Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject	: Vaccination against pandemic influenza A/H1N1 2009: target groups and prioritization (2)	
Your reference	: PG/CI-2.955.307	
Our reference	: U-5488/HH/mj/842-K	Publication no. 2009/12E
Enclosure(s)	: 1	
Date	: September 17, 2009	

Dear Minister,

On 17 August 2009, the Health Council of the Netherlands and the National Institute of Public Health and Environmental Protection/Centre for Infectious Disease Control Netherlands presented a joint advisory report on the target groups and the prioritisation of vaccination against pandemic influenza A/H1N1 2009.[1] On 15 September 2009, you requested additional advice. Your questions were discussed by a panel of experts that same day. The answers to your questions are set out below.

Question 1. Is any new data available concerning the epidemiology of influenza A/H1N1 2009 in the Netherlands (numbers, ages, severity of disease, medical high-risk groups), or can such data be expected in future on the basis of international developments in this area, which might justify adding to, or further clarifying, the previous advisory report on target groups and the way in which they are prioritised?

The picture emerging from recent international epidemiological data is consistent with the assessment given in the advisory report that was presented on 17 August 2009. The general picture in the Netherlands is no different from that in other Western countries. The data currently being reported by Southern Hemisphere countries like Australia and New Zealand is of particular interest in this regard. These countries' effective surveillance systems have been accumulating data on the first flu season in which the A/H1N1 2009 influenza virus was involved. Their flu season is now drawing to a close, but the data obtained may well be indicative of the upcoming flu season in the Northern Hemisphere. In the Southern Hemisphere, the A/H1N1 2009 influenza virus appears to have partially – but not completely – supplanted the other flu viruses. Although it

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has been quite short, the 2009 flu season in Australia and New Zealand has placed a heavy burden on these countries' healthcare systems, especially intensive care units.[2,3]

In the course of their meeting on 15 September 2009, the experts mainly addressed the question of whether, in addition to the previously identified target groups, healthy children and healthy pregnant women should also be eligible for vaccination.

In most cases, the course of this infection is quite mild, however there are sporadic instances in which it has a severe or complicated course – primarily in individuals with a known medical risk factor. Data on the severity of cases of disease reported by other countries cannot automatically be extrapolated to the Dutch situation. In Australia, New Zealand and Canada, for example, the percentage of patients with complications was clearly elevated in specific population groups (Aboriginal, Maori and Inuit) which are sparsely represented in the Netherlands. Furthermore, these findings might be partially due to differences in the quality of care.[2,4] For reported cases, the estimated death rate is less than one in a thousand.

In terms of the age distribution of patients, unlike seasonal flu, it is young people who are primarily affected. While there are a relatively large number of cases among children and adolescents below the age of 19, instances of a complicated course and mortality in this age group are no more common than would be expected with seasonal flu.

The incidence of A/H1N1 2009 influenza among older people is relatively small. However, infections in this age group involve a greater risk of complications and mortality than is the case in young people.

At this early stage of the pandemic, there are relatively few scientific publications that could be used to properly assess the risk posed by influenza A/H1N1 2009 to pregnant women. However, reports from various countries consistently indicate that the group of patients with a complicated course includes relatively large numbers of pregnant women, some of whom had no previously known risk factors.[5-9]

To date, no major mutations of the virus have been reported. While there have been sporadic reports of cases of resistance to the usual anti-virals (neuraminidase inhibitors), none of these cases have led to the spread of resistant viral strains.[10]

Based on the above considerations, the experts advise that the recommendations made in the advisory report of 17 August (concerning the target groups for vaccination) be maintained. The latter groups are individuals with medical risk factors, pregnant women in medical risk groups during the second and third trimesters of pregnancy, health-care personnel who may have direct

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contact with patients in the medical risk groups, and the family members and informal carers of individuals who are at very high risk of serious illness and mortality from influenza. For all such groups, the clinching argument is that the health benefits yielded by vaccination clearly outweigh the associated adverse effects (which are expected to be minimal).

In addition, the experts recommend that vaccine be made available to healthy pregnant women in the second and third trimesters. Reports from several countries suggest that even healthy pregnant women can become seriously ill, and some may even die, as a result of infection with influenza A/H1N1 2009. Vaccination might have been useful in cases such as these. It should be borne in mind, however, that there is virtually no scientific data on the use, during pregnancy, of the adjuvants (agents used to boost the immune response) that are contained in vaccines. This lack of data is particularly significant for the first trimester, as it is during this phase that the organs develop and the foetus is most vulnerable. Given this uncertainty, the experts believe that vaccination during the first trimester of pregnancy should be discouraged. The experts take a different stance, however, with regard to the second and third trimesters of pregnancy. Here, as with the first trimester, little is known about the possible side effects of adjuvanted vaccines. Nevertheless, at this stage, the theoretical risk to the foetus is much smaller. Moreover, it is anticipated that the risk of flu will be higher during the second and third trimesters. In view of the reported increased risk to healthy pregnant women, the experts conclude that vaccination should be made available to any healthy pregnant women in their second or third trimester who want it. In this connection, the experts stress the importance of fully informing pregnant women (including those of foreign origin) about these issues. This will enable them to make a considered choice, in consultation with their physician or obstetrician.

The experts advise against extending the provision of vaccination to include healthy children. While that group can be expected to suffer an excessive level of disease, no extra risk of mortality is involved. Children in medical high-risk groups are already included in the target groups for vaccination. The admittedly limited amount of data available reveals a strong correlation between children in medical risk groups and a complicated course.[11] Given the observed burden of disease, the experts feel that the vaccination of all children cannot be justified. An additional consideration is that there is little data on the efficacy and safety of vaccination in children.

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Question 2. On the basis of medical/immunological and registration considerations, can you indicate the maximum period of time allowed between the two vaccinations?

The registration dossiers for the vaccines that will soon be available in the Netherlands cite a minimum period of three weeks between the two doses. On the basis of medical/immunological considerations, there is no fixed maximum period that must be allowed to elapse between the two vaccinations. However, if there is indeed a good case for administering two doses (a point that we will return to later), then the experts feel that the logical approach is to wait no longer than is strictly necessary before administering the second dose. The goal is to synchronise the point of maximum protection for vaccinated individuals with the moment at which the spread of influenza A/H1N1 2009 reaches epidemic proportions in the Netherlands.

In their advisory report of 17 August 2009, the experts stated their intention of returning at a later date to the issue of balancing vaccination against seasonal flu with vaccination against influenza A/H1N1 2009. This was mainly prompted by the fact that the administration of both vaccines leads to a total of three vaccination sessions.[1] The timing of the single dose of seasonal flu vaccine has been brought forward. As a result, that vaccination now precedes the administration of two doses of vaccine against the pandemic virus. The experts recommend that vaccination against influenza A/H1N1 2009 should take place at a separate time from vaccination against seasonal flu. Ideally, these vaccination sessions should be separated by an interval of at least two weeks. If necessary, it would be possible to shorten this interval to just one week. The experts advise against the simultaneous administration of vaccines against seasonal influenza and influenza A/H1N1 2009, as this would make it difficult to separately document the adverse effects associated with each type of vaccination. In their previous advisory report, the experts emphasised the importance of registering any such adverse effects.[1]

Question 3. Does administering one rather than two vaccinations provide sufficient protection for healthy individuals aged 60 or above?

In recent weeks, the initial results have been published of a study into the administration of just one vaccination instead of the two that are currently being proposed.[12,13] This appears to show that a single vaccination may be sufficient to provide protection against infection with influenza A/H1N1 2009.

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However, the experts feel that there is not yet sufficient evidence to proceed on this basis. These results are based on research which involved very small study populations of healthy adults between the ages of 18 and 60. Furthermore, the vaccines used differed from those that are to be deployed here in the Netherlands. No data whatsoever has yet been published concerning the vaccines that are to be used here. Nor can the experts exclude the possibility that these preliminary results may, to some extent, have been influenced by the use of an overly sensitive technique or by previous contacts between the study's subjects and influenza A/H1N1 2009. Effects such as these could have led to an overestimation of the impact of a single vaccination. On the basis of currently available data, the experts recommend that the use of two vaccine doses be continued, even in healthy individuals aged sixty and above. In formulating this recommendation, they took account of the fact that frail elderly people exhibit a relatively weak post-vaccination immune response.

Question 4. Can you indicate the point on the epidemic curve at which (in theory) the benefits to be gained by preventing health impairment no longer outweigh the disadvantages (adverse effects, the effort involved), thereby rendering vaccination superfluous?

On the basis of the current (revised) delivery schedule, the experts anticipate that vaccination of the selected groups will require virtually every dose of vaccine that will be delivered up to the end of November 2009. It is not yet possible to say whether it will be necessary for any batches of vaccine delivered after this period to be earmarked for the vaccination of other target groups.

The experts also take the view that, if the situation surrounding the pandemic remains effectively unchanged, there will be no medical basis for recommending that additional groups be vaccinated. In the previous advisory report, however, they were at pains to point out that there is no way to predict the future course of the pandemic and its effects.1 These events are influenced by factors such as the population's susceptibility to influenza A/H1N1 2009, changes in the virus's pathogenicity, the timing of the peak of the pandemic in the Netherlands, and the possible emergence of resistance to anti-virals.

The experts therefore feel that the limitations of currently available scientific data make it impossible for them to identify a point at which it would no longer make sense to continue with the vaccination programme.

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Question 5. Has further information come to light concerning the safety and efficacy of the vaccines?

The efficacy and safety of the purchased vaccines have primarily been assessed on the basis of mock-up dossiers. In this context, much of the research that was conducted in advance involved model vaccines based on a potential pandemic influenza virus of subtype H5N1. Following identification of the pandemic virus in April 2009, the viral antigen in the vaccines was replaced by that of influenza A/H1N1 2009. The efficacy and safety of the modified vaccines are currently being investigated. This work is still in progress, however. No data has yet been published concerning the vaccines that have been purchased.

A provisional registration has been granted to the manufacturers of the vaccines, on the basis of the data contained in the mock-up files.[14,15] A clinical trial focusing on safety and immunogenicity will be conducted to assess the quality of the vaccines that specifically target pandemic influenza virus A/H1N1 2009. Further modifications, concerning dosage recommendations for example, will be guided by the results of ongoing studies, as and when these become available.

To date, only moderate scale studies have been conducted into the adverse effects of these model vaccines. Currently available data gives no cause for alarm. The adverse effects that have been described to date, while frequent, are nevertheless mild and transient in nature. As yet, little is known about the safety of these vaccines in children and the elderly, and there is no data whatsoever concerning their safety in individuals with a medical risk factor.[14,15]

The methods used in the production of vaccines against influenza A/H1N1 2009 are based on those developed for seasonal flu vaccines. As a result, the safety data for existing vaccines can, to some extent, be extrapolated to the new vaccines. Traditional seasonal flu vaccines have been used extensively over the years, accordingly they can be characterised as very safe.[16] However, health authorities have only limited experience with the adjuvants (agents used to boost the immune response) that have been incorporated into the new vaccines. This therefore limits the extent to which safety data on existing vaccines can be extrapolated to the new vaccines. In this connection it is worth noting that adverse effects (albeit transient ones) occur more frequently with new

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vaccines than is the case with conventional influenza vaccines. MF59, the adjuvant added to one of the two vaccines to be deployed in the Netherlands, has been used in Italy for several years, in a vaccine to protect the elderly against seasonal flu.

As previously mentioned, the recent publications in the New England Journal of Medicine relate to different vaccines than those that are to be used in the Netherlands.[12,13]

The ultimate test of the effectiveness of vaccination will be the pandemic itself. Based on data from the mock-up dossiers and on experience with 'conventional' flu vaccines, the experts consider it highly likely that the new vaccines will prove to be effective against influenza A/H1N1 2009. The use of adjuvants will probably enhance and expand the new vaccines' efficacy relative to traditional flu vaccines, to which no adjuvants are added. The experts take the view that vaccination will probably lead to a significant reduction in disease burden.

In the advisory report of 17 August 2009, the experts indicated that the efficacy and safety of vaccination must be closely monitored from the outset.[1]

Yours sincerely,

(signed)

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

(signed)

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Annex **A**

The request for advice

Date of request: 15 September 2009; reference: PG/CI-2.955.307

On 17 August, you sent me the advisory report entitled 'Vaccination against pandemic influenza A/H1N1 2009: target groups and prioritisation'. In this document, you stated that the panel of experts would meet again in September to review the situation.

I would ask that you address the following questions in the course of that meeting.

1.Is any new data available now concerning the epidemiology of influenza A (H1N1) 2009 in the Netherlands in (numbers, ages, severity of disease, medical high-risk group), or can such data be expected in future on the basis of international developments in this area, which might justify adding to, or further clarifying, the previous advisory report on target groups and the way in which they are prioritised?

2.On the basis of medical/immunological and registration considerations, can you indicate the maximum period of time allowed between the two vaccinations?

3.Does administering one rather than two vaccinations provide sufficient protection for healthy individuals aged 60 or above?

4.Can you indicate the point on the epidemic curve at which (in theory) the benefits to be gained by preventing health impairment no longer outweigh the disadvantages (adverse effects, the effort involved), thereby rendering vaccination superfluous?

5. Has further information come to light concerning the safety and efficacy of the vaccines?

I look forward to receiving the report of your deliberations.

The Minister of Health, Welfare and Sport,
(signed)

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 15 September 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. Koopmans PhD
  Professor of Virological Research for Public Health, Erasmus Medical Centre, Rotterdam, National Institute of Public Health,Bilthoven
- Professor T.W. Kuijpers PhD
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  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
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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.