Health Council of the Netherlands

On the role of vaccination in preparation for an influenza pandemic

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

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Dear Minister,

At your request, the Health Council of the Netherlands has incorporated details of the lessons learned from influenza A/H1N1 2009 (also known as Mexican Flu or Swine Flu) into its advisory report on the role of vaccination in preparation for an influenza pandemic. As a result, the advisory report contains both a review and an evaluation, as well as advice for the future.

When reviewing this hectic period with a degree of objectivity, my attention was drawn to a number of points. I very much appreciate the willingness of experts to make their knowledge and experience available, often at short notice and with tight deadlines, to create a careful, scientifically-based advisory report. The Netherlands is fortunate to have so many experts of such high international standing. This enabled us to rapidly gain access to the best data. As I look back, I am also struck by the fact that there are few areas in which we might have reached a different conclusion, even given the benefits of science and the more advanced knowledge that we possess today.

Yet the public perception of this episode is not unequivocally positive. In the press, in debates held in the Lower House of the Dutch Parliament, and in society at large, there is a feeling that we may have overreacted. People feel that money was wasted on unnecessary vaccines, and that this was partly due to a conflict of interest involving experts from the Health Council and RIVM, and the vaccine manufacturers themselves. It is a worthwhile exercise to explore those perceptions in greater depth.

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In my analysis of the issues involved in that public debate, I have identified four individual points:

1 In the public debate, the term "pandemic" has taken on a life of its own. Strictly speaking, the term simply refers to a disease that is spreading around the world. In popular parlance, "pandemic" has now come to mean a severe influenza epidemic, possibly involving many deaths. Once it became clear that this form of influenza was generally not as serious as expected, many concluded that the WHO had wrongly declared the epidemic to be a pandemic.

2 The severity of a pandemic is not only determined by how seriously ill people become and by the number of related deaths, it is also reflected by the number of people who become ill. The real concerns – for the Minister, the Health Council, RIVM, and others – were the consequences of large numbers of people simultaneously becoming ill with influenza. This possibility, which is not inconceivable in an epidemic caused by a new virus, may have received too little attention in the media. If large numbers of people were to call in sick, this could disrupt the very fabric of society. Moreover, given large enough numbers of influenza patients, even a very low rate of complications could involve large numbers of seriously ill patients. Indeed, there could be so many of them that hospitals and ICUs would no longer have the capacity to treat everyone. Accordingly, the severity of a pandemic is not determined by the severity of disease symptoms in individual patients.

3 Future decisions on whether or not to order vaccines will also be taken in the context of significant scientific uncertainty. The experts can analyse the available data as much as they wish, but this is ultimately a political decision involving the public health impacts of various scenarios. I am in favour of presenting the details of such scenarios to the House, so that others can contribute proactively and appropriately to the Minister's assessment of the situation. In the case of pandemics, as with decisions relating to defence or bank rescues, it may also be necessary to involve the Parliamentary Standing Committee on Public Health at an early stage in the proceedings.

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4 The Health Council is keenly aware that the debate on conflicts of interest is becoming increasingly important. In some areas of health research there is a long tradition of collaboration between academia and industry aimed at quickly transforming research results into new forms of diagnosis or treatment. This certainly applies to infectious diseases, where mortality and the burden of disease have been significantly reduced by the development of vaccines and antibiotics. Such close collaboration (which this government also aims to use in other areas of science) involves the possibility that individual experts may often carry out research that has been commissioned by industry, or that they may serve industry in an advisory capacity. For quite some time now, the Health Council has been wrestling with the issue of how to obtain advice from the best people in their field while at the same time being able to guarantee that such advice is truly independent. After going through the procedures again, I have made changes to some sections. I believe that the current procedures deliver maximum transparency both with regard to possible interests and to the prevention of undue influence on the advisory process in Health Council committees. I would like to consult with you, and with the Parliamentary Standing Committee on Public Health, to see whether this view is shared by others. After all, we cannot afford to have the Health Council's authority undermined at times when that very advisory process is absolutely essential.

Swine flu has come and gone, but the threat of a new pandemic is undiminished. This advisory report sets out details of the best stance to take in anticipation of any such development. The advisory report has been reviewed by the Standing Committee on Infection and Immunity. I endorse the conclusions of the Committee.

Now that no specific decisions need to be taken, I feel that some thought should be given to how to conduct a social debate on the significance of a major epidemic of infectious disease. Consideration should also be given to ways in which the government can limit the impact of such an event on public health. Most Dutch people routinely underestimate both the dangers of infectious diseases and the health gains from vaccination. Perhaps this would be a good time to consider how we might be able to change this situation. The Health Council would be delighted to engage in that particular debate.

Yours sincerely
(signed)
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to:

the Minister of Health, Welfare and Sport

No. 2011/40E, The Hague, December 15, 2011

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

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INAHTA

This report can be downloaded from www.healthcouncil.nl.

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Executive summary

Background and requests for advice

In this advisory report, the Health Council of the Netherlands addresses three requests for advice from the Minister of Health Welfare and Sport concerning the role of vaccination during influenza pandemics. A new category of influenza vaccines, capable of targeting the agents of potential future influenza pandemics, is now available. In 2007, with this in mind, the Minister asked whether the Netherlands would be better advised to use one of these *prepandemic* vaccines (against avian influenza virus (H5N1), for example).

Early in 2009, the advisory report was almost ready for publication when the Committee's work was overtaken by the news that a new influenza virus from Mexico (influenza A/H1N1 2009) was spreading round the world. This prompted the Minister to submit a second, urgent, request for advice concerning the role of vaccination in combating that particular virus.

Finally, in a third request for advice, the Minister asked the Health Council to include in the general advisory report (on the role of vaccination in preparation for an influenza pandemic) details of the lessons learned from pandemic influenza A/H1N1 2009 (also known as New Influenza A or Swine Flu).

Influenza: familiar, but unpredictable

Over the centuries there have been many human epidemics and associated deaths which, in retrospect, are thought to have been caused by influenza viruses. These vary considerably in terms of scope and severity. Epidemics in relatively limited areas of the world are interspersed with pandemics that affect entire continents or even the whole world. The latter are caused by novel influenza viruses against which the population has little or no resistance. Between 1510 and 2009, Europe suffered sixteen influenza pandemics, eight of which killed many more people than the annual seasonal flu. Inevitably, influenza pandemics will continue to occur from time to time.

New knowledge about influenza, the risk of a pandemic remains

Why is it so hard to predict when a pandemic will occur and what course it will take? The swine flu from Mexico generated significant new knowledge and insights, but that new understanding has not changed our assessment of the threat of pandemic influenza in general. It is still possible that mutation, or genetic reassortment (gene swapping) with other influenza viruses, might allow a virulent animal influenza virus to acquire traits that would facilitate its pandemic spread among people.

The influenza A/H1N1 pandemic produced important new insights into the virology, immunology, and epidemiology of influenza infections. The Committee summarises its main findings and describes their implications in terms of preparing for a future pandemic. Based on this improved understanding, the Committee concludes that our knowledge of the determinants governing the occurrence, nature, scope, and course of influenza pandemics is still incomplete. It is this very uncertainty that makes influenza pandemics so difficult to predict.

What can the government do?

A severe influenza pandemic is a major public health emergency, one that carries the risk of social disruption. One of the measures that the government can take is to vaccinate vulnerable individuals. These are primarily people with chronic cardiac and pulmonary diseases, those with reduced immunity, and the elderly. However, if a completely new flu virus is involved, then even healthy people are at risk. In such cases, it may be necessary to vaccinate the entire population. At the beginning of a pandemic, a vaccine may not yet be available. However, an

attempt can be made to ameliorate the effect of the pandemic as much as possible by rapidly deploying antiviral drugs to treat influenza patients and to protect their contacts against infection. It is also possible to take social measures aimed at limiting infections, such as avoiding public gatherings and high-risk contacts. This advisory report focuses on the role of vaccination.

New influenza vaccines on the way

Any assessment of the role of vaccination in preparation for future influenza pandemics must take account of three major developments. Firstly there are the above-mentioned prepandemic vaccines, which are based on the potential agents of future pandemics, such as H5N1. In theory, this makes it possible to be better prepared for a pandemic, by ensuring production capacity, or even by building up stocks of vaccine.

The second such development is that, thanks to improved production methods, the spectrum of activity of modern influenza vaccines can extend beyond the specific viral strain that was used to develop them. As a result, their versatility is greatly enhanced.

Finally, it is important to note that, over the longer term (at least ten years), vaccines based on proteins common to all influenza viruses are expected to become available. These will have an even wider spectrum of activity, against a range of virus sub-types.

Conclusions and recommendations

Influenza A/H1N1 2009 had probably been circulating in pigs for some time before it first caused disease in people, an event which led to its discovery. The improved monitoring of influenza viruses, together with the routine exchange of information between those veterinary and medical authorities who are responsible for such surveillance, means that it should be possible to identify and investigate pandemic threats at an earlier stage. The Committee recommends that the surveillance of influenza infections in pigs and poultry be carried out at international level. This should also be routinely supplemented by the monitoring of influenza infections and related complaints in people who work with such animals.

It has proved difficult to carry out an early and rapid assessment of the H1N1 influenza pandemic’s impact. The Committee recommends a cooperative

approach, involving international networks for combined clinical and public health research, to accelerate information flows during future pandemics.

Influenza is even less predictable than we thought. Partly for this reason, the Committee cautions against entering into contracts with manufacturers, at this stage, for the supply of vaccine in the event of a pandemic. Experience has shown that it is important to be fully conversant with the material in question, and to exchange information with fellow institutes in other countries. This enables recommendations concerning the role of vaccination (and government decisions in this regard) to be made quickly and adequately during an influenza pandemic.

Inevitably, during a pandemic, it is necessary to make decisions before scientific research data becomes available in any detail. Accordingly, it must be accepted that risk assessment and precautionary measures also have a part to play in influenza prevention. In each individual decision, efforts will be required to find a balance between precautionary measures and the avoidance of unnecessary vaccinations.

Chapter 1

Introduction

1.1 Global flu

In 2009, it again became clear that influenza is often full of surprises. While experts throughout the world were preparing for a pandemic involving the H5N1 avian influenza virus, a new virus (A/H1N1 2009) emerged, causing influenza on a massive scale across the southern hemisphere. Also, contrary to the general expectation, this virus did not originate in birds in Asia, but in pigs in Mexico. For the Health Council of the Netherlands, this "surprise" meant that the pandemic advisory report (on which a specially appointed committee had started work in late 2007) had to be put on the back burner. This enabled the Council to rapidly assist the Minister of Health, Welfare and Sport by providing advice on measures to counter the threat of pandemic "Mexican Flu" (influenza A/H1N1 2009 or "Swine Flu"). That turbulent interlude has generated a great deal of new knowledge about influenza and vaccination against this disease. In this advisory report, the Committee responds to the Minister's question concerning the role that vaccination might play in preventing and limiting the effects of an influenza pandemic in the future. Here, it draws on its own evaluation of recent experience, and on specific aspects of that experience.

1.2 Several questions and interim advisory reports

Typically, an advisory report is based on a single request for advice, but here the advisory report in question derives from three such requests (Annex A), plus a number of interim questions.

The Minister posed the first question on 12 November 2007. This was prompted by the introduction of new category of influenza vaccines. These prepandemic vaccines target the potential agents of future pandemics, such as influenza virus A/H5N1. The Minister wanted to know what part vaccination might play in preparing for an influenza pandemic (see Annex A). To answer this question, the President of the Health Council established the Committee on Vaccination Against Pandemic Influenza on 18 September 2007 (Annex B). Early in 2009, the advisory report was almost ready for publication when the Committee's work was overtaken by the news that a new influenza virus from Mexico (influenza A/H1N1 2009) was spreading round the world. On 29 April 2009, this prompted the Minister of Health, Welfare and Sport to request an emergency advisory report (Annex A). The Committee issued the requested report on 8 May 2009.[1] Finally, in a supplementary request for advice (Annex A), the Minister asked that details of experiences with pandemic influenza A/H1N1 2009 be included in the advisory report.

During the pandemic of influenza A/H1N1 2009, the Minister of Health, Welfare and Sport asked the Health Council, together with the National Institute for Public Health and the Environment (RIVM), to advise on target groups and vaccination doses. The objective was to link scientific advice with practical implementation. In all, four advisory reports were issued in these areas, drawn up on the basis of meetings involving panels of experts.[2-5] Advisory reports issued after the pandemic, in April and August 2010, included assessments of the extent to which it makes sense to vaccinate children and pregnant women against influenza outside the context of the pandemic.[6,7]

In the summer of 2011, the Committee resumed work on the advisory process relating to the role of vaccination in general, as part of the preparations for an influenza pandemic. The Committee held hearings on 29 June 2011 with the most relevant manufacturers in the Netherlands, to fully acquaint itself with recent advances in the development of new influenza vaccines. Ten questions were submitted to each of these manufacturers (Annex C).

1.3 Structure of this advisory report

In Chapter 2, the Committee describes the main aspects of our current understanding of influenza. The Swine Flu from Mexico came as a surprise and provided many new insights. It is worth noting that the pandemic threat has not changed substantially since then, as this is associated with the continued presence of influenza viruses in animals.

Chapter 3 outlines the advice given by the Health Council during the Swine Flu pandemic. At that time, allowance always had to be made for numerous uncertainties. Efforts were made to find a balance between precautionary measures and the avoidance of unnecessary vaccinations. The Committee gives details of the contents of those advisory reports. It also examines the issues of what went right and what can be done better next time.

Chapter 4 describes the latest developments in vaccinology. What can we expect from prepandemic vaccines, pandemic vaccines, and, finally, from future types of vaccine?

The advisory report closes with conclusions and recommendations concerning the role of vaccination in a future influenza pandemic.

Chapter 2

Influenza: familiar, but unpredictable

Human populations have been infected by waves of influenza at regular intervals for many centuries. Why is this, and why is it so hard to predict when a pandemic will occur and what course it will take? In this Chapter, the Committee describes the main aspects of our current understanding of influenza. It also addresses the issue of why experts were particularly fearful of the risk of an avian influenza pandemic spreading from Asia. The Swine Flu from Mexico came as a surprise and provided many new insights both in terms of what we do know, and of what we don't know. The main conclusion of this Chapter is that there has been no substantial change in the pandemic threat.

2.1 Previous pandemics

For more than five hundred years (and possibly for well over a thousand years) there have been many human epidemics involving morbidity and mortality which, in retrospect, are thought to have been caused by influenza viruses. With regard to the epidemics of the twentieth century, virological tests have shown that this was indeed the case. These epidemics varied considerably in terms of scope and severity. Some involved mass fatalities, others did not. Annual epidemics in relatively limited areas of the world (North and South hemispheres) are interspersed with pandemics that affect entire continents, or even the entire globe. The latter are caused by novel influenza viruses against which the population has little or no resistance (the term "pandemic" derives from the

Greek: παν (pan)= all; δεμος (demos)= the people). As phenomena, influenza pandemics are not easy to explain. They are the result of a number of interacting, poorly understood, viral evolutionary events.[8]

There were three influenza pandemics in the twentieth century: the Spanish Flu of 1918-1919 (H1N1), the 1957 Asian Flu (H2N2), and the Hong Kong Flu in 1968 (H3N2). The Spanish Flu in particular, which caused an estimated fifty million to one hundred million deaths worldwide (about 20 000 in the Netherlands), is a nightmarish example of how severe an influenza pandemic can be.

Despite the experience gained during these three pandemics, it is still not possible to predict, with any certainty, whether a new influenza virus will spread pandemically. At the start of 1976, in response to an impending pandemic based on human infections with the Hsw1N1 virus (Swine Flu), the Centers for Disease Control (CDC) in the United States sounded the alarm. In January 1977 it emerged that the Hsw1N1 virus was incapable of pandemic spread. The mass vaccination campaign that was already in progress was then abandoned.

Similarly, it is no easy task to predict the burden of disease associated with an influenza pandemic. In 1977, for example, an H1N1 virus spread throughout the world. This had clear similarities to the variants of Spanish flu virus that had continued to circulate until 1957. Unlike the earlier form of Spanish Flu, however, the worldwide spread of that particular H1N1 virus was associated with relatively low morbidity and mortality.

2.2 Avian influenza viruses

All influenza A virus infections originate from epizootic infections, i.e. infectious diseases of animals. Infections with influenza A viruses are wide-spread in the animal kingdom, especially in waterfowl. These viruses, which are well adapted to their host, occur in the gastrointestinal tract and generally do not cause any disease symptoms. Waterfowl, including ducks and waders, are the natural reservoir of influenza A viruses. Accordingly, the greatest diversity of viruses is seen in these hosts. Aside from waterfowl, influenza A viruses occur in chickens, pigs, horses, dogs and cats.

Influenza A viruses are divided into subtypes based on the composition of proteins on the surface of the virus particles. This involves 16 different subtypes of haemagglutinin (H) and 9 different subtypes of neuraminidase (N). All of these subtypes are found in birds. However, the influenza viruses that have infected humans on a large scale in the past, or which continue to circulate in the form of seasonal influenza viruses, are much less diverse (H1N1, H2N2, H3N2).

Furthermore, subtypes H5N1 and H7N7 have been virologically confirmed in human infections (and, occasionally, H7N2, H7N3, and H9N2) without widespread circulation.

The influenza viruses found in water birds and waders are not easily transmitted to humans. For instance, infections with avian influenza viruses are seldom found in duck hunters and others who come into contact with wild birds.[9,10] One possible explanation is the presence of specific α-2,3-neuraminic acid receptors in the epithelium of the intestinal and respiratory tracts of waterfowl, for which specific influenza viruses have a high affinity (binding propensity). These bird-like receptors differ from the human-like α-2,6-receptors found in the human upper respiratory tract, for which human influenza viruses have a particular affinity.[11] However, bird-like receptors are found in the lower respiratory tracts of humans.[12,13]

2.3 Pigs and poultry as intermediate hosts

An important question is "Under what circumstances can avian influenza viruses cause infections in humans?". Intermediate hosts can play an important part in this respect. In addition to receptors for avian influenza viruses (bird-like receptors), the respiratory tracts of pigs and poultry, for example, also contain receptors to which human influenza viruses can bind (human-like receptors). Once they have entered an intermediate host, avian influenza viruses can acquire – by mutation or genetic reassortment (gene swapping) – an affinity for receptors in the human respiratory tract.

Influenza A viruses in pigs can be transmitted to humans relatively easily. Accordingly, infections with swine influenza viruses are common among pig farmers.[14] In this way, avian influenza viruses can pass through pigs (as intermediate hosts) and ultimately cause infections in humans. Poultry, too, is seen as an important intermediate host for avian influenza viruses, and as a "melting pot" for influenza viruses. Human-like receptors have been found in the respiratory tracts of chickens. Through, as yet, poorly understood selection processes, these viruses can become more virulent as they circulate in poultry, ultimately causing avian influenza. H5N1 is an example of a virus that is pathogenic to both waterfowl and poultry, as well as to humans.

2.4 Fear of avian influenza in humans

H5N1 influenza viruses have been causing epidemics among birds since 1997. Remarkably, in contrast to previous years, highly pathogenic forms of these

viruses were also found in wild birds. Hundreds of cases of human illness, due to H5N1 infections, have also been reported. Sixty percent of these individuals died, hence the heightened focus on H5N1 as a potential agent of a future pandemic. The H5N1 avian influenza virus meets two important conditions for causing a pandemic. Firstly, the virus can infect humans and, secondly, there is little immunity against the virus in the population. However, it does not meet an important third condition – the virus is not yet easily transmitted from one person to another.

Ever since the emergence of highly pathogenic H5N1 avian influenza viruses in Asia, experts have feared that mutation or genetic reassortment will enable these viruses to spread through the human population, creating the launch pad for a new pandemic virus. Many cases of H5N1 infection in humans have been reported from Indonesia, Vietnam, Thailand, China, and Egypt. It is thought that there is a particularly high risk of an H5N1 pandemic developing in Asia. In that part of the world in particular, large numbers of people live cheek by jowl with potentially infected chickens and other types of poultry. The pressure on ecosystems is compounded by the poor screening of domestic poultry from wild birds. The region is densely populated, and live poultry and wild birds are sold at markets. This high population density provides the ideal conditions for viruses to spread between people, even those viruses that cannot be easily transmitted. Under these conditions, it is deemed that there is a substantial risk of influenza viruses from birds making the jump to humans, and causing morbidity and mortality on a significant scale. [15-17]

The fear is that, either through mutation or genetic reassortment with other influenza viruses, H5N1 will acquire the ability to be readily transmitted from one individual to another. A recent report in New Scientist suggested that this is indeed possible. The article concerned the results of a Dutch study in ferrets, which has yet to be published in a peer reviewed journal. According to New Scientist, that study revealed that just a few mutations might be all that is needed to bring this about.[18]

H5N1 is not the only influenza virus from which a pandemic variant could develop. In 2003, a remarkable epidemic of avian influenza broke out in the Netherlands. This was caused by an H7N7 virus. A novel feature of this epidemic was the unprecedented ease with which this virus could be transmitted to humans, and also give rise to symptoms.[19,20] Symptomatic infections were confirmed in 86 individuals working in the poultry sector and in three of their family members. One veterinarian who had acquired an infection died from acute respiratory distress syndrome.[21] Serological testing indicated that at least a

thousand people became infected.[22] Thirty million chickens either died from influenza or were "preventively" culled.[20]

2.5 The surprise of 2009

In 2009, while the experts' fears were still centred around a pandemic caused by the H5N1 avian influenza virus, a pandemic of influenza A/H1N1 2009 developed, caused by a new type of H1N1. This new virus had characteristics found in both North American and Eurasian swine flu viruses. Some of its gene segments had, at different times, jumped the species barrier between birds, pigs, and humans. This form of influenza was initially named Swine Flu, after its intermediate host. Others referred to it as Mexican Flu, after its country of origin. Here, we will refer to it using its neutral scientific designation: influenza A/H1N1 2009.

The "surprise of 2009" does not mean that the risk of a pandemic caused by H5N1 or another avian influenza virus has gone away. The lesson here is that, where influenza is concerned, we should always be prepared for surprises.

2.6 New knowledge about influenza

2.6.1 Influenza appears to be even less predictable than we previously thought

Influenza A/H1N1 2009 has clearly given a strong impetus to research into the underlying processes of an influenza pandemic. It has also greatly enhanced the body of knowledge in this area. Based on this improved understanding, the Committee concludes that our knowledge of the determinants governing the occurrence, nature, scope, and course of influenza pandemics is still incomplete. It is this very uncertainty that makes influenza pandemics so difficult to predict.[8]

Aside from the source of a pandemic, it is also difficult to predict the extent to which a virus (pandemic or otherwise) will cause disease symptoms. Studies of H5N1 viruses, H7N7 viruses and previous pandemic viruses have identified combinations of mutations that were associated with increased virulence. However, this combination was not found in the new pandemic H1N1 virus, nor was the literature of any assistance in predicting the course of this outbreak.[23]

2.6.2 Worldwide spread, but not in all age groups

The term "pandemic" refers to the worldwide spread of a virus. This form of influenza A/H1N1 2009 had not previously been encountered in humans or

animals. Furthermore, there was a substantial antigenic difference between its haemagglutinin and that of the circulating H1N1 seasonal influenza virus. These considerations led people to expect that there would be little immunity to the new virus. It was feared that there might be a great many infections, possibly resulting in considerable morbidity and mortality. However, things did not work out that way. Many people over the age of 65 were found to possess antibodies that limited their susceptibility to the virus. The majority of deaths occurred among children and adolescents. In the United States, the respective risks of mortality in these age groups were 4 to 7 and 8 to 12 times greater than that from seasonal influenza in the period from 1976 to 2001.[24]

In retrospect, older people were probably protected against influenza A/H1N1 2009 by previous contact with H1N1 strains descended from the Spanish Flu virus. The H1N1 variant that circulated until 1945 is now known to elicit antibodies that cross-react with influenza A/H1N1 2009. Another H1N1 variant has circulated since 1945. Antibodies against that variant do not cross-react with influenza A/H1N1 2009. The immune system provides two-pronged protection against infectious diseases. This involves a humoral immune response via antibodies and a cellular immune response that is mediated by T cells. If present, antibodies can prevent such infections. If infection does occur, then T cells are needed to clear the virus once the disease has run its course. While cellular immunity, as such, does not prevent infection, it may help to alleviate disease symptoms. The relatively mild course of influenza A/H1N1, even in those below the age of 65, might mainly be due to priming of the cellular immune system by H1N1 viruses from 1945 to 1957, and after 1977. This would create an immunological memory that, on exposure to A/H1N1 2009, triggers rapid anamnestic antibody production that protects against this type of influenza. Studies using animal models have clearly demonstrated the feasibility of similar wide-spectrum protection based on cellular immunity.[25,26]

The influenza A/H1N1 pandemic has therefore helped to create a new understanding of the immune response. Cellular immunity plays a greater part than previously thought in the protection derived from previous exposure to other influenza viruses.

2.6.3 *It is difficult to rapidly assess the burden of disease in a pandemic*

It is difficult to make a rapid, early assessment of how seriously ill the victims of an influenza pandemic will become. All pandemics involve a range of serious and more mild disease symptoms. Initial reports from Mexico and the southern U.S. indicated that the influenza A/H1N1 2009 pandemic was associated with a

relatively wide range of severe disease symptoms. Subsequent details from other parts of the U.S. indicated that many infected individuals in those areas exhibited only mild disease symptoms. Some groups were being prospectively monitored, but it took a long time before this data became available. Ultimately, however, this enabled systematic information about the clinical course of this disease to be collected. It is crucial to obtain information on the spectrum of disease symptoms, and on the course of the disease in hospital patients and individuals in the general population. This is the only way to assess the impact of a pandemic, determine the best response, and identify essential, effective measures.[27] Finally, it is important to realise that, mutations and/or genetic reassortment can change the burden of disease associated with a pandemic (as a function of virulence, infectivity and immunity in the population; see Section 2.6.6). The risk of this is probably greatest at the start of a pandemic, when there are numerous infections (involving rapid viral replication) in a population.

2.6.4 *Significant time savings at the start of a pandemic*

On the advice of the Health Council, the government had previously purchased stocks of antiviral drugs for use in an influenza pandemic.[28,29] There were sufficient antiviral drugs (the neuraminidase inhibitors oseltamivir and zanamivir) for one third of all inhabitants of the Netherlands. These drugs were to be used to delay the initial stages of a pandemic, and to subsequently treat all patients with an influenza-like clinical picture. The Health Council had recommended the use of post-exposure prophylaxis (with neuraminidase inhibitors) at the start of a pandemic. The target group would be new patients' family members, housemates, and other close contacts. This approach is subject to the provision that there are only a limited number of cases of illnesses involving a small number of patients and that these patients can be traced shortly after becoming ill. It has been shown that seven or ten days of post-exposure prophylaxis can cut the incidence of influenza in treated families. Furthermore, it reduces viral shedding in those individuals who, despite post-exposure prophylaxis, go on to become ill.[28,29] This policy was implemented in the pandemic of influenza A/H1N1 2009. The provision of antiviral drugs was restricted when it became clear that the influenza A/H1N1 2009 virus had only a low level of virulence.[30]

It was indeed the case that, at the start of the pandemic in the Netherlands, individual infections seldom led to further spreading of the disease.[31,32] Similar results were obtained elsewhere.[33] There are several possible explanations for this. One involves lower rates of transmission of infection in the summer (or late

summer), due to environmental factors such as higher humidity and/or less crowding, as well as to the effectiveness of antiviral prophylaxis. If these findings can be extrapolated to other situations, it is reasonable to conclude that the use of post-exposure prophylaxis could result in significant time savings before a vaccine becomes available.

2.6.5 *Influenza A/H1N1 2009: did it start in pigs or people?*

The viruses that gave rise to the influenza A/H1N1 2009 virus, through a process of genetic reassortment, had already been circulating for some time among pigs in Eurasia and North America. The A/H1N1 2009 virus also has some characteristics of avian influenza viruses and human influenza viruses, but it is unclear exactly when this genetic reassortment occurred. At the time of the pandemic, the A/H1N1 2009 virus had never before been detected in pigs, despite the surveillance activities carried out by such countries as China.[34]

It might be possible to detect the virus at an earlier stage through the improved monitoring of potential pathogens and of disease in animal populations (from which infections might jump to humans). Whether or not this would facilitate more effective disease control, however, is very much open to question. The possibility cannot be excluded that the final genetic reassortment occurred in another species or, indeed, in humans.[34-36]

Another problem is that influenza is common in pigs and is not regarded as being sufficiently serious to justify large-scale monitoring in this group of animals. Accordingly, relatively little is known about the occurrence of influenza in pigs. To date, human surveillance has not focused on the early detection of human infections resulting from contact with animals. As a result, it is likely that new infections will either go unnoticed or that they will only be detected when severe symptoms occur.

2.6.6 *The impact of a pandemic*

The various influenza viruses certainly differ in terms of their pathogenicity. As stated, H5N1 infections in humans, for example, are associated with a high level of mortality. As many as 60 percent of those who develop symptoms ultimately die from this disease. The Spanish Flu of 1918-1919 is also thought to have been caused by a highly virulent virus. Indeed, there is evidence that the mortality rate at that time was around 2.5 percent, a factor of 10 to 100 higher than those of recent pandemics. Scientists recently succeeded in reconstructing this virus from the bodies of two groups of American soldiers who died of Spanish Flu during

the First World War. The first group died before the disease began to spread pandemically, while the second group died during the pandemic. In 13 cases, RNA sequence analysis of the domain encoding the part of the virus that binds to the haemagglutinin receptor suggested that a shift from avian-like to human-like specificity took place between the early and later cases. However, no commensurate difference was found between the two groups in terms of the distribution of viral antigen in the upper and lower respiratory tracts. Accordingly, it is not clear whether the identified mutations were fundamentally responsible for the pandemic spread of this virus.[37]

Aside from their virulence, pandemics mainly differ in terms of the scale of the disease burden involved. In all cases, the vast majority of infections have a benign course. However, complications and mortality still occur in a small percentage of patients. In the case of very large-scale pandemics, however, even that small percentage corresponds to a large number of patients. This can have a large impact, and a corresponding risk of social disruption. Thus the scale of a pandemic is the most important determinant of its impact. That scale, in turn, mainly depends on the infectivity of the influenza virus in question, and on the susceptibility of the population concerned. Finally, the impact of a pandemic appears to be related to the season in which the peak occurs. Half of the sixteen influenza pandemics that struck Europe between 1510 and 2009 were associated with significantly increased mortality, and all eight of them occurred during the winter. The mild pandemics either peaked in the summer or emerged during the spring and spread more slowly during the summer, with a small peak in the winter. That pattern was also seen in the pandemic of influenza A/H1N1 2009.[8]

2.7 There has been no substantial change in the pandemic threat

In the aftermath of the influenza A/H1N1 2009 pandemic, there has been no substantial change in the pandemic threat. That relatively mild pandemic generated significant knowledge and insights, but this has not changed our assessment of the threat of pandemic influenza in general. It is still possible that mutation, or genetic reassortment with other influenza viruses, might allow H5N1 to acquire traits that would facilitate its pandemic spread. Recent research has shown that only a few mutations might be sufficient to bring this about.[18]

The possibility remains that an influenza virus other than H5N1 could evolve into a form that is capable of causing a pandemic. More influenza pandemics are likely to occur in future, but no accurate predictions can be made concerning the exact timing of these events, or about the identity of the viral agents involved. All preparations for a future pandemic should allow for a small, but real, risk of a

large-scale public health emergency. These measures should also be sufficiently flexible to be able to respond to unexpected developments.

Chapter 3

Influenza A/H1N1 2009: looking back and looking forward

Any advisory report into the role of vaccination in preparation for an influenza pandemic must, of necessity, allow for numerous uncertainties. Wherever possible, the Health Council bases its recommendations on the current level of knowledge. In areas where that approach falls short, the group of experts harness their knowledge and experience to give the Minister the best possible advice. In the case of the influenza A/H1N1 2009 pandemic, efforts had to be continually made to find a balance between precautionary measures and the avoidance of unnecessary vaccinations. This Chapter first sets out details of the Council's advisory reports and the considerations involved (3.1), followed by a review and a look forward (3.2).

3.1 The advisory process on vaccination against influenza A/H1N1 2009

3.1.1 In situations of uncertainty, decisions are based on risk assessment and the precautionary principle

During a pandemic, it is sometimes necessary for the Health Council to issue advisory reports, and for the government to make decisions, before scientific research data becomes available. Under such circumstances, policy is shaped more by risk assessment and precautionary considerations than by scientific data.[38]

One example of this is the Minister's decision to order vaccine. On 29 April 2009, the Minister of Health, Welfare and Sport asked the Health Council to prepare an advisory report on this matter. At that time, there was still a great deal of uncertainty and the question of whether or not to order vaccine was a political decision. In the advisory report that it issued on 8 May 2009, the Council set out the pros and cons of the various options. It stated: "In this uncertain situation, there are various policy options: 1) adopt a wait-and-see policy until there is greater clarity concerning the risk of the Mexican flu virus giving rise to a pandemic, and 2) take steps now to purchase a vaccine against the virus. The first option saves money now but suffers from the disadvantage that ordering vaccine at a later date (if this eventually proves to be necessary) may mean that it will be delivered too late to be of any use, or that none can be delivered at all. One advantage of the second policy option is the sure and certain knowledge that, in an uncertain situation and within the bounds of what is reasonable, every possible measure has been taken to minimise a serious health risk. (...)". On 19 June 2009, the Minister ordered adjuvanted vaccine against influenza A/H1N1 2009 which, once it became available in the autumn of 2009, could be used to combat the pandemic. To reduce the risk of limited or delayed delivery, the Minister ordered vaccines from two different manufacturers: Novartis and GSK.

As stated, the Minister of Health, Welfare and Sport asked the Health Council, together with the National Institute for Public Health and the Environment (RIVM), to advise on target groups and vaccination doses. The objective was to link scientific advice with practical implementation. The Health Council and RIVM have always emphasised that a decision to purchase vaccine should be seen as a distinct and separate issue from a decision to actually deploy these vaccines. The latter decision should be based on a subsequent, separate, and careful evaluation of epidemiological, clinical and virological data.

3.1.2 *An assessment framework and criteria*

During the advisory process on vaccinations in public programmes, the Health Council remains mindful of the fact that the public must be provided with the best possible protection against infectious diseases, and that this is particularly true of vulnerable groups. In addition, the continuity of the health service must also be guaranteed. To assess whether vaccination contributes to these goals, the Health Council uses clear criteria (see Frame) which are explained in its advisory report entitled "The future of the National Immunisation Programme: towards a programme for all age groups" (2007).[39,40]

Criteria for the inclusion of vaccination (of a particular group) in a public programme.[39,40]

Seriousness and extent of the disease burden

1 The infectious disease causes considerable disease burden within the population
   - The infectious disease is serious for individuals, and:
   - The infectious disease affects or has the potential to affect a large number of people.

Effectiveness and safety of the vaccination

2 Vaccination may be expected to considerably reduce the disease burden within the population.
   - The vaccine is effective for the prevention of disease or the reduction of symptoms.
   - The necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought).
3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4 The inconvenience or discomfort that an individual may be expected to experience *in connection with his/her personal vaccination* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
5 The inconvenience or discomfort that an individual may be expected to experience *in connection with the vaccination programme as a whole* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

Efficiency of the vaccination

6 The balance between the cost of vaccination and the associated health benefit compares favourably to that associated with other means of reducing the relevant disease burden.

Priority of the vaccination

7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

The Health Council and RIVM used the assessment framework during the advisory process on vaccination against influenza A/H1N1 2009 (and during the advisory process relating to the role of vaccination in general, as part of the preparations for an influenza pandemic). Based on the available scientific literature and the associated arguments, vaccination for the various potential target groups was tested against seven criteria for inclusion in a public programme. The strength of the evidence obtained in published studies, and their limitations, are factors that are always taken into consideration. In this case, many details were still missing, however the framework itself provided a degree of guidance. The framework was also helpful in identifying areas in which vital scientific data was missing. Accordingly, risk assessment and the precautionary principle have a part to play in evaluation and in the advisory process. Details are given of the contexts in which they were used.

3.1.3 Vaccination for high-risk groups only

At various points in time, the Health Council and RIVM assessed the situation to see whether they should advise the government to offer vaccination to the entire population. On each of these occasions, however, their assessment was negative. If the virus had mutated into a more pathogenic strain, then it would have been appropriate to make a positive recommendation, to keep the health risks within acceptable limits. This situation did not arise.

The main objective of vaccination against influenza A/H1N1 2009 was to protect medically vulnerable groups. To protect such groups, in their advisory reports of 17 August and 17 September 2009, the Health Council and RIVM recommended vaccination for everyone in those medical high-risk groups that are eligible for the annual vaccination against seasonal influenza, as well as for all healthy individuals aged 60 and above. They also recommended that any healthcare workers coming into contact with these individuals should also be vaccinated. This would also make it possible to meet the second objective, of guaranteeing the continuity of the health service.[2,3]

Scientific publications reported that even healthy pregnant women can become seriously ill, and some may even die, as a result of infection with influenza A/H1N1 2009. Accordingly, on 9 November 2009, the Health Council and RIVM recommended that vaccinations should be given to all expectant mothers who are at least four months into their pregnancy. The same advisory report extended the recommendation on vaccination to infants/children from 6 months to 4 years of age, and to the housemates of babies up to five months of age. The latter recommendation was prompted by the increased burden of disease

in this age group and by the increasing risk that intensive care units for children would become overloaded.[4]

At the time of the pandemic, vaccination was offered to all of the above-mentioned groups. Two new target groups – pregnant women and young children – were added to the list of those eligible for the usual seasonal influenza vaccination. The question then arose of whether these new target groups should also be offered vaccination against seasonal influenza in the following season. The main causes of seasonal influenza in 2010-2011 were, in Europe, the new A/H1N1 influenza virus and, in North America, influenza A/H3N2.

On 8 April 2010, the Health Council and RIVM concluded that, outside the context of the pandemic, it would not be appropriate to vaccinate young children or the housemates of babies up to five months of age. It had meanwhile emerged that, during the 2009-2010 season, the incidence of illness and complications resulting from influenza A/H1N1 2009 was no greater than is normal for seasonal influenza, even in young children. The healthcare system did not become overloaded.[6] The same was true in the United States.[41]

On 31 August 2010, the Health Council examined at greater depth the issue of whether healthy pregnant women should be offered vaccination during the flu season (as was the case during the pandemic). This is the usual procedure in most other countries. Meanwhile, more data on the effects of influenza A/H1N1 during pregnancy was now available than had been the case during the pandemic. Pregnant women were found to have an increased risk of hospitalisation, of admission to an ICU, and – potentially – of death. However, it appeared that other medical risk factors were mainly responsible for the greater vulnerability of pregnant women (compared to other women of childbearing age). While hospital admissions do occur in the group of pregnant women without a medical risk factor, there are few cases of admission to an ICU, and even fewer deaths (to date, in the Netherlands, none at all). In this group, it is estimated that at least fifteen hundred women would have to be vaccinated to prevent just a single hospital admission. The Council concluded that, given the limited burden of disease in healthy pregnant women, a general offer of vaccination to this group outside the context of the pandemic could not be justified. The Council took the view that, when providing information to pregnant women with medical risk factor, general practitioners, obstetricians and gynaecologists should give the greatest possible emphasis to the importance of vaccination for this group of patients.[7]

In summary, both during a pandemic and at other times, the advisory process relies primarily on the available scientific knowledge. Unavoidably, however, the

Council's advisory reports sometimes anticipate data from scientific research. In such cases, risk assessment and precautionary considerations are also taken into account. This meant that the Committee was sometimes compelled to deliver recommendations in the absence of conclusive scientific evidence. These recommendations were revised, if this was deemed necessary in the light of increasing knowledge.

3.1.4 *Sole use of adjuvanted vaccine*

To ensure the timely delivery of vaccine, it was necessary to take decisions about the nature of the vaccine in question at an early stage. Based on an analysis of its genetic and antigenic properties, the WHO found that influenza A/H1N1 2009 differed markedly from the H1N1 strain then being used in the seasonal influenza vaccine. This finding indicated that the vaccine's efficacy would probably be substantially reduced as a result. Based on studies of vaccines against avian influenza viruses, a non-adjuvanted vaccine based on the pandemic virus A/H1N1 2009 was expected to have only limited efficacy. Given that a completely new influenza virus was involved, it was anticipated that full immunity would have to be developed from scratch, even with the existing target groups for vaccination against seasonal influenza.[42-44] This reasoning would be all the more applicable if the decision was taken to extend vaccination to target groups that would not normally be vaccinated against seasonal influenza, such as children. The Committee endorsed these considerations in its advisory report of 8 May 2009.[1]

Scientific research into the H5N1 and H5N3 influenza viruses revealed that non-adjuvanted vaccine was relatively ineffective in immunologically naive populations.[42-44] Accordingly, where exposure to a completely new influenza virus is involved, adjuvant (an agent that enhances the immune response) is added to the vaccine. Adjuvants are very commonly used in vaccines. Indeed, most vaccines (including those against common childhood diseases) contain one or more of these substances. Influenza vaccines have always been an exception to this rule, as conventional adjuvant has always been relatively ineffective in such vaccines. However, adjuvants have now been developed that do work well with influenza vaccines.

The Council also stated that the virus might mutate into a more pathogenic strain. Here too, effective protection requires a robust, broad-spectrum immune response. Accordingly, if the Minister decided to proceed with the purchase of a vaccine, the Committee concluded that it would be preferable to use an adjuvanted vaccine based on the A/H1N1 influenza virus.[1] A vaccine based on

whole killed virus, without added adjuvant, was also an option. One such vaccine, which contains "natural" adjuvant, was produced by Baxter. That vaccine, too, was characterised by broad-spectrum efficacy, however there was no guarantee that it could be supplied in sufficient quantities.

On 19 June 2009, partly in response to this advisory report, the Minister of Health, Welfare and Sport placed orders with two separate manufacturers for adjuvanted vaccine against influenza A/H1N1 2009 which, when it became available in the autumn of 2009, could be used to combat the pandemic. The Novartis vaccine (*Focetria*) was used to vaccinate individuals in medical high-risk groups, healthy pregnant women, those aged 60 and above, and healthcare workers. The GSK vaccine (*Pandemrix*) was used for the vaccination of infants/children from 6 months to 4 years of age.

MF59, the adjuvant used by Novartis, had already been used extensively in vaccines against seasonal influenza. GSK's adjuvant, AS03, had been tested in a Phase III trial of prepandemic vaccine against H5N1. Yet data about the possible adverse effects of these new, adjuvanted, influenza vaccines overall was limited. For this reason, the Health Council and RIVM have always insisted that particular attention should be paid to the monitoring of adverse effects, and to the link between vaccination and disease registries.

Especially with regard to vaccination during pregnancy, some object to the fact that the only vaccine available in the Netherlands was adjuvanted vaccine. The WHO's stated preference is that pregnant women should only be immunised with non-adjuvanted vaccines. However, the WHO also indicated that, if no such vaccines were available, health authorities could also opt for an adjuvanted vaccine. On theoretical grounds, the possibility of a risk to the foetus cannot be excluded, particularly in the first trimester. Theoretically, there should be a much smaller risk to the foetus during the second and third trimesters of pregnancy, and this period coincides with the greatest risk of influenza. Accordingly, the Health Council and RIVM recommended that vaccination should be restricted to the second and third trimesters of pregnancy. This would eliminate any objections to the use of adjuvanted vaccine.[3,4]

Adjuvanted vaccines may not be entirely risk-free. An increased frequency of narcolepsy was reported among adolescents in Sweden and Finland following the use of *Pandemrix* (a vaccine that was also used in the Netherlands). While no such increase was reported for this vaccine in other European states, these countries did not generally classify adolescents as a target group for vaccination against pandemic influenza. Recent reports from China indicate an increased frequency of narcolepsy at the time of the pandemic. Vaccination was not an issue here, so a possible explanation for the occurrence of narcolepsy might be

the influenza infection itself.[45] Research is currently under way in Europe to find an explanation for these symptoms.

In summary, the decision to use adjuvanted vaccine was prompted by a consideration of the available scientific data on the efficacy of such vaccines, coupled with the assessment that the new virus was so different that a significant proportion of the population would have little protective immunity against it. In the absence of any known or suspected risks, the use of adjuvanted vaccine was also recommended for pregnant women in the second and third trimesters of pregnancy.

3.1.5 *Two injections, or is one enough?*

The vaccination schedule (one or two doses) offered more scope for postponing a decision on this matter than had been the case with regard to the decision to purchase vaccine. In its 8 May 2009 advisory report, the Health Council stated that it could not yet say whether one or two doses were required for effective protection. However, the Council considered it likely that two doses would be needed. As with the use of adjuvant, its reasoning was based on studies involving vaccination against antigenically very distinct viruses. This was even more applicable to population groups that are known to generate a weaker immune response after vaccination, such as individuals in medical high-risk groups, the elderly, and young children. The Minister of Health, Welfare and Sport then ordered sufficient vaccine to provide two doses for the entire population of the Netherlands, should that prove necessary.

A/H1N1 2009 was the first influenza pandemic in which – in some parts of the world – governments succeeded in making sufficient amounts of specific vaccine available more or less on time. The requisite preliminary research was conducted on H5N1, the influenza virus which had previously given rise to fears of a pandemic. In the case of H5N1, it was found that two doses of adjuvanted vaccine were required for vaccination to be fully effective. Using a special, fast-track procedure, the European Medicines Agency (EMA) assessed the suitability of vaccines in which the H5N1 virus had been replaced by the pandemic H1N1 virus. Based on this assessment, these vaccines were registered for administration in a two-dose vaccination schedule.

In the advisory reports issued on 17 September 2009 and 9 November 2009, the Health Council and RIVM explored the question of whether just a single dose of vaccine could offer sufficient protection. It was concluded that the protection required for vaccinated individuals themselves, or for vulnerable individuals

entrusted to their care, should be as comprehensive and effective as possible. Based on the scientific data available at that time, the Council took the view that it was advisable to keep to the two-dose vaccination schedule prescribed by the medicines authorities. At that point in time, this was the only schedule whose efficacy had been established with any certainty.[3,4] There was no data on the effectiveness of a reduced vaccination schedule in either medical high-risk groups or the elderly (the target groups for vaccination in the Netherlands).

On 20 November 2009, the European Medicines Agency (EMA) and the Dutch Medicines Evaluation Board announced their acceptance of evidence from new research showing that a single dose of vaccine may be sufficient to generate an adequate immune response in healthy individuals from 9 to 60 years of age (in the case of Focetria) and in those aged 10 and above (for Pandemrix). The EMA gave no details concerning the number of vaccinations per person in the high-risk groups and the elderly, many of whom have compromised immune systems. For children below the age of 10 (for Pandemrix) or 9 (in the case of Focetria) and for adults above the age of 60 (for Focetria) it was recommended that two doses be given, regardless of the health status of the individuals in question.

Accordingly, with the exception of disease-free healthcare workers, the target groups for vaccination in the Netherlands were unaffected by these changes in recommended dose.

At the request of the Minister of Health, Welfare and Sport, the Health Council and RIVM issued an advisory report on 25 September 2009 in which they explored the question of whether a single dose of vaccine would be sufficient for the vaccination of target groups in the Netherlands. As previously mentioned, no specific data was available concerning the vaccination of those target groups defined in the Netherlands. It was therefore concluded that a two-dose vaccination schedule should be maintained.[5]

Based on preliminary research with H5N1 vaccines, the European Medicines Agency had established a vaccination schedule of two doses for the pandemic vaccines. In the case of seasonal influenza, the efficacy of influenza vaccines is evaluated differently. This involves an assessment of these vaccines' ability to generate antibodies above a certain limit value. It was initially thought that this method would be inappropriate for a pandemic, partly due to the difficulty of determining a new limit value for protection against an entirely new form of influenza virus. Also, the testing methods used by the various manufacturers to measure antibody levels were not standardised, which made it difficult to compare data from different studies. Later research has shown that, in individuals aged 10 and above, a single dose of most pandemic vaccines against A/H1N1 2009 (unlike H5N1) was sufficient to generate an antibody level that

was believed to provide protection against infection.[46,47] Based on that data, it was stated that a single dose of vaccine would have been sufficient. The Committee notes that, here too, there is a lack of specific data concerning those high-risk groups for which it is generally more difficult to achieve protection.

In summary, the dosage recommendations were based on the scientific data available at that time, and on recommendations by the medicines authorities. Even with an improved understanding of this problem, there was no indication that the recommended two doses for high-risk groups (which, in the Netherlands, correspond to the target groups for vaccination) could to be adjusted to a one-dose schedule.

3.2 Overall review of the advisory reports

3.2.1 The evaluation is influenced by the outcome of the pandemic

Some commentators in the lay media and in professional journals have expressed the view that policy (and the related advisory process) did not reflect the fact that the actual situation was not particularly serious.[48,49] Key topics were the target groups for vaccination, the use of adjuvanted vaccines only, and a two-dose vaccination schedule. Any retrospective assessment should take account of the fact that the advisory process was always based on the limited, and often fragmentary, data available at that time. Moreover, there was always a lag time before this material appeared in scientific journals, if at all.

Given the potentially serious consequences involved, it is vital to take every possible precaution during an influenza pandemic. If the impact turns out to be less than expected, as it did in the case of the last pandemic, then some will criticise the response as being excessive. If the impact had been far greater (e.g. if the virus had mutated to develop increased virulence, or resistance to antiviral drugs) then critics would have argued the opposite standpoint just as vociferously. Accordingly, any evaluation of the advisory process on vaccination (and of the policy in question) is, to some extent, determined by the outcome of the pandemic.

The first part of this Chapter gives details of the risk assessments and scientific considerations underpinning the advisory reports by the Health Council and RIVM. The question of whether the policy itself, and the related advisory process conducted by the Health Council and RIVM, were adequate and well-considered is something that the Committee is content to leave to others. At the instigation of the Ministry of Health, Welfare and Sport, Berenschot and

Crisislab conducted an evaluation of the national decision-making during this crisis.[50] At international level, a committee chaired by Professor Harvey V. Fineberg (of the U.S. Institute of Medicine) evaluated the way in which the World Health Organization and other bodies responded to the pandemic. The goal was to enable lessons to be learned that might be of use when preparing for a future pandemic, or other type of public health emergency.[51] The European Academies Science Advisory Council, the Editor-in-Chief of the journal *Vaccine*, and others have also formulated the lessons to be learned from the pandemic of influenza A/H1N1 2009.[52,53]

3.2.2 *Practical, science-based advisory process*

Short lines of communication make for fruitful cooperation. RIVM advisors are often involved in Health Council advisory reports. The purpose of this is to ensure that these reports reflect the situation on the ground as accurately as possible, to set up a direct link with surveillance data, and to facilitate follow-up. With regard to vaccination against influenza A/H1N1 2009 also, it was considered important to link scientific advice with practical implementation. To this end, the Minister of Health, Welfare and Sport asked the Health Council and RIVM to advise jointly on target groups and vaccination doses. Such cooperation was facilitated by existing close contacts, and by each organisation's familiarity with the other's procedures. This facilitated a rapid, practical, and science-based advisory process, as well as effective follow-up. This partnership between the Health Council and RIVM is a good model of how to respond to a public health emergency.

3.2.3 *Restrict protocols to key issues*

The influenza A/H1N1 2009 pandemic put the existing system to the test. The Netherlands proved to be well prepared for an influenza pandemic. The various risks were intensively assessed in advance, and many areas were covered by existing protocols containing details of the procedures to be followed. Overall, it worked well.

When developing protocols, it is important that those concerned jointly think through the relevant steps and procedures. This can save time when a crisis actually occurs. However, there is a tendency to draw up protocols or guidelines that are more extensive than is useful or necessary. As already stated, influenza is difficult to predict, so the next pandemic scenario might not be quite what we expect. Accordingly, there is a risk that – rather than helping – the procedures

and consultative structures set out in protocols might actually be a hindrance. Hence it is best to restrict protocols to key issues only. An emergency procedure can be used to fill in the details later, based on the actual situation pertaining at that time, and the data then available.

3.2.4 *Communication with the public is key*

Public vaccination, of course, requires a clear communication strategy based on sound scientific principles. This is even more important in the case of vaccination campaigns carried out against the background of a pandemic. The provision of information alone is not enough. In a previous advisory report, entitled "The future of the National Immunisation Programme: towards a programme for all age groups", the Health Council addressed recent ideas on information provision and communication in the context of vaccination.[39] In the advisory report in question, the Council outlined areas in which the scientific basis of the communication strategy could be strengthened. As the pandemic of influenza A/H1N1 reminded us, the importance of an effective communication strategy cannot be over-emphasised. Once again, it has been shown that the acceptance of public vaccination programmes is by no means a foregone conclusion.[54]

3.2.5 *Procedures to avoid conflicts of interests need to be more rigorous*

To deliver the best advisory reports possible, the Health Council employs the services of people who are experts in their own fields. These individuals regularly place their expertise at the disposal of other agencies, including patient organisations, government, or industry. The Health Council has, for many years, actively pursued a policy of avoiding conflicts of interest, or even the appearance thereof. The risk of vested interests is ever present. Scientists further their knowledge using research funding from universities, research funds, and other sources. The government actively encourages cooperation between science and industry. A given individual may well have various roles and contacts, but this is not necessarily a problem. There is a general requirement that members of a committee must have no direct personal or financial interest in a given advisory report. The Council sees to it that there is full transparency with regard to any potential interests. Careful consideration is always given to the question of whether a conflict of interest might arise, and to whether there are sufficient checks and balances to compensate for possible vested interests within a committee.

Whenever experts are invited to sit on a committee, they are asked to submit a detailed official statement, to provide information about their sources of research funding, and to declare any personal financial interests. Based on this information, the Health Council decides whether or not a given individual may sit on a committee. The official statements are discussed during the establishment meeting, to ensure that the various members are fully aware of each other's positions and ancillary activities. These declarations of interest are periodically updated and available upon request. On occasion, if the area in question is a highly specialised one, there may be a limited choice of suitably qualified experts. In the case of those whose contribution is deemed essential to a given advisory report, but where an apparent conflict of interest makes them ineligible for committee membership, an advisory role is an option. While advisors provide input, they have no voting rights and bear no responsibility whatsoever for the contents of the advisory report in question.

The Health Council's final safeguard against conflicts of interest is a process of peer review. The Council's advisory reports are usually drawn up by a committee of experts specially appointed to deal with the request for advice in question. A peer review process always takes place before an advisory report is issued. This usually involves an assessment by one or more standing committees. The Health Council has eight standing committees, each of which supervises a wide range of public health issues.

The advisory process on influenza A/H1N1 2009 was not exempt from these considerations. For the reasons outlined above, some experts served on that Committee in an advisory capacity rather than as members. The first advisory report (of 8 April 2009) and the current report were both prepared under the auspices of the Committee on Vaccination Against Pandemic Influenza (Annex B). The 31 August 2010 advisory report on the vaccination of pregnant women outside the context of the pandemic was drawn up by the Committee on the National Vaccination Programme. In all of these advisory reports, full use was made of the Health Council's usual procedures for the avoidance of conflicts of interest. Given the unusual circumstances and the degree of urgency involved, a slightly different procedure was followed during the intervening period when drawing up five advisory reports on target groups and dosages. These advisory reports were drawn up on the basis of what were occasionally very large meetings of experts. In such cases, the declarations of interest were omitted and the actual advisory reports were issued by the President of the Health Council and the Director of RIVM's Centre for Infectious Disease Control Netherlands (CIB).

All advisory reports on vaccination during the influenza A/H1N1 2009 pandemic were reviewed by the Standing Committee on Infection and Immunity and/or by the Presidency of the Council. Prior to the pandemic, the broader framework for the advisory process on the role of vaccination in preparation for an influenza pandemic was assessed by the Standing Committee on Infection and Immunity, the Standing Committee on Health Ethics and Health law, and the Standing Committee on Medicine.

Despite all of these precautions, the advisory process on influenza A/H1N1 2009 has sparked a debate about Health Council advisors' alleged conflicts of interest. In 2010, partly in response to this situation, it was decided that the declarations of committee members' and advisors' interests should be actively published on the Health Council's website. That new policy has now been put into effect with respect to standing committees. This will soon be extended to semi-permanent committees, such as the Committee on the National Vaccination Programme. Details of the declarations of interest of the members and advisers of all of the Council's committees were already available upon request.

3.2.6 There does not appear to be a need for an advance purchase agreement

There is a worldwide shortage of production capacity for influenza vaccine. The available capacity is determined by the annual production of vaccine against seasonal influenza, which amounts to less than one billion doses per year. The actual requirement exceeds the available capacity many times over, especially during a pandemic. Accordingly, it has been stated that a supply contract must be concluded with a manufacturer prior to a pandemic. At the start of influenza A/H1N1 2009 pandemic, the Netherlands had no such contract with the manufacturers. Despite this, the Netherlands was one of the first countries to obtain supplies of pandemic vaccine. This was made possible by the fact that the Netherlands was fully conversant with the available options, knew what it wanted, and was able to act quickly. The effective and timely delivery of vaccine was not, apparently, dependent on the conclusion of an advance purchase agreement (APA).

This does not necessarily mean that it will always be possible to obtain sufficient amounts of vaccine in good time. For instance, no vaccine was available to combat influenza A/H1N1 2009 in the southern hemisphere (where the pandemic started), not even in those countries that had concluded an APA with the manufacturers in advance. Nevertheless, countries that do have an APA may well take priority in terms of vaccine deliveries during a future pandemic.

Chapter 4

Developments in vaccinology

In this Chapter, the Committee outlines relevant developments in the field of influenza-vaccine development (4.1). It also reports on hearings into the role of industry in this area (4.2).

4.1 Improved production methods and a broader spectrum of efficacy

The production of "normal" influenza vaccines does not generally involve the use of adjuvants (additives that help the vaccine to generate a strong immune response). Recent research into the influenza vaccines to be used in an influenza pandemic has underscored the importance of these additives, in terms of achieving optimum efficacy.[42,44] The use of adjuvants can broaden a vaccine's spectrum of efficacy, offering the prospect of cross-protection against different – ut related – viral strains. Moreover, the use of adjuvants means that less antigen (virus) is required. This, in turn, will deliver efficiency gains in the production of sufficient quantities of viral material (currently a bottleneck in vaccine production, due to the relative shortfall in production capacity).

The use of adjuvants has opened the way for the development of prepandemic influenza vaccines. These vaccines are developed using virus strains that are already in circulation and which are believed to be potentially capable of causing a pandemic. The assumption here is that, in the event of a severe pandemic, significant health gains could be made by quickly vaccinating the population.

Some concepts explained

prepandemic vaccine	-	a vaccine that is developed prior to a possible pandemic, using a circulating virus strain with potential – but not yet proven – pandemic potency (WHO Phases 1 to 3)
pandemic vaccine	-	a vaccine that is developed during a pandemic, using the circulating pandemic virus (WHO Phase 4 and beyond)
adjuvanted vaccine	-	a vaccine to which adjuvants (agents that boost the immune response) are added to increase its potency and expand its spectrum of efficacy
mock-up vaccine	-	a vaccine based on a known influenza virus whose genetic material is ultimately replaced by that of the pandemic strain in question

Boosted by adjuvants, the vaccine strain would not even have to be a perfect match for the circulating virus. In this scenario, work on the production of prepandemic vaccines could start straight away. These vaccines would then be available at the very beginning of a possible pandemic, which would be a major advantage. In other words, prepandemic vaccines would be available on time, as their development (or further refinement) does not hinge on information that is only available once a pandemic has actually broken out.

Currently, the development of influenza vaccines is based on immunity against the surface proteins of influenza viruses. As a result, the protection they offer is very specific, being limited to certain subtypes of the influenza virus. Work is in progress on a long-term solution, but this is likely to take ten years or more to come to fruition. The goal is to develop more universal influenza vaccines based, not on surface proteins, but on various highly conserved, general proteins of influenza viruses. Other approaches might involve vaccines based on recombinant viral vectors, and improved live, attenuated influenza vaccines. Such vaccines can be expected to have a broader spectrum of efficacy against a range of virus sub-types, both in seasonal influenza and pandemic influenza.[55-60]

4.2 Hearings into the role of industry

The Committee held hearings on 29 June 2011 with the most relevant manufacturers in the Netherlands, to fully acquaint itself with recent advances in the development of new influenza vaccines. The companies in question were Baxter, GlaxoSmithKline (GSK), Novartis and Sanofi Pasteur MSD. Ten questions were submitted to each of these manufacturers in advance (Annex C). The Committee has incorporated the information obtained in these hearings into its conclusions concerning the role of vaccination in preparation for future influenza pandemics.

GSK (AS03) and Novartis (MF59), in particular, have developed expertise in the use of adjuvanted influenza vaccines. Both found that adjuvants have beneficial effects on efficacy. There have been no reports of significant adverse effects associated with the use of MF59-adjuvanted vaccines. This also applies to groups such as children, the elderly, pregnant women, newborns, and those with medical risk factors. Novartis has been using MF59 in vaccines against seasonal influenza for more than ten years, particularly in the elderly, for whom non-adjuvanted vaccines are less effective.

However, a safety issue has arisen in connection with the use of GSK's AS03-adjuvanted vaccine. An increased frequency of post-vaccination narcolepsy was reported in Sweden and Finland, however adolescents were the only group affected. Unlike Novartis, GSK does not favour the use of adjuvants in vaccines against seasonal influenza.

GSK and Novartis have continued their development work on adjuvanted prepandemic and pandemic vaccines. The latter category involves mock-up dossiers, to which – during a pandemic – a seed strain based on the pandemic virus is appended.

Baxter follows a different approach, using vaccines derived from whole killed virus that has been produced on Vero cell cultures. This delivers wide-spectrum efficacy without the addition of adjuvant.

At the beginning of the A/H1N1 2009 pandemic, Sanofi Pasteur MSD had no pandemic mock-up vaccine available (adjuvanted or otherwise). During the pandemic, the company developed and produced *Panenza*, a classic, non-adjuvanted vaccine based on A/H1N1 2009. *Humenza*, an A/H1N1 2009 vaccine adjuvanted with AF03, was registered in June 2010, after the pandemic. However, this registration was withdrawn by the company in June 2011.

Remarkably, Sanofi Pasteur MSD has terminated all research into adjuvants and adjuvanted vaccines. This major manufacturer of influenza vaccines no longer has any prepandemic or pandemic (mock up) vaccines in its portfolio.

4.3 Conclusion

Any assessment of the role of vaccination in preparation for future influenza pandemics must take account of three major developments. Firstly there are the prepandemic vaccines, which are based on the potential agents of future pandemics, such as H5N1. In theory, this makes it possible to be better prepared for a pandemic (caused by a specific influenza virus), by ensuring production capacity, or even by building up stocks of vaccine. The second such development is that, thanks to improved production methods, the spectrum of efficacy of modern influenza vaccines can extend beyond the specific viral strain that was used to develop them. As a result, versatility is greatly enhanced. Finally, it is important to note that, over the longer term (at least ten years), vaccines based on proteins common to many influenza viruses are expected to become available. These will have an even broader spectrum of efficacy, against a range of virus sub-types.

Chapter 5

Conclusions and recommendations

Based on its review of the scientific literature and the experience that has been gained with influenza A/H1N1 2009, the Committee has made a number of recommendations (see Section 5.1) concerning the preparations for, and the advisory process during, any future pandemics. In the second part of this Chapter, the Committee then makes a number of statements concerning the role of vaccination in this regard. Starting with prepandemic vaccines, it proceeds to pandemic vaccines, and finally deals with future types of vaccine.

5.1 Concerning preparation and the advisory process

5.1.1 Accept that risk assessment and precautionary measures also have a part to play

The Health Council's advisory process on vaccinations in public programmes is governed by a clear framework, with associated criteria. These criteria were formulated to protect both the entire population and specific groups within it, for whom protection is a priority (high-risk groups). The Health Council has based its recommendations on the available scientific data, taking both the strength of the evidence obtained in published research and the limitations of such studies into consideration. During a pandemic, decisions usually have to be taken quickly, often before scientific research data becomes available. Where there is a lack of direct scientific data, risk assessment and precautionary considerations

take on an important role in the advisory process. When answering questions of policy in its advisory reports, the Health Council clearly indicates where supporting scientific data is available and where it is not. Policy and decision-making are the responsibility of the minister in question.

5.1.2 *Improve monitoring and surveillance in humans and animals*

Influenza A/H1N1 2009 had probably been circulating in pigs for some time before it first caused disease in people, an event which led to its discovery.[34] The improved monitoring of influenza viruses, together with the routine exchange of information between those veterinary and medical authorities who are responsible for such surveillance, should make it possible to identify and investigate pandemic threats at an earlier stage than is presently the case. While there is an international network for the monitoring of human influenza viruses, there is no systematic monitoring of animals on a global scale. It is important to invest in this, in an international context.[61,62]

When interpreting the findings in animals, it is important to determine whether there has been any transmission to humans. If transmission were to occur, then the first cases might be expected to involve those who come into contact with these animal species on a regular basis, in the course of their professional activities. Accordingly, the surveillance of influenza infections in pigs and poultry should be routinely supplemented by the monitoring of influenza infections and related complaints in people who work with such animals. This will also help us to better interpret the findings in animals.

5.1.3 *Prepare clinical research for pandemics*

During the influenza A/H1N1 2009 pandemic, not only was information on disease in humans slow to emerge, but even data that became available proved difficult to interpret. During the pandemic, work started on a system for systematic syndrome surveillance. If such data were available in real-time, this would deliver vital information about the impact of the pandemic.[63] The ground has been prepared for the establishment of pandemic and inter-pandemic clinical research networks. This will streamline operations and make international coordination a reality. The Netherlands has effective facilities for combined clinical and public health research. The Committee recommends that the Dutch centres be allowed to actively contribute to this consortium or to similar international networks. In this way, in the event of a future pandemic, we will

have access to the clinical and epidemiological data that have proven essential in decision-making.

It will sometimes be necessary to carry out random testing for the presence of a new influenza virus, to quickly understand its clinical effects. This might involve blood donations with limited but relevant background information. The material obtained could then be tested for cross-reactivity, using antibodies and cellular immunity.[64,65] Under current regulations in the Netherlands, testing of this kind is subject to time-consuming procedures, including assessment by a medical ethics committee. With regard to such testing, the Committee recommends that as much preparatory work as possible should be completed in advance, and evaluated for medical ethics issues. Then, in the event of a public health emergency, testing could be carried out immediately.

5.1.4 *A joint Health Council/RIVM advisory process should be used during public health emergencies*

The existing partnership between the Health Council and RIVM, which was further enhanced during the 2009 pandemic, is a good model of how to respond to a public health emergency. It is also recommended that, in any future emergency, the scientific advisory process and practical implementation be linked together in a similar fashion.

5.1.5 *Publish declarations of interest*

To deliver the best advisory reports possible, based on the latest scientific data, the Health Council employs the services of people who are experts in their own fields. These individuals regularly place their expertise at the disposal of other agencies, including patient organisations, government, or industry. The Health Council has detailed procedures aimed at avoiding conflicts of interest, or even the appearance thereof. These include comprehensive screening for ancillary activities and personal interests. In this way, the Council can guarantee that its advisory reports will be produced in the absence of any conflicts of interest, or even the appearance thereof. In the past, statements concerning possible personal interests and sources of research funding used in this context have always been made available on request. In response to the events that took place during the pandemic of influenza A/H1N1 2009, the Health Council has decided to actively publish these statements on its website from now on.

5.1.6 Offer advice from an international perspective

In the event of global public health emergencies, such as influenza pandemics, it is essential for policy and the advisory process to be framed in an international context. In future pandemics (more so than during the pandemic of influenza A/H1N1 2009), greater efforts should be made to achieve international cooperation. This will help to prevent any unnecessary confusion, which might damage people's confidence in the advisory process. From the perspective of international public health, the World Health Organization's advisory process serves as a guideline. In Europe, the European Centre for Disease Prevention and Control (ECDC), which was established a few years ago, could be of use in this regard.

5.2 Concerning vaccination

The role of vaccination in an influenza pandemic should be considered in the wider context of seeking to mitigate the effects of these events. One option is to purchase the antiviral drugs needed for a rapid response (involving the treatment of patients and the protection of their contacts) at the very beginning of a pandemic. It is also possible to take social measures aimed at limiting public gatherings and contacts where people might become infected. Another essential aspect of preparing for an influenza pandemic is international cooperation and coordination in areas such as the effective monitoring of influenza virus infections in humans and animals.

A fundamental question in this connection is whether it makes sense to conclude a contract with a manufacturer for the supply of vaccine. This may involve prepandemic vaccines (developed and produced in advance) based on a currently circulating strain of influenza virus that is believed to be potentially capable of causing a pandemic. prepandemic vaccines are readily available as soon as a pandemic is confirmed. Moreover, if a vaccine is a good enough match for the pandemic virus in question, it can immediately provide a degree of protection. Another option is a contract for pandemic vaccine. The final form of such vaccines is not developed and produced until the pandemic has actually started. Once the virus behind the pandemic has been characterised, it takes another six months for the pandemic vaccine to be developed and produced.

5.2.1 *Prepandemic vaccines*

One candidate with the potential to trigger pandemic influenza is H5N1, a highly pathogenic avian influenza virus. The bulk of the research effort into prepandemic vaccines involves vaccines based on the H5N1 virus. This virus meets two important conditions for causing a pandemic. Firstly, the virus can infect humans and, secondly, there is little immunity to it in the population. However, it does not meet an important third condition – he virus is not yet transmitted from human to human. The fear is that, either through mutation or genetic reassort-ment with other influenza viruses, H5N1 might yet acquire that ability. Based on current scientific data, it is impossible to say whether that particular scenario will ever become a reality. Given our inability to predict how such a mutant virus might differ from the H5N1 virus used to develop prepandemic vaccine, it is impossible to say whether such vaccines will be able to provide sufficient protection.

Aside from H5N1, there are a number of other influenza viruses that could develop into forms capable of causing pandemics. This applies to the H1N1 and H3N2 subtypes that cause seasonal influenza. Other candidates are the H2N2 subtype responsible for the Asian flu in 1957, and the H7 and H9 subtypes that have yet to cause large-scale serious illness in humans. As was shown in the case of A/H1N1 2009, however, this is not something that lends itself to scientifically-based predictions.

Thus, in scientific terms, there is no well-founded answer to the question of whether it makes sense to conclude a contract with a manufacturer for the supply of prepandemic vaccine against a specific influenza virus.

5.2.2 *Pandemic vaccines*

Not until a new influenza virus is found to be capable of human-to-human transmission, and the WHO issues a pandemic alert (WHO Phase 4), does it become clear that it may no longer be possible to avert a pandemic. At that point, the virus behind the potential pandemic can be characterised, and the development of a pandemic vaccine can begin. Its availability is limited by the fact that development and production take at least six months. In the case of A/H1N1 2009, epidemiological developments in the northern hemisphere allowed time for production to commence. Indeed, there was just enough time for the vaccine to be made available at the very peak of the epidemic curve. While this probably prevented a great many infections, it illustrates the point

that, in future pandemics, the timely availability of pandemic vaccine cannot be guaranteed.

Recent research into the vaccines to be used in an influenza pandemic has underscored the importance of additives (adjuvants), in terms of achieving optimum efficacy for the influenza vaccines currently in common use. The use of adjuvants widens a vaccine's spectrum of efficacy, offering potential cross-protection against different – but related – viral strains. Moreover, the use of adjuvants means that less antigen (virus) is required. This, in turn, will deliver efficiency gains in the use of vaccine (currently a bottleneck, due to the relative shortfall in global production capacity). Several manufacturers are capable of supplying vaccines of this kind. Pandemic vaccine can also be developed and produced using whole killed virus which, without the addition of adjuvant, is also characterised by wide-spectrum efficacy.

Pandemics can have a major social impact. This argues in favour of entering into contracts with the manufacturers of the vaccines in question, right away, for the supply of vaccine in the event of a pandemic. However, experience has shown that it is important to be fully conversant with the material in question. This enables adequate recommendations (and government decisions in this regard) to be made quickly. Accordingly, the Committee cautions against entering into contracts, at this stage, for the supply of vaccine in the event of a pandemic.

5.2.3 *Future types of vaccine*

Currently, the development of influenza vaccines (including adjuvanted vaccines) is based on immunity against the surface proteins of influenza viruses. As a result, the protection they offer is very specific, being limited to certain subtypes of the influenza virus. Other types of vaccine may eventually become available, but it is estimated that this will take at least ten years to come to fruition. The goal is to develop more universal influenza vaccines based not exclusively on generating an immune response to surface proteins but mainly on cellular immunity to more general, internal influenza virus proteins. Other approaches might involve vaccines based on recombinant viral vectors, and improved live, attenuated influenza vaccines. Such vaccines may be expected to have a broader spectrum of efficacy than current vaccines. If these new types of influenza vaccine become available, they may eliminate the need for a specific pandemic vaccine.

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Annexes

Annex **A**

The request for advice

On 12 November 2007, the Minister of Health, Welfare and Sport approached the President of the Health Council for advice concerning vaccination in the event of an influenza pandemic. The following is an extract from the Minister's letter (reference: PG/CBV-2.804.624):

In recent years, both at national and international level, great emphasis has been given to preparations for an influenza pandemic. Partly on the basis of an advisory report issued by your Health Council, the Dutch government proceeded with the purchase of an emergency supply of antiviral drugs. The Netherlands now has sufficient antiviral drugs to treat the 30% of the population that is expected to become ill as a result of infection with the pandemic virus. In addition, a contract has been signed with a vaccine supplier for the delivery of a pandemic vaccine. Once this vaccine becomes available, all batches from the first eight weeks of production will be delivered to the Netherlands. If the vaccine is sufficiently effective, and if it can be produced in sufficient quantities, then there will be enough to vaccinate the entire population of the Netherlands.

Rapid developments are taking place in the area of anti-pandemic-influenza-virus vaccines. Several companies are taking steps to develop a vaccine that can be used – before the onset of a pandemic – to build up the population's resistance to an expected pandemic virus. These efforts have partly been prompted by doubts about the feasibility of effectively deploying a pandemic vaccine during the first phase of a developing pandemic. The development of current prepandemic vaccines is aimed at alleviating the impact of a pandemic caused by an H5N1 virus. The WHO has already identified four different H5N1 strains that are seen as the most suitable choices for use in the development of prepandemic vaccines.

While H5N1 is a good candidate for a pandemic virus, it is highly unlikely that a pandemic strain will be identical to the current variant of the virus. This has important implications for the development of a prepandemic vaccine, as the efficacy of such a vaccine depends on its ability to build up resistance in the population. It is also important to be able to produce properly effective vaccines as soon as possible, and for as many people as possible. To this end, the search is on for new ways of producing vaccine, some involving methods based on cell culture. Other lines of research are exploring new delivery methods and adjuvants capable of delivering adequate protection while using a smaller quantity of active ingredient.

Reports on the development of these prepandemic vaccines are quite encouraging. Yet, on the basis of the results to date, there is still no certainty about the efficacy of such vaccines during a pandemic. Accordingly, there is some question concerning the usefulness of these vaccines in the context of government campaigns to protect public health during a pandemic. I assume that the results of recent research by the European Centre for Disease Prevention and Control will feature prominently in your advisory report.

I would be grateful for your advice on the following questions:

Pandemic vaccine:

- What requirements (particularly with regard to short-term and long-term adverse effects and effectiveness at individual and population level - assuming that people are willing to be vaccinated) must a pandemic vaccine meet? How can we reliably identify these requirements, given the short time available once a pandemic has started?

Prepandemic vaccine:

Usefulness

- In what way (or ways) might a prepandemic vaccine (in combination with other medical or non-medical interventions) be able to prevent or combat an influenza pandemic?
- What requirements (e.g. with respect to effectiveness at individual and population level, short-term and long-term adverse effects, availability, shelf-life) must prepandemic vaccines meet? Does this depend on the role of the prepandemic vaccine in combating the pandemic? To what extent do these requirements differ from those imposed on a pandemic vaccine?
- What is the replacement time for a prepandemic vaccine? To what extent does the replacement time depend on the extent to which the vaccine matches viruses circulating in wild fauna and/or those found (regardless of the exact cause) in H5 patients?
- What assumptions underpin the cost effectiveness of a prepandemic vaccine? In particular, to what extent is cost effectiveness dependent on the risk of a pandemic occurring within a given period of time, on the characteristics of the pandemic virus in question, on the properties of the

prepandemic vaccine itself, and on the replacement time of that vaccine, assuming that people are willing to be vaccinated?

Vaccine development

- Do those prepandemic vaccines that have already been developed meet the above requirements? If so, in what ways? If not, why not?
- In your view, how likely is it that current developments will lead to a prepandemic vaccine that does meet the above requirements?
- If you consider this to be quite likely, how long do you expect it to take before an effective prepandemic vaccine becomes available?
- Given the above-mentioned details, how do you rate the different strategies adopted by vaccine developers to create a prepandemic vaccine?
- How do the current private-sector initiatives measure up, in terms of the effort required to create a prepandemic vaccine (assuming that this is possible)?

Purchase

- What are the arguments for or against signing a contract for the delivery of prepandemic vaccine? If so, what conditions should it include with regard to production, delivery, storage, efficacy, safety, registration, liability, and replacement? What developments might affect the weight given to these arguments, both now and in the future?

Deployment

- If the Netherlands were to proceed with the purchase of a prepandemic (H5) vaccine, how would this fit into the existing preparations for prepandemic and pandemic scenarios?

Complementary request for advice

On 29 April 2009, the Minister of Health, Welfare and Sport asked the Health Council to prepare an emergency report on the following points: The following is an extract from the e-mail in question:

1 Can the current seasonal vaccine be expected to offer any degree of protection against serious complications resulting from infection with the "Mexican flu virus" that is now in circulation?
2 If so, could any protection offered by the current seasonal vaccine be enhanced by the addition of new generation adjuvants?
3 Would it be advisable - in the light of the current epidemiological situation - to opt for the development/acquisition of a vaccine that is based on the Mexican flu virus?
4 What conclusions can be drawn concerning the possible patterns of protection and adverse effects associated with each of these options?

5 Should greater demands now be placed on production capacity, how would you assess the risks involved in terms of normal vaccine production for the upcoming influenza season?
6 Any other considerations that, in your view, could usefully be communicated in this regard.

Complementary request for advice

In a supplementary request for advice (dated 20 August 2009; reference: PG/CI-2.948.935), the Minister asked the Council to postpone the general advisory report (on the role of vaccination in preparation for an influenza pandemic) until the pandemic of influenza A/H1N1 2009 was over. The Minister also asked that details of the lessons from that pandemic be included. The following is an extract from his letter:

On 12 November 2007, I sent you a letter (reference: PG/CBV-2.804.624) in which I asked you to advise me on the role of vaccination in the context of preparations for an influenza pandemic. Your advisory process on this subject is now well advanced. In this connection, I would like to express my appreciation of the fact that, in a meeting held on 29 July, you brought the Director-General of Public Health up to date regarding progress on this matter.

The outbreak of the H1N1 pandemic has resulted in a situation of considerable complexity. Steps are currently being taken (and others are in preparation) to limit, as far as possible, the H1N1 pandemic's impact on the Netherlands. Partly based on a targeted emergency report from the Health Council, I recently ordered the procurement of vaccines based on the pandemic H1N1 virus.

In addition to H1N1, there are other viruses that pose a risk of pandemic influenza. I therefore attach great importance to the completion of your advisory report. I am, however, convinced of the need to include in that document details of our experiences during the current pandemic.

Accordingly, further to my previous request for advice, I would ask that you include details of the implications of the H1N1 pandemic in that general report. In that connection, I am interested in matters such as the general method used to assess a pandemic (epidemiological developments, trends in number of infections, its extent and rate of spread, and its severity), the experience currently being gained in the field of vaccine development and production, and any other events that you deem to be of relevance in this regard.

Please send me your advisory report as soon as your Committee has assessed the necessary details on the current influenza (when these become known).

Annex **B**

The Committee

The composition of the Committee on Vaccination Against Pandemic Influenza was as follows:

- Prof. E.J. Ruitenberg, *Chairman*
  Emeritus Professor of Immunology; University of Utrecht; Professor of International Public Health; VU University Amsterdam
- Dr. E. Hak
  Professor of Clinical Pharmacoepidemiology, University of Groningen
- Prof. M.D. de Jong
  Professor of Clinical Virology (from May 2011), Academic Medical Center, Amsterdam
- Dr. G. Koch
  Central Institute for Animal Disease Control, Lelystad, Wageningen University Research Centre
- Prof. M. Koopmans
  Professor of Public Health Virology, ErasmusMC, Rotterdam; National Institute of Public Health and the Environment, Bilthoven
- Dr. W. Opstelten
  GP, Dutch College of General Practitioners (NHG), Utrecht
- Dr. J. Wallinga
  Population Biologist, National Institute of Public Health and the Environment, Bilthoven

- Dr. H Houweling, *scientific secretary*
  physician/epidemiologist; Health Council, The Hague

The Committee employed the services of the following advisors:
- Prof. R.A. Coutinho
  Professor of Epidemiology and Infectious Disease Control, Utrecht University; National Institute of Public Health and the Environment, Bilthoven
- Prof. T.W. Kuijpers
  Professor of Paediatric Immunology; Academic Medical Center, Amsterdam
- Dr. W. Luytjes
  National Institute of Public Health and the Environment, Bilthoven
- Prof. A.D.M.E. Osterhaus
  Professor of Virology, ErasmusMC, Rotterdam
- Dr. A.C.G. Voordouw
  physician, Master of Public Health, Medicines Evaluation Board, The Hague
- Prof. J.C. Wilschut
  Professor of Viral Infection Mechanisms and Vaccine Development, University Medical Center Groningen

Dr. P.J. van Dalen was attached to the Committee as an observer from the Ministry of Health, Welfare and Sport.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Questions for hearings into the role of industry

The four manufacturers of influenza vaccine of greatest relevance to the Netherlands (Baxter, GlaxoSmithKline, Novartis, Sanofi Pasteur MSD) attended the hearings on 29 June 2011. The following company representatives were in attendance, and responded to the questions set out below (details of which had been submitted to them in advance).

- Baxter (O. Kistner, D. Broeke)
- GSK (M. Wettendorff, D. Campens, R. Remorie)
- Novartis (K. Stöhr PhD, A. Banzhoff)
- SPMSD (A. Abelin, B. Slierendrecht)

Questions on prepandemic and pandemic influenza vaccines, Health Council of the Netherlands, June 2011

1 What lessons has your company learned from the A/H1N1 pandemic and what conclusions do you draw from these?

2 Which *prepandemic* vaccines does your company currently have in portfolio?
Please give details of vaccine type, virus subtype, egg or cell culture, adjuvant, number of doses needed, micrograms of antigen per dose, and market registration status.

3 Which of these *prepandemic* vaccines could actually be produced and delivered in quantity?

4 Which registered *pandemic* mock up vaccines does your company currently have in portfolio?
Please give details of vaccine type, virus subtype, egg or cell culture, adjuvant, number of doses needed, micrograms of antigen per dose and market registration status.

5 Which of these *pandemic* vaccines could actually be produced and delivered in quantity?

6 What preparations is your company making for a potential future influenza pandemic?

7 What future does your company see for the use of adjuvant in influenza vaccines? In your answer, please address prepandemic and pandemic influenza vaccines, and seasonal influenza vaccines separately.

8 What future does your company see for the use of live attenuated vaccines against seasonal influenza? How soon could live attenuated vaccines go into mass production?

9 What future does your company see for the use of multivalent vaccines against seasonal influenza? How soon could multivalent vaccines go into mass production?

10 What future does your company see for the use of wide-spectrum influenza vaccines based on universal epitopes? How soon could wide-spectrum vaccines go into mass production?