MEASLES VACCINATION

Before the Measles-Mumps-Rubella Vaccine

Jan Hendriks, MSc, and Stuart Blume, PhD, MA

At the beginning of the 1960s, it was clear that a vaccine against measles would soon be available. Although measles was (and remains) a killer disease in the developing world, in the United States and Western Europe this was no longer so. Many parents and many medical practitioners considered measles an inevitable stage of a child's development. Debating the desirability of measles immunization, public health experts reasoned differently. In the United States, introduction of the vaccine fit well with Kennedy's and Johnson's administrations' political commitments. European policymakers proceeded cautiously, concerned about the acceptability of existing vaccination programs. In Sweden and the Netherlands, recent experience in controlling polio led researchers to prefer an inactivated virus vaccine. Although in the early 1970s attempts to develop a sufficiently potent inactivated vaccine were abandoned, we have argued that the debates and initiatives of the time during the vaccine's early history merit reflection in today's era of standardization and global markets. (*Am J Public Health*. 2013;103:1393–1401. doi:10.2105/AJPH.2012.301075)

EXAMINING THE INTRODUCTION of four pediatric vaccines (diphtheria antitoxin and the pertussis, polio, and measles vaccines), Baker has argued that the middle years of the 20th century displayed distinctive national styles of vaccine innovation[1]: whereas US vaccine development and implementation were marked by a "current of urgency," the more cautious British set much higher standards for the evidence required to prove the safety and effectiveness of a new vaccine before deciding on its introduction. This, in turn, could be attributed to the influence that the statistical pioneers of the randomized clinical trial had gained in Britain. We have looked in detail at the introduction of the measles vaccine, focusing not only on the United States and Britain but on two other European countries (the Netherlands and Sweden) as well.

Responses to the development of the first measles vaccines confirm Baker's contrast between American and British styles, the one marked by a sense of urgency, the other by a cautious insistence on randomized trial data. But our analysis suggests that, in addition, two other considerations influenced policymakers: one was the national experience with polio vaccination just a few years previously, which differed in these four countries; the other was the European public health authorities' concern with the implications of introducing a new vaccine for the national immunization program, as a whole, and for popular confidence in it, in particular.

THE SEARCH FOR A MEASLES VACCINE

By the early 1960s the epidemiology of measles was well understood. It was known that the disease occurred throughout the world, generally in regular periodic cycles. With the exception of

some isolated population groups, almost all children contracted measles before they reached adolescence. No nonhuman sources of infection were known.[2] By 1960, thanks to the use of antibiotics and improvements in living conditions, measles mortality was declining steadily in industrialized countries (although not in the developing world). For example, in the United Kingdom deaths from measles had fallen from 307 in 1949 to 98 in 1959.[3] Parents largely came to see measles as an unpleasant, although more or less inevitable, part of childhood. Many primary care physicians shared this view.

"The situation in the early 1960s was thus that live attenuated vaccines appeared to offer long-term protection against measles. Their side effects, however, were a matter of concern, and attempts to develop further attenuated, less reactogenic strains continued."

In the early 1960s researchers in numerous US and European laboratories were, nevertheless, trying to develop a measles vaccine. Building on their earlier success with the poliovirus, in 1954 John Enders and his Harvard colleagues succeeded in culturing the measles virus. Because their initial sample was taken from a boy named David Edmonston, the strain became known as the Edmonston strain. By 1960, Katz, Enders, and Holloway had shown that their Edmonston strain, suitably attenuated, stimulated production of measles antibodies in susceptible children.[4]

Because it was found to be too reactogenic, Enders and his colleagues set about attenuating it further. Enders wanted to encourage other investigators and made the strain freely available. Very soon numerous other researchers (including Anton Schwarz at American Home Products and Maurice Hilleman at Merck) were also working at attenuating it further.[5] In addition, inspired by Salk's earlier development of an inactivated polio vaccine, other laboratories were developing inactivated (killed virus) vaccines. One or more safe and effective vaccines seemed within reach. But were they needed and would they be used? Although measles claimed the lives of 1 to 2 million children annually in developing countries, few of these countries had adequately organized immunization programs at this time.[6] In the United States and Western Europe, which did, measles mortality was low and declining and parents seemingly accepted it as an unpleasant part of childhood. What reasons could there be for introducing a measles vaccine?

In March 1963 the first two measles vaccines were approved for use in the United States: a live vaccine produced by Merck (*Rubeovax*) and a formalin-inactivated one produced by Pfizer (*Pfizer-Vax Measles–K*).[7] In September 1963 the US Surgeon General Luther Terry published a statement on the status of measles vaccines.[8] The live vaccine had by this time been given to some 25 000 people in the United States. A single dose produced an effective antibody response in more than 95% of susceptible children—a response that trials had shown persisted for at least three years. Although 30% to 40% of these children showed signs of temporary high fever and a rash after vaccination, side effects could be reduced by coadministration of γ globulin. The inactivated vaccine was generally administered, in field trials, on a three-dose monthly schedule. Although this produced no side effects, antibody levels were lower than with the live vaccine, and it was not known whether they persisted beyond six months.[9] A combined schedule had also been tried. If a dose of inactivated vaccine was given a month or so before the live vaccine, reactions caused by the live vaccine were greatly reduced. The surgeon general recommended that children without a history of measles be immunized at approximately aged nine months.[10] There seemed to be no reason to begin a mass immunization program; the decision to immunize could be left to individual medical practitioners and parents.

The situation in the early 1960s was thus that live attenuated vaccines appeared to offer long-term protection against measles. Their side effects, however, were a matter of concern, and attempts to develop further attenuated, less reactogenic strains continued. (The Schwarz strain would be licensed in 1965, and Merck's more attenuated "Moraten" strain in 1968.) Inactivated vaccine produced no side effects, but it was unclear whether it could provide protection of adequate duration. If protection was of too short duration, there was a risk of measles infection being postponed to an older age, when its effects could be more serious.

US AND UK IMMUNIZATION POLICY, 1963–1968

Any decision to begin mass measles vaccination in the early 1960s thus involved numerous

uncertainties. Was the disease serious enough? Would parents feel it worth having their children vaccinated? And if mass vaccination did seem justified, should the live or the killed vaccine (or a combination of both) be used? In the United States, experience with the polio vaccines played a major role in shaping the consensus that gradually emerged.

Colgrove has explained how, after an initially euphoric response to the Salk vaccine, demand in the United States for the polio vaccine fell rapidly.[11] By the late 1950s polio was again on the rise, with cases now concentrated in socially deprived areas with large numbers of unvaccinated people.[12] Overcoming this problem seemed more feasible with the live Sabin vaccine, which required just one drop in place of the three Salk vaccine shots. It also fitted well with the priorities of the administration of President John F. Kennedy, who took office in 1961.

In 1962 Congress passed the Vaccine Assistance Act, which authorized financial assistance to states specifically for vaccination programs against polio, diphtheria, whooping cough, and tetanus.[13] In 1965, when this act came up for renewal, officials were anxious to avoid the socioeconomic disparities in coverage that had emerged with polio and that were now appearing with measles vaccine coverage. An amendment to the act added measles to the diseases for which federal subsidies were available.

> As the problem of infectious disease became increasingly coterminous with the issue of socioeconomic disadvantage, the federal war on poverty provided an ideal conceptual framework for the fight that would soon be launched against measles.[14]

Approximately 15 million children were given one of the new measles vaccines starting with their licensing in 1963 and continuing until mid-1966, and the reported incidence of the disease fell by half.[15] On the basis of this success, with material and financial support from the Centers for Disease Control and Prevention, and inspired by the social and political climate of the time, in 1967 a campaign was launched to eliminate measles from the United States. "To those who ask me 'Why do you wish to eradicate measles?'" wrote Alexander Langmuir, chief epidemiologist at the Centers for Disease Control and Prevention from 1949 to 1970,

> I reply with the same answer that Hillary used when asked why he wished to climb Mt. Everest. He said "Because it is there." To this may be added, ". . . and it can be done."[16]

Some were skeptical, notably the eminent bacteriologist René Dubos, but President Lyndon B. Johnson gave the program his support.[17] Rapid success was anticipated:

> The availability of potent and effective measles vaccines, which have been tested extensively over the past 4 years, provides the basis for the eradication of measles in any community that will raise its immune thresholds to readily attainable levels. Effective use of these vaccines during the coming winter and spring should insure the eradication of measles from the United States in 1967.[18]

Some 11.7 million doses of measles vaccine were distributed in 1967–1968, and the estimated number of cases of measles fell from 900 000 to 250 000. However, because budgetary politics subsequently led to fluctuating federal support for community-based immunization programs, the expectation that measles would soon be eradicated was to prove wildly overoptimistic.[19]

In the United Kingdom it took longer for a consensus regarding the desirability of measles vaccination to emerge. As the editor of the *British Medical Journal* warned in 1962,

> There is a real danger that the general public may become weary of the ever-increasing number of immunizing injections which are being urged upon their children. The administration of this [inactivated] vaccine would require three further injections. Measles is often regarded as a normal part of childhood development, and though this view is misguided parents may not easily be persuaded to depart from it.[20]

D.L. Miller of the UK Central Public Health Laboratory Service's epidemiological section[21] was among those arguing most forcefully for mass measles immunization. A large-scale survey of general practitioners and hospitals had shown that "serious complications of measles are commoner than is generally supposed."[22] In an average epidemic year, more than half a million notified cases of measles could be expected in England and Wales. Extrapolating on the basis of the survey, 35 000 patients with serious complications could be expected, of whom 6000 would be hospitalized.[23] As a percentage, this was small, but the numbers were considerable and represented a significant burden to families and to the state. It seemed unlikely that further reductions in measles morbidity could be expected from improvements in hygiene, nutrition, or housing.

> Further advance is likely to come only from prevention of the disease by immunization,

> and on the available evidence this would seem to be well worth doing.[24]

The editor of the *BMJ*, commenting on the survey, was not convinced: "Does this present survey . . . add up to a strong argument for mass vaccination as Miller argues?"[25] There were other factors that would have to be considered, such as the reactions the child might suffer from currently available vaccines. How often would the doctor have to see vaccinated children when they had a severe reaction? What if immunity was short lived? According to the editorial,

> [it] would be tragic if its action was merely to postpone an attack of measles into the age-group when complications such as encephalitis would be common.[26]

The editorial ended,

> In Great Britain at the moment it is not necessarily logical to say, "We can produce a vaccine; let us therefore use it."[26]

The editor of the *The Lancet,* however, reviewing the evidence reported by Miller, was convinced that measles should be prevented,

> not only as Langmuir has said "because it is there and it can be done," but also because of the toll it takes in human misery.[27]

Still, even if it was agreed that measles vaccination was desirable, the question of how it should be done remained open. On this the editors of the two journals agreed. The live vaccine was problematic by virtue of the side effects it often produced, whereas protection provided by the inactivated vaccine was of questionable duration. However, there was the possibility that a more powerful inactivated vaccine would be developed

> and work along these lines as is being done in Sweden, where success has clearly been achieved in eliminating poliomyelitis by the use of killed polio vaccine.[28]

British experience with the polio vaccines had led to a clear preference for the live (Sabin) vaccine by 1964.[29] But because hard evidence relating to measles specifically was felt to be needed, in early 1964 the Medical Research Council (MRC) started a study of measles vaccines. A preliminary study among children aged 10 to 18 months involved the comparison of four schedules. Two groups of children received a highly attenuated strain produced either by Glaxo or by Wellcome Research Laboratories, and two groups were given the Pfizer killed vaccine before one of the live vaccines.[30] The study focused only on short-term clinical and serological responses. It was found that although all four schedules were "acceptable and practical," children on the single-dose schedule seemed on average to have higher antibody titers.

Why this should be was unclear and needed to be studied further, especially because other investigators had reached the opposite conclusion. A large-scale trial began later in 1964. Meanwhile, although the various vaccines were available for doctors to use at their discretion, there was as yet no national policy. In a letter to doctors dated February 21, 1966, the Ministry of Health left the choice of vaccine to the individual physician.[31]

In 1965 the first reports of a strange measles-like illness in children exposed to natural measles after receiving the inactivated vaccine appeared in the United States,[32] and it appeared that this could also occur when live vaccine was administered after inactivated vaccine. There was a growing sense, internationally, that the inactivated virus vaccine should be avoided.[33] In August 1967 a letter from Vincent Fulginiti, a specialist in pediatric infectious diseases at the University of Colorado, appeared in *The Lancet.*[34] He and his colleagues had started trials using three doses of killed vaccine (KKK schedule) and two doses of killed plus one live attenuated vaccine (KKL schedule) some years earlier. Results showed that in some of the children on the KKK schedule, immunity waned after six months:

> We are receiving increasing reports of natural disease in both the KKK and KKL vaccinees. In addition, 10 of these vaccinees, all of whom have required admission to hospital, have had a new disease which we have termed "atypical measles."[35]

How this came about was not understood.

In May 1968 a second report of the MRC measles vaccine trial was published.[36] This trial involved more than 36 000 children, aged from 10 months to 2 years, across Great Britain. Some children were assigned to a control group and received no vaccine, whereas others in the trial received either a single dose of Glaxo's live attenuated (Schwarz strain) vaccine or a single dose of the Pfizer killed vaccine followed one month later by a single dose of the live vaccine.[37] Both schedules were found to give good protection in the first nine months. With time, however, differences appeared. After two years the single-dose schedule produced a higher degree of protection (95%) than did the

double-dose schedule (89%). The MRC concluded that "there is a strong case for the use of live measles vaccine alone." Not only did this give a higher degree of protection, but it also had the additional advantage that only a single injection was required.

> It is desirable, however, that parents should be informed that live vaccine alone sometimes induces a febrile disturbance or a mild measles-like illness which is non-infectious, to avoid undue concern if such reactions should occur.

No case of the atypical measles Fulginiti reported was found.

> Such reactions, which have been reported entirely from the USA, have so far occurred only in children who have had repeated doses of killed vaccine. They have not been observed in any of the children in the British trial in which only one dose of killed vaccine was given and was followed after a relatively short period of a month by live vaccine. Nevertheless, it would be wise not to use killed vaccine at all until more information is available about the mechanism of such reactions and how they can be avoided.[38]

Meanwhile, in November 1967, the Joint Committee on Vaccination and Immunisation, the British government's principal expert advisory body on vaccination policy, recommended that all children aged one year and older who had not had measles and had not been vaccinated should be offered live attenuated vaccine.[39] The recommendation was accepted, and in February 1968 local health authorities were informed. In 1968, by which time the inactivated vaccine had been withdrawn in the United States,[40] the mass vaccination campaign using live vaccine began in Britain.[41]

Although the duration of protection was still uncertain, the MRC trials using the Schwarz strain suggested that immunity lasted for at least two years. This was likely to be true also of the other attenuated vaccine then available in Britain, Wellcome's Beckenham-31. The editor of *The Lancet* agreed that the killed vaccine then available offered protection that was too short lived to be of value, and when used before an attenuated vaccine there was the possibility of unusual reactions. Although it was possible that a more satisfactory killed vaccine would be produced, "killed measles vaccine of the type made so far is clearly unsatisfactory and it is no longer available in Britain."[42]

THE SEARCH FOR AN IMPROVED INACTIVATED VACCINE

Unlike Britain, the United States, and virtually all other countries, the Netherlands and Sweden had successfully controlled polio with Salk's inactivated vaccine (IPV) and had not switched to the Sabin vaccine. Influenced by this experience, vaccinologists in both countries had a clear initial preference for an inactivated measles vaccine. As Sven Gard, professor of virology at the Karolinska Institute in Stockholm, told an international conference on measles vaccine in 1964,

> In my opinion the use of live vaccines should be avoided if possible. By introducing an autonomous organism in the individual a reaction-chain is initiated which we probably are unable to control in all conditions. The immediate consequences may seem harmless, but a cytopathogenic agent does not disappear without leaving traces. . . .
>
> In the controversy between living and inactivated poliovirus the axiom was that this goal would not be obtained with dead virus alone. In Sweden however, it appears that 7 years after application of IPV neither the diseases nor the virus seem to occur. Hopefully we shall see the same development with the use of inactivated measles vaccine.[43]

Gard's research assistant and later successor Erling Norrby had started research on inactivated measles vaccines in 1959. Whereas the Pfizer vaccine was grown in a culture of monkey kidney cells, Norrby used dog kidney cells and, crucially, a different inactivation method. Rather than using formalin as researchers in the United States were doing, Norrby inactivated the virus with an organic solvent, Tween 80 and diethyl ether (TE). This treatment caused disintegration of the virus, and the Swedish researchers' objective was a measles vaccine consisting only of a purified hemagglutinin (a surface protein of the virus).[44] The expectation was that this process would remove the sensibilizing agents responsible for the strange reactions observed in the United States. Tests in guinea pigs showed that vaccines inactivated in this way were three to four times more potent than were those inactivated with formalin. A series of studies designed to analyze the possible usefulness of a killed measles vaccine for elimination of measles began in Sweden.

In 1965 Norrby justified working on inactivated virus vaccine by referring to earlier experiences with polio vaccines:

> The killed measles vaccines are generally supposed to give immunity quantitatively and qualitatively inferior to that after natural measles. For this reason they are usually recommended

> for use only in combination with live vaccine. Similar arguments were raised against inactivated and for live poliovirus vaccines. However, the excellent results achieved in the Scandinavian countries with inactivated poliovirus vaccine appear to invalidate those arguments, and for this reason it would seem unwise to discount inactivated measles vaccines before they have been given a fair trial.[45]

In an initial study, Swedish children who had previously received three monthly doses of the Pfizer inactivated vaccine were revaccinated 22 to 23 months later, either with a fourth dose or with the new TE-inactivated preparation. They were then followed for a further 8 months and then tested after 18 months and after 29 months. In a second study children were given either three monthly doses of formalin-inactivated vaccine plus a booster of TE vaccine 17 months later, or they were given three monthly doses of TE vaccine and, again, a TE booster after 17 months.[46] These children were followed for three years after the final booster.

Initial results with the TE-inactivated vaccine were promising:

> The mean haemagglutination-inhibition titer eight months after revaccination was 600 in the group of children given formalin-killed vaccine, and 7800 in the group given Tween-ether vaccine.[47]

However by 1969 despite "theoretical advantages," earlier promise seemed not to be borne out. The antibodies induced by the killed virus vaccine seemed to be of low protective value, and it was becoming clear that intact surface antigens other than hemagglutinin would have to be included in a killed virus vaccine. It was not known what these were or how they should be isolated. Norrby et al. concluded, "In the present situation inactivated measles vaccines cannot be recommended for general use."[47,48] In 1971 Sweden began mass measles immunization using the live vaccine.

Like their Swedish colleagues, Dutch investigators preferred an inactivated vaccine. In the Netherlands too, polio had been successfully controlled with IPV.[49] This was done by adding IPV to the diphtheria-pertussis-tetanus (DPT) vaccine already in use, thereby avoiding disruption of the national immunization program. The country's high immunization rate (more than 95%) was attributed to the simplicity of the immunization schedule used. When work on development of a measles vaccine began at the Dutch Institute of Public Health (Rijksinstituut voor Volksgezondheid [RIV]) in 1964, the intention was to replicate the earlier strategy.[50]

In 1965 Merck's subsidiary in the Netherlands (MSD) requested permission to import the company's live measles vaccine. Obliged to respond to this request, in October 1965 the minister of health turned to the health council (Gezondheidsraad) for advice.

Meanwhile, RIV intensified its contacts with two European manufacturers working on Tween-ether inactivated vaccines: first Glaxo in the United Kingdom (where John Beale was working on a TE-inactivated vaccine in parallel with the company's work on attenuated vaccine)[51] and subsequently Behringwerke in Germany. This company had developed a pentavalent combination vaccine (Quintavirulon), including an inactivated measles strain (Marburg) that it claimed was less reactogenic. In the late 1960s RIV considered using this Marburg virus strain, and a provisional licensing agreement with Behringwerke was drafted in 1969. However, Quintavirulon seemed less potent and produced more side effects than did the combination that RIV itself was developing, and this collaboration also ended. RIV finally decided to use a TE-treated measles seed strain obtained from Norrby in Sweden. They set about combining this with the tetravalent DPT-IPV combination vaccine that had become the cornerstone of the Dutch National Immunization Program. By 1967 a production process and the necessary controls had been established.[52]

In December 1967 the health council published its report on measles vaccines.[53] The council's view was that although measles vaccination should eventually be included in the National Immunization Program, it was not yet the time to do so. It was still unclear which vaccine was to be used, how it was to be used, or how disruption of the National Immunization Program could best be avoided. The council therefore recommended that further studies, particularly of the inactivated vaccine, be carried out before any definitive decision was made. Meanwhile, import of both live and inactivated vaccines should be permitted and the decision to use one or the other left to the individual medical practitioner.

As measles vaccines then became available, medical practitioners needed guidance on their use. Unlike in the United Kingdom, there had been relatively little discussion of measles vaccination in the Dutch medical press, and (also unlike in the United Kingdom) physicians at this time were not obliged to report cases of measles. The principal source of information

was a national survey of general practitioners conducted under the auspices of the Dutch Association of Family Doctors (Nederlands Huisartsen Genootschap). Between October 1965 and April 1966, the 247 physicians who responded had seen 10 700 cases of measles.[54] The authors of the study estimated that approximately 16.1% of children contracting measles were likely to show some complications. Extrapolating, some 2700 children would be seen by a specialist and 900 admitted to a hospital.

In October 1968 the head of the RIV's epidemiology department published a long article in the main Dutch medical journal.[55] Polak explained to doctors that whereas the application of a safe and effective vaccine would yield considerable benefit, the relative advantages of the attenuated and killed vaccines were still unclear. The Schwarz vaccine had been shown effective elsewhere and with few side effects, and its use certainly merited consideration in the Netherlands. There were also inactivated vaccines that were produced by inactivation either with formalin or Tween 80 and ether.

> Inactivated vaccines can provide good protection against measles, in any event in the short term and after repeated application.

A mixed schedule was also a possibility, although (for unknown reasons) this had sometimes led to serious reactions.

> It is conceivable that these complications, associated with use of inactivated vaccine, can be avoided by the correct choice both of vaccine and of mode of delivery.[55]

Because at the time these conditions were not known, use of the (commercially available formalin-)inactivated vaccine was not advisable. It remained to be seen whether a different inactivated vaccine might eventually prove of value. Individual use of the vaccine was advisable: the consequences of vaccination were far less than of the disease itself. But introducing measles vaccination into the National Immunization Program raised additional questions. From this viewpoint, combining measles vaccine with existing combinations had major organizational advantages. The overall success of the National Immunization Program was crucial.

One must consider whether those caring for the child will readily accept prevention of what is generally an unproblematic illness and/or whether this could lead to resistance against vaccination and attendance at the children's clinic.[55]

As experience with the use of the vaccine accumulated, parents as well as doctors would be able to form an opinion regarding the burden associated with the effects of the vaccine. This would aid preparation for large-scale application in the framework of the existing national vaccination program.

The director general of RIV wrote to the state secretary for health explaining the progress of the pentavalent combination vaccine project. Particular attention was being paid to the risk of adverse effects of the kind reported in the United States, although no such reactions had been observed in Europe when (purified) TE vaccines had been used. Live attenuated vaccines were being used effectively elsewhere, and side effects were now far less a problem than they had been, but their inclusion in the National Immunization Program would be more challenging than would an inactivated vaccine.

> Development and production of an inactivated measles vaccine will increase the chance that the number of injections in the program remains limited or more spread.[56,57]

In August 1970, the RIV was ready to begin a clinical trial. Permission was sought from the Dutch regulatory authority. "We think this is justified," wrote the new director general, "despite the adverse events as reported in the literature after administration of a killed measles vaccine from an American firm."[58] Using killed vaccine from another supplier (Behringwerke), these side effects did not appear. In 1971 the trial began, with 1207 children enrolled.

Children placed in one arm of the trial were given Merck's live *Attenuvax* at 12 months, whereas those in the other arms received either four doses of one of the inactivated (pentavalent DKTP-M) vaccines at 3, 4, 5, and 12 months or three doses of one of the DKTP-M vaccines followed by one dose of live vaccine at 12 months.[59] Clinical data were collected till about two years after the fourth injection. No case of atypical measles was found, there was no interference between the component antigens, and there were no side effects. However, the results clearly showed that antibody titers declined rapidly in children given either of the preparations containing an inactivated vaccine. The conclusion was now inescapable, and the fate of the inactivated measles vaccine approach in the Netherlands sealed.[60] In 1973 the decision was taken to stop the program. In 1974 live *Attenuvax* was purchased from Merck, and in 1976 mass measles immunization began in the Netherlands.

CONCLUSIONS

Our comparison of the beginnings of mass measles vaccination in the United States and in Great Britain bears out Baker's allusion to two distinctive styles of vaccine innovation. Pursuing its war on poverty and concerned by socioeconomic disparities in infectious disease incidence, the Johnson administration in the United States made federal funds for measles vaccination available starting in 1965 and embarked on a measles eradication campaign in 1967. The British, more cautiously, established a large-scale clinical trial to establish the relative benefits of the different available vaccines and possible immunization schedules. Parents, it was hoped, would gradually come to accept the desirability of vaccinating against what was widely seen as an unpleasant, although inevitable, childhood illness.

Maintaining popular confidence in the country's immunization program had to be given due weight when introduction of a new vaccine was under consideration. Mass measles immunization began in Britain in 1968. In Sweden it began in 1971 and in the Netherlands not until 1976. These delays reflect not only the greater British caution to which Baker refers but also a concern in all three countries about the implications for a national immunization program as a whole. There was a fear that introducing a vaccine most parents did not see as needed could undermine popular confidence.[61]

The Dutch and Swedish cases show something else as well. Both countries, unlike the United States and Britain, succeeded in controlling polio using Salk's

inactivated virus vaccine despite almost universal skepticism elsewhere. This very recent experience led virologists in both countries to prefer, and to continue to develop, inactivated measles vaccines long after their US and British counterparts had rejected them. Unlike in the United States and the United Kingdom, the issue in the Netherlands was not choosing between commercially available alternatives. As a public sector institution, RIV was responsible for providing the vaccines to be used in the National Immunization Program. It could do this by developing and producing them itself or, when appropriate, by purchasing them from a commercial supplier.

In its work on a measles vaccine, conducted from 1964 to 1972, RIV was trying to develop the vaccine that could best—effectively and safely but also with minimal disruption—be accommodated in the National Immunization Program. Following the strategy that had been so successful in the case of the polio vaccine, this was attempted by combining an inactivated measles vaccine with the existing DPT-P. The significance of these efforts, we suggest, is not that they ultimately failed; it is to remind us of an approach to vaccine development, taking the needs of a national immunization program as its starting point, which in the past three decades has all but vanished. Vaccine development and production in public sector institutions such as RIV, tailored in the first instance to national health care needs and only in the second instance to market opportunity, has come to seem an anachronism. Although local vaccine producers are now accepted as having an important role to play in ensuring adequate vaccine supplies,[62] the wider relevance of the few remaining public sector vaccinology institutes' (e.g., in Brazil and in Cuba) distinctive approach to innovation is rarely acknowledged.[63] ■

About the Authors

Jan Hendriks is with International Support, Vaccinology Unit, National Institute of Public Health and the Environment, Bilthoven, the Netherlands. Stuart Blume is with the Department of Sociology and Anthropology, University of Amsterdam, Amsterdam, the Netherlands.

Correspondence should be sent to Stuart Blume, University of Amsterdam, o.z. Achterburgwal 185, 1012 DK Amsterdam, The Netherlands (e-mail: s.s.blume@uva.nl). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This article was accepted September 6, 2012.

Contributors

J. Hendriks was responsible for archival research in the Netherlands and participated in collection and review of secondary sources. S. Blume participated in collection and review of secondary sources and in drafting the article.

Acknowledgments

The authors would like to thank Suzette Westling for research assistance, Hans Cohen and Rob van Binnendijk for advice, and Christoph Gradmann and William Muraskin for comments on an earlier version of this article.

Endnotes

1. J.P. Baker, "Immunization and the American Way: 4 Childhood Vaccines," *American Journal of Public Health* 90, no. 2 (2000): 199–207.

2. D.J. Sencer, H.B. Dull, and A.D. Langmuir, "Epidemiological Basis for Eradication of Measles in 1967," *Public Health Reports* 82, no. 3 (1967): 253–256.

3. "Editorial: Vaccination Against Measles," *British Medical Journal* 2, no. 5262 (1961): 1274–1275.

4. S.L. Katz, J.F. Enders, and A. Holloway, "Studies on an Attenuated Measles-Virus Vaccine. Clinical, Virologic and Immunologic Effects of Vaccine in Institutionalized Children," *The New England Journal of Medicine* 263, no. 4 (1960): 159–161.

5. S.L. Katz, "John F. Enders and Measles Virus Vaccine—A Reminiscence," in *Measles: History and Basic Biology,* ed. D.E. Griffin and M.B.A. Oldstone (Heidelberg, Germany: Springer, 2009), 3–11.

6. As Morley's work in Nigeria, in particular, was beginning to demonstrate, e.g., D.C. Morley, "Measles in Nigeria," *American Journal of Diseases of Children* 103 (1962): 230–233; D. Morley, M. Woodland, and W.J. Martin, "Measles in Nigerian Children: A Study of the Disease in West Africa, and Its Manifestations in England and Other Countries During Different Epochs," *Journal of Hygiene* 61, no. 1 (1963): 115–134. In 1960, responding to a request from Morley, Samuel Katz had taken measles vaccine prepared by Merck to the Nigerian village in which Morley was working and a trial was conducted successfully (Katz, "John F. Enders," 8).

7. Merck's development of the measles vaccine is discussed in L. Galambos with J.E. Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895–1995* (Cambridge, UK: Cambridge University Press, 1995), 86–98.

8. L.L. Terry, "The Status of Measles Vaccines," *Journal of the National Medical Association* 55, no. 5 (1963): 453–455.

9. The Centers for Disease Control and Prevention, in collaboration with the Colorado State Department of Public Health, carried out a placebo-controlled trial of the inactivated vaccine in 1961–1962. An outbreak of measles two to six months later showed the vaccine to be "82% effective in preventing any evidence of measles and 93% effective in preventing regular measles" (p. 64). The authors of the report were, nevertheless, skeptical regarding the possibility of longer protection. W.H. Foege, O.S. Leland, C.S. Mollohan, V.A. Fulginiti, D.A. Henderson, and C.H. Kempe, "Inactivated Measles-Virus Vaccine. A Field Evaluation," *Public Health Reports* 80, no. 1 (1965): 60–64. On the other hand, a study in Buffalo, NY, found inactivated vaccine promising enough to merit further study. W. Winkelstein, D.T. Karzon, D. Rush, and W.E. Mosher, "A Field Trial of Inactivated Measles Virus Vaccine in Young School Children," *Journal of the American Medical Association* 194, no. 5 (1965): 106–110.

10. Younger children would be unresponsive because of residual maternal antibodies.

11. J. Colgrove, *State of Immunity. The Politics of Vaccination in Twentieth-Century America* (Berkeley, CA: University of California Press, 2006).

12. Ibid., 132.

13. Office of Technology Assessment, *A Review of Selected Federal Vaccine and Immunization Policies Based on Case Studies of Pneumococcal Vaccine* (Washington, DC: Congress of the United States, Office of Technology Assessment, September 1979), http://www.fas.org/ota (accessed February 10, 2012).

14. Colgrove, *State of Immunity,* 156.

15. Office of Technology Assessment, *A Review of Selected Federal Vaccine and Immunization Policies,* 182.

16. A.D. Langmuir, D.A. Henderson, R.E. Serfling, et al., "The Importance of Measles as a Health Problem," *American Journal of Public Health* 52, no. 2 (1962): 1–3.

17. Colgrove, *State of Immunity,* 159.

18. Sencer, Dull, and Langmuir, "Epidemiological Basis," 256.

19. For fiscal years 1969 and 1970, Congress authorized no federal funding for community immunization programs. The number of doses distributed fell to 9.4 million, and the estimated cases of measles rose to 533 000 in 1970 and to 847 000 in 1971. Thereafter, federal funding was restored, and measles cases fell to 400 000 in 1972. The Office of Technology Assessment suggests a direct connection (*A Review of Selected Federal Vaccine and Immunization Policies,* 182–183).

20. "Editorial: Inactivated Measles Virus Vaccine," *British Medical Journal* 1, no. 5294 (1962): 1746–1747.

21. The 1946 act setting up the United Kingdom's National Health Service established the Public Health Laboratory Service, which the MRC administered until 1960. In that year it acquired a new status under, but somewhat independent of, the Ministry of Health. See Linda Bryder, "Public Health Research and the MRC," in *Historical Perspectives on the Role of the MRC,* ed. J. Austoker and L. Bryder (Oxford, UK: Oxford University Press, 1989), 59–81.

22. D.L. Miller, "Frequency of Complications of Measles, 1963. Report on a National Inquiry," *British Medical Journal* 2, no. 5401 (1964), 75–78.

23. Of these, 2000 would be expected to have a neurological condition, 13 000 a middle ear infection, and 20 000 a respiratory problem. Miller, "Frequency of Complications of Measles, 1963."

24. D.L. Miller, "The Public Health Importance of Measles in Britain Today," *Proceedings of the Royal Society of Medicine* 57 (1964): 843–846.

25. "Editorial: Measles and Measles Vaccination," *British Medical Journal* 2, no. 5401 (1964): 72–74.

26. Ibid., 72.

27. J.F. Bourdillon, "Immunisation Against Measles," *The Lancet* 284, no. 7353 (1964): 239–240.

28. "Editorial: Vaccination Against Measles," *British Medical Journal* 1, no. 5485 (1966): 435–436.

29. George Dick, a leading member of the British government's vaccine advisory committee, had carried out a trial of Koprowski's live polio vaccine in Belfast. Its failure led him to oppose the use of live vaccines. However, a government campaign to encourage Salk vaccine uptake in 1958 made little headway until a famous soccer player died of polio in spring 1959. That stimulated huge numbers to seek vaccination, and incidence fell sharply. Nevertheless, in September 1961 a polio outbreak occurred in the city of Hull. The city's health officials sought permission from the Ministry of Health to use the live (Sabin) vaccine for the first time in Britain. The ministry agreed, and vaccine was supplied by the British subsidiary of Pfizer. Within two weeks the epidemic was over. In early 1962 the ministry gave local health authorities permission to change to the Sabin vaccine, and by 1963 medical opinion had swung in favor of its exclusive use. See T. Gould, *A Summer Plague. Polio and Its Survivors* (New Haven, CT: Yale University Press, 1995).

30. E. Norrby, R. Lagercrantz, and S. Gard, "Vaccination Against Measles: A Study of Clinical Reactions and Serological Responses of Young Children. A Report to the Medical Research Council by the Measles Vaccination Committee," *British Medical Journal* 1, no. 5438 (1965): 817–823.

31. "Editorial: Measles Vaccination," *The Lancet* 1, no. 7435 (1966): 473–474.

32. L.W. Rauh and R. Schmidt, "Measles Immunization With Killed Virus Vaccine. Serum Antibody Titers and Experience With Exposure to Measles Epidemic," *American Journal of Diseases of Children* 109 (1965): 232–237.

33. In August 1966, C. Cockburn of the World Health Organization wrote to Pfizer saying, "My epidemiological colleagues in Czechoslovakia are rather unwilling to proceed with these studies because of the reports of rather severe reactions when live vaccine is given after killed vaccine." Cockburn initiated a study of this reaction. "So far there is very little evidence of untoward reactions except from Dr Fulginiti who has not answered my letter but whose report to a recent meeting was made available to me." On August 15, Pfizer's assistant medical director replied, "We have had a few isolated reports of reactions following live vaccine, but Dr Fulginiti is the only investigator to report its occurrence in a number of cases." In December 1966 Cockburn wrote to M. Sharif at the United Nations Relief and Works Agency (which had been offered the inactivated vaccine for use in Palestinian refugee camps), saying that although information was still rather fragmentary, it seemed possible that an "unexpected antigen antibody reaction may occur as the effect of the inactivated vaccine wears off" and that "the climate of opinion is for the present veering away from the killed measles vaccine" (World Health Organization Archives; Geneva, Switzerland; file M11/445/2).

34. V.A. Fulginiti and C.H. Kempe, "Killed-Measles-Virus Vaccine," *The Lancet* 290, no. 7513 (1967): 468.

35. Characteristics of atypical measles were high fever, coughing, and myalgia, followed by a distinctive rash and accompanied by pneumonia-like symptoms.

36. Medical Research Council, "Vaccination Against Measles: Clinical Trial of Live Measles Vaccine Given Alone and Live Vaccine Preceded by Killed Vaccine. Second Report to the MRC by the Measles Vaccines Committee," *British Medical Journal* 2, no. 5603 (1968): 449–452.

37. Vaccines for these children were offered after nine months and, if accepted, the children were then excluded from the remainder of the trial.

38. Medical Research Council, "Vaccination Against Measles," 452.

39. Joint Committee on Vaccination and Immunisation, "Minutes of Meeting Held on Monday November 13, 1967. Document CHSC(VI) 1967 Second Meeting," http://www.dh.gov.uk/ab/JCVI/DH_095054 (accessed June 30, 2012).

40. Also, in 1968, Merck's Moraten strain had been licensed, and the earlier *Rubeovax* was replaced by *Attenuvax*. See Galambos, *Networks of Innovation,* 97–98.

41. However, supplies initially available were insufficient, so between May and July only susceptible children aged between four and seven years, plus children aged between one and seven years who attended nursery schools or lived in residential establishments, would be vaccinated. Joint Committee on Vaccination and Immunisation, "Minutes of Meeting of July 23, 1968. Document CHSC (VI)(68). First Meeting," http://www.dh.gov.uk/ab/JCVI/DH_095054 (accessed June 30, 2012).

42. "Vaccination Against Measles," *The Lancet* 292, no. 7568 (1968): 616–618. The Beckenham-31 vaccine was withdrawn by its manufacturer in 1969.

43. R. Brouwer, "Internal Report," International Symposium on Standardization of Measles Vaccine and the Serology of Measles and Rubella, Institut Mérieux, Lyon, France, June 18–20, 1964 (in Dutch), n.p.

44. E. Norrby, R. Lagercrantz, and S. Gard, "Measles Vaccination IV. Response to Two Different Types of Preparations Given as a Fourth Dose of Vaccine," *British Medical Journal* 1, no. 5438 (1965): 813–817.

45. Norrby, Lagercrantz, and Gard, "Measles Vaccination IV," 816.

46. E. Norrby, R. Lagercrantz, and S. Gard, "Measles Vaccination VII. Follow Up Studies in Children Immunized With Four Doses of Inactivated Vaccine," *Acta Paediatrica Scandinavica* 58, no. 3 (1969): 261–267.

47. Norrby, Lagercrantz, and Gard, "Measles Vaccination IV," 817.

48. "H-protein (causing hemagglutination) and F (fusion) protein (causing hemolysis) are surface proteins on the envelope of the virion needed to penetrate host cells. The H-protein reacts with a specific receptor on the host cells. After adsorption of the virion, the F protein is involved in the fusion of the viral and the plasma membrane. The existence of the F protein was not known at this time" (S. Westling, Interview with E. Norrby, Stockholm, November 2011). Only later were Norrby and Gollmar able to show that both formalin and TE inactivation destroyed the F-protein, i.e., the surface component of the virus that produced these so-called non-HI hemolyzing-inhibiting antibodies. E. Norrby and Y. Gollmar, "Identification of Measles Virus-Specific Hemolysis Inhibiting Antibodies Separate From Hemagglutinating-Inhibiting Antibodies," *Infection and Immunity* 11, no. 2 (1975): 231–239.

49. U. Lindner and S. Blume, "Vaccine Innovation and Adoption. Polio Vaccines in the UK, the Netherlands and West Germany, 1955–1965," *Medical History* 50, no. 4 (2006): 425–446.

50. It has not been possible to establish how far the needs of developing countries, where an inactivated vaccine could have certain advantages, also influenced the decision to work on an inactivated measles vaccine. Hans Cohen, head of the RIV's vaccine division and later its director general, was an active member of the World Health Organization's Expert Committee for Biological Standardization, which established vaccine requirements. In the 1980s, new attempts to develop a (subunit) inactivated measles vaccine began at the RIV.

51. Beale had previously worked on inactivated polio vaccine as well at Connaught in Canada. At Glaxo, he tested a measles vaccine inactivated using Norrby's process in a small trial in Ireland. The conclusion, that a single dose of inactivated vaccine given one month before live vaccine does not interfere with antibody response and may even enhance it, was different from what MRC found. They attributed the difference to the different inactivated vaccines used.

52. R. Brouwer, "De productie en controle van een geinactiveerd en gezuiverd mazelenvaccin." Unpublished internal report (in Dutch; 1967).

53. Gezondheidsraad, *Rapport Inzake de Vaccinatie tegen Mazelen.* Report 68-430-6 (The Hague, the Netherlands, 1968).

54. Quoted by M.F. Polak, "Mazelenvaccinatie," *Nederlands Tijdschrift voor Geneeskunde* 112, no. 42 (1968): 1905–1906.

55. Ibid., 1905–1909.

56. J. Spaander, Letter dated April 26, 1968 (U222/68 Dir Sp/mp) to the Dutch secretary of state regarding the development of a pentavalent vaccine (in Dutch; The Hague, the Netherlands: Dutch National Archives, 1968). Box No. 3937.

57. At Merck, Maurice Hilleman was by this time also investigating the possibilities of combining (live) measles vaccine with other antigens. But Merck did not produce DPT, and Hilleman eventually decided to combine measles vaccine with mumps and rubella. Merck's measles-mumps-rubella vaccine was licensed in 1971.

58. H. Cohen, Letter dated August 7, 1970 (U234/70 Dir Co/ms) to the head of the National Control Laboratory H.P. Lansberg (in Dutch; The Hague, the Netherlands: Dutch National Archives, 1970). Box No. 3937.

59. R. Brouwer, "Vaccination of Infants in Their First Year of Life With Split Inactivated Measles Vaccine Incorporated in a Diphtheria-Pertussis-Tetanus-Polio (Inactivated) Vaccine (DPTP-M), Compared With Live Measles Vaccination," *Journal of Biological Standardization* 4, no. 1 (1976): 13–23.

60. Subsequent support for this decision came from Norrby's discovery that inactivated vaccine fails to generate antibodies against the fusion protein, which later turned out to be critical for protection. The special feature of this deficiency is that it can provide a basis for immune pathological effects that may aggravate the situation of vaccinated individuals.

61. As subsequent developments have illustrated all too well. See H.J. Larson, L.Z. Cooper, J. Eskola, S.L. Katz, and S. Ratzan, "Addressing the Vaccine Confidence Gap," The Lancet 378, no. 9790 (2011): 526–535.

62. e.g., S. Jadhav, M. Datla, H. Kreeftenberg, and J. Hendriks, "The Developing Countries Vaccine Manufacturers' Network (DCVMN) Is a Critical Constituency to Ensure Access to Vaccines in Developing Countries," *Vaccine* 26, no. 13 (2008): 1611–1615.

63. H. Thorsteinsdottir, "The Role of the Health System in Health Biotechnology in Developing Countries," *Technology Analysis & Strategic Management* 19, no. 5 (2007): 659–675; A. Lage, "Connecting Immunology to Public Health: Cuban Biotechnology," *Nature Immunology* 9, no. 2 (2008): 109–112.