



# Towards a History of “The Vaccine Innovation System,” 1950-2000

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## Introduction

The most familiar histories of vaccines and vaccination are variants on a narrative of progress. Written by practitioners in the field, scattered through the professional literature, they recount the contributions that vaccination has made to reductions in mortality and morbidity from one infectious disease after another: polio, diphtheria, measles, and whooping cough among others. The eradication of smallpox is, rightly, hailed as one of the greatest of vaccination's successes. Senior vaccine scientists are frequently inclined to remind us of the remarkable advances in vaccine science and technology that have made all this possible. To be sure, progress has not always been at the same pace. In the early 1960s an optimistic view of the future seemed particularly appropriate. Control of viral diseases seemed within reach, despite continuing and heated debate concerning the relative merits of live and killed virus vaccines. Jonas Salk's inactivated (killed) polio vaccine and then Albert Sabin's rival live vaccine had, together, vastly reduced the ravages of this terrible disease. Jonas Salk, in particular, had achieved world renown. Soon afterwards, successes in developing vaccines against other diseases of childhood, less feared than polio but in much of the world still killers, followed. Measles was the first, with a vaccine introduced in the United States in 1963. In the 1950s only two vaccines had been given to all children in the United States: against smallpox, and a compound DTP (diphtheria, tetanus and pertussis) vaccine. By the late 1980s, smallpox

vaccination was no longer needed, and children were given four vaccines by the time they entered school: DTP, oral polio, MMR (measles, mumps, and rubella) and Hib (*Haemophilus influenzae type b*). By 2005, American children received nine vaccines, offering protection against twelve diseases.<sup>1</sup>

Past successes and recent discoveries seem to imply that we can continue to look forward with optimism. Such extrapolations are common. For example, in his foreword to a 1996 government report, the British Chief Medical Officer of Health, Sir Kenneth Calman, uses characteristic language:

Two hundred years after Jenner's first observations, we are seeing a new era beginning for vaccines. With the application of genetic manipulation techniques, better understanding of processes of infection and immunity, and a widespread recognition that investment in disease prevention is one of the best uses of resources, we can expect ever more vaccines, and ever more diseases eradicated.<sup>2</sup>

The history that I want to try to sketch out in this paper is a less familiar and a less comforting one. It will not be an account of progress in vaccine technology, or of the scientific breakthroughs on which progress has been built. Rather, my focus will be on the institutional changes, and the changes in rhetoric, associated with successes and failures in developing and producing vaccines. An apology is required at the very start, for what I will have to say is more an agenda for future research than an account of what we know. Most of the work still has to be done, and for two reasons. One has to do with the power of the familiar narrative of progress: a narrative that speaks to the professional and institutional interests that helped shape it, and that at the same time provides reassurance in a world beset by risks and by doubts. It is difficult to escape its influence. The second reason has to do with the kind of scholarly enterprise entailed. Writing the history of the institutions involved in developing and supplying the tools of public health, and their interrelations, is a much more formidable task than writing a history that takes a vaccine or group of vaccines as its focus.

The history of what I am calling the “vaccine innovation system” must draw its materials from around the globe, for some of the institutions that comprise it are located far from the scientific metropolis. We know a little of how they came to be there: of the important roles played by colonial relations, by the Rockefeller Foundation<sup>3</sup> and by the Institut Pasteur<sup>4</sup> a century ago. We know much less of what happened thereafter, or of their evolution—let alone interrelations—in an era marked by decolonization, the Cold War, and free trade ideologies. Underlying what I shall have to say, therefore, is not so much a set of convictions regarding the (unquestionable) benefits of vaccines and vaccination, as it is a set of questions regarding the changing roles of states, supranational organizations, and private corporations in this vaccine innovation system. I hope that in this paper I can at least hint at the fruitfulness and the significance of this alternative agenda for future historical research.

### The Social Organization of Vaccine Innovation

The middle decades of the twentieth century were a turbulent time in the vaccines field. At the end of World War II, interest on the part of the pharmaceutical industry, that in the 1930s had been substantial, had now turned elsewhere. This was partly a consequence of the emergence of new and powerful, and potentially profitable, antibiotics. For example, a pneumonia vaccine developed in the 1940s was virtually ignored because treatment with the new penicillin and sulfonamide drugs was much the more attractive option. The pharmaceutical industry was expanding the scope of its research and production into several therapeutic areas, all of which appeared more profitable than vaccines. Elsewhere, however, research was going on that was to change matters dramatically. Notably, at Harvard University, John Enders, Thomas Weller, and Frederick Robbins were developing new and far safer methods of culturing live viruses: work for which they were later to receive a Nobel Prize.<sup>5</sup> This work was to lead to the development of a range of new viral vaccines (attenuated polio vaccine, measles, rubella, mumps...), but, most important for the argument here, the prospects of breakthroughs in this area catalyzed new attention for vaccine development.

The career of Maurice R. Hilleman, possibly the twentieth century's most renowned and successful developer of new vaccines, shows the changes taking place in the vaccine world.<sup>6</sup> Having completed graduate work at the University of Chicago, he joined the virus laboratories of E. R. Squibb and Sons of New Jersey in 1944. There he worked on development of a vaccine against Japanese encephalitis B, needed by troops fighting in the Pacific. In 1948 he left Squibb to join the Walter Reed Army Institute of Research, where he worked principally on influenza: the "drift and shift" in antigens, and how a future flu pandemic could be averted. In 1957, by which time the implications of the Harvard research were clear, Vannevar Bush, then chairman of the newly merged Merck, Sharp & Dohme, decided that the company needed a new push in the virus field. Hilleman was recruited to establish and run a virus vaccine research initiative that would encompass basic research, development, and (through a collaboration with the University of Pennsylvania School of Medicine) clinical research. Hilleman was provided with ample support, and launched a major and ambitious program of work directed at the major diseases of childhood, starting with measles.<sup>7</sup>

There was little or no patent protection for vaccines in those days, and knowledge of vaccine production techniques was either exchanged or leaked out as discoveries were disclosed to government regulatory bodies. However, lack of patent protection—which was to continue as the norm in the vaccines field until the 1980s—was not a barrier. Spurred by the new scientific possibilities, and by the more active role being taken by the federal government in promoting the use of selected vaccines (starting with Salk's polio vaccine), by the late 1950s the number of manufacturers licensed to produce vaccines in the United States was growing. Industrial commitment, however, was to remain uncertain and unreliable.

By the 1970s, the vaccine market was once more losing its appeal for pharmaceutical companies: a situation to which the swine flu fiasco of 1976 certainly contributed.<sup>8</sup> And now, in the United States in particular, this was becoming a matter of political concern. Like the majority of Western industrialized countries, the United States was wholly dependent on private pharmaceutical companies for its supplies of vaccines. In the United States it was noted that from the mid-1960s to the end of the 1970s (a twelve-year period) the number of licensed vaccine

manufacturers had dropped from thirty-seven to eighteen, whilst the number of licensed vaccine products was also falling.<sup>9</sup>

The Office of Technology Assessment (OTA) of the United States Congress, investigating the matter, felt that “The apparently diminishing commitment—and possibly capacity—of the American pharmaceutical industry to research, develop, and produce vaccines...may be reaching levels of real concern.”<sup>10</sup> As far as nineteen vaccines, including the polio vaccine, were concerned, the United States was dependent on only a single American pharmaceutical company. What if that producer decided to exit the vaccine field? There were precedents enough. For example, in the mid-1970s, Eli Lilly was working on an experimental pneumococcal vaccine with support from the National Institutes of Health (NIH). Then the company decided to terminate almost all its vaccine research and development (R&D) and production activities. Company executives told the OTA that this reflected the costs and difficulties of developing vaccines, market considerations, and carrying out the testing of each batch of vaccine as required by federal regulations.<sup>11</sup> Vaccines were more difficult to develop, test, and license than pharmaceutical products. They were also less profitable, and there were much greater risks of liability actions and huge damages if anything went wrong. After all, vaccines were typically administered to millions of healthy children.

Influential vaccine spokesmen, including D. A. Henderson, who had spearheaded the World Health Organization’s smallpox eradication program, were now arguing for a more active federal government role in stimulating and coordinating vaccine R&D. In the United States, these concerns, and the desirability of government policies aimed at facilitating vaccine development and stimulating industrial commitment, remained an issue.<sup>12</sup> William Jordan, director of the Microbiology and Infectious Diseases Division of the National Institute of Allergy and Infectious Diseases (NIAID), estimated that all federal agencies (NIH, Center for Disease Control, Food and Drug Administration, Army, Navy, and USAID) had together spent only \$23 million on vaccines R&D addressing eleven domestic and seven tropical diseases in 1978. “Clearly the vaccine effort needed to be expanded.”<sup>13</sup> In 1986 the U.S. Congress established a National Vaccine Program (NVP), with the task of coordinating the vaccine-related activities of federal agencies and

private industry, and of determining what vaccines are needed. But the NVP led an uncertain existence, with “little money and less clout” as a *Science* reporter put it in 1994.<sup>14</sup> By that time leading vaccine scientists were arguing for the creation of a more powerful National Vaccine Authority.<sup>15</sup> The proper role of the federal government continued to be a matter of political debate. Some argued, for example, that the 1993 Vaccines for Children Act, providing an entitlement to free vaccines for uninsured and certain other groups of children, acted as a serious disincentive to vaccine manufacturers<sup>16</sup>

Whilst political discussion continued, in the 1980s more American pharmaceutical companies left the vaccine business. By the mid-1990s, only four private wholly owned United States firms were active, of which only two (Lederle-Praxis Biologicals and Merck) were active developers of new pediatric vaccines. However, the picture is more complex than this suggests, and other elements have to be added. One is the influx of small biotechnology companies into the field, the result of the emergence of new biotechnology-based ways of making vaccines. A second is 1986 legislation that provided important encouragement to vaccine manufacturers. In that year, driven largely by widespread popular concern at side effects of the pertussis vaccine, and the concomitant surge in damage actions against manufacturers, the U.S. Congress passed legislation establishing the National Childhood Vaccine Injury Compensation Program. This limited the liability of manufacturers and established a public fund from which possible compensation claims could be paid. Reassured by the protection this act afforded, pharmaceutical firms began to reconsider their commitment to vaccines.

Changes in the vaccine field in the 1980s and 1990s did not affect the United States alone. Far from it. In 1998 Seung-il Shin, of the International Vaccine Institute (IVI), then recently established in Korea, characterized these changes as follows:

The most important thing driving the transformation of the vaccine enterprise (which encompasses the development, clinical testing, production, licensure and distribution of vaccine) is the increasingly complex scientific and technological base that is required....

The second factor...is the changing nature of technology ownership...vaccine development has become primarily the purview of large industrial laboratories.... In Pasteur's day, and even as recently as forty years ago when the polio vaccines were first developed, most of the new technologies needed to manufacture vaccines were owned by the public. The scientists and organizations that developed them often assisted and funded the technology transfer to institutions in developing countries....

The third factor is the globalization of international commerce.... The global vaccine industry in 1998 is thus dominated by a small number of large multinational companies, instead of the smaller, publicly owned and public-spirited national vaccine production centers that were until recently the norm. Consequently, some of the key decisions regarding which vaccines to develop and how to distribute (market) them are no longer made by scientists and public health officials but by business executives....

Finally, the increasingly stringent international product safety standards required of vaccines.<sup>17</sup>

What consequences have these changes, and in particular the growing role of business executives, had for institutions involved in developing and producing vaccines? A comprehensive answer to this question must await a good deal of further research, for consequences certainly differed from country to country, and between the public and private sectors. One of the few detailed studies we have is Louis Galambos's comprehensive history of vaccine development at Merck: one company that has maintained its commitment throughout.<sup>18</sup> This is a success story, attesting to the crucial role that the company has played in vaccine development and production. The study shows how Merck was able successfully to adapt to new scientific opportunity. As the focus in vaccine development shifted from bacteriology to virology (starting in the 1940s and lasting through the 1980s), and then to recombinant DNA technology, so Merck (and the companies it absorbed) modified their organizational structures and—crucially—their scientific capabilities and networks.

To be successful, however, Merck had to respond not only to changes in vaccine science, but changes in the vaccine market also. This is a market that is particularly sensitive to changing government policies. From a business point of view government policies, in the United States, had two sorts of effect: one negative and one positive. On the negative side, Galambos refers to the growth of the public sector market, both nationally and internationally. The Vaccines for Children Program had been just one in a series of measures through which public sector agencies negotiated rock-bottom prices for their bulk vaccine purchases, and so drove down the profits available for investment in R&D. The share of this public market was growing, to the extent that, according to Galambos, economic motives for remaining in the vaccine business were continuously eroding. On the positive side, Galambos refers to relaxation in antitrust laws in the 1980s and 1990s. These changes had made it possible for large companies like Merck to establish strategic alliances “that broadened the front across which it innovates and enabled it to strengthen its position in global markets.”<sup>19</sup> And this is what it did.

As David Mowery and Violaine Mitchell wrote in 1995, “the extent of acquisitions and alliance formations among vaccine manufacturers during the past decade, especially from 1990 to 1993, is staggering.”<sup>20</sup> The diagram that they provide to illustrate their argument links Merck with a number of other major manufacturers (notably Pasteur-Mérieux in France), with a number of smaller biotech companies (including Biogen and Medimmune), and with a few public sector institutes (RIVM [National Institute for Public Health and the Environment] in the Netherlands and the Commonwealth Serum Laboratory in Australia).

Reflecting the developments listed by Shin, the vaccine system was changing in shape and size. But the implications of these changes varied greatly from country to country. Consider, for example, the implications for what Shin refers to as the “publicly owned and public-spirited national vaccine production centers,” that had previously been the mainstay of vaccine production. In both China and India private vaccine manufacturers emerged and flourished alongside the older public sector ones. In some countries, including Sweden and Australia, the public sector institutes (the Swedish State Bacteriological Laboratories and the Australian Commonwealth Serum Laboratory), were privatized (in



1993 and 1994, respectively). There were other countries, including Colombia, where public sector production was gradually phased out.<sup>21</sup> In the Netherlands, by contrast, private sector attempts at acquiring the public sector vaccine facility (then part of the Dutch Institute of Public Health, RIV, later renamed RIVM) continued to be resisted. Though vaccine production remained in the public sector, the institute was not immune to developments taking place in the vaccine field at large. In order to understand how it was affected, however, we have to focus down to consider the vaccine development work being conducted there.

With responsibilities for vaccine supply (including development, manufacture and/or purchase) of vaccines located in a single public sector institution, the Netherlands<sup>22</sup> was not faced with the concerns regarding security of supply that were arising in the United States in the late 1970s. But the point to be made here concerns not security of supply but incentives to innovate. Since their foundation early in the twentieth century, state vaccine institutes like the Dutch Institute of Public Health were concerned with meeting the vaccine requirements of national public health systems. The incentives to innovate were not principally commercial but could be public health needs. Innovation could indeed fly in the face of commercial reasoning. This is shown clearly by RIV's collaboration with Jonas Salk in developing an improved inactivated polio vaccine (IPV).<sup>23</sup>

Disputes regarding the relative merits of live and killed vaccines, compounded by personal animosity between the principal investigators, had marked the search for a polio vaccine since the early 1950s. Though Salk's killed (IPV) vaccine was first to be licensed, in the course of the 1960s most major manufacturers abandoned it and switched to production of the rival Sabin oral polio vaccine (OPV). In doing this they responded to majority scientific and medical opinion. There seemed reason to believe that the OPV would be quicker acting and would control the disease more effectively. Thus, whilst in the mid 1960s, some 4 to 5 million doses of IPV were being distributed annually in the United States, 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. With the exception of a few small West European countries with very high rates of vaccination coverage, the whole world switched to OPV.

By the 1970s, as evidence that, in a small number of cases, the weakened virus used in the OPV reverted to virulence and led to vaccine-induced disease, matters became more complex. By then, choice for one vaccine or the other should have 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. 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. In the event, the virtually complete consensus around the OPV was not threatened. Few experts were willing to take the risk of recommending a switch back to the Salk vaccine.

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. In the Netherlands, children were (and still are) vaccinated using a combination diphtheria tetanus pertussis polio (DTPP) vaccine, of which the inactivated polio vaccine was one component. The Sabin vaccine, which is taken orally, could not replace IPV in the Dutch cocktail. Introducing it would necessitate major changes in immunization practice, and given the success of the existing program there was no reason to make these changes. But there were problems with the IPV being produced by the institute. One was the enormous supply of monkeys needed for culturing the polio virus and in testing the vaccine. Ways were thus found of using cultured kidney cells for growing the virus, in place of tissue taken directly from live monkeys. In this way the need for live monkeys was reduced from 5000 per annum in 1970 to just 50 by 1975. In other ways, too, the production process was improved and the strength of the vaccine enhanced. Crucial here is that these developments were motivated in part by perceived inadequacies in the production process, and in part by the attempt to provide the Netherlands with a more powerful weapon in the fight against infectious disease, given existing vaccination practices.

In the 1970s, the RIV succeeded in developing a technology for efficiently producing a high potency, standardized IPV, on a scale sufficient for domestic needs. There was little interest in exploring the possibilities

of (re)developing an international market for IPV. Both Jonas Salk and the (French) Institut Mérieux, with which they were also collaborating, *were* interested in demonstrating that the enhanced IPV was as effective in tropical countries as the OPV that was by now in virtually universal use. Field trials were organized in Africa, though not without difficulty and even opposition. According to Philippe Stœckel, (then with the Institut Mérieux, now of the Fondation Mérieux) the improved 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.”<sup>24</sup> As Stœckel sees it, it was protection of their home market by pharmaceutical companies with no IPV production facilities that was principally at stake here.

In his review of “the ten most important discoveries in vaccinology during the last two decades”<sup>25</sup> Stanley Plotkin places the acellular pertussis vaccine first on his list. Although it had been widely used for decades, the older “whole cell” pertussis (or whooping cough) vaccine was long acknowledged to have nasty side effects: mostly not serious but worrying to parents. Far more worrying were reports in the 1970s linking the vaccine with possibly permanent brain damage in a small number of cases. In the light of these suggestions, and of the declining incidence of the disease in the industrialized world, widespread resistance to pertussis vaccination emerged in a number of countries. Japan and Sweden stopped vaccinating children against pertussis in the late 1970s, whilst in some other countries vaccination levels fell precipitously (e.g., in the United Kingdom from 70/80 percent to 40 percent).<sup>26</sup> In the United States a spate of law suits against vaccine manufacturers, demanding compensation for damage, led all but two manufacturers to abandon production of pertussis vaccine. This was a major stimulus to introduction of the National Childhood Vaccine Injury Compensation Program, designed to protect manufacturers against crippling claims, in 1986.

By the mid-1980s several research groups were working on the development of alternative “acellular” pertussis vaccines from which reactogenic and non-protective components had been removed.<sup>27</sup> By the early 1990s the global pharmaceutical industry had made a clear commitment to the new acellular pertussis vaccine. Indeed, it has been suggested that

the market prospects of acellular pertussis vaccine (costing approximately three times as much as the older vaccine) were an important factor in the expansion of the global vaccine market since 1992.<sup>28</sup> Clinical trials were initiated in a number of countries, with the NIAID playing a major role.

The results of the trials were complex. Just as in the case of the polio vaccines earlier, data did not lend themselves to unambiguous interpretation. Some of the older whole cell vaccines were clearly very good (for example, those used in Britain and France), whilst others (including that used in Canada) seemed to be poor. Some acellular vaccines seemed to be as effective as good whole cell vaccines, others less so. Side effects, however, were generally less with the new vaccines. "Health authorities are thus faced with a difficult choice. Should the better efficacy of certain whole cell vaccines be traded for the better tolerance of acellular vaccines?"<sup>29</sup> Recognizing that this trade-off is not only political but also depends upon the particular whole cell vaccine in use, there is no simple and unambiguous answer. "The answer may vary in different parts of the world. In the U.S. the greater safety afforded by acellular vaccines, as well as the recent demonstration of the lower efficacy of one of the whole cell vaccines used in a three-dose regimen, will elicit recommendations to favor acellular over whole cell vaccines. The same will be true of those countries of Europe where pertussis vaccine has not been accepted for fear of reactions."<sup>30</sup>

Today the majority of industrialized countries, including the United States, Canada, and most West European countries, have switched to one or other commercially available acellular vaccine. In the Netherlands, the Health Council has repeatedly advised that the country should switch to acellular vaccine. Disease incidence suggests that the whole cell vaccine being used, and produced by the Dutch institute, is not effective enough (or, not as effective as it used to be). However, Dutch scientists were not convinced that, in the long term, the acellular vaccine would prove the optimal solution for the Netherlands.

The answer to the pertussis problem in the Netherlands, these scientists agree, is a whole cell vaccine—but a better one than the one they had been producing. Though instructed by the Dutch Minister of Health to develop a combination vaccine incorporating a (commercial) acellular

component, the Dutch vaccine institute (by now called NVI)<sup>31</sup> was also trying to produce a combination vaccine incorporating a good whole cell pertussis component. Though they had failed to produce the vaccine they wanted themselves within the time they had, good whole cell vaccines do still exist. They are used, officially, in both France and the United Kingdom. The next best thing would be to import one of these. However, it appeared that import of the British or the French vaccines was not possible, since their manufacturers appeared unwilling to expand production: perhaps a consequence of the fact that they were also producing the new (and more profitable) acellular alternative. In the meantime, the Minister of Health, responding to yet a further recommendation of the Health Council, and a growing public furore over side effects, decided that the country would switch to the acellular vaccine. This it recently did.

This example shows two views of the relative merits of the distinct kinds of vaccine locked in uneasy equilibrium. Grounded in epidemiology and appeal to the (positive) experience of other countries, the view of the Health Council reflects what has become the orthodoxy in the industrial world. The view of the NVI is rather different. Bacteriologists and immunologists interpret the current state of knowledge differently than do epidemiologists. Dutch vaccine scientists have doubts regarding the long-term advantages of acellular vaccines. The current “uneasy equilibrium” contrasts with the situation in the 1970s and 1980s. It is more difficult than it was then to diverge from majority opinion and practice. As one microbiologist put it:

I think that the variation in vaccines between different countries will get less and less. This is of course on the one hand dangerous, but I see it as a factor that makes it more and more difficult for individual countries to escape from international advice or international consensus regarding what a vaccination scheme should or can be. [...] You see how experts have tried to get consensus, at the level of South America, North America, at the European and Australian levels, regarding how it should be.... I think more and more synchronization is taking place, as the world becomes increasingly global.<sup>32</sup>

Neither with respect to polio nor to pertussis did Dutch “vaccinologists” accept that the vaccine that had achieved, or seems set to achieve, global dominance was best for the Netherlands. In the case of polio, reasoning from the health needs of the population as well as from their technical mastery of the production process, the scientists decided that the Netherlands needed a better version of the IPV already being used, and that a more efficient production process was necessary. There was no good reason, in their view, to follow most of the world in introducing the alternative vaccine. Expertise needed to solve the technical problems was available. An improved IPV was developed not because of commercial considerations, which initially played no role. Crucial was the institute’s responsibility for producing and providing the vaccines the country’s vaccination program needed. Twenty years later, in the face of the controversy over pertussis, scientists at the Dutch Vaccine Institute were again convinced that the Netherlands needed a vaccine like the one they had, but better. Again, they reached this conclusion on the basis of scientific arguments and analysis of the epidemiology of the disease in the Netherlands itself. The preferred pertussis vaccine is not the one in which the pharmaceutical industry, sensitive to the growing political weight of public concern, had invested so much. Again the scientists tried to act on their convictions, but this time they faced difficulties of a kind that had not arisen twenty years earlier.

Global preference for the OPV had only become problematic for the RIVM when attempts were made to test their enhanced IPV in developing countries. Trials in Africa, and any demonstration of the efficacy of the enhanced IPV there, were a potential threat to investments (financial and symbolic) in the OPV, and to the strategy the WHO had built around it. Today, by contrast, the fact that acellular pertussis vaccine has become the preferred solution to disease control in the industrialized world inhibits producing the improved DTP-P even for domestic needs. Technical problems are greater, and the pharmaceutical industry, possibly looking to abandon the older and less profitable vaccine, may be less willing to collaborate. It has become more difficult to go against the grain of global consensus or, in more sociological language, the force of “institutional isomorphism”<sup>33</sup> has become far greater.

Underlying this “force” is a change in the structure of the vaccine field: one marked by changing relationships both between individual scientists and between institutions. Prior to the mid-1980s, vaccine researchers were a relatively homogeneous and relatively small group, mostly microbiologists and virologists. Knowledge was freely available and freely exchanged irrespective of place of work. That changed. Vaccines-related research is now pursued not only by microbiologists and virologists but also by molecular biologists, geneticists, immunologists, and organic chemists; working in competing networks jealously guarding their findings.

Scientists who have been in the field long enough are well aware of the changes in the vaccine field that have taken place:

In terms of the way in which the whole vaccine community talks to each other, my experience in going to meetings in the last two or three years is that in the vaccines field the number of commercial companies involved is really quite large. In the old days, you’d go to a conference and it would be mainly your colleagues, people from universities throughout the world. Now you see a lot of representation from companies, who are certainly willing to talk about their data, often talking about their data far more freely than academics would. Probably knowing that their basic technologies, or basic ideas, have been covered by patenting anyway. I’m sure that that’s a key issue in the whole thing.<sup>34</sup>

Institutional relationships have changed in a similar way. Decades ago they were rooted in a common commitment to public health. Hans Cohen, who was for many years director general of the Dutch Institute of Public Health responsible for producing/supplying the country’s vaccine needs, tells of his earlier relationships with industry, specifically with Pasteur Mérieux

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 <sup>35</sup>

The knowledge generated in the new networks is no longer freely available or freely exchanged. A 1983 survey of United States vaccine manufacturers had revealed only two patents for twenty-seven vaccine products. A decade later, SmithKline Beecham had to assemble fourteen patents to produce and market its recombinant hepatitis-B vaccine.<sup>36</sup> Vaccine development and production had become “privatized.” Despite the important role of governments in funding basic research and in subsidizing vaccine distribution, it was the private sector that had acquired “the pivotal intermediate role in deciding whether research gets translated into products available for public use.”<sup>37</sup> That this “privatization” had been accompanied by remarkable scientific progress is in no doubt. Between the 1950s and the 1980s, vaccines offered to children in the United States (and through the WHO Expanded Program of Immunization in much of the world) had multiplied. By 2005, at least in the United States, they had multiplied again, with the IPV having replaced the OPV, acellular pertussis having replaced whole cell vaccine, and new hepatitis B, varicella, influenza, and pneumococcal conjugate vaccines having been added to the schedule. But progress had come at a price. The new vaccines were expensive. Whereas vaccines provided through the public sector in 1987 had cost \$33.70 per child, by 2005 this figure had risen to \$517.12.<sup>38</sup>

### Discursive Change: From *Scientific Discipline* to *Global Enterprise*

With changing structures comes a changing discourse. Historians and sociologists of science have long been intrigued by the kinds of disciplinary histories that practitioners write: their functions, and their publics. Most of these practitioner histories have some kind of a legitimating function. Not infrequently, they are directed towards the public, governments, and foundations that provide financial support for science.



“Legitimations of this sort typically assume the format of popularised accounts of heroic achievements and adventures at the frontiers of knowledge.”<sup>39</sup> So it is here. The vaccine literature is studded with references to past heroes (Edward Jenner, Louis Pasteur, Jonas Salk...); to the extension of vaccination programs into the world’s poorest regions; and to the dramatic decline in infant mortality that has been achieved. Despite the recalcitrance of HIV/AIDS and of malaria, the range of diseases against which effective vaccines are available is constantly growing. The significance of these references to the past, typically and commonly to be found in prefaces and in personal memoirs, is not only a matter of their reasonableness or veracity. Their significance, evident in the fact of their constant reiteration, derives from their function as a source of confidence for the public and of motivation and inspiration for the professionals involved. They attest to what has been possible in the past and by implication, but crucially, to what will be possible in the future.

Confronting the prospect of an apparently imminent and devastating epidemic of SARS a few years ago, or of bird flu more recently, we are routinely consoled by the idea that soon there will be a vaccine to protect us. Scientists are already hard at work and they are making rapid progress. Industry is ready, and will be in a position rapidly to produce millions of doses of the vaccine, just as soon as the last hurdles have been cleared. We allow ourselves to find consolation in statements such as Sir Kenneth Calman’s partly because we want to—the alternative, after all, is rather unpleasant to contemplate—and partly because they seem to be justified by the past. Great strides are being taken, and there is reason for optimism. Yet progress is not easy. What stands in the way is not only the recalcitrance of the natural world, but organizational failings too. To provide ourselves with the vaccines we need, and quickly, we need to do things better, more effectively. But how? The answer to this question depends upon the way in which vaccine development is seen as taking place, and in this respect—I shall now argue—a change has taken place that parallels the structural changes discussed above. We can think of it as the replacement of one metaphor (one representation of how the vaccine innovation system works) by another.

By the 1970s vaccines were widely viewed as an effective tool of preventive health. Earlier scepticism, shown by the hesitant responses of some

national public health authorities to the availability of vaccines,<sup>40</sup> had abated. And science was making gigantic strides forward, as the new viral vaccines showed. Nevertheless, vaccine development in the 1970s was not only risky and uncertain, it was scientifically and technically difficult, requiring, in Maurice Hilleman's words:

the cooperative team play of a wide variety of disciplines, including, at the very least, the fields of virology, cell biology, biochemistry, biophysics, pathology, clinical medicine, epidemiology and applied biology. The effort is doomed from the outset unless the cooperating scientists of these diverse disciplines can be brought to focus on the multifaceted problems which are involved and for whose solution the guidelines may be hazy or nonexistent.<sup>41</sup>

Reflecting on such issues, a few years later Jonas Salk suggested a kind of discursive integration. He proposed the concept of "vaccinology" to refer to "the study and application of the basic requirements for effective immunization."<sup>42</sup> Salk elaborated his concept a few years later:

"Vaccinology" might be defined as the study and application of the requirements for effective immunization. This body of knowledge would include an understanding of the fundamental properties of the immune system and of specific immunogens.... Applied vaccinology would involve the application of basic knowledge and practical solutions to the development of effective vaccination programs suitable for particular population groups.<sup>43</sup>

Anne-Marie Moulin has explained further what Salk intended with his neologism. "For the study of vaccines," she writes, "Salk called upon all disciplines, including the human sciences. Indeed, vaccinology brings together the research laboratory, the pharmaceutical industry, the governments, international agencies, epidemic cycles and the suffering flesh, body and psyche."<sup>44</sup> Vaccinology was thus conceived as a single body of knowledge: a field of science in which not only the biomedical, but also the social and cultural considerations underlying development, provision, and acceptance of vaccines have their place.

The concept of vaccinology not only pointed to a shared endeavor, it also helped constitute a shared past. By providing a rhetorical integration of two powerful and reassuring images, it permitted the construction of a common history and a common culture. The concept of vaccinology could draw on two well-established images: that of the successful fight against disease and the promise of science. It then became possible to state that “Of all the branches of modern medicine, vaccinology can claim to be the one that has contributed most to the relief of human misery and the spectacular increase in life expectancy in the last two centuries.”<sup>45</sup>

What vaccine history there was, a decade ago, fitted rather well with the success story as well as with Salk’s metaphorical integration.<sup>46</sup> The successes of vaccinology give rise to historical accounts that are not only reasonable and inspirational. Thanks to their constant reiteration they are also familiar, they are authoritative, and they are welcome. Faced with what can seem to be a fearful reservoir of pathogens laying in wait in the animal kingdom, they give us grounds for confidence. Even when current problems have to be acknowledged, new science always gives grounds for hope.<sup>47</sup> On the whole, we are happy to accept such histories of vaccinology. As they imply, the development, production, and use of vaccines against infectious diseases *can be* conceived as a single and remarkably successful medical discipline.

Within a few years of Salk’s suggestion, concerns were shifting in such a way that a new integrative metaphor would be needed. Convinced that development and effective deployment of new vaccines was hampered by cognitive and social gaps between the contributing disciplines, Jonas Salk had conceived of an integrative *discipline*–vaccinology—as the means to overcome fragmentation. *Institutional* relationships, on the other hand, had been easy and unproblematic, as Cohen pointed out. For example, announcing the licence of the new rubella vaccine in 1969, *Science* noted simply and without comment that its development “resulted from the combined efforts of government, university, and industry scientists over an 8-year period.”<sup>48</sup> This was now changing. Past successes have to be re-attributed, as Salk’s integrative metaphor of a scientific discipline fades, to be replaced by a very different metaphor. Twenty years after Salk, the U.S. National Vaccine Advisory Committee wrote:

The United States has been extraordinarily successful in vaccine research and development, contributing more than two thirds of all new vaccines approved worldwide in the last 20 years. This success is the product of a fragile network of interdependent industrial, governmental, and academic partners engaged in vaccine research and development in the United States. This highly effective, yet fragile, network was not designed, but evolved, in response to scientific, public health, and economic forces during the past 50 years.<sup>49</sup>

History is being rewritten. Past vaccine achievements are no longer the result of untiring efforts in the scientific field of vaccinology, but are now the result of an “unplanned” and “fragile” network of collaborations between heterogeneous institutions. And the problem, by the late 1990s, is no longer located in the laboratory, but in institutional relationships and in the marketplace.

In the mid-1980s, reports from the Institute of Medicine in the United States had detailed, separately, the vaccines needed domestically, and those needed in the developing world, and for which the basic knowledge was said to be available. Their list of vaccines needed in the developing world included those against rotavirus and *Shigella*, *Plasmodium* (responsible for malaria), hepatitis B, and the *Streptococci*. Some of these vaccines have since been developed, of course, but what—in the 1980s—were seen as the obstacles to their development? Laboratory research was not being translated into effective vaccines, despite unquestioned health care needs, in part because of the lack of market incentives. Pharmaceutical companies were devoting little or no effort to the search for a malaria vaccine (or indeed vaccines against any human parasitic diseases), because parasitic diseases were a problem of poor countries that would not be able to afford expensive new vaccines. Somehow or other, the incentive structure had to be changed. Perhaps the solution had to be found in new forms of collaboration between the public and private sectors, and in new mechanisms by which this collaboration could be orchestrated. The term that came to capture the new forms that would be needed was “public private partnerships.” The editor of the *British Medical Journal* expressed the emerging consensus: one from which few would have dissented,

the public and private sectors will need to work together in new ways to make vaccines and drugs available to the world's poor. The public sector alone cannot solve the problem because almost all new vaccines and drugs come from private companies. Yet private companies cannot solve the problem alone because their obligations to their shareholders mean seeking the highest returns—which tend to come from developing products for the rich world.<sup>50</sup>

Buse and Walt explain emergence of a range of Global Public Private Partnerships in terms of an ideological shift in the 1990s from “freeing” to “modifying” the market, of emerging notions of corporate responsibility, and as a response to changing notions of global governance.<sup>51</sup> A longer historical view suggests something else. We see how relationships that had been taken-for-granted, unworthy of comment, in the 1970s have now become the crux of the issue, providing us with a new metaphor: “Public-private partnerships exist at the nexus of several diverse organizations necessary to achieve equitable, improved treatment. Like a successful venture capital firm, partnerships must effectively orchestrate the resources within and across these organizations...”<sup>52</sup>

In the 1980s, the U.S. National Vaccine Program had been a response to the lack of leadership and coordination in the field. But the issue remained: a 1994 *Science* survey of leading vaccine scientists, business executives, and policy makers found many concerned at “lack of strong leadership and funding.”<sup>53</sup> But at what level was this leadership required? What exactly was to be led? There is a second crucial aspect of the rhetorical construction that was emerging by the early 1990s. This is the emphasis on the “international” and, gradually, “the global.”

The eradication of smallpox, certified by international declaration at the end of 1979, was one of the most magnificent and impressive successes of vaccination. The history of this success, as subsequently recounted by the health officials who masterminded it,<sup>54</sup> provided a powerful symbol of what was possible. For one thing, it showed that disease eradication was feasible. This was important because, at the time, conventional wisdom increasingly held that human pathogens were ecologically so well adapted that the concept of eradication was untenable.

No less important, the smallpox eradication program created a cadre of professionals whose ideas and enthusiasms continued to dominate the international immunization effort,<sup>55</sup> and it

demonstrated the potential of WHO as an organisation within which all countries, whatever their beliefs and politics, could cooperate successfully in the pursuit of a common global objective. It encourages the hope that other challenges might likewise be addressed...an important impetus was provided for new initiatives in, for example, immunization, diarrhoeal disease control and the prevention of blindness.<sup>56</sup>

Inspired by these experiences, the World Health Organization launched the Expanded Program on Immunization (EPI) with the objective of taking vaccines of demonstrated value in the industrialized world and facilitating their use in developing countries. Despite the minimal starting point (less than 5 percent vaccine coverage overall) and lack of infrastructure in much of the world, the EPI rapidly succeeded in immunizing most children, even in the poorest regions, with its six chosen vaccines. A succession of international (or global) goals and initiatives followed: aimed in part at mobilizing financial and political support for immunization in the developing world.<sup>57</sup>

William Muraskin has provided a detailed study of one of the first and most influential global initiatives taken in the early 1990s, the Children's Vaccine Initiative (or CVI). In its beginnings, the CVI was a humanitarian endeavor, with as its initial goal "the creation of a single 'magic bullet' vaccine that could be given orally—at or near birth—for more than a dozen different diseases."<sup>58</sup> The CVI's founders hoped to establish a mechanism whereby the public sector could influence the way in which industry was deploying the new possibilities of biotechnology, and so get new and better vaccines to children in the Third World. Gradually, however, the goal diversified, to become nothing less than "rationalizing the entire system."<sup>59</sup> The CVI established a Task Force on Situation Analysis, and this it was that drove the transformation in the CVI's objectives. The Task Force began to address the whole range of issues: vaccine demand, procurement, production, relations with donors, global vaccine strategies...<sup>60</sup> However, the CVI found itself confronting

insuperable difficulties in the international arena (turf battles between international organizations, differences in ideology between European and American donors, its own lack of resources) that led to its being closed down in 1999, in an atmosphere of bitter recrimination. Lessons had been learned, however, and the institutions that followed, though recognizably related, were to be differently structured.

Like the CVI, today, too, the public-private partnerships that have to do the orchestrating are not national or international, but global in scope. For example, in considering how barriers to the development and delivery of a vaccine against HIV/AIDS can best be overcome, a group of experts drawn from the Gates Foundation, the WHO, the NIH, and many other organizations plead for “a well-coordinated global enterprise.”<sup>61</sup>

A metaphor such as this is but one small element in the discursive framework that serves to underpin the transformed vaccine innovation system. Many more elements can be identified. Here is one. Basing his account on the SARS outbreak a few years ago, and its containment, David Fidler argues that the era of national approaches to public health problems (which he refers to as “Westphalian public health”) is now over.<sup>62</sup> Collaboration between nation states is no longer adequate. If this is assumed, then the need for global initiatives in the field of vaccine development is justified in a way they never could have been previously. Another element is the changed language used to characterize public sector vaccine institutes and their roles in the system. Under resourced, badly managed, ineffectively regulated, at the mercy of political whim, these institutions are said to be ill-equipped to compete in a world in which vaccine economics have changed dramatically. Their contribution can but be a strictly limited one.

Perhaps most intriguing and significant of all is the global logic that has been crafted over the past decade: a representational structure in which the proper place of each country and each organization, as well as the relationships between them, can be rationally characterized. In the early 1990s, whilst working at the WHO, Batson and Evans developed a graphic representation, a Grid, on which countries were plotted according to their income and population size. This Grid played an important role in the work of the CVI Task Force on Situation Analysis (on the staff of which Batson and Evans served), and, most important

of all, it provided a guide to the optimal use of resources that donor organizations could use. Rich countries with large populations can be assumed to have the resources needed to produce vaccines for their own use, and populations large enough to make production viable. In other words, a large population implies a large enough market and so provides an economic justification for local production facilities. Where the population is large but the country is poor, though the potential for local production exists, technical assistance from outside is required if it is to be realized. Such countries, for example, Indonesia, should be helped to attain vaccine self-sufficiency. In poor small countries the assumption is that local production cannot be justified, so that donor support should be directed towards subsidizing procurement.<sup>63</sup>

The emergence of this discursive framework, and its associated global logic, has itself been critically deconstructed. Nicholas B. King has suggested that its roots lie in the perception of *emergent diseases* as a major threat to the national security of the United States.<sup>64</sup> Viewing disease emergence as the result of the interplay of various factors, dislocations and crises, a 1992 study by the National Academy of Sciences proposed that steps be taken in the areas of surveillance, training and basic research, vaccine development and coordination between local, national and international public health institutions.<sup>65</sup> This report, media coverage, popular books such as Laurie Garrett's 1994 bestseller<sup>66</sup> and a later (1997) report from the Institute of Medicine<sup>67</sup> were turning the threat of emerging diseases into a crucial new challenge to United States security and economic interests. King notes that the 1997 report laid great stress on the notion of global interconnectedness, and the importance of cooperative actions and solutions. New, according to King, is a "set of anxieties and solutions, envisioning a world in which the security of territorial borders has faded, to be replaced by one in which vast networks are not only conduits of infection but also prophylactic tools."<sup>68</sup>

The United States, according to the view that King teases out of a number of reports from the CDC and other central institutions, can best protect itself against this envisaged threat, by "the use of American technoscience in the establishment of global networks of information and exchange. 'International' projects, conducted through treaties between and cooperation among sovereign states, would be replaced by 'global'



projects, conducted by coalitions of public, private and non-governmental organisations”<sup>69</sup> Drawing in particular on the 1997 Institute of Medicine report, King argues that in the course of the 1990s, the dominant view in the United States was becoming one in which the nation’s interest in protecting the health and security of its citizens was best served by a global system that ensured the efficient production, distribution and consumption of vaccines and other products of the pharmaceutical industry in all corners of the globe.

The metaphorical shift implied in moving from a disciplinary integration to the concept of a network of institutions, a “global enterprise,” or something “like a venture capital firm,” represents acknowledgment and acceptance of two transformations in the vaccines world no less fundamental than the science and technology deployed. Focusing on the science suggests a trajectory of constant progress, stretching back to Pasteur and endlessly forwards. A focus on the ways in which the metaphors of global business are now used to represent vaccine development offers far less comfort. So too does an analysis of the changing locus of innovation, and the difficulty—today—of innovating in the health interests of a territorially-defined population.

## Charting the History of the Vaccine Innovation System

The starting point of this paper was the claim that perceptions of vaccine history are dominated by notions of progress, reaching back to Jenner and Pasteur and forwards to the conquest of HIV/AIDS, malaria, and tuberculosis. The vaccine literature is replete with expressions of what Daniel Sarewitz calls the “myth of infinite progress.”<sup>70</sup> A myth it may be, but it is a powerful and a consoling one. Professional historians, in so far as they have interested themselves in vaccines, have tended to tell rather different stories, relating (for example) vaccination policies to national cultures or politics, public health aspects of colonial relations, or the association between vaccination and compulsion or the use of force.<sup>71</sup> Where and how vaccines are developed, produced and supplied (and to whom) has tended to receive little attention. Even James Colgrove’s recent history of vaccine politics in the United States has little to say about debates regarding the role of the government in developing and

producing vaccines.<sup>72</sup> One of few major contributions to the “history of the vaccine innovation system” is Galambos’s study of Merck, Sharp & Dohm, and valuable though this is, I have tried to suggest that what is needed is more complex and more heterogeneous. The history that remains to be written is one that will acknowledge and explore the differential impact of the changes that have occurred: changes that have impacted on (national) institutions and their interrelations, on the roles of states, and on the articulation of vaccine innovation with responsibilities and priorities in the field of public health.

This paper has suggested that the scope for state action, for vaccine innovation driven by assessment of national public health needs, has declined. That is the principal conclusion of my analysis of Dutch public sector vaccine development. In discussing the social organization of vaccine development, I concluded that it seems to be increasingly difficult to make choices, or pursue a line of development work, on the basis of the public health needs of a defined population. As in the Netherlands, in Britain too there has recently been heated discussion of the desirability of switching from the whole cell pertussis vaccine to the new acellular vaccine. When Elliman and Bradford write, in the *British Medical Journal*, “The voice in the wilderness is not always wrong, and we should resist the temptation to change our policy just to conform,”<sup>73</sup> they put their finger on a critical feature of current vaccine politics. The “temptation” is becoming an irresistible pressure. It seems that today, whatever the scientific and technical competences available, it is difficult—if not impossible—for choices to be made on the basis of what is believed to be the public health interest of a territorially defined population. Similarly, an Indian scholar has suggested that “vaccine policy in India, rather than being determined by disease burdens and demand-pull, is increasingly driven by supply push, generated by the industry and mediated by international organisations.”<sup>74</sup> Focusing specifically on the controversial introduction of hepatitis B vaccination in India, she argues that decisionmaking took place in the absence of adequate epidemiological data and equivocal results from the cost-efficacy studies that were conducted. Far more important, according to Yennapu Madhavi, were pressures from industry (both multinational and local manufacturers) and from international organizations.

I have suggested that social organization of vaccine development and production and its metaphorical representation are related, and that both are key elements of a history of the vaccine innovation system. Thirty years ago, vaccine history helped legitimate faith in future progress. The infectious diseases that threatened us would be conquered with new vaccines in the future, just as they had been in the past. Today, as threats have become globalized, so—it is taken for granted—must responses be too. The metaphorical representation of vaccine development and vaccine history, constantly reiterated and constantly enacted, is slowly being adjusted to changes in the social organization of the vaccine field. With threats of global epidemics, or pandemics, constantly held before us, the need for a global approach to public health seems self-evident: far removed from debates on economic globalization. Yet, as we consider what it might mean to write the history of the emerging global vaccine system, we should bear in mind the question preoccupying political scientists. Have states, asks Suzanne Berger in reviewing the political science literature on globalization, “lost the ability to sustain...distinctive configurations of market and non-market institutions that reflect societal preferences and national traditions?”<sup>75</sup>

## Notes

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