplasmic neuronopathy in at least one case. It is noteworthy that while the surviving patients ultimately recovered completely without atrophy, it occasionally took eight to ten months, with slight muscle weakness and hyporeflexia still being present in a few one year after onset.

It is clear, from what has just been said, that as paralytic poliomyelitis caused by polioviruses is increasingly controlled by vaccination, reported cases of lower motoneuron paralytic disease, with and without pleocytosis, must be carefully analyzed, and that the mere isolation of a poliovirus (vaccine-like or nonvaccine-like) can no longer per se constitute evidence of its etiologic relationship to the paralytic disease. It is also clear that cases of lower motoneuron paralytic disease which occur in children who have had multiple doses of either IPV or OPV or both are very likely not to be paralytic poliomyelitis caused by polioviruses. I can never forget a front-page story in a 1963 Colombo, Ceylon (Sri Lanka) newspaper which, during a severe polio epidemic, asked what good are polio vaccines when a rich man's child who had seven doses of Salk vaccine and five doses of Sabin vaccine can die of the disease. It turned out that she had died of Guillain-Barré syndrome with typical albuminocytological dissociation.

Use of Highly Immunogenic Potent IPV for Elimination of Paralytic Poliomyelitis in the Tropics

There is no question that more potent and very much more expensive IPV can be highly immunogenic and after multiple doses can produce very high titers of antibody that will persist for longer periods of time. However, as long as a large propor-

tion of children receive either no vaccine at all or only one dose, IPV cannot be expected to accomplish more than OPV and, for a variety of other reasons, not as much. Melnick's recent recommendation [21] that multiple doses of IPV and OPV be used in routine vaccination as a means of eliminating paralytic poliomyelitis in the tropics is, in my judgment, based not only on an improper evaluation of the continuing greater incidence of paralytic disease among Arab children in Israel, the West Bank, and the Gaza strip than among Jewish children in Israel, but also on a disregard of the procedure by which OPV produces its maximum effect in such populations. He also failed to appreciate the impracticality of his proposal for impoverished populations with limited health services.

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