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Lock in, the state and vaccine development: Lessons from the history of the polio vaccines

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Abstract

Over the past two decades pharmaceutical industry interest in the development of vaccines against infectious diseases has grown. At the same time various partnerships and mechanisms have been established in order to reconcile the interests of private industry with the needs of public health systems (especially in the developing world). The general assumption is that, lacking resources and competences, the public sector has little or no role to play in vaccine development. Drawing on the concept of 'lock in', and the history of vaccines against poliomyelitis, this paper advances a different set of considerations relevant to the role of the public sector. It was thanks to public sector R&D, driven by technical and public health considerations, not commercial ones, that a vaccine that had been virtually 'locked out' of the world markets was improved, and expertise in its production sustained. This vaccine now plays a crucial role in current attempts at eradicating polio. It is suggested that despite subsequent changes in vaccine technology, their different incentive structure requires acknowledgement in current discussion of the potential contribution of public sector vaccine institutes to vaccine innovation.

Keywords: Lock in; Vaccine development; Polio vaccine

1. Dilemmas of vaccine development

Vaccination is generally considered one of the great success stories of public health. Measured in terms of deaths prevented, vaccines against infectious disease are widely viewed as the most effective, and most *cost*-effective medical technology ever developed (Plotkin and Mortimer, 1988). Thanks to a determined, and some would say ruthlessly efficient vaccination programme, smallpox was eradicated from the globe two decades ago (Greenough, 1995). When, in late 1979, the World Health Organisation (WHO) declared the world to be smallpox-free the victory was symbolic as well as practical (Blume, 1998). It showed that with a determined and internationally co-ordinated vaccination campaign it was possible to conceive of eradicating diseases that had plagued humankind since time

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immemorial. The next candidate was to be poliomyelitis. In 1988 the World Health Assembly resolved that by the year 2000 poliomyelitis would have been eradicated too. Though this target date has since had to be pushed back to 2005, partly due to cost and partly to problems in certain regions of the world (West Africa, South Asia), the goal is still believed to be within reach. Epidemiological statistics can easily be used to construct a highly gratifying history of vaccines and vaccination.

A more disturbing and critical history can also be written. It has a number of elements. The slogans under which international donor interest—essential for maintaining financial support for vaccine procurement in the developing world—has been sustained may have been counter-productive in other respects. Recent global emphasis on the introduction of expensive new vaccines may have compromised the sustainability of existing programmes (Hardon and Blume, 2005). Various analyses have pointed to the lack of effective vaccines against diseases that cost hundreds of thousands of lives annually. For example, there is no vaccine against malaria (or any other human parasitic disease) endemic in many tropical countries. Indeed until recently very little R&D was being devoted to the search for an effective malaria vaccine (Anon., 1997; Anderson et al., 1996). Even vaccines that expert opinion considered scientifically feasible were not necessarily being developed, whatever the health need (Institute of Medicine, 1986).

In that they are commonly a tool of preventive, public health, rather than of individual therapy vaccines are rather unusual among medical technologies.[1] Effective demand for vaccines, measured in money terms, is limited. Poor countries (some 60% of the vaccine market in volume terms) cannot pay much, and the international organisations, such as UNICEF, that supply part of their need negotiate rock-bottom prices through a tendering system.[2] Vaccines have never been a commercially attractive area of pharmaceutical industry activity. The worldwide vaccine market represents no more than 2–3% of the industry's turnover; development costs are high; and past events have shown how real are the risks of crippling law suits in the event of injury. In the 1960s and 1970s many pharmaceutical companies abandoned vaccines totally, and the industry's commitment to vaccine development and production became a matter of political concern, especially in the USA (OTA, 1979; Galambos, 1995; Grabowski and Vernon, 1997). Was the nation's vaccine supply in jeopardy? How could industrial commitment to vaccine production be sustained? Although the desirability of a public sector role in vaccine development and production has since been raised by a number of analysts (Bloom, 1994; Mowery and Mitchell, 1995), in practice this role has declined over many decades.

Despite continued, even increased commitments to *basic vaccine research* by the US National Institutes of Health and other national laboratories, public sector institutions now seem to have a negligible role in vaccine *product development*. The roots of this trend go back to the early 20th century. For example, we see research on, and the production of diphtheria antitoxin in the United States gradually shifting from State and local boards of health to private pharmaceutical firms. But even well into the 1980s, relationships between public and private sectors were typically rooted in a common commitment to public health. Knowledge was freely available and freely exchanged. Hans Cohen, who was for many years Director General of the Netherlands State Institute (RIVM) responsible for producing and supplying the country's vaccine needs, tells of his earlier relationships with industry, specifically with Pasteur Mérieux (now Aventis).[3]

> They [Mérieux] got all our know-how, and we weren't always happy about that, but on the other hand we got a great deal of know-how back in return. For example, I got a rabies vaccine. We exchanged. It took three minutes. A matter of "what do you want from me?" then the boss says "I'll have some polio, and what do you want?" And I'd say "Give me a measles strain, and some of that and some of that. . ." It was good. Really a free exchange.

A change has taken place, from largely discipline-based research conducted in relatively well-defined but

[1] For a comparison of the diffusion of vaccines with other medical technologies see Hollingsworth et al. (1990).

[2] For example in 1992 UNICEF purchased and supplied 850 million doses of vaccine at a total cost of $65 million. Mitchell et al. (1993), p 71.

[3] Interview with Hans Cohen, Bilthoven 1998, quoted in Blume and Geesink (2000a).

co-operative public and private sector institutions, to research carried out in multidisciplinary settings linked in fluid networks (Blume and Geesink, 2000a). Vaccine-related research is now pursued by molecular biologists, geneticists, immunologists and organic chemists, among other relatively "newer" (sub)specialties and (sub)disciplines, as well as by microbiologists and virologists, working in competing networks that jealously guard their findings (cf. Powell et al., 1996). With the emergence of new, promising and less risky ways of making vaccines in the 1980s, industrial interest was rekindled The knowledge generated in these newer "vaccinological" networks is no longer freely available, and is increasingly protected by patents. For example, by 1983 a government survey found that only two patents for 27 vaccine products existed; a decade later, SmithKline Beecham had to assemble 14 patents to produce and market its recombinant hepatitis-B vaccine (Mowery and Mitchell, 1995).[4]

Changes over the past two decades have led a number of informed commentators to express their concern at the "privatization" of vaccine development and production (Freeman and Robbins, 1991). In the industrialised world at least, the state is retreating from its traditional responsibilities in the vaccine area. Some countries, including Australia and Sweden, have sold their state vaccine institutes to the private sector. (Matters are rather different in the developing world, and a number of countries in Asia and Latin America have major public sector producers.)[5] What values, what commitments, now guide the search for new vaccines, and how does this affect potential users? The historian William Muraskin quotes a senior British official as saying that "the manufacturers were developing new [vaccines] without any regard for public health priorities, and by ignoring the problem of need, left public sector officials open to being pressured into switching to new vaccines that had been designed to meet commercial, not public health needs" (Muraskin, 1998, p. 117).

Much of the discussion in the global arenas in which, these days, vaccine supply and development strategies are debated, is designed to promote fruitful dialogue between public health officials from North and South, and the multinational pharmaceutical industry. The implicit assumption is that the public sector is unable to make any significant contribution to vaccine development. When this assumption is made explicit it is typically expressed in terms of inadequate resources, poor management structures and skills, and weak R&D.

> In theory, public sector vaccine developers ... could play a major role in developing new vaccines with potentially great public health impacts, since they are not especially sensitive to considerations of market size. However ... these institutions do not have sufficient resources to undertake major programs—by private sector standards—in these areas (Hausdorff, 1996).

Or as a WHO team puts it

> To access research and development technology and scale up know-how, national producers will need to enter into agreements with commercial producers or wait until the knowledge enters the public domain. However, commercial producers will contemplate agreements only with national facilities who can assure quality and are economically viable (Milstien et al., 1997).

Underlying all this is a fundamental concern with optimising the deployment of global resources and with stimulating rapid development and introduction of new vaccines. Important though these concerns are, they are not the only ones relevant to the proper organisation of vaccines R&D. In this paper I will approach the question of a public sector role in vaccine development from a rather different angle and using rather different (historical) data. The argument will be built on the concept of 'lock in', introduced by David and by Arthur (David, 1985; Arthur, 1989). This is one of various approaches to understanding 'successions' of technologies: in other words, the ways in which experience in the use of a technology shapes attempts at its improvement, whilst excluding alternative technological approaches. Rosenberg's notion of 'focussing devices' and Hughes' notion of 'reverse salients' are other conceptualisations of related processes (Rosenberg, 1969; Hughes, 1987). Though all of these concepts have proven valuable in the study of innovation, they seem not to figure at all in the substantial literature on vaccine

[4] Hepatitis B vaccines produced by Smith Kline Biologicals (now Glaxo SmithKline) and by Merck/Chiron, first marketed in 1984, were the first of the vaccines produced by rDNA technology.

[5] Local production in developing countries accounts for 50–60% of world production (Mitchell et al., 1993; Shin and Shahi, 1994).

R&D. How and why might the public health system become 'locked in' around a vaccine that becomes suboptimal as needs and epidemiological profiles change?

A few words of introduction are required. On the one hand, thanks to a century's commitment to innovation, and thanks to the high degree of inter-relatedness between technologies and complex user-skills, health care seems a promising domain to search for Paul David's 'QWERTY worlds' (Rothman, 1997). On the other hand there are also reasons for thinking that health care is precisely where we should not expect lock in around 'wrong' or 'sub optimal' technologies. Decision-making in the medical area is supposedly based on comprehensive evaluations, with much medical research devoted to assessing the effectiveness of specific interventions. Since the 1970s, with the rise of health economics and more recently pharmacoeconomics, the analytic armamentarium has become ever-more powerful. At a time in which so much weight seems to be attached to Evidence Based Medicine, to the meta-analyses of clinical trials, the possibility of health care having become locked in around an inappropriate, or no longer appropriate technology ought to be very small indeed (see Pope, 2003). The notion of 'Evidence Based Medicine' and that of 'lock in' clearly derive from very different approaches to understanding medical innovation. An initial sense that they have little or nothing to do with each other would be mistaken. Fundamental to the argument of this paper will be the scope of and interplay between these two logics.

This paper takes the history of polio vaccine—or more precisely the history of the polio *vaccines*—as its empirical focus. The history has been reconstructed on the basis of documentary and archival sources, and of interviews with a number of those involved. The paper uses the concepts sketched out above to open a new line of debate in consideration of the role of the public sector in vaccine development.

2. The origins of the polio vaccine controversy

In the late 1930s, there was a tremendous social pressure to do something about polio. People were scared and, especially in the USA, very aware of the disease thanks to the Presidency of Franklin Roosevelt. Roosevelt, himself a polio survivor (Fairchild, 2001), played an important role in founding the National Foundation for Infantile Paralysis[6] to support research on poliomyelitis and to provide support to its victims.

Although it was known that polio was a viral disease, in the 1930s little was known of the nature of the virus or of its propagation. Even though "trying to develop a polio vaccine in 1935 was somewhat like a Stone Age man trying to invent an automobile" (Klein, 1972, p. 20) some researchers thought they could do it. Two ways of making vaccine were tried. Some researchers tried to kill, or 'inactivate' the virus whereas others tried to weaken or 'attenuate' it. Neither was successful. The early trials were such disastrous failures that work stopped. Indeed, many scientists doubted whether a safe vaccine of any kind against polio could be made. The problem was that the virus seemed only to survive and grow in nerve tissue. It was known that injecting nerve tissue culture carried a potential risk of brain damage: you could not use anything grown in nerve tissue culture as a vaccine.

By the late 1940s, this vital barrier to the development of a polio vaccine had been cleared (Robbins, 1988). Scientists at Harvard University had shown that polio virus could be propagated in non-nervous tissue cultures (Enders et al., 1949). This opened the way to a safe vaccine. By 1948, too, it had also been shown that there were *at least three* different types of polio virus. This was crucial, since an effective vaccine would have to protect against all types.

Earlier uncertainty regarding the relative merits of 'killed' or 'inactivated' virus and a 'weakened' or 'attenuated' one remained. Jonas Salk, at the University of Pittsburgh, chose to try to develop an inactivated virus vaccine. The more common view was that such a vaccine would not be adequate: that it would only provide a few months' protection. Nevertheless, with support from the National Foundation Salk pushed ahead. Thanks to publicity, social pressure to produce a vaccine was building up. By late 1952 it was decided that the Salk vaccine was ready for a large scale trial. It would have to be clearly independent of any vested interests, and people would have to have confidence in the results. Thomas Francis, a highly respected epidemiologist at the University of Michigan, agreed to take responsibility, and in April 1954 the trial began. A year later the results were in.

[6] On the National Foundation and its establishment see Paul (1971) pp. 300–323.

In April 1955, surrounded by cameras, hordes of reporters, floodlights, Francis presented the results of the trial, declaring the vaccine over 90% effective against Types II and III and 60–70% effective against Type I polio virus. Whatever the proponents of an attenuated vaccine might have thought, the American nation breathed a sight of relief. Within 2 hours the Salk vaccine was licensed for use. In 1955 five million American children would have to be vaccinated.

Immediately, discussion of the desirability of polio vaccination began in many countries. In Denmark, which had been shaken by an epidemic of unprecedented severity in 1952, action was rapid. Experts from the Danish Serum Institute had already been in touch with Salk and the Institute quickly set about vaccine production. Other European countries moved more cautiously. In the Netherlands a specially-established committee of the Dutch Health Council (Gezondheidsraad) doubted whether an inactivated vaccine would be adequate. The Minister of Health was advised not to permit import of the vaccine. In 1956 the country experienced a serious polio epidemic. That fact, combined with the clear evidence of what had been achieved in the USA, led to a change of heart. In December 1956 the Dutch Minister announced that import of polio vaccine would begin. Other European countries were moving in the same direction.

Meanwhile, some manufacturers were still having problems with the production process. Many batches of vaccine had to be discarded because of the presence of live virus. It soon became known that six children in California had become paralysed as a result, it was concluded, of vaccine produced by one of the American manufacturers, the Cutter company. Faced with an agonising decision—whether to take the Cutter vaccine off the market or suspend the whole programme (after all, everyone was having problems and the disaster could easily recur) the Surgeon-General of the USA decided on the former course of action. The Cutter company stopped production and withdrew supplies of its vaccine. Unfortunately, even after close examination of the Cutter plant and procedures, it was not clear why the accident had happened. Cutter had followed Salk's procedure carefully (Klein, 1972, p. 120). Congressional hearings followed, and the Secretary of Health Education and Welfare resigned. What had gone wrong? Some virologists thought the problem lay in the inactivation time used: Salk had got his kinetics wrong. Others thought that complete inactivation using formalin (the procedure used) was not possible: ultraviolet radiation would be better.[7] In May 1955 the US vaccination programme was briefly suspended. Public faith in the Salk vaccine had been severely shaken.

Meanwhile Albert Sabin at the University of Cincinnati and Harold Cox and Hilary Koprowski (both at that time with the pharmaceutical company Lederle), who had never believed in the killed vaccine, were working on attenuated polio vaccines. By 1956, large scale trials of attenuated vaccines were being planned. These could not be held in the USA. Widespread use of the Salk vaccine meant that most children already had too high antibody levels for a different vaccine to be tested.[8] Albert Sabin, himself of Russian birth, succeeded in having his vaccine tested on a huge scale in the Soviet Union: nearly 15 million people had swallowed his vaccine by July 1960.[9] US authorities, unwilling to be once more rushed into licensing (as they felt they had been with the Salk vaccine) were concerned by the possibility of the attenuated virus vaccine reverting to virulence. Joseph Melnick, Professor of virology and epidemiology at Baylor University, was asked to conduct a comparative study of the Sabin and Cox vaccines. Melnick's results clearly favoured the Sabin strains over those of Lederle-Cox (Melnick and Brennan, 1959).

In August 1960, the US Surgeon General announced that he would recommend licensing of the Sabin vaccine, despite the protests of the National Foundation (that had sponsored Salk's work) to the effect that the efficacy of the Salk vaccine had not yet been fully established. On the same day "Lederle made it known that it had contracted to manufacture Sabin vaccine" (Klein, 1972, p. 147). The vaccine was, in fact, licensed on a strain-by-strain basis: in August 1961 Pfizer was

[7] Later work suggested that the problem was a technical, not a virological one. Some of the virus seemed to become embedded in clumps of cell debris which protected it from the formalin. At Glaxo, they improved the filtration process, after which the problem of residual living virus was solved (see Beale, 1996, p. 224).

[8] George Dick, professor of Microbiology in Belfast, organised a first trial of Koprowski's vaccine in Northern Ireland. A trial in the Belgian Congo followed.

[9] "Though no one questioned the overall success of Sabin's mission in Russia, it was, as Smorodintsev belatedly admitted during a visit to the United States in 1964 'a public-health measure not a field trial'. Sabin's live vaccine was never subjected to the kind of rigorous field trial that Salk's killed vaccine had undergone in 1954" (Gould (1995) p. 183).

granted a licence to produce and market a Type I vaccine, Type II followed in October, and Type III in March 1962.[10] A trivalent vaccine, including all three types, became available in 1963. The stage was set for protracted discussion of the relative merits of the Salk and Sabin vaccines.

3. Dominance of the oral polio vaccine (OPV) in the 1960s and 1970s

Through the 1960s and early 1970s, Sabin's attenuated vaccine (usually known as oral polio vaccine or OPV because it was and is administered orally) achieved almost total dominance. How did this occur?

In 1961 the Committee advising the British Health Minister was still of the opinion that IPV remained the vaccine of choice (Anon., 1961a). But when the city of Hull experienced a polio outbreak, in September 1961, the city's public health authorities "sought permission from the Ministry of Health to use live vaccine for the first time in Britain" (Gould, 1995, p. 175). Pfizer's British subsidiary, already producing OPV in the event of "just such an emergency", was rapidly able to provide a supply. Within a week more than the city's entire population was vaccinated and within 2 weeks the epidemic was over. The authorities were convinced that the vaccine had been responsible for bringing the epidemic to so abrupt an end, and the evidence now seemed to indicate that a change in national vaccination strategy would be appropriate (Anon., 1961b). In 1962 the British Health Minister issued a circular permitting local health authorities and family doctors to change to the Sabin vaccine. For a time, both vaccines were then used in Britain. By early 1963 the BMJ was arguing for a more determined attack on the virus using the live vaccine (Anon., 1963).

Thus the view that the live vaccine was to be preferred was based on a number of distinctive hypotheses. One concerned ease of administration Taken orally, it should be more acceptable to the public. Second, the repeated booster jabs said to be needed with IPV would not be necessary. OPV was believed to confer longer-lasting immunity. Third, it was quicker acting, immunity being achieved in a matter of days rather than months (Paul, 1971, p. 451), which meant that it could be used in the event of a local epidemic. And finally was the argument that OPV provides protection to the community as a whole and could indeed offer a route to eradication of the virus. The point here was that attenuated live virus, excreted and entering the sewage system, would give indirect protection to people who had not been vaccinated. Note that issues relating to production, quality control or price, scarcely figured in this discussion.

These are powerful arguments. By 1964 the Committee on Control of Infectious Diseases of the American Academy of Pediatrics was writing that evaluation "reveals a clearcut superiority of the OPV from the point of view of ease of administration, immunogenetic effect, protective capacity, and potential for the eradication of poliomyelitis" (quoted Robbins, 1988, p. 104)

In the course of the 1960s, paralleling growing medical preference for OPV, pharmaceutical companies abandoned production of the Salk vaccine. Whilst in the mid 1960s, some four to five million doses of IPV were being distributed annually in the USA, by 1967 this had fallen to 2.7 million and a year later to zero. By contrast distribution of OPV had reached some 25 million doses annually.[11] The history of polio vaccines in the 1960s provides a fine illustration of the process of lock-in initiated, in the first instance, by a set of clear cut scientific arguments. We can see an emerging preference for one alternative, the OPV, based essentially on scientific—epidemiological and virological—reasoning. These arguments played a vital part in the socio-economic logic which was leading to lock in.

There was, however, a cloud on the horizon. By summer 1962, with millions of doses of OPV having been administered in the USA, there was a growing suspicion that in a small number of cases the attenuated virus in the vaccine had reverted to virulence and itself caused disease. Careful analysis suggested that 16 cases of polio were probably due to the vaccine itself. Whilst some now recommended that the live vaccine programme be suspended, others were worried

[10] John Beale recalls that "three companies were invited to bid, by a sealed bidding process. In fact two companies made no bid when their envelopes were opened. This left the field open to the third company, Pfizer, who had bid very low to secure the business anyway" (John Beale, personal communication).

[11] Figures quoted by Salk and Salk (1977).

that public faith in the vaccine would be shaken, and vaccination levels would fall. Two years later a new committee of enquiry once more reviewed the data. Of the 87 cases of paralytic polio reported since 1961, 57 were judged "compatible" with having been caused by the OPV itself. This time there was no association with specific lots of vaccine or particular manufacturers. Although it could not be proved conclusively that a particular case had been caused by a vaccine, the Committee believed that "at least some of these cases were caused by the vaccine". It advised that the risk was low enough for vaccination of children to be safely continued, but that care was needed in the immunization of older people.

Whilst in 1960 arguments in favour of the live vaccine seemed irrefutable—and had initiated the process of lock in—by the mid 1960s matters were more complex. Choice for one vaccine or the other now entailed weighing the presumed benefits of OPV (greater acceptability, community protection and so on) against what were now known to be small but definite risks associated with its use. Were the risks acceptable, and should society take them? Posed in this way, the issue is the fundamentally political one of trading off risks against benefits. If it were a matter of politically re-weighing relative risks against relative benefits, we might expect that a number of countries would change course. There now seemed reason to believe that one country's choice would not necessarily be the other's. Perhaps there was no universally best solution.

Much depended upon how successful reduction in the incidence of polio had been and—perhaps still more importantly—what still needed to be accomplished. Though incidence of the disease had fallen dramatically both the USA and Britain were still faced with hundreds of cases per year. Making matters complicated was the fact that three small countries, Finland, the Netherlands and Sweden, had never introduced the attenuated vaccine. These three countries, uniquely, had continued to use the Salk vaccine alone, and with great success. Lock in had not, in fact, been complete. How was the example of these countries to be balanced against what were still believed to be the valid arguments in favour of the attenuated vaccine? It is not difficult to imagine that the potential advantage of indirect protection for unvaccinated populations would weigh more heavily the greater the distance still to go. In other words, where there were still hundreds of cases annually among the unvaccinated, and where vaccination levels were only 60–70% (as in the USA), indirect protection could seem a more important advantage than where only 5 or 10 cases occurred annually and vaccination levels exceeded 80% (as in Sweden or the Netherlands).

Partly as a result of Salk's efforts, in the USA in particular the controversy would not die down. Could the country, in fact, rely exclusively on the live vaccine? Concerned by the question of safety, and under pressure from manufacturers worried about possible liability, the US Secretary of Health Education and Welfare asked the Institute of Medicine to review the matter yet again.

In early 1977 the Institute of Medicine Committee delivered its report. A major issue is the small but politically significant risk associated with use of the attenuated vaccine: estimated at one in anything between 4 and 23 million depending on way risk is calculated. "Such a risk would be acceptable," Dr. Nightingale (the project study director) writes, "except that countries using only IPV report no serious complications" (Nightingale, 1977). Did it thus make sense for the USA to abandon the attenuated (Sabin) vaccine in favour of the inactivated (Salk) vaccine? Using IPV the Netherlands and Sweden managed to protect their populations without the risk of vaccine-attributable disease . . . but they had vaccinated more than 80% of their populations. This was not the case in the USA.

On 1 April 1977 *Science* devoted a two page article in its 'news and comments' section to the controversy. Salk's attempts to rehabilitate his vaccine in the USA were reviewed. "His warmest reception," wrote Philip Boffey, "seems to have been before the Senate health subcommittee . . . the committee's ranking Republican, Senator Jacob Javits of New York, said he found it "amazing" that the government had not "reversed its field" and reinstated the Salk vaccine. The views of organised medical groups, Javits suggested, are now "outdated". Similarly, the subcommittee's chairman, Senator Edward M. Kennedy, pushed hard on the theme that parents should be given a choice and enough information . . . but none of the expert groups that have reviewed the data seems ready to jump on Salk's bandwagon". The evidence was ambiguous and could be read as showing the superiority of the OPV, or of the IPV, or as suggesting the need for some intermediate strategy using both vaccines.

The Institute of Medicine Committee took the same view as Senator Kennedy, recommending use of both vaccines and some degree of personal choice on the part of parents. But in the event the virtually complete consensus, virtually complete lock in, around the OPV was not threatened. Few experts were willing to take the risk of recommending a switch back to the Salk vaccine, or even of allowing parents to choose. In his *Science* article Philip Boffey suggested that the medical profession would be opposed to the possibility of choice. Individual parents could after all choose for the vaccine that carried no individual risk even when the medical profession was convinced that the alternative was in the collective interest. Moreover, if IPV was to be offered, even as an option to parents, where was it to be obtained? There no longer was any US-based manufacturer of IPV.

The relationship between evidence-based argument, and socio-economic process, has changed. We saw that around 1960 it had been the arguments in favour of the OPV that had initiated the process of (almost complete) lock in. By the 1970s, the evidence no longer plays the determinant role it had played as the mechanisms underlying 'lock in' begin to act. The agents responsible were to be found both on the user and on the producer sides. So far as public health authorities were concerned existing immunisation schedules, established routines of health care workers, the familiarity and faith of the public, all provided reasons for not changing course. For the vaccine manufacturers, needless to say, a major concern was with the investments tied up in existing facilities. The costs of setting up IPV production would be considerable.

"Eli Lilly & Co, which used to make Salk vaccine, estimates that a $30 to $50 million investment would be required over 3 years time. There is also some doubt that there would be an adequate supply of monkey kidney cells, which are used to grow the viruses for both vaccines but which are needed, some say, in greater quantity for the Salk vaccine than for the Sabin vaccine" (Boffey, 1977).

This does not mean that evidence and argument have become unimportant. It remains necessary to justify any strategy in terms of the vocabularies of biomedical science and of public health. But the evidence, and the arguments, are no longer conclusive. Perhaps they can no longer be conclusive. For example, did the fact that wild polio virus had been eradicated from Finland prove that the Salk vaccine offered herd immunity? Salk argued that it did, whilst others disagreed. It is hard to see how the relevance for one country of another country's experience could be proven. Lock in was almost complete. With the exceptions of The Netherlands, Finland and Sweden, attenuated vaccine was in universal use. Though concerns at the possible risks of this attenuated vaccine had clearly arisen, these concerns were not strong enough to force any country seriously to reconsider its use of the OPV. The commitments that had been made by the late 1970s in virtually all countries, both on the production/supply side and within the public health system, placed far weightier demands on the evidence, for a change of course to seem necessary, than had been the case earlier.

4. A protected niche in the public sector[12]

No less feasible, as we move into the 1980s, was that the countries that had remained faithful to the IPV would ultimately capitulate. Even if the scientific evidence was inconclusive, socio-economic logic of vaccine production and use would eventually bring matters to a conclusion. Processes of 'lock in' could still lead to the elimination of IPV as a weapon in the fight against polio. This is not what happened.

From an economic point of view, devoting R&D resources to improvement of the technology which is being 'locked out' is not rational. With growing economies of scale, as practices become increasingly established and investments all the greater, the chances of recouping investments would decline. Devoting resources to improvement of the Salk vaccine, at a time when most of the world had committed itself to the Sabin vaccine, would then seem to make little economic sense. That expertise in IPV production did not disappear was due to the existence of a 'niche' largely protected from economic forces. Although two commercial companies (Pasteur Mérieux in France and Connaught in Canada) did maintain some competence in IPV production, it was at the Dutch state institute, the *Rijks Instituut voor Volksgezondheid*, that ways of more

[12] A preliminary version of this section was published as Blume and Geesink (2000b).

efficiently producing an enhanced Salk vaccine were sought and found. It is thanks largely to the work of the RIV that the Salk vaccine survived as a weapon the in fight against infectious disease. It is through that institute's collaboration with Pasteur-Mérieux-Connaught (merged from 1990) that the enhanced IPV was later re-launched onto world markets.

Tracing the process by which the IPV was reconstituted as a credible option leads us to an innovation process driven, in its beginnings at least, by a logic that did not derive from economic incentives. Innovation was motivated by the attempt to provide the Netherlands with a more powerful weapon in the fight against infectious disease,[13] and by perceived inadequacies in the production process. An important 'inadequacy', as we will see, was the dependency on a continuous supply of wild monkeys.

When the Netherlands started its national vaccination programme in 1957 the combined vaccine against diptheria pertussis and tetanus (DPT, in Dutch DKT) was produced by the RIV, which already had considerable experience in production of bacterial vaccines. Production of DKT on the scale needed posed technical problems that could not be solved with the skills available in the Institute. Investments in new technology, and personnel to develop it, would be required.

When it was decided to vaccinate against polio, vaccine was initially imported from Belgium. In 1959 RIV received government permission to produce polio vaccine itself. A chemical engineer Paul Van Hemert adapted a type of vessel initially designed for the production of antibiotics—the 'fermentor'—to the production of vaccines (van Hemert, 1971, p. 20–33). This work led to what became known as The Bilthoven Unit, named after the institute's location. The new system was a vast improvement on the previous one. Previously, explains Hans Cohen, at that time head of vaccines production, "They did a few hundred flasks per day, perhaps 500. Four technicians were engaged on that. A few hundred cc were removed from each flask, and then you had a hundred litres . . . but God knows of what. I can still see it . . . quite an operation. The contents of all the flasks were thrown in together, filtered, centrifuged, washed. You had such trouble with moulds. Such an old institute . . . there was no bacteria or dust-free space. The Bilthoven Unit was a breakthrough in terms of sterility alone, because everything took place in a closed system. You didn't have to pour things anymore. Through applied pressure in such a system you could keep bacteria out, and the inside stayed sterile". Using this fermentor, within a relatively short time RIV had a system in which polio virus was being grown continuously, under controlled conditions on monolayers of monkey kidney cells, themselves growing on the surface of these fermentors. By combining the polio vaccine with the DKT, thought Cohen, it ought to be possible to increase vaccination coverage, since fewer injections would be required. Thus, a start was made, in parallel, with development of a combination DKTP vaccine. This led to new technical problems. The antiseptic substance, merthiolate, contained in the DKT component, proved to inactivate the polio vaccine and had to be left out. This led to new demands on purity and sterility. Nevertheless, by 1962 RIV had succeeded in producing a combination DKTP vaccine, for use in the national child vaccination programme.

Used both as the substrate on which the virus was grown, and for testing the vaccine, monkeys played a major role in polio vaccine production. The supply of monkeys had been a major problem since the start of polio vaccine development, with producers constantly complaining both about the shortage of monkeys and the health of the monkeys. By 1970, the RIV was importing 5000 Cynomolgous monkeys each year, largely from India. Many were sick on arrival, 15–20% died, and some carried infectious agents potentially hazardous to those handling them. Working with wild monkeys was difficult, a health risk, and expensive. Not only that, a number of countries (including India) were beginning to ban export of monkeys. By 1970, finding ways to reduce the dependency on the kidneys of captured monkeys was becoming urgent. The RIV established a monkey breeding colony. But monkey breeding had its own problems, and other approaches were sought. This led to use of the so-called 'trypsinisation' technique, introduced by van Wezel in 1971, and which led to a fourteen fold increase in cell yield per monkey. Ways were found of using cultured kidney cells, in place of tissue taken directly from a live monkey. Thanks to these innovations, by 1972 the RIV had reduced its need for monkeys to about 500 per annum. The prospect of bringing numbers down much further

[13] Interview with H. Cohen 25.11.1998, interview with J. Ruitenberg 21.12.1998.

seemed within reach, and was indeed soon achieved. The number had fallen to 50 by 1975 and by 1978 to just 7.

To the 'unit process' previously developed by van Hemert for culturing bacteria (van Hemert, 1971), Anton van Wezel, who had been trained both in chemical engineering and biochemistry, added a further crucial innovation. The surface on which cells were cultured could be vastly increased by filling the vessel with small plastic (Sephadex) beads held in suspension through rotation in the vessel (van Wezel et al., 1979). Now cells and the virus could be grown on a large scale, in units wherein temperature, pH and oxygen concentration (all crucial) could be continuously monitored and adjusted. This approach was much less labour-intensive and the chance of product-loss through infection was much reduced. In place of the 2000 glass bottles they had used previously, the RIV now had stainless steel fermentors, filled with plastic beads, of a capacity of some 125 l.

The unit process, trypsinisation, the use of microcarriers . . . these were three of the important 'process' innovations made by the Bilthoven group, with major implications for the economics of IPV production.

5. From local niche to global alternative

The RIV had developed a technology for efficiently producing a high potency, standardized vaccine, on a scale sufficient for the needs of the Netherlands. There was little interest in exploring the possibilities of (re)developing an international market for IPV.[14] So how did the enhanced IPV reach international markets? Put in another way, through what processes was the technology taken from its local niche in a renewed attempt at reversal of the lock out process? Here evidence, the reflexive level, once more plays an important role. But there is a difference from the earlier period. Collecting evidence has become problematic by the late 1970s, given virtually global lock out. What is more, public health experts were by now unwilling to be convinced of the benefits of IPV.

The small group that set about rehabilitation of the IPV called itself the Forum of Advanced Immunization Research (FAIR). Among its members were Jonas Salk, Hans Cohen, John Beale, and the industrialist, philanthropist, and campaigner for world health Charles Mérieux. They would have to accomplish a lot. The international public health community would have to be convinced. The argument that, unlike the OPV, there was no risk (of reversion to virulence) was insufficient. They would have to show that there was some formulation of the enhanced IPV which was at least as good as the OPV under a wide range of conditions, but most importantly in tropical countries. The fact that the OPV was sensitive to temperature, and in tropical countries required an extremely expensive 'cold chain' right through to the point of vaccination, was an acknowledged weakness (Robbins, 1988). The next problem was how and where to conduct the trials that were needed?

Much effort went into establishing trials in francophone Africa, a region in which Mérieux's company and charitable foundations had many contacts. On 5 May 1977 Salk wrote to Mérieux's associate Philippe Stoeckel, then in Upper Volta (now Burkina Faso), explaining that[15]

One of the purposes in conducting the proposed study is to reduce the cost of using killed poliovirus vaccine (KPV). This would be accomplished by reducing costs related to administration, by diminishing the number of doses required for effective immunization and by eliminating costs of special refrigeration since KPV is stable under normal conditions of refrigeration.

Salk goes on to express the "hope that you will be able to obtain the necessary permission to organize this investigation. . ." Stoeckel was successful. In June the Minister of Public Health and Social Affairs of the Republic of Mali granted official permission for a study of the vaccine in the country. Further trials followed, both in French West Africa and in Finland and Sweden, that had continued to use IPV.

At a meeting of FAIR, held in the Netherlands in December 1977, findings and strategy were reviewed "From [studies in France and the Ivory Coast] it can

[14] Interview with P. van Hemert 25.3.1999. Thus, J. Melnick wrote to van Wezel The Israeli government is also interested in obtaining inactivated p + oliovirus vaccine (types 1 and 3). Is there any way in which your vaccine can be obtained for Holland. I have been told that it is not for sale outside of your country (Melnick to v. Wezel, November 2, 1977. RIVM archives).

[15] Letter from Salk to Stoeckel, RIVM archives.

be concluded that the protection against polio in developing countries was more satisfactory after vaccination with IPV than with OPV". In the Middle East "there are still a large number of polio cases each year although the population is well vaccinated with OPV. Even after three to four doses of OPV some children did not develop antibodies". Jonas Salk, chairing the meeting, pointed out that "The intention of this meeting is to establish working groups on the production, control and application of IPV to initiate and co-ordinate [the various studies needed]. The results of these studies will be forwarded to WHO and the regulation authorities of the different countries".[16]

These efforts were slowly having an impact. A WHO Advisory Group, meeting in Delhi in November 1979, agreed on the need of "additional data on the effectiveness and the costs of both killed and live poliomyelitis vaccines under various conditions of use" And as practical medium term goals the experts referred to the need of both a more stable OPV and a cheaper IPV.[17] A Dutch participant at this meeting reported "renewed interest for the inactivated polio vaccine, partly as a result of recent field trials in Africa, Finland and Sweden using in part IPV prepared by the RIV". There were valid objections, to be sure, relating to the relatively high price of the IPV, and the number of monkeys used. But thanks to the technological advances recently made "these objections are no longer valid".

Salk was delighted. The possibility of enhanced IPV really becoming a global alternative was starting to affect the Dutch too . . . in contrast to the domestic contours of their earlier perspective. Early in 1980 Hans Cohen visited Geneva, authorized to discuss a donation to WHO/EPI of one million guilders, part of which was to be reserved for purchase of IPV from the RIV.

Unlike the RIV, the Mérieux company was certainly interested in world markets. They recognized that if IPV was to be produced on a much greater scale the production process would have to be modified still further. Although van Wezel had succeeded in greatly improving the vaccine yield per monkey, it still was not good enough, especially given the concerns with animal rights that were increasingly emerging. Could some substitute be found for monkey cells as substrate? Or rather, in place of the sub-cultured cells (which could be used two to three times before dying) was it possible to find cell lines which would continue to propagate: that is, which would reproduce themselves (and so could be used) indefinitely? The problem is that cells having that property of continuous propagation look suspiciously like cancer cells. There was the risk that they might contain a gene that would induce cancer in humans. Whilst the Dutch were not interested in pursuing this line of investigation Mérieux saw it as a prerequisite to any substantial increase in the scale of production of IPV. John Pettriciani, a virologist with the NIH, had identified three types of cell from the monkey kidney which could potentially be used in virus cultivation. Encouraged by Salk, scientists at the Institut Mérieux eventually opted for so-called VERO cells, derived from kidney cells of the African green monkey, but which could be used continuously and which appeared to be free of viral contaminants. From an industrial point of view it looked promising[18]

The problem then was to have the world scientific community accept it as a cell substrate for human vaccine production . . .. Anyway, eventually this was agreed to in '78 at the Lake Placid meeting, that we would go on with VERO. That was the step that Mérieux took: the adaptation to the microbeans and fermentor of Van Wezel of the VERO cell.

The accumulating data were leading epidemiologists to reconsider their earlier certainties. In 1980 the RIVM hosted a Symposium on the 'reassessment of inactivated poliomyelitis vaccine', organised for the International Association of Biological Standardization. One of the speakers was J.L. Melnick, who had evaluated the Sabin and Cox strains of live virus vaccine 20 years previously. Melnick explained to his audience that "in a number of studies, live poliovaccine has been found to be less effective in inducing antibodies and immunity in children living in tropical areas than among children residing in temperate climates" (Melnick, 1981). He reviewed, once more, the advantages and disadvantages of the inactivated and live vaccines. Interestingly, Melnick was sceptical about one of the features of the live vaccine which had previously been presented as an advantage: "some people

[16] document in RIVM archives.
[17] WHO document EPI/GAG/79/REP, RIVM archives.
[18] Interview with Dr. Philippe Stœckel, ex-Secretary General of FAIR, Marnes-la-Coquette, 29 January 1999.

consider this spread into the community to be an advantage, but the progeny virus excreted and spread by vaccines often is a mutated virus. Obviously it cannot be a safety tested vaccine, licensed for use in the general population". Melnick concluded that "it may be that only the combined use of killed and live polio vaccines will ultimately lead to the total conquest of the disease and possibly the eradication of the virulent polioviruses". A few years later this was the strategy recommended by a committee of the Institute of Medicine in the United States (Institute of Medicine, 1988). However, not only did data still allow of alternative interpretations, but there were other things to be taken into account in thinking about any change of course. For the WHO, in particular, cost was a major concern. IPV was considerably more expensive, was not available in sufficient quantities, and as far as WHO was concerned its advantages, "particularly where only low proportions of susceptibles are being immunized" had not been sufficiently demonstrated. The WHO continued to recommend OPV for routine use in countries expanding their immunization programmes.[19]

Despite suggestions in the literature that the costs of IPV could be brought down, and that eIPV could even be more cost-effective in tropical countries (Mouliapelat et al., 1988), little changed in the late 1980s and early 1990s. According to Philippe Stœckel (now of the Fondation Mérieux) the rejuvenated IPV threatened political and economic interests: "we were bothering the WHO. We were an alternative, we were another solution. We were, they said, distracting people. With one goal, the use of OPV. We were sort of challenging them and they didn't like that". As Stœckel sees it, it is protection of their home market by pharmaceutical companies with no IPV production facilities that is principally at stake here. Whatever academic advisory committees may say, whatever the epidemiological evidence, no practical role for IPV can be allowed.

But by the mid 1990s things were starting to change in a number of countries: in Canada, France, Germany, among others. In the USA a working group of the Advisory Committee on Immunization Practices (ACIP) was established in late 1994, to once more review polio vaccination. In late 1996, acting on the advice of the ACIP, the Center for Disease Control and Prevention (CDC) recommended that the then-current four-dose OPV vaccination schedule be replaced by a two-plus-two schedule.

This change of course in the USA provoked widespread rethinking in Britain and other countries (Finn and Bell, 1998). The WHO, still committed to the eradication of polio by 2000, remained convinced that only OPV should be used in most of the world. The arguments were the familiar ones: passive vaccination, ease of administration . . . and cost. The WHO was worried that across the globe public health authorities would interpret the US recommendation as implying that OPV was not safe, or that it was not sufficient to control polio (Hull and Lee, 1996). If they then insisted on introducing the same mixed schedule as in the United States there would be a resource problem. A similar argument was made in the UK, where IPV was said to cost the National Health Service ten times as much as OPV (Heath et al., 1998). Early in 2000 the United States took a further step. Backed by its ACIP and by other professional bodies, the CDC recommended complete phasing out of OPV and a complete switch to IPV in the USA. At the WHO the view remained that use of IPV was appropriate only for the USA and a few other rich countries. At the global level, the eradication date had had to be pushed back to 2005 and new estimates were that $1.23 billion more than currently available would be needed to get the job done. No one was looking for extra costs or disruption of present goals and strategies.

6. Lessons from history

One conclusion from this historical study is that the concept of lock does have explanatory value in the field of health technology. Though dominance of the OPV was initiated by scientific and practical arguments, as experience and data accumulated the argument became less clear-cut, and processes of lock in came into play. The utility of the concept of lock in is that it directs our attention beyond the technological options that have become excluded to the practices and the interests that give rise to this exclusion.

The second conclusion concerns the role of public sector vaccine institutes (PSVI). When the Dutch state vaccine institute, RIV, invested in IPV R&D the incentive to innovate was not global markets and eco-

[19] R H Henderson, commenting on Melnick, Bilthoven 1980.

nomic returns, but local vaccination practices and local production bottlenecks. Conceived in terms of normal market economics, R&D investment directed at a 'locked out' product makes no sense. But as a public sector institute, closely related to the Ministry of Health, it was public health and not commercial considerations that shaped the work of the RIV. It was thanks to this that an enhanced IPV became available for subsequent re-introduction in a number of industrialised countries. The relevance of the analysis derives from what it adds to current discussion of PSVI: a discussion now focussed on resources, competences, and novelty. As pointed out in the introduction, the dominant view today is that lack of resources and competences greatly restricts the role of PSVI (e.g. Milstien et al., 1997).[20] To look at the potential contribution of PSVI in terms of processes of lock in that may be occurring, and in terms of distinctive incentives to innovate, is to look quite differently. At a time in which concentration in the vaccines industry is increasing rapidly the possibilities of lock in such as described here are becoming all the greater. Given growing awareness of regional variation, through mutation, in circulating pathogens, and given differences in modes of transmission and in public health priorities,[21] support for local or regional competences may be of increasing importance.

That incentives for the pharmaceutical industry to invest in developing new vaccines are far less than in the case of drugs has become common knowledge. Total global revenue for vaccines is estimated to be $US 4–5 billion annually today: a tiny fraction of turnover and less than some individual blockbuster drugs can yield (Gold, 2002). How to commit the pharmaceutical industry to the search for vaccines whose market will be exclusively in poor countries? The question has been endlessly debated. Public-private partnerships, such as the International Aids Vaccine Initiative (IAVI), are one approach that currently finds favour. Other proposals have included a substantial fund from which purchases could be guaranteed and, on the supply side, a large fund for subsidising R&D to be managed perhaps by WHO (Archibugi and Bizzarri, 2004). The implication of this paper is complementary and slightly different. Coupled as they typically are to national vaccination programmes, PSVI should respond to quite different incentives to innovate than do multinational pharmaceutical companies. These differences will be manifest both in the search for new vaccines and in improvements to existing ones. This crucial difference, giving PSVI a distinctive character and implying that they have a distinctive contribution to make, finds no reflection in current debate at the global level. This debate, to reiterate, seems largely focussed on the ways in which they can best be assimilated as subordinate partners in a commercially-dominated vaccine innovation system (WHO, 2000). A principal conclusion of this paper must then be that the terms of this debate require reconsideration.

[20] For example, at a meeting of International PSVI in 2000, Julie Milstien of the WHO "concluded that the role of PSVIs as manufacturers of 'old vaccines' may not be sustainable and that PSVMs must expand capacity to produce new vaccines via joint ventures or bulk-filling agreements" (WHO, 2000, p. 10).

[21] See for example Girard's conclusion regarding pertussis: that there may be no single vaccination strategy appropriate for all countries (Girard, 2002).

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