Vaccination against pandemic influenza A/H1N1 2009: target groups and prioritisation

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory report *Vaccination against pandemic influenza A/H1N1 2009: target groups and prioritisation*
Our reference : U 5444/HH/tvdk/824-I
Enclosure(s) : 1
Date : August 17, 2009

Dear Minister,

We hereby present the advisory report Vaccination against pandemic influenza A/H1N1 2009: target groups and prioritisation. This document presents the findings of an expert meeting held on Monday 10 August 2009. The report has been reviewed by the Health Council of the Netherlands' Standing Committee on Immunology and Infectious Diseases.

In the opinion of the experts, the primary objective of any vaccination programme addressing the pandemic influenza A/H1N1 2009 virus should be to protect those groups at increased medical risk. The experts therefore recommend that vaccination should be made available to the members of the high-risk groups, as well as to the health service workers who will come into contact with them. By offering vaccination to this latter group, it will also be possible to meet the secondary objective of vaccination, i.e. to ensure the continuity of health services. The healthcare professionals who are to be eligible for vaccination can be identified by the Centre for Infectious Disease Control in consultation with your ministry and the relevant professional organisations. At this time, the experts do not advise a full-scale vaccination programme for the Dutch population as a whole. We, the undersigned, endorse this opinion.

P.O.Box 16052
NL-2500 BB The Hague
Telephone +31 (70) 340 56 88
Telefax +31 (70) 340 75 23
E-mail: k.groeneveld@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 VX The Hague
The Netherlands
www.healthcouncil.nl

Gezondheidsraad **President**
Health Council of the Netherlands

Of necessity, some aspects of this advisory report are based on rather limited knowledge of the patients who have been affected to date and the probable course of the pandemic in future. The nature of the pandemic may well change over time. The experts are therefore to reconvene in September 2009 when they will discuss the situation at that time. Given the unpredictability of the pandemic in terms of both progression and effects, it is possible that additional recommendations with regard to vaccination will be made.

Yours sincerely,

(signed)

Professor J.A. Knottnerus
President, Health Council of the Netherlands

(signed)

Professor R.A. Coutinho
Director, RIVM Centre for Infectious Disease Control

P.O.Box 16052
NL-2500 BB The Hague
Telephone +31 (70) 340 56 88
Telefax +31 (70) 340 75 23
E-mail: k.groeneveld@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 VX The Hague
The Netherlands
www.healthcouncil.nl

Vaccination against pandemic influenza A/H1N1 2009: target groups and prioritisation advies

to:

the Minister of Health, Welfare and Sport

No. 2009/10, The Hague, August 17, 2009

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, Housing, Spatial Planning & the Environment, Social Affairs & Employment, Agriculture, Nature & Food Quality, 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.

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with *health technology assessment*.

INAHTA

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

Preferred citation:
Health Council of the Netherlands. Vaccination against pandemic influenza A/H1N1 2009: target groups and prioritisation. The Hague: Health Council of the Netherlands, 2009; publication no. 2009/10E.

ISBN: 978-90-5549-769-0

Contents

Executive Summary

This report presents the findings of an expert meeting held on 10 August 2009 to discuss the target groups and possible prioritisation for any vaccination programme against pandemic influenza A/H1N1 2009. Some aspects of the discussion were, of necessity, based on relatively limited knowledge about the patients affected to date and the course of the pandemic. The meeting was nevertheless able to offer the following recommendations.

Vaccination is recommended for the following (risk) groups:

- Individuals at medical risk, in line with the existing indication for the annual seasonal flu vaccination, together with all those aged 60 and above, regardless of health status.
- Pregnant women in the medical risk groups, but *only* during the second or third trimester of pregnancy. The experts do not recommend the vaccination of expectant mothers who do not belong to one of the recognised risk groups.
- Healthcare staff who may come into contact with patients belonging to the previously defined medical risk groups.
- Family members and (informal) carers of individuals at extremely high risk of death or serious illness from influenza.

At this time, the experts do not recommend a general vaccination programme for the entire Dutch population.

According to the current delivery schedule, vaccines will be available in sufficient quantities whereby prioritisation will probably not be necessary. If this situation changes, the experts advise that healthy individuals aged 60 and over should be vaccinated *after* the other groups listed above. If further prioritisation within the medical risk groups proves necessary, the experts propose the following order of priority:

- Patients with a serious disorder and functional deficiency of the airways and lungs; patients with a serious (acute or chronic) disorder of cardiac function; patients with insulin-dependent diabetes.
- Patients with a disorder and functional deficiency of the airways and lungs; patients with a chronic disorder of cardiac function which can be stabilised and compensated to a reasonable degree by medication; patients with chronic renal insufficiency (dialysis and kidney transplant patients); children and adolescents aged from 6 months to 18 years who have been taking salicylates on a long-term basis; patients with a non-insulin-dependent form of diabetes; individuals with a mental handicap, in residential care; all other individuals in residential care and having a general predisposition to respiratory infections.
- Individuals aged under 60 with reduced resistance to infections.

Given the current uncertainty with regard to both the course and the seriousness of the pandemic, and the possibility of new knowledge about the specific characteristics of patients and vaccines becoming available in the short term, the experts have decided to reconvene in September 2009. At this next meeting, a possible broadening of the indication for vaccination, perhaps to include children and adolescents, will be discussed.

Chapter 1

Introduction

1.1 Background

The possibility of an influenza pandemic with major medical and societal consequences has been foreseen for some time. Until recently, it was thought that this would most likely involve the human-to-human transmission of the H5N1 'avian influenza' virus which emerged in Asia a few years ago. In early 2009, however, a new H1N1 virus with pandemic potential began to occupy the world's attention. The first cases were seen in Mexico, whereupon the new disease was dubbed 'Mexican Flu'. On 21 April 2009, the American Centers for Disease Control and Prevention (CDC) confirmed that there was indeed a new influenza virus strain in circulation and that it contains genetic material from an avian influenza virus in combination with genetic material from a virus generally seen in pigs. Accordingly, the new virus also became known as 'Swine Flu'. Later, the World Health Organisation (WHO) proposed that the virus should bear the official name A/H1N1 2009, and this designation was adopted by the Netherlands on 12 May 2009.

On 25 April 2009, the WHO declared 'an emergency of public health concern'.[1] Following close monitoring and successive upgradings of the threat, a pandemic (phase 6) was declared on 11 June 2009. This classification simply means that the H1N1 virus had then spread to more than one WHO region; it does not represent any opinion of the seriousness of the resultant illness. In fact, the clinical

symptoms of influenza A/H1N1 2009 have thus far proven very similar to those of 'regular' seasonal flu, although a relatively high proportion of younger people seem to have been infected.

In 2005, prompted in part by an advisory report produced by the Health Council of the Netherlands[2], the Dutch Minister of Health ordered the procurement of antiviral drugs to be used in the event of an outbreak of a new influenza virus. These drugs have been used to treat the first patients who had contracted H1N1 influenza while abroad (the first such case dating from 28 April 2009). Initially, the antivirals were used for both therapeutic and prophylactic purposes, and were also prescribed to close (family) contacts of the confirmed cases in order to slow the spread of the disease. Prophylactic use has since been discontinued, since the virus has now spread too widely to warrant such interventions.

The first case of influenza A/H1N1 2009 contracted within the Netherlands was confirmed on 8 June 2009. By 14 August, the Centre for Infectious Disease Control (RIVM-CIb, part of the National Institute for Public Health and the Environment) had recorded 1473 laboratory-confirmed cases, of which 883 (60%) had definitely been contracted abroad and 289 (20%) in the Netherlands itself. The source of the remaining 301 cases (20%) could not be established with certainty.[3] It seems likely that there has been a degree of under-reporting, whereby the actual number of influenza A/H1N1 2009 cases in the Netherlands will have been significantly higher. Laboratory diagnostics are no longer used in every suspected case.

1.2 Terms of reference

On 19 June 2009, and prompted in part by the advisory letter submitted by the Health Council on 8 May 2009[4], the Minister of Health authorised the procurement of 34 million doses of adjuvanted vaccine against A/H1N1 2009. The vaccine will be used to counter the pandemic as soon as it becomes available later this year. The ministry is currently working alongside many other stakeholders (ActiZ, GGD-NL, GHOR, LHV, NHG, NVI, RIVM-CIb, RIVM-CvB, SNPG, VNG) to produce a logistical plan for the administration of the vaccine to members of the public. A communication plan is also to be produced.

In anticipation of the delivery of the vaccine, on 20 July the Minister of Health requested the Health Council and the Centre for Infectious Disease Contol (RIVM-CIb) to produce a joint advisory report on how the vaccines should be

deployed, with particular reference to the main target groups and, in the event of any shortage, the prioritisation of those target groups. The full text of the minister's 'Request for Advice' is given as Appendix A to this document.
To answer the minister's questions, the Health Council and the RIVM-CIb convened an expert meeting on 10 August 2009. Throughout this report, the term 'the experts' refers to those who attended this meeting.

1.3 Previous Dutch advisory reports and contingency plans; advisory reports produced in other countries

The Health Council has been responsible for a number of previous advisory reports concerning the control of influenza outbreaks.[2,4-7]

These advisory reports have defined the risk groups which should be offered vaccination against 'regular' seasonal flu[7] or, in the event of a pandemic, should be given priority for vaccination.[5] The order of priority for vaccination in a pandemic is given in the LCI plan *Bestrijding influenzapandemie*, produced in 2006.[8] The risk groups are also listed in the Health Council's advisory reports with regard to the distribution of antiviral agents during a pandemic.[2,6] When these documents were produced, it was assumed that the main threat was posed by the H5N1 virus. In view of the (as yet) relatively low virulence of the H1N1 influenza virus, the RIVM-CIb requested an expert group chaired by Prof. J.T. van Dissel to advise on the use of antiviral agents in the current circumstances.[9] The resulting report, *Neuraminidaseremmers bij pandemie door nieuwe influenza A/H1N1* ('The role of neuraminidase inhibitors in a New Influenza A/H1N1 pandemic') has been reviewed by the Health Council's Standing Committee on Immunology and Infectious Diseases.

Recommendations covering the selection of target groups for vaccination in the face of an influenza pandemic have now been issued by the World Health Organisation, the Centers for Disease Control and the British Department of Health.[1,10,11]

The WHO advises the vaccination of the following groups, in order of priority[1]:
- Healthcare personnel
- Pregnant women
- Individuals aged six months and above with a chronic health condition
- Healthy adolescents and (young) adults aged 15 to 49
- Healthy children

- Healthy adults aged 50 to 64
- Healthy adults aged 65 and over.

These are general recommendations which can and should be adapted according to the situation in each country.

The order of priority given by the CDC is[10]:
- Pregnant women
- Individuals caring for children under six months of age and their (family) contacts
- Healthcare personnel, including emergency room staff
- All individuals aged between six months and 24 years
- Individuals aged 25 to 64 suffering from a chronic condition and immuno-deficiency
- Individuals aged 25 to 64 and not belonging to one of the risk groups
- Individuals aged 65 and over.

The British Department of Health advises the vaccination of the following groups, listed in order of priority[11]:
- Individuals aged between six months and 65 years and belonging to the groups for which vaccination against seasonal flu is advised
- Pregnant women (depending on the registration of the vaccines for use in the various trimesters)
- Family members of individuals with immuno-deficiency
- Individuals aged 65 and over belonging to those groups for which vaccination against seasonal flu is advised. (In the United Kingdom, vaccination is not automatically offered to those aged 65 and over, regardless ofhealth).

In the current report point of departure are the previous advisory reports issued by the Health Council. Relevant recommendations produced by other countries are discussed and incorporated where appropriate.
In producing this report, the experts relied on purely medical grounds to select those groups who should be offered vaccination.

1.4 Structure of this report

The Minister of Health presented a number of specific questions with regard to the target groups for vaccination in the event of an influenza pandemic. Before addressing these questions, the experts first considered whether a general vacci-

nation programme should be implemented at the earliest possible opportunity, or whether vaccination should be limited to certain risk groups, at least for the time being. This question has been designated ‘Question 0’.

This report is divided into six chapters, the first two of which examine the (probable) course of the pandemic and the objectives of vaccination. Each of the remaining four chapters examines a specific aspect of the influenza pandemic, presenting a summary of the information available at this time and the relevant recommendations or considerations arising from experience in other countries. Each chapter also addresses the minister’s questions relating to the aspect concerned.

Chapter 2

The current status of the pandemic

In the case of ‘regular’ seasonal flu, many people will have developed some immunity through earlier exposure to the virus or a closely related strain (‘cross-reactivity’). In a pandemic of ‘New Influenza’, however, this will not be the the case and the virus could affect a significant number of people. It is possible that during the first year of the pandemic, one in every three people will suffer the associated symptoms (although it should be remembered that they will not all be ill at the same time: this is the cumulative total over a period of months). Accordingly, even if morbidity and mortality remain relatively low, the pandemic can have major consequences. It is still too early to offer any accurate assessment.

This chapter opens with a summary of the current knowledge with regard to the patients who have contracted the virus thus far. We then go on to examine the various factors which render it so difficult to predict the course of the pandemic.

2.1 The patients

As of mid-August 2009, the symptoms of illness associated with the current H1N1 pandemic appear to be relatively mild. They are, in any event, less serious than those associated with the H5N1 (avian) influenza circulating in parts of Asia, and are broadly comparable to a bout of ‘regular’ seasonal flu. However, it must not be forgotten that even seasonal flu can have serious effects. To counter seasonal flu, which causes some one thousand additional deaths each year and

has a major impact on public health, the Dutch government has instituted the National Influenza Prevention Programme, under which free vaccination is offered to approximately five million people, including the elderly and the members of certain designated high-risk groups.

The RIVM-CIb's recent advisory report on the provision of antiviral drugs includes an account of the clinical and epidemiological data relating to patients who have contracted the A/H1N1 2009 virus to date.[9] It is unnecessary to repeat this information here, and we may confine ourselves to the additional information which has since become available. This information relates to patient age, the incidence and outcomes of illness among pregnant women and among overweight patients, and the current situation in the Netherlands.

2.1.1 *Patients of different ages*

Alongside the 'usual' flu patients, the patient group to date includes a disproportionately high number of younger patients. A similar situation was noted during the 'Spanish Flu' pandemic of 1918/1919. The WHO's Briefing no. 4 (24 July 2009) states a median age of 12 to 17.[1] However, the briefing also notes that the average age appears to be rising, which can be explained in terms of increased transmission among the general population. In the United States, illness and hospital admissions due to the A/H1N1 2009 virus are more common among the younger age groups (0 to 4 years and 5 to 24 years), but mortality in these groups has remained relatively low. The majority of deaths (in absolute numbers) have been in the 25 to 49 age group. In approximately two thirds of fatal cases, the patient was also suffering from some underlying medical condition. In the United Kingdom (DoH report of 6 August 2009), most new cases of A/H1N1 2009 seem to be in the age groups of 5 to 14 and 15 to 24. The lowest number is to be seen in individuals aged 25 and above, with the incidence reducing in direct proportion to age. The number of cases in the 0 to 5 age group falls somewhere in the middle but the hospitalisation rate in this group is higher: 3.6 per 100,000 cases compared to 1.1 per 100,000 for the population as a whole. It should be noted that these figures relate to clinically diagnosed cases which have not been confirmed by laboratory testing. In the very youngest group, treatment with antiviral drugs is often an indication for hospital admission.

2.1.2 *Illness in pregnant women*

Influenza A/H1N1 2009 seems to cause relatively high morbidity and mortality among pregnant women. In a study conducted by Jamieson and involving a group of 34 infected expectant mothers in the USA, the hospitalisation rate was shown to be higher (0.32 per 100 000) than in the general population (0.076 per 100 000).[12] However, this study concerns a small group of patients, whereupon (as the authors concede) the findings have a high degree of uncertainty. Moreover, and once again the authors stress this point, there are indications that only those cases in which serious symptoms develop are tested and reported. With regard to the probability of hospitalisation, the picture may be distorted as there is a tendency to admit pregnant women with influenza as a precautionary measure.

2.1.3 *Illness in overweight patients*

Anecdotal reports have been received from the United States to the effect that people with morbid obesity are more likely to become ill from Influenza A/H1N1 2009. Patients in this category are overrepresented among those admitted to intensive care units. However, in view of the possible causes of distortion in this observation, the experts are not yet convinced that people who are extremely overweight but do not fall into any of the other risk groups are at any significant additional risk. In many cases, extreme overweight is accompanied by some other chronic condition whereupon vaccination will be offered anyway.

2.1.4 *Patients in the Netherlands*

On 14 August 2009, a total of 1473 people in the Netherlands were recorded as having been infected with influenza A/H1N1 2009. The majority of these patients were between 4 and 46 years of age (median: 20), but the number of confirmed cases in extremely young children was low compared to that in the United Kingdom. In most cases, the progression of the disease prompted no cause for concern. There was no reported overrepresentation of pregnant women, nor of more serious symptoms or complications in pregnant women. A total of 28 patients required hospitalisation; the majority have since been discharged. Clinical information is available for 23 patients, of whom 13 had some underlying medical condition. As of 14 August, only one fatal outcome had been

reported in the Netherlands: a male patient aged 17 with a serious underlying medical condition.

2.2 Factors which may influence the course of the pandemic

There are various factors which may influence the course of the pandemic and which render it difficult to make any accurate predictions about its nature, form or extent. Similarly, it is difficult to make any predictions about the precise effects of any preventive measures.

First, it is by no means certain if the general public is indeed susceptible to the new virus in any great numbers. A pandemic virus – no matter how 'new' – bears similarities to viruses which have previously been in circulation. It is created by a series of random mutations of the genome of the virus, or via a process of 'reassortment'. The question is therefore always: how closely related is the current virus to its predecessors, and do certain people have some (partial or residual) immunity to the new virus? Soon after it was confirmed that a new influenza virus had been isolated and could cause illness in humans, the CDC conducted sera tests on subjects in various age groups. The results showed some cross-protection among those who had been exposed to the 'Spanish Flu' virus in 1918-1919. Similarly, those born prior to 1957 seem to have some degree of protection against the pandemic A/H1N1 2009 virus, presumably acquired through cross-reactivity. The clinical significance of these findings remains unclear at this time.

A second complicating factor is that it is unclear how the pandemic will develop in 2009 and beyond. Will it remain relatively innocuous, responsible for largely mild symptoms? We must take into account the possibility of further mutations or gene reassortment, which may affect the virulence of the virus and its ability to cause serious illness. Such mutations have been seen in previous pandemics. In that of 1918-1919, for example, there was a higher mortality rate during the second wave of the pandemic.

Third, it remains unclear when the pandemic will reach its peak in the Netherlands. This could be in September, before the vaccine is even available, or it could be somewhat later, in which case there will be more time to vaccinate those at greatest risk.

In the United Kingdom, where the pandemic struck earlier and with greater virulence, the first wave now seems to be subsiding. In the early stages of the

pandemic, the increase in the number of cases was far more rapid than in the Netherlands. It would seem that the conditions for large-scale transmission were in place in the United Kingdom to a greater extent than in other European countries. It is possible that there were more frequent introductions of the virus from countries in which it had already taken hold, such as the United States and Mexico.[13] The current decline of the epidemic in the United Kingdom may be due to the summer vacation and the closure of schools and colleges. After all, it is known that the transmission of influenza is dependent in part on seasonal influences, including school holidays. It is estimated that only a very small proportion of the British population has been infected to date, whereupon the possibility of a second wave cannot be excluded.

A fourth factor, directly related to the virus itself, is the possible development of resistance to antiviral agents. If resistance does indeed develop, this could have a major influence on the choice of groups to be offered vaccination, since the opportunity to provide effective post-infection treatment will no longer be available.

The fifth and final factor is the availability of a vaccine. This is of particular importance in relation to the precise time at which the pandemic reaches its peak in the Netherlands. The vaccines currently on order will not be available until October, and delivery of the 34 million doses will be ‘staggered’ in successive batches (see below). If there is an early large-scale outbreak, vaccination will be difficult or perhaps impossible.

Chapter 3

Objectives of vaccination

In any public vaccination programme, it is important to define clearly the purpose of vaccination. In the case of influenza A/H1N1, the objectives are:

1 to preclude or reduce serious illness and mortality by:
   a protecting vulnerable groups
   b countering transmission of the virus, particularly to vulnerable groups;
2 to safeguard the continuity of healthcare services.

In assessing the desirability of a vaccination programme, whether for all members of the public or one or more specific groups, the Health Council applies seven criteria[14], namely:
1 the seriousness and extent of the disease burden
2 the effectiveness of the vaccination
3 the safety of the vaccination
4 the acceptability of the individual vaccination
5 the acceptability of the vaccination within the overall programme
6 the efficiency of vaccination
7 the urgency of vaccination.

These criteria informed the discussions on which this report is based. The most important criteria were adjudged to be the first (seriousness and extent of the disease burden), the second (the effectiveness of vaccination in mitigating the dis-

ease burden), and the third (the safety of vaccination). The seventh criterion – the urgency of vaccination – must also be taken into account when designating those groups for whom vaccination is to be prioritised.

Chapter 4

Decision to begin vaccination

Prompted in part by a previous Health Council advisory report, the Minister of Health has ordered the procurement of a sufficient quantity of vaccine to vaccinate the entire population of the Netherlands (including the Netherlands Antilles) against influenza A/H1N1 2009, should this prove necessary. The Committee responsible for the previous advisory report determined that the decision to procure the vaccine should be separate to that of actually administering it to the general public. The latter decision must be based on a careful consideration of the epidemiological, clinical and virological information available at the time. Although international recommendations such as those issued by the WHO are important, it is evident that the Netherlands has its own responsibilities.

The Netherlands has ordered supplies of vaccine from two companies: Novartis (which is to market its vaccine under the trade name Focetria) and GlaxoSmithKline (Pandemrix). As of 30 July 2009, the contracted delivery schedule for the vaccines was:[15]

- Late October 2009: 2.25 to 3 million doses of Pandemrix and 17 million doses of Focetria;
- Late November 2009: 2.25 to 3 million doses of Pandemrix and 8 million doses of Focetria;
- Late December 2009: 2.25 to 3 million doses of Pandemrix;
- Late January 2010: 2.25 million doses of Pandemrix.

Based on the current information, the experts conclude that adequate protection will be afforded by the admistration of *two* doses of vaccine, at least three weeks apart. If the majority of the vaccine doses are indeed delivered before the end of November as per the contract schedule, there is unlikely to be any shortage. The decision whether to offer the vaccine to certain groups at the earliest possible opportunity can therefore be taken entirely on medical grounds, although logistic factors (such as the availability of enough qualified staff to administer the vaccine) will also be involved.

Given the limited experience with the new vaccines, each patient must be given the same vaccine (Focetria or Pandemrix) on both occasions. No data regarding the compatibility or exchangeability of the two vaccines is available.

Question 0
Should vaccination of certain (risk) groups commence as soon as the vaccine becomes available?

To date, the illness associated with the new influenza A/H1N1 2009 appears relatively mild. The seriousness of clinical symptoms is broadly comparable to that of 'regular' seasonal flu. For the general population, the risk of complications is relatively small. Although the pandemic is known to have caused serious symptoms in a few previously healthy patients, those symptoms have been readily treatable with antiviral agents or other medication (such as antibiotics for bacterial pneumonia) in the vast majority of cases. At the same time, there is very little information about the potential side effects of the vaccines, although these are not expected to be either serious or common. The experts have taken these (potential) advantages and disadvantages into account when considering the vaccination of the general population.

Based on a careful consideration of all factors, the experts currently are not in favour of a general vaccination programme for the entire Dutch population. However, the experts do advise that vaccination should be offered to those groups who are already eligible for vaccination against seasonal flu, together with a number of additional target groups, as defined in Chapter 5.

The uncertainties with regard to the likely course of the pandemic (as outlined above) make it essential to monitor developments very closely. It is possible that those developments will prompt a revision of the current recommendation to desist from general vaccination. The experts therefore plan to reconvene in the latter half of September 2009, or earlier if circumstances demand, to reassess the

situation in the light of any new information which becomes available in the meantime.

Chapter 5

Groups to be considered for vaccination

As stated in Chapter 4, the experts are of the opinion that the 'traditional' risk groups for seasonal influenza should be offered vaccination against the new pandemic form. This chapter examines the other groups which require discussion: pregnant women, healthcare personnel, and the family members and (informal) carers of those with a significantly high health risk.

Question 1
Which groups should be offered vaccination against H1N1?

5.1 Selection on medical grounds

5.1.1 Groups who are already eligible to receive vaccination against seasonal influenza

Already the earliest accounts of patient series suggested that the 'traditional' risk groups are vulnerable to the new influenza virus A/H1N1 2009. The experts therefore conclude that vaccination is appropriate for all groups at medical risk, as per the indication for seasonal influenza vaccination, together with all individuals aged 60 and over, regardless of health status. Although it has been suggested that the latter group may be less susceptible to A/H1N1 2009, perhaps further to

cross-immunity following exposure to a similar virus strain in the past, the research data currently available does not provide sufficient scientific evidence to support this hypothesis. Accordingly, the experts advise that all groups who are currently eligible for the annual influenza vaccine should be offered vaccination against influenza A/H1N1, assuming an adequate quantity of the vaccine is available. According to information provided by the RIVM Centre for Population Screening, which is responsible for coordinating the National Influenza Prevention Programme, the breakdown of these risk groups is as follows:

The target group of individuals under 60 with a medical indication includes approximately 1.5 million people. That of individuals with a medical indication and aged 60 or over numbers 2.1 million. The target group of individuals aged 60 and above with no medical indication numbers 1.3 million. The envisaged target group therefore totals approximately 5 million, including approximately 100 000 patients in residential care.

5.1.2 Pregnant women

According to some reports, influenza A/H1N1 2009 appears to lead to higher morbidity and mortality among pregnant women. In reaching any conclusion about the desirability of offering vaccination to this group, various factors must be taken into account. It is, for example, necessary to distinguish between those women who, regardless of pregnancy, fall into one of the existing risk groups and those who are in good health. The Health Council has previously advised that pregnant women in good health need not be vaccinated against seasonal flu.[7] In some other countries, however, seasonal flu vaccinations are offered to all expectant mothers. One consideration in this context is that pregnant women are more susceptible to the complications of influenza, particularly in the final trimester when breathing can be impaired by a raised diaphragm. The WHO advises that pregnant women should be vaccinated against seasonal flu. In its 2007 advisory report, however, the Health Council notes no additional risk to expectant mothers who are in good health.

In the case of pregant women, the risks associated with (pandemic) flu must be carefully weighed against the safety and effectiveness of the vaccine. Pregnant women with a medical risk factor are already included in the target group for seasonal influenza vaccination, since the risks associated with the disease clearly outweigh any disadvantages associated with the vaccine. For pregnant women

who do not belong to one of the established risk groups, however, the balance is somewhat different.

One important factor in this context is the current lack of information with regard to the potential side effects of the vaccines which are soon to become available. There is very little data relating to the use of the new vaccine during pregnancy, or indeed about the use of the alternative non-adjuvanted vaccines which will not be available in the Netherlands.[16]

Given this lack of information, the WHO recommends that an inactive vaccine without adjuvant should be administered to pregnant women. However, if such a vaccine is not available, the WHO states that an adjuvanted vaccine can be used. The recommendations of the American CDC are based on the use of inactive non-adjuvanted vaccine.

Based on these considerations, the experts recommend that pregnant women who do not belong to one of the recognised risk groups should not automatically be offered vaccination against influenza A/H1N1 2009. For those women who do belong to one of the risk groups, the risk of complications further to infection clearly outweighs any potential adverse effect of vaccination, whereupon the balance falls in favour of vaccination using the adjuvanted vaccines which are to be available in the Netherlands. However, the experts advise that vaccination should only be offered during the second and third trimesters of pregnancy. The experts regard the lack of information, whereupon it is not possible to exclude all risk to the foetus particularly during the first trimester, as a contra-indication to vaccination at this time.

This recommendation implies that special attention must be devoted to women in the existing risk groups who are of child-bearing age. When deciding whether such women should be offered vaccination, the doctor should ask if there is any possibility that the individual in question is pregnant, or intends to become so in the short term. During the first trimester of pregnancy, vaccination should be avoided. Moreover, the patient should take precautions to avoid becoming pregnant within a period of eight weeks following vaccination.

In line with the earlier recommendations with regard to treatment, pregnant women who contract new influenza during the third trimester should be prescribed antiviral drugs. To ensure that the treatment can begin promptly following the onset of symptoms, pregnant women should be given a ‘standby’ prescription for oseltamivir (trade name: Tamiflu), with instructions to begin treatment in the event of fever, following due consultation with the GP.

5.1.3 *Children*

Both the WHO and the CDC recommend that healthy children should be vaccinated against A/H1N1 2009.[1,10] The American data available at this time shows a possible overrepresentation of children and adolescents among patients requiring hospital admission for influenza, but not among the deaths attributable to influenza A/ H1N1 2009 (see Section 2.1.1). Although a similar picture has been seen in the United Kingdom, the British Department of Health does not recommend the vaccination of healthy children.[11]

The Dutch experts believe that, given the mild nature of illness seen in children thus far, the balance between any possible major health benefit and the as yet unknown safety risks of vaccination suggests that it is inappropriate to vaccinate children and adolescents at this time. The Health Council has previously advised that children should not automatically be vaccinated against seasonal flu in the absence of other medical indications.[7]

As stated above, the experts intend to reconvene in September 2009 to discuss the latest developments. The desirability of vaccinating children and adolescents will be reviewed on this occasion.

5.2 Prioritisation for vaccination

Question 2
In what order should the groups selected for vaccination on the basis of medical risk actually be vaccinated if the vaccine becomes available only gradually?

According to the most recent delivery schedule, the vaccine will be available in sufficient quantities to vaccinate all medical risk groups and individuals over the age of sixty at the same time. If this proves not to be the case, the experts advise that the medical risk groups should be given priority over the healthy seniors. This will reduce the number of people to be vaccinated in the first round by approximately one million, leaving a group of approximately 3.7 million. If further prioritisation based on medical risk is required, the experts propose that the order given in the LCI contingency plan *Bestrijding Influenzapandemie* should be observed.[8] In practice, the order will then be:

1 Patients with a serious disorder and functional deficiency of the airways and lungs, patients with a serious (acute or chronic) disorder of cardiac function, and patients with an insulin-dependent form of diabetes.
2 Patients with a disorder and functional deficiency of the airways and lungs, and patients with a chronic disorder of their cardiac function which can be stabilised and reasonably compensated with medication, patients with chronic renal insufficiency (dialysis and kidney transplant patients), children and adolescents aged from six months to eighteen years who have been taking salicylates on a long-term basis, patients undergoing immunosuppressive therapy following bone marrow or organ transplantation, patients with a non-insulin-dependent form of diabetes, individuals with a mental handicap in residential care, others in residential care with a medical condition which predisposes them to respiratory infections.
3 Individuals below the age of 60 with reduced resistance to infections.

5.3 Vaccination of healthcare personnel

Question 3
Should medical personnel be one of the first groups to be offered vaccination and, if so, which specific professionals should be targeted? How will this affect the prioritisation of the medical risk groups?

5.3.1 Healthcare personnel

In 2007, the Health Council advised that all healthcare workers with direct patient contact should be vaccinated against seasonal influenza.[7] This recommendation was not based on any higher risk of personal infection, but on the fact that the vaccination of healthcare workers will help to protect vulnerable patients, particularly since vaccination of the patients themselves does not always provide full protection. Based on the research data available at this time, the Health Council believes that the vaccination of healthcare personnel will reduce the adverse health impact among patients. The experts further cite a specific professional responsibility to reduce the risk of transmission during a pandemic. An additional factor is that vaccination will help to safeguard the continuity of adequate care and will reduce absenteeism through illness.

The experts therefore recommend that vaccination is offered to all healthcare personnel with possible direct contact with patients belonging to one of the defined medical risk groups.

5.3.2 *Family members and (informal) carers of individuals at high risk*

In its earlier recommendations concerning vaccination against seasonal influenza, the Health Council advised that vaccination should be offered to the family members of individuals at extremely high risk of serious illness or death from the effects of an influenza infection.[7] The Committee responsible for this advisory report was unable to define this group precisely, but nevertheless stated that it should include patients with serious disorders of cardiac or pulmonary function who, despite pharmaceutical treatment, were at risk of decompensation, patients with serious liver or kidney failure, and patients with immunodeficiency further to HIV, chemotherapy or immunosuppressive therapy. The experts have adopted this recommendation in the current advisory report on vaccination against influenza A/H1N1 2009.

Should prioritisation nevertheless prove necessary, the experts state that highest priority should be given to healthcare personnel and the other groups listed in Section 5.3, and to the previously defined medical risk groups.

Chapter 6

Practical aspects of vaccination

Question 4

Should the first priority groups be given two doses of vaccine before the next group is called for vaccination, or will one dose (for the time being) be enough for certain groups?

The experts advise that the first dose should be given to all target groups and that the second dose should not be reserved prior to the vaccination. The second dose is usually given three weeks after the first. This interval can be extended if necessary, whereupon the second dose can be given a month later once the second delivery of the vaccine has been received. The American CDC makes the same recommendation.

Question 5

Simultaneous vaccination against pandemic influenza and seasonal influenza

The experts advise against the simultaneous administration of non-adjuvanted seasonal influenza vaccine and adjuvanted pandemic vaccine, as insufficient information concerning the safety and effectiveness of this approach is available at this time. Accordingly, those individuals for whom both types of vaccination is indicated will require three separate vaccination sessions over a period of several weeks.

It will be possible to postpone the seasonal influenza vaccination until the end of November (but no later). Further information may become available in the meantime, whereupon it may be appropriate to give the seasonal influenza vaccination at the same time as the second dose of the pandemic vaccine.

One potential complication is that the virus responsible for influenza A/H1N1 2009 will supplant the strains responsible for seasonal influenza. If this indeed the case, there could be consequences in terms of the need for seasonal influenza vaccination.

As stated above, the experts intend to reconvene in September 2009, by which time new information about this aspect could be available. If so, it will be taken into consideration during the experts' deliberations.

Question 6
Other relevant considerations

6.1 Monitoring

In planning vaccination against pandemic influenza, there remain uncertainties with regard to the course of the pandemic (in terms of scope, extent and duration) as well as uncertainties with regard to the new vaccines. Monitoring is therefore extremely important to enable policy to be modified promptly in the light of new insights regarding the virulence of the virus, the groups who are affected, and the safety of the vaccines. Monitoring is also essential to the effective evaluation of the policy adopted.

The vaccination programme must be conducted with the greatest possible diligence. Monitoring of the epidemiological, clinical and virological characteristics of the pandemic is essential to developing a full understanding of the epidemic and the effects of the preventive measures. The Netherlands possesses top-level expertise in all relevant areas, while the infrastructure in place will greatly facilitate this process. It seems advisable to implement an adequate monitoring system *before* proceeding to undertake the vaccination programme itself.

The monitoring of the vaccine's possible side-effects is of particular importance. Special attention must be devoted to the safety assurance of this new generation of adjuvanted influenza vaccines. A reliable assessment calls for linkage between the vaccination registers and disease registers. It must be possible to see which

vaccine has been given to an individual patient, and when. In addition to the existing passive surveillance system ('Adverse Events Following Immunisation') whereby patients and medical professionals are encouraged to report suspected side-effects, it is recommended that an active surveillance system examining possible side-effects among a sample group of vaccine recipients should be implemented. It is also important to ensure that good written information is provided to all those who receive the vaccine, setting out the anticipated effectiveness of the vaccine and any possible side-effects known thus far.

6.2 Follow-up assessment

In producing this report, the experts have occasionally been forced to rely on incomplete knowledge. The number of cases has been relatively low so far, but the further course of the pandemic is far from clear. It is possible that the nature of the pandemic will alter in the weeks and months ahead.
As stated above, the experts intend to reconvene, most probably in the latter half of September 2009. The question of vaccination for children and adolescents will again be considered at this meeting.

References

1 WHO. Pandemic (H1N1) 2009. 2009. Internet: http://www.who.int/csr/disease/swineflu/en/index.html.

2 Gezondheidsraad. Gebruik van antivirale middelen en andere maatregelen bij een grieppandemie. Den Haag: Gezondheidsraad; 2005: 2005/05.

3 Nieuwe Influenza A (H1N1). 2009. Internet: http://www.rivm.nl/cib/themas/nieuwe-influenza/index.jsp.

4 Gezondheidsraad. Vaccinatie tegen Mexicaanse griep. Den Haag: Gezondheidsraad; 2009: 2009/08.

5 Gezondheidsraad. Vaccinatie bij een grieppandemie. Den Haag: Gezondheidsraad; 2000: 2000/01.

6 Gezondheidsraad. Antivirale middelen bij een grieppandemie; gebruik bij schaarste. Den Haag: Gezondheidsraad; 2004: 2004/05.

7 Gezondheidsraad. Griepvaccinatie: herziening van de indicatiestelling. Den Haag: Gezondheidsraad; 2007: 2007/09.

8 Landelijke coördinatiestructuur infectieziektenbestrijding. Operationeel deeldraaiboek 3. Bestrijding influenzapandemie. 2006. Internet: http://www.rivm.nl/cib/binaries/DB%20Bestrijding%20influenzapandemie%20november%2006_tcm92-33565.doc.

9 Centrum voor Infectieziektebestrijding. Neuraminidaseremmers bij pandemie door Nieuwe Influenza A(H1N1). 2009.

10 CDC. Novel H1N1 Vaccination Recommendations. 2009. Internet: http://www.cdc.gov/h1n1flu/vaccination/acip.htm.

11 Department of Health. Pandemic vaccine priority for most at risk. 2009. Internet: http://www.dh.gov.uk/en/News/ Recentstories/DH_104295.

12 Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS *et al.* H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009; 374(9688): 451-458.
13 Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van K, Hollingsworth TD *et al.* Pandemic potential of a strain of influenza A (H1N1): early findings. Science 2009; 324(5934): 1557-1561.
14 Gezondheidsraad. De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden. Den Haag: Gezondheidsraad; 2007: 2007/02.
15 W. Luytjes, Netherlands Vaccine Institute, written communication, 2009.
16 Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis 2008; 8(1): 44-52.

A Request for advice

B The experts

Annexes

Annex **A**

The request for advice

Date of request: 20 July 2009; reference: PG/CI-2944999

On 8 May 2009, the Health Council of the Netherlands produced the advisory report I had requested on the matter of New Influenza A (N1H1) and possible vaccination against this strain of flu virus. Since then, based in part on the contents of your report, I have ordered the procurement of a sufficient quantity of vaccine to offer every person in the Netherlands two doses, should this prove necessary.

A logistical plan for the vaccination programme is currently in preparation. I am aware that a number of uncertainties remain with regard to the new Influenza A virus. My decision to proceed with a vaccination programme, and the exact form of that programme, will very much depend on the transmission pattern and virulence of the virus itself. Nevertheless, I wish to prepare as thoroughly as possible for the wave of cases which is expected to occur in the autumn, and to plan the various possible scenarios for the vaccination programme. Advice concerning the specific target groups to whom vaccination can and should be offered is of particular importance in this context.

I therefore request the Centre for Infectious Disease Control to prepare a report which answers the following questions, and to liaise with the Health Council of the Netherlands, thereby providing me with the benefit of a joint advisory report. The questions to which I require answers are:

1 Which groups should receive vaccination against New Influenza A (H1N1), based on the international information currently available regarding the morbidity and mortality caused by the new virus?

2 It is unlikely that the vaccine against A (H1N1) will be delivered as a single consignment, but in several successive batches over a period of months. Based on the medical risks, which groups should be the first to be offered vaccination, and what order of priority should be observed?

3 During an influenza pandemic, the healthcare system will be under particular pressure. Moreover, certain groups of healthcare professionals will be exposed to the virus on an extremely regular basis through their contact with patients. In view of this, do you consider it necessary for healthcare staff to be among the first groups to be offered vaccination? Can you identify the particular subgroups or professionals for whom vaccination is particularly important, and how this will affect the proposed prioritisation of the medical risk groups?

4 When procuring the vaccine, we assumed that every individual will require two doses. Should the priority groups you identify be given both doses before vaccination is offered to other groups, or will one dose be sufficient for the time being? This could, for example, be the case with elderly people, who may already have some degree of residual immunity.

5 In the autumn, all individuals aged 60 and over and the members of certain designated risk groups will be offered vaccination against the 'regular' seasonal influenza viruses (i.e. influenza A H3N2/H1N1 and influenza B). Can the new vaccine against influenza A (H1N1) be administered at the same time, or are there contra-indications to this approach? If simultaneous vaccination is not possible, what would be the optimal vaccination schedule?

I further request you to inform me of all other aspects that you consider to be of importance in this context.

I assume that you will base your answers to these questions in part on the findings and current recommendations of the WHO and the ECDC. Because your advisory report will play a decisive part in shaping the plans for the vaccination progamme, I would appreciate its prompt submission. I therefore look forward to receiving your report no later than 15 August 2009.

The Minister of Health, Welfare and Sport,
(signed)
Dr Ab Klink

Annex **B**

The experts

This advisory report has been produced jointly by the Health Council of the Netherlands and the Centre for Infectious Disease Control (part of the National Institute for Public Health and the Environment; RIVM), based on a document produced by the secretaries of these organisations and discussed at an expert meeting held on 10 August 2009. The meeting was attended by:

- Professor J.A. Knottnerus, *chairman*
  President, Health Council of the Netherlands, The Hague
- Professor J.G. Aarnoudse
  Gynaecologist, University Medical Center, Groningen
- Professor R.A. Coutinho
  Epidemiologist/ virologist, Director of the RIVM Centre for Infectious Disease Control, Bilthoven
- Dr. P.J. van Dalen, *observer*
  Ministry of Health, The Hague
- Professor J.T. van Dissel
  Internist-infectiologist, University Medical Center, Leiden
- Professor W. van Eden
  Immunologist, Utrecht University
- Dr. E. Hak
  Clinical epidemiologist, University Medical Center, Groningen
- Dr. C. Herberts
  Medical Devices and Technology division (RIVM), Bilthoven

- Professor M.D. de Jong
  Virologist, University of Amsterdam Medical Center
- Professor J.W.M. van der Meer
  Internist-infectiologist, University Medical Center St Radboud, Nijmegen
- Professor F. Miedema
  Immunologist, University Medical Center, Utrecht
- Professor J. van der Noordaa
  Virologist
- Dr. W. Opstelten
  General practitioner and staff member of the Netherlands Society of General Medical Practitioners, Utrecht (consulted in writing)
- Professor A.D.M.E. Osterhaus
  Virologist, National Influenza Center, Erasmus Medical Center, Rotterdam
- Professor J. van de Velden
  University Medical Center St Radboud, Nijmegen
- Dr. M. Verweij
  Ethicist, Utrecht University
- Professor M. de Visser,
  Chairman, Standing Committee on Immunology and Infectious Diseases, Vice President of the Health Council of the Netherlands, The Hague
- Dr. J. Wallinga
  Population-biologist, RIVM Centre for Infectious Disease Control, Bilthoven
- E.G. Wijnans
  Clinical assessor, Medicines Evaluation Board, The Hague
- Dr. M.A.E. Conyn-van Spaendonck, *scientific secretary*
  Epidemiologist, RIVM-CIb, Bilthoven
- Dr. K. Groeneveld, *scientific secretary*
  Medical immunologist, Health Council of the Netherlands, The Hague
- Dr. H. Houweling, *scientific secretary*
  Epidemiologist, Health Council of the Netherlands, The Hague

This report has been reviewed by the Standing Committee on Immunology and Infectious Diseases of the Health Council of the Netherlands.

The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – 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 President 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 establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.