Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory letter *Vaccination against Mexican flu*
Your reference : -
Our reference : U-5242/JAK/msj/824-E
Enclosure(s) : 1
Date : May 8, 2009

Dear Minister,

On 29 April 2009 you requested the Health Council of the Netherlands to prepare with the necessary expedition an advisory report on a number of questions about the Mexican flu and possibilities of vaccination against it. Referring to your request I asked the Committee which is currently preparing a general advisory report on the role of vaccination in preparation for an influenza pandemic, to report at the shortest possible notice on these questions. The Committee, which has been enlarged with a number of specially invited experts, met on 7 May 2009.

Professor M. de Visser, Vice President of the Health Council and chairperson of the Standing Committee on Infectious Diseases and Immunity, professor H. Verbrugh, and I myself attended the meeting.

In preparing this advisory report various external consultations have been conducted. Also the President of the US Institute of Medicine has been consulted.

I herewith present you the Committee's report.

I can subscribe to the evaluation and conclusions of the Committee.

Yours sincerely,

(signed)
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Gezondheidsraad
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Advisory letter
Vaccination against Mexican flu

Publication no. 2009/08E

1 Requests for advice

On 29 April 2009, the Minister of Health, Welfare and Sport asked the Health Council of the Netherlands to prepare an advisory report on the following points:

1 Can the current seasonal vaccine be expected to provide any degree of protection against serious complications resulting from infection with the 'Mexican flu virus' that is now in circulation?
2 If so, could the 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 flu season?
6 Any other considerations that, in your view, could usefully be communicated in this regard.

1 Background

The Minister has asked the Council to deal with the above questions as a matter of urgency. This task must take priority over the current advisory process, which is addressing the role of vaccination in preparation for influenza pandemics in

general. He has asked the Committee to deliver an advisory report (or advisory letter) in the week of 4-9 May 2009, if possible. Publication of the more general advisory report is scheduled for the beginning of July 2009.

After discussing the matter, the President of the Council and the Committee chairperson have called for an extra meeting of the Committee on *Vaccination during an influenza pandemic*. An important point in this advisory report is to distinguish between assessing the scientific and policy aspects. The decision on whether or not to purchase a vaccine is a political one, and is therefore the Minister's responsibility

2 Preparatory work

As part of the current advisory process concerning the role of vaccination in preparation for an influenza pandemic, the Committee has already gathered and evaluated a great deal of relevant information. This work has already shown that it is very difficult to predict the actual occurrence of an influenza pandemic and the form that it might take. It was partly for this reason that, in the general advisory report, the Committee opted for a flexible approach capable of responding to a range of potential pandemics caused by influenza viruses of various subtypes. The validity of that choice has been borne out by the current wave of Mexican flu. The Committee has answered the Minister's questions with reference to the preparatory work for a general advisory report that is scheduled for publication in early July 2009. That report addresses the role of vaccination in preparation for an influenza pandemic. The Committee has met on one occasion in the context of this specific advisory letter.

3 Answering the questions

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?

As yet it is not possible to give a definitive answer to this question. Laboratory research is currently under way to assess the efficacy of antibodies generated by the seasonal vaccine. It might conceivably have some degree of efficacy, as the current vaccines against seasonal flu include an H1N1 strain. However, genetic analysis of the Mexican flu virus has shown it to be significantly different to the strain used in these vaccines, which is likely to produce a substantial reduction in

efficacy. The Committee concludes that current vaccines against seasonal flu can only be expected to confer a very limited degree of protection at best.

2 If so, could any protection offered by the current seasonal vaccine be enhanced by the addition of new generation adjuvants?

Previous research has shown that the addition of newly developed adjuvants of the oil-in-water emulsion (MF59, AS03) type results in a stronger immune response. This would enable a vaccine to produce a more widespread response and the limited stocks of available antigen to be used more sparingly. It is therefore probable that the addition of such an adjuvant to a vaccine based on the normal H1N1 seasonal strain would confer broader efficacy against H1N1 influenza virus infections. However, in the absence of relevant research data, the Committee cannot yet assess the extent to which an adjuvant-enhanced seasonal flu vaccine would provide protection against the Mexican flu. Given the major antigenic difference between the Mexican flu virus and the H1N1 seasonal strain, an enhanced seasonal vaccine would be unlikely to provide adequate protection.

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?

As yet, there is insufficient data for an adequate assessment of the epidemiological situation. The virus has probably undergone large-scale dispersal within Mexico. The future course of the epidemic outside Mexico remains uncertain. The virus could simply continue to cause scattered infections, but large-scale dissemination is also possible.

Meanwhile, researchers have learned quite a lot about the virus itself. Its capacity for human-to-human transmission seems to be about the same as that of ‘normal’ seasonal flu. To date, infection with this virus has resulted in relatively mild symptoms and low mortality. Unlike seasonal flu, Mexican flu patients include a relative large proportion of young adults.

There is a possibility that the virus will mutate into a more pathogenic strain. As stated in the answer to the first question, any protection offered by the current vaccine against seasonal flu is likely to be very limited (despite the relationship between the H1N1 strain used in that vaccine and the Mexican virus).

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, every reasonably possible measure has been taken to minimise a serious health risk. There is one way of avoiding a situation in which money is spent on a vaccine that ultimately proves to be unnecessary. The terms of purchase should, if possible, enable the antigen (virus) used in this vaccine to be switched for another antigen, if there is a threat of a pandemic caused by a different flu virus.

4 What conclusions can be drawn concerning the possible patterns of protection and adverse effects associated with each of these options?

The Committee assumes that 'each of these options' refers to: 1) an adjuvanted vaccine based on an H1N1 seasonal strain, and 2) a similarly adjuvanted vaccine based on the Mexican flu virus.

In response to the second question, the Committee has already indicated that – in view of the major antigenic difference between the Mexican flu virus and the H1N1 seasonal strain – an adjuvanted seasonal vaccine would be unlikely to provide adequate protection against the Mexican flu virus. No research data is yet available concerning the protection offered by an enhanced (adjuvanted) vaccine based on the Mexican flu virus. However, based on experience with other influenza viruses and vaccines targeted against them, the Committee considers it likely that a vaccine of this kind would indeed be able to provide adequate protection. It is not yet possible to give a definitive answer to the question of whether one or two doses would be needed to provide effective protection. However, two doses would probably be required, at least for certain groups in the population.

Traditional seasonal flu vaccines have been used extensively over the years, accordingly they can be characterised as very safe. Since they have not yet been used so widely, there is less certainty concerning the safety of adjuvanted vaccines. On the basis of currently available data, the possibility cannot be entirely eliminated that such vaccines might cause serious adverse effects in sporadic cases. The importance of maintaining an adverse-effect monitoring system in a state of operational readiness was demonstrated in 1976, in the US, when vaccination against swine flu was followed by a number of cases of paralysis caused by Guillain-Barré syndrome. Although the vaccine involved in that instance was

not adjuvanted, the production process involved differed from those that are normally used in the production of vaccine against seasonal flu.

The Committee has also considered a third option, involving the use of a classic non-adjuvanted vaccine against seasonal flu which incorporates the Mexican H1N1 strain. There are three reasons which argue against the use of an approach of this kind. Firstly, vaccination against seasonal influenza and vaccination in the event of a pandemic involve different target groups. Secondly, a non-adjuvanted vaccine would only be expected to have limited efficacy against an entirely new flu virus. Finally, an adjuvanted vaccine would enable much more economical use to be made of the limited stocks of viral antigen.

If the Minister decides to proceed with the purchase of a vaccine, the Committee concludes that it would be preferable to use an adjuvanted vaccine based on the Mexican flu virus. The efficacy and safety of vaccination should be very closely monitored from the outset (see point 6).

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 flu season?

Vaccine production for the 2009-2010 season is already underway. Some manufacturers have finished (or virtually finished) the viral culture stage in the production of seasonal vaccines. Accordingly, the production of seasonal vaccine by these manufacturers would not be jeopardised, as it would be at a different phase from the production of a possible H1N1 vaccine based on the Mexican flu virus. Other manufacturers have devoted their entire capacity to the production of seasonal vaccine. In their case, a request that they switch to the production of specific H1N1 vaccine might well impair the production capacity for seasonal vaccine. The decision on whether to formally request manufacturers to switch production from seasonal vaccine to pandemic vaccine rests with the World Health Organization (WHO). Based on information provided by manufacturers, the Committee estimates that a possible Dutch decision to proceed with the purchase of vaccine against Mexican flu would not necessarily impair the production of vaccine against seasonal flu. In all probability, an H1N1-specific vaccine would not be available until mid-August, at the earliest.

6 Any other considerations that, in your view, could usefully be communicated in this regard.

- A decision to purchase vaccine against Mexican flu should be seen as a distinct and separate issue from a decision to actually deploy the purchased vaccines. The latter decision should be based on a careful evaluation of epidemiological, clinical and virological data. While the Dutch government naturally has the final say, the Committee takes the view that the authorities should allow themselves to be guided in this matter by the recommendation of the WHO.
- It is vital that great care be exercised if a vaccination programme is put into effect. It is essential that epidemiological, clinical and virological characteristics be closely monitored, in order to keep track of the progress of the epidemic and the impact of preventive measures. It is particularly important to monitor any adverse reactions to vaccination; in this connection it should be possible to link vaccination records to disease registries. In addition to possessing expertise in all of the above fields, the Netherlands also has the requisite infrastructure. It is advisable that experts from the relevant organisations be convened soon, to ensure that an adequate monitoring system is put in place prior to the start of a possible vaccination programme.
- A significant proportion of the morbidity and mortality associated with an influenza pandemic is caused by bacterial super-infection, particularly by pneumococci. With this in mind, the Committee wondered whether vaccination against pneumococcal infections can or should form part of the strategy adopted in preparation for an influenza pandemic. Two types of vaccine are available for use against pneumococcal infections. One is the traditional polysaccharide vaccine, and the other is the more recently introduced conjugate vaccine that is given to infants as part of the National Immunisation Programme. The polysaccharide vaccine is not effective in children, and there is uncertainty about its efficacy in adults and the elderly. The conjugate vaccine has been shown to be highly effective in children and, by means of herd immunity, in the rest of the population as well. The conjugate vaccine may also provide protection for adults, especially the elderly, against pneumococcal infections. However, this cannot be confirmed until current studies have been completed. As yet, the vaccine has not been registered for use in these age groups. In the advisory report entitled ‘Use of antiviral agents and other measures in an influenza pandemic’ (2005/05) the Health Council advised against the use of pneumococcal vaccination during a pandemic. On the basis of current data, the Committee concludes that there is no compelling reason

to review this recommendation. It will explore this subject in greater depth as part of the general advisory report into the role of vaccination in preparation for an influenza pandemic.

- If the decision is taken to proceed with vaccination and a situation arises in which there is insufficient vaccine for the entire population, then the Committee recommends that priority be given to those with a medical condition that places them in the high-risk group, as defined in the advisory report entitled ‘Antiviral agents in an influenza pandemic: use in the event of shortage’ (2004/05). In accordance with the advisory report entitled ‘Influenza vaccination: revision of the indication’ (2007/09), it is recommended that all healthcare workers who have direct contact with patients should also be vaccinated.

Annex **A**

The committee

This advisory letter has been written by the Committee on Vaccination During a Pandemic. Members and advisors of this committee were the following persons:

- Professor E.J. Ruitenberg PhD, *chairman*
  Emeritus Professor of Immunology, University Medical Centre Utrecht; Professor of International Public Health, Free University, Amsterdam
- Professor R.A. Coutinho PhD, *advisor*
  Professor of Epidemiology and Prevention of Infectious Diseases, Academic Medical Centre, Amsterdam; National Institute of Public Health, Bilthoven
- P.J. van Dalen PhD, *advisor*
  Ministry of Public Health, Welfare and Sport, The Hague
- E. Hak PhD
  Clinical epidemiologist, University Medical Centre Groningen
- G. Koch PhD
  Central Veterinary Institute, Lelystad, Wageningen University Research Centre
- Mrs. 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, *advisor*
  Professor of Child Immunology, Academic Medical Centre, Amsterdam
- W. Luytjes PhD, *advisor*
  Netherlands Vaccine Institute, Bilthoven

- W. Opstelten PhD
  General Practioner, Netherlands College of General Practioners (NHG), Utrecht
- Professor A.D.M.E. Osterhaus PhD, *advisor*
  Professor of Virology, Erasmus Medical Centre Rotterdam
- Mrs. A.C.G. Voordouw MPH PhD, *advisor*
  Medicines Evaluation Board (CBG), The Hague
- J. Wallinga PhD
  Population Biologist, National Institute of Public Health, Bilthoven
- Professor J.C. Wilschut PhD, *advisor*
  Professor of Viral Infection Mechanisms and Vaccine Development, University Medical Centre Groningen
- H. Houweling PhD, *scientific secretary*
  Medical Epidemiologist, Health Council, The Hague

The following persons participated as guest scientists in the extra meeting of the Committee for this advisory report:
- G.A. van Essen PhD, Research Fellow in General Practice, Julius Centre, Utrecht
- J. IJzermans PhD, Research Fellow in Public Health Aspects of Acute Care and Disasters, NIVEL, Utrecht
- Professor dr. M. de Jong, Professor of Virology, Academic Medical Centre, Amsterdam

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.