The erosion of public sector vaccine production: the case of the Netherlands

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Introduction

Despite earlier resistance to compulsory smallpox vaccination, by 1900 the possibility of protection against diphtheria was greeted with hopeful anticipation. Diphtheria, a bacterial infection of the respiratory tract, caused the deaths of many children. At the end of the nineteenth century it was discovered that the disease could be treated with an antitoxin. Subsequently, Emil von Behring found that combining a small amount of the diphtheria toxin with the antitoxin produced a serum that offered long-term immunity to the disease. As states increasingly concerned themselves with public health (though in ways and to extents that varied greatly from one country to another)¹ a variety of institutions set about meeting demand for the new public health technologies. Some were commercial manufacturers. In Germany, in 1904, von Behring established Behringwerke to produce them. In Italy Achille Sclavo founded the *Istituto Sieroterapico e Vaccinogeno Toscano 'Sclavo'* in Siena in the same year. In Britain, the Burroughs-Wellcome pharmaceutical company, established in 1880, began producing diphtheria anti-toxin in 1894. Some were state institutions. Thus, the Danish Statens Serum Institut (State Serum Institute or SSI) was established to produce diphtheria antitoxin in 1902, and a Swedish institute (SBL) in 1909. In the Netherlands, production of the anti-toxin began in a private institution, the Bacterio-therapeutisch Instituut. However, problems in meeting national needs during the First World War, coupled with political anxieties regarding security of supply and a sense of

political responsibility, led the Dutch government to take over the Institute in 1919.²

Driven in part by the economic and political interests of the colonial powers, new public health technologies and practices also diffused far beyond Europe and North America.³ Inter-governmental organisations, and private foundations such as the Rockefeller Foundation and the Pasteur Institute all played important roles in this process.⁴ A consequence was that institutes combining bacteriological research with the production of vaccines and sera were established in much of Asia, in parts of Africa and in Latin America (as discussed by Carillo and Benchimol in Chapters 5 and 7). Many of these institutes were established by (colonial) governments, and many of their directors had been trained at one of the leading European institutes.

A hundred years ago, in other words, states' demands for the new bacteriology-based tools of public health were met by a mix of public and private institutions. In some countries primary responsibility lay with state institutes of bacteriology or of public health. Indeed, in the Netherlands and the Scandinavian countries this remained the case until well after the Second World War. Since the 1980s, however, various governments (including those of Sweden and the Netherlands), have abandoned vaccine and serum production. Because vaccines have become ever more central to public health programmes, this seems odd. How should we understand this withdrawal of states from vaccine production? I argue here that in trying to answer this question we must attend to the complex interplay of a number of factors, operating over a period of two or more decades.

Changing technology and a changing industry

With the exception of those against smallpox and yellow fever, the vaccines in widespread use before the Second World War offered protection against bacterial diseases: diphtheria, tuberculosis, whooping cough (pertussis) and tetanus. Experimental vaccines against other viral diseases, notably polio, had been disastrous failures.

However, in the late 1940s research by John Enders and his Harvard colleagues showed how polio virus could be safely cultured. This vital breakthrough opened the way to development of vaccines against a variety of viral diseases. A vaccine against polio, that 'dread disease',

was the first priority, and – encouraged in the USA by President Roosevelt – it attracted the attention of numerous research groups, in universities as well as in pharmaceutical companies. Jonas Salk, at the University of Pittsburgh, developed the first polio vaccine to be successfully tested and licensed (in 1955).⁵ By the 1960s, with vaccines against both polio and measles in production and others under development, the vaccine business looked promising. Pharmaceutical companies increased their commitment. However, by the 1970s this was changing. Vaccines were proving more difficult to develop and produce than drugs. Because their production involved handling live pathogens they carried particular risks, and required particularly stringent testing. Some pharmaceutical companies abandoned vaccine production. In the USA, in particular, this was becoming a matter of political concern. The Office of Technology Assessment of the US Congress (OTA), 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.’⁶ As far as nineteen vaccines, including the polio vaccine, were concerned, the USA was dependent on only a single American pharmaceutical company. What if that producer decided to exit the vaccine field?

In the 1980s more American pharmaceutical companies left the vaccine business, influenced not only by the resources and risks involved, but now also by fear of punitive liability claims if anything went wrong. In 1986, driven largely by widespread popular concern at side effects of the pertussis vaccine, and the resulting surge in damage actions against manufacturers, the US 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. However, another change was also taking place, and one which affected vaccine development worldwide. In the 1980s new, biotechnology-based ways of making vaccines emerged. Expertise in this area tended to lie not with the old, established manufacturers, but with small biotechnology firms. Because these new methods promised to reduce the safety concerns in vaccine production, and allow more ‘targeted’ development, accessing

them became important to large pharmaceutical companies.⁷ Frequently, the easiest way of doing so was by purchasing the small companies that possessed it. And finally, patents, which had previously played no role in the vaccines field, were becoming increasingly important.

Looking at the structure of the US vaccine industry, in the mid-1990s Mowery and Mitchell noted that 'the extent of acquisitions and alliance formations among vaccine manufacturers during the past decade, especially from 1990 to 1993, is staggering'.⁸ A brief look at the European industry shows a similar process of alliances and increasing concentration. The pioneers, their names and their companies, have vanished.⁹ Nor have public sector institutes been immune to this process of agglomeration. For example Sweden's State Biological Laboratories (SBL) had been producing vaccines and sera since 1909. In 1993 its production department was separated from the Institute's other functions and turned into a private company, SBL-Vaccin.¹⁰ In 2006 SBL-Vaccin was acquired by the Dutch biotechnology company Crucell.¹¹

Something similar happened in the Netherlands, though more recently. In 2009 the Dutch government decided to terminate public sector vaccine production and sell the production facilities. But negotiations with potential purchasers took time, and it was only in July 2012 that the government announced that a buyer had been found.

Bare facts like these show the outcome of the process, but they reveal very little about underlying rationales. The reason given by the Dutch Minister of Health was a financial one.¹² The costs of producing vaccines for the small Dutch population (around 180,000 births per year) were too great. Meeting the ever more stringent international standards of 'good manufacturing practice' for so small a market resulted in prices far above those on the commercial market. However, this official explanation is by no means the whole story. The processes of which these privatisations and acquisitions are the outcomes can better be viewed as the outcome of a cascade of events that began years before. In order to understand how and why welfare states like the Netherlands and Sweden, justly proud of their long and successful records in public health, decided to divest themselves of the capacity to develop and produce vaccines, we have to dig deeper. This question is addressed in the remainder of this chapter, with specific reference to the Dutch situation.

Public sector vaccine development and production in the Netherlands

RIV from the Second World War to the 1970s

The Bacterio-therapeutisch Instituut, which the Dutch government had taken over in 1919, was soon renamed the Rijks-Serologisch Instituut. It was later merged with the central public health laboratory, and in 1934 became the Rijks Instituut voor Volksgezondheid (State Institute for Public Health), or RIV. Then followed the Second World War and the country's occupation. As in much of Europe, the years after 1945 were a time of reconstruction. RIV was to produce vaccines against pertussis and diphtheria, but lack of facilities, space and manpower hindered its attempts to do so. In 1950 the Institute was reorganised, its tasks more clearly set out, and new staff appointed.¹³ By 1952 the Institute had succeeded in producing a combined diphtheria pertussis and tetanus (DPT) vaccine. A new facility for smallpox vaccine was constructed, and the Institute was later to be given an important role in the WHO smallpox eradication campaign. A 1956 polio epidemic, to which more than 2,000 people succumbed, had two important consequences. It led to the establishment of a centralised national vaccination programme. It also led the RIV to begin work on the production of viral vaccines.

The Netherlands started its national vaccination programme in 1957 using the DPT vaccine produced by the RIV. However, production on a sufficiently large scale demanded personnel with new skills: people who would be able to develop the production technology required. When the Dutch government decided to vaccinate against polio, problems became still more acute. Polio vaccine was first purchased from the RIT in Belgium. In 1959 the RIV received government permission to produce polio vaccine itself. This would be the killed virus vaccine, or IPV, developed by Jonas Salk. (Alternative live vaccines were still undergoing field trials. Albert Sabin's live oral vaccine – OPV – would only be licensed in the USA in 1960.)

With the aid of new technology developed in the Institute, within a relatively short time RIV had an innovative system in which polio virus was grown continuously on layers of monkey kidney cells, themselves growing on minute beads or 'microcarriers'.¹⁴ Hans Cohen, head of the Institute's vaccine department¹⁵ saw that by combining the polio vaccine

with the DPT already in use, it should be possible to avoid additional vaccinations and so maintain coverage levels. Thus, a start was made, in parallel, with development of a combination DPT-P vaccine, and by 1962 RIV had succeeded in producing it. Success in controlling polio with IPV was such that the Netherlands felt no need to switch to the Sabin OPV as almost all other manufacturers, and countries (except Sweden and the other Scandinavian countries) were doing in the 1960s. On the contrary, the Institute invested considerable resources in further improving the production process and in enhancing the potency of the vaccine.¹⁶

The crucial point is that RIV production, and also the research and development (R&D) carried out, were wholly shaped by the interests of the national immunisation programme (NIP). The decision not to switch to OPV, whatever the rest of the world was doing, reflected the country's high coverage rate and near-success in controlling the disease.¹⁷ Polio vaccine was combined with the existing DPT vaccine in order to avoid the need for an additional visit to the doctor or child health centre, which could have brought down the coverage level. A stronger ('enhanced') IPV was developed in order to reduce the number of vaccinations required. Sustaining the national vaccination programme and avoiding any changes were at the heart of the Institute's strategy. There was little or no interest in developing markets outside the Netherlands – a non-commercial culture which some members of staff would later find uncongenial.¹⁸

In the mid-1960s, and in parallel with many institutions elsewhere, RIV turned its attention to two other viral diseases: measles and rubella (German measles). As with polio vaccine development, these vaccines could be produced either by *inactivating* the virus, so producing a 'killed' virus vaccine, or by *attenuating* it by passing it through an appropriate cell culture. Salk's polio vaccine had been produced in the former manner, Sabin's in the latter. While many virologists had always been sceptical about the efficacy of killed virus vaccines, they did seem to be safer. There was no chance of their reverting to virulence, as occasionally happened with the live polio virus vaccine. Still, whichever route was chosen difficult decisions were unavoidable. How best to inactivate the virus? Or, if it were to be attenuated, in what medium, and how much attenuation was required to produce a vaccine that was both safe and effective?

Influenced by their earlier successes with inactivated polio vaccine, both Dutch and Swedish scientists began work on inactivated measles vaccine.¹⁹ The Dutch researchers hoped to combine an inactivated measles vaccine with the four component vaccine then being used in the national vaccination programme. This work was continued despite an emerging consensus in the USA that the protection provided by inactivated vaccine was unacceptably short, and that the vaccine could even induce an unusual form of measles.²⁰ Erling Norrby in Sweden, who had been working on an inactivated measles vaccine since 1959, believed that a different inactivation process from that used in the USA could yield an effective vaccine. The RIV adopted Norrby's method of inactivation, and by 1967 had established a production process.

In December 1967 the Dutch Health Council (the government's principal advisory body on medical research and innovation) issued a report on measles vaccines.²¹ The Council argued that the country should wait before beginning measles vaccination on a national scale. It was still unclear which vaccine should best be used, and how disruption of the NIP could best be avoided. The Council recommended that further studies, particularly of the inactivated vaccine, should first be carried out. Meanwhile, import of both live and inactivated vaccines should be permitted. Individual medical practitioners could decide whether or not to recommend measles vaccination to their patients, and with which vaccine.²²

In 1971 the RIV was ready to begin a clinical trial of its pentavalent DPTP-M vaccine. The results of the trial were, however, so disappointing that this line of work was aborted in 1973.²³ In 1974 live *Attenuvax* was purchased from Merck, and in 1976 mass measles immunisation began in the Netherlands. The country's very high immunisation rate was not compromised, and measles incidence declined rapidly.

By 1976, a vaccine against another potentially serious viral disease was added to the NIP. This was rubella, or German measles. RIV had begun studying the possibilities of producing a rubella vaccine in the early 1960s, more or less at the same time as work on a measles vaccine began. It had been established long before that rubella contracted during pregnancy could lead to spontaneous abortion, to central nervous system defects, or to one of a range of other serious and debilitating conditions in a new-born child (congenital rubella syndrome, or CRS). The epidemic that struck the USA in 1963–65 was said to be

responsible for some 20,000 fetal deaths and a similar number of brain-damaged children. There was growing public and political pressure to produce a vaccine.²⁴

Attempts to develop an inactivated virus rubella vaccine were soon abandoned. However, because investigators in different places used different virus strains, and attenuated them in different ways, competing vaccines emerged. These included the 'HPV77' developed at the NIH Division of Biologics Standards; the 'Cendehill' developed at RIT in Belgium (soon to be taken over by SmithKline & French); and 'RA27/3' developed by Stanley Plotkin in Philadelphia, using a culture made from aborted fetuses.²⁵

By 1970 a number of rubella vaccines were commercially available. In the UK SmithKline's 'Cendevax' (using the Cendehill strain) and Burroughs Wellcome's 'Almevax' (an RA27/3 vaccine) were licensed. Discussion of the relative merits of these vaccines was more protracted and more complex than was the case with measles vaccines. Control of rubella presented a unique problem, because its 'ultimate goal ... is a remote one, namely the protection of some future fetus against damage from intrauterine infection.'²⁶ This meant that the possibility of immunity declining with time was particularly important, since it could result in a more susceptible population of women of childbearing age.²⁷

By 1971 the RIV had obtained an HPV77 strain from the USA and had attenuated it further. Trials suggested that this further attenuated vaccine was comparable with commercial vaccines in terms of effectiveness and safety, and by 1973 the RIV was convinced that it should be added to the NIP. Starting in 1974, 11-year-old girls (only) were vaccinated. Reported cases fell from 2,000–3,000 per year in the early 1970s to roughly 700–800 in the years thereafter. However, it was still unclear whether the protection would last until the time of an eventual pregnancy. Unlike most European countries, strategy in the USA was to vaccinate both boys and girls. The objective was then not protection of the individual woman, as in Europe, but to halt circulation of the virus. The relative benefits of the two approaches would become a matter for discussion in the Netherlands and in Europe more widely.²⁸

RIVM in the 1980s and 1990s

In 1984 two other institutes, working in the field of environmental health, were merged with RIV, and the expanded institute was renamed

the Rijksinstituut voor Volksgezondheid en Milieuhygiene (RIVM). Hans Cohen, Director General of RIV, became head of the RIVM. Internal reorganisations followed. What had previously been separate departments, one for vaccine production and the other for microbiology (diagnostics, epidemiology), were integrated. This would enable the Institute's vaccine work to more effectively reflect the changing disease patterns shown by epidemiological surveillance. As the ex-head of the vaccine sector later explained;

That is both structurally and psychologically an important point because earlier vaccines had been something of a separate world within the RIV. The advantage now was that you could say: so, why are we making vaccines. Because we want to control the infectious disease problem in the Netherlands. So not as a kind of independent thing ... we're a vaccine producer, but also – and that is politically very important – you can say that infectious disease control in the Netherlands is possible partly because we have a RVP. And what do you need for that? Vaccines.²⁹

Far-reaching changes were, however, taking place in the broader vaccine field. These included the new approaches to developing vaccines based on genetic engineering, and they included changes in the structure of the vaccine industry (the mergers that were starting to take place). Still more profound changes were taking place in the world of politics and business within which vaccine development and production took place. One such change was an increasingly aggressive attitude to the protection of intellectual property rights. Years before, knowledge and expertise had been freely exchanged, even between public and private sector vaccine institutions. By the 1980s this was no longer the case. Commercial vaccine producers were starting to patent everything they could, and to enforce secrecy on academic researchers whose work they funded.³⁰ The free play of market forces was coming to be seen as the only efficient way of allocating resources, and the role of the state (and public expenditure) was to be reduced as far as possible. All these developments, taking place in the 1980s, had inevitable implications for the Dutch Institute's functioning.

One consequence of the changing ideological climate was that in the early 1980s state production of vaccines came to be questioned for the first time. Given the ideologically inspired wave of free-market thinking that was then sweeping the world, it is hardly surprising that some

Dutch politicians began to question the Institute's role. For the first time, it was becoming necessary to defend the existence of RIVM as a state vaccine producer.

At about this time (the early 1980s) the Canadian Connaught Laboratories (not yet taken over by Pasteur Mérieux) talked with the agency that represented the Dutch Ministry of Economic Affairs in North America. It was suggested to Connaught that acquisition of RIVM's vaccine production could offer the firm a means of entering the European vaccine market. Whereas the Ministry of Economic Affairs appears to have encouraged the Connaught initiative, the RIVM, which fell under (and was funded by) the Ministry of Health, did not wish to be taken over. RIVM felt itself perfectly capable of meeting the country's vaccine needs. Resisting takeover, the RIVM was supported by its parent ministry. In the late 1980s Berna, a commercial producer based in Switzerland,³¹ also attempted a takeover of RIV vaccine production. This too was successfully opposed. But it was clear that the Institute's future as a vaccine producer was far from secure.

This episode illustrates a change in how vaccines were perceived, politically. In the Netherlands they had been viewed almost exclusively as tools of public health: the tools with which the state could best protect its citizens against infectious disease. Paediatric vaccines were paid for by the state and provided freely. But vaccines could also be viewed as sophisticated technologies with economic/export potential. Friction between the ministries of health and of economic affairs (responsible for industrial policy) reflected the gap between these two perspectives, not easily bridged in the increasingly polarised ideological climate of the 1980s.

The changing political climate, and the threat of privatisation, led to a number of organisational initiatives being taken. Thus at the end of the 1980s vaccine production was separated from the RIVM's other responsibilities in vaccine R&D, regulatory control and epidemiological surveillance. Production was brought under a new entity, SVM. SVM was a foundation, wholly owned by RIVM, but no longer a government agency. The Director General of RIVM functioned also as chair of the board of the SVM. This restructuring was intended to protect public sector vaccine production against private sector challenges, but also to provide a buffer against fluctuations (reductions) in funding from the state budget. Moreover, it provided a clearer separation of vaccine

production from the government's control function. A single institution that combined a quasi-commercial manufacturing role with both regulatory functions (ensuring that products were of proper quality) and advisory responsibilities (advising on which products were to be used) was coming to be seen as inappropriate.³² The WHO insisted on the importance of independent quality control if safety were to be guaranteed. Others argued that state production represented an unacceptable interference with 'fair trade'.

RIVM began to explore the possibility of strategic partnerships with comparable institutions in Scandinavia. It might be possible to pool expertise, share production and benefit from some economies of scale. Discussion with sister institutes in Denmark, Finland, Norway and Sweden led to the idea of a Dutch-Nordic consortium, and this was formally established in 1990. One of its functions would be to facilitate technology transfer to developing countries. Thus, in 1991 an agreement was signed to jointly develop a conjugate pneumococcal vaccine for use in developing countries. Tasks were divided among the five countries according to their specific expertise.³³ However, problems soon arose. These included confusion over the ownership of the technology, a lack of funding and privatisation. The SBL, one of the participants in the consortium, was privatised in 1993. In Denmark there was talk of privatising the SSI's vaccine production (though this step was ultimately not taken). These accumulating difficulties led to collapse of the consortium. Nevertheless, under WHO auspices RIVM continued to emphasise and develop its role as a non-commercial centre of expertise for developing countries.³⁴

However, to understand the challenges confronting the Institute from the 1980s onwards it is not enough to focus only on the macro politics. Resisting 'assaults' from the private sector, changing legal status and cooperation agreements were institutional responses to a profoundly changing world. But the fact is that the Institute's expertise and its functioning were being eroded by more subtle changes over which it could have no possible influence, and which it was powerless to resist. In order to see how this was so we need to look in more detail at the Institute's substantive work in the vaccine field.

Since 1974, Dutch girls had been vaccinated against rubella at the age of 11 with a vaccine produced by the Institute. By the early 1980s, there was a growing international consensus that the rubella

vaccination strategy should aim not at protection of the individual woman before she became pregnant, but at stopping circulation of the virus. Further, research elsewhere suggested that this could only be done by vaccinating both boys and girls: the strategy followed by the USA.³⁵ Discussions in the Dutch government's Health Council were leading to a consensus regarding the need to change the rubella vaccination strategy. These discussions also challenged the Institute's choice of rubella virus strain.³⁶

Whereas RIV made use of the HPV77 strain, commercial manufacturers were all switching to the RA27/3 strain, which was claimed to have a higher immunogenicity. Members of a Health Council committee urged the Institute to change its rubella vaccine. In response, in 1981, the RIV carried out a study in Rotterdam. Half of the girls in the study were given the existing RIV vaccine, and half were given a commercial RA27/3 vaccine. RIV researchers concluded from this study that both vaccines produced a more than adequate response and saw no reason to switch to an RA27/3 vaccine.³⁷ The Institute argued that both vaccines were perfectly good, a switch would be expensive and would yield virtually no benefit. Not everyone agreed. A Belgian member of the Health Council committee, a virologist, argued that the Netherlands *should* switch, as Belgium had done, mainly in the interests of public confidence. Whatever research showed, there was a risk of controversy and public loss of trust if people believed they were being given an inferior vaccine. Despite the results of its own studies in 1984 the Institute started working with the RA27/3 strain.

A further challenge followed. The Minister of Health had asked the Health Council to consider the desirability of beginning vaccination against mumps. Mumps mortality was minimal, and many general practitioners considered it an unpleasant but fairly routine phase in a child's development. Because of this RIV had not done any work on mumps vaccine. However, a number of manufacturers had, and commercial mumps vaccines had been available since the late 1960s.

By the early 1970s Merck had combined mumps vaccine with measles and rubella vaccines to produce MMR. In 1984 the Health Council advised the minister that vaccination against mumps was desirable, and that MMR vaccine be introduced in the Netherlands. Its arguments in support of this recommendation had nothing to do with mumps mortality (which remained minimal). They were in part

economic (looking at the costs of school absences and treatment of children who contracted mumps), and in part they reflected the conviction on the part of some experts that the Netherlands should harmonise its immunisation practice with those of other European countries. This argument was to be made with increasing stridency in subsequent years.³⁸

Foreseeing that it would ultimately be required to provide a vaccine against mumps, the RIVM had begun considering the options. They would try to provide an MMR vaccine which included their existing measles and rubella vaccines, and a mumps strain obtained from one of the commercial manufacturers. A number of different strains were being used in commercial vaccines. The preference was for the Jeryl Lynn strain, which was used by Merck. Negotiations with Merck's European subsidiary (MSD) regarding the production of mumps vaccine under licence began in 1982. They broke down, however, when it became clear that Merck would consider licensing its combined MMR vaccine, but not the single mumps component. When the Minister of Health, following Health Council advice, decided that the country would switch to a combined MMR vaccine, the Institute would have to provide it. How was this to be accomplished? Looking back, the then head of the RIVM's vaccine department recalls that

The end of the story is that we had to forget about our own measles and rubella. We could only do it by producing the threefold vaccine under licence from one of the companies. That's what happened. I negotiated with the Belgians, and the French, and with Merck and we ultimately chose for Merck. It was impossible otherwise.³⁹

This was not an isolated episode. Subsequent events show further erosion in the Institute's expertise. They also show that the Institute could no longer engage with commercial vaccine manufacturers in the way that it once had.⁴⁰ These developments, and the changing environment in which the Institute worked, are well illustrated by its involvement in the production of whooping cough vaccine.

Whooping cough (pertussis) vaccines had been in widespread use for decades. Nevertheless, they were known to have more side effects than most other vaccines. Though these were worrying for parents they were generally soon over and rarely serious. However, in the 1970s reports appeared suggesting that the vaccine could cause encephalitis.⁴¹

These reports were greeted with alarm, and in both Sweden and Japan vaccination against whooping cough was halted and numbers of cases rose rapidly.⁴² In the USA hundreds of lawsuits were filed, claiming billions of dollars in damages from vaccine manufacturers. Fearful of crippling litigation, all but two US manufacturers of DTP withdrew from the market, provoking fears of a vaccine shortage. This was a major incentive to the establishment of the National Childhood Vaccine Injury Compensation Program in 1986. Vaccine manufacturers set about developing so-called 'acellular' pertussis vaccines which would not have these side effects, and by the early 1990s many were offering a new combination DTP vaccine in which the old 'whole cell' pertussis component had been replaced by the new acellular vaccine.

However, the results of the trials, in which different acellular vaccines were compared with each other but also with some of the older vaccines, were not easy to interpret. The problem of the side effects had been solved, but the efficacy of the new vaccines was less clear. Some of the old whole cell vaccines were more effective than the new vaccines, though not all were. What did this imply? What should public health authorities do? According to one authoritative review '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?'⁴³ Because this trade-off depends on the particular whole cell vaccine in use, there is no simple and unambiguous answer.

The fears that had led to suspension of pertussis vaccination in Japan and Sweden did not affect the Netherlands. In 1988 the Dutch Health Council advised that though a switch to an acellular vaccine might ultimately be desirable the time was not yet right. Too little was known of their efficacy. By the 1990s it was becoming clear that there was nevertheless a problem. Not only was the incidence of whooping cough rising, but there seemed to be a shift in the population groups principally at risk. What had been a disease largely of young children was coming to affect older children and adults.⁴⁴ From the late 1990s onwards, in a series of reports, the Health Council advised that, for whatever reason, the locally produced vaccine no longer worked. The Netherlands should switch to the acellular vaccine being used elsewhere, and the Institute was instructed to work towards introduction of an acellular vaccine.

The Institute's scientists were not all convinced that an acellular vaccine was the answer to the long-term control of pertussis.⁴⁵ Some believed that in the long term the answer lay with a good whole cell vaccine such as was still being used in the UK and France. However, manufacturers of these 'good whole cell vaccines' were unwilling to supply them under licence. Development of the new acellular vaccine had required a considerable investment, and it was being sold for approximately three times the price of the old vaccine. Manufacturers wished to phase out production of the old vaccine.

As the introduction of acellular vaccine became inevitable the Institute had two options: it could replace the whole combination DPTP, or else it could combine a commercial acellular vaccine with the other locally produced components. The Institute preferred the latter course, for reasons that had much to do with its perception of its status and functions.

We could have just bought a vaccine of course but in the first place it's much more expensive. In the second place, if you buy it, you buy the whole combination then you lose all the knowledge and production here. Then you just become a sort of warehouse, no longer a knowledge institute. It could have been injected immediately, but that's less important.⁴⁶

These views were not universally shared, even within the public sector itself:

We found from the very beginning that a DTaP-P had to be imported and however important an RIVM/SVM/NVI is for all the knowledge and expertise that we have in the Netherlands, that the interest of children had to be the primary consideration, and that a more effective vaccine is always more important than maintenance of our own production capacity. We still believe that.⁴⁷

The difficulties that the Institute confronted in the 1980s and (increasingly) in the 1990s, were of a different order from the technical difficulties they had previously faced in trying to develop an inactivated measles vaccine. By the mid-1980s the Institute was confronting a changed industry. Pharmaceutical companies, increasingly multinational, jealously guarded knowledge that had now become 'intellectual property'. They no longer offered the easy collaboration they had once done, and the relationships that RIV had enjoyed with Mérieux in the

1960s and early 1970s were unthinkable by the 1990s. Moreover, at the political level perspectives were also changing. Reflecting moves towards European integration, there was a growing sense that the Netherlands should do the same as neighbouring countries. The implications for policy making and for the evidence on which policy should be based were profound. Were national boundaries and national populations the best way to think about public health? Did national experience and local epidemiological data offer the appropriate evidential base for policy?

The Institute's experiences in the 1980s and 1990s highlight a number of developments which were increasingly influencing its functioning and reducing its room for manoeuvre. The first one derives from changes in technology, industry and economic ideology. New and improved vaccines were being produced by sophisticated biotechnological processes, and the technology involved had been appropriated – and patented – by large pharmaceutical manufacturers. In sharp contrast to earlier decades, these private corporations were no longer willing freely to collaborate or to share knowledge. Second, and largely based on surveys of public sector producers in developing countries, it was increasingly taken for granted that public sector producers lacked the resources, the freedom from political interference and the expertise to produce good quality vaccines.⁴⁸ The third development was an increasing emphasis on standardisation: on the harmonisation of immunisation policies between countries. The fourth development, clearly related to the third, concerns the declining weight attached to 'local' research evidence. RIVM's experience with the alternative rubella strains in the early 1980s fits in a pattern that has become clearer over time. Policy options based on national research are no longer a match for policies based on international research and promoted internationally.⁴⁹ Though the relations between these developments is still to be disentangled, the hypothesis that the third and fourth were a consequence of the first has a certain plausibility.

In 1991 Europe's commercial vaccine manufacturers joined together to form the European Vaccine Manufacturers,⁵⁰ as a special group within the European Federation of Pharmaceutical Industries Associations, an influential lobby in Brussels. Vaccine manufacturers began to criticise the idea of national immunisation programmes, in the light of moves to European integration.

EVM argued that given the free movement of persons within the EC (now EU) the concept of herd immunity had to be seen in a European context. Europe should move gradually towards a standardised immunisation schedule and a Europe-wide system for testing and evaluation of vaccines. This was not only desirable, in the view of manufacturers, but likely to occur anyway, since 'the availability of new vaccines, coupled to the development of more precise concepts in vaccinology ... drive separate national systems towards similarity in their respective approaches'.⁵¹ The growing involvement of the EU in public health, and subsequent moves toward a European procurement system, are clearly in line with the views of European manufacturers.

By the mid-1990s it was starting to seem that further legal protection was required if the Institute's tasks were to remain a state responsibility. In 1996 legislation was passed, the Law on the RIVM ('Wet op de RIVM') giving a firmer legal basis to the Institute's functioning and independence.

RIVM-NVI: the new millennium

At the beginning of the new millennium the Dutch Cabinet was still committed to maintaining the close link between infectious disease control and vaccine development and supply that the RIVM/SVM structure represented. This commitment was made clear in early 2002. However, there was to be a reorganisation. The vaccine R&D, the responsibility of RIVM, and SVM's production facilities, would be integrated in a new entity to be called the Netherlands Vaccine Institute (NVI). There would be a clearer separation between entities with development/production and control/advice functions.

The government would seek independent advice regarding the NIP and would arrange for a continuous evaluation of vaccination policy independent of the views of the NVI. The Health Council is the most important advisor in this area. The most important reason for ensuring such independent advice is that *because the government itself produces vaccines through the NVI, there is the danger of giving the impression that the interests of the producer weigh more heavily than those of the public health.* In fact it is impossible wholly to neglect the interests of the public sector producer. This is not only a matter of psychological factors, but also of material arguments such as the importance of continuity in production if the capacity to produce vaccines is to be sustained.⁵²

The core tasks of the NVI would be: (1) provision of vaccines for the NIP, for influenza, for travellers, and in case of calamities such as an influenza epidemic; (2) vaccine R&D in the interests of the vaccination programme (including longer-term strategic research not coupled to a specific product); and (3) research to support policy development. The inter-departmental group that planned the restructuring acknowledged that changes in vaccine science and technology, and the costs of developing new vaccines (and vaccine combinations), had profound implications for how the new Institute would work. There would have to be more intensive collaboration, both with international research institutes and with private vaccine manufacturers:

dependence on industry has increased in recent years, and the availability of (combination) vaccines is less easy to guarantee than was previously the case. In order to guarantee provision in the future, as effectively as possible, requires, among other things, strengthening of public sector collaboration (with the Scandinavian countries and England).⁵³

Reorganisation took time, but by 2005 NVI was functioning as intended.

However, by this time the context within which the Institute had to function had become still more complex. The forces with which the Dutch institute had had to contend in the 1980s and 1990s derived from global changes in industrial organisation and economic ideology, and a pressure to standardisation. Now, however, domestic politics were increasingly impacting on vaccine policy. Many authors have written of the growing involvement of 'health care consumers' in policy making, and of an erosion of trust in official pronouncements regarding risks and benefits to public health. In the Netherlands too, it was starting to seem that popular trust in the vaccination programme could no longer be taken for granted. There was a growing reluctance to accept vaccine recommendations on trust and unquestioningly. While NVI's planners had foreseen conflict of interest issues, they had underestimated the extent to which the state's involvement in vaccine production came to be presented as biasing its public health policies.

Yet this is what happened in 2004, when a newly established Vaccination Damage Foundation (Stichting Vaccinatieschade) began a campaign against the whole cell pertussis vaccine then being used in the

Netherlands. In their view the government had for years ignored evidence for the dangers of the existing vaccine. 'The thing is that the old vaccine is being made by the government itself, in the Netherlands Vaccine Institute. If that cannot produce those 800,000 jabs per year, you can just as well close it down. So they are working on their own stuff. That will be available in 2008/2009 at best.'⁵⁴

A few days later the controversy was aired on television and questions were asked in Parliament.⁵⁵ Growing numbers of parents were objecting to their children being obliged to accept what they had come to see as an old, inferior vaccine. More and more Dutch parents were demanding that their children be given the new (and therefore better) vaccine. However valid the reasons which led some Dutch scientists to question the long-term value of acellular vaccines, they had been unable to convince the general public. The Health Council, pointing out that the Institute had not been able to develop the vaccine it said was needed, once again advised the Minister that a commercial acellular vaccine be purchased.⁵⁶ The country should be brought into line with practice in other Western countries. The Minister of Health finally agreed that in 2005 commercial acellular pertussis vaccine would replace the old whole cell vaccine in the NIP. Explaining his decision in Parliament, he stated that he had been most concerned, and influenced, by the actions of parents. The crucial thing, and the ground for his decision, had been the need to reassure parents and to restore their faith in the vaccination programme as a whole.⁵⁷

In 2009 the commitment that had been reiterated seven years previously – that the state should retain the capacity to produce vaccines – was given up. There was a different government of a different political complexion. In February 2009 the Minister of Health informed Parliament that public sector vaccine production would cease. The production activities were said to be losing money and 'for a small producer such as the NVI it is increasingly difficult to meet increasingly stringent quality standards at an acceptable cost':

The Netherlands is one of the last European countries with vaccine production in the hands of the government. With this privatization the Netherlands is following the example of other European countries.⁵⁸

Despite the initiatives taken by NVI 'profitable production within the framework of a public sector institution and above all without

major investment, is not possible'. Therefore, and despite the opposition of left-wing parliamentary parties, the decision was taken to seek a purchaser for the NVI's production facilities, and in July 2012 their sale to the Serum Institute of India (a private corporation) was announced.

Conclusion

In the 1960s and 1970s the Dutch Institute of Public Health was a significant and respected participant in vaccine development and production. Though it enjoyed good relations with commercial manufacturers, Mérieux in particular, RIV was resolutely non-commercial. Its production and its vaccine development work were oriented to the needs of the country's national immunisation programme. It would provide the public health service with the tools with which the nation's children could best be protected against infectious diseases. Such tools would thus reflect the country's specific epidemiological patterns and threats, its resources, and the functioning of the NIP. As the example of the polio vaccines shows, these tools would not necessarily be the same as those most other countries were purchasing from commercial manufacturers.

In the course of the 1980s, a number of developments began to threaten the way in which vaccine production and development had been steered by the needs of national policy. They included changes in vaccine technology. There were new vaccines, produced by new biotechnological processes, and the technology involved had been patented by large pharmaceutical manufacturers. As a result of mergers and acquisitions, the industry was increasingly dominated by a few multinational corporations. In contrast to the more distinctively national companies that had come before, these multinational corporations were unwilling freely to collaborate or to share knowledge. An ideological shift – the growing influence of free-market economics – provided conceptual support for these giant corporations' attempts to capture global markets. So too did the increasingly aggressive defence – and enforcement – of rigorous intellectual property regimes. The old idea that knowledge essential to safeguarding people's health should be a public good (Salk's ironic 'Can you patent the sun?')⁵⁹ no longer held. Now it was 'intellectual property rights' which had to be

safeguarded at all costs. It was becoming more and more difficult for the Dutch institute to access the knowledge with which it could provide the country with the new tools that the pharmaceutical industry was offering.

No less important, however, was a change on what, following economic convention, we can call the demand side. The officials and experts responsible for formulating Dutch vaccine policy not only insisted on the introduction of the new biotechnology-produced vaccines, but increasingly insisted that policy must be harmonised with the policies of neighbouring countries. Coincidentally or not, this was the view of the European pharmaceutical industry, with its interest in standardised markets. It was also justified by reference to European integration. The very idea of a nationally autonomous policy, reflecting the distinctive health needs and profile of the Netherlands, was losing credibility. It was because of this that local evidence – the results of local epidemiological studies – was of less and less relevance. Standardised decisions should best be based on ‘international’ studies from which ‘place’ had been stripped away and which claimed universal generalisability.

The Institute’s history between the late 1980s and the first years of the new millennium is marked by a series of reorganisations, legal protections and struggles against commercial assaults, designed to preserve the Dutch state’s ability to provide itself with the public health tools it required. These initiatives ultimately proved inadequate because the real challenge was conceptual and ideological. In a world in which talk of ‘public health’ is giving way to talk of ‘global health’ the responsibilities of nation-states are becoming subordinate to those of global institutions.⁶⁰ It follows that nation-states no longer require, or have any legitimate reason to seek to preserve, the tools or the competences with which national policies can be developed and pursued. It is, of course, conceivable that the relative weight of the arguments in political discourse will change again. As the ‘securitisation’ of public health proceeds, European states might feel a need to secure the competences with which to protect their populations against biological assault.⁶¹ Moreover, mistrust provoked by recent insights into commercial influences on global policy making, as manifest in relation to the H1N1 ‘pandemic’, may have more enduring consequences.⁶² Time will tell.

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Notes

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- 2 H. van Zon, *Tachtig Jaar RIVM* (Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiëne, 1990), pp. 85–96.
- 3 See for example D. Arnold, *Colonizing the Body. State Medicine and Epidemic Disease in Nineteenth Century India* (Berkeley and Los Angeles: California University Press, 1993); A. Bashford, 'Foreign Bodies. Vaccination, Contagion and Colonialism in the 19th Century', in A. Bashford and C. Hooker (eds), *Contagion. Historical and Cultural Studies* (New York and London: Routledge, 2001), pp. 39–60.
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- 14 S. S. Blume, 'Lock In, the State and Vaccine Development. Lessons from the History of the Polio Vaccines', *Research Policy*, 34:1 (2005), p. 167.
- 15 Cohen became Director General in 1979.
- 16 These developments are discussed at length in Blume, 'Lock In, the State and Vaccine Development'.
- 17 'Near success' because in deference to the beliefs of the country's highly orthodox Protestant community, immunisation was and is voluntary. Orthodox communities in the country's so-called Bible Belt generally do not vaccinate their children and are subject to epidemics that the rest of the country escapes.
- 18 It is worth noting that Jonas Salk and the Institut Mérieux, RIV's collaborators in improving the IPV, *did* have an interest in markets outside the Netherlands. In order to restore IPV as a credible alternative to the then dominant OPV, clinical trials in tropical countries would have to show that there was some formulation of the enhanced IPV which was as effective as OPV, and less sensitive to temperature. See F. C. Robbins, 'Polio – Historical', in S. A. Plotkin and E. A. Mortimer (eds), *Vaccines* (Philadelphia: W. B. Saunders, 1988), pp. 98–114.
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- 31 In 2006 Berna merged with the Dutch biotechnology company Crucell, the same year in which Crucell acquired SBL-Vaccin.
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- 33 J. Hendriks, in *Report of a Meeting of International Public Sector Vaccinology Institutions* (Geneva: World Health Organization, 16–17 March 2000), p. 24.
- 34 J. Hendriks, 'Technology Transfer in Human Vaccinology. A Retrospective Review on Public Sector Contributions in a Privatizing Science Field', *Vaccine*, 30:44 (2012), pp. 6230–40.
- 35 Interview with E. Miller, Centre for Infectious Diseases, London, 15 October 2007.
- 36 This decision is discussed at greater length in S. S. Blume and J. Tump, 'Evidence and Policymaking: the Introduction of MMR Vaccine in the Netherlands', *Social Science & Medicine*, 71:6 (2010), pp. 1049–55.
- 37 RIV(M) *Berichten uit het RIV(M)*, 1981.
- 38 See Blume and Tump, 'Evidence and Policymaking', p. 1054.
- 39 Interview with J. Ruitenberg, 21 December 1998.
- 40 Notes on an interview with a senior scientist who had resigned from RIVM to join (what was then) SmithKlineBeecham. 'We talked about the relations between commercial and state institutes. At one point he used the word "versus" ... about which I asked him "why one versus the other?" He corrected himself: "Of course it's not like that but that is how it was seen in RIVM"' (interview by the author, Amsterdam, 10 November 1997).

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- 46 Interview with laboratory scientist responsible for quality control of biological products, quoted in Blume and Zanders, 'Vaccine Independence, Local Competences and Globalization', p. 1831.
- 47 Interview with public health physician, government adviser, quoted in Blume and Zanders 'Vaccine Independence, Local Competences and Globalization', p. 1831.
- 48 For example, an inquiry by the Children's Vaccine Initiative (CVI) found: 'The private sector, particularly commercial pharmaceutical and vaccine manufacturers in industrialized countries, research institutions which were characterized by outdated technology and facilities, cheap labour and uncertain and unreliable products.' The indicators with which Milstien and colleagues evaluated local producers – including the right to hire and fire and to set salary levels, and a multi-year business plan – could be seen as unfavourable to public sector producers. See J. Milstien, A. Batson and W. Meaney, 'A Systematic Method for Evaluating the Potential Viability of Local Vaccine Producers', *Vaccine*, 15:12–13 (1997), pp. 1358–63.
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