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A Brief History of Polio Vaccines

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In 1988, the World Health Assembly resolved that by the year 2000 paralytic poliomyelitis would be wiped off the face of the Earth. The global eradication campaign is now moving into its final stages, with valiant efforts under way to maintain polio vaccination programs, implement surveillance systems, and eliminate the last remaining reservoirs of poliovirus. As the smallpox eradication campaign showed in the 1970s, immunizing the last few hard-to-reach villagers in remote or war-stricken regions is a formidable task. But the goal of global eradication has mobilized everyone from politicians and vaccine manufacturers to health workers in the field.

The notion of a polio-free world encourages us to look beyond 2000 with optimism, but there are also reasons to look back at the history of polio vaccine development. The first is the renewed interest in the hypothesis that HIV, the virus that causes AIDS, evolved from a monkey virus that contaminated early batches of polio vaccine used in trials in the Congo in the late 1950s. This has led to the suggestion that the few remaining batches of the original polio vaccine stocks used in the Congo trials should be tested for the presence of HIV. A second reason, less widely appreciated, is the recommendation of the U.S. Advisory Committee for Immunization Practices that, beginning in January this year, children in the United States should be immunized with the inactivated (killed) polio vaccine (IPV) developed by Jonas Salk in place of the oral (live-attenuated) polio vaccine (OPV) developed by Albert Sabin (used almost exclusively in the United States for the past 35 years). This change in policy is a result of the epidemiology of the disease but also has implications for the economics of vaccine production. By comparing how the United States (where polio vaccines were developed and manufactured by private companies) and the Netherlands (where government-funded laboratories designed, developed, tested, and manufactured the entire country's supply of polio vaccine) implemented their polio vaccine programs, it becomes clear how economics and market forces mold vaccine policy.

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The bitter rivalry between the developers of the original polio vaccines, Salk and Sabin, was a contributory factor to the United States and the Netherlands choosing to pursue different polio vaccination programs. In April 1955, the results of the largest clinical trial ever held (at that time) were made public. More than 400,000 U.S. children had been immunized with Salk's IPV and, as the results of effective protection against this dreaded disease were declared, Americans breathed a collective sigh of relief. The Salk vaccine was declared 90% effective against Types II and III poliovirus and 60 to 70% effective against Type I. Within 2 hours, Salk's IPV was licensed for use. Thanks to guarantees from the National Foundation for Infantile Paralysis (now the March of Dimes), industrial production facilities were already built and ready to operate. The goal was to have five million U.S. children vaccinated by July 1955. Across the Atlantic, some European countries imported the Salk vaccine from the United States whereas others, including Denmark, Sweden, and the Netherlands, began vaccine production in their own government facilities.

Many virologists were of the opinion that Salk's vaccine could not provide long-lasting protection and that this could only be achieved with Sabin's live-attenuated version. Only a live vaccine, it was argued, had sufficient immunogenicity to provide protection. In contrast, an inactivated vaccine would have to be re-administered regularly. Undeterred by Salk's popular success, Cox and Koprowski at Lederle (Koprowski later took his candidate vaccine to the Wistar Institute) and Sabin at the University of Cincinnati continued to work on their live-attenuated virus preparations. Trials of their vaccines took place largely outside the United States because widespread immunization with the Salk vaccine meant that most U.S. children had antibody levels that were too high to enable evaluation of a second vaccine. Instead, Koprowski tested his vaccine in Northern Ireland and in (and around) the Congo, Cox in Latin America, and Sabin in the Soviet Union. By July 1960, more than 15 million Soviet citizens were said to have received Sabin's oral vaccine.

On the basis of these trials, Sabin's vaccine was deemed the better of the two. It was found to confer longer-lasting immunity, so that repeated boosters were not necessary, and acted quickly, immunity being achieved in a matter of days. Taken orally (on a sugar cube or in a drink), the vaccine could be administered more readily than the Salk vaccine, which had to be injected. Most importantly, the Sabin vaccine offered the prospect of passive vaccination because it caused an active infection of the bowel that resulted in the excretion of live-attenuated virus. Thus, through fecal matter and sewage the Sabin vaccine could help to protect those who had not been vaccinated. In August 1960, the U.S. Surgeon General recommended licensing of the Sabin vaccine. The oral vaccine gradually supplanted its rival and by 1968, Salk's vaccine was no longer being administered in the United States, and U.S. pharmaceutical companies had stopped producing it. This interplay—between emerging consensus on the part of health authorities and physicians, and growing commitment on the part of the manufacturing industry to carry out the consensus—is a good example of technological "lock in," a theory propounded by evolutionary economists.

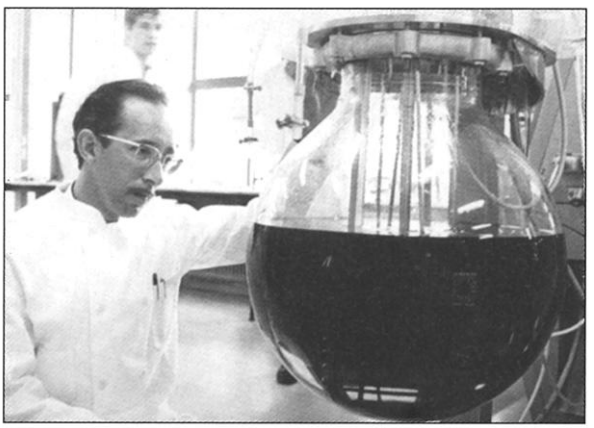
Despite the switch from the Salk to the Sabin vaccine by the United States, other countries including the Netherlands and Scandinavia continued exclusive use of the Salk vaccine even though the advantages of the live-attenuated vaccine seemed clear-cut. As early as 1962, there were growing suspicions that in a very small number of cases, largely adults, the live-attenuated vaccine could lead to paralytic poliomyelitis. In 1964, an advisory committee established by the U.S. Surgeon General reviewed the incidence of the disease be-

tween 1955 and 1961 (when only the Salk vaccine was used) and between 1961 and 1964 (when the Sabin vaccine predominated). They concluded that of the 87 cases of paralytic polio reported in the United States since 1961, 57 were judged "compatible" with having been caused by the attenuated poliovirus regaining its virulence. By the mid-1960s, health officials had to weigh the many benefits of the live-attenuated vaccine against the small but definite risks that were now known to be associated with its use.

The rational language of risk-assessment does not reflect the real politics of decision-making. We suspect that politicians and their advisers looked at matters rather differently in the 1960s when polio was still rampant than they would now, with global eradication of this dreaded disease within reach. Given the commitments made to the general public about the Sabin vaccine and the immunization programs and manufacturing facilities already in place, was there sufficient reason for the U.S. government to change course? The costs involved in switching back to the Salk vaccine and the risk of affecting public confidence in vaccination were profound. But authorities in different countries interpreted risks and benefits differently, depending on the progress that had already been made in their own countries in reducing the incidence of the disease. Perceiving that a formidable public health battle had still to be waged to stamp out polio, the United States maintained its exclusive loyalty to Sabin's live-attenuated vaccine.

By the early 1970s most of the world was using Sabin's oral vaccine. Because of its lower cost and long-term efficacy, the World Health Organization included the Sabin vaccine in the packet of subsidized vaccines that it provided to poor countries under the auspices of the Expanded Program of Immunization (EPI). The Sabin vaccine market was huge and continued to grow as the EPI extended its reach to more and more countries. Economics suggests that devoting resources to a technology that is being "locked out," in this case the Salk vaccine, is not rational. Yet the Netherlands continued not only to manufacture the Salk vaccine, but also to improve upon it. Nearly half a century later, this improved Salk vaccine can be produced to current GMP (good manufacturing practice) standards and supplied to the United States. U.S. children are once more to be immunized with the Salk vaccine principally because the tiny risk of vaccine-induced poliomyelitis attributable to the Sabin vaccine is of far more concern as global eradication of polio approaches. After eradication is officially declared, vaccination will continue for a few more years, both in the United States and elsewhere. Precisely for how many more years is under international discussion.

In the 1960s, the Dutch government research laboratory, *Rijksinstituut voor Volksgezondheid* (RIV), in Bilthoven was responsible for producing the country's entire supply of Salk vaccine. Hans Cohen, a physician and microbiologist at RIV who oversaw vaccine production, decided to combine Salk's inactivated polio vaccine (produced at RIV for domestic use) with the combination vaccine that protected children against diphtheria, whooping cough, and tetanus (known as DKT in the Netherlands and DPT elsewhere). To do this, he needed to improve the potency of the Salk vaccine. This necessitated overcoming a major production problem: the short supply of monkey kidneys necessary to produce and test polio vaccines (both the inactivated and live-attenuated versions). The RIV used about 5000 Rhesus monkeys annually for production and testing of the Salk vaccine. These animals were largely imported from Asia, many were sick and 15 to 20% died soon after arrival. Reducing the institute's dependence on imported monkeys became a priority.



The "Bilthoven Unit," designed by the Dutch microbiologists van Hemert (pictured) and van Wezel, generated large quantities of poliovirus for vaccine production in the 1960s.

Two microbial engineers, Paul van Hemert and Anton van Wezel, came up with a solution. Van Hemert had already developed a series of 300 to 1000 liter fermentors, the so-called "Bilthoven Unit," in which bacteria could be grown under standard conditions (see the figure). Van Wezel adapted this unit to grow large quantities of monkey kidney cells (derived from live monkeys) and poliovirus. The area for culturing cells was increased by filling the stainless steel vessels with medium containing small plastic beads ("microcarriers"). By allowing the monkey kidney cells to grow on the surface of the beads, he increased the yield of cells and hence of poliovirus a thousandfold. By 1975, RIV's annual consumption of monkeys had been reduced to 50, and by 1978 to just 7. These could be bred at the institute so that importing monkeys was no longer necessary.

Van Wezel was able to develop vaccines of any desired poliovirus concentration. In 1978 an improved Salk vaccine was tested in field trials in Mali and Upper Volta (now Burkino Faso), under the auspices of the Forum for the Advancement of Immunization Research, an organization established by Salk, Cohen, and Charles Mérieux. The vaccine was shown to confer full protection with just two doses. The Institut Mérieux (now Aventis Pasteur) subsequently succeeded in improving the Bilthoven process still further by propagating the virus in a cultured monkey kidney cell line.

The improvements to Salk's original vaccine by RIV were not stimulated by market forces because RIV had limited interest in producing vaccines for export. On the contrary, the stimulus for improvement came both from the country's commitment to a particular immunization schedule (the combined polio and DPT vaccine) and from technical achievements that reduced dependence on wild monkeys and enabled vaccine of a high enough quality to be manufactured. Because RIV is a Dutch Ministry of Health institute, it has been insulated from market forces, and thus has not been subjected to the pressure of "lock-in" economics that affected polio vaccine manufacture in the United States.

There has been growing international concern over the security of worldwide vaccine supplies because most vaccines are manufactured by a limited number of companies. If a particular vaccine is produced only by one company at a single facility, there is a potential risk that the supply of vaccine could dry up if the company decides for economic reasons to cease production or if the facility breaks down. There has been talk in the United States of the desirability of a publicly owned "standby vaccine production facility," but this suggestion has not received much support. Internationally, the role of the public sector in vaccine development and production is under debate. By closing off options, "lock in" economics provide a barrier to the reintroduction of older technologies for producing vaccines and drugs. Herein lies a good reason for governments to ensure that the public sector retains the competence to produce vital vaccines and drugs.

CREDIT: PAUL VAN HEMERT