Societal vaccinology
Hendriks, J.T.

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Global health has improved remarkably through the introduction of a multitude of vaccines in childhood vaccination programmes since the 1950s. New vaccines that are now increasingly becoming available result from the science and technology field commonly called vaccinology which has become the domain of multinational pharmaceutical companies. The “privatisation” of vaccinology has been accompanied with the gradual erosion of public sector vaccine development and production. This thesis analyses the global impact of public sector vaccine manufacturing in the Netherlands before it was partially taken over in 2012 by the Serum Institute of India Ltd., one of the world’s largest private vaccine manufacturers that plays a key role in the supply of affordable vaccines for developing countries.

The main finding of this study is that national public sector vaccinology institutions, in particular the Netherlands public health institute, have over the past decennia had a hitherto hardly acknowledged but profoundly positive impact on the global vaccine system that aims to increase access to vaccines in developing countries. This impact is the result not of supply of vaccines, but through enabling vaccine manufacturing entities (public or private) in developing countries to set up or improve their capacity. From a societal and horizontal angle this study illustrates that a divergence between policies and practices between different ministries within the same government may lead to missed opportunities for global health.
SOCIETAL VACCINOLOGY

The Netherlands public sector vaccine development, production and technology transfer in the context of global health

Jan Hendriks
SOCIETAL VACCINOLOGY
The Netherlands public sector vaccine development, production and technology transfer in the context of global health

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Promotiecommissie:

Promotor:
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# Acronyms and abbreviations

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<th>Description</th>
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<tr>
<td>AMC</td>
<td>Advanced Market Commitment</td>
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<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
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<td>BSL2</td>
<td>Bio Safety Level 2</td>
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<td>CNIP</td>
<td>Chinese National Immunisation Programme</td>
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<td>CVI</td>
<td>Children's Vaccine Initiative</td>
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<td>DCVM</td>
<td>Developing country vaccine manufacturers</td>
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<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers Network</td>
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<tr>
<td>DNC</td>
<td>Dutch Nordic Consortium</td>
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<tr>
<td>DTaP</td>
<td>Diphtheria, Tetanus and acellular Pertussis</td>
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<td>DTwP</td>
<td>Diphtheria, Tetanus and whole cell Pertussis (=DTP)</td>
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<tr>
<td>ECDC</td>
<td>European Centre for Disease Control, Stockholm, Sweden</td>
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<tr>
<td>EPI</td>
<td>Expanded Programme on Immunisation</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>GAVI</td>
<td>GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation)</td>
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<tr>
<td>GLO-VQ</td>
<td>WHO’s Global Learning Opportunities for Vaccine Quality</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>GPG</td>
<td>Global Public Good</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>GSPoA</td>
<td>WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property</td>
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<tr>
<td>GVAP</td>
<td>Global Vaccine Action Plan</td>
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<tr>
<td>HepB</td>
<td>Hepatitis B</td>
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<tr>
<td>Hib</td>
<td><em>H. influenzae</em> type b</td>
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<tr>
<td>HPV</td>
<td>Human papilloma virus</td>
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<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers and Associations</td>
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<tr>
<td>Intravacc</td>
<td>Institute for Translational Vaccinology</td>
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<td>IP</td>
<td>Intellectual property</td>
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<tr>
<td>IPV</td>
<td>Inactivated polio vaccine</td>
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<tr>
<td>KIMB</td>
<td>Kunming Institute of Medical Biology, China</td>
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<tr>
<td>MMR</td>
<td>Mumps, measles and rubella vaccine</td>
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<tr>
<td>MNC</td>
<td>Multinational companies</td>
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<tr>
<td>MSD</td>
<td>Merck, Sharp and Dome</td>
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<td>MSF</td>
<td>Médecins Sans Frontières/Doctors Without Borders</td>
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<td>MVP</td>
<td>Meningitis Vaccine Project</td>
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<td>NATO</td>
<td>North Atlantic Treaty Organisation</td>
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<tr>
<td>NCL</td>
<td>National control laboratory</td>
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<tr>
<td>NGO</td>
<td>Non-governmental organisation</td>
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<td>NIBSC</td>
<td>National Institute for Biological Standards and Control, United Kingdom</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health, United States</td>
</tr>
<tr>
<td>NIP</td>
<td>National Immunisation Programme</td>
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<td>NMA</td>
<td>Noordwijk Medicines Agenda</td>
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<tr>
<td>NRA</td>
<td>National regulatory authority</td>
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<tr>
<td>NVI</td>
<td>Netherlands Vaccine Institute</td>
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<tr>
<td>ODA</td>
<td>Overseas Development Assistance</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Cooperation and Development</td>
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<tr>
<td>OPV</td>
<td>Oral polio vaccine</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organisation</td>
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<tr>
<td>PATH</td>
<td>Programme for Appropriate Technology in Healthcare, Seattle, United States</td>
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<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
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<tr>
<td>PDP</td>
<td>Product Development Partnership</td>
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<tr>
<td>QC</td>
<td>Quality control</td>
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<tr>
<td>RF</td>
<td>Rockefeller Foundation</td>
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<tr>
<td>RIV</td>
<td>Rijksinstituut voor Volksgezondheid (National Institute of Public Health)</td>
</tr>
<tr>
<td>RIVM</td>
<td>Rijksinstituut voor Volksgezondheid en het Milieu (National Institute for Public Health and the Environment)</td>
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<tr>
<td>SAGE</td>
<td>Scientific Advisory Group of Experts on Immunisation</td>
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<td>SBL</td>
<td>Swedish Bacteriological Laboratory</td>
</tr>
<tr>
<td>SFDA</td>
<td>China Food and Drug Administration</td>
</tr>
<tr>
<td>SIIDC</td>
<td>Swedish Institute for Infectious Disease Control</td>
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<tr>
<td>SIIL</td>
<td>Serum Institute of India Ltd.</td>
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<tr>
<td>SIREVA</td>
<td>Sistema Regional de Vacunas: PAHO’s laboratory-based surveillance system</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SRID</td>
<td>Single Radial Immunodiffusion</td>
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<tr>
<td>SSI</td>
<td>Statens Serum Institut (Denmark)</td>
</tr>
<tr>
<td>SVM</td>
<td>Stichting tot Bevordering van de Volksgezondheid en het Milieu (Foundation for the Advancement of Public Health and Environment)</td>
</tr>
<tr>
<td>TE</td>
<td>Tween 80 and diethyl ether</td>
</tr>
<tr>
<td>TFCS</td>
<td>Task Force for Child Survival</td>
</tr>
<tr>
<td>TFSA</td>
<td>Task Force for Situation Analysis</td>
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<tr>
<td>TT</td>
<td>Tetanus toxoid</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>UNICEF</td>
<td>United Nations International Children’s Emergency Fund</td>
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<tr>
<td>UNIDO</td>
<td>United Nations Industrial Development Organisation</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
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<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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Introduction
INTRODUCTION

The global vaccine system

Governments have policies in place to prevent infectious diseases by national vaccination programmes, mainly targeting infants and young children. Over the last decades, these programmes have proven to be one of the most beneficial preventive measures in terms of health outcome and cost effectiveness. Vaccination is commonly associated with global public goods and, due to the increased availability of new vaccines, countries are spending increasing amounts of their national health budgets to maintain and expand national vaccination programmes, usually following recommendations by national, regional or global health bodies.

Vaccines and vaccination programmes for public health

Used for prevention in healthy individuals, usually babies or young children, rather than for therapy or treatment in older age groups, vaccines have a complex biological structure which makes them more subject to widespread variation even between individual production batches. Vaccines differ in this way from pharmaceuticals which in contrast have remarkable identity between batches and even between manufacturers. Because of this variation, vaccine regulation is more complex; even after licensure, each produced vaccine lot must be independently released by a national authority. For pharmaceuticals this is not required. Vaccines further usually require cold storage, while pharmaceuticals mostly do not. Another differential characteristic is that vaccines are usually bought by governments for national immunisation programmes for the entire population or large parts of their population, whereas pharmaceuticals are usually purchased on an individual basis.

Today’s growing vaccine scepticism in some high income countries notwithstanding, there is no doubt that vaccines and vaccination programmes have proven to be one of the most effective health interventions reducing childhood mortality and morbidity due to infectious diseases.

The triumphant declaration of the global eradication of smallpox in 1980 after a campaign led by the World Health Organisation (WHO) marked an unprecedented and historical success in global health. For the first time ever a virus, cause of a devastating disease that had caused millions of deaths and human suffering over centuries, had been eliminated from the planet. This achievement was the result of a 14 years long collaborative effort of virtually all nations in the world driven by the WHO, the prime global health agency of the United Nations. A global public good had been created.

The critical instruments in this public health success story were the principle of vaccination and the existence and worldwide application of an effective and affordable vaccine against smallpox, discovered already by Jenner in the United Kingdom (UK) in the 18th century. Since the second half of the 19th century, vaccines against other infectious diseases were developed and applied successfully, largely by gifted and dedicated micro-
biologists such as Louis Pasteur in France and Robert Koch in Germany, and their collaborators. Both scientists created national research institutions that bear their names and that last to this day⁴.

Since the early 70s, building on the imminent smallpox eradication success, WHO had begun to advise developing countries to integrate routine immunisation and surveillance programmes against other infectious diseases in their public health programmes. In 1974 a resolution was adopted at the World Health Assembly (WHA) to establish an Expanded Program of Immunisation (EPI), recommending countries to maintain immunisation and surveillance programmes against diphtheria, pertussis, tetanus, measles, poliomyelitis, tuberculosis and smallpox. With the exception of tuberculosis, mortality and morbidity against these diseases have been greatly reduced worldwide as a result. Polio eradication has reached its final stage and measles elimination is progressing.

Besides beneficial public health outcomes of vaccination, to which obviously other health interventions such as sanitary hygiene and improved socio-economic conditions also contributed, an appreciation of economic benefits of vaccination has come to dominate global policy thinking from early 2000 onwards [1, 2].

The globally adopted way to monitor progress has become the annual recording of metrics of vaccination coverage against these diseases through WHO and UNICEF. These figures have shown a steady increase since 1980. For example, DTP-containing vaccine coverage rose rapidly from around 20% in 1980 until reaching a plateau of around 75% in 1990. Since 2010 the coverage level rose sustainably above 85% (Figure 1). However, this still falls short of the 90% target for DTP containing vaccines as agreed at the 2012 WHA, when Ministers of Health of all WHO Member States endorsed the Global Vaccine Action Plan (GVAP). The GVAP is a “framework to prevent millions of deaths by 2020 through more equitable access to immunisation for all people in all communities”. The GVAP aims to “meet vaccination coverage targets, accelerate control of vaccine-preventable diseases with polio eradication as the first milestone, introduce new and improved vaccines and spur research and development for the next generation of vaccines and technologies” [3].

A 2016 mid-term assessment by the Scientific Advisory Group of Experts on Immunisation (SAGE), the principal advisory group to WHO for vaccines and immunisation, noted with concern that progress towards the GVAP goals (“to eradicate polio, eliminate measles and rubella, eliminate maternal and neonatal tetanus and increase equitable access to lifesaving vaccines”) was too slow and that only a marginal improvement in vaccination coverage and equity had been achieved since 2011 [4].

⁴ By the end of the 19th century and throughout the first half of the 20th, the Pasteur Institute also established sister institutions in French colonies in different parts of the world. Nowadays, while all these countries have become independent, 33 Pasteur Institutions in 26 countries together constitute the Institute Pasteur International Network.
Where do vaccines come from?

Where do vaccines come from and who makes them? Today, the development and manufacture of vaccines and their introduction into national programmes is a complex and multifaceted undertaking involving a variety of scientific and technological disciplines from academia, the public and the private sectors. At a national level, even in the Western world, there are only a few countries that possess the entire spectrum of vaccinology, which comprises the science, technology and industrial manufacturing capacity to successfully complete the entire cycle of innovative product development, combined with the regulatory capacity and established health policies to add a new vaccine to the programme. Notably the licensing and manufacturing of new vaccines is now almost exclusively done by large multinational pharmaceutical companies, operating on a global scale.

It used to be different: vaccine manufacturing in the second half of the previous century was seen as a governmental responsibility and many of the vaccines in the current immunisation schedules stem from that era. National vaccine institutes in Europe and some state laboratories in the United States used to supply their country programmes, but for several reasons have ceased the development and manufacturing of vaccines. In the United Kingdom, for instance, a 2008 parliamentary report concluded that public...
sector production would not be cost-effective and offer few advantages over existing arrangements [6]. Other factors often quoted to explain the gradual disappearance of vaccine manufacturing in the public domain are lack of economy of scale, failure to meet new and stricter international regulatory standards and lack of innovative development capacity. Costs to develop and commercialise a new vaccine have become huge, leading to a focus on protection of intellectual property, which results in price increases. In recent years vaccines are seen as becoming more profitable and a renewed interest by the private sector and by public private partnerships can be observed in all regions of the world.

Over the past decennia, this gradual privatisation of the vaccinology science field has continued in the industrialised world and nowadays there are only a few large pharmaceutical companies that dominate the supply of vaccines and vaccine combinations to Western markets.

For many countries in Asia, Africa and Latin America, a global system has evolved that has assumed the responsibility to provide vaccines. In this system, United Nations procurement organisations such as UNICEF, WHO and PAHO (for the Latin American region) are the key international organisations promoting children immunisation programmes in developing countries for the essential childhood infectious diseases. UNICEF and PAHO, and more recently also the GAVI Alliance for the newer and underused vaccines, play a significant agenda-setting role for immunisation programmes in developing countries because they simultaneously act as procurement organisations. In this system, WHO’s main role is to assure the quality of procured vaccines through a so-called WHO prequalification procedure. The GAVI Alliance, established in 2000, is a global public-private partnership funded for 75% by governments and for 15% by foundations, corporations and individuals. Its role in the global vaccine system has been described as

“a hypothetical “world government” for overcoming the collective action problem associated with the provision of immunisation. It brings various donors and technical partners together, acts as a conduit for funds, creates rules and regulations for the dissemination of those funds, and ultimately, purchases high-value vaccines that increase access to vaccination in developing countries” [7].

The four permanent GAVI Board seats are taken by UNICEF, WHO, The World Bank and the Bill and Melinda Gates Foundation (BMGF). Vaccines are procured through this system at lower prices than common in the industrialised world from the pharmaceutical vaccine industry and mostly, in terms of volume, from private or public vaccine manufacturers with their origin in low and middle income countries. These manufacturers are members of the Network of Developing Countries Vaccine Manufacturers (DCVMN). Both the pharmaceutical vaccine industry and the DCVMN occupy non-permanent seats in the GAVI Board.

One of the frequently recurring issues in the global vaccine arena is the debate on pricing of vaccines for the developing world. The current system is based on neoliberal thinking that primarily assumes that market mechanisms, in part shaped by GAVI, will eventually lead to access to vaccines in all countries of the world. Yet, despite GAVI’s 15
fifteen years of existence, serious disparities remain, as repeatedly highlighted around 
the annual World Health Assembly in Geneva by civil society organisations, united in 
Global Health Watch, but also by other NGO’s. Médecins Sans Frontières/Doctors With- 
out Borders (MSF), for example, launched a global petition in 2015 calling on pharmaceu-
tical companies Pfizer and GlaxoSmithKline (GSK) to reduce the price of the pneumonia 
conjugate vaccine to US$5 per child (for all three doses) for all developing countries and 
for humanitarian organisations.

Global public goods

Infectious disease control, especially through immunisation, is a way to improve 
public health outcomes worldwide. Certain aspects of vaccines and vaccination thus fall 
under the commonly accepted (economic) definition of a Global Public Good (GPG) as 
they fulfil its three basic criteria: non-excludability, non-rivalry and world wide availability. 
Non-rivalrous means that if one person consumes the good this does not deprive any- 
one else from using that same good, for example scientific knowledge. Non-excludable 
means that we cannot stop someone from using the good, for example the atmosphere. 
A good is excludable if it is possible to limit the benefit to those who pay for it.

Clearly, the benefit of the eradication of a disease fulfils all GPG criteria. In addition 
to smallpox eradication and the ongoing global polio eradication programme, another 
vaccine-related example of a public good is the herd immunity provided by a measles 
vaccination campaign. The vaccination against measles itself is not a public good; the 
measles vaccine dose used for one person cannot be used for another. However, if 
95% of the population gets vaccinated, no epidemic will spread. Thus even those who 
have not had the (rivalrous and excludable) vaccine are protected from the disease as 
well. So herd immunity is indeed non-rivalrous and non-excludable. Finally, Archibugi [8] 
has made the case that vaccine research and development know-how can be seen as 
intermediate global goods, necessary for reaching the final public global good of commu-
nicable disease control.

Generally a public good cannot be provided by the market because everyone gets 
it whether or not they pay for it [9]. The economic challenge with public goods being 
that in a free market private actors will invest less in producing them than desirable 
from a societal perspective. It is difficult to earn money: if anyone can use it, and this 
doesn't deprive anyone else from doing so, how can a profit be made to cover the costs 
of production? So, in many cases global public goods are associated with market failure 
and an international organisation as the World Bank regard GPGs as those goods whose 
supply critically depends on international collective action.

Failure to provide global public goods by collective action has been analysed by 
Gartner [10], taking the work of Barrett [11] as a starting point. Barrett distinguished 
three different categories of GPGs: 1) the weakest link GPGs, requiring the participation 
of every country to reach success (example: small pox eradication: unless every single
country successfully vaccinates its population, no country would benefit from the elimination of the disease; 2) aggregate GPGs, requiring cooperation by some but not all countries (example: climate change mitigation: reducing carbon dioxide production will succeed if the major emitters commit to reduce their emissions, but it does not necessarily require the participation of all countries); and 3) single-best effort GPGs, requiring action only by a single country (example: one country that would develop the technology to protect against the planetary threat of an asteroid and by doing so providing a GPG that might protect the entire human population).

**Increasing role of non-state actors**

Gartner [11] has pointed out that the weakness in Barrett’s approach is that many global public goods do not seem to fit into only one of these 3 categories, but rather in different stages in all three. As example he argues that vaccines can be placed in all three categories: as a weakest link GPG in terms of difficulty in eliminating disease in failed states; as a single best effort GPG in terms of discovery of vaccines and as an aggregate GPG in terms of financing mass vaccination campaigns (Table 1). He therefore proposed to regard these categories as different stages of the production of GPGs: innovation, financing and compliance. Innovation in the global health context is usually a single best effort problem; global health financing is usually an aggregate challenge and compliance generally reflects a weakest link problem. Innovation requires a better alignment of incentives with results; financing increasingly depends upon more automatic mechanism for capturing resources and compliance demands more decentralized means of enforcement. Gartner further highlighted the need to better incorporate the role of non-state actors into an analysis of global public goods and taking the polio eradication as an example he places the role of non-state “financing” actors such as the Rockefeller Foundation (RF) and more recently the BMGF in the aggregate stage of GPG production. Gartner suggests that different strategies and institutions are required to respond to different stages of GPG production. Innovation in the context of global health can be done by a single country or single actor. Financing rarely requires all countries to participate. Compliance however depends often on nearly universal cooperation. Gartner sees the incorporation of non-state actors into the governance of global health as an advantage, as many of the current international institutions have proven not to be well placed to overcome the underlying free rider problem. He further describes two outstanding vaccination-related examples of increasing non-state actor involvement in two different stages of the production of global public goods. At the innovation stage the BMGF is actively “reshaping the vaccine and drug markets” in developing countries by investing $12 billion over the period 1994-2008. At the financing stage, he highlights the GAVI Alliance’s success in resource mobilization as a new form of global health governance that strengthens the global capacity to deliver GPGs. Adopting a GPG perspective has allowed the GAVI Alliance to mobilize innovative sources of finance through collective action. These resources would not have become available without GAVI’s existence, thereby demonstrating that collective action can be used to advance global public goods like immunisation. It offers
INTRODUCTION

a rational reason for why developed countries take an interest in and invest in the health problems and health systems of developing nations.

**Table 1.** Global Public Good (GPG) categories regarded as different stages of GPG production [10, 11].

<table>
<thead>
<tr>
<th>GPG categories</th>
<th>examples from vaccine field</th>
<th>stages of GPG production</th>
<th>strategies and institutions that can be involved</th>
<th>role of non-state actors in GPG creation</th>
</tr>
</thead>
<tbody>
<tr>
<td>single best effort</td>
<td>discovery of a new vaccine</td>
<td>innovation</td>
<td>single country or single actor</td>
<td>BMGF reshaping vaccine market</td>
</tr>
<tr>
<td>aggregate</td>
<td>financing mass vaccination campaigns</td>
<td>finance</td>
<td>rarely requiring all countries to participate</td>
<td>RF and GAVI financing in polio eradication. Successful resource mobilization by GAVI</td>
</tr>
<tr>
<td>weakest link</td>
<td>elimination of disease in failed states</td>
<td>compliance</td>
<td>depends often on nearly universal cooperation</td>
<td></td>
</tr>
</tbody>
</table>

The core question: the Dutch case in international perspective

This thesis describes the specific case of public sector vaccine development and manufacturing in the Netherlands, from its emergence and initial successes in the 70s and 80s through a process of gradual decline and privatisation in the 90s, till the eventual take-over by the private sector in 2012.

How to understand the effects of globalization upon a renowned national vaccine institute such as the National Institute of Public Health and the Environment (RIVM) with a strong technological and scientific reputation? Specifically this thesis seeks to assess the institute’s impact on global health of international activities undertaken as a collateral to the national mandate to develop and produce vaccines for the Netherlands Immunisation Programme (NIP) and raises the question what the effect of the 2012 privatisation will be on global health. While in the Netherlands the public sector has now ceased to function as a supplier of vaccines for the national programme, its greater societal relevance is perhaps to be found by the creation of global public goods when viewed over a sixty-year period of local vaccinology knowledge and technology sharing with other countries, continuing to this day.

Already in 1979 this was recognized by Jonas Salk, the renowned inventor of the inactivated polio vaccine, when he described the Netherlands’ national institute’s contribution to global polio eradication and global health as follows:

“the significance of the work at the Rijksinstituut lies in the development of the technology that can produce an economic and reliable polio vaccine for world wide application and opens the prospect of eradication at such time as adequate supplies of vaccines can become available to be administered in a timely fashion”. [12]

and
“In addition to these technological advances, an essential ingredient in the control of poliomyelitis is a spirit of generosity and cooperation of the Netherlands not only in its invaluable gifts of specially prepared vaccine and the testing of serum samples collected in the studies carried out in other parts of the world, but in making available to all who wish to learn the methods developed in Bilthoven. The Rijksinstituut’s contributions in the field of poliomyelitis immunisation is an example of the potential of medical immunology for public health, for the health of the global community”. [12]

The national health institute consistently maintained an open-door policy and until the mid-nineties of the previous century shared production technology with other countries. This took place either under the UN-umbrella of WHO or UNIDO or through direct agreements with public and private manufacturers, most of which are now members of the DCVMN. From a global perspective, the Dutch case of vaccinology privatisation is of particular interest because the eventual buyer turned out to be the Serum Institute of India Ltd. (SIIL), one of the world’s largest private vaccine manufacturers. SIIL plays a key role in the supply of affordable vaccines for developing countries made available through the global UN procurement system. Since the mid-sixties of the previous century, SIIL had also been one of the most successful partners benefitting from established vaccine know how and technology transfer programmes executed from the Dutch public domain. The 2012 take-over has therefore by some insiders been described as “the ultimate success of technology transfer”.

Outline of the thesis

**Chapter 1** provides a short overview of public vaccine manufacturing in the Netherlands. It starts with an outline of the vaccines and vaccination schedules used today in the national childhood immunisation programme (NIP), followed by a chronological description on new vaccine introductions since the NIPs establishment in the early 50s. It further summarizes several technological innovations and challenges in local vaccine research and development that led the institute from early success as sole provider of vaccines to the NIP, to institutional transformations with increasing difficulty to meet the NIP requirements, and eventually to a situation that none of the components of the NIP are any longer provided by the public sector.

The next two chapters describe case studies from the institute’s history that illustrate the complexity of development of a new vaccine within a public setting.

**Chapter 2** describes an attempt in the 60s and early 70s to develop an inactivated measles vaccine for the NIP, despite the availability of a highly effective commercial live measles vaccine that had been developed in the United States. One reason for this persistent effort was high confidence in its own ability to overcome the technical (safety-related) challenges that had caused other countries to abandon the development of an inactivated measles vaccine. The key driving factor however appeared to be the dominating institutional strategy to prefer measles vaccine introduction into the NIP as a
component of a combination vaccine.

Chapter 3 analyses a regional network initiative driven by the RIVM to develop and clinically test a conjugate pneumococcal vaccine for the developing world, undertaken with public health institutions from Sweden, Denmark, Norway and Finland between 1990 and 2000. A tetravalent prototype vaccine was made that proved safe and immunogenic in phase 1 trials in adults and toddlers in Finland. The planned next step, to test the vaccine in Asia in infants, did not meet approval by the local authorities in Viet Nam nor later in the Philippines and the project eventually stopped. The premature termination of the project was less due to technological and scientific challenges, but more to managerial challenges and institutional policies. Key success factors and important lessons learned on technology transfer from this consortium were later applied in other international projects, resulting in the availability at affordable prices for the developing world of another conjugate vaccine.

The following three chapters appraise the impact on global health through selected case-studies on RIVM’s international activities directed at members of the DCVMN.

Chapter 4 highlights the role of capacity building in previous “producer - producer” collaborations between the RIVM and emerging manufacturers over the past 40 years and in specific technical training courses developed in collaboration with the WHO and describes the Netherlands' government decision to transform RIVM’s vaccinology research and development capacity into a new not-for-profit entity: “the Institute for Translational Vaccinology (Intravacc)”. It proposes a common initiative from Europe for a practical vaccinology course for emerging countries with particular focus to the African region.

Chapter 5 is a comprehensive review on international technology transfer initiatives starting from the insight that the vast majority of vaccines are nowadays produced in middle income countries. It illustrates that the production capacity increase in those countries is to a major part due to technology transfer from the public sector sometimes but not always in collaboration with WHO. It specifically highlights the RIVM activities in providing access to vaccine technology in these countries not only through multilateral frameworks but also on a bilateral basis including a major project in the 90s to three national institutes in China on diphtheria, pertussis, tetanus, measles and polio vaccine production funded through a soft loan from the World Bank. It argues that connecting innovative enabling platforms with competent developing country vaccine manufacturers (DCVM) is critical to ensure a sustainable supply of affordable and quality vaccines to national immunisation programmes in developing countries.

Chapter 6 comprises a short description of an influenza vaccine technology platform (or “hub”) that was established in Bilthoven at the request of WHO to enable developing country manufacturers to establish or improve their pandemic influenza vaccine production capacity. A transferable pilot process for egg-based inactivated influenza vaccine production was established under GMP, together with release assays and a course
curriculum, including a practical handbook for hands-on training.

Chapters 7 and 8 provide insights in the way that developing country vaccine manufacturers (DCVM) are now positioned in the recent transformations taking place in the global vaccine system.

**Chapter 7** represents a 2008 status report of the Developing Countries Vaccine Manufacturers Network (DCVMN) as main representing body of emerging vaccine manufacturers from the developing world within the global vaccine system. This chapter focuses on the achievement, within 8 years from its establishment, of the Network’s main strategic priority: increase of access to DTP-based combination vaccines containing vaccines against hepatitis B (HepB) and *H. influenzae* type b (Hib). This has been due in part as a result of the transfer of conjugation technology from Bilthoven to various manufacturers of the Network. To ensure the long-term viability of domestic or regional vaccine manufacturing, this article advocates for more push mechanisms at the international level for product development involving DCVM, and at national level for more financial incentives to manufacturers to develop and import new technologies.

**Chapter 8** gives a comprehensive overview of the Chinese vaccine industry in 2009 which is developing rapidly due to an emerging and large market for current and new vaccines, a large potential for local vaccine manufacturing both in the public and private domain, and a governmental orientation towards national vaccine self-sufficiency. The innovative development capacity of state vaccine institutions is stimulated by significant government investments. Various Chinese influenza manufacturers were in 2009 among the first worldwide to obtain a national license for their pandemic H1N1 influenza vaccines. The expectation expressed in this article, that WHO prequalification for at least one product from a Chinese manufacturer will be obtained soon, proved correct: in October 2013 the Japanese encephalitis vaccine from the Chengdu Institute of Biological Products (CIBP) was officially prequalified by WHO, followed in June 2015 by a second WHO prequalification of a Chinese-made seasonal influenza vaccine from Hualan Biological Engineering Ltd. [13].

In the concluding section, called the *Endgame*, the findings from the previous chapters are reviewed and the narrative on the Netherlands public sector manufacturing and its technology sharing discussed in the wider context of the global vaccine system. An apparent misconnection (“policy incoherence”) is noted between national vaccine development practices and overseas development assistance policies towards the provision of vaccines to the developing world.
Chapter 1
Public sector vaccine development and production in the Netherlands
CHAPTER 1

This chapter gives a brief chronological description on the origin and key features of the development of local vaccine manufacturing in the Netherlands over half a century with its innovations, successes (seen from a national perspective) and gradual decline.

The Netherlands National Immunisation Programme (NIP)

The Netherlands takes great pride in its national childhood immunisation programme. Traditionally, vaccine coverage levels are high, also in comparison with other countries in Europe and elsewhere, and a recent historical analysis covering many decades clearly indicates the beneficial public health impact and the cost-benefits of the programme [14]. Over time, the schedule for children has evolved from a simple package of a few classical vaccines in the 50s to its current (2016) composition, containing vaccines against 12 infectious diseases (Table 2).

Although other vaccines are licensed and available on the Dutch market, chief characteristics of NIP vaccines are that they are recommended by the Ministry of Health and provided free of charge. A particular feature of the NIP is the policy to restrict the number of injections per session to two, which puts limitations to the number of vaccines that can be applied in a single vaccination moment. This policy requirement has been a driver for the development of combination vaccines.

The introduction of this state sponsored programme started in 1951 with the vaccination against diphtheria (D) primarily in schoolchildren. From 1953 onwards it was extended to neonates with two vaccines against tetanus and pertussis in a trivalent combination vaccine (DTwP). In 1957 an inactivated vaccine against polio (IPV) was added to make it a four valent combination (DTwP-IPV). In 1974 a rubella vaccine was added as a separate vaccine, initially for 11-year old girls, but from 1987 onwards as part of the new combination vaccine MMR. A stand-alone vaccine against measles was introduced to the NIP in 1976. This was also to become part of the MMR combination vaccine from 1987 onwards. A vaccine against mumps was introduced in 1987 as part of the same combination vaccine. Six years later in 1993 a conjugate vaccine against H. influenzae type b infection was added, followed in 2002 by another conjugate vaccine against meningitis disease caused by meningococcus C. In 2003 a recombinant vaccine against hepatitis was taken up in the NIP for all neonates born to a mother infected with hepatitis B. In 2005 the whole cell pertussis component (wP) was replaced by an acellular component (aP) by introduction of a DTaP-IPV-Hib combination vaccine. A HepB component was added to this combination vaccine for those neonates that had an indication for HepB vaccination. In 2011, hepatitis B has become a universally applied component of a combination vaccine also containing DTaP, IPV and Hib. A 7-valent pneumococcal conjugate vaccine (PCV) was added in 2006, which was replaced in 2011 by a 10-valent PCV. Finally, a HPV vaccine against human papilloma virus infections was introduced in 2009 for 12 year old girls.
Table 2. The 2016 National Immunisation Programme (NIP) in The Netherlands [15].

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<td>H. influenzae type b infection</td>
<td>cHib</td>
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<td>rubella</td>
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<tr>
<td>human papillomavirus infection</td>
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Footnotes:  
1) Babies born to a mother infected with hepatitis B will be offered a first dose at birth  
2) The booster dose of DT-IPV offered at nine years is the only vaccine that is currently manufactured in Bilthoven.

Dynamics of supply to the National Immunisation Programme

Since the 50s, vaccines to supply the NIP have been developed and produced by the National Institute of Public Health in Bilthoven.

After the Second World War, in 1950, the Institute received financial support from Marshall Aid to make the Netherlands independent from vaccine imports and, in case of a war with the Eastern Block, to make sufficient sera and vaccines for the military apparatus of NATO. Production facilities for smallpox vaccine and bacterial vaccines were constructed, leading in a few years to local production of a trivalent combination vaccine: diphtheria, pertussis and tetanus (DTP) for supply of the national immunisation programme which had started in 1957.

Inactivated vaccines against diphtheria, pertussis, tetanus and polio

A polio vaccine was to be added soon. In 1956 a serious polio epidemic had oc-

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Footnotes:  
1 The Dutch National Institute of Public Health or Rijksinstituut voor Volksgezondheid (RIV) was created in 1934 and moved in 1953 to its current location in Bilthoven; from 1984 onwards it became the RijksInstituut voor Volksgezondheid en Milieu (RIVM); from 2003 till 2012 vaccines were developed and produced within the Netherlands Vaccine Institute (NVI).

2 RIV later played an important role in global eradication of smallpox by supplying vaccines to the WHO smallpox campaign and by acting as a WHO smallpox quality control reference to test smallpox vaccines from other suppliers to the programme for safety and potency.
CHAPTER 1

curred, which led the Dutch Health Council (the committee that advises the Government
on the relevance of introducing new vaccines) to recommend mass vaccination to all
children up to fourteen years of age against polio with the inactivated polio vaccine (IPV)
as had been developed by Salk in the US. In 1956, IPV was imported from a Belgium
manufacturer, but in 1957 the government decided to produce IPV itself. This triggered
the development of a combination DTP-IPV vaccine, under the dynamic leadership of
Hans Cohen (head of vaccine production at RIV who became director of the Institute in
1979) which would reduce the number of injections to four instead of the previous seven
or eight (four times DTP plus three or four times IPV). In 1962 the DTP-IPV combination
vaccine replaced the separate DTP and IPV vaccines in the NIP [16].

Key to this success story was the development and introduction of innovative pro-
duction technology by two RIV microbial process engineers Paul van Hemert and Anton
van Wezel. They made large scale bacterial and viral vaccine production technically and
economically feasible. Van Hemert developed medium to large scale bacterial production
and purification processes based upon stainless steel fermenters (bioreactors) under
standardized conditions and in closed systems, increasing product yield and quality. Van
Wezel succeeded in producing large quantities of polio viruses, which need adherent
cells, in these bioreactors by introducing small plastic beads (“micro carriers”) on which
cells, susceptible to polio viruses, had been grown. Use of micro carriers increases the
total surface on which cells are grown per given bioreactor volume, thereby increasing
the yield of viral production dramatically. Van Wezel also developed and improved the
then existing purification procedures by introducing size exclusion chromatography and
anion exchange chromatography. The resulting IPV polio vaccine process (the “van
Wezel” process) has become a standard for IPV production and is still being used today
by the majority of IPV manufacturers worldwide [17-20].

Live vaccines against measles, mumps and rubella

In a case study on vaccination against measles, mumps and rubella, Blume and
Tump [21] have described the reasoning and complex negotiations that resulted in the
eventual introduction of an MMR vaccine. Partly in parallel with an in-house development
of an inactivated measles vaccine to be added to the existing DTP-IPV combination vac-
cine (described in further detail in Chapter 2), RIV concluded a licensing agreement with
Merck in the United States for making a live measles vaccine in Bilthoven with Merck’s
“Moraten” strain. From 1981 onwards, this RIV-measles vaccine replaced the imported
Merck’s measles vaccine in the National Immunisation Programme. By 1973, RIV had
developed its own rubella vaccine from a HPV77 strain that had been obtained from
the US and had been further attenuated. By 1974 it was introduced in the NIP. From
1981 onwards, RIV had started negotiations with commercial manufacturers to obtain a
mumps vaccine strain, anticipating an expected forthcoming advice of the Health Council
to add mumps to the NIP. Since MSD (Merck’s European subsidiary) would not consider
licensing a single mumps component, RIV eventually decided to take a license for MSD’s
combined MMR vaccine and from 1987 onwards, RIV supplied the live MMR vaccine
made in Bilthoven under license from MSD to the NIP.

**Replacement of the whole cell pertussis vaccine with an acellular pertussis vaccine**

By the end of the 90s, when a pertussis epidemic occurred in the Netherlands, an international advisory committee established by the Dutch Health Council suggested a declining efficacy of the existing vaccine and recommended a switch to a new acellular vaccine that had come on the market [22]. In 2000, the Health Council recommended a booster vaccination with acellular pertussis for children aged 4 years and urged to change over to acellular vaccine in the primary series. The RIVM had worked from 1997 onwards (after 2002 within a new entity known as the Netherlands Vaccine Institute (NVI)) on the replacement of the whole cell pertussis component in its DTP-IPV combination vaccine with a commercial acellular pertussis component. This raised considerable technical and formulation challenges. When vaccine components are put together they do influence each other, with possible safety or potency implications for each of the individual component, thus requiring time-consuming and costly clinical trials for the entire combination vaccine, as it is regarded by the regulatory authorities as a new product. By 2004, the Health Council observed that NVI had not succeeded in producing its own new vaccine in a reasonable time frame and therefore recommended purchase of a commercially available combination vaccine. The Minister of Health followed this advice and from 2005 onwards a commercial DPaT-IPV vaccine was procured for the national immunisation programme [22]. This also implied that the local production capacity for diphtheria, pertussis, tetanus and polio became obsolete for the requirements of the NIP.

**Gradual decline (inability to meet local demand)**

The revolutionary process development in the 60s of the application of semi industrial production in bioreactors of bacterial and viral childhood vaccines (polio and rabies) has been the hallmark of the Dutch public sector production success, which generated substantial international interest. The strongest characteristic in those early decades was that the national demand could be supplied. Development costs were not clearly known, and most needed technological competences were available in house. Over time, as progressively more introductions of new vaccines were required, the capability to meet this national demand diminished until eventually all vaccines and vaccine combinations that are used today in the NIP have to be procured from international commercial manufacturers (Figure 2)\(^d\).

\(^d\) The only exception being the DT-IPV booster dose given at nine years which is still manufactured in Bilthoven. See footnote 2 under Table 2.
Institutional reforms following changes in government policy

From the mid-80s onwards, a succession of several institutional and legal reforms began, reflecting changes in government policies to adapt to new challenges in the preservation of national vaccine development and production capacity for the NIP.

In 1988, the Stichting voor Volksgezondheid en het Milieu (Foundation for Health and Environment) or SVM was created: a not for profit foundation separate from the Ministry of Health in order to separate medium preparation and pharmaceutical filling from vaccine research development and production which remained within RIVM. The relevant RIVM staff was transferred to SVM, located on the RIVM premises. In 1998 this was followed by transfer of the production personnel to SVM. Research and development and quality control functions including animal facilities remained within RIVM. The rationale was to reach cost efficiency. Installed manufacturing and pharmaceutical filling capacity under a foundation structure could also be used for (private) customers, which had not been possible under the government umbrella of the RIVM.

There was another reason to place the vaccine manufacturing in a legal entity separate from RIVM. The vaccine regulatory authority (NRA) had its national quality control laboratory (NCL), responsible for independent lot release of all vaccines released to the Dutch market, within RIVM’s premises. This meant efficiency in a sense because some resources such as experimental animals and experienced animal technicians could be shared between the vaccine department of RIVM and the national quality control labo-
In February 2002, in the aftermath of the 11 September 2001 events in the US, the Netherlands’ government decided that “the possibility to develop and produce vaccines within the public domain needed to be preserved to ensure the timely availability of sufficient vaccines of assured quality”. The perceived risk in the Western world for a potential smallpox pandemic by intentional release played a role in this decision. The production of a national smallpox vaccine stockpile was commissioned to the RIVM in 2002. The rationale was that maintaining a production capacity in the public domain would counterbalance the risk of market failure caused by a decrease in the number of commercial manufacturers. This led to the creation of the Netherlands Vaccine Institute (NVI), bringing together the SVM and the vaccine research and development department of the RIVM. All vaccine development and production related facilities and staff were now merged into a separate state agency separated from RIVM. NVI’s mission was to guarantee (by procurement or production) the supply of vaccines necessary to protect the Dutch population against infectious diseases for the use in the NIP and in crisis situations, such as an epidemic or pandemic [23].

In 2009 however, the Netherlands Minister of Health decided to cease all vaccine manufacturing in the public domain. The main reason for this decision was economical, since the manufacturing of vaccines had been consistently losing money over years. Through a part-privatisation process the vaccine manufacturing capabilities of NVI were eventually sold in 2012 to the Serum Institute of India Ltd. (SIIL), for €32 million [24]. Prior to the sale, several public vaccine tasks of the NVI such as vaccine procurement, warehousing, distribution and the vaccine research and development division had been re-incorporated into the RIVM.

The re-integration of the vaccine research and development into RIVM turned out to be very short-lived, because already in 2012, the Director-General Public Health and the Director-General RIVM together agreed to place the RIVM vaccinology research and development capacity outside the RIVM in a new not-for-profit entity: “the Institute for Translational Vaccinology” (Intravacc), with a mission to bridge the so-called translational gap between vaccine research in academia or small/medium enterprises including biotech and the vaccine industry. Intravacc is expected to become the key entry in the Netherlands for partners that wish to take advantage of its broadly accessible and comprehensive infrastructure for translational vaccine research and development. Although Intravacc currently still belongs to the Ministry of Health, a ministerial decision to privatize or semi-privatize (“placing it outside the public domain, but with the preservation of certain public tasks”) is expected in 2017. In a letter sent to parliament on 22 December 2016, the Minister of Health, Edith Schippers, announced and clarified the governments’ approach towards Intravacc’s privatisation. While mentioning the public interests which
need to be safeguarded after privatization\textsuperscript{6}, she emphasized the expected economic advantages for the Government \cite{ref25}. Should this decision be taken, it would mark the beginning of the end of a multi-annual privatisation process of the Dutch public sector vaccinology capacity that began in 2009.

\textbf{Summarizing remarks}

Under a national mandate and strong leadership by Hans Cohen, a comprehensive infrastructure covering the entire product value chain was laid in the 60s and 70s based upon van Hemert and van Wezel process technologies in combination with analytical in-house capabilities for in process control, quality control and quality assurance, resulting in a critical mass of vaccinology expertise and capacity in well-resourced facilities. This infrastructure also included advanced laboratory animal science and technical capabilities, required for quality control testing of vaccines.

The key technological innovations in the 60s and 70s were the successful development and application of semi-industrial bioreactor/micro carrier process technology which increased quality (closed systems) and quantity (economy of scale), combined with formulation technology for combination vaccines and adjuvants. One of the world’s first DTP-IPV combination vaccines was developed and taken up for many years in the NIP. Local MMR manufacturing under a unique license agreement with Merck was similarly successfully implemented to serve the NIP. When by the 90s the call for adding more vaccines to the NIP arose, the privatisation of the global vaccinology field that started from the 80s onwards began to influence the Institute’s capacity to meet the national vaccine requirements. As new vaccines were developed and patent protected it became more difficult. Hepatitis B was initially not seen as a priority by the Institute. When from the early 90s onwards recombinant DNA technology and conjugation technology resulted in new vaccines against hepatitis B and Hib, the Institute ran into trouble because it could not acquire these technologies fast enough against acceptable conditions from commercial sources. Moreover, the demand for these vaccines threatened the other components in the NIP’s cornerstone DTP-IPV combination vaccine since negotiations with commercial suppliers learned that they (like MSD in the case of acellular pertussis mentioned above) were not so much interested to provide bulk components, but rather preferred to sell the entire combination. In addition, increasing regulatory pressure made development, especially the clinical development, of a new vaccine more complex and therefore more costly. In a country with a small population size and by mandate restricted to its very small national market, the Institute was unable to upscale for export which is a requirement for economic sustainability.

\textsuperscript{6}The priority public interests mentioned are: 1) continued contributions to vaccine development and vaccine improvement, 2) access to critical facilities for vaccine development in case of calamities, 3) worldwide access to affordable vaccines of assured quality and 4) reduction and replacement of animal experiments.
Chapter 2

Measles vaccination before MMR: Perspectives from Europe
CHAPTER 2

Abstract:

At the beginning of the 1960s, it was clear that a vaccine against measles would soon be available. Although measles was (and remains) a killer disease in the developing world, in the United States and Western Europe this was no longer so. Many parents and many medical practitioners considered measles an inevitable stage of a child’s development. Debating the desirability of measles immunisation, public health experts reasoned differently. In the United States, introduction of the vaccine fitted well with Kennedy’s and Johnson’s administrations’ political commitments. European policymakers proceeded more cautiously, concerned about the acceptability of existing vaccination programmes. In Sweden and the Netherlands, recent experience in controlling polio led researchers to prefer an inactivated virus vaccine. Although in the early 1970s attempts to develop a sufficiently potent inactivated vaccine were abandoned, we have argued that the debates and initiatives of the time during the vaccine’s early history merit reflection in today’s era of standardisation and global markets.

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

Examining the introduction of four paediatric vaccines (diphtheria antitoxin, and the pertussis, polio and measles vaccines), Baker has argued that the middle years of the 20th century display distinctive national styles of vaccine innovation. Whereas US vaccine development and implementation were marked by a “current of urgency”, the more cautious British set much higher standards for the evidence required to prove the safety and effectiveness of a new vaccine before deciding on its introduction. This, in turn, could be attributed to the influence that the statistical pioneers of the randomized clinical trial had gained in Britain. We have looked in detail at the introduction of measles vaccine, focusing now not only on the United States and Britain, but on two other European countries (the Netherlands and Sweden) as well. Responses to the development of the first measles vaccines confirms Baker’s contrast between American and British styles, the one marked by a sense of urgency, the other by a cautious insistence on randomized trial data. But our analysis suggests that, in addition, two other considerations influenced policymakers: one was national experience with polio vaccination just a few years previously, which differed in these four countries; the other was the European public health authorities’ concern with the implications of introducing a new vaccine for the national immunisation programme, as a whole, and for popular confidence in it, in particular.

The search for a measles vaccine

By the early 1960s the epidemiology of measles was well understood. It was known that the disease occurred throughout the world, generally in regular periodic cycles. With the exception of some isolated population groups, almost all children contracted measles before they reached adolescence. No nonhuman sources of infection were known.

By 1960, thanks to the use of antibiotics and improvements in living conditions, measles mortality was declining steadily in industrialised countries (although not in the developing world). For example, in the United Kingdom deaths from measles had fallen from 307 in 1949 to 98 in 1959. Parents largely came to see measles as an unpleasant, although more or less inevitable, part of childhood. Many primary care physicians shared this view.

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

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

In March 1963 the first two measles vaccines were approved for use in the United States – a live vaccine produced by Merck (Rubeovax) and a formalin-inactivated one produced by Pfizer (Pfizer-Vax Measles-K). In September 1963 the US Surgeon General Luther Terry published a statement on the status of the measles vaccines. The live vaccine had by this time been given to some 25,000 people in the United States. A single dose produced an effective antibody response in more than 95% of susceptible children - a response that trials had shown persisted for at least 3 years. Although 30 to 40% of these children showed signs of temporary high fever and a rash after vaccination, side effects could be reduced by coadministration of gamma globulin. The inactivated vaccine was administered, in field trials, on a three-dose monthly schedule. Although this produced no side effects, antibody levels were lower than with the live vaccine and it was not known whether they persisted beyond six months. A combined schedule had also been tried. If a dose of inactivated vaccine was given a month or so before the live vaccine, reactions caused by the live vaccine were greatly reduced. The surgeon general recommended that children without a history of measles be immunized at approximately nine months.

There seemed no reason to begin a mass immunisation programme: the decision to immunize could be left to individual medical practitioners and parents.

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

US and UK immunisation policy, 1963-1968

Any decision to begin measles vaccination in the early 1960s thus involved a number of uncertainties. Was the disease serious enough? Would parents feel it worth having their children vaccinated? And if mass vaccination did seem justified, should the live or the killed vaccine (or a combination of both) be used? In the United States experience with the polio vaccines played a major role in shaping the consensus that gradually emerged.
Colgrove has explained how, after an initially euphoric response to the Salk vaccine, demand for the polio vaccine in the United States fell rapidly\textsuperscript{IX}. By the late 1950s polio was again on the rise, with cases now concentrated in socially deprived areas with large numbers of unvaccinated people\textsuperscript{XII}. Overcoming this problem seemed more feasible with the live Sabin vaccine, which required just one drop in place of the three Salk vaccine shots. It also fitted well with the priorities of the administration of President John F. Kennedy, who took office in 1961. In 1962 Congress passed the Vaccine Assistance Act, which authorized financial assistance to states specifically for vaccination programmes against polio, diphtheria, whooping cough and tetanus\textsuperscript{XIII}. In 1965, when this act came up for renewal, officials were anxious to avoid the socio-economic disparities in coverage that had emerged with polio, and which were now appearing with measles vaccine coverage. An amendment to the act added measles to the diseases for which federal subsidies were available.

\textit{As the problem of infectious disease became increasingly coterminous with the issue of socioeconomic disadvantage, the federal war on poverty provided an ideal conceptual framework for the fight that would soon be launched against measles.}\textsuperscript{XIV}

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

I reply with the same answer that Hillary used when asked why he wished to climb Mt. Everest. He said ‘Because it is there.’ To this may be added, ‘...and it can be done’.\textsuperscript{XVI}

Some were sceptical, notably the eminent bacteriologist René Dubos, but President Lyndon B. Johnson gave the programme his support\textsuperscript{XVII}. Rapid success was anticipated:

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

Some 11.7 million doses of measles vaccine were distributed in 1967-1968 and the estimated number of cases of measles fell from 900,000 to 250,000. However, because budgetary politics subsequently led to fluctuating federal support for community-based immunisation programmes, the view that measles would soon be eradicated was to prove wildly over-optimistic\textsuperscript{XIX}.

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

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

D.L. Miller, of the UK Central Public Health Laboratory Service’s epidemiological section, was among those arguing most forcefully for mass measles immunisation. A large-scale survey of general practitioners and hospitals had shown that “serious complications of measles are commoner than is generally supposed.” In an average epidemic year, more than half a million notified cases of measles could be expected in England and Wales. Extrapolating on the basis of the survey, 35,000 patients with serious complications could be expected, of whom 6,000 would be hospitalized. As a percentage this was small, but the numbers were considerable, and represent a significant burden to families and to the state. It seemed unlikely that further reductions in measles morbidity could be expected from improvements in hygiene, nutrition or housing.

*Further advance is likely to come only from prevention of the disease by immunisation, and on the available evidence this would seem to be well worth doing.*

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

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

The editorial ended,

*In Great Britain at the moment it is not necessarily logical to say, “We can produce a vaccine; let us therefore use it.”*

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

*not only as Langmuir has said “because it is there and it can be done”, but also because of the toll it takes in human misery.*

Still, even if it were agreed that measles vaccination was desirable, the question of how it should be done remained open. On this the editors of the two journals agreed. The live vaccine was problematic by virtue of the side effects it often produced, whilst protection provided by the inactivated vaccine was of questionable duration. However, there was the possibility that a more powerful inactivated vaccine would be developed.
British experience with the polio vaccines had led to a clear preference for the live (Sabin) vaccine by 1964\textsuperscript{XXIX}. But because hard evidence relating to measles specifically was felt to be needed, in early 1964 the Medical Research Council (MRC) started a study of measles vaccines. A preliminary study among children aged 10 to 18 months involved comparison of four schedules. Two groups of children received a highly attenuated strain produced either by Glaxo or by Wellcome Research Laboratories, and two groups were given the Pfizer killed vaccine before one of the live vaccines\textsuperscript{XXV}. The study focused only on short term clinical and serological responses. It was found that whilst all four schedules were “acceptable and practical”, children on the single-dose schedule seemed on average to have higher antibody titers. Why this should be was unclear and needed to be studied further, especially because other investigators had reached the opposite conclusion. A large-scale trial began later in 1964. Meanwhile, although the various vaccines were available for doctors to use at their discretion, there was as yet no national policy. In a letter to doctors, dated February 21 1966, the Ministry of Health left the choice of vaccine to be used to the individual physician\textsuperscript{XXXI}.

In 1965 the first reports of a strange measles-like illness in children exposed to natural measles after receiving the inactivated vaccine had appeared in the United States\textsuperscript{XXXII}, and it appeared that this could also occur when live vaccine was administered after inactivated vaccine. There was a growing sense, internationally, that the inactivated virus vaccine should be avoided\textsuperscript{XXXIII}. In August 1967 a letter from Vincent Fulginiti, a specialist in paediatric infectious diseases at the University of Colorado, appeared in the \textit{Lancet}\textsuperscript{XXXIV}.

He and his colleagues had started trials using three doses of killed vaccine (KKK schedule) and 2 doses of killed plus one live attenuated vaccine (KKL schedule) some years earlier. Results showed that in some of the children on the KKK schedule, immunity waned after six months:

\begin{quote}
We are receiving increasing reports of natural disease in both the KKK and KKL vaccinees. In addition, 10 of these vaccinees, all of whom have required admission to hospital, have had a new disease which we have termed ‘atypical measles’\textsuperscript{XXXV}.
\end{quote}

How this came about was not understood.

In May 1968 a second report of the MRC measles vaccine trial was published\textsuperscript{XXXVI}. This trial involved more than 36000 children, aged 10 months to 2 years, across Great Britain. Some children were allocated to a control group and received no vaccine, whereas others in the trial received either a single dose of Glaxo’s live attenuated (Schwarz strain) vaccine, or a single dose of the Pfizer killed vaccine followed one month later by a single dose of the live vaccine\textsuperscript{XXXVII}. Both schedules were found to give good protection in the first 9 months. With time, however, differences appeared. After 2 years the single dose schedule produced a higher degree of protection (95%) than the double dose schedule (89%). The MRC concluded that “there is a strong case for the use of live measles vaccine alone”. Not only did this give a higher degree of protection, but it also had the additional
advantage that only a single injection was required.

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

No case of the atypical measles Fulginiti reported was found.

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

Meanwhile, in November 1967, the Joint Committee on Vaccination and Immunisation, the British government’s principal expert advisory body on vaccination policy, recommended that all children aged one year and older who had not had measles and not been vaccinated should be offered live attenuated vaccine. The recommendation was accepted, and in February 1968 local health authorities were informed. In 1968, by which time the inactivated vaccine had been withdrawn in the United States, the mass vaccination campaign using live vaccine began in Britain. Although the duration of protection was still uncertain, the MRC trials using the Schwarz strain suggested that immunity lasted for at least two years. This was likely to be true also of the other attenuated vaccine then available in Britain. The editor of the Lancet agreed that the killed vaccine then available offered protection that was too short lived to be of value, and when used before an attenuated vaccine there was the possibility of unusual reactions. Although it was possible that a more satisfactory killed vaccine would be produced, “killed measles vaccine of the type made so far is clearly unsatisfactory and it is no longer available in Britain.”

The search for an improved inactivated vaccine

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

In my opinion the use of live vaccines should be avoided if possible. By introducing an autonomous organism in the individual a reaction-chain is initiated which we probably are unable to control in all conditions. The immediate consequences may seem harmless, but a cytopathogenic agent does not disappear without leaving traces...

In the controversy between living and inactivated poliovirus the axiom was that
this goal would not be obtained with dead virus alone. In Sweden however, it appears that 7 years after application of IPV neither the diseases nor the virus seem to occur. Hopefully we shall see the same development with the use of inactivated measles vaccine.\textsuperscript{XLIII}

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

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

The killed measles vaccines are generally supposed to give immunity quantitatively and qualitatively inferior to that after natural measles. For this reason they are usually recommended for use only in combination with live vaccine. Similar arguments were raised against inactivated and for live poliovirus vaccines. However, the excellent results achieved in the Scandinavian countries with inactivated poliovirus vaccine appear to invalidate those arguments, and for this reason it would seem unwise to discount inactivated measles vaccines before they have been given a fair trial.\textsuperscript{XLV}

In an initial study, Swedish children who had previously received three monthly doses of the Pfizer inactivated vaccine were revaccinated 22-23 months later, either with a fourth dose, or with the new TE-inactivated preparation. They were then followed for a further 8 months, and then tested after 18 months and after 29 months. In a second study children were given either three monthly doses of formalin-inactivated vaccine plus a booster of TE vaccine 17 months later, or they were given 3 monthly doses of TE vaccine and, again, a TE booster after 17 months\textsuperscript{XLVI}. These children were followed for 3 years after the final booster. Initial results with the TE-inactivated vaccine were promising:

The mean haemagglutination-inhibition titer eight months after revaccination was 600 in the group of children given formalin-killed vaccine, and 7800 in the group given Tween-ether vaccine.\textsuperscript{XLVII}

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

Like their Swedish colleagues, Dutch investigators preferred an inactivated vaccine. In the Netherlands too, polio had been successfully controlled with IPV\textsuperscript{LIX}. This had been done by adding IPV to the diphtheria-pertussis-tetanus (DTP) vaccine already in use, thereby avoiding disruption of the national immunisation programme. The country’s high immunisation rate (more than 95%) was attributed to the simplicity of the immunisation schedule used. When work on development of a measles vaccine began at the Dutch Institute of Public Health (RIV) in 1964 the intention was to replicate the earlier strategy.\textsuperscript{1}

In 1965 Merck’s subsidiary in the Netherlands (MSD) requested permission to import the company’s live measles vaccine. Obliged to respond to this request, in October 1965 the Minister of Health turned to the Health Council (Gezondheidsraad) for advice.

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

In December 1967 the Health Council published its report on measles vaccines\textsuperscript{LIII}. The Council’s view was that although measles vaccination should eventually be included in the National Immunisation Programme, it was not yet the time to do so. It was still unclear which vaccine was to be used, how it was to be used, or how disruption of the National Immunisation Programme could best be avoided. The Council therefore recommended that further studies, particularly of the inactivated vaccine, be carried out before any definitive decision was made. Meanwhile, import of both live and inactivated vaccines should be permitted and the decision to use one or other left to the individual medical practitioner. As measles vaccines then became available, medical practitioners needed guidance as to their use. Unlike in the United Kingdom, there had been relatively little discussion of measles vaccination in the Dutch medical press, and (also unlike in the United Kingdom) physicians at this time were not obliged to report cases of measles. The principal source of information was a national survey of general practitioners, conducted under the auspices of the Dutch Association of Family Doctors (Nederlands Huisartsen Genootschap). Between October 1965 and April 1966, the 247 physicians who responded had seen 10,700 cases of measles\textsuperscript{LIV}. The authors of the study estimat-
ed that approximately 16.1% of children contracting measles were likely to show some complications. Extrapolating, some 2700 children would be seen by a specialist and 900 admitted to hospital.

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

\begin{quote}
\textit{Inactivated vaccines can provide good protection against measles, in any event in the short term and after repeated application.}
\end{quote}

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

\begin{quote}
\textit{It is conceivable that these complications, associated with use of inactivated vaccine, can be avoided by the correct choice both of vaccine and of mode of delivery.}\textsuperscript{LV}
\end{quote}

Because at the time these conditions were not known, use of the (commercially available formalin-) inactivated vaccine was not advisable. It remained to be seen whether a different inactivated vaccine might eventually prove of value. Individual use of the vaccine was advisable: the consequences of vaccination were far less than of the disease itself. But introducing measles vaccination into the National Immunisation Programme raised additional questions. From this viewpoint, combining measles vaccine with existing combinations had major organisational advantages. The overall success of the National Immunisation Programme was crucial. One must consider whether those caring for the child will readily accept prevention of what is generally an unproblematic illness and/or whether this could lead to resistance against vaccination and attendance at the children’s clinic\textsuperscript{LV}. As experience with the use of the vaccine accumulated, parents as well as doctors would be able to form an opinion regarding the burden associated with the effects of the vaccine. This would aid preparation for large scale application in the framework of the existing national vaccination programme.

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

\begin{quote}
\textit{Development and production of an inactivated measles vaccine will increase the chance that the number of injections in the programme remains limited or more spread.}\textsuperscript{LV, LV}
\end{quote}
In August 1970, the RIV was ready to begin a clinical trial. Permission was sought from the Dutch regulatory authority. “We think this is justified,” wrote the new director general, “despite the adverse events as reported in the literature after administration of a killed measles vaccine from an American firm\textsuperscript{LVIII}. Using killed vaccine from another supplier (Behringwerke) these side effects did not appear. In 1971 the trial began, with 1207 children enrolled.

Children placed in one arm of the trial were given Merck’s live \textit{Attenuvax} at 12 months, whereas those in the other arms received either four doses of one of the inactivated (pentavalent DKTP-M) vaccines at 3, 4, 5, and 12 months, or three doses of one of the DKTP-M vaccines followed by one dose of live vaccine at 12 months\textsuperscript{LIX}. Clinical data were collected till about 2 years after the fourth injection. No case of atypical measles was found, there was no interference between the component antigens, and no side effects. However the results clearly showed that antibody titers declined rapidly in children given either of the preparations containing an inactivated vaccine. The conclusion was now inescapable, and the fate of the inactivated measles vaccine approach in the Netherlands sealed\textsuperscript{LX}. In 1973 the decision was taken to stop the programme. In 1974 live \textit{Attenuvax} was purchased from Merck, and in 1976 mass measles immunisation began in the Netherlands.

\textbf{Conclusions}

Our comparison of the beginnings of mass measles vaccination in the United States and in Great Britain, bears out Baker’s allusion to two distinctive styles of vaccine innovation is born out. Pursuing its war on poverty and concerned by socio-economic disparities in infectious disease incidence, the Johnson administration in the United States made federal funds for measles vaccination available starting in 1965 and embarked on a measles eradication campaign in 1967. The British, more cautiously, established a large-scale clinical trial in order to establish the relative benefits of the different available vaccines and possible immunisation schedules. Parents, it was hoped, would gradually come to accept the desirability of vaccinating against what was generally seen as an unpleasant, although inevitable, childhood illness. Maintaining popular confidence in the country’s immunisation programme had to be given due weight when introduction of a new vaccine was under consideration. Mass measles immunisation began in Britain in 1968. In Sweden it began in 1971 and in the Netherlands not until 1976. These delays reflect not only the greater British caution to which Baker refers but also a concern in all three countries about the implications for the national immunisation programme as a whole. There was a fear that introducing a vaccine most parents did not see as needed could undermine popular confidence\textsuperscript{LXI}.

The Dutch and Swedish cases show something else as well. Both countries, unlike the United States and Britain, succeeded in controlling polio using Salk’s inactivated virus vaccine, despite almost universal scepticism elsewhere. This very recent experience led
virologists in both countries to prefer, and to continue to develop, inactivated measles vaccine long after their American and British counterparts had rejected them. Unlike in the United States and the United Kingdom, the issue in the Netherlands was not choosing between commercially available alternatives. As a public sector institution, RIV was responsible for providing the vaccines to be used in the National Immunisation Programme. It could do this by developing and producing them itself or, when appropriate, by purchasing them from a commercial supplier. In its work on a measles vaccine, conducted from 1964 to 1972, RIV was trying to develop the vaccine that could best – effectively and safely, but also with minimal disruption – be accommodated in the National Immunisation Programme. Following the strategy that had been so successful in the case of polio vaccine, this was attempted by combining an inactivated measles vaccine with the existing DTP-P. The significance of these efforts, we suggest, is not that they ultimately failed; it is to remind us of an approach to vaccine development, taking the needs of a National Immunisation Programme as its starting point, which in the last three decades has all but vanished. Vaccine development and production in public sector institutions such as RIV, tailored in the first instance to national health care needs and only in the second instance to market opportunity, has come to seem an anachronism. Although local vaccine producers are now accepted as having an important role to play in ensuring adequate vaccine supplies, the wider relevance of the few remaining public sector vaccinology institutes’ (e.g. in Brazil and in Cuba) distinctive approach to innovation is rarely acknowledged.
CHAPTER 2

Endnotes Chapter 2


VI. As Morley’s work in Nigeria, in particular, was beginning to demonstrate e.g. D. C. Morley, “Measles in Nigeria.” Am J Dis Child. 103 (1962) 203; D. Morley, M. Woodland and W. J. Martin, “Measles in Nigerian children.” Journal of Hygiene 61 (1963) 115-134. In 1960, responding to a request from Morley, Samuel Katz had taken measles vaccine prepared by Merck to the Nigerian village in which Morley was working and a trial was conducted successfully (Katz, “John F. Enders”:8)


IX. The Centers for Disease Control and Prevention in collaboration with the Colorado State Department of Public Health, carried out a placebo-controlled trial of the inactivated vaccine in 1961-1962. An outbreak of measles two to six months later showed the vaccine to be “82% effective in preventing any evidence of measles and 93% effective in preventing regular measles” (p.64). The authors of the report were nevertheless sceptical regarding the possibility of longer protection. W. H. Foege, O. S. Leland, C. S. Mollohan, V. A. Fulginiti, D. A. Henderson and C H Kempe, “Inactivated measles-virus vaccine. A field evaluation” Public Health Reports 80 (1965) 60-64. On the other hand a study in Buffalo NY, found inactivated vaccine promising enough to merit further study. W. Winkelstein, D. T. Karzon, Dush and W. E. Mosher, “A field trial of inactivated measles virus vaccine in young school children.” Journal of the American Medical Association 194, 5, (1965) 106-110

X. Younger children would be unresponsive, because of residual maternal antibodies


XII. Colgrove, Ibid, p 132


XIV. Colgrove, Ibid, p 156

XV. Office of Technology Assessment, A Review of Selected Federal Vaccine and Immunization Policies, 1979, p 182


XVII. Colgrove, Loc cit, p 159


XIX. For fiscal years 1969 and 1970 Congress authorized no federal funding for community immunization programmes. The number of doses distributed fell to 9.4 million and estimated cases of measles rose to 533000 in 1970 and to 847000 in 1971. Thereafter federal funding was restored, and measles cases fell to 400000 in 1972. The Office of Technology Assessment suggests a direct connection (A Review of Selected Federal Vaccine and Immunization Policies 1979, pp 182-3)

XX. Editorial: “Inactivated measles virus vaccine.” British Medical Journal (June 231962) 1746-7

XXI. The 1946 act setting up the United Kingdom National Health Service established the Public Health Laboratory Service, which the MRC administered until 1960. In that year it acquired a new status under, but


XXIII. Of these 2000 would be expected to have a neurological condition, 13,000 a middle ear infection, and 20,000 a respiratory problem. Miller, “Frequency of complications of measles, 1963.”


XXV. Editorial: “Measles and measles vaccination.” British Medical Journal (11 July 1964) 72-4

XXVI. Ibid p 72

XXVII. J.F. Bourdillon, “Immunization against measles.” The Lancet 284 (August 1, 1964) 239-240


XXIX. George Dick, a leading member of the British government’s vaccine advisory committee, had carried out a trial of Koprowski’s live polio vaccine in Belfast. Its failure led him to oppose the use of live vaccines. However, a government campaign to encourage Salk vaccine uptake in 1958 made little headway, until a famous soccer player died of polio in spring 1959. That stimulated huge numbers to seek vaccination, and incidence fell sharply. Nevertheless, in September 1961 a polio outbreak occurred in the city of Hull. The city’s health officials sought permission from the Ministry of Health to use the live (Sabin) vaccine for the first time in Britain. The Ministry agreed and vaccine was supplied by the British subsidiary of Pfizer. Within 2 weeks the epidemic was over. In early 1962 the ministry gave local health authorities permission to change to Sabin vaccine and by 1963 medical opinion had swung in favor of its exclusive use. See T. Gould, A Summer Plague. Polio and its Survivors (New Haven and London: Yale University Press, 1995)


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


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

XXXVI. Medical Research Council “Vaccination against measles: clinical trial of live measles vaccine given alone and live vaccine preceded by killed vaccine. Second Report to the MRC by the Measles Vaccines Committee.” British Medical Journal 25 May 1968 2 pp 449-52

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

XXXVIII. Medical Research Council “Vaccination against measles.”, 1968, p 452

CHAPTER 2

XL. Also in 1968, Merck’s Moraten strain had been licensed, and the earlier Rubeovax was replaced by Attenu-vax. See Galambos, Networks of Innovation, pp 97-98

XLI. However supplies initially available were insufficient, so that between May and July only susceptible children aged between four and seven years, plus children aged between one and seven who attended nursery schools or living in residential establishments, would be vaccinated. Joint Committee on Vaccines and Immunization, “Minutes of meeting of 23 July 1968. Document CHSC (VI) (68) First meeting” http://www.dh.gov.uk/ab/JCVI/DH_095054 (accessed June 0, 2012).


XLIV. E. Norrby, R. Lagercrantz and S. Gard, “Measles vaccination IV. Response to two different types of preparations given as a fourth dose of vaccine” British Medical Journal 1965, 1, 813-817.

XLV. Norrby et al “Measles vaccination IV”, (1965), Ibid p 816


XLVII. Norrby et al “Measles vaccination IV”, 1965) p 817

XLVIII. “H-protein (causing hemagglutination) and F (fusion) protein (causing hemolysis) are surface proteins on the envelope of the virion needed to penetrate host cells. The H-protein reacts with a specific receptor on the host cells. After adsorption of the virion, the F protein is involved in the fusion of the viral and the plasma membrane. The existence of the F protein was not known at this time. TS. Westling, Interview with E. Norrby, Stockholm, November 2011). Only later were Norrby and Gollmar able to show that both formalin and TE inactivation destroyed the F- protein, i.e. the surface component of the virus that produced these so-called ‘non-HI hemolyzing-inhibiting antibodies.’ E. Norrby and Y. Gollmar, “Identification of measles virus-specific –hemolysis inhibiting antibodies separate from hemagglutinating inhibiting antibodies” Infection and Immunity 11 (1975)231-239


L. It has not been possible to establish in how far the decision to work on an inactivated measles vaccine was also influenced by the needs of developing countries, where an inactivated vaccine could have certain advantages. Hans Cohen, head of the RIV’s vaccine division, and later Director General, was an active member of the WHO’s Expert Committee for Biological Standardization, at which vaccine requirements were established. In the 1980s new attempts to develop a (sub-unit) inactivated measles vaccine began at the RIV.

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


LV. Ibid., 1905-1909

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

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

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

LIX. R. Brouwer, “Vaccination of infants in their first year of life with split inactivated measles vaccine incorpo-
rated in a diphtheria-pertussis-tetanus-polio (inactivated) vaccine (DTPP-M), compared with live measles vaccination. Journal of Biological Standardization 4 (1976) 13-23

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

LXI. As subsequent developments have illustrated all too well. See H. J. Larson, L. Z. Cooper, et al “Addressing the vaccine confidence gap” The Lancet 378 (2011) 526-535

LXII. e.g. S. Jadhav, M. Datla, H. Kreeftenberg and J. Hendriks, “The Developing Countries Vaccine Manufacturers’ Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries” Vaccine 26 (2008) 1611-1615

Chapter 3
Why might regional vaccinology networks fail?
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Abstract:
We analysed an attempt to develop and clinically test a pneumococcal conjugate vaccine for the developing world, undertaken by public health institutions from the Netherlands, Sweden, Denmark, Norway and Finland: the Dutch Nordic Consortium (DNC), between 1990 and 2000. Our review shows that the premature termination of the project was due less to technological and scientific challenges and more to managerial challenges and institutional policies. Various impeding events, financial and managerial challenges gradually soured the initially enthusiastic collaborative spirit until near the end the consortium struggled to complete the minimum objectives of the project. By the end of 1998, a tetravalent prototype vaccine had been made that proved safe and immunogenic in phase 1 trials in adults and toddlers in Finland. The planned next step, to test the vaccine in Asia in infants, did not meet approval by the local authorities in Viet Nam nor later in the Philippines and the project eventually stopped. The Dutch DNC member, the National Institute of Public Health and the Environment (RIVM) learned important lessons, which subsequently were applied in a following vaccine technology transfer project, resulting in the availability at affordable prices for the developing world of a conjugate vaccine against *H. influenzae* type b. We conclude that vaccine development in the public domain with technology transfer as its ultimate aim requires major front-end funding, committed leadership at the highest institutional level sustained for many years and a competent recipient-manufacturer, which needs to be involved at a very early stage of the development.

At the national level, RIVM’s policy to consolidate its national manufacturing task through securing a key global health position in support of a network of public vaccine manufacturers proved insufficiently supported by the relevant ministries of the Dutch government. Difficulties to keep up with high costs, high-risk innovative vaccine development and production in a public sector setting led to the gradual loss of production tasks and to the 2009 Government decision to privatize the vaccine production tasks of the Institute.

Keywords: Globalization, pneumococcal conjugate vaccine development, regional networks, public sector consortium, privatisation, WHO, developing countries

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Background

In May 1974, the World Health Assembly adopted a resolution formally establishing what became known as the Expanded Programme of Immunisation (or EPI). The principal objective was to help countries “develop or maintain immunisation and surveillance programmes against some or all of the following diseases: diphtheria, pertussis, tetanus, measles, poliomyelitis, tuberculosis, smallpox and others, where applicable, according to the epidemiological situation in their respective countries” [26]. Recognizing that this would only be possible if public health authorities had access to good quality vaccines at reasonable cost, the resolution also committed the WHO to studying the possibilities for expanding vaccine supply including “developing local competence to produce vaccines at the national level”. In the years that followed, as an increasingly globalized pharmaceutical industry increased its commitment to vaccine production, and as a consequence of the ideological shifts of the 1980s, this commitment to stimulating local vaccine production, to ‘vaccine self-sufficiency’ gradually vanished from international policy statements and resolutions.

Today there are growing signs from different regions that low and middle-income countries, concerned to ensure affordable access to vaccines for their growing populations, have a renewed interest in stimulating vaccine self-reliance. In Asia, an initiative to increase regional vaccine security started in 2014 under the Association of South East Nations, ASEAN [27]. Also in 2014 the Organisation of Islamic Countries (OIC) established a Vaccine Manufacturers Group under a programme called “self-reliance in vaccine supply and production” with a focus to the Middle East and North Africa [28]. In 2015, the African Vaccine Manufacturing Initiative (AVMI) brought together stakeholders in 2015 to “develop a roadmap to reach a strategy for vaccine manufacturing and procurement in Africa. This was followed in February 2016 by a declaration by African Ministers at a Ministerial Conference on Immunisation in Africa, to increase the use of vaccines by - among other actions - promoting and investing in regional capacity for the development and production of vaccines in line with the African Union Pharmaceutical Manufacturing Plan [29]. In this paper, we analyse a previous comparable initiative, in the hope that the lessons that can be drawn from its ultimate failure will be of value to those planning these initiatives.

Vaccine policy in the 80s

In the 80s, responding to priorities of the new ‘global health’ policy, to the availability of new sources of funds as well as more comprehensive epidemiological data, and to the efforts of the pharmaceutical industry seeking new markets, developing countries acknowledged their need for vaccines beyond the classical vaccines supplied in the context of the EPI.
In 1984 at a conference at the Rockefeller Foundation’s Bellagio Conference Centre, the Taskforce for Child Survival (TFCS) was installed to energize and transform existing international vaccine programmes committed to immunizing the world’s children. Antony Robbins, director of the vaccine development and production initiative of the TFCS, initiated a more pro-active public sector role in vaccine development and strongly promoted a research incentive system called frond-end funding. Robbins and others had analysed obstacles to development, testing, mass production and distribution of needed vaccines and observed that whilst the UN was not equipped to produce them, manufacturers had little interest in doing so. They concluded that the impediments to develop new vaccines were chiefly of an economic and political nature rather than scientific nature. The classic EPI vaccines could be sold cheaply because there were no more development costs. The main obstacle for development of new vaccines with little commercial interest was that the decision to develop is left in the hands of a few institutes or commercial manufacturers in the developed world, who consider it necessary to recoup the research and development costs before selling at cost price.

Capitalizing on the new opportunities for vaccine development created by the biotechnology revolution, the TFCS subsequently developed an initiative to accelerate development of new and improved vaccines for use in developing countries through a “front end” funding programme. UNDP had suggested a revolving fund to cover cost of development. EPI buyers were to agree on long-term purchase agreements with a small surcharge to replenish these development costs over a 5 or 10 year period. The TFCS would establish such fund with a Standing Committee to manage and oversee it. WHO would select the vaccines and the TFCS would establish contracts with developers [30]. These plans for frond-end funding were presented at another Bellagio conference entitled “Protecting the World’s Children” in March 1988, which ended in the Declaration of Talloires.

The Talloire Declaration called for the global eradication of poliomyelitis by the year 2000, but also called for research and development including technology transfer on acute respiratory diseases by:

> urging national governments, multi- and bilateral development agencies, United Nation agencies, non-governmental organisations and private and voluntary groups to commit themselves to pursue research and development, including technology transfer, in support of the initiatives to control respiratory infections which hold promise in the years ahead of averting many of the 3 million childhood deaths from acute respiratory infections each year in developing countries and that are currently not prevented by immunisation [31].

After interacting with the TFCS during the 1988 Bellagio conference, public sector vaccine institutions from the Netherlands and Scandinavia, responded actively to this Call for Action, which eventually led to the establishment of a ‘Dutch Nordic Consortium’ (DNC) and the pneumococcal vaccine project described below. The private industry also

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\*At that time, a new conjugate vaccine against *S. pneumoniae* was regarded to be of little commercial interest.
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considered the analysis of Robbins as a step in the right direction but added that more incentives would be needed to get real commitment from industry: increased protection for another product of that company, extended patents or monopolies for certain countries, or higher prices [32]. In July 1989, the TFCS solicited specific proposals from manufacturers who wished to be considered for “front end” assistance in developing vaccines of high value to the EPI [31]. Independent scientists reviewed proposals on vaccines against Meningococcus A/C and Meningococcus B, cholera, Japanese encephalitis and pneumococcal infections, the latter being submitted from Finland on behalf of the Finnish, Swedish and Dutch institutes. The idea was that the TFCS would commit to seek funds from its members, foundations and bilateral development programmes for one or more selected proposals. The reviewers considered the proposals on conjugate vaccines against Meningitis A/C and \textit{S. pneumoniae} as most promising and the Task Force subsequently undertook to acquire funds [33].

**New consortia in the 90s**

In September 1990, at the World Summit for Children in New York City, WHO, UNICEF, UNDP, the Rockefeller Foundation and the World Bank launched the Children’s Vaccine Initiative (CVI) as a major new global initiative to connect new technologies to advance childhood immunisation. All organisations had come to realize that the manufacture of vaccines cannot be assured without taking into account the prospective development of new vaccines [34].

Around the same time, with increasingly widespread political commitment to reducing the role of the state, public sector vaccinology institutions in Europe and other regions were facing increasing challenges to their traditional responsibilities. In this context, George Siber from the Massachusetts Biological Public Health Laboratories in the US proposed the establishment of a public sector vaccine consortium. Public sector manufacturers in industrialised and developing countries and could share technology for manufacturing existing vaccines and could develop orphan “low-profit vaccines for diseases occurring mainly in developing countries or for rare or emerging diseases” [35].

In Latin America, PAHO established SIREVA in 1993 [36]. A regional system for the America’s, SIREVA supported regional initiatives among countries with vaccine production capacities (Brazil, Mexico, Cuba, Argentina, Colombia and Chile) [37]. SIREVA initiated regional pneumococcal conjugate vaccine development initially in Brazil, but this was not continued. Luciana Leite from the Butantan Institute in São Paulo, Brazil, when asked in 2011 to look back on the initiative, remembered:

\textit{within the SIREVA consortium, Butantan in Brazil started with pneumococcal vaccine development; they started fermentation of the polysaccharides. Different countries were to make different polysaccharides. The know-how for conjugation was developed in-house from studying the literature. Butantan in Sao Paulo and the Oswaldo Cruz Institute in Rio de janeiro produced the serotypes 23 and 19 respectively. Chile and Cuba joined later. The collaboration failed, because PAHO}
had no money: not even money to hold meetings, so people did not interact. Then SIREVA continued in terms of surveillance (Leite, L., 2011, personal communication).

In Geneva, plans to establish a public sector consortium were also under discussion. In January 1995, the CVI Task Force for Situation Analysis (TFSA), held a meeting on fostering partnerships on DTP and DTP based combination vaccines, where several ongoing initiatives were discussed [38]. Julie Milstien from WHO subsequently drafted a strategic background document: “Strengthening Vaccine Production: A Consortium of Public Sector Vaccine Manufacturers” [39]. The WHO had taken part in visits by the TFSA to a series of developing countries that were producing EPI vaccines predominantly in the public sector for their national immunisation programmes. These visits to manufacturers and the national control authorities and laboratories in those countries had identified significant gaps in quality and quantity of vaccines. The TFSA had noted that technical support to those countries had often not been effective because of “a lack of receptive management structure leading to frustration with donors and countries”. The proposed solution was a three-step process. First, countries should critically look at the cost-effectiveness and viability of vaccine production in the public sector. Second, vaccine manufacturers should develop a receptive organisational structure to be based on elements of viability of local production. Third, a coordinated system at the international level to support these processes in individual countries needed to be set up. This proposed coordinating system of a global consortium of manufacturers would be managed by WHO and would enable the sharing of management expertise and technical knowledge among its members and to ensure that international consultant advice would be consistent. It would also promote partnerships and interactions with public sector manufacturers in industrialised countries.

This global WHO plan referred to earlier similar proposals made by the Netherlands Institute of Public Health (RIVM) [40] and the Massachusetts Public Health Laboratories in the US and it aimed to build on the ongoing SIREVA initiative. The emphasis of the proposed activities was on quality, production rationalization, regional national control laboratories, and training in Good Manufacturing Practices (GMP). The plan did not elaborate on specific work plans and research priorities [39]. However, when presented to the Fifth Annual Meeting of CVI’s Consultative Group in São Paulo in October 1995 [41], it was rejected. Despite support from several developing country producers, such as the Brazilian Butantan Institute, several experts and representatives from the international vaccine industry were sceptical and expressed doubts about the viability of public sector manufacturing. Soon after, WHO silently shelved the plan. Some supporting participants, such as Isaías Raw from Brazil later expressed their opinion that the international vaccine industry saw the proposed consortium as a “cartel” (Raw, I., 2011, personal communication).

Interestingly, about 5 years later, several of the elements and proposed activities of this plan were taken on by the creation of the DCVMN in 2001 [42].
The Dutch Nordic Consortium (DNC)

On 25 October 1990, RIVM celebrated its 80th year of existence with an international seminar highlighting its international cooperation in the field of health and the environment. At this seminar, four Scandinavian health institutes from Norway, Finland, Sweden and Denmark agreed with the RIVM in a Letter of Intent to cooperate in the development of new vaccines for third world countries (Figure 3).

![Figure 3: Signing of the Dutch Nordic Consortium Letter of Intent by the Directors of the Public Health Institutes in Scandinavia and the Netherlands, at the occasion of the 80th year of existence of the RIVM, 25 October 1990.](image)

From left to right: B. Hareide (Norway’s Institute of Public Health), J. Huttunen (Finland’s Public Health Institute), Mrs R. Norberg (Sweden’s National Bacteriological Laboratory), L. Pallesen (Denmark’s Statens Serum Institute) and R. van Noort (Netherlands’ RIVM). Source: Proceedings of the Seminar on International Cooperation in the Field of Health and Environment, RIVM Archives, 1991.

They decided, “to carry out projects and programmes in the field of public health in the developing countries, starting with the development of a vaccine against pneumococci” [43]. Other institutional strategic considerations also played a role. Since all Institutes were tasked by their governments to supply the national immunisation programmes by production or procurement it was thought that an Europe collaboration could reduce costs and benefit procurement in the event of any emergency [44]. This would be also advantageous for the TFCS objectives, as work would progress quicker if distributed among members. The DNC would combine the accumulated experienced expertise of the five institutes, and benefit from financial support from the TFCS as well as from Nordic and Dutch bilateral development aid programmes. Resulting products would be given
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to WHO and countries in the third world. Several proposals for new vaccine development were submitted to the TFCS [45].

Looking to connect the DNC plans with the recently established Children’s Vaccine Initiative (CVI), in early 1991 RIVM hosted a CVI workshop on “the Role of the Public Sector Institutions in Developing and Industrialised Countries” [46]. Participants were from UNDP, UNICEF, WHO, PAHO, RF and representatives from public sector manufacturers from the DNC, China, Brazil, Mexico and individual international vaccine experts. With initial funding from the Dutch Ministries of Economic Affairs and of Foreign Affairs (Development Cooperation), RIVM had initiated a Centre for training and technology transfer to establish or strengthen vaccine production facilities in a selected number of highly populated developing countries” [47]. It was expected that building on the contacts and the work by the TFCS, CVI could support public health institutes in the DNC and use them to aid the public sector institutions in the developing world [48]. RIVM anticipated to become a major pillar of the CVI because, as historian William Muraskin has pointed out: “it saw its ability to help transfer vaccine technology to the third world as a major justification of RIVM’s continued existence” [48]. The objective of the workshop was to define critical issues to successful implementation of the CVI. In fact, the workshop was an effort to integrate the starting and ongoing regional initiatives (SIREVA and DNC) into CVI’s strategic plan. The workshop proceedings [46] state that participants recognized amongst others that,

the SIREVA initiative is committed to improve the scientific and technological infrastructure and management of science for public health in Latin America; that the DNC is committed to the joint development of new vaccines and to transfer its expertise to developing countries and that regional cooperation needs to be promoted in the CVI.

On the occasion of the First European Conference on Vaccinology, held in Annecy, March 1992, RIVM’s Director-General re-iterated his opinion on the role of public sector manufacturers in the CVI [49]. After expressing concerns about the slow development of the CVI, he proposed, referring to the DNC as an example, a more action-oriented approach with the role of the public sector in the CVI mainly in research and in providing scientific and technical support to developing countries and organisations, with a limited role with respect to vaccine production. Referring to an earlier paper by Robbins [50], he stated that:

The new set of initiatives (such as CVI) share a recognition that public institutions must assume a central role in managing decisions about vaccine research, development, production, and distribution.

However, when the CVI’s strategic plan was finally published in 1993, none of these proposals had been adopted. The public sector institutions were not seen as an essential part of CVI’s strategy neither individually nor acting as regional networks.
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### The tetravalent pneumococcal conjugate vaccine project

The DNC embarked on the development of a conjugate vaccine project because it was thought that the pooled scientific and technical experience and expertise in the five institutions would ensure a reasonable chance of success. The Swedish and the Dutch institutes had in earlier projects \[51, 52\] accumulated pioneering experience in the innovative conjugation technology, and with the added capacity of the other Scandinavian institutes on serotyping, animal assays and clinical study design, the consortium basically possessed all knowledge and infrastructure to succeed. *S. pneumoniae* was chosen as a vaccine target, because of its high morbidity and mortality in developing countries.

Of the 8,8 million global annual deaths amongst children under 5 years of aged in 2008, WHO estimated in 2012 that 476,000 were caused by pneumococcal infections \[53\]. Disease rates and mortality are higher in developing than in industrialised settings, with the majority of deaths occurring in Africa and Asia. Although there existed a polysaccharide vaccine against the bacterium it appeared not to be effective in children under 2 years of age. There was evidence that a conjugated vaccine, made by attaching a poorly immunogenic (polysaccharide) antigen to a carrier protein, would stimulate a more vigorous immune response and would effectively protect young children.

This choice for a, in itself rather complex\[^5\] \[54\], conjugation technology approach for a vaccine against pneumococcal infections proved to be correct as shown by the subsequent emergence of a highly profitable global market for pneumococcal conjugate vaccines (PCVs) in developing countries, now shared between Pfizer and GSK \[55-57\].

After the signing of the DNC Letter of Intent, it still took a long time before start-up grants from the respective governments and the European Union were in place and the project could take off. Detailed bilateral collaboration agreements were made in advance to describe each partner’s specific contributions and responsibilities in proportion to the financial reimbursements from received grants.

Initially a vaccine was envisaged with the four serotypes that were globally the most frequent cause of pneumococcal disease in children under two years of age (6B, 14, 19F and 23F). When successful, another four serotypes, with specificity for developing countries would be added to make it an eight-valent vaccine.

The laboratory scale development of saccharide-protein conjugates started at the RIVM in the Netherlands and at the Swedish Bacteriological Laboratory (SBL) in the second half of 1993. RIVM and SBL had both independently from each other developed Jan Poolman, who left RIVM in 1996 to join GSK, co-authored a review on the history of pneumococcal conjugate vaccine development in 2013. That paper describes the strategic importance of choosing the right combination of technical factors that illustrate the complexity of manufacturing of polyvalent conjugate vaccines, such as establishing the correct dose, the best carrier-protein for each of the serotypes and the most appropriate conjugation technology.

\[^5\] Jan Poolman, who left RIVM in 1996 to join GSK, co-authored a review on the history of pneumococcal conjugate vaccine development in 2013. That paper describes the strategic importance of choosing the right combination of technical factors that illustrate the complexity of manufacturing of polyvalent conjugate vaccines, such as establishing the correct dose, the best carrier-protein for each of the serotypes and the most appropriate conjugation technology.
different conjugation technologies\textsuperscript{\textit{H}} [58-60]. The DNC management committee decided to use the Swedish technology for the DNC vaccine and chose tetanus toxoid from RIVM as the carrier protein. Norway would apply an animal model to measure experimental conjugate vaccines. The Statens Serum Institut (SII) in Denmark, that housed the WHO Reference Laboratory on pneumococcal isolates and typing, was to develop assays to measure the immune response in animals against each of the specific pneumococcal serotypes that were to be in the DNC vaccine. Finland’s National Institute would take responsibility for the design and operational activities needed for the clinical studies.

In the course of the project, which lasted about ten years, various impeding events and managerial challenges, described in detail below, then gradually soured the initially enthusiastic spirit of collaboration. By the end of the decade the parties that had remained in the consortium had to struggle to complete the minimum objectives agreed with the European Commission, which by then remained as the only financial sponsor. Despite these and other obstacles, the DNC managed by the end of 1998 to produce a prototype vaccine that was ready for field-testing in developing countries (Figure 4). This

\textbf{Figure 4}. The DNC tetra-valent pneumococcal conjugate vaccine made in 1998.

The left and middle single-dose glass vials contain respectively a low-dose (LD) and a high dose (3xLD) freeze-dried formulation with the four serotypes 6B, 14, 19 and 23F all conjugated individually to tetanus toxoid. The vial on the right contains the reconstitution fluid in which the vaccine is dissolved just prior to the vaccination. Source: private collection Dr P. Hoogerhout; photograph taken by J. Uittenboogaard (Intravacc).

\textsuperscript{H} The Swedish and Dutch conjugation technologies employed in the DNC project differ in the way how the polysaccharide is linked to the carrier protein. The Swedish method used thiolation of polysaccharides with 2-iminothiolane, followed by coupling to the bromoacetylated carrier protein to obtain thioether-linked polysaccharide-protein conjugates. The advantages are that it is fast and suitable for larger polysaccharides and causes less cross-linking. The RIVM method used reductive amination of polysaccharides with cystamine to obtain thiolated polysaccharides.
prototype proved safe and immunogenic in animals. Two subsequent small-scale phase 1 clinical studies in adults and toddlers in Finland confirmed its safety and indicated immunogenicity [61, 62]. The planned next step, to test the vaccine in Asia in infants, did unfortunately not meet approval by the local authorities in Viet Nam nor later in the Philippines and the project had eventually to be abandoned.

The challenges that faced the DNC

Financial and managerial constraints

Funding was a major challenge throughout the project, as it had to be obtained from different sources each requiring tedious and time consuming application procedures. In addition to the Institutes' own financial contribution, the DNC managed to obtain grants from the European Commission, the Netherlands Ministry of Development Cooperation and the Scandinavian Development Agencies for the development, testing and production of the vaccine at RIVM. The European Commission initially contributed with a grant for a five year period (1993 - 1997) for the vaccine development, that was followed by a second grant for another five-year period (1997 - April 2002), later extended with 18 months until October 2003. The second EU grant served to clinically test the DNC vaccine in Finland and Viet Nam and formed part of another EU funded project (ARIVAC2), coordinated by the Finnish DNC partner, which was to test an eleven-valent pneumococcal conjugate vaccine developed by Pasteur Merieux Vaccines (now Sanofi Pasteur) in the Philippines.

Overall, the DNC programme suffered from too little and insufficient upfront funding that had to be collected from different sources, requiring substantial energy and time of investigators. Despite the long-term preparations and hopeful early indications, in the end, neither the TFCS nor the CVI contributed any funds at all. The modest funds that were raised eventually came with many administrative restrictions, making it hard to proceed fast. Moreover, the EU was not interested in financing the collaboration with SIREVA that the DNC hoped for.

Privatisation and patent claims

In 1993, the Swedish Government decided to privatise the vaccine production of the SBL into a new entity (SBL-Vaccin) and simultaneously established the Swedish Institute for Infectious Disease Control (SIIDC), which included the academic and government part of the previous SBL. The responsibilities of the Swedish partner in the DNC were from this moment on taken over by the SIIDC. This major organisational chance within one of the partners had a major negative impact upon the institutional collaboration. Added to this, in 1994 some controversy arose between RIVM and SIIDC regarding a patent application filed independently by SIIDC on the Swedish conjugation technology, selected for use in the DNC vaccine. The scientific paper describing the technology, published in
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2000, expressed the hope that the application of the “Swedish” conjugation technology would reduce vaccine costs for developing countries:

*Taking into account their simplicity and feasibility for large-scale preparation of pneumococcal polysaccharide conjugate vaccines at costs appropriate for the general use in developing countries, we hope that the described techniques will be further exploited* [59].

In return, RIVM also decided to independently file a patent application on its own technology with a plan to provide later non-exclusive licenses to partners in developing countries. In retrospect, these cases of unilateral patent applications had a negative impact on the working relations within the consortium.

**The project’s leader moves to the private sector**

In the second half of 1996, the key scientist and informal leader of the DNC pneumococcal vaccine project Jan Poolman, decided to join the private sector. Heading the RIVM laboratory for bacterial vaccine development for 10 years, he had become increasingly frustrated in his ambition to drive development of bacterial vaccines forward in an institutional climate that at times seemed to restrict instead of facilitate progress. Poolman had repeatedly argued for more capacity and investments in development programmes targeting the introduction of new meningococcal and pneumococcal vaccines into the Netherlands Immunisation Programme. Conflicts with other units and projects in the vaccine division on competing for access to essential experienced technical staff and specialized laboratory suites for vaccine production emerged. In addition to its national tasks, the Institute was at that time struggling with several international vaccine projects, such as a large technology transfer project on EPI vaccines with the Chinese Government funded by a soft loan from the World Bank [63]. Pressures were such that the Institute’s management offered little support to Poolman’s development projects. As a national institute under the Netherlands Ministry of Health, convincing decision makers at the Ministry to increase budgets for costly vaccine development and clinical testing, with no promise of measurable short-term returns was becoming increasingly difficult. Poolman grew increasingly disappointed and in 1996 accepted an offer to join GSK in Belgium, where he later became one of the co-developers of GSK’s ten-valent pneumococcal conjugate vaccine PCV10 (Synflorix) and several new vaccines against pertussis, *H. influenza* type b (Hib) and meningococcus. His personal conclusion at that time was that,

“vaccine development and production is not any longer possible in the public sector due to inadequate resources, lack of infrastructure and too little will to make it a success”. (Poolman, J., 1997, personal communication)

The DNC was left without a leader during the transition period that followed. Perhaps coincidentally, at around the same time, another advocate of collaborative public sector vaccine development, George Siber from the Massachusetts Public Health Biologics Laboratory, had come to a similar conclusion and moved as well to private industry. He jointed Wyeth-Lederle in 1996 where he subsequently played a role in the development and commercialization of the world’s first licensed pneumococcal conjugate vaccine, the
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seven-valent PCV7 (Prevnar).

**Viet Nam and the Philippines withhold approval for immunogenicity studies in infants**

Around mid-1995, DNC members began to consider the region or country where the vaccine could be tested in the field. SIREVA/PAHO with its network in Latin America seemed a logical choice [64]. Bilaterally, RIVM also had good contacts with PAHO on training programmes about vaccine quality control and quality assurance. It also had contacts with vaccine manufacturers in Latin America, such as the Butantan Institute in São Paulo, also involved in SIREVA.

The DNC management proposed to the European Commission to field-test the DNC vaccine therefore in the Latin American region, by first building up local capacity for pneumococcal quality control and analytical tests followed by vaccine production technology transfer, for example to the Butantan Institute. However, this did not fit the European Commission policy at that time. The relevant EU working programme had prioritized the Asian region over the Latin America region. As a result there were no funds for a SIREVA-DNC collaboration [65]. On top of this, the Butantan management appeared not interested in facilitating a field test in Brazil with a DNC vaccine if this vaccine had not been produced in Brazil first. Thus, for its second grant proposal to the EU, the DNC then focused to Asia and in Viet Nam. The Danish DNC member, SSI, had good contacts there through the Academic Hospital in Copenhagen and a large paediatric hospital in Ho Chi Minh City.

With the second EU grant in place, sites for the clinical studies in infants were prepared in southern Viet Nam and Vietnamese staff was sent for training to Denmark, where the serological analysis was to be done. The Vietnamese study investigators submitted a formal application to the regulatory authorities in Hanoi. The application included a protocol for clinical trials and a brochure for clinical investigators, made by the DNC and proposed a field study in southern Viet Nam with the tetravalent DNC pneumococcal conjugate vaccines produced by RIVM. However, the regulatory body’s ethical review committee withheld approval. Unaccustomed to authorizing new investigational vaccines not yet licensed in other countries and that had not been produced in Viet Nam, their main concern was with the possibility of serious adverse events. This was despite the documented evidence of successful safety phase testing in the Finnish phase 1 trial. At the time of application, rumours were circulating on adverse events caused by locally made vaccines and the regulatory body did not want to take any risks [66, 67]. This rejection was a major setback and it necessitated a search for a new study site in another country.

By the end of 2002, the consortium management agreed with the European Commission to transfer the site of the phase 2 trial in infants from Viet Nam to the Philippines. By this time, RIVM had announced that due to other priorities it would not continue the clinical development of the vaccine. Nevertheless, the reasoning was that, if the vaccine...
proved immunogenic, the prototype could be offered for further development by another
manufacturer, possibly in a developing country. However, the ethical review board of the
partner institute in the Philippines, the RITM, also withheld its approval. Since RIVM would
not continue the clinical development, the availability of the vaccine was uncertain. In
view of this, the risks of subjecting these infants to an experimental vaccine outweighed
its uncertain benefits [68]. This second refusal marked the end of the DNC pneumococcal
vaccine development project.

The decision by the Vietnamese regulatory body is best understood as due to its
weak regulatory capacity. At that time it had no procedures for dealing with applications
for investigational new vaccines not made in Viet Nam. In fact, the weakness of the
Vietnamese national regulatory authority has been a concern for many decades, and
very recently, after an intensive capacity building programme, the Vietnamese NRA has
reached the international status of being fully competent to exercise the six essential
regulatory functions seen as essential by WHO [69]. The rejection by the ethical review in
the Philippines was due in part by the information that RIVM would not continue the vac-
cine development. It also reflected the availability of a commercial seven-valent vaccine
that covered all the serotypes (and more) that were contained in the DNC vaccine. The
only justification for continuation, that the technology might be transferred in the future
to manufacturers in developing countries, proved not to be a convincing argument. No
such manufacturer had been identified.

What can we learn from this experience?

The consortium was not endorsed by the global vaccine community

Despite the initially active interactions between the DNC and the TFCS, and later the
CVI, eventually neither concrete collaboration nor front-ending funding materialized from
that side. The CVI, once established, became the international forum for UN organisations,
policymakers, technical agencies, academia and industry to discuss all matters regarding
vaccine development and vaccine supply for developing countries. The DNC was unable
to become incorporated into the CVI, one of the reasons being that the Netherlands and
the Scandinavian countries, as important donor countries to WHO’s EPI programme ex-
pressed concerns that the “US-driven” research and technology-focused CVI movement
would jeopardize EPI country delivery programmes [48]. On several occasions the RIVM
management, emphasizing its international technology transfer experience, reflected in
a 1995 RIVM International Vaccine Policy Brochure [40], called for an action-oriented
approach and promoted a stronger role of public sector vaccine manufacturing in the
CVI, but the impact remained minimal. Over time, the CVI movement developed gradually
towards more partnerships with the international vaccine industry.
The lack of a recipient vaccine manufacturer proved a major weakness

The attempt to establish a “bridging” relationship between the SIREVA/PAHO with the DNC did not materialize. In retrospect, we argue that it was a major weakness that no developing country partner had been engaged from the early stages onwards. By not including such partner from the beginning, the research-focused consortium did insufficiently manage the project from the perspective of either a manufacturing or a regulatory recipient. Little attention was paid to process-upscaling or to preparing a technology transfer package to engage the Butantan Institute in Brazil. There had been no early interactions with regulatory authorities in Viet Nam and the Philippines in anticipation of the clinical studies.

Privatisation policies hindered public sector collaboration

Over time, the Institutes’ senior management had less and less interest to the pneumococcal vaccine development project. The plan to hold regular meetings of the DNC Board of Directors was never implemented. Due to ever-continuing institutional reorganisations and shifts in institutional vaccine development priorities, the research-based consortium team worked in an environment that lacked a real sense of urgency. The Boards of the respective Institutes turned out not to remain fully committed to the pneumococcal vaccine project. Peter Bootsma, who co-managed the DNC project from the side of RIVM, remembered in 2015:

*When it suited politically the “Dutch Nordic Consortium” concept was enthusiastically exploited, but real commitment, backed with substantial funding, that was an entirely different matter (Bootsma P., 2015, personal communication).*

The privatisation of vaccine production has since continued among all the Institutes that formed the DNC. The small populations of each of the DNC countries makes vaccine manufacturing economically unsustainable. Sweden stopped production in the public domain in 1993 (Olin, P., 1998, personal communication). Finland stopped in 2003 [71]; the Netherlands in 2009 [72]. In December 2014, Denmark has initiated the privatisation of its vaccine production activities [73]. Norway still maintains a contract development and manufacturing organisation to serve biotechnology companies, but this facility will be shut down in 2017 (Nokleby, H., 2016, personal communication). At the Board level of the Institutes, the initial need to guard their interests through a regional consortium mechanism, started to decline almost as soon as it was expressed. As early as 1996 Lars Pallisen, Director of the Danish SSI, told European manufacturers:

*The DNC was useful in the beginning because at that time some countries were...*
CHAPTER 3

not yet members of the EU; but it was not so successful with the exception of R&D pneumococcal vaccine development. [74]

Since meanwhile all DNC countries have now stopped vaccine manufacturing in the public domain, DNC collaboration on vaccine issues has ceased to exist at the policy level. The one common interest in vaccines that has remained is the sharing of best practices on vaccine purchases from industry for their respective national immunisation programmes of vaccines. Increasingly, such common interests are guarded through mechanisms of joint procurement through the European Union [75].

Concluding remarks

In conclusion, collaborative vaccine development on common political grounds, but with insufficient upfront funding and unclear end-goals is a risky undertaking and unlikely to succeed. Although a promising tetravalent prototype resulted from this effort, it was not taken further due to a variety of policy-related factors described in this case study.

The sobering Dutch Nordic Consortium experience formed the basis within RIVM to design, towards the end of the 90s, a less ambitious and technically simpler development and technology transfer project for a monovalent conjugate vaccine against *H. influenza* type b (cHib).

The key difference with the DNC programme was that this time the management approach was entirely partner- and regulatory driven. The goal of the cHib project was straightforward: transfer of vaccine technology for an already licensed vaccine, making it a “me too” product and therefore easier for regulators. Most importantly, the early involvement of future recipient manufacturing partners (who co-financed the research and development) ensured that every decision taken was evaluated from a receiving partner’s perspective as well as from a regulatory perspective and possible impact on the time to license [76, 77].

The profile of the RIVM as an advanced European public sector vaccine development and manufacturing institute actively sharing technology with developing countries has faded over the last decades. Despite several notable successes in international vaccine technology capacity building and transfer [63] and the cHib project, the national mission to develop and produce new vaccines for the Dutch national immunisation programme, became politically unsustainable. The Institute’s policy to consolidate its national manufacturing task through securing a key global health position in support of a network of public vaccine manufacturers [14] found insufficient support from the Dutch government, nor from WHO, despite a strong appeal in 1999 by the Dutch Minister of Health for a core-membership in the GAVI Board for RIVM’s Director-General [78]. Difficulties to keep up with high costs, high risk innovative vaccine development and production in a public sector setting led to the gradual loss of production tasks and to the 2009 decision by the Government to privatize the vaccine production tasks of the Institute.
Chapter 4

Vaccinology capacity building in Europe through innovative platforms serving emerging markets
**CHAPTER 4**

**Abstract:**

The 2012 Terrapinn World Vaccine Congress held from 16 to 18 October in Lyon addressed in a dedicated session the transfer of innovative vaccine technologies from Europe to emerging markets. Past and recent transfers and experiences from Europe’s public domain were summarized by the Netherlands’ National Institute for Public Health and the Environment (RIVM) in Bilthoven. The role of capacity building through training courses for developing country partners was highlighted in several recent technology transfer programmes developed in collaboration with the World Health Organisation (WHO). In another stream of the Congress, a case of human vaccine technology transfer from Europe’s private sector to an emerging economy recipient in India was presented. The continuing globalization of vaccinology is further illustrated by the recent acquisition in 2012 of the Netherlands’ public vaccine manufacturing capacity in Bilthoven by the Serum Institute of India Ltd., an emerging vaccine manufacturer. In a parallel development, the Netherlands’ government decided to transform RIVM’s vaccinology research and development capacity into a new not-for-profit entity: “the Institute for Translational Vaccinology”. Under a public private partnership structure, Intravacc’s mission will include the fostering of global health through international partnerships in innovative vaccinology. Projected activities will include training courses and curricula, capitalizing on various currently established platform technologies and the legacy of previous “producer - producer” collaborations between the RIVM and emerging manufacturers over the past 40 years.

It is suggested to consider this as a basis for a common initiative from Europe to develop and implement a practical vaccinology course for emerging countries with particular focus to the African region.

**Keywords:** Vaccinology capacity building, training, technology transfer, global health, developing country vaccine manufacturers’ network (DCVMN)

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Technology transfer and manufacturers in developing countries

Most vaccine doses are nowadays produced in emerging economies. Technology transfer from public and private providers has significantly contributed to this increase in production capacity in such economies [63]. During the World Vaccine Congress in Lyon, Dr Goetz Reider from BiologicalE Ltd. (Hyderabad, India) described an example of technology transfer from Europe’s private sector to India: the successful in-licensing of an inactivated Japanese Encephalitis vaccine by BiologicalE Ltd. from Intercell AG’s manufacturing site. Transfer of Intercell’s proven production technology on Vero cells in roller bottles resulted in a license in India within 5 years. In his presentation, Dr Reider emphasized strong project management as a key element in the success. Examples of international technology transfer initiatives from Europe’s public domain have recently been reviewed with a specific focus to projects between RIVM in Bilthoven, the Netherlands and vaccine manufacturers in developing countries, assembled in the Developing Countries Vaccine Manufacturers Network (DCVMN).

The DCVMN is an international alliance of governmental and private vaccine manufacturers from countries with fast growing emerging economies, such as Brazil, India and China. Their common goal is the supply of high quality vaccines at affordable prices [79]. One objective of the Network is to help members to understand the most up-to-date status of vaccine development and assist them becoming a supplier to international markets, thereby improving the health of people in developing countries. A key feature distinguishing this alliance from the western vaccine industry, usually represented by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and the European Vaccine Manufacturers Association (EVM), is that a substantial part of DCVMN members are state-owned or public manufacturers, tasked with providing vaccines to their national immunisation programmes. For example, over 60% of doses used in Brazil’s 2010 immunisation programme were manufactured and supplied by Brazil’s two state-owned producers Butantan (Saô Paulo) and Biomanguinhos (Rio de Janeiro) [80]. Next to their national markets, various DCVM also supply to other developing countries through international procurement agencies such as UNICEF, PAHO and the GAVI Alliance. Currently, 9 DCVMN members from a total of 36 have obtained a WHO pre-qualification status for one or more of their vaccines: a quality status required to export to international markets. The DCVMN highly values technology transfer and expressed in its recent 2012 annual meeting a commitment to promote “south-south” technology transfer between their members [81, 82].

Capacity building as prerequisite for successful vaccine technology transfer

In RIVM’s experience, capacity building by training has been a consistent and necessary ingredient in every technology transfer initiative undertaken. From the Institute’s
comprehensive knowledge base in developing and making (at semi-industrial scale and with all associated analytical assays) vaccines for the Netherlands’ national immunisation programme, a variety of international generic training courses on DTP production and quality control (QC) have been realized in collaboration with the WHO from the 1970s [63]. In the period 1990 - 2000 various bilateral training courses were delivered as part of technology transfer projects to Asian manufacturers in China, Indonesia and Viet Nam. The majority of these tailor-made courses were contained in the training programme of the World Bank China Vaccine Project that lasted from 1990 till 1997. From around 2000 onwards till today, a combination of dedicated training activities under bilateral agreements and courses were designed and realized under the WHO Global Training Network as well as in WHO driven courses on \textit{H. influenzae} type b (Hib) conjugate vaccines, pandemic influenza vaccines and, more recently, on a safer injectable polio vaccine for the post oral polio vaccine (OPV) cessation period.

As part of WHO’s Global Learning Opportunities for Vaccine Quality (GLO/VQ) [83], RIVM’s courses have always been characterized by “learning by doing”. International vaccine experts enrich the curriculum by presenting latest advances in the field. The curricula further include workshops, theoretical lectures and practical hands-on training in laboratories, production and QC facilities. Next to training personnel from manufacturing entities, capacity building on quality aspects took place by regulatory agencies, like National Regulatory Authorities and National Control Laboratories (NRA/NCL) in lower and middle income countries as they increasingly monitor the introduction and use of new vaccines.

In a rough estimate, these combined efforts since the 70s have allowed well over 400 staff members from emerging manufacturers and NRA/NCL’s from developing countries to receive training for extensive periods in RIVM’s facilities. A large part of this took place in about 20 certified hands-on training courses and workshops under the umbrella of the WHO GLO-VQ. Over this extended time period, various comprehensive course manuals and instruction handbooks were made and distributed for future reference to course participants (Figure 5).

The RIVM technology transfer programmes over the years evolved from initial “producer to producer collaboration” into platform technology developed and sharing using different models of technology transfer. Hereunder three recent examples of capacity building are briefly described. Two examples relate to generic training courses: on QC for Hib-conjugate vaccines and on production and QC of egg-based influenza vaccines respectively; both developed as parallel activities next to specific technology transfer projects. The third example, on a new and safer vaccine against polio, highlights the training capacity building component as an integral part of a strategy that entails a comprehensive technology transfer and licensing package. A key principle of this approach is that receiving partners play an interactive role in adapting pilot scale processes for local large-scale vaccine production. In this latter programme, a polio vaccine production process based upon inactivated attenuated (Sabin) strains has been developed (Sabin-IPV). This is
Vaccinology capacity building in Europe through innovative platforms serving emerging markets

Currently transferred to various emerging manufacturers in close collaboration with the WHO Polio Eradication Initiative [84].

**Quality control of Hib conjugate vaccines**

A simple, robust and easily-to-implement Hib vaccine production process based on public knowledge was developed and transferred to several public and private industrial partners. After 8-10 years, licenses and WHO prequalification were granted for both lyophilized and liquid presentations, with Hib alone or in combination vaccines. This increased the sustainable supply of affordable Hib vaccines in developing countries [76].

The Hib Quality Control course was derived from this technology transfer project. Several production and QC methods had been specifically developed and the RIVM staff had acquired a practical experience of training personnel from its vaccine manufacturing partners during the technology transfer phase. It was then felt that the QC aspects could be shared with a larger group, because it would then benefit public health worldwide by increasing awareness about Hib conjugate vaccines. The course was designed to enable staff from vaccine manufacturers and NRA/NCL to upgrade their knowledge in relevant areas of QC of Hib conjugate vaccines and related products (e.g. multivalent formulations). The course was targeted for senior scientific QC personnel, including managers involved in QC testing of conjugate vaccines. Since 2007, 26 participants from 25 institutes have completed the course.

The programme of the course consisted of daily practical bench work sessions in the laboratory (about 80% lab time during a 2-week period), complemented by workshops and theoretical lectures provided by visiting experts.
A practical approach was preferred, because it would allow trainees to fully participate in all QC tests and data interpretation. During the course, the participants were exposed to typical problems facing manufacturers and NRA/NCL when they have to control, analyse, review and approve Hib conjugate vaccines. This training course was based on the WHO recommendations and the European Pharmacopoeia monograph for Hib conjugate vaccines. In addition to the practical and theoretical learning sessions, a comprehensive course manual complemented by software calculation templates was provided to all participants. In recent years, many more conjugate vaccines have been tested in clinical trials, and some brought to market. To meet this growing need for improved technical knowledge on QC issues pertaining to these vaccines, the Hib QC course could in time be transformed into a generic conjugate QC course, eventually covering e.g. pneumococcal, meningococcal, typhoid and Shigella conjugate vaccines.

**Influenza vaccine for manufacturers**

The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property adopted at the World Health Assembly in 2008, brought a new emphasis to local production as a means of contributing to the overall goals of promoting technology transfer, innovation, capacity-building and improving access to medicines including vaccines [85]. Upon WHO’s request, the RIVM established in 2007 a training centre for the technology transfer of egg-based influenza vaccine production to developing countries to contribute to a sustainable global access to influenza vaccines [86, 87]. Besides training courses in Good Manufacturing Practice (GMP) production and QC facilities, several tailored technology transfers were also initiated on a bilateral basis.

A production process for whole-virion pandemic vaccines has been designed that is transferable to DCVM. This basic process was complemented with a split process step, to accommodate DCVM who also wish to manufacture seasonal influenza vaccines, where split vaccines are the common standard. In 2009 the first trainees were welcomed in a dedicated GMP pilot plant training facility. Since then, 65 participants from 18 institutes have received training in the production and quality control of influenza vaccine. The generic 3-week course includes theoretical background information and a complete production run with assays, and a shorter 2-week practical training focusing on QC and production facilities. Just as in the Hib QC courses, these courses are for small groups so that each participant has the chance to perform either every step in the production process or every step in the QC assays. During each course a complete production run is performed.

In some cases follow up training on site of the DCVM was provided as part of a bilateral agreement. This has been done for instance with VACSERA in Egypt and with Viet Nam’s Institute of Vaccines and Biologicals (IVAC); both countries with a high H5NI endemicity that have decided to build national H5NI influenza vaccine production capacity. In the aftermath of the 2009 H1N1 pandemic the demand for this kind of practical training
has declined, raising doubts on the sustainability of retaining this training infrastructure in the public domain.

**A safer polio vaccine (Sabin-IPV)**

RIVM and WHO entered into collaboration to establish and completely document a Sabin based injectable polio vaccine (IPV) production process based on the RIVM Salk technology followed by non-exclusive transfer to vaccine manufacturers in developing countries capable of producing Sabin-IPV vaccine securely [84, 88]. Since the start in 2008, Sabin master and working seed lots have been made from certified seeds and characterized. From these working seed lots GMP-grade candidate vaccines of different formulations have been produced for (pre-) clinical and stability studies. A phase 1 clinical trial in adults and a limited phase 2 study in infants were recently successfully completed.

This Sabin-IPV production process and related QC testing is in the process of being transferred to a number of emerging vaccine manufacturers. Recipients are selected using pre-defined criteria through an annual selection process that starts with a call for expression of interest at the website of the WHO Polio Eradication Initiative. Even though the current IPV, made from wild type virulent (Salk) seed strains could continue to be successfully used following global OPV cessation, a safer vaccine such as an IPV made from the attenuated (Sabin) strains would be preferable for reasons of biosecurity and containment. By developing a new IPV vaccine a price reduction, compared to the existing Salk IPV, may be achieved for example by dose reduction or by using a more efficient process. Further, developing a new vaccine gives the opportunity to modernize the process and to characterize the product better using more updated techniques. Producing Sabin-IPV by vaccine manufacturers in developing countries may also lead to a more competitive price for IPV.

For transferring the Sabin-IPV technology to selected partners, an overall approach is followed covering 5 phases: preparation, start-up, implementation, evaluation and trouble shooting, (Table 3).

**Table 3.** Training components in Sabin-IPV technology transfer.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Main components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation</td>
<td>Non-Disclosure Agreement and other contractual agreements; work plan; project planning</td>
</tr>
<tr>
<td>Start-up</td>
<td>Exchange information and documentation; three-week hands-on training in Bilthoven; follow-up training</td>
</tr>
<tr>
<td>Implementation</td>
<td>Exchange information and documentation; make materials available; experimental lots at partner’s site; on-site training</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Discuss data findings; decide on future training needs</td>
</tr>
<tr>
<td>Troubleshooting</td>
<td>Provision of advice/consultancy to support marketing/license application of partner</td>
</tr>
</tbody>
</table>
CHAPTER 4

Capacity building by training is incorporated in at least a start-up phase and an implementation phase. During the start-up phase, the first training is at RIVM using a lab scale bioreactor (20 litre total volume). This instructional three-week hands-on training covers all process-related aspects (upstream, downstream and formulation) and relevant QC testing. Further, during the training various presentations and seminars on for example QA and up-scaling aspects are delivered. For this first training, participation of R&D staff from the partner’s side is highly recommended. The ideal composition of the group to be trained would be two to four persons with a process-background and two to four persons from QC. The main aim is to get thoroughly familiarized with all the required unit operations and process steps. During the implementation phase, at least one on-site training is scheduled. This is a “custom-made” training of about two weeks predominantly targeting production staff members. The focus is on all aspects that are of importance for the partner. Following the first on-site training, the training needs of the partner can be defined and arrangements for more hands-on trainings can be determined. In order to define the training needs different aspects are taken into consideration, such as: progress achieved and data generated by the partner, available infrastructure, personnel available for the project and partner’s commitment to the project. The number of participants in the on-site training is decided by the partner.

Since the Sabin-IPV project is on a non-exclusive basis, on-site training may differ for each individual partner; however the first hands-on training at RIVM is similar for all partners. Until now, four DCVM have been selected for participation since the start of this programme in 2010. Actual technology transfer has started meanwhile in 2011 with one of these: Panacea Biotec Ltd. in India) [89].

Perspective: a new European Institute for Translational Vaccinology

In September 2012, the Netherlands’ government decided to transform from 2013 onwards, RIVM’s current vaccinology research and development capacity into a new not-for-profit entity: “the Institute for Translational Vaccinology “(Intravacc). Under a public private partnership structure, Intravacc’s mission will include the fostering of global health through international partnerships in innovative vaccinology. Intravacc intends to bridge the so-called translational gap between vaccine research in academia or small/medium enterprises including biotech and the vaccine industry. The Institute aspires to become the key entry in the Netherlands for partners that wish to take advantage of its broadly accessible, complete and comprehensive infrastructure for translational vaccine research and development.

Using innovative platform technologies that have in part originated from the Netherlands’ decade-long experience of human vaccine development and production in the public domain, new idea’s, leads or concepts from academia are “translated” on the long and winding road towards licensable and economically sustainable vaccines with public health relevance. Available platform technologies comprise cell-based upstream
and downstream production technology for viral vaccines, conjugation technology and outer membrane vesicle technology for bacterial vaccines and finally various formulation, adjuvant and delivery platform technologies, including lyophilisation.

Using its core basic disciplines, Intravacc is capable to assess the feasibility of vaccine concepts as regards working mechanism (pre-clinical and clinical immunological parameters of vaccines) and safety. Where necessary, these concepts can be further optimized and improved, using molecular biology techniques. Other services to be rendered to partners include GMP knowledge and valorisation assessments, using core know how and experience of design of proof-of-concept tests in animal models and of regulatory pathways including clinical phase 1 and phase 2 studies.

To achieve its mission, the Institute will work together with partners and clients, some of those close to its premises, such as Bilthoven Biologicals (BBio). BBio represents the previous Netherlands human vaccine manufacturing capacity that was acquired as a wholly owned subsidiary by Serum Institute of India Ltd. (Pune, India) in July 2012. Internationally, the Chief Scientific Officer (C.B.) of Intravacc is on the board of the European Vaccine Initiative and on the board of trustees of the International Vaccine Institute (IVI) in Seoul, South Korea. Existing strategic RIVM partnerships with DCVM will be continued by Intravacc. These include for example existing bilateral Memoranda of Understanding on innovative vaccinology between RIVM and China’s state-owned manufacturer China National Biotech Group (CNBG) and Indonesia’s state-owned Perum Bio Farma respectively. Recently, a Letter of Intent was signed with the Institute Pasteur in Tunis, a potential emerging manufacturer in the Africa region. The primary focus of Intravacc’s mission will be to serve the Netherlands’ national public interest by promoting valorisation of vaccines of public health relevance thereby enhancing a stronger national knowledge economy. In conjunction, it is expected that at the international level, Intravacc’s know-how and experience in vaccine development and production will contribute to global enhancement of access to vaccines.

**Concluding remarks**

The rapidly changing global context and the growing recognition of the needs and capacities of emerging economies, reinforce the necessity to build or strengthen local vaccine manufacturing capabilities in those regions. Access to technical knowledge is a main constraint for developing countries manufacturers. From these perspectives, there is much value in sustaining knowledge transfer and exchange from Europe to emerging economies through training curricula, courses and Technology Transfer programmes.

A recent workshop realized by WHO and the U.S. Department of Health and Human Services on November 30 and December 2, 2011 in Cape Town, South Africa, addressed the role of capacity building and training to realize sustainable vaccine production capacity in developing and emerging economy countries [90]. An important point that
arose was that international support should include appropriate efforts to recruit, train and retain a skilled local workforce, seen as essential to support long term sustainability and viability of developing country vaccine manufacturers. Since then, the Institute of Biotechnology in Hyderabad, India has, with participation of faculty from Bharat Biotech Ltd., a DCVM, developed a curriculum for a 2 month practical training course in industrial biotechnology for frontline supervisors of Biotech and DCVM staff. The first edition of this course was successfully delivered in August 2012. Complementary to this Indian initiative, mainly targeting emerging manufacturers in Asia, a common initiative from Europe is conceivable to develop and implement a similar practical vaccinology course with particular focus to the African region in view of Africa’s current paucity in vaccine manufacturing capacity. Various European partners and stakeholders from public and private origin could contribute to such a curriculum, by sharing expertise as faculty or allowing access to vaccine development facilities for trainees. Financial support could be requested from the European Union and European governments committed to improving access to vaccines in Africa.
Chapter 5
Technology transfer in human vaccinology: a retrospective review on public sector contributions in a privatizing science field
CHAPTER 5

Abstract:
As health intervention, vaccination has had a tremendous impact on reducing mortality and morbidity caused by infectious diseases. Traditionally vaccines were developed and made in the western, industrialised world and from there on gradually and with considerable delay became available for developing countries. Today that is beginning to change. Most vaccine doses are now produced in emerging economies, although industrialised countries still have a lead in vaccine development and in manufacturing innovative vaccines. Technology transfer has been an important mechanism for this increase in production capacity in emerging economies. This review looks back on various technology transfer initiatives and outlines the role of WHO and other public and private partners. It goes into a more detailed description of the role of the National Institute of Public Health and the Environment (RIVM) in Bilthoven, the Netherlands. For many decades RIVM has been providing access to vaccine technology by capacity building and technology transfer initiatives not only through multilateral frameworks, but also on a bilateral basis including a major project in China in the 90s of the previous century. Looking forward it is expected that, in a globalizing world, the ambition of BRICS countries to play a role in global health will lead to an increase of south-south technology transfers. Further, it is argued that push approaches including technology transfer from the public domain, connecting innovative enabling platforms with competent developing country vaccine manufacturers (DCVM), will be critical to ensure a sustainable supply of affordable and quality vaccines to national immunisation programmes in developing countries.

Keywords: Vaccine production technology transfer, developing country vaccine manufacturers network (DCVMN), historical framework, public sector contribution, global access, BRICS

Acknowledgements: Key persons in the RIVM technology transfer projects and courses described in this paper include Rudy Tiesjema (deceased), Hans Kreeftenberg, Michel Beurret, Ahd Hamidi, Otto de Boer, Marit Holleman, Willem Luytjes, Wilfried Bakker, Coenraad Hendriksen, Johan van der Gun, and Geert van Amerongen. Stuart Blume, Hans Kreeftenberg, Ben van der Zeijst, Joost Ruitenber and Claire Boog kindly provided helpful suggestions and comments to the first draft of this manuscript. Martin Friede kindly provided unpublished data from WHO’s landscape review on technology transfer initiatives.

Introduction

One way in which vaccines differ from other pharmaceuticals is that the vaccine industry operates in a highly monopolized fashion. Liability issues in the US in the 70s, increased regulatory compliance in the 80s and increased mergers and acquisitions in the 90s, are all factors that caused a considerable decline in the number of international vaccine manufacturers [91]. Contributing to this oligopoly situation is the virtual disappearance over the past decades of development and production of vaccines in the public domain in Europe and the US. This gradual shift of innovative vaccine development towards the private sector prompted Blume and Geesink in 2000 to ask whether vaccinology should be regarded as an “Industrial” Science: a science of and for the pharmaceutical industry [92].

Yet at the global level a paradigm change seems to evolve, due to globalisation and the increasing economic power and self-confidence of BRICS countries. UN vaccine procurement institutions such as UNICEF and PAHO, but also GAVI now increasingly recognize the growing importance of emerging manufacturers from these countries in the supply of underutilised and new vaccines for low and middle income countries. They can have either a public or a private status; some of them primarily serve national immunisation programmes, while others focus increasingly to export markets as well.

How did and do these manufacturers acquire know how and capacity to manufacture high quality vaccines of international standards?

This paper is a retrospective review on the role that technology transfer has played in the growing importance of vaccine manufacturing in developing countries. For the purpose of this paper, technology transfer is seen as a tool that is used by developing countries to achieve goals which they themselves have established. From a recipient’s perspective, the rationale for vaccine technology transfer is that local production of vaccines is often seen as a potential way to meet national demands for new vaccines thereby improving public health [93, 94]. At the same time, such production may also support other national policy goals such as economic development, industrialization and accelerated technological capacity. With the overwhelming majority of the world’s population living in developing countries and emerging economies it is inevitable that vaccine production capacity needs to be in place locally or at least regionally to mitigate global threats such as pandemic influenza. Various countries have now come to regard local production capacity almost as a matter of national emergency for which arguments other than mere economic considerations apply. Transfer of vaccine technology is thus increasingly regarded as a global public good.

For the purpose of this review, only those initiatives are considered that are international (i.e. from country to country, but not cross country transfers between branches or subsidiaries within a multinational company) and that include production process and quality control technology together with considerations of sustainability and affordabil-
CHAPTER 5

It is. The latter meaning that the vaccines resulting from the technology transfer will be accessible to public markets in developing countries either nationally or through UN procurement mechanisms. A recent landscape inventory report on vaccine technology transfer and local vaccine production from WHO followed the same approach [95]. Cases of licensing of a proprietary technology are not taken into account unless associated with training in the use of the technology and technical support to the recipient. This approach thus restricts the term of technology transfer to activities that involve a capacity-building component at the recipient site intended to enable the recipient to produce quality vaccines.

International technology transfer initiatives

Recent landscape, approaches and trends

A recent WHO overview of technology transfer and local production of vaccines in developing countries [94, 95], identifies around 90 confirmed international initiatives for over 14 different vaccines in the past 20 years. Providers come from both the public and the private sector and also transferred technology to both domains. The initiatives were subdivided over 6 different approaches: bilateral know how transfer, joint ventures and acquisition, de novo manufacture, single recipient joint development with a facilitation entity, a shared technology platform and a technology transfer hub. These different approaches, each with one typical example of a partnership, are shown in Table 4.

From Figure 6 it is apparent that since 2003 the diversity of different approaches has increased considerably, particularly in 2008 and 2009 when WHO and the US National Institutes of Health (NIH) launched various new initiatives and when multinational companies (MNCs) increased the number of joint ventures and acquisitions into BRICS countries remarkably. Another trend is the evolution from bilateral technology transfer to transfer facilitating hubs or platforms where a technology is established and multiple recipients can receive training and know how.

The raw data of this WHO survey were made available for the current review to obtain a further indication of impact of technology transfer on global access to vaccines over time. Of the 73 initiatives for which the dataset was complete, 29 (40%) had resulted in a national license of which 9 (12%) also obtained WHO prequalification. This strongly suggests that technology transfer initiatives have significantly enhanced vaccine availability for global health [95].
Table 4. Approaches of technology transfer in WHO's 2010 landscape analysis [95]

<table>
<thead>
<tr>
<th>Approach</th>
<th>Provider (legal status)</th>
<th>Recipient (legal status)</th>
<th>Vaccine</th>
<th>Reference on example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Bilateral know-how transfer or joint development</td>
<td>Biken (private)</td>
<td>GPO\textsuperscript{a} (public)</td>
<td>Japanese encephalitis</td>
<td>[95]</td>
</tr>
<tr>
<td>2 Joint venture and acquisition</td>
<td>Sanofi (private)</td>
<td>GPO-Merieux (private)</td>
<td>various</td>
<td>[95]</td>
</tr>
<tr>
<td>3 De novo manufacture</td>
<td>GSK (private)</td>
<td>GSK-Singapore (private)</td>
<td>various</td>
<td>[95]</td>
</tr>
<tr>
<td>4 Single recipient joint development with active</td>
<td>NIH\textsuperscript{b}</td>
<td>SIIL\textsuperscript{d} (private)</td>
<td>meningitis A</td>
<td>[110, 112]</td>
</tr>
<tr>
<td>input by facilitation entity</td>
<td>with PATH\textsuperscript{c} (public)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Shared technology platform</td>
<td>NIH with PATH (public)</td>
<td>Shantha (private)</td>
<td>rotavirus</td>
<td>[163]</td>
</tr>
<tr>
<td>6 Technology transfer hub</td>
<td>RIVM/NVI with WHO (public)</td>
<td>Several DCVM\textsuperscript{e} (public and private)</td>
<td>influenza</td>
<td>[86, 87, 137]</td>
</tr>
</tbody>
</table>


Figure 6. Diversity in technology transfer approaches increases [95]. Legend: JV: Joint venture
CHAPTER 5

Examples from the private sector

As the global representative organisation of the MNCs, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has in a position paper recently elaborated on her approach and successes of technology transfer [96]. The rewards to companies transferring pharmaceutical technology to emerging countries are described as both reputational as well as commercial. A more specific IFPMA pamphlet on influenza vaccines [97], states that technology transfer and local production itself will be inadequate to prepare for a global pandemic. Advanced purchase agreements established prior to a pandemic and early use of pre-pandemic vaccines are seen as better instruments. In general, MNCs emphasize their experience that firm long term commitments (at least 7 years) of both partners are needed to reach success and preference is expressed for a stepwise progression of bilateral technology transfer between partners [98] [91].

An example of successful technology transfer by the private sector is the bilateral know how transfer of recombinant hepatitis B (HepB) vaccine to China by Merck. Through a progressive technology transfer agreement in 1989 between the Chinese government and MSD, Chinese scientists and engineers were trained in HepB vaccine production in the US. Next, Merck assisted the Chinese teams to help scale up two state-of-the art recombinant DNA vaccine plants, in Beijing and Shenzhen [99]. Thanks to this project, China’s Ministry of Health was able to integrate HepB vaccination into its nationwide EPI programme in 2002, resulting in a reduction in infant hepatitis B carriers from around 10% in 1992 to less than 1% in 2006. The carriers in the total population dropped from 10% to around 7% [100, 101].

A second example of technology transfer by MNCs is a number of supply-agreement/tech transfer partnerships with manufacturers in Latin America, notably Brazil. Cortez et al. have summarized the current public vaccine manufacturing and perspectives in Latin America [102]. Together with Cuba, Brazil is one of the few countries in this region with a strong national policy towards vaccine self-sufficiency, and several strong partnerships between external providers and Brazilian national manufacturers have been established. Sanofi transferred influenza vaccine technology to the state owned Butantan Institute in São Paulo in a stepwise manner, starting with bulk importation in 1999 and ending with the transfer of the complete production process. This partnership has now resulted in a fully installed capacity for local production of influenza vaccines.

GSK has since 1997 a long standing collaboration with the Oswaldo Cruz Institute/Biomanguinhos using the same stepwise model. This partnership is consistent with Brazil’s national policy for vaccine self-sufficiency [98]: it involves at least 5 different vaccine technology transfers on respectively OPV, MMR, H. influenzae type b (Hib) conjugate vaccine (formulated in combination with DTwP-HepB from the Butantan Institute), pneumococcal conjugate and rotavirus vaccine. These agreements with MNCs for transfer
Technology transfer in human vaccinology: a retrospective review on public sector contributions in a privatizing science field

Examples from the US public sector

The US developed legislation to promote transfer of technology from the federal level to industry. The Bayh-Dole Act (1980) was created from the thought that private (not government) ownership of inventions, motivated by the prospect of financial gain, will lead to commercialization of public funded inventions [105]. This legislation has enabled the U.S. National Institutes of Health (NIH) to develop an active policy for international vaccine technology transfer. Enhancing technology transfer to developing countries is seen as an important humanitarian endeavour consistent with NIH’s mission to improve health and save lives [106]. The NIH IP portfolio on neglected diseases included in 2005 multiple distinct technologies, issued patents and patents pending for dengue, rotavirus, HPV, Lyme disease, tuberculosis and malaria[107]. Based on this portfolio, international partnerships are formed that may include a technology license, know-how or patent rights, usually from industrialised country academic or public entities and that involve additional in-house development by the emerging supplier.

In particular the rotavirus case is of interest: the technology of the human-bovine reassortant rotavirus vaccine was developed by Kapikian in the NIH[108]. With financial support from the Gates Foundation, PATH established partnerships through an enabling platform [109] between the NIH Technology Transfer Office and not for profit institutions in Brazil (the Butantan Institute) and China (the Chengdu Institute of Biological Products, the Wuhan Institute of Biological Products), as well as with for-profit companies in India (Bharat Ltd., Biological E Ltd., Shantha Ltd., Serum Institute of India Ltd. (SIIL)). The transfer of this public intellectual property and technology goes along with public financial support for research and development, technical assistance and cost sharing of clinical development and trials. Some of the recipient manufacturers of rotavirus vaccine may soon reach the market as a result.

A second example from the US public sector is the meningitis A project for Africa (MVP): development and transfer of a meningitis A conjugate vaccine to a single recipient (the Serum Institute of India, Ltd.: SIIL) through a facilitating entity (PATH/WHO). With an upfront $70 million grant in 2001 of the Gates Foundation, this partnership between PATH and WHO with the goal of eliminating meningococcal epidemics in Africa is a real
success story of technology transfer from the public sector [110]. By transfer of conjugation technology from CBER/FDA [111, 112] to SIIL in 2003 an affordable vaccine was developed. From the start, SIIL was committed to a maximal per dose price of $0.40 cents. WHO prequalification was obtained in June 2010 and six months after the introduction of the new vaccine in sub-Saharan Africa, Burkina Faso, Mali, and Niger reported the lowest number of confirmed meningitis A cases ever recorded during an epidemic season [113]. In July 2012, not a single case of group A meningitis has been notified in the more than 54 million individuals who received the vaccine since 2013 [114]. This product development partnership is an example of a successful “push” model where a competent DCVM was instrumental in providing access to a much needed vaccine that was of limited interest to MNCs [110].

These two examples on rotavirus and meningitis A seem to indicate that technology transfer success from the public domain requires additional support in the form of grants from donors, such as the Bill and Melinda Gates Foundation.

South – south collaboration

Whilst the current contribution of south-south transfer to the total landscape is still modest compared to north-south (10% versus 90% in WHO’s 2010 overview [95]), this is likely to increase since BRICS countries’ ambitions to play a role in global health clearly include vaccine manufacturing and capacity building [115].

Two vaccines in the current range of 23 WHO-prequalified vaccines, originate from south – south collaborations: a cholera vaccine was transferred from the state owned company Vabiotech, Viet Nam to Shantha Ltd., India, facilitated by the International Vaccine Institute [116] [117] and polysaccharide meningitis AC vaccine produced in bulk by the Finlay Institute, Cuba is filled and finished and supplied to UN markets by Biomanenguihos, Brazil [118].

Contributions from Europe’s public sector: RIVM

From Europe, the NIBSC in the UK, as the WHO International Laboratory for Biological Standards, fulfils a prominent role in the global provision of biological reference materials, reagents and international standards. This supports the vaccine industry, also in developing countries, as these materials are critical to vaccine quality control and release assays. Further, NIBSC provides developing country specific training courses in laboratory quality management systems under the WHO [83]. Finally, in the particular case of influenza vaccines, NIBSC is one of the WHO collaborating centres on influenza that annually supplies vaccine manufacturers with the strains of virus used to make influenza vaccine. It also prepares and supplies the reagents needed by manufacturers to quantify each dose of their vaccine [119].
The European public sector contribution as regards technology transfer of human vaccine production process and analytical technology to developing countries is illustrated by the activities of the RIVM, the Netherlands' public health institute, under the Ministry of Health. The institute's experience in vaccine technology transfer, capacity building over the past 40 years is summarized in Tables 5a and 5b respectively. The description hereunder is based upon the institute's archives, insiders' information and the author's own experience, as a long term employee of the RIVM.

Vaccines in the Netherlands Immunisation Programme (NIP) were for many years manufactured by RIVM. Since the early 70s, the programme’s cornerstone, a tetravalent adjuvanted combination vaccine DTwP-IPV, was made using a semi-industrial “unit”-approach in large scale bioreactors and the use of micro carrier technology developed in-house [18, 20, 120].

Live attenuated measles vaccine and later measles, mumps and rubella vaccines were manufactured from 1982 onwards after technology had been transferred from Merck to Bilthoven. Local manufacture of both combination vaccines ensured the sustained supply of vaccines for the Dutch population for many years [17, 18].

The need to introduce new vaccines such as *H. influenzae* type B from 1992 onwards followed by acellular pertussis gradually led to an increasing need to procure from MNCs. In 2003, all vaccine development, production and procurement tasks responsibilities were transferred to a newly established vaccine agency: the Netherlands Vaccine Institute (NVI).

In 2009, the Dutch government decided to cease, primarily on the basis of economic considerations, all vaccine manufacturing in the public domain. The institute was no longer able to sustainably meet the increasing quality requirements against acceptable costs for the small public market in the Netherlands, with an annual birth cohort of less than 200,000.

In July 2012, the Dutch government announced that NVI's production capabilities were sold to the private sector [121]. Interestingly, the buyer is SIIL from India, indicating an increasing presence of emerging manufacturers in the global vaccine community. The vaccine research and development unit of the NVI, including the international activities has, at least for the moment, been re-merged within RIVM, under the Ministry of Health’s assurance that running international technology transfer agreements will be respected.

Open door policy

Because of its obvious up scaling advantages, the semi-industrial “Bilthoven unit”-bioreactor approach for bacterial and viral “EPI”-vaccines developed in the 70s and 80s attracted worldwide interest from many parties including WHO and developing countries with large birth cohorts. The way contacts and collaborations took place then is best described as an open door policy. Public and private entities all “learned from each other”
<table>
<thead>
<tr>
<th>Project</th>
<th>Period</th>
<th>Vaccine(s)</th>
<th>Recipients</th>
<th>Country</th>
<th>Approach</th>
<th>Predominant driver</th>
<th>Impact, Public Health benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 5a. RIVM contribution to global vaccinology capacity: I. Technology transfer initiatives.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro-carrier technology</td>
<td>1970-1980</td>
<td>for viral vaccines (IPV, Rabies)</td>
<td>Sanofi, GSK</td>
<td>Several</td>
<td>“open-door” exchange for Ravel products of several MNCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China Vaccine Project</td>
<td>1990-1998</td>
<td>DTWP, Measles, OPV</td>
<td>SIBP, LIPB, KMB</td>
<td>China</td>
<td>Turn-key</td>
<td>WHO, China, Global Health Foundation, Dutch ODA</td>
<td>Technology used in global vaccines (IPV, Rabies) products of several MNCs</td>
</tr>
<tr>
<td>Tri-Parte Project</td>
<td>1997 -2002</td>
<td>DTwP, Tt</td>
<td>Bio Farma, MAC</td>
<td>Indonesia,</td>
<td>Turn-key</td>
<td>World Bank, Rockefeller Foundation, Dutch ODA</td>
<td>Tt vaccine technology was developed</td>
</tr>
<tr>
<td>Animal Free Cultivation</td>
<td>2000-2003</td>
<td>Viral Vaccines</td>
<td>gPVI</td>
<td>Tunisia</td>
<td>Joint development of vaccine seeds</td>
<td>NIP Tunisia</td>
<td>Am medium fee from financial contributions was developed</td>
</tr>
<tr>
<td>Upgrading/Combo Project</td>
<td>2000-2002</td>
<td>DTwP-HepB</td>
<td>Bio Farma, SIBP</td>
<td>Indonesia, Vietnam</td>
<td>Consultancy on formulation of DTwP-HepB</td>
<td>WHO, Global Health</td>
<td>DTwP and DTwP-HepB from Bio Farma prequalified by WHO and available for UN market</td>
</tr>
<tr>
<td>Hib Project</td>
<td>1999 - now</td>
<td>Hib Vaccine</td>
<td>Bio Farma, SBI, Biogovax - SIBP</td>
<td>India, China, Vietnam</td>
<td>Development of Hib vaccine</td>
<td>WHO, Global Health</td>
<td>Hib conjugate technology was developed</td>
</tr>
<tr>
<td>Sabin-IPV Project</td>
<td>2008 - now</td>
<td>New safer polio vaccine</td>
<td>Panacea</td>
<td>India</td>
<td>Bilateral agreements</td>
<td>WHO, Global Health</td>
<td>To be determined; contributes to risk containment policy in post OPV cessation period</td>
</tr>
<tr>
<td>ITPI Project</td>
<td>2007 - now</td>
<td>Egg-based inactivated influenza vaccine</td>
<td>Up to 15, including VACSERA, IVAC</td>
<td>Up to 15, including Egypt, Viet Nam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>development of flu vaccine</td>
<td>WHO, Global Health</td>
<td>Robust flu manufacturing process plus entire package including clinical data</td>
</tr>
</tbody>
</table>

a NIP: National Immunisation Programme; MNCs: Multinational Companies; DTWP: Diphtheria whole cell Pertussis-Tetanus vaccine; SIBP: Shanghai Institute of Biological Products; China; LIPB: Lanzhou Institute of Biological Products; China; KMB: Kunming Institute of Medical Biological Products, China; ODA: Overseas Development Assistance; ITPI: Tetanus Toxoid vaccine; Glovax: Glovax Ltd., South Korea; SIBP: Shanghai Institute of Biological Products; China; VACSERA: VACSERA, Egypt; Panacea: Panacea Ltd., India; Bio Farma: Perum Bio Farma, Indonesia; SBI: Serum Institute of India Ltd., India; Biogovax: Biogovax Ltd., India; Global Health: Global Health; UN market: To be determined; contributes to risk containment policy in post OPV cessation period.
and exchanged production and quality control methodology often through WHO expert consultations and expert meetings such as the annual meetings of the Expert Committee of Biological Standardization (ECBS). Nowadays MNCs such as Sanofi Pasteur and GSK have incorporated the micro carrier technology in several of their licensed vaccines, e.g. Salk-IPV and rabies vaccines. Because of its national public mission, the Institute’s focus was on know how exchange and supply for the national programme and not on generation of intellectual property or increasing sales in export markets. In the early/mid-eighties a Rabies Vero technology transfer project from the Rockefeller Foundation to Colombia in the early 80s was also initiated from the Institute’s technology-resource base [122, 123].

From the late 80s onwards, several alternative in vitro quality control tests to replace and reduce the use of animals have been developed, validated and transferred to various developing countries. The toxin binding inhibition (ToBI) test proved to be a reliable in vitro alternative to the toxin neutralization test in mice for the estimation of tetanus antitoxin in humans [124] and appeared also to be suitable for the estimation of the potency of tetanus toxoid, thus replacing the in vivo lethal challenge test in mice [125, 126]. Also, a mouse model, developed to estimate the potency of diphtheria toxoid components in vaccines using Vero cells, proved capable to replace in routine control the challenge test in guinea-pigs, leading to a considerable reduction in the number of animals used and costs [127, 128]. Both assays, when properly validated, are acceptable according to WHO requirements [129] and are currently being used routinely by several manufacturers and national control laboratories in various developing countries [130].

<table>
<thead>
<tr>
<th>Course Subject</th>
<th>Period</th>
<th>No of courses (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General production of EPI vaccines</td>
<td>1972 - 1983</td>
<td>9</td>
</tr>
<tr>
<td>General quality control of EPI vaccines</td>
<td>1984 - 1987</td>
<td>2</td>
</tr>
<tr>
<td>Quality control of DwPT vaccines</td>
<td>1998 - 2003</td>
<td>6</td>
</tr>
<tr>
<td>Animal husbandry for quality control</td>
<td>1998 - 2006</td>
<td>4</td>
</tr>
<tr>
<td>Production of DwPT group vaccines</td>
<td>1998 - 2001</td>
<td>3</td>
</tr>
<tr>
<td>Quality control for Hib-conjugate vaccines</td>
<td>2007 - 2008</td>
<td>3</td>
</tr>
<tr>
<td>Production and control of egg-based influenza vaccines</td>
<td>2009 - 2011</td>
<td>5</td>
</tr>
</tbody>
</table>

(*) Course duration varied between 2 and 6 weeks. No of participants per course varied between 7 and 18. All courses were hands-on and included extensive course manuals, documentation and in most cases take-home reagents and materials.
CHAPTER 5

Capacity building by international courses

Through many international contacts, the institute gradually became engaged in transfer of technology of classical EPI vaccines to other countries through training in production and quality control methods, consultancies and bilateral and multilateral projects with international agencies.

From the mid-seventies onwards till today, the international interest in the Institute’s technologies and this open door policy has resulted in the realization of over 30 international training courses in vaccinology, for a large part under the auspices of WHO’s Global Learning Opportunities for Vaccine Quality Network (Table 5b).

The detailed course documentation on production and control technologies, has been extensively used in developing countries and in some instances formed the core content of WHO manuals, such as for instance the WHO manual of laboratory methods for quality control of EPI vaccines [131].

These courses are “hands-on” and are also open to employees of national regulatory agencies. Over the entire period about 54% of the participants came from public producers, 10% from private producers and 36% from national control laboratories or authorities. Taken together these courses are a substantial contribution to global vaccinology capacity building in the public domain over the past 50 years.

Bilateral transfer to state owned Asian manufacturers

In the 90s, several bilateral technology transfer projects were initiated with governmental institutions and state-owned enterprises in Indonesia, Viet Nam and in particular in China.

Strong ties existed already well before 1990 with Bio Farma, Bandung, Indonesia's sole manufacturer of human vaccines, dating back from the Dutch colonial rule: Bio Farma was established in the 19th century as a smallpox inoculation centre. For DTwP, a consultancy/training approach from 1990 onwards resulted in an upgrade of the already existing DTwP production within Bio Farma. A step-by-step approach was followed: starting at the end of the process and upgrade towards bulk production. This approach differs from the partnerships between MNCs and Brazil in the sense that there were no associated vaccine supply agreements from the Netherlands to Indonesia. Also consultancy was provided to assist Bio Farma to prepare for WHO prequalification for DTwP; successfully obtained in the mid-90s.

A tripartite collaboration between Bio Farma, RIVM and Rhein Biotech Ltd. on formulating Bio Farma’s DTwP with the recombinant hepatitis B vaccine from Rhein Biotech Ltd. [132], resulted in 2004 in WHO prequalification of Bio Farma’s DTwP-Hepatitis B combination vaccine.

An example of south-south cooperation between two public manufacturers IVAC, Viet Nam and Bio Farma, Indonesia, was facilitated through RIVM and financed in part
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by a Dutch’ overseas development aid (ODA) grant. After IVAC's DTwP vaccines had been licensed nationally following a comparative field trial executed with RIVM’s assistance [125], this tripartite project succeeded in upgrading IVAC's DTwP and tetanus vaccine (TT) production and quality control capability to WHO requirements. Bio Farma (as a WHO prequalified manufacturer) acted as the main host for the training of IVAC staff, whereas RIVM coordinated a flow of GMP/QA know how from Bio Farma and RIVM to IVAC. From a global perspective, a weakness in this project was the insufficient performance of Viet Nams’ regulatory authority in WHO’s competence assessment for the six regulatory functions [133], essentially preventing any WHO prequalification procedure for IVAC products.

The World Bank China Vaccine Project intended to improve vaccine production in the 90s in China through construction and rehabilitation of three national production centres for EPI (measles, DTwP, TT and OPV) vaccines meeting European quality standards [134]. A Dutch consortium was selected with an engineering firm as the leading partner to design and construct the facilities, RIVM to provide technical knowledge and a Dutch supplier for bioreactor equipment. Included were design, construction and validation of new state of the art GMP plants in three different state-vaccine institutions respectively in Shanghai, Lanzhou and Kunming. The Lanzhou and Shanghai state institutions have meanwhile become part of China's current state-owned vaccine manufacturing agency: the China National Biotec Group Company, Limited (CNBG) [110].

Between 1990 and 1997, over 550 person months training were provided in the Netherlands: more than 80 Chinese employees from the three locations attended practical hands-on training on production, quality control and quality assurance for different periods ranging from 2 till 18 months.

The project suffered numerous challenges and by 1995 a strained relationship between the implementing parties had arisen due to payment disputes, engineering drawing delays, supervision inadequacies and delays in the completion of some of the process development programmes. By then the Chinese government realized that the cost of “better quality” vaccine from the new facilities would be substantially above cost of production and exceed UNICEF price levels. Completion of the project as originally planned lost its incentive and the Chinese government decided to release the engineering firm from its responsibilities after settling all claims in amicable manner around 1997.

At that time three new and fully equipped cGMP facilities were ready; the training programmes in the Netherlands had been completed to satisfaction, and seed strains, Vero master and working cell banks (for OPV), quality assay tests and standards and extensive documentation, including Standard Operating Procedures (SOPs) had been transferred to China. Production of consistency batches in the new facilities in China however had not yet started.

The end goals of this large and capital intensive technology transfer project were never reached. Many lessons to all parties were learned. The complexity clearly exceeded the combined “provider” capacities of the Dutch consortium as well as the “recipient”
capabilities of the Chinese Ministry of Health at that time for a project that was perceived
as a community health project, but turned out to be a complex industrial transfer un-
dertaking. As the World Bank stated in her final evaluation: “in hindsight it not surprising
that project design, procurement arrangements, as well as implementation and fund-
ing requirements often exceeded domestic and professional, managerial and financial
resources throughout project implementation” [134]. On the positive side, the project
realized in the 90s in China in the public domain significant human capital development,
new concepts of GMP, QA and validation, and state of the art production plants in state-
owned facilities, still in use today, in three different regions. In one facility in the Shanghai
Institute of Biological Products, licensed H1N1 pandemic flu vaccines were made in 2009
by a workforce, some of which had been trained previously in this World Bank China
project.

Resource institute to developing country vaccine manufacturers
Since 2000 RIVM/NVI has been a resource member to developing country manu-
facturers by providing specific training courses and through direct technology transfer
programmes. Three main programmes are described hereunder: the Hib conjugate
project and two broader programmes under WHO umbrella on pandemic influenza and
on a new safer polio vaccine for the post-OPV cessation period (Sabin-IPV).

Over a period of about 7 years, RIVM/NVI developed a robust Hib conjugate vaccine
production process based on a proven conjugation method[135] [76] and transferred
this to several DCVM partners in India, Indonesia, and China. The project and its lessons
learned are described in two publications [76, 136]. The project started in 1997 with the
sole purpose of transferring the technology to developing countries; a licensed Hib vac-
cine (from a MNC) had already been incorporated the Netherlands’ national programme
since 1993. The project had no upfront funds and there was no international involve-
ment, in contrast to the PATH/WHO Meningitis A conjugate project that started with a
$70 million grant from the Gates Foundation. A seed capital to develop an up scalable pi-
lot-scale production process was provided by the RIVM. Further investments were made
by the recipients. In the transfer model applied, the recipients played a large role in scale
up, clinical trials and licensing. As a result of this project, two of the Indian recipients (SIIL
and BE) have reached WHO prequalification status for their Hib containing pentavalent
combination vaccines. This increase in supplier-base is now leading to a decrease of the
price for pentavalent vaccines in the UN market [76].

With financial support from WHO, a generic non-proprietary influenza vaccine technol-
gy hub was set up in 2008 at RIVM/NVI as a training centre to assist manufacturers in
low- and middle-income countries in establishing or improving their pandemic influenza
vaccine production capacity [86]. A robust and transferable egg based monovalent pi-
lot process for inactivated whole virus or split influenza A vaccine production with the
corresponding in-process and release assays was established under international GMP
standards. Clinical material has been made and a recent phase I clinical study in Europe
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shows that influenza vaccines made with this basic process are safe and immunogenic (van Boxtel et al. [137]). Various generic hands-on training courses have been delivered since 2009 for employees from 15 developing country manufacturers [87]. The current hub also collaborates in a consultative capacity with the Vaccine Formulation Laboratory at the University of Lausanne in Switzerland, a technology transfer hub for generic non-proprietary adjuvant formulation [138].

In the WHO containment policy for the post-OPV cessation period, an increased demand for IPV is anticipated. For safety reasons, new manufacturers are encouraged by WHO to use the attenuated Sabin virus instead of wild polio strains in the production of IPV. In line with its role as a DCVM resource institute, NVI/RIVM started in 2009, upon request of WHO, to develop such a Sabin-based inactivated polio vaccine process for technology transfer [88]. This process for transfer is based on the OPV development experience previously obtained in the World Bank China project and on a scale-down model of the current, and well-established, Salk-IPV process in Bilthoven using Vero cell based micro-carrier technology [84]. It is anticipated that at least 6 DCVM will eventually obtain this technology through bilateral, non-exclusive agreements. A first bilateral contract for technology transfer was signed in 2011 with one manufacturer in India. Selection of other potential recipients is ongoing and takes place in close consultation with WHO [89].

**Impact and effectiveness**

Bozeman has proposed a ‘contingent effectiveness model of technology transfer’ that assumes that technology effectiveness can take a variety of forms. In addition to the more traditional effectiveness criteria (measured in market impacts) the model considers various alternative effectiveness criteria, such as political effectiveness and scientific and technical human capacity-building [139]. Applying these criteria for comparing RIVM’s contributions, it is clear that RIVM’s Hib conjugate project has had the most significant market impact. Of the current 23 WHO prequalified vaccine types [140], 2 products and 3 manufacturers are directly related to this project: DTwP-HepB from Bio Farma and pentavalent vaccine from SIIL and BiologicalE Ltd. respectively. UN vaccine prices will go down as a result of this increase in supplier’s base.

Taken together the impact is broader when the alternative effectiveness criteria are taken into consideration: politically/economically for recipients in India, Indonesia and Viet Nam the impact is increased availability of licensed EPI and combination vaccines (DTwP and DTwP-based combo’s) for national programmes. Finally, considerable human scientific capital was generated not only through international WHO courses, but also in the three state-owned companies involved in the China Project in the 90s.
Factors and actors in shaping the developing world vaccine industry

Several market and "market pull" mechanisms contributed to shaping the developing world vaccine industry. The innovation of new highly priced vaccines in developed countries fundamentally changed the economics of vaccine development and delivery. Recognizing this, actors and talented entrepreneurs from particularly Brazil, India, and China entered the international field and the general increase in the scientific and technological capabilities of these countries is leading to increased capabilities to undertake vaccine research, development and production. Finally, the establishment of GAVI fundamentally changed the market for vaccines in poor countries and encouraged the developing country manufacturers to invest more.

A historical perspective on the role of vaccine technology transfer was proposed in a working paper by John Barton, a renowned author about Global Public Goods [141, 142] who passed away unexpectedly in 2009, before the paper was published. A 2006 public lecture on this manuscript and the accompanying slides can be downloaded from the internet.

Barton argues that the key legal and policy factors shaping the developing world industry are those associated with safety regulation and with the purchasing procedures of major international procurement mechanisms. He distinguishes 4 distinct eras in the previous century: one of heroic individuals going into the developing world in the early 20th century, one of public sector health ministry production with slowly improving technology during the mid-century and up until about 1990, one of centralization of vaccine production in the developed world as a corollary of global health programmes during the last part of the century, and finally, one in which the global authorities turned to a few leading developing-world manufacturers during the last decade (see Table 6) [143].

WHO's evolving policy towards technology transfer over the past 40 years and its impact on the developing world vaccine industry can be distinguished in three phases, shown in Table 7.

Local production was initially encouraged between 1970 and 1990 to support the EPI programme, for example by publication of WHO manuals for the production and quality control testing of diphtheria toxoid, tetanus toxoid and pertussis vaccine in the 70s [144-146]. In line with this position, WHO contributed to an effort to promote vaccine production in developing countries, initiated by UNIDO with input also from UNICEF in the early eighties. Aim was to assist developing countries in the establishment of a pharmaceutical industry. Local manufacture of classical vaccines was seen as the only viable solution to meet the demand of densely populated countries like India [147] [148]. Finally, UNIDO published a document in 1986 entitled "A model programme for the production of vaccines in developing countries" [149]. This extensive document was based mainly on knowledge and experience from RIVM. Another example of direct WHO support for technology transfer to national vaccine manufacture in this period is the provision of the
Table 6. Factors shaping the developing world vaccine industry (updated from J. Barton, 2006 [143]).

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>TECHNOLOGY</th>
<th>ECONOMICS</th>
<th>POLITICS</th>
<th>REGULATION</th>
<th>LEGAL AND INTELLECTUAL PROPERTY</th>
<th>TRANSFER OF TECHNOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEROIC: &lt;1930</td>
<td>Low</td>
<td>Low cost</td>
<td>Colonial policy plus altruism</td>
<td>Nearly absent</td>
<td>Absent</td>
<td>Institute Pasteur</td>
</tr>
<tr>
<td>MID-CENTURY: DIVERGENCE 1930 - 1990</td>
<td>Moving</td>
<td>Increasing cost</td>
<td>National health programmes</td>
<td>Strengthening from a low base</td>
<td>Absent</td>
<td>WHO, national institutes, meetings, education</td>
</tr>
<tr>
<td>CURRENT: 2000 → 2012</td>
<td>Global authorities turning to a few leading developing-world manufacturers</td>
<td>High</td>
<td>High cost/ low margin, economies of scale</td>
<td>Self-sufficiency, biotechnology, donor politics, privatisation</td>
<td>Very high domestic and parallel WHO prequalification</td>
<td>Strengthening but mainly on intermediates and processes</td>
</tr>
</tbody>
</table>
In 1990, UNICEF, WHO, World Bank, the Rockefeller Institute and UNDP together launched the Children’s Vaccine Initiative (CVI). The idea was to work with all the players in immunisation, including industry, to find a new approach to vaccine development that launched the Children’s Vaccine Initiative (CVI). The idea was to work with all the players in immunisation, including industry, to find a new approach to vaccine development that

Table 7. Evolving dominant WHO policy towards technology transfer (1970-2010) and RIVM initiatives in the same periods.

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>GLOBAL PROGRAMMES</th>
<th>WHO POLICY</th>
<th>EXAMPLES RIVM TECHNOLOGY TRANSFER INITIATIVES &amp; CAPACITY BUILDING</th>
<th>RECIPIENT COUNTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970 - 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970 - 1990</td>
<td>Smallpox Eradication, start EPI, start Polio Eradication</td>
<td>Encouragement of local vaccine production</td>
<td>Rabies/Vero – Rockefeller Foundation EPI - UNIDO model programme</td>
<td>Colombia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WHO courses mainly on production</td>
<td>various</td>
</tr>
<tr>
<td>1990 - 2000</td>
<td>Children’s Vaccine Initiative</td>
<td>Encouragement of local vaccine production</td>
<td>EPI - World Bank</td>
<td>China</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quality policy: focus to regulatory agencies, viability studies for manufacturers</td>
<td>WHO courses mainly on quality control</td>
<td>Indonesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>various</td>
</tr>
<tr>
<td>2000</td>
<td>Start GAVI</td>
<td>Foster technology access Hubs</td>
<td>Hib-conjugate containing combo vaccines WHO courses on flu production and control</td>
<td>India</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>various</td>
</tr>
<tr>
<td>2012</td>
<td>Start Decade of Vaccines</td>
<td></td>
<td>Sabin-HPV – WHO; Gates Foundation</td>
<td>India, others</td>
</tr>
</tbody>
</table>
could be sustained in developing countries. However, the CVI never really got off the
ground for many reasons, one being “lack of money” [151, 152]. The period between CVI’s
inception until around 2005 is characterized by increasing reluctance towards directly
supporting local manufacturers due to concerns of quality associated in WHO policies.
According to WHO earlier efforts to support local manufacturers had not resulted in
sustainable vaccine production. In 1995 a WHO/CVI survey of 63 public sector manufac-
turers focused to quality aspects in the production and in the regulatory oversight [153].
Eventually the findings from several successive studies were summarized in a WHO qual-
ity policy published in 1990 [154], [155, 156]. This entailed that WHO would not provide
technical or financial support unless the manufacturer worked under the oversight of a
functional NRA and had a strategic plan for viability [157]. In hindsight, this “late-CVI and
early-GAVI” period has not been supportive to stimulate transfer of technology.

In the mid-90s, the Bill and Melinda Gates Foundation started to invest in global
health and created the Children’s Vaccine Program that provided seed funding for the
launch of GAVI. Simultaneously the Foundation provided a grant of $750 million to es-
establish the Vaccine Fund. Eventually, the Vaccine Fund was merged into GAVI in 1999
[151]. In this period, the developing world industry began to take shape; new research
programmes were established and a political and entrepreneurial climate emerged for
vaccines from developing countries. Several meetings were held under WHO’s umbrel-
la to bring public sector vaccine institutions together. This turned out to become the
pre-cursor of the Developing Country’s Vaccine Manufacturers Network (DCVMN), a net-
work of public and private manufacturers, established with a strategic plan to contribute
to access to combination vaccines [42, 79].

Simultaneously, new markets are shaped by GAVI in emerging economies for “high
value”- new vaccines such as Hib-containing pentavalent vaccines, rotavirus, pneumo
conjugate vaccines and HPV vaccines. GAVI uses predominantly “pull” mechanisms, such
as the Advanced Market Commitment (AMC) for conjugate pneumococcal vaccines to
attract manufacturers. Initially these markets were taken by MNCs, but increasingly UN
global vaccine procurement institutions begin to rely on developing country manufacturer-
s, who compete with equal quality and lower prices for these GAVI markets. To sustain
their role, the DCVM have expressed their need for more “push” mechanisms, including
transfer of technology [79]. They have also stated to consider the AMC mechanism to be
inappropriate for supporting their innovative activities on pneumococcal vaccines [158].

From around 2005 onwards new global policies by WHO result in a return of local
production and technology transfer on the international agenda. One of the underlying
reasons for this changing WHO position is the international debate on equity and virus/
benefit sharing of pandemic influenza strains, strongly promoted by several emerging
economies, notably Indonesia. This is reflected in WHO’s Global Strategy and Plan of
Action on Public Health, Innovation and Intellectual Property and Trade (GSPOA) [85], that
includes action “to promote transfer of technology and production of health products in
developing countries through identification of best practices, and investment and capaci-
ity building provided by developed and developing countries where appropriate”. In this context, WHO started a project on the local production of medical products (including vaccines) for improved access in developing and least developed countries, resulting in 2011 in a framework to assist governments in assuring that local production contributes to economic development while also meeting public health needs [159].

In practice, WHO has initiated various vaccine technology transfer projects in the area of pandemic influenza [86, 160].

**Sustainability of public sector contribution**

The sustainability of public sector vaccinology input as illustrated in this review faces challenges of a legal, financial and regulatory nature.

As is the case in the US, successful technology transfer initiatives from Europe’s public sector require third party financing from donors as well as strong industrial partners capable of absorbing and up scaling the technology. National institutes with vaccine development capabilities in Europe, with the possible exception of the NIBSC in the UK, do not have any international mandate. They have to focus therefore on their national health priorities, in a time of increasing financial restraints. Consequently there are decreasing budgets for global health activities. The costs for taking part in international initiatives need to be recovered from the receiving partners through upfront and milestone payments and/or licensing or royalty agreements. In practice, this appears however difficult to reconcile with the national public vaccine tasks of the institute, which (in the case of RIVM in the Netherlands) may include vaccine procurement advisory tasks for the national immunisation programme, requiring strict independence from industry. Another potential constraint of a regulatory nature in a public institute is that national control tasks such as vaccine batch release for the national market require a strict independence from any vaccine development or production activity. Perhaps a public private partnership foundation, dedicated to translational vaccinology for global health, separated from the national institute, would be a solution to these potential conflicts of interest.

From an overseas development aid perspective, several European countries, are committed to increase global access to vaccines; for instance, the Dutch contribution and pledges to GAVI over the period 2011-2015 amounts to $240 million [161]. Countries could consider investing part of such funds within their own borders in translational vaccinology centres of excellence that have shown a track record on technology transfer to improving local vaccine manufacturing capacity in the developing world.
Conclusion and perspective

This review indicates the gradual transformation over the last twenty years in the public sector from initially bilateral “producer-producer” collaborations into non-exclusive partnerships between internationally endorsed innovative enabling platforms or hubs and developing country manufacturers. It further observes that a substantial part of the current emerging vaccine industry finds its early roots in the early heroic era when the Pasteur Network started the transfer of vaccine technology within the public sector [143] and in the various RIVM contributions from 1970 onwards as described above.

The privatisation of vaccinology in the western world as noted by Blume and Gee-sink [92] is also ongoing in the developing world. A large part of the DCVMN consists of private companies, in particular from India. A consequence of ongoing privatisation is that vaccine production technology is increasingly difficult to obtain since commercial market-oriented business models focus to know how and intellectual property protection.

GAVI has developed a global policy approach largely dominated by market-oriented pull mechanisms, such as the AMC. Yet this overview shows that various innovative “push” technology transfer approaches through “open innovation” between enabling platforms and hubs and competent DCVM can lead to success and are in fact critical to ensure a sustainable supply of affordable quality vaccines to the national immunisation programmes in developing countries.

Archibugi [8] argues that vaccine know how and development are intermediate global goods, necessary for reaching the final public global good of communicable disease control. The economics of technological/scientific innovation has shown that optimal knowledge production is reached through a highly cooperative approach to scientific enquiry [162]. Together, these are convincing arguments for the public sector to preserve a major role in vaccine lead discovery and development for global health.
Chapter 6
An international technology platform for influenza vaccines
CHAPTER 6

Abstract:

Since 2008, the World Health Organisation has provided seed grants to 11 manufacturers in low- and middle-income countries to establish or improve their pandemic influenza vaccine production capacity. To facilitate this ambitious project, an influenza vaccine technology platform (or “hub”) was established at the Netherlands Vaccine Institute for training and technology transfer to developing countries. During its first two years of operation, a robust and transferable monovalent pilot process for egg-based inactivated whole virus influenza A vaccine production was established under international Good Manufacturing Practice standards, as well as in-process and release assays. A course curriculum was designed, including a two-volume practical handbook on production and quality control. Four generic hands-on training courses were successfully realized for over 40 employees from 15 developing country manufacturers. Planned extensions to the curriculum include cell-culture based technology for viral vaccine production, split virion influenza production, and generic adjuvant formulation. We conclude that technology transfer through the hub model works well, significantly builds vaccine manufacturing capacity in developing countries, and thereby increases global and equitable access to vaccines of high public health relevance.

Keywords: Pandemic influenza, developing country vaccine manufacturers network (DCVMN), technology transfer, hub, access

Introduction

Until recently, international efforts to boost capacity in low- and middle-income countries along the vaccinology value chain have been limited to quality control, regulatory support and clinical trials. The direct transfer of knowledge and technology for vaccine manufacturing itself has received very little attention. This trend mirrors a decline in the number of domestic and regional vaccine manufacturers in all parts of the world.

The (re)emergence of infectious diseases such as highly pathogenic avian influenza changed this picture. Governments saw investment in health security and pandemic influenza preparedness to be of increasing strategic importance. In several countries, this has resulted in significant national investment in manufacturing capacity. At the global level, the threat of an influenza pandemic has led to an acknowledged need for technical know-how and vaccine production capacity in developing countries.

In 2006, in response to the human-to-human transmission of A(H5N1), the World Health Organisation (WHO) took steps to enhance global access to influenza vaccine as part of its Global Pandemic Influenza Action Plan [165]. This included a pioneering project to strengthen the capacity of developing countries to produce influenza vaccine. WHO has to date provided seed grants for this purpose to 11 manufacturers that belong to the Developing Countries Vaccine Manufacturers Network (DCVMN), a voluntary, public health driven network supported by international organisations and vaccinology resource institutions such as the Netherlands Vaccine Institute (NVI) [42, 79, 166]. As the national vaccine agency of the Ministry of Health, NVI is tasked with the supply of vaccines for the Netherlands Immunisation Programme, either through production or procurement. Over the last decades, NVI has carried out a number of technology transfer projects to developing country manufacturers in various settings (Table 8) [79, 88].

Table 8. Netherlands Vaccine Institute technology transfer projects.

<table>
<thead>
<tr>
<th>Project</th>
<th>Vaccine</th>
<th>Approach</th>
<th>Recipient</th>
<th>Developing country</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenza type b (1999–now)</td>
<td>H. influenza type b conjugate</td>
<td>Development and transfer of pilot process</td>
<td>Bio Farma, SIIL, BE, Glovax/SIBP</td>
<td>Indonesia, India</td>
</tr>
<tr>
<td>WHO Sabin-IPV (2008–now)</td>
<td>New safer polio</td>
<td>1) Generic, hub 2) Bilateral technology transfer agreements with royalties</td>
<td>Potentially several</td>
<td>Republic of Korea/China</td>
</tr>
<tr>
<td>To be determined WHO/NVI (2007–now)</td>
<td>Egg-based inactivated influenza</td>
<td>1) Generic, hub 2) Bilateral agreements</td>
<td>1) 15 DCVM 2) Vacsera, IVAC</td>
<td>1) 12 countries; 2) Egypt, Viet Nam</td>
</tr>
</tbody>
</table>

SIBP, Shanghai Institute of Biological Products; LIBP, Lanzhou Institute of Biological Products; KIMB, Kunming Institute of Medical and Biological Products; SIIL, Serum Institute of India Ltd.; BE, BiologicalE Ltd.; WHO, World Health Organisation; IPV, inactivated polio vaccine; NVI, Netherlands Vaccine Institute; IVAC, Institute of Vaccines and Medical Biologicals.
"Hub-based" transfer of technical know-how

In early 2007, to address numerous requests from countries for support to their pandemic influenza vaccine production capacity, WHO developed the concept of a centralized technology and training platform (a "hub"). The objective of the hub was to pool public sector knowledge and expertise on a generic pilot process for influenza vaccine production that could be transferred to and easily scaled up in developing countries. Following a transparent bidding process, WHO selected NVI to fulfil this role, and an International Technology Platform for Influenza Vaccines was thus created in Bilthoven, the Netherlands [86]. A collaborative agreement between WHO and NVI was signed with the aim to establish an egg-based production process for inactivated whole virion influenza vaccine and relevant documentation (standard operating procedures, batch process records, validation methods, analytical methods and release criteria). The choice of technology was based on its simple and robust production process, and therefore its feasibility for transfer to developing countries to produce pandemic influenza vaccine. In addition, whole virus vaccines evoke the broadest immune responses, are largely exempt from intellectual property hurdles and can be produced without using licensed adjuvants [167]. This said, the ability to produce rapidly a pandemic vaccine invariably depends on the existence of annual seasonal influenza vaccine production; since split-virion vaccine is by far the most widely used technology in seasonal influenza programmes, NVI has added a process for split vaccine to its curriculum.

Establishment and validation of the basic process

The process established at pilot scale (10,000 eggs) follows the international quality and safety regulations of WHO [168] and the European Pharmacopoeia [169] (Figure 7).

To determine robustness, we used one monovalent seasonal strain to set up and test a classical egg-based process in our facilities. The main steps outlined in Figure 7 can be summarized as follows. The primary seed virus obtained from the National Institute for Biological Standards and Control (NYMC X-175C reassortant derived from A/Uruguay/716/2007) was processed to working seed on specific pathogen-free eggs before propagating the bulk virus at pilot scale for 48–72 h in fertilized hen eggs at 35 °C. The virus-containing fluid was harvested semi-automatically and clarified by centrifugation and depth filtration. The virus was purified and concentrated by sucrose gradient zonal ultracentrifugation and then inactivated by β-propiolactone, filtrated using depth filters and further purified by subsequent ultrafiltration/diafiltration. Finally, the product was formulated and filtrated at 0,22 μm to obtain monovalent vaccine.

After producing 12 monovalent batches, the final production settings were defined and consistency runs performed. The average recovery from zonal ultracentrifugation to monovalent vaccine was 53% and the average yield 1.1 dose/egg. The sucrose density
An international technology platform for influenza vaccines

Gradient purification method – the international standard for influenza virus purification – resulted in the purification profile shown in Figure 8. The performance per process step and the impurity profile for the consistency runs are shown in Table 9 and Table 10, respectively. The ovalbumin, total protein and endotoxin content meet the specifications set by WHO and the European Pharmacopoeia.

Comparison with other industrial processes is difficult, as most international manufacturers do not publish their process results. We found one publication on density gradient yields [170] and another comparing six European influenza vaccines for impurities [171]. Our data on hemagglutinin antigen yield (Table 9) and impurity profile for ovalbumin and endotoxin (Table 10) fitted well within the ranges reported in these two studies.

**Figure 7.** Egg-based pilot influenza vaccine production process.
Table 9. Performance per process step.

<table>
<thead>
<tr>
<th>Process step</th>
<th>Hemagglutinin recovery (%)</th>
<th>Bioburden removal Log (%)</th>
<th>Total protein removal (%)</th>
<th>Ovalbumin removal (%)</th>
<th>Sucrose removal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonal ultracentrifugation</td>
<td></td>
<td>Up to 1.3</td>
<td>92</td>
<td>99.993</td>
<td></td>
</tr>
<tr>
<td>Inactivation</td>
<td>89</td>
<td>Complete</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration/diafiltration</td>
<td>101</td>
<td>-</td>
<td>1</td>
<td>93.4</td>
<td>99.9</td>
</tr>
<tr>
<td>Formulation</td>
<td>98</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile filtration</td>
<td>66</td>
<td>Complete</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

Average values obtained in three consistency runs. Bioburden reduction values were the maximum values achieved (removal depends on initial bioburden load of a batch).

Table 10. Impurity profile of three consistency runs.

<table>
<thead>
<tr>
<th>Impurity</th>
<th>Min.</th>
<th>Max.</th>
<th>Spec [8;9]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovalbumin/HA</td>
<td>0.7</td>
<td>3.6</td>
<td>≤2000</td>
</tr>
<tr>
<td>Total protein/HA</td>
<td>225</td>
<td>245</td>
<td>≤600</td>
</tr>
<tr>
<td>Endotoxin/HA</td>
<td>0.09</td>
<td>4.19</td>
<td>≤200</td>
</tr>
<tr>
<td>Sucrose/HA</td>
<td>0.09</td>
<td>0.18</td>
<td>≤0.4</td>
</tr>
</tbody>
</table>

HA, hemagglutinin.
Hands-on training courses

In the preparatory phase, a suitable production training facility meeting international Good Manufacturing Practice standards within NVI was fitted with all necessary equipment. Process steps and test assays were set up and validated, and a two-volume course book written. Extensive documentation on the entire process was generated including all standard operating procedures for manufacturing and testing, and a Bill of Testing.

Participants for the training courses were selected in collaboration with WHO. Of the 15 public and private entities trained to date, 11 have represented manufacturers or regulatory agencies supported by the WHO influenza technology transfer project.

In June 2009, the first one-week interactive workshop was held on quality assurance and GMP aspects, including biosafety risk analysis and management, for 13 participants. This was followed in late 2009 and early 2010 by three courses of three weeks each on influenza production and quality control for a total of 29 participants. These courses addressed the production process in general, as well as specific quality control and release assays of each individual process such as 50% of the egg infectious dose (EID50) and single radial immunodiffusion (SRID). Regulatory issues related to influenza vaccines were covered, as well as the insights and skills needed to work safely and securely. Each course included a demonstration run at 10,000 egg pilot scale, and excursions to external suppliers such as a private egg-breeding facility. Invited international experts complemented the course faculty of NVI scientists and researchers. Participants who successfully completed the course were awarded a WHO certificate.

In addition to the training courses, bilateral technology transfer agreements have been signed with two WHO grantees to ensure further technical support to their vaccine manufacturing projects. Additional staff from both institutions attended tailor-made training programmes at NVI in 2010. The surge of interest in these courses from many countries and regions across the world, created by the 2009 H1N1 pandemic, has led to a waiting list for the next course which is scheduled for early 2011. The International Technology Platform for Influenza Vaccines has a dedicated web site as a communication tool for interested parties (www.itpiv.nl).

Discussion

On the basis of evaluations held after our courses, and in order to serve a broader range of developing countries interested in influenza manufacturing, we are now extending the knowledge base of our Centre. The basic process established for monovalent seasonal strains will be used for pandemic strains, allowing practical training in BSL2-plus conditions. To validate the processes developed and immunogenicity of the NVI vaccine, clinical batches of a candidate pandemic H5N1 strain (NIBRG23 A/turkey/Turkey/1/2005) are being produced under GMP for clinical studies in early 2011. We will also extend the
CHAPTER 6

process to include a step to serve parties that prefer split over whole virus pandemic vaccine and those interested in seasonal vaccine production.

A major challenge of the hub model is its sustainability. The need to secure NVI’s international role in building capacity for common public goods such as those described here have led to other initiatives and innovative approaches that will be introduced into the curriculum. For instance, we plan to develop and introduce cell-culture based technology modules for viral vaccine production. Developing countries may thereby enhance their capacity to manufacture not only influenza, but also other vaccines of high public health relevance, such as rabies or rotavirus. In addition, we serve as a training partner within the recently launched project for the technology transfer of an oil-in-water adjuvant for pandemic influenza vaccines in developing countries.

Summary and concluding remarks

The first years of operation have shown the International Technology Platform for Influenza Vaccines to be a highly successful capacity-building tool. The egg-based pilot-scale process established is robust, consistent and meets all international specifications. The technology is easy to scale up and has proven suitable for transfer to developing country manufacturers. The training and technology transfer objectives have been met, since participants at the fully booked generic courses are successfully using the technology and know-how gained in their facilities, and two bilateral consultancy agreements for follow-up activities have been signed. The generic hub approach to technology transfer can thus be seen as complementary to the bilateral partnerships for domestic influenza vaccine production reported by the International Federation of Pharmaceutical Manufacturers & Associations, which usually focus on fill/finish activities [172].

In conclusion, technology transfer from the public domain to emerging developing country manufacturers and regulators will increase global and equitable access to vaccines of high public health relevance. The hub approach is thus meeting a critical international need, and may be worth considering for other vaccines needed in low- and middle-income countries [173].
Chapter 7

The Developing Countries Vaccine Manufacturers Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries.
CHAPTER 7

Abstract:
Six years after its establishment, the Developing Countries Vaccine Manufacturers’ Network (DCVMN) has become the main representing body for emerging vaccine manufacturers from the developing world. The Network’s main strategic priority (increase access to DTP-based combination vaccines containing vaccines against hepatitis B (HepB) and *H. influenzae* type b (Hib)) has now come close to fulfilment due in part to the transfer of conjugation technology from The Netherlands Vaccine Institute (NVI) to various manufacturers of the Network. It is argued that at the international level more push mechanisms for product development involving DCVM are needed, including those promoting access to technology and transfer of technology, know-how and technical skills from Organisation for Economic Co-operation and Development (OECD) countries to developing countries. At the national level, governments of countries in which DCVMN manufacturers operate should provide more generous funding for all aspects of vaccines and immunisation including incentives to manufacturers to develop and import new technologies. These two approaches will contribute to the long-term viability of domestic or regional vaccine manufacturing, which in itself is critical to ensure global equity of access to vaccines.

Keywords: Developing countries, vaccines, hepatitis B, Hib conjugate, combination vaccines, access to technology, technology transfer

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Introduction

The OECD recently held a high level forum on policy coherence in Medicines for Neglected and Emerging Infectious Diseases in the regal Hotel Oranje in Noordwijk-aan-Zee, The Netherlands. The forum brought together representatives of developed and developing countries, industry, academia, non-governmental organisations and international organisations and agreed on a coherent “Noordwijk Medicines Agenda” [174].

This agenda calls for improving global health by accelerating development and delivery of medicines, vaccines and diagnostics for infectious diseases affecting developing countries.

Coincidently the DCVM-Network (see Table 11), the international representing body of emerging vaccine manufacturers, originated some 6 years ago in the same Hotel Oranje in Noordwijk at the 2001 Partner’s meeting of the Global Alliance for Vaccines and Immunisation (GAVI).

This communication highlights the development of the Network and lessons learned since, with a particular perspective towards increased recognition of domestic or regional vaccine development and manufacturing as a critical step for increasing access to neglected and underused vaccines in developing countries.

DCVMN origin

DCVMN is a voluntary public health driven alliance of vaccine manufacturers owned by and located in developing countries that offer a consistent and sustainable supply of quality vaccines that are affordable and accessible to developing countries [42]. These countries account for the majority of new-borns in the world and DCVMN members supply (next to most of their own local public markets) currently the vast majority of all the vaccines procured by UNICEF and PAHO for the developing world. For example, the DCVMN contribution in vaccine doses to PAHO’s 2007 tenders ranged from 5 to 100%, the average being 70% (Table 12). In fact, two out of every three children born in the world get immunized with at least one vaccine that comes from a manufacturer from the DCVMN.

When the DCVMN was created following a series of WHO meetings of public sector vaccinology institutions, the majority of initial members were focused to their local markets only. Interestingly, this is now no longer the case; in fact, the transition from “suppliers to the local market” to “suppliers to the global market” signifies most clearly a major development that has taken place among DCVMN since it originated. Its main purpose is now “to provide a consistent and sustainable supply of quality vaccines at an affordable price to developing countries and also to the entire globe” [175].
Table 11. Members of the DCVMN in 2008.

<table>
<thead>
<tr>
<th>NAME</th>
<th>CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Biomanguinhos (Fiocruz-Fiotec), Brazil</td>
<td>(1)</td>
</tr>
<tr>
<td>2  Bio Farma, Indonesia</td>
<td>(1)</td>
</tr>
<tr>
<td>3  Finlay Institute, Cuba</td>
<td>(1)</td>
</tr>
<tr>
<td>4  LG Life Sciences Ltd., Seoul, Korea</td>
<td>(1)</td>
</tr>
<tr>
<td>5  Panacea Biotech Limited, India</td>
<td>(1)</td>
</tr>
<tr>
<td>6  Serum Institute of India, India</td>
<td>(1)</td>
</tr>
<tr>
<td>7  Biological E. Limited, India</td>
<td>(2)</td>
</tr>
<tr>
<td>8  Bharat Biotech International Ltd., India</td>
<td>(2)</td>
</tr>
<tr>
<td>9  Indian Immunologicals Limited, India</td>
<td>(2)</td>
</tr>
<tr>
<td>10 Zydus Cadila Healthcare Limited, India</td>
<td>(2)</td>
</tr>
<tr>
<td>11 Instituto Fundacao Butantan, Brazil</td>
<td>(2)</td>
</tr>
<tr>
<td>12 Laboratories De Biologicos Y Reactivos De Mexico S.A. De C.V. (BIRMEX), Mexico</td>
<td>(2)</td>
</tr>
<tr>
<td>13 The Biovac Institute, South Africa</td>
<td>(2)</td>
</tr>
<tr>
<td>14 Queen Saovabha Memorial Institute, Thailand</td>
<td>(2)</td>
</tr>
<tr>
<td>15 Razi Vaccine &amp; Serum Research Institute, Iran</td>
<td>(2)</td>
</tr>
<tr>
<td>16 China National Biotec Corporation, China</td>
<td>(2)</td>
</tr>
<tr>
<td>17 Dalian JGAD Bioproducts Co. Ltd., Dalian, China</td>
<td>(2)</td>
</tr>
<tr>
<td>18 Xiamen YST Biotech Co. Ltd., China</td>
<td>(2)</td>
</tr>
<tr>
<td>19 IVAC (National Institute of Vaccines &amp; Biological Substances), Viet Nam</td>
<td>(2)</td>
</tr>
<tr>
<td>20 Vabiotech, The Company for Vaccine &amp; Biological Production No. 1, Viet Nam</td>
<td>(2)</td>
</tr>
</tbody>
</table>

(1) members holding WHO-prequalification of one or more of their products, located in countries with fully functional National Regulatory Authorities (NRA) as defined by WHO
(2) members working towards attaining the status of WHO prequalification

Strategic goal: availability of Hib-containing combo vaccines

In 2007, a dedicated website has come on air (www.dcvmn.com) that outlines mission, vision and objectives of the Network and also provides useful company profiles of its members and supportive organisations [175]. To be eligible for DCVMN membership a company must be either a public sector manufacturer in a developing country or must be majority held (51% or greater) by a person or combination of people citizens of the developing country in which the company produces vaccines.

The Network’s main strategic priority formulated at the start was to increase access to HepB and Hib containing DTP combination vaccines. This was in line with the objectives of GAVI, which was just launched after an initial subsidy of the Gates Foundation [176]. It was hoped at that time that GAVI would support the Network by “push” mechanisms such
The DCVMN is a critical constituency to ensure access to vaccines in developing countries

Table 12. Vaccines procured by the Pan American Health Organisation (PAHO) from members of the DCVMN in 2007.

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>TOTAL QUANTITY</th>
<th>QUANTITY AWARDED</th>
<th>DCVM-MEMBER</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BCG 10 dose vial</td>
<td>11,440,000</td>
<td>6,520,800</td>
<td>Manufacturer A</td>
<td>57</td>
</tr>
<tr>
<td>2. DTP 10 dose vial</td>
<td>11,182,204</td>
<td>10,623,094</td>
<td>Manufacturer A</td>
<td>95</td>
</tr>
<tr>
<td>3. DT (Adult) 10 dose vial</td>
<td>32,400,000</td>
<td>32,400,000</td>
<td>Manufacturer A</td>
<td>100</td>
</tr>
<tr>
<td>4. DT (Ped) 10 dose vial</td>
<td>612,000</td>
<td>183,600</td>
<td>Manufacturer A</td>
<td>30</td>
</tr>
<tr>
<td>5. Hep B 1 dose recom (Ped)</td>
<td>7,000,000</td>
<td>5,000,000</td>
<td>Manufacturer B</td>
<td>71</td>
</tr>
<tr>
<td>6. Hep B 1 dose recom</td>
<td>364,286</td>
<td>364,286</td>
<td>Manufacturer B</td>
<td>100</td>
</tr>
<tr>
<td>7. Hep B 10 dose recom</td>
<td>6,240,486</td>
<td>6,240,486</td>
<td>Manufacturer B</td>
<td>100</td>
</tr>
<tr>
<td>8. MR 10 dose</td>
<td>4,000,000</td>
<td>2,800,000</td>
<td>Manufacturer A</td>
<td>70</td>
</tr>
<tr>
<td>9. MMR 1 dose</td>
<td>9,750,000</td>
<td>6,250,000</td>
<td>Manufacturer A</td>
<td>64</td>
</tr>
<tr>
<td>10. MMR 10 dose</td>
<td>5,914,286</td>
<td>3,414,286</td>
<td>Manufacturer A</td>
<td>58</td>
</tr>
<tr>
<td>11. Polio</td>
<td>42,000,000</td>
<td>2,000,000</td>
<td>Manufacturer C</td>
<td>5</td>
</tr>
<tr>
<td>12. TT 10 dose</td>
<td>430,000</td>
<td>265,000</td>
<td>Manufacturer A</td>
<td>62</td>
</tr>
<tr>
<td>13. Yellow fever 5/10 dose</td>
<td>11,000,000</td>
<td>11,000,000</td>
<td>Manufacturer D</td>
<td>100</td>
</tr>
</tbody>
</table>

Average from DCVM A-D = 70%.

as facilitating access to technology [42]. Most DCVM at that time were DTP manufacturers serving a substantial part of the developing country vaccine demand for paediatric vaccines and, although this had not been investigated in a study, it was assumed that GAVI goals would be most cost-effectively be obtained when the new vaccines to be introduced (HepB and Hib) would be combined with DTP made by DCVM. Thereby GAVI would also make effective use of their existing DTP manufacturing infrastructure and distribution channels. For DCVM such international support was important as access to technology is one of the main conditions determining the long-term viability of local vaccine manufacturing [154]. The expected donor support to the Network at that time did not materialize, partly due to international concerns for unfair subsidizing certain individual manufacturers. Despite this initial lack of donor support the Network’s main strategic priority has now nearly been reached at a global scale. As reported by Kreeftenberg and Hamidi in 2004, the key factors to this success included the transfer of conjugation technology from The Netherlands Vaccine Institute (NVI), the ability of the “receiving” DCVMN members to invest upfront in this conjugation technology and their ability to absorb the transferred technology [136].

Recently in 2006 USAID has provided some funding to the Network for training purposes.
CHAPTER 7

Development and technology transfer of Hib conjugation technology by NVI

NVI developed since 1999 an up-scalable and patent-free process for the production of a conjugate vaccine against Hib, based on the Robbins conjugation technology [135, 177] and transferred the process at pilot scale to three different DCVMN members: Bio Farma (Bandung, Indonesia), Serum Institute of India Ltd./SIIL (Pune, India) and Biological E. Limited (Hyderabad, India) [136]. This wider NVI Hib technology transfer programme, as well as the up-scaling, clinical trial and licensing, was financed mainly by three involved DCVMN members themselves. Lessons learned in this programme have been described elsewhere [136].

Due to a near monopoly situation, the GAVI market price for Hib containing combination vaccines has not decreased for nearly 5 years. GAVI now expects that the entry into the market by DCVM will lead to this needed decline for Hib containing vaccines, just as the price of DTP-HepB combo vaccines dropped 40% since 2001 mainly as a result of entry into the market of new manufacturers from developing countries [176].

Recently, one DCVM, the Serum Institute of India Ltd. (SIIL) obtained with the NVI Hib process technology a license from the Indian Government for the indigenous production of monovalent Hib and also for pentavalent (DTP–Hep B–Hib) vaccine. In the near future, SIIL expects to get the necessary clearance for supply to United Nation Organisations. With a capacity to produce over 100 million doses of the vaccine, it is expected that with the imminent availability of additional Hib vaccine products there will be a reduction of the global vaccine price in the next few years. When licensure is obtained by the other DCVM that have absorbed the NVI technology (Biological E and Bio Farma) such reduction will be further sustained.

These kinds of joint development and technology transfer projects with DCVM will increase the availability of Hib vaccines for affordable prices on the global vaccine market. Next to this successful example of technology transfer from an OECD public sector institution as NVI, other approaches to obtain Hib conjugation technology were recently summarized in a case study on access to vaccine technologies [103]. These involve OECD Industry and include importing Hib bulk by Biomanguinhos in Brazil with eventual technology transfer and importing Hib bulks for formulation and marketing in India by Bharat Biotech and Panacea Biotech [103].

Vaccines for development: access is key

Involving DCVM in the development and creation of vaccines will increase the likelihood that any given vaccine or vaccine combination needed in those countries will become available because DCVM are by nature closely interacting with their national or (in the case of India) regional immunisation programmes. They also liaise closely with
The DCVMN is a critical constituency to ensure access to vaccines in developing countries. Therefore DCVM are more likely to develop and manufacture affordable products targeted to the needs of the population.

Currently new and promising policy innovations [178] for new generation vaccines\(^9\) and possible future vaccines\(^1\) are developed in the global vaccine landscape. These build on the existing GAVI Alliance that was created initially mainly for under-used vaccines\(^4\). With GAVI funds, UNICEF has in the past 5 years predominantly purchased under-used vaccines for low-income countries from OECD manufacturers, in particular monovalent HepB and Hib vaccines and combination vaccines containing Hib and HepB.

The new policy innovations that have received much media attention lately include the International Finance Facility for Immunisation (IFFIM), Product Development Partnerships (PDP’s like the International AIDS Vaccine Initiative (IAVI), the Malaria Vaccine Initiative (MVI) and the Meningitis Vaccine Project (MVP)) and Advance Market Commitments (AMCs) [178]. These innovations will be applied mainly for new generation and future vaccines and (with the exception of PDP’s, which can activate push mechanisms) seem focused to pull mechanisms.

We argue here that more push mechanisms should be put in place at the international level to attain DCVM’s involvement. In particular this can be achieved by increasing access to technology (also critical for viability of the manufacturer) by joint research and development programmes and by transfer of technology and know-how (including how to deal with IP issues [103] and [179]. DCVM are now on the one hand expected to lower the global vaccine prices for underused vaccines such as pentavalent combinations, but at the same time they have like any other manufacturer to invest in product development and to meet the costly international cGMP quality standards and regulatory requirements for clinical studies necessary to prequalify through WHO for supply of vaccines to UN agencies.

At the national level, governments of countries in which DCVMN manufacturers operate should provide more generous funding for all aspects of vaccines and immunisation including incentives to manufacturers to develop and import new technologies. A good example of this approach is Brazil, where 80% of the vaccines distributed come from two DCVM. Successive governments have over the last decades substantially invested in a public industrial complex including two DCVM [Instituto Butantan in São Paulo and the Biomanguinhos in Rio de Janeiro]. Both have attained a GMP status. Similarly, the establishment of a strict national control authority, entirely independent from the manufacturers, was created ensuring international quality levels. This was done in the framework of a national self-sufficiency programme for vaccines and sera based upon competitiveness [180].

\(^{9}\) New generation vaccines: Pneumo, Rota, HPV, Japanese Encephalitis
\(^{1}\) Possible future vaccines: HIV/AIDS, TB, Malaria
\(^{4}\) New and under-used vaccines: HepB and Hib conjugate-containing combination vaccines, including the traditional EPI DTP vaccines, Typhoid, Cholera
CHAPTER 7

Perspectives: influenza vaccine production capacity in developing countries

The threat of a potential new flu pandemic has sparked a renewed interest at the global level in domestic or regional vaccine production in developing countries. Currently, influenza vaccine production capacity is vastly insufficient to meet the global demand in case of a pandemic. Influenza vaccine manufacturing is now mainly located in Europe. Developing countries, notably in Asia rightly fear that in case of a pandemic they will not have access in time to affordable pandemic influenza vaccines, if they have to rely entirely on the European-based influenza vaccine industry, which will primarily serve OECD markets. The latest World Health Assembly reached after 6 days of closed-door meetings a tedious agreement on a new resolution on best practices for sharing virus samples to address new pandemics such as avian flu. This resolution addresses in part the concerns of a group of developing countries led by Indonesia focusing on access to vaccines for developing countries [181]. The WHA resolution acknowledges the need for facilitation of acquisition by developing countries of capacity for manufacturing in-country influenza vaccines.

The Global Pandemic Influenza Action Plan to increase vaccine supply of WHO aims to close the current influenza vaccine production gap of several billion doses [182]. In line with this plan, WHO has taken recent steps to engage DCVM: six members in Brazil, India, Indonesia, Mexico, Thailand and Viet Nam were awarded grants in 2007 for technology transfer to establish manufacturing capacity for influenza vaccine [183].

The Noordwijk Medicines Agenda (NMA) calls for the need to explore models to promote innovation and stimulate the development of new vaccines for neglected and emerging infectious diseases. Amongst several others mechanisms, the promotion of transfer of technology, knowledge and technical skills from OECD countries is encouraged. The NMA also calls for new partnership models between developing and developed countries to accelerate R&D for neglected diseases.

The DCVMN has evolved over the last years into a significant international constituency critically involved in matters of global vaccine security concern. The experiences between DCVMN-members and the NVI described here on the Hib conjugate vaccine are an example of such a model that could be applicable also to other neglected vaccines. To foster the contribution by developing countries to global R&D efforts, incentives are to be designed to strengthen and utilize their capacity and institutions. This includes a good understanding of intellectual property and strengthening their capacity to manage IP issues [103]. In this respect it is encouraging to note that the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, due to convene in November 2007, drafted a new global strategy containing specific elements on transfer of technology and management of IP [184].
Chapter 8

China’s emerging vaccine industry
CHAPTER 8

Abstract:

The Chinese vaccine industry is developing rapidly due to an emerging and large market for current and new vaccines, a large potential for local vaccine manufacturing both in the public and private domain, and a governmental orientation towards national vaccine self-sufficiency. There are currently over 40 companies and institutions manufacturing a large variety of traditional (EPI) and some new vaccines. The innovative development capacity of state vaccine institutions is stimulated by significant government investments. Various Chinese influenza manufacturers were in 2009 among the first worldwide to obtain a national license for their pandemic H1N1 flu vaccines. It is of interest to note that private but also governmental entities are committed to raise manufacturing quality standards to reach WHO prequalification. It is expected that WHO prequalification for at least one product from a Chinese manufacturer will have been obtained by 2011. This will open the door to the global market for Chinese vaccines.

Keywords: China, national immunisation programme, pandemic influenza, developing country vaccine manufacturers’ network (DCVMN)

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Introduction

The global human vaccine market is expected to grow rapidly in the coming decades, fuelled by re-emerging vaccine preventable health threats such as pandemic influenza, an increasingly more coordinated international response thereto, and the availability of licensed new vaccines combined with several international philanthropically public-private partnerships, such as GAVI. On top of this, countries with emerging economies are introducing these new vaccines in a more rapid pace than ever. At the same time, equitable access to vaccines for the global community remains a subject of intensive international public health concern, as for example the recent case of pandemic influenza caused by the new H1N1 virus illustrates [185]. The importance of local or regional vaccine manufacturers, coordinated in the Developing Countries Vaccine Manufacturers’ Network (DCVMN), to reduce this global vaccine inequity has been highlighted before [79]. The DCVMN (www.dcvmn.com) is a voluntary public health driven alliance of vaccine manufacturers in developing countries, under advocacy of WHO [79]. The members include vaccine manufacturers in developing countries, international organisations and resource institutions such as the Netherlands Vaccine Institute (NVI) and the Programme for Appropriate Technology in Health (PATH), based in Seattle, USA. The objective of the Network is to help the vaccine manufacturers in developing countries understand the most up-to-date status of vaccine development and assist them becoming a supplier to international markets, thereby improving the health of people in developing countries [42, 79]. Members of the DCVMN include public and private manufacturers mainly from countries with fast growing emerging economies, such as Brazil, India and China. It is remarkable that at the international level, little is known about the vaccine situation in China, a country with a very large part of the world population. Due to China’s impressive economic growth figures in latest years, the Chinese market is becoming very attractive for pharmaceutical companies. Because of its huge population, national vaccination policies in China are influenced by the ability of domestic manufacturers to supply needed vaccines at an affordable price.

This commentary aims to give a recent overview of the emerging human vaccine industry in China in view of the increasing global awareness of the importance of regional or local vaccine manufacturing to tackle international vaccine availability issues [186]. Although the focus of most Chinese vaccine manufacturers is at this moment their domestic market, they have a clear ambition and potential to play a role in the global market. This became apparent at the latest Annual Meeting of the DCVMN that was hosted by the China National Biotec Group (CNBG) in Beijing in September 2009. Currently 4 Chinese manufacturers are DCVMN members, including CNBG. CNBG’s national status was actually reconfirmed end 2009, when China’s State-owned Assets Supervision and Administration Commission (SASAC) announced a merger of the CNBG with the China National Pharmaceutical Corporation (Sinopharm). Sinopharm is one of China’s largest pharmaceutical companies and is believed to become one of China’s three giant pharmaceutical conglomerates over the next few years [187].
The National Immunisation Programme and vaccine markets

China, with its 1.3 billion inhabitants and over 17 million new-borns annually, is the world largest vaccine consuming country. The current vaccine market in China was valued in 2009 to be around $700 million with a compound annual growth rate expected to increase from around 15% now to 30% over the next few years, thanks to recently announced governmental healthcare reforms that emphasize prevention and aim to bring wider insurance coverage to the population [188].

The Chinese government has traditionally over the years managed a successful vaccine-preventable disease programme. Polio-eradication was for example already achieved in 1994 and childhood immunisation continues to be a high priority [189]. A law was passed in 2005 ensuring provision of vaccines free of charge through the Chinese National Immunisation Programme (CNIP). The CNIP currently includes 14 (mainly paediatric) vaccines against 15 diseases (Table 13). Several new antigens including recombinant Hepatitis B were introduced since 2007.

**Table 13.** The Chinese National Immunisation Programme (CNIP) in 2009.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Vaccine</th>
<th>Year of introduction</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepB</td>
<td>Hepatitis B Vaccine</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>BCG Vaccine</td>
<td>1978</td>
<td></td>
</tr>
<tr>
<td>OPV</td>
<td>Oral Poliomyelitis Vaccine</td>
<td>1978</td>
<td></td>
</tr>
<tr>
<td>DTP</td>
<td>Combined Vaccine of Pertussis, Diphtheria &amp; Tetanus</td>
<td>1978</td>
<td></td>
</tr>
<tr>
<td>MV</td>
<td>Measles Vaccine</td>
<td>1978</td>
<td></td>
</tr>
<tr>
<td>DT</td>
<td>Combined Vaccine of Diphtheria &amp; Tetanus</td>
<td>2008</td>
<td>Booster for 6 year olds</td>
</tr>
<tr>
<td>DTaP</td>
<td>Acellular DTP Vaccine</td>
<td>2008</td>
<td>To replace DTP</td>
</tr>
<tr>
<td>HAV</td>
<td>Hepatitis A Vaccine</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>MenA/MenAC</td>
<td>Meningococcus Vaccine</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>JE</td>
<td>Japanese Encephalitis Vaccine</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>Combined Vaccine of Measles, Mumps &amp; Rubella</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic Fever Renal Syndrome Vaccine</td>
<td>2008</td>
<td>Only for certain risk groups in endemic regions</td>
<td></td>
</tr>
<tr>
<td>Anthrax Vaccine</td>
<td>2008</td>
<td>Only for certain risk groups in endemic regions</td>
<td></td>
</tr>
<tr>
<td>Leptospira Vaccine</td>
<td>2008</td>
<td>Only for certain risk groups in endemic regions</td>
<td></td>
</tr>
</tbody>
</table>
Several vaccines in the CNIP are in short supply, for example the demand for Diphtheria Tetanus acellular-Pertussis Vaccine (DTaP) was nearly 64 million doses in 2008, whereas manufacturers supplied only about 18 million doses, resulting in a market gap of 46 million doses in 2008. For MMR, the market gap is estimated at 23 million doses each year and there are also shortages for live attenuated hepatitis A vaccines, inactivated hepatitis A vaccines, and inactivated Japanese Encephalitis vaccines [190].

The priority and cost-effectiveness of introduction of new vaccines such as conjugate Hib vaccine, pneumococcal and rotavirus vaccines, IPV replacement for OPV and combination vaccines to reduce the number of injections into this CNIP is currently actively being assessed in collaboration and consultation with international bodies such as WHO and GAVI [191]. These studies are expected to lead in the coming years to the uptake of new vaccines in the CNIP. Currently, the introduction of a cHib vaccine (widely promoted by GAVI) is seriously being considered by the Chinese authorities and several domestic manufacturers have already started to develop and manufacture this conjugate vaccine.

Vaccines used outside the CNIP in the private market are produced by manufacturers based on market demand (Table 15). Examples are seasonal influenza vaccines and rabies vaccines. These may be purchased by consumers on a voluntary basis.

The vaccine regulatory authority

Vaccines are regulated in China by the State Food and Drug Administration (SFDA). The SFDA with provincial FDA’s supervises and controls throughout the country the entire vaccine supply chain, from production, trading, to supply and administration. Since China aims to produce and export vaccines, it is a pre-requisite that China’s regulatory authority, the SFDA, is able to exercise the six regulatory functions that are recognized by WHO as essential to ensure that vaccines manufactured in China are of international assured quality. The Government has thus embarked since 2003 with WHO support on a programme to improve the vaccine regulatory capacity of the SFDA up to international standards [192]. Currently WHO is preparing for a re-assessment of the SFDA which is expected to take place by the end of 2010. A successful outcome of this re-assessment will start the process of submission to WHO of prequalification dossiers of vaccines made by Chinese manufacturers, which will pave the way of China’s entry into the global market. One of the first candidate vaccines for WHO prequalification will be the Japanese Encephalitis vaccine made by the Chengdu Institute for Biological Products in collaboration with PATH.
Table 14. Chinese vaccine manufacturers registered at SFDA [195].

<table>
<thead>
<tr>
<th>Vaccine Manufacturer</th>
<th>Location</th>
<th>No of products</th>
<th>Legal Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Vaccine &amp; Serum Institute (NVSI)</td>
<td>Beijing</td>
<td>2</td>
<td>Public; Sinopharm</td>
</tr>
<tr>
<td>Changzhou Institute of Biological Products (CiBP)</td>
<td>Changzhou, Jilin</td>
<td>7</td>
<td>Public; Sinopharm</td>
</tr>
<tr>
<td>Lanzhou Institute of Biological Products Co. Ltd. (LiBP)</td>
<td>Lanzhou, Gansu</td>
<td>13</td>
<td>Public; Sinopharm</td>
</tr>
<tr>
<td>Shanghai Institute of Biological Products (SiBP)</td>
<td>Shanghai</td>
<td>3</td>
<td>Public; Sinopharm</td>
</tr>
<tr>
<td>Wuhan Institute of Biological Products (WHiBP)</td>
<td>Wuhan, Hubei</td>
<td>4</td>
<td>Public; Sinopharm</td>
</tr>
<tr>
<td>Chengdu Institute of Biological Products (CDiBP)</td>
<td>Chengdu, Sichuan</td>
<td>6</td>
<td>Public; Sinopharm</td>
</tr>
<tr>
<td>Huanan Biological Engineering Inc. (Huanan)</td>
<td>Xinxian, Henan</td>
<td>7</td>
<td>Private</td>
</tr>
<tr>
<td>Yunnan Yuexishangcheng Biotech Co. Ltd.</td>
<td>Yuxi, Yunnan</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Sinovac Biotech Co., Ltd. (SinoVac)</td>
<td>Beijing</td>
<td>3</td>
<td>Private</td>
</tr>
<tr>
<td>Rong’an Pharma Co. Ltd. (RongAn)</td>
<td>Ningbo, Zhejiang</td>
<td>2</td>
<td>Private</td>
</tr>
<tr>
<td>Guangzhou Nuocheng Bio-product Co. Ltd. (Nuocheng)</td>
<td>Guangzhou, Guangdong</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Beijing Qweike Biotech Co. Ltd.</td>
<td>Beijing</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Shanghai Zerun Biotech Co. Ltd. (Zerun)</td>
<td>Shanghai</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Tianshi Jinna Biotech Co. Ltd.</td>
<td>Tianjin</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Shandong Hengeye Biotech Co. Ltd.</td>
<td>Qingdao, Shandong</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Hanen Puxin Bio-engineering Co. Ltd. (Puxin)</td>
<td>Zhengzhou, Henan</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Changchun Institute Co. Ltd. of Biological Products</td>
<td>Changchun, Jilin</td>
<td>2</td>
<td>Private</td>
</tr>
<tr>
<td>Zhejiang Pukang Biotechnology Co. Ltd. (Pukang)</td>
<td>Hangzhou, Zhejiang</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Changchun Wei-er-sai Pharma Co. Ltd.</td>
<td>Changchun, Jilin</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Zhejiang Tianyuan Bio-Pharma Co. Ltd. (Tianyuan)</td>
<td>Hangzhou, Zhejiang</td>
<td>4</td>
<td>Private; (85% Novartis)</td>
</tr>
<tr>
<td>Dalian Kunyang Pharma Co. Ltd.</td>
<td>Dalian, Liaoning</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Changzhou Changhai Life Science (Changsheng)</td>
<td>Changchun, Jilin</td>
<td>7</td>
<td>Private</td>
</tr>
<tr>
<td>Luoyi Bio-pharma Co. Ltd. (Luoyi)</td>
<td>WuXi, Jiangsu</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Walvas Biotechnology Co. Ltd. (Walvax)</td>
<td>Yunnan</td>
<td>4</td>
<td>Private; (65% GSK)</td>
</tr>
<tr>
<td>Shenzhen Kangtai Biological Products Co. (SKBP)</td>
<td>Shenzhen, Guangdong</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Jiangsu Yanshen Biological Tech Co. Ltd. (Yanshen)</td>
<td>Changzhou, Jiangsu</td>
<td>4</td>
<td>Private</td>
</tr>
<tr>
<td>Xinkexian Biotech Co. Ltd.</td>
<td>Fuyang, Anhui</td>
<td>5</td>
<td>Private</td>
</tr>
<tr>
<td>Liaoning Yisheng Pharma Co. Ltd. (Yisheng)</td>
<td>Shenyang, Liaoning</td>
<td>2</td>
<td>Private</td>
</tr>
<tr>
<td>Liaoning Chengda Bio-tech Co. Ltd. (Chengda)</td>
<td>Shenyang, Liaoning</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Future Pharma Co. Ltd. (Fuer)</td>
<td>Hebei</td>
<td>2</td>
<td>Private</td>
</tr>
<tr>
<td>Zhejiang Weixin Pharma Co. Ltd. (Weixin)</td>
<td>Ningbo, Zhejiang</td>
<td>2</td>
<td>Private</td>
</tr>
<tr>
<td>Shenzhen Qinghuayuanxing Bio-pharma Tech Co. Ltd.</td>
<td>Shenzhen, Guangdong</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Beijing Hua-er-dun Bio-tech Co. Ltd.</td>
<td>Beijing</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Dalian Hanxin Pharma Co. Ltd. (Hanxin)</td>
<td>Dalian, Liaoning</td>
<td>2</td>
<td>Private</td>
</tr>
<tr>
<td>Beijing Lvyu Pharma Co. Ltd. (Lvyu)</td>
<td>Beijing</td>
<td>3</td>
<td>Private</td>
</tr>
<tr>
<td>Shenzhen Sanofi Pasteur Biological Products Co. Ltd. (Pasteur)</td>
<td>Shenzhen, Guangdong</td>
<td>4</td>
<td>Private; (Stakeholder Sanofi)</td>
</tr>
<tr>
<td>Shenzhen Jieling Biotech Co. Ltd. (Jieling)</td>
<td>Shenzhen, Guangdong</td>
<td>1</td>
<td>Private; (JV 40% GSK)</td>
</tr>
<tr>
<td>Jinan Yatai Bio-pharma Co. Ltd. (Yatai)</td>
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<td>1</td>
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<td>Jinan Maiying Pharma Co. Ltd. (Maiying)</td>
<td>Changchun, Jilin</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Beijing Wansai Bio-Pharma Co. Ltd.</td>
<td>Beijing</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Huabei Pharma Jiantin Bio-tech Co. Ltd. (Jiantin)</td>
<td>Shijiangzhuan, Hebei</td>
<td>1</td>
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</tr>
<tr>
<td>Shenzhen Neptunus Interlong Biotech Co. Ltd.</td>
<td>Shenzhen, Guangdong</td>
<td>1</td>
<td>Private; (Stakeholder Sanofi)</td>
</tr>
<tr>
<td>Beijing Tiantan Biological Products Co. Ltd. (BTBP)</td>
<td>Beijing</td>
<td>3</td>
<td>Private (holding company of Sinopharm)</td>
</tr>
<tr>
<td>Shanghai Rongsheng Pharma Co. Ltd.</td>
<td>Shanghai</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Shenzhen Weiwu Guangming Bio-product Co. Ltd.</td>
<td>Shenzhen, Guangdong</td>
<td>1</td>
<td>Private</td>
</tr>
<tr>
<td>Dalian Aleph Biomedical Co., Ltd. (Aleph)</td>
<td>Dalian, Liaoning</td>
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</table>
China’s emerging vaccine industry

Vaccine manufacturing in China

China ranks as the world’s largest vaccine manufacturing country with an annual output of more than one billion doses [193]. The Chinese government has a policy to provide vaccines for the CNIP by Chinese manufacturers and, with the exception of BCG and OPV, does not encourage supply of CNIP vaccines by international vaccine manufacturers, according to a “Guidance Catalogue of Foreign Investment Industries” issued by the National Development and Reform Commission and the Ministry of Commerce in 2007 [194]. Currently the website of the Chinese national regulatory authority (SFDA) lists 46 Chinese registered vaccine manufacturers, of public and private status, collectively manufacturing 24 licensed vaccines [195]. Table 14 shows an overview with an indication of the number of vaccines they each manufacture and their legal status.

CNBG/Sinopharm. It is interesting to note from this list that the six subsidiary manu-

Table 15. Major vaccine products in China [195].

<table>
<thead>
<tr>
<th>Product Name</th>
<th>No. of Manufacturers</th>
<th>Reference no. in Table 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Recombinant HepB</td>
<td>8</td>
<td>2, 3, 5, 6, 25, 34, 41, 43</td>
</tr>
<tr>
<td>2 BCG</td>
<td>5</td>
<td>1, 2, 3, 4, 6</td>
</tr>
<tr>
<td>3 OPV</td>
<td>2</td>
<td>36, 43</td>
</tr>
<tr>
<td>4 DTP</td>
<td>6</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>5 MV</td>
<td>5</td>
<td>3, 4, 5, 6, 43</td>
</tr>
<tr>
<td>6 DT</td>
<td>6</td>
<td>2, 3, 4, 5, 6, 43</td>
</tr>
<tr>
<td>7 DTaP</td>
<td>7</td>
<td>2, 3, 4, 5, 6, 22, 43</td>
</tr>
<tr>
<td>8 HAV</td>
<td>6</td>
<td>2, 9, 13, 18, 22, 36</td>
</tr>
<tr>
<td>9 Meningococcus A and A+C Vaccine</td>
<td>9</td>
<td>2, 3, 4, 5, 6, 20, 23, 24, 35, 43</td>
</tr>
<tr>
<td>10 JE</td>
<td>9</td>
<td>1, 2, 3, 4, 5, 6, 20, 29, 43</td>
</tr>
<tr>
<td>11 MMR</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>12 Haemorrhagic Fever with Renal Syndrome Vaccine, Inactivated</td>
<td>6</td>
<td>2, 3, 4, 20, 23, 31</td>
</tr>
<tr>
<td>13 Anthrax vaccine</td>
<td>2</td>
<td>3, 6</td>
</tr>
<tr>
<td>14 Leptospira Vaccine</td>
<td>3</td>
<td>4, 5, 6</td>
</tr>
<tr>
<td>15 Adsorbed Tetanus Vaccine</td>
<td>6</td>
<td>2, 3, 4, 5, 6, 43</td>
</tr>
<tr>
<td>16 Combined Vaccine of Hepatitis A and B</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>17 Rabies Vaccine</td>
<td>14</td>
<td>2, 3, 5, 10, 11, 16, 22, 26, 28, 29, 30, 34, 38, 39</td>
</tr>
<tr>
<td>18 Tracheitis Vaccine</td>
<td>4</td>
<td>2, 4, 5, 26</td>
</tr>
<tr>
<td>19 Typhoid Vi Polysaccharide Vaccine</td>
<td>6</td>
<td>2, 3, 4, 5, 6, 43</td>
</tr>
<tr>
<td>20 Tick-borne encephalitis vaccine</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>21 Split A (H1N1) Influenza Vaccine</td>
<td>10</td>
<td>2, 3, 4, 7, 9, 20, 22, 26, 43, 46</td>
</tr>
<tr>
<td>22 Seasonal Influenza Vaccine</td>
<td>11</td>
<td>2, 3, 4, 7, 9, 20, 22, 26, 37, 42, 43</td>
</tr>
<tr>
<td>23 Pandemic (H5N1) Influenza Vaccine</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>24 Brucella Vaccine</td>
<td>2</td>
<td>2, 3</td>
</tr>
</tbody>
</table>

NB. The first 14 vaccines are used in the Chinese National Immunisation Programme (see also Table 13).
facturers of the CNBG group, located in Beijing, Changchun, Chengdu, Lanzhou, Shanghai and Wuhan, have the widest diversity of vaccines as compared to the private manufacturers. Collectively they provide 90% of the doses of the 14 CNIP vaccines (Table 15). To bolster innovative development capacity, CNBG/Sinopharm established in Beijing in 2004 a corporate R&D centre to maximize the synergies of the 6 Institutions. The construction of a New National Vaccine Engineering Research Centre, China’s first national-level research, development and industrialization base for new vaccines started in 2009 in Beijing. The centre will aim to upgrade traditional vaccines and solve technical problems occurring during the R&D and industrialization of new vaccines, focusing on R&D including pilot scale production of new vaccines and biomedicines.

CNYB/Sinopharm has also interests in several private companies, for instance CNBG/Sinopharm is a majority shareholder of Beijing Tiantan Biological Products Co. Ltd. (no 43 in Table 14).

Recently, multinational vaccine companies show an increasing interest in expanding their presence and are entering the Chinese market by taking majority shares in Chinese companies. GSK announced in 2009 to take a 65% stake in a joint venture with the Chinese firm Walvax (no. 24 in Table 14) for the development, manufacture and supply to China’s public vaccine market of MMR. This followed GSK’s earlier announcement of a 40% stake in a JV with another Chinese company, Shenzhen Neptunus Interlong Biotech Co. Ltd. (no. 42 in Table 14) to develop and manufacture flu and rabies vaccines. Sanofi Pasteur has a majority in Shenszen Sanofi (no. 36 in Table 14) and has announced investments of over $700 million in a flu vaccine facility with a 25 million doses annual capacity. Novartis obtained in November 2009 a majority (85% stake) in Zhejiang Tianyuan Bio-Pharmaceutical Co. Ltd. (no 20 in Table 14), subject to government and regulatory approval in China.

Influenza vaccines

Seasonal influenza vaccines. There is a big potential market for seasonal flu vaccines considering the current low vaccination rates and China’s huge population. The overall seasonal flu vaccination rate in China was about 1.5% in the 2007-2008 season. For certain risk groups (the aged population) it was only about 0.3%. Under the current SFDA regulation, provinces and municipalities can develop their own policies. This explains that regional differences on flu vaccination practices exist. For example, the Beijing municipality offered in the 2007/2008 season free flu vaccines to the registered elderly population, and half-price flu vaccines to students in primary and junior middle schools, totalling together over 1.5 million persons. Five flu manufacturers (Table 14; nos. 9, 20, 26, 43, and 37) supplied seasonal influenza vaccines to this Beijing city programme. Obviously there is a marked interest by various manufacturers both domestically and internationally to obtain a market share of the influenza vaccine market in China, as is apparent from the relatively large number of influenza manufacturers in Table 14 as well as the interest of the international companies to get a stake in China’s flu vaccine market.
Pandemic influenza vaccines. The recent global threat for a new avian flu pandemic and in particular the 2009 new (H1N1) influenza pandemic amplified galvanized the emerging Chinese flu vaccine industry. Due to very pro-active pandemic vaccine preparedness decisions at the Government level, China made global headlines in 2009 becoming the first country to complete clinical trials for the new H1N1 pandemic flu, to approve domestically made pandemic flu vaccines and to start mass immunisations. The Chinese government’s strategy was to vaccinate in 2009 five percent of the total population, or about 65 million people. By November 2009, SFDA had provided a national license to 10 Chinese manufacturers (see Table 14 nos: 2, 3, 4, 7, 9, 20, 22, 26, 43 and 46). By February 2010 around 77 million persons had received the vaccine. The Chinese vaccines were made in eggs with the NYMCX-179A virus seed strain obtained from WHO. An extensive clinical study coordinated by the Chinese Centre for Disease Control in 7 provinces involving over 13,000 volunteers showed that a one dose regimen of a 15 ug split formulation without adjuvant yielded a protection of about 85% [196]. The Chinese government purchase price was set to about 22 RMB (€2.2) per dose. The vaccines were provided to the public (especially high risk groups: public health workers, students and patients with chronic diseases) free of charge. The estimated national flu vaccine production capacity was estimated by the first quarter of 2010 at around 100 million doses.

Concluding remarks

The recent developments described here will lead to an increased uptake of traditional and new vaccines in the Chinese public immunisation programme. In the years to come the domestic vaccine market in China will grow at an accelerated pace. Besides stimulating the domestic industry, this has attracted the interest of international manufacturers who are now engaging in China through different strategies, such as taking interests in Chinese private companies. This may lead to competitive supply of vaccines to Chinese markets including the EPI- markets. Because the Chinese regulatory authorities are striving to meet international criteria for vaccine manufacturing and regulation, it may be expected that in the years to come the number of domestic vaccine companies will decrease, as they are forced to meet international quality standards. China’s national policy to stimulate domestic vaccine manufacture is becoming more internationally oriented, as exemplified by the increasing presence of Chinese manufacturers in the DCVMN. Several Chinese manufacturers are making significant investments in their facilities to meet international GMP standards and regulations. CNBG/Sinopharm and others have embarked on an ambitious programme to meet WHO prequalification for one or more of their products opening the way to provide vaccines for the global market. The remarkable, very fast and significant up scaling of Chinese pandemic flu vaccine production capacity in 2009 illustrates the enormous potential and global relevance of the emerging Chinese vaccine industry. This will in the near future no doubt benefit global access to vaccines.
The endgame
THE ENDGAME

This section provides some perspectives drawn from the preceding chapters. It places the narrative on the Netherlands public sector manufacturing and its technology sharing in the wider context of the global vaccine system. An apparent misconnection ("policy incoherence") is noted between national vaccine development practices and overseas development assistance policies towards the provision of vaccines to the developing world.

Institutional tensions and transformations

It was Jonas Salk who first introduced the term vaccinology as “the study and application of the basic requirements for effective immunisation”. This definition includes the application of basic knowledge of the immune system and of specific immunogens and practical solutions to the development of effective vaccination programmes. Vaccinology thus includes vaccine research and development but also production, licensing and implementation in national programmes. In 1998, Joost Ruitenberg, at that time RIVM's Deputy Director, saw vaccinology as a science that should also incorporate social and cultural aspects concerning development, provision and acceptability of vaccines, since vaccine use in the population is in essence a political matter and of great public health importance [92].

The dynamics of the Netherlands public sector vaccine development and production described in Chapter 1, are in line with what Blume and Geesink observed in 2000 as two influencing transformations, when they proposed to consider vaccinology as an industrial science: the influence of the biotechnology revolution and the dominant role which the private industry has come to play in this science discipline [92]. Zooming out, the case studies described in this thesis illustrate the place of a national vaccinology institute in a globalising world. They represent different aspects of privatisation and globalisation processes that over a period of 50 years transformed a public health driven vaccinology expertise centre with a semi-industrial infrastructure into what became three different parts. The privatisation of the Dutch vaccine production capacity was completed in 2012, whereas the privatisation of the research and product development and technology transfer capacity (i.e. Intravacc) is pending [25]. Other tasks that relate to advising the government on vaccination schedules monitoring vaccine coverage and on procurement of vaccines have been re-integrated into the RIVM.

The preceding chapters also show that from an institutional public perspective different vaccine development routes or vaccine choices were sometimes made in the Netherlands in comparison to other countries, such as the United States. Not market considerations but reflections on programmatic suitability to optimally meet the needs of the National Immunisation Programme justified the persistent effort in the early 70s to develop an inactivated measles containing combination vaccine (Chapter 2).

The foregoing illustrates further that, acting from a public perspective, the institute
began to focus its activities towards developing countries to contribute to the production of global public goods. This process which one could call “public health globalisation” occurred despite government policies which gradually evolved from a basic public health focus into a policy dominated by cost reductions and economic performance, with higher expectations on return of investments in national infrastructure. This transformation from a national public health mandate towards global public good creation through “push” mechanisms originated from a few strong-willed and capable individual scientists and leaders. Over time this ambition increasingly met closed doors at the Ministry of Health, whereas policy makers in the Dutch Overseas Development Assistance Ministry, disconnected from this ongoing non-mandated institutional globalisation, appeared more attracted to a divergent logic of market “pull” globalisation as promoted by the GAVI Alliance.

Under a national mandate and by technological development and innovation the institute was for several decades well able to meet the mandate for provision of the national immunisation programme. As a corollary, the contributions to the creation of GPGs became an increasingly relevant function, but perhaps as a paradox this process of globalisation resulted in a situation of high vulnerability, when measured along economic and market considerations alone. Since increasingly most vaccines or vaccine combinations required for the Netherlands Immunisation Programme were no longer manufactured in-house, continuation of a fully integrated national vaccinology centre came under scrutiny and was eventually considered unsustainable.

**Impact on the National Immunisation Programme**

Similar privatisation/globalization processes of previously public sector driven national vaccinology institutions have taken place in most if not all countries of the Western world. As a consequence, vaccine innovation and supply to national vaccination programmes in the US and Europe are now increasingly driven by a remarkable small number of multinational pharmaceutical companies that are market (profit) driven. Countries find themselves in an increasingly vulnerable position when negotiating annual vaccine supply agreements for their existing national immunisation programmes with less than a handful companies. New vaccine introductions have become even more problematic not only because of increasing mistrust by the public (vaccine hesitancy), but also due to their high pricing, non-transparency of actual cost of goods and research and development costs by the pharmaceutical companies. This is accompanied by an erosion of scientific and technical vaccinology expertise in the public domain. The European Commission has since 2002 started a tedious process for a joint procurement mechanism which should assist the smaller countries in the EU to negotiate better prices, but progress in the implementation of this approach is painstakingly slow.
Impact on the global vaccine system

The main finding of this thesis is that national public sector vaccinology institutions, in particular the Netherlands public health institute, have over the past decennia had a hitherto hardly acknowledged but profoundly positive impact on the global vaccine system that aims to increase access to vaccines in developing countries. This impact is the result not of supply of vaccines, but through enabling capable vaccine manufacturing entities (public or private) in developing countries to set up or improve their capacity. Various vaccines now in massive routine use globally, like the pentavalent (DTP-HepB-Hib) vaccines made by SIIL and BE in India and procured by GAVI) or the recently licensed Sabin-IPV vaccine made by the Kunming Institute of Medical Biology (KIMB) for the Chinese market\(^1\) find their origin in Bilthoven. The scientific and technical ability to develop and manufacture vaccines in-house in combination with a public health driven mission, enabled the sharing of vaccine seed strains, manufacturing knowledge, know-how and expertise through capacity building and technology transfer. This was initially mainly to public sector institutions but since 2000 increasingly to private manufacturers in developing countries. These emerging manufacturers, welcomed by GAVI as new competitors, now increasingly supply the global vaccine system, which will drive prices down.

After the sale of the production capacity in 2012, transfer of large scale technologies from the Netherlands has come to an end because access to manufacturing expertise and facilities have become inaccessible. Whether the vaccine development capacity within Intravacc will continue to play a supportive role for the global vaccine system supply is currently uncertain. This will depend to a large degree on the success of the pending sale under conditions that should preserve certain public tasks currently executed by Intravacc [25].

From a participant observer perspective, I conclude that the larger societal value for global health has received too little attention in the privatisation process of vaccinology in the Netherlands. This is remarkable because in the overseas development assistance arena, the Netherlands always supported the goal of providing access to vaccines for all children. Since GAVI’s inception, the Netherlands has been one of the main donor countries to a total of $742,5 million over the period 2000-2020, or about $37 million annually for twenty years [198]. GAVI until now predominantly favours pull mechanisms thereby creating global markets for multinational pharmaceutical companies and manufacturers in developing countries. The Dutch vaccinology public sector has, as described in Chap-

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\(^{1}\) The World Bank China Vaccine Project, briefly described in Chapter 5, successfully transferred in the 90s the “Bilthoven” micro carrier/ bioreactor-based production technology for Sabin oral polio vaccine (OPV) to the Kunming Institute of Medical Biology. This included the provision of WHO approved virus seeds, qualified cell banks, numerous Standard Operating Procedures and extensive hands-on training programmes. KIMB scientists later independently adapted this OPV process into a process for IPV by adding an inactivation step. They further succeeded in defining an optimal vaccine formulation and in steering this Sabin-IPV vaccine through various clinical studies until it was licensed for the Chinese market in January 2015.
ters 3 to 8, by push mechanisms significantly supported developing country manufacturers to enter GAVI markets. Take for instance the Hib containing pentavalent vaccine, for which prices did not decrease until Serum Institute of India and BiologicalE from India, both beneficiaries of technology transfer from the Netherlands, started to supply this vaccine. Yet, this technology transfer project never received any financial support from national or international donor agencies [77].

A large chunk of GAVI funding now goes to new and underused vaccines such as the pneumococcal conjugate vaccine, supplied by Pfizer and GSK and, according to some, still too highly priced [57]. It is tempting to speculate what would be the GAVI price of this vaccine today if the DNC pneumococcal vaccine project in the 90s described in Chapter 2 had succeeded in its’ ultimate objective to transfer the conjugate technology to a DCVM in that time period.

Success factors in the global system

The two dominant reasons that the DNC pneumococcal vaccine initiative failed were insufficient and inflexible upfront funding and the lack of continuous strong leadership. Both conditions are frequently mentioned by key global vaccinology players as critical success factors in product development partnerships, as illustrated by the following quotes from personal interviews with respectively Marie-Paule Kieny, presently WHO’s Assistant Director General Health Systems and Innovation, and Adar Poonawalla, SIIL’s Chief Executive Officer and son of billionaire SIIL owner Cyrus Poonawalla.

Kieny, at the time Director of WHO’s Initiative for Vaccine Research in the early stages of WHO/PATH’s highly successful Meningitis Vaccines for Africa project (MVP), reflected in 2015:

“Part of the MVP success was the $70 million upfront grant without ties from the Gates Foundation. At that time the Gates Foundation was different. Now it is a micromanagement organisation. Gates had just started and they did not have an army yet. Therefore, they gave us in one bit an unconditional $70 million; even a large part in cash. So in the course of the project we got a lot of problems, when the programme chose to go with SIIL and not GSK or another. But they couldn’t stop us because we had the cash. So, part of the success is the $70 million upfront without ties. Second: Marc LaForce: you need a champion. He was amazing: he goes straight to his goal; when he bumps, he turns and goes into another direction and then another bump; that doesn’t matter him and he goes into yet another direction” [199].

In current days, such large flexible upfront investments for push oriented vaccine development and technology transfer projects with associated risks have become out of reach for the public sector. Also the public sector’s ability to take risks and to flexibly manage complex technological and clinical development to industrial scale levels can be questioned.

Perhaps paradoxically, while the development and manufacture of children’s
vaccines over the years turned out to be economically unsustainable within the Dutch national setting, it was the decades-long practice of international knowledge and technology-sharing that convinced the Serum Institute, the largest global supplier of vaccines for developing countries, to acquire this facility which in the long run may turn out to increase access to vaccines for all children in the world. When interviewed on SIIL's reasoning to acquire the Netherlands' public sector vaccine production in 2011, Adar Poonawalla illustrated the difference between the public and private sector as follows:

"Because we only had one manufacturing base in India, we felt financially strong enough to make an acquisition to get access to the EU and US markets. That was the secondary objective. The primary objective was that we knew that IPV was required for the endgame of polio. And because of the ban on manufacturing a polio vaccine based on the wild strain in India, we had no choice but to invest in a loss-making Dutch public sector company. That's why we said: look, it's a no-brainer; we have to go for it. And that's what we did. We are taking 3 years turning it around and hopefully in the next year we should break-even on the operations. So we don't take losses anymore. It will take maybe 7 - 8 years to recover the money we have sunken in. The acquisition was €30 million; then another acquisition of €50 million for the land and the buildings and then we spent €30 million upgrading and €10-15 million other things, working capital etc. In all, we'll spend about €200 million. Public sector units are not able to capture a global market. This is a very important point: no vaccine company can survive on a one-country market. They are restricted to supply their products to one or two countries. If for example $20 million had to be spent to comply with GMP or whatever they won't get the budget as the Ministry will ask how it is going to benefit the Dutch. My answer is: at least it is bringing the company figures out of the red and into the black. The governments don't look from that angle because every financing they give they have to be politically accountable to it and if they can't justify, then it is a political fight; they have to deal with parliament. Those are the kind of restrictions that have prevented a lot of these companies to remain in business. Their privatisation is taking place because they can't self-sustain" [200].

Finally, returning now to one of the core questions of this thesis what the impact will be of the 2012 privatisation on the Institute's contribution to the production of global public goods? Has the case of privatisation of the Dutch vaccinology been good or detrimental for global health? I think that there are two answers to this question, depending on the observer's angle. From a neoliberal, market oriented and vertical perspective one could argue that the private take-over will benefit global health because the new owner SIIL, currently the largest provider of low cost vaccines to the world, will increase global access to IPV, and IPV is an essential requirement for reaching polio eradication, a commonly accepted global public good. From a societal and horizontal angle however, and this is where I stand, one can see it as an illustration that in the current global vaccine system a divergence between policies and practices between different ministries within the same government leads to missed opportunities for global health. The unique national “open door” vaccinology infrastructure that once existed has vanished, and this represents a great loss to the horizontal capacity building in developing countries which took place over so many decades.
References


27. Thanormwat, Y. NVI initiates ASEAN collaboration for regional vaccine security. 2015 [cited 2016 April 7]; Available from: https://www.google.nl/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=NVI+initiates+ASEAN+collaboration+for+regional+vaccine+security.


29. Robbins, A., Letter to Dr Foege (TFCS ) to start front-end funding of vaccine development for the developing world. RIVM Archives, 1988.


32. Freeman, P., Letter to RIVM Director General van Noort on the TFCS review on proposals for front-end support for vaccine development, in RIVM Archives. 1989.


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55. GAVI. About the Pneumococcal AMC. 2016 [cited 2016 April 8]; Available from: http://www.gavi.org/funding/pneumococcal-amc/about/.
REFERENCES

www.who.int/immunization_standards/vaccine_quality/gtn_index/en/.


101. WHO. Meeting of the Global Advisory Committee on Vaccine Safety. December 2010. Wkly Epidemiol Rec,


REFERENCES


WHO, Brochure: Ensuring the quality of locally produced vaccines and the viability of local production. WHO/ VSQ/90.82. 1990.


Rourou, S., A. van der Ark, T. van der Velden, and H. Kallel, A microcarrier cell culture process for propagating


183. WHO. Press Release. WHO facilitates influenza vaccine technology transfer to developing countries, April 24, 2007.


199. Hendriks, J., Interview with Marie-Paule Kieny, Assistant Director General Health Information Systems and Innovation, World Health Organization. 2015.

200. Hendriks, J., Interview with Adar Poonawalla, Chief Executive Officer of Serum Institute of India Ltd. 2014.
Appendix
APPENDIX

List of publications and contributions by respective authors

i. Jadhav, S., Datla, M., Kreeftenberg, H. and Hendriks, J. *The Developing Countries Vaccine Manufacturers' Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries.* Vaccine, 2008. 26 (13): p. 1611-1615. [Chapter 7 in this thesis]

   Author contributions: J. Hendriks wrote the first draft and subsequently incorporated comments and suggestions from the other authors. S. Jadhav provided the data that were used to create Table 12.

ii. Hendriks, J., Liang, Y., Zeng, B. *China's emerging vaccine industry.* Human Vaccines and Immunotherapeutics, 2010. 6 (7), p. 602-607. [Chapter 8 in this thesis]

   Author contributions: J. Hendriks wrote the first draft and subsequently incorporated some comments and suggestions from the other authors. Y. Liang translated Table 14 from Chinese into English.


   Author contributions: J. Hendriks wrote the first draft and subsequently incorporated comments and suggestions from other authors. P. de Jong provided Table 9, 10 and Figure 8. O. de Boer provided Figure 7.


   Author contributions: J. Hendriks wrote the first draft and subsequently incorporated some comments and suggestions from the other authors. A. Hamidi provided Table 3.


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


   Author contributions: J. Hendriks was responsible for archival research, participated in collection and review of secondary sources and in drafting the article. S. Blume participated in collection and review of secondary sources and in drafting the article.
Summary

Global health has improved remarkably through the introduction of a multitude of vaccines in childhood vaccination programmes since the 50s of the previous century. The successful global eradication of smallpox and the imminent global eradication of the polio virus are but two examples of global public goods which only became a reality through widely available safe and effective vaccines against these viruses. New vaccines that are now increasingly becoming available result from the science and technology field commonly called “vaccinology”. Recent global introductions include vaccines against hepatitis B, H. influenzae type B, rotavirus, pneumococcus and human papillomavirus. While early classical vaccines against diphtheria, pertussis, tetanus, polio and measles were made mainly in state owned laboratories and institutions under a national mission to provide these goods for the population, nowadays the manufacture and supply of new vaccines and combination vaccines have in the Western world become the domain of only a handful of multinational companies. This “privatisation” of the vaccinology science field has been accompanied with the gradual erosion of public sector vaccine development and production. As regards vaccine provision in low and middle income countries, non-state actors and public-private-partnerships such as the Bill and Melinda Gates Foundation and the GAVI Alliance have become dominant in agenda setting and prioritisation, once the remit of WHO and countries themselves. Within this “global vaccine system”, counterbalancing developments are also noticeable. These include the growing importance of public and private vaccine suppliers in developing countries themselves and is associated with an increase in innovative capacity within these countries.

This thesis describes the specific case of public sector vaccine development and manufacturing in Bilthoven, the Netherlands. After successes from the 1960s onwards, there followed a period of institutional transformations and gradual decline. This culminated in the eventual partial take-over by the private sector in 2012. For nearly three decades until the 90s, the National Institute of Public Health was successful in producing and supplying all the vaccines required for the national immunisation programme. Production technologies and quality control assay techniques for diphtheria, pertussis, tetanus and polio vaccines that had been developed largely in-house were widely shared in the public domain with various developing countries through extended practical training courses under WHO auspices but also on a bilateral basis. From the 90s onwards, when it became progressively more challenging to meet the national demand for newer or better vaccines, the institute increasingly engaged in several vaccine development and technology transfer activities and projects focused on the developing world.

The dynamics described in this thesis illustrate the effects of globalisation upon a public health driven vaccinology expertise centre with a semi-industrial infrastructure that over the period of study disintegrated into three legally separated parts. The sale of the national production capacity to the private sector in 2012 was accompanied by the re-integration of public advisory tasks on vaccination schedules and vaccine procure-
ment into the National Institute of Public Health and the Environment (RIVM), whereas the privatisation of the national vaccine development and technology transfer capacity, the Institute for Translational Vaccinology (Intravacc), is imminent.

From a global perspective, this case of privatisation is of particular interest because the buyer, the Serum Institute of India Ltd. (SIIL), is one of the world’s largest private vaccine manufacturers playing a key role in the supply of affordable vaccines for developing countries made available through the global United Nations vaccine procurement systems. Since the mid-1960s, SIIL had also been benefitting from vaccine know-how and technology transfer programmes from the Netherlands’ public domain.

The main finding of this thesis is that national public sector vaccinology institutions, in particular the Netherlands public health institute, have over the past decennia had a hitherto hardly acknowledged but profoundly positive impact on the global vaccine system that aims to increase access to vaccines in developing countries. This impact is the result not of supply of vaccines, but through enabling vaccine manufacturing entities (public or private) in developing countries to set up or improve their capacity. From a participant observer perspective, I conclude that this larger societal value for global health has received too little attention in the privatisation process of vaccinology in the Netherlands. This is remarkable, because in the overseas development assistance arena, the Netherlands always supported the goal of providing access to vaccines for all children. From a societal and horizontal angle this study illustrates that in the current global vaccine system a divergence between policies and practices between different ministries within the same government may lead to missed opportunities for global health. It is to be hoped that the conditions set by the government for the pending privatisation of Intravacc, planned for 2017, will ensure at least the partial continuation of global public good creation from Bilthoven as has been done so successfully in the past decades.
Samenvatting (Dutch Summary)

De mondiale volksgezondheid is aanzienlijk verbeterd door de introductie van meerdere vaccins in kindervaccinatie programma's sinds de jaren vijftig van de vorige eeuw. De wereldwijde uitoering van pokken en de aanstaande uitoering van het poliovirus zijn twee aansprekende voorbeelden van verworven mondiale publieke goederen, welke slechts mogelijk werden dankzij de wereldwijde beschikbaarheid van veilige en effectieve vaccins tegen deze virussen. Nieuwe vaccins, welke met enige regelmatig op de markt komen, zijn afkomstig van de wetenschappelijke en technologische discipline, aangeduid als "vaccinologie". Recentelijk wereldwijd geïntroduceerde vaccins zijn onder andere gericht tegen hepatitis B, *H. influenzae* type B, rotavirus, pneumococcen en human papillomavirus. Terwijl de klassieke kindervaccins tegen difterie, kinkhoest, tetanus, polio en mazelen meestal werden vervaardigd in nationale laboratoria of instellingen, welke vanuit de overheid de opdracht hadden om deze producten te maken voor de eigen bevolking, is in de Westerse wereld vandaag de dag de productie van vaccins het domein geworden van slechts een zeer klein aantal multinationale bedrijven. Deze "privatisering" van de vaccinologie discipline is gepaard gegaan met de geleidelijke uitholling van de ontwikkelings- en productiecapaciteit van vaccins binnen de publieke sector. Wat de vaccinvoorziening in lage en middeninkomenslanden betreft, geldt dat het bepalen van de agenda en de prioriteiten, lange tijd het domein van de Wereldgezondheidsorganisatie (WHO) en de landen zelf, steeds sterker beïnvloed wordt door niet-gouvernementele actoren en publiek-private-partnerschappen zoals de Bill en Melinda Gates Stichting en de GAVI Alliance. Binnen dit "mondiale vaccinsysteem" zijn er ook tegenstromen waarneembaar, zoals het toenemende belang van vaccinfabrikanten, zowel publiek als privaat, uit ontwikkelingslanden welke gepaard gaat met een toename in de innovatieve capaciteit binnen deze landen.

Dit proefschrift beschrijft de specifieke casus van vaccinontwikkeling en -productie in het publieke domein in Bilthoven, Nederland, vanaf het begin en de aanvankelijke successen sinds de jaren zestig van de vorige eeuw, gevolgd door een periode van institutionele veranderingen en geleidelijke afname tot tenslotte een gedeeltelijke overname door de private sector in 2012. Gedurende een periode van bijna dertig jaar was het Rijksinstituut voor Volksgezondheid in staat om alle vaccins, welke werden vereist voor het Rijksvaccinatieprogramma, zelf te produceren en te leveren. Technologieën voor productie en kwaliteitscontrole voor difterie, kinkhoest, tetanus en polio vaccins, welke grotendeels binnenshuis waren ontwikkeld, werden tevens op wijde schaal gedeeld in het publieke domein met verschillende ontwikkelingslanden door intensive praktische trainingscursussen onder de vlag van de WHO, maar ook op bilaterale basis. Vanaf de jaren negentig, toen het nationaal steeds moeilijker werd om aan de vraag naar nieuwe en betere vaccins te voldoen, raakte het Instituut steeds meer betrokken bij verschillende activiteiten, waarin kennis van vaccins en technologie werd overgedragen, primair aan ontwikkelingslanden.
APPENDIX

De hier beschreven ontwikkelingen illustreren de effecten van globalisering op een door een publieke missie gedreven centrum van vaccinologie expertise met een semi-industriële infrastructuur, welke gedurende de bestudeerde periode uiteen is geraakt in drie gescheiden onderdelen. De verkoop van de nationale productiecapaciteit naar de private sector in 2012 ging gepaard met de re-integratie van de publieke adviestaken over vaccinatie schema’s en jaarlijkse vaccinaanschaf in het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), terwijl de privatisering van de nationale capaciteit voor vaccinontwikkeling en voor overdracht van kennis en technologie, het Instituut voor Translationele Vaccinologie (Intravacc), aanstaande is. Vanuit mondiaal perspectief is deze casus van privatisering intrigerend omdat de koper, het Serum Institute of India Ltd. (SIIL), een van 's werelds grootste private vaccinfabrikanten is die een cruciale rol speelt in de voorziening van betaalbare vaccins aan ontwikkelingslanden. SIIL heeft ook vanaf de jaren zestig jaren van de vorige eeuw kunnen profiteren van de vaccinkennis en van de overdracht van technologie vanuit het Nederlandse publieke domein.

De belangrijkste bevinding van dit proefschrift is dat nationale vaccinologie instituten, in het bijzonder het Nederlandse volksgezondheidsinstituut, gedurende meerdere decennia een tot nu toe nauwelijks erkend, maar aantoonbaar positief effect hebben uitgeoefend op het mondiale systeem van vaccinvoorziening dat toegang tot vaccins in ontwikkelingslanden beoogt te bevorderen. Dit effect is niet het gevolg van vaccinleveranties, maar is toe te schrijven aan het ondersteunen van vaccinfabrikanten in ontwikkelingslanden met het doel hun capaciteit (kennis en kunde) te verbeteren. Vanuit het perspectief van een participerende waarnemer concludeer ik dat deze maatschappelijke waarde creatie voor de mondiale volksgezondheid te weinig aandacht heeft gekregen in het privatiseringsproces van de vaccinologie in Nederland. Dit is opmerkelijk, omdat Nederland in de wereld van ontwikkelingssamenwerking altijd internationale doelstellingen om vaccins toegankelijk te maken voor alle kinderen in de wereld sterk heeft ondersteund. Vanuit een maatschappelijk en horizontaal perspectief illustreert deze studie dat in het huidige mondiale vaccinsysteem een divergentie tussen politiek, beleid en praktijk tussen verschillende ministeries binnen een overheid kan leiden tot gemiste kansen voor de mondiale volksgezondheid. Het is te hopen, dat de verkoopvoorwaarden verbonden aan de te verwachten privatisering van Intravacc, voorzien in 2017, in ieder geval voor een deel zullen zorgdragen voor het voortzetten van de creatie van mondiale publieke goederen in Bilthoven, zoals dat de afgelopen decennia zo succesvol heeft plaatsgevonden.
APPENDIX

About the author

Graduated in 1978 as a biologist (Drs, University of Leiden) and in 1980 as an immunologist (MSc, University of Amsterdam), Jan Hendriks worked in the early 80s for a period of five years in Jamaica and Brazil as PAHO associate expert in the field of cellular immunology of tropical diseases, before returning to the University of Amsterdam, to become project coordinator of various immunology training and capacity building projects with institutes and universities in Viet Nam. Since 1990, he is employed by the Netherlands Ministry of Health, working in several international staff and project management positions within the respective vaccinology entities described in this thesis: the National Institute for Public Health and Environment (RIVM), the Netherlands Vaccine Institute (NVI) and currently the Institute for Translational Vaccinology (Intravacc). Between 2002 and 2006, he was seconded as a national expert to the Public Health Directorate of the European Commission in Luxembourg. A second secondment followed from 2013 to 2015 to WHO in Geneva, where he was the coordinator of WHO’s Global Action Plan on Influenza Vaccines. Including the publications contained in this thesis, he has (co-) authored over forty peer-reviewed papers.