Use of antiviral agents and other measures in an influenza pandemic

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport
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Subject	: report regarding measures to be taken in an influenza pandemic
Your reference	: POG/ZP 2.393.860
Our reference	: -1202/KG/ts/768-I
Enclosure(s)	: 1
Date	: February 14, 2005

Dear Minister,

I am pleased to enclose my Council's advisory report on influenza pandemic response strategy. The advisory report has been drawn up by a specially created committee and reviewed by the Health Council's Medical Standing Committee and Standing Committee on Infection and Immunity. The advisory report addresses the questions posed in your ministry's letter of 7 August 2003 on this topic (your reference POG/ZP 2.393.860) and follows on from the interim report presented in February 2004 (*Antiviral agents in an influenza pandemic; use in the event of shortage* no. 2004/05).

As in the interim report, the committee makes certain recommendations about ways of reducing the temporal concentration of the pandemic and mitigating the consequences of infection. Expanding on the content of the interim report, which outlined how the current limited stock of antiviral agents should be deployed in the event of a pandemic, the committee recommends that the amount of antiviral agents held in stock should be increased to the point where, if a pandemic occurred, it would be possible to treat every resident of the Netherlands exhibiting influenza-like symptoms with neuraminidase inhibitors. I endorse the committee's conclusions.

The committee makes the point that a pandemic is a very unpredictable phenomenon. Therefore, even with a larger stock of antiviral agents, proper 'pandemic preparedness' is very important. The value of being properly prepared has been illustrated by the outbreak of avian influenza ('bird flu')

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in South-East Asia, which has been gathering momentum again in recent weeks, again claiming human victims. Furthermore, cases of person-to-person[1] transmission have very recently been reported in the academic press. In its advisory report, the committee refers to such transmission as one of the key factors in the development of a pandemic.

Yours sincerely,

(signature)

Professor M de Visser,
Vice-president

[1] Ungchusak K, Auewarakul P, Dowell SF, Kitphati R, Auwanit W, Puthavathana P et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med 2005; 352: 333-40.

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to:

the Minister of Health, Welfare and Sport

No. 2005/05E, The Hague, 14 February 2005

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..." (Section 21, 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, and Agriculture, Nature & Food Quality. 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.

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Contents

Executive summary

Influenza viruses give rise to epidemics virtually every year and they occasionally also lead to pandemics (i.e. epidemics on a global scale). Unlike the epidemics, influenza pandemics are, to a great extent, unpredictable. Thus although it is generally expected that another influenza pandemic *will* occur, we cannot predict when this will be. Furthermore, if a pandemic arises abroad it is difficult to predict how long it will be before it reaches our own country. And once it has arrived here, we can only make a partial estimate of how many people will fall ill, which population groups are at greater risk and which individuals, being ill, run a greater risk of complications.

The massive incidence of avian influenza in South-East Asia appears to have increased the risk that a virus strain may emerge that is capable of triggering an influenza pandemic. In preparation for a possible pandemic, the Dutch government has begun to build up a stock of compounds known as neuraminidase inhibitors for use as antiviral agents. On 24 February 2004 the Health Council published the interim advisory report *Antiviral agents in an influenza pandemic*, in which the Committee responsible for preparing the advisory report indicated the measures that it believes would need to be taken if such a pandemic were to reach the Netherlands in the not-too-distant future, and particularly if there were to be a shortage of antiviral agents. In this second advisory report, the Committee puts the recommendations from the interim advisory report into a broader context. The objectives underlying the Committee's recommendations here are the same as in the interim advisory report, namely: to distribute the pandemic over time by reducing the number of infected people and clinical cases and to contain the impact of infection by means of antiviral therapy with neuraminidase inhibitors.

General measures

The Committee reaffirms its medically based recommendation from the interim advisory report that, for the duration of the pandemic, schools should be closed down and events at which large numbers of people gather in a confined space should be cancelled. The Committee realises that this measure would have major social and economic consequences. It therefore understands that the decision to close schools will depend on the anticipated severity and extent of the pandemic, which would largely be determined by the characteristics of the virus (for example its pathogenicity and the speed at which it spreads).

The Committee regards vaccination against influenza as the best means of protecting the population against an influenza pandemic. Should vaccine stocks prove inadequate, the Committee recommends that priority should be given to the particular groups defined in its interim advisory report (i.e. people who fall into a [pandemic-specific] risk group and "professionals").

The Committee also recommends that risk groups should not be vaccinated against pneumococci during an influenza pandemic, since there is no evidence that pneumococcal vaccination confers protection in these groups.

Use of neuraminidase inhibitors in the first clinical cases

When the first clinical cases are recorded, it is likely that outbreaks will be isolated and affect a small number of patients only. If this is the case, and if these patients are traced shortly after they fall ill, the Committee recommends treating the patient and administering postexposure prophylaxis (neuraminidase inhibitors after exposure – or possible exposure – but before clinical symptoms have emerged) to his/her family or household and other close contacts. The aim here is to slow down the pandemic or even to nip it in the bud. The Committee's advice is that these measures should even be adopted when stocks of neuraminidase inhibitors are limited (as is the case at present). This is an extension of the recommendation made in the interim advisory report, where the Committee advocated treatment only (both of the patient and his/her family or household).

Use of neuraminidase inhibitors in a manifest pandemic or in the event of the large-scale introduction of virus from abroad

During a manifest pandemic, the Committee recommends that any resident of the Netherlands displaying a clinical picture that resembles influenza should be treated with neuraminidase inhibitors – preferably as soon possible, but no later than 48 hours after the onset of the first clinical symptoms. This approach serves to mitigate the course of

the disease and helps patients to build up immunity to the virus, meaning that they will not fall ill (or at least that they will be far less affected) in the event of a second infection. The Committee's advisory report implies that stocks of neuraminidase inhibitors need to be expanded to such an extent that there is enough to treat all residents of the Netherlands with influenza. Since it is estimated that up to 30 percent of the population could become ill during a pandemic, the Committee anticipates that a total stock of five million courses of the neuraminidase inhibitor oseltamivir is sufficient.

The Committee does not even advocate prophylaxis in the presence of adequate stocks of neuraminidase inhibitors, because then protection would only be conferred for as long as the compound is used. After the therapy is stopped, the person would still be vulnerable to the virus owing to a lack of immunity. During a manifest pandemic, however, the Committee can envisage that the neuraminidase inhibitors might be used prophylactically in particular groups or under particular circumstances. What it has in mind here are patients whose immune system is compromised (e.g. as a result of bone marrow transplantation) or the occurrence of influenza in a department of a care home or nursing home that can easily be isolated. The Committee recommends that the decision on whether to administer prophylaxis should be left to the individual patient's attending physician.

Comments

The Committee regards the procurement of a sufficiently large stock of neuraminidase inhibitors as just one of the elements required in order to prepare for the use of these compounds during a pandemic. The Committee does not believe that its remit includes a detailed elaboration of the logistical implications of its recommendations. It therefore confines itself to noting that the success of the use of neuraminidase inhibitors will depend to a great extent on the way in which this strategy is implemented.

The Committee is not currently in a position to quantify the cost-effectiveness of its recommendations (e.g. in terms of the cost per quality-adjusted life-year). It believes that there are too many uncertainties – not only of a factual nature (e.g. the timing of the pandemic and the characteristics of a future pandemic virus) but also uncertainties that can only be eliminated through (possibly arbitrary) policy choices. The Committee provides a summary of the elements that feature in an evaluation of cost-effectiveness, but feels that it is not incumbent upon it to make these choices.

The Committee's recommendations are based on the current, limited, state of knowledge. Its advice is therefore that its recommendations should be kept in line with advances in knowledge and that the opinion of experts should be sought when making

decisions on what action is to be taken (for example from the new centre for infectious disease control).

The chances of gaining some insight into the pandemic will improve if it begins abroad and only reaches the Netherlands after some time has elapsed. Use can then be made of data from the countries that have already been affected.

Chapter 1

Introduction

Ministerial commission

On 7 August 2003, the Health Council was commissioned by the Minister of Health, Welfare and Sport to report on the use of antiviral agents in an influenza pandemic. More specifically, the minister asked the Health Council to describe the latest scientific thinking and developments concerning antiviral agents and to review the RIVM report *Development of Scenarios for Care Demand in an Influenza Pandemic*. The minister also requested that, using the recommendations as a basis, the Health Council should outline a number of scenarios describing the course that a pandemic might take in the Netherlands and indicate what response would be appropriate under each scenario. Once preparatory work had been started in autumn 2003, the Vice-President of the Health Council set up a special committee on 20 January 2004 to produce the requested report.

The interim report

The large-scale outbreak of avian influenza in South-East Asia has increased the likelihood of a virus strain emerging, which is capable of being transmitted from person to person and thus causing an influenza pandemic. In order to deal with any such pandemic, the Dutch government has started stockpiling neuraminidase inhibitors (a type of antiviral agent). In view of the exceptional circumstances, the Health Council issued an interim report on 24 February 2004 entitled *Antiviral agents in an influenza pandemic; use in the event of shortage*. In this report, the committee identified various measures

that it believed should be taken in the early stages of a pandemic affecting the Netherlands, if there were a shortage of antiviral agents. The interim report also indicated the population groups that should have priority in terms of the administration of neuraminidase inhibitors. The Minister of Health, Welfare and Sport accepted these recommendations.

The second advisory report

The document now before you – the committee's second advisory report on this topic – places the interim report's recommendations in a wider context. Chapter 2 describes the characteristics of the influenza virus that are relevant in relation to pandemic response strategy. In chapters 3 and 4, consideration is given to various supplementary measures. As part of this review, a number of population groups are identified that are regarded by the committee as recipients of neuraminidase inhibitors for treatment or prophylaxis; in addition, the committee describes the approach that should be taken if neuraminidase inhibitor stocks are sufficient. In the report's concluding chapter, the committee makes a number of comments concerning its recommendations.

Finally, the committee wishes to emphasise that its advice is necessarily based upon limited scientific data. Little is yet known, for example, regarding the effect of administering neuraminidase inhibitors to the 'classic' risk groups, such as older people. Furthermore, in the event of a pandemic, a great deal would depend on the properties of the virus strain involved. Without a pandemic in progress, the committee can make general recommendations only.

Chapter 2

Influenza

The influenza virus is capable of causing both epidemics and pandemics. Here, the committee describes each phenomenon individually, examining the various genetic mechanisms involved. In this context, the committee gives particular attention to the unpredictable nature of pandemics, since this unpredictability is a complicating factor in the formulation of advice regarding an appropriate response strategy.

2.1 Epidemics and antigen drift

In countries where the climate is moderate, influenza viruses cause influenza epidemics on an almost annual basis. Influenza epidemics are able to recur in this way because of what is known as 'antigen drift' in the influenza A and B viruses, brought about by mutations in the genes for the virus proteins haemagglutinin and neuraminidase[1]. Antigen drift means that minor changes are constantly occurring in the antigen make-up of the virus, enabling it to re-infect people who have already had influenza.

During an epidemic, healthy people endure influenza in general well. The antibodies formed in response to the infection protect against re-infection by the same virus strain and – by a process known as cross-protection – against a strain with a similar antigen composition. The further the process of antigen drift has gone, and therefore the more different a strain is from anything an individual has previously encountered, the less benefit is afforded by cross-protection and the greater the risk that the new strain will cause influenza in the individual in question.

Among risk groups, such as older people, vaccination is used to reduce the chances of influenza infection. The composition of the vaccine is adjusted annually in line with the virus strains in circulation. Vaccination provides adequate protection as long as the antigen composition of the strain with which a person comes into contact is reasonably similar to that of the strains used for preparation of the vaccine.

2.2 Pandemics and antigen shift

Much less frequent than epidemics, but also much more unpredictable, are pandemics caused by the influenza A virus. A pandemic is a global epidemic caused by a virus that, in terms of antigen composition, is very different from those that have previously circulated. Three such pandemics occurred during the twentieth century[2]. The 'Spanish influenza' pandemic of 1918 claimed tens of millions of lives, making it one of the most serious outbreaks of infectious disease on record[3].

The process underpinning the occurrence of influenza pandemics is 'antigen shift'[1]. Antigen shift is brought about by the transfer of genetic material (particularly the genes for haemagglutinin (H) and neuraminidase (N)) from one virus strain to another. Such transfer can occur when a single organism is simultaneously infected by two virus strains. The most commonly cited example of such 'co-infection' involves a pig infected by both a 'human' strain of influenza A and an 'avian' strain of influenza A[4]. Antigen shift leads to the development of a virus subtype whose antigen composition is very different from its predecessors, with the result that the population has insufficient (cross-) protection against such a virus and existing vaccines are ineffective. If a 'new' subtype of this kind can infect humans and can be transmitted from person to person, there is a risk of a pandemic.

2.3 Unpredictable nature of a pandemic

Influenza pandemics are very unpredictable. So, while it is generally anticipated that there will be another influenza pandemic at some time, no one can say when[2,5]. Nevertheless, one can say that the large-scale outbreak of avian influenza in South-East Asia has increased the likelihood of a pandemic[6,7].

Although it is now more likely that another pandemic will begin in Asia, one can only estimate approximately how long any such pandemic would take to reach the West. On the basis of data on the spread of pandemics and on air travel, various authors have suggested periods of up to four months[2,8]. However, the committee believes that – as one of the authors in question suggests[2] – the spread of a pandemic could be greatly hastened by modern air travel patterns.

Earlier pandemics have tended to spread in waves: there have been alternate highs and lows in the rates of infection and mortality[9]. Whether a future pandemic would follow a similar pattern cannot be stated with certainty. In previous pandemics, a wave typically lasted six to eight weeks; however, the periods between waves varied, as did the numbers of people infected and killed in each wave[9].

It is difficult to estimate how many people would be affected in the event of a pandemic reaching the Netherlands, to indicate which groups are most likely to get ill, or to indicate which ill people develop complications. During the last three pandemics (1918 to 1919, 1957 to 1958 and 1968 to 1969), roughly 25 to 30 per cent of the population in the affected countries became ill[10-13]. Data on the last pandemic of the nineteenth century indicate that the percentage on that occasion was even higher[13]. In contrast to the situation during an influenza epidemic, when fatalities are confined mainly to older people, during a pandemic higher levels of mortality are also seen amongst people who do not belong to the classic risk groups[14]. In the interim report, the committee already mentioned to the increased rate of mortality recorded among twenty-to-forty-year-olds during the 'Spanish influenza' pandemic[14,15]. This pattern was also evident in the data that the Health Council gathered at the time and published in 1921[16]. During the pandemics of 1957 and 1968, the mortality pattern was more consistent with that seen in 'ordinary' epidemics: most deaths involved either very young children or older people[3]. Most of the people who died during the recent outbreak of avian influenza in South-East Asia were under the age of twenty[6,7]. It is not entirely clear why different age groups should have been most at risk in successive pandemics. It is worth pointing out that an equally virulent virus would probably claim fewer victims in the Netherlands today than Spanish influenza claimed, because the Dutch population is generally in better health and because medical science has moved on considerably both in terms of insight and in terms of available treatments. At the time of the Spanish influenza pandemic, for instance, there were no antibiotics to treat people who developed secondary bacterial pneumonia.

Chapter 3

Measures

In its interim report, the committee indicated that, in the event of a pandemic reaching the Netherlands, the aims should be to reduce the temporal concentration of the pandemic by reducing the number of people becoming infected and falling ill, and to mitigate the consequences of infection by antiviral therapy[15]. The committee also identified a number of measures that it regarded as necessary for realisation of these aims, including the avoidance of large gatherings, vaccination, and treatment with antiviral agents during a shortage.

In this chapter, the committee describes the first of these two measures in more detail. The use of antiviral agents is covered in chapter 4. The basic aims of the measures are as previously stated in the interim report.

Before describing the proposed measures in detail, the committee wishes to emphasise the importance of general measures to prevent infection. For example, good manual hygiene, particularly among healthcare workers, can help to control the spread of the virus. Whether wearing masks over the nose and mouth is also beneficial is less clear; in the Canadian Pandemic Influenza Plan, the use of masks is advocated primarily for healthcare workers in the early stages of the pandemic[2]. There is no evidence that mask-wearing by the population at large offers any protection during a manifest pandemic[2].

In this context, the following point is also worth making ahead of the committee's recommendations. Because pandemics are inherently unpredictable, and because circumstances in the early stages of a pandemic differ considerably from those that prevail once

a pandemic is in full swing, the committee can at present indicate only what it regards as *theoretically* the most appropriate measures. The committee therefore advises that its recommendations should be reviewed in line with medical advances and to consult appropriate experts and expert bodies, such as the fledgling Centre for Infectious Diseases, before taking action.

3.1 Preventing concentrations of people

In the interim report, the committee recommends that, during a pandemic, schools should be closed and events at which people gather in large numbers should be cancelled in regions where influenza is prevalent[15].

RIVM's scenario analysis suggests that at the peak of a pandemic the closure of schools would also lead to a reduction in the number of infected people[8]. The committee accordingly believes that, from a medical viewpoint, it is best that schools remain closed and that public events do not go ahead for the duration of (the various waves of) a pandemic. The committee nevertheless recognises that this could have serious social and economic consequences and therefore recommends that a decision as to whether schools are closed should depend on the anticipated seriousness and scale of the pandemic. These mainly depend on the properties of the virus, such as its virulence and the speed of its spread.

3.2 Vaccination

3.2.1 Vaccination against influenza

As indicated in the interim report, the committee regards vaccination against influenza as the best means of protecting the population against an influenza pandemic[15]. In the present context, the committee wishes only to reiterate its view that the development of a vaccine should be the absolute priority. However, even if everything possible is done in this regard, it is likely to be six to twelve months before a vaccine against the relevant pandemic strain can be developed and produced in sufficient quantities. Furthermore, a vaccinated individual does not have adequate immunological protection against an influenza virus until several weeks after inoculation.

If vaccine stocks are insufficient for general vaccination, the committee advises giving priority to vaccination of the special groups defined in its interim report, people in (pandemic-specific) risk groups and professionals[15].

3.2.2 *Pneumococcal vaccination*

The committee responsible for the Health Council's 2000 report *Vaccination in an influenza pandemic* advised that, in the event of a shortage of influenza vaccine, certain defined risk groups should be vaccinated against pneumococci[17]. This recommendation was made with a view to protecting the population against secondary bacterial pneumonia, which is caused by pneumococci in many cases.

However, the committee that subsequently drew up the 2003 advisory report *Vaccination of older people and risk groups against pneumococci* indicated that there was no evidence that pneumococcal vaccination was beneficial either to the over-sixty-fives or to people in the most urgent risk group referred to in the 2000 report[18]. The 2003 committee's conclusions were based partly on the findings of a 2001 meta-analysis by the *Dutch Cochrane Centre*[19], which had not been available to the earlier committee.

The present committee endorses the conclusions of the 2003 advisory report on pneumococcal vaccination and accordingly advises against pneumococcal vaccination in the event of an influenza pandemic.

Chapter 4

The use of antiviral agents

In the interim report, the committee indicated that neuraminidase inhibitors were preferable to first-generation antiviral agents, because the latter have relatively strong side-effects on the central nervous system in particular and because of the relatively rapid emergence of resistant virus strains[15,20]. Research into new neuraminidase inhibitors is in progress[21], but it is unlikely that such agents will be available in ample quantities for several years, mainly because development work on a number of them has been halted[22]. In the context of this advisory report, the committee has therefore confined itself to the neuraminidase inhibitors oseltamivir and zanamivir, since sufficient data are available on the clinical use of these antiviral agents.

4.1 Neuraminidase inhibitors

Definitions

The neuraminidase inhibitors are registered both for treatment (in the case of both oseltamivir and zanamivir) and for prophylaxis (in the case of oseltamivir)[23,24]. The committee has applied the following definitions.
Prophylaxis: the use of oseltamivir (a single daily dose of 75 mg for a period of up to six weeks) by a person who shows no symptoms of illness, with a view to preventing infection.

Postexposure prophylaxis: the use of oseltamivir (a single daily dose of 75 mg for seven days) by a patient's family, housemates and other contacts after possible exposure but before the manifestation of symptoms.
Treatment: the use of oseltamivir (two daily doses of 75 mg for five days) or zanamivir (two inhalations of 5 mg twice a day for five days) by a patient showing symptoms of illness consistent with infection by the influenza virus, such as fever, a suddenly acquired cough and, for example, headache or aching muscles[25]. When an influenza virus is in circulation, it is very likely that a patient displaying such symptoms has been infected with the virus[26]. The committee emphasises the importance of beginning treatment as soon as possible after the appearance of the first symptoms, and certainly within forty-eight hours.

Effects

In its interim report, the committee indicated that the treatment of otherwise healthy influenza patients with neuraminidase inhibitors reduced the duration of the illness by one to two days, and was associated with lower levels of antibiotic use and a lower incidence of pneumonia[15]. This statement was based primarily on the findings of a systematic review of the research data published up to that time, which had appeared in 2003[27]. The effects of treating people in risk groups is much less clear, mainly because much less research has been done in this field. However, a recent publication suggests that the treatment of risk-group influenza patients with oseltamivir is also associated with reduced antibiotic use because of the lower levels of influenza-related respiratory infection[28].

Knowledge regarding the use of neuraminidase inhibitors for prophylaxis is similarly sketchy[27]. Nevertheless, the available data suggest that both oseltamivir and zanamivir have a strong protective effect. It should be noted, however, that the latter agent is not registered in the Netherlands for prophylactic use.

Side-effects

The clinical trial data published to date indicate that neither oseltamivir treatment nor zanamivir treatment has significant side-effects[27]. Only in exceptional cases have the reported side-effects been sufficiently serious to require treatment to be abandoned.

The Committee for the Safety of Medicines recommends adjusting the dosage of oseltamivir when treating an adult who suffers from serious renal insufficiency[24]. Because zanamivir is administered by inhalation, it has occasionally been known to trigger a bronchospasm or impair pulmonary function. The latter Committee has indicated that, because of the limited number of patients studied, it is not possible to say whether

zanamivir is safe for the treatment of people with serious asthma or other serious chronic respiratory conditions, people with unstable chronic conditions or people whose immunity has been compromised[23]. Reports suggest that the inhaler system can be difficult to use with older hospitalised patients[29].

The Committee for the Safety of Medicines has additionally indicated that insufficient data are available regarding the use of oseltamivir or zanamivir for the treatment of pregnant women or breastfeeding mothers[23,24]. The Committee therefore suggests that neuraminidase inhibitors should be given to women in these groups only if the potential benefits for the mother outweigh the potential side-effects on the foetus or infant.

4.2 Use of neuraminidase inhibitors for treatment of early cases

If a pandemic takes hold abroad, the first cases in the Netherlands are likely to be isolated, involving a small number of so-called 'index patients'. Under such circumstances, if the index patients are identified within a short time of becoming ill, the committee recommends the treatment of these patients and the postexposure prophylaxis of their families, housemates and other close contacts, such as the doctors and nurses caring for them[30]. In a recent publication, the phrase 'ring prophylaxis' has been coined to describe this type of strategy[31]. The committee expects that the effects of postexposure prophylaxis will be greater if at the same time steps are taken to prevent people gathering in large groups, as described in subsection 3.1.

This recommendation goes beyond what was proposed in the interim report, where the committee suggested only the treatment of patients and the prompt treatment of their families and housemates[15]. The committee has revised its interim advice because there is a growing body of evidence that postexposure prophylaxis for a period of seven[32] or ten[33,34] days reduces the incidence of influenza in treated households and diminishes excretion of the virus by people who become ill in spite of such prophylaxis[32]. Mathematical analyses, including the RIVM's scenario analysis, indicate that the recommended strategy could mitigate or even stop a pandemic[8,35]. Interestingly, the model developed by Longhini *et al*[35] suggests that postexposure prophylaxis is most effective if continued for eight weeks. Nevertheless, the committee recommends a prophylactic period of seven days, mainly because the effect of such limited prophylaxis has been clinically demonstrated[32], but also because an eight-week prophylaxis period would have serious implications for neuraminidase inhibitor stocks. Although the evidence is limited, it does not appear that postexposure prophylaxis is more effective if maintained for ten days than if maintained only for seven days[32-34].

The success of the recommended strategy would depend on identifying the index patients quickly. The committee believes that the surveillance mechanisms in the Netherlands are sufficiently good to make this possible. Furthermore, the medical profession

is very alert to the dangers following the large-scale outbreaks of avian influenza in the Netherlands and now in South-East Asia.

The committee regards postexposure prophylaxis as advisable in the event of a pandemic even with the limited existing stocks of oseltamivir (200 000 to 250 000 courses, assuming the quantity required for treatment). This agent would then not be available for the treatment of people who become ill, but would be used to slow the spread of the pandemic or perhaps even nip it in the bud[8] – either of which would be a worthwhile objective.

The committee regards the use of neuraminidase inhibitors for postexposure prophylaxis with a view to halting or slowing the spread of a pandemic, as desirable only while the scale of the outbreak remains limited. The committee therefore advises that any decision to initiate or cease postexposure prophylaxis should be taken in consultation with appropriate experts and expert bodies, such as the fledgling Centre for Infectious Diseases.

4.3 Use of neuraminidase inhibitors in a manifest pandemic or in the event of large-scale virus introduction from abroad

4.3.1 Treatment

The committee advises that, during a manifest pandemic, all residents of the Netherlands showing symptoms of illness consistent with infection by the influenza virus should be treated with neuraminidase inhibitors as soon as possible following the appearance of the first symptoms, and certainly within forty-eight hours. In the interim report, the committee outlined how such treatment influences the course of the illness while the development of immunological protection against the virus still occurs, as a result of which someone who is infected a second time will not become ill or will become much less seriously ill. If treatment is started later, it may not be effective[3,20].

The thinking behind the committee's advice is that, because of the current shortage of antiviral agents, most people in the Netherlands would receive neuraminidase inhibitors only if they were admitted to hospital with a complicated influenza infection. In the interim report, the committee pointed out that there was little or no clinical evidence that the treatment described is beneficial[15]. It is worth noting that there are also gaps in the evidence supporting neuraminidase inhibitor administration immediately following appearance of the first symptoms. Comparatively little is known, for example, about the effect of treating children, older people and people in risk groups.

The committee's advice implies increasing stocks of antiviral agents to the point where, if a pandemic occurred, it would be possible to treat everyone in the Netherlands

who appears to have influenza with neuraminidase inhibitors. On the basis of what happened during earlier pandemics (see subsection 2.3), the committee anticipates that up to 30 per cent of the population could become ill during a future influenza pandemic. A total stock of five million courses of oseltamivir should therefore be sufficient.

The committee reiterates the proposal made in its interim report[15], namely that the purchase of the neuraminidase inhibitor zanamivir should be considered if the recommended number of courses of oseltamivir cannot be obtained.

4.3.2 *Prophylaxis*

In the interim report, the committee indicated that, if there should be a shortage of neuraminidase inhibitors during a pandemic, prophylaxis would not be appropriate[15]. The committee also believes that neuraminidase inhibitors should be used for treatment (as opposed to prophylaxis) even if stocks are ample. The reason being that prophylaxis offers protection only for the duration of the course of administration. Once the therapy stops, the person has no immunological protection and is therefore vulnerable to the virus. Hence, if the initial wave of a pandemic should prove to be prolonged, or if there should be a second wave, prophylaxis recipients would require a second course of therapy or would be at just as much risk as if they had never received the first course. The committee therefore recommends that, during a manifest pandemic, neuraminidase inhibitors should be given on a prophylactic basis only to certain special groups of people or under special circumstances.

Special groups

The committee believes that prophylaxis should be considered for certain groups of patients for whom a policy of treatment only in response to the appearance of the first symptoms would entail excessive risk. Particularly, the committee has in mind people whose immune systems have been compromised, such as those who have undergone bone marrow transplantation or who are suffering from AIDS and have a very low CD4-positive T-cell count. The committee advises that it should be up to the doctor in charge to decide whether prophylaxis is appropriate.

The committee does not favour prophylaxis for all nursing home or care home residents; in principle, such people should be treated as soon as possible in response to the appearance of the first symptoms. Research findings from the United Kingdom suggest that the provision of prophylactic therapy to all the residents of a nursing home or care home as soon as one resident shows symptoms consistent with influenza would require large quantities of neuraminidase inhibitors[36]. Nevertheless, the committee can imagine that, where one or more patients are very weak, or where special circumstances exist

(e.g. where influenza is confirmed within a readily isolated ward at a particular establishment), the doctors in charge may consider prophylaxis advisable.

A report published by the Canadian authorities identifies certain essential service workers, such as police officers and fire-fighters[2], for whom prophylaxis with antiviral agents is recommended. However, the present Health Council committee does not advise a similar policy in the Netherlands; the recommended strategy is immediate treatment of essential service workers only in response to the development of influenza symptoms, so that such individuals also acquire immunological protection.

Special circumstances

As indicated earlier in this report, one may not be fully resistant to infection for several weeks following influenza vaccination, since it takes some time to build up immunity (see subsection 3.2.1). If sufficient stocks are available, while the virus is circulating, the committee advises giving neuraminidase inhibitors on a prophylactic basis to the predefined (pandemic-specific) risk groups and professionals during the period that they are building up immunity following vaccination[15].

The committee's recommendations regarding the use of neuraminidase inhibitors in an influenza pandemic are summarised in Table 1.

Table 1 Use of neuraminidase inhibitors in an influenza pandemic.

	treatment	prophylaxis
when the pandemic first reaches the Netherlands	index patients[a]	Families, housemates and other contacts of index patients[b]: postexposure prophylaxis
in a manifest pandemic or in the event of large-scale virus introduction from abroad		
if neuraminidase inhibitors are in short supply	risk groups[c], professionals[d] and (where relevant) people in pandemic-specific risk group; otherwise healthy people: in the event of hospitalisation due to complications	
if neuraminidase inhibitors are NOT in short supply	patients displaying symptoms consistent with influenza	individual patients[e] and risk groups, professionals and (where relevant) people in pandemic-specific risk group[f]

a As soon as possible following the appearance of the first symptoms; if treatment is not started within forty-eight hours, it may not be effective
b Not previously recommended in the interim report
c Patients with serious respiratory, pulmonary or cardiovascular abnormalities or dysfunctions, who if infected with the pandemic influenza virus would be at serious risk of pulmonary or cardiovascular function decompensation, patients with an insulin-dependent form of diabetes
d All persons responsible for the diagnosis, treatment and care of influenza patients, or for logistic management of the necessary resources
e Where considered appropriate by the doctor in charge of the individual patient
f Following vaccination and while the virus is circulating

Chapter 5

Qualifying comments and implications

The committee advises increasing the stock of neuraminidase inhibitors held by the Dutch authorities to the point where it is sufficient for large-scale administration in the event of a pandemic. While not wishing to dilute this advice, the committee feels that its recommendation should be qualified in certain respects and that a number of points should be made regarding the implications of the recommended strategy.

5.1 Insufficiency of the available scientific data

In its interim report, the committee made reference to two systematic reviews of data on the use of neuraminidase inhibitors, which had appeared in 2003. The authors of these reviews concluded that the data on the relevance of the effects associated with the use of such agents were insufficient[20,27]. The paucity of data has also been highlighted in this advisory report. Where treatment is concerned, the gaps in knowledge relate primarily to the effects on people in risk groups and to the impact on hospitalisation and mortality rates. Where prophylaxis is concerned, there is a general shortage of data. Since the 2003 reviews appeared, more information has been published concerning the use of oseltamivir for both prophylaxis[34] and the treatment of people in risk groups[28].

The committee's recommendations are based on current scientific knowledge and thinking. It is important to recognise that the situation during a future pandemic may be very different from the situation during an epidemic (the type of outbreak on which most research is based); for example, the illness may take a different clinical course during a pandemic, or it may emerge that certain groups are at risk in the specific context of the

pandemic (see subsection 2.3). The committee therefore advises reviewing its recommendations in the light of the constantly increasing scientific insight and adjusting the response strategy as appropriate. There will be more scope for strategy revision if any future pandemic starts elsewhere and takes some time to reach the Netherlands, since the Dutch authorities will be able to learn from knowledge gained in other countries. In this context too, the committee advises that the fledgling Centre for Infectious Diseases should be consulted before any decision is taken regarding the use of neuraminidase inhibitors.

In view of the paucity of scientific data available, the committee would also reiterate the recommendation made in its interim report that, during any future pandemic, proper arrangements should be made to document the use of neuraminidase inhibitors and the results of such use, in order to provide data for subsequent research purposes.

5.2 Resistant virus strains

Until recently, virus strains resistant to neuraminidase inhibitors were very rarely encountered, either in the laboratory[22] or in a clinical setting[37,38]. Those that were encountered were (much) less infectious than the strains from which they had evolved.

However, Japanese researchers have very recently published study findings that appear to point to a change in this picture: in nine of fifty child subjects who had been treated with oseltamivir, virus strains were isolated that were resistant to this neuraminidase inhibitor[39]. It is not (yet) clear whether the resistant strains are transferable to other people, or how infectious the new strains are. Further research in this field is strongly recommended[40].

The committee considers the results of the initial Japanese study to be noteworthy. How significant the discovery of the resistant virus strains ultimately proves to be will depend on their virulence and on whether similar incidences of resistance are observed in other patient populations. The published results emphasise the importance of monitoring the emergence of resistance in the context of the neuraminidase inhibitor use documentation programme referred to earlier.

5.3 Costs and effectiveness

With a view to ensuring that neuraminidase inhibitors are put to the most cost-effective use, the committee wishes to see the emphasis placed on treatment as opposed to prophylaxis (with the exception of ring prophylaxis in the context of the first reported cases).

The committee believes that the use of neuraminidase inhibitors should be geared to mitigating the seriousness of the illness as far as possible and minimising mortality among those who contract it, while allowing for the development of immunological protection against the pandemic virus. With these aims in mind, the committee advises that, if there is a shortage, neuraminidase inhibitors should be used for the treatment of professionals and people in risk groups, provided that such treatment can be started within forty-eight hours of the first symptoms appearing, and for the treatment of other people only in the event of hospitalisation[15]. If there is no shortage of antiviral agents, neuraminidase inhibitors should be used to treat anyone in the Netherlands showing symptoms consistent with influenza, again provided that such treatment can be started within forty-eight hours of the first symptoms appearing.

The committee does not regard prophylaxis for the entire population of the Netherlands as efficient, because the protection thus afforded would last only as long as neuraminidase inhibitor use continued. As soon as prophylaxis stops, an individual is just as vulnerable to the virus as he or she had been before starting prophylaxis, since no immunological protection has been acquired. For this reason, the committee advises keeping the number of people considered for prophylaxis down to the minimum, even during a manifest pandemic.

The committee does nevertheless see a role for prophylaxis when the first cases are detected in the Netherlands. Neuraminidase inhibitor use is recommended for the treatment of index patients and for the postexposure prophylaxis of such patients' contacts with a view to slowing or possibly halting the spread of the pandemic.

No economic evaluation or efficiency analysis of the committee's recommendations is presented in this report. The committee did not feel that its remit extended to the performance of any such evaluation or analysis, partly because the minister had not requested anything of the kind. Nevertheless, the committee does wish to highlight a number of points that should be taken into account if an exercise of this kind were undertaken. The reasons for highlighting these points are that in academic literature, economic considerations are often instrumental in shaping opinion and that this case involves an unusual number of uncertain factors. The uncertainties concerned come under various headings: factual uncertainties (*when the next pandemic will occur, how many people will fall ill*), uncertainties arising from the complexities of measuring relevant variables concerning which consensus exists (*how much economic damage a pandemic would cause, what effect popular fear of the pandemic would have*), and uncertainties arising from the arbitrary decisions necessarily preceding any efficiency analysis in the narrow sense. These decisions are considered briefly below.

First, a somewhat arbitrary choice needs to be made concerning the time frame of the evaluation, since the measures recommended by the committee involve a combina-

tion of large capital expenses and ongoing costs incurred in order to prepare the nation for a very rare phenomenon. Second, it is essential to define the alternative or alternatives with which the recommended strategy should be compared. In this advisory report, the committee has focused on the most medically desirable outcome. Third, one needs to consider exactly which costs and effects are to be taken into account. Finally, in the context of policy formulation, it is necessary to address the question of whether the prevention of a disaster such as a pandemic should in principle be viewed purely from a public health perspective or in a wider context. The committee examines these four issues more closely in Annex C.

It is anticipated that, once decisions have been made in the areas identified above, quantitative policy-support information can be generated using economic models. Researchers in the United Kingdom have already demonstrated that this is possible[27].

5.4 Logistics

The committee regards the acquisition of an adequate stockpile of neuraminidase inhibitors as merely one aspect of preparing for the use of such agents in a pandemic. Numerous steps need to be taken to ensure that antiviral agents held in storage are made available at the right moment, both when the first cases are detected in the Netherlands and during the course of a manifest pandemic. The committee feels that working out the logistic implications of its recommendations in detail is beyond its remit, but does wish to make the point that the successful use of neuraminidase inhibitors would in practice depend to a considerable extent on the quality of the logistic arrangements made.

In this context, the committee believes that the government has two important tasks: enforcing its decisions and providing the public with information.

Chapter 6

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A Request for advice

B The Committee

C Arbitrary decisions underpinning an efficiency analysis

Annexes

Annex **A**

Request for advice

On 7 August 2003, the Minister of Health, Welfare and Sport wrote as follows to the President of the Health Council (letter reference POG/ZP 2.393.860):

On 7 July 2003, representatives of the Health Council and the Ministry of VWS held one of their periodic meetings to discuss the advisory reports that the council will be asked to work on in 2003/2004. The meeting was attended by the President of the Health Council, the Deputy Secretary of the Health Council and the ministry's Director General for Public Health. Among the topics discussed were the scope and timing of the following three advisory report requests:

1 Antiviral agents in an influenza pandemic
2 The threats posed by infectious diseases originating from the veterinary domain within Europe
3 The threats from (as yet) unknown pathogens

You indicated that the Health Council was willing to incorporate the three topics referred to above into your work programme for 2003/2004. The point was made that you would like to treat the three topics as a trilogy and produce three interlinked advisory reports. I am very happy with this proposal.

In the context of this correspondence, I shall address only the question of antiviral agent use in an influenza pandemic. Requests concerning the other two advisory reports will be prepared in the near future, in consultation with you. I would like to receive your advisory report on the use of antiviral agents in an influenza pandemic before 1 December 2003. In addition, I wish to receive a report on the threats posed by infectious diseases originating from the veterinary domain by 15 May 2004, because the report's publication should be

coordinated with the Dutch presidency of the EU. Finally, I would like to receive your advisory report on the threats from (as yet) unknown pathogens before 15 October 2004.

Antiviral agents in an influenza pandemic

The Ministry of VWS has for several years been preparing for an influenza pandemic, with a view to enabling the Netherlands to deal with the consequences of such an event as effectively as possible. An influenza pandemic is a serious form of influenza outbreak that is likely to claim many more victims than the illness claims in an ordinary season. This is partly because the virus involved has undergone a sudden mutation, making it capable of spreading through a large population in a short space of time. Furthermore, a vaccine capable of protecting the population against the responsible virus strain will not be available, at least not in sufficient quantities.

In 1997, the then Minister of VWS asked the Health Council for practical advice regarding the order in which medical risk groups should be vaccinated, if vaccine were gradually made available in the course of a pandemic. The Health Council reported back on this topic in April 2000. The Minister of VWS incorporated the Council's recommendations into the policy statement published on 15 November 2000.

The advisory report contained several observations regarding the role of antiviral agents in controlling an influenza pandemic in the absence of a vaccine. On the basis of what was known at the time, it was not possible to draw definite conclusions regarding the role that these agents might play under such circumstances.

However, further research into the efficacy of antiviral agents has since been performed. I would therefore like you to review the advice that your Council gave in 2000 regarding antiviral agents, in the light of current scientific thinking and developments.

Specific questions

More specifically, I would like you to address the following questions:

1 What effect would the use of antiviral agents have on the incidence of secondary complications and mortality in an influenza pandemic? (In this context, please give separate consideration to first-generation and second-generation antiviral agents and to therapeutic and prophylactic use.)
2 Considering the relative efficacy and side-effects of first-generation and second-generation antiviral agents, which type of agent would be preferable for use in an influenza pandemic?
3 Medically speaking, is it desirable to use antiviral agents to control the consequences of an influenza pandemic?
4 Are any new agents under development that might be used against influenza? If so, when are they likely to become available?

When formulating your advice, you should disregard the fact that certain agents might not be available in sufficient quantities. However, where that might be the case, I would like to know whether you feel the gov-

ernment could possibly choose to acquire a stock of the agent in question. I would also like to hear if there are any logistic matters or storage/retention issues that you believe should be taken into consideration.

Scenarios for an influenza pandemic

No one can predict the course that an influenza pandemic will take. When preparing for such an eventuality, it is therefore useful to adopt a scenario-based approach. By formulating scenarios, it is possible to estimate the effect of certain forms of intervention, such as the use of antiviral agents.

In 2003, the RIVM undertook an influenza pandemic scenario study on behalf of the Ministry of VWS*. For the purposes of the study, a number of assumptions were made. For example, estimates were made of the size of the affected population and the percentage of people contracting the illness that would require hospitalisation following the development of serious complications, and the percentage that would die. The researchers then calculated how effective various intervention measures might be in reducing hospitalisation and mortality rates.

Because the assumptions made in the context of such a scenario-analysis have a major influence on the projected effects of the various intervention measures modelled, I would like you to address the following questions. Where it is not possible to give a precise answer, please indicate the range within which the variables concerned are likely to lie.

How long would it take for a pandemic that has started elsewhere to reach the Netherlands?

4 How long would a pandemic last?

5 What percentage of the population is likely to fall ill during an influenza pandemic?

6 What percentage of those that fall ill will require hospitalisation or die as a result of contracting influenza?

7 How will case numbers be distributed over time? (Will there be a normal distribution pattern, for example?)

8 Do you anticipate that a vaccine will become available during a pandemic?

In this context, I would like you to use your recommendations as the starting point for the formulation of a number of scenarios, which differ from one another in terms of scale, and to indicate in general terms the control measures that would be most appropriate under each scenario.

In this context, please take account of the fact that the need to make use of antiviral agents is related to the availability of vaccines. It is likely that the availability of vaccines will increase as a pandemic progresses.

Minister of Health, Welfare and Sport
(signed)
H Hoogervorst,

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* Report 282701003/2002 MLL van Genugten, MLA Heijnen, JC Jager

Annex **B**

The committee

- Professor J van der Noordaa, *Chairman*
  Emeritus Professor of Virology; University Medical Centre, Amsterdam
- Professor GJ Bonsel
  Professor of Social Medicine; University Medical Centre, Amsterdam
- Dr PJ van Dalen, *consultant*
  Ministry of Health, Welfare and Sport, The Hague
- Professor JT van Dissel
  Professor of Infectious Diseases; Leiden University Medical Centre
- Dr GA van Essen, general practitioner
  Julius Centre for Health Science and Primary Healthcare; Utrecht University Medical Centre
- Professor JWM van der Meer
  Professor of Internal Medicine; St Radboud University Medical Centre, Nijmegen
- Professor ADME Osterhaus
  Professor of Virology, Erasmus MC, Rotterdam
- Dr RRR Huijsman-Rubingh, *consultant*
  Ministry of Health, Welfare and Sport, The Hague
- Professor EJ Ruitenberg
  Professor of International Public Health; Free University, Amsterdam
- Professor P Smits
  Professor of Pharmacology; St Radboud University Medical Centre, Nijmegen

- Dr EW Steyerberg
  Institute for Social Healthcare, Rotterdam
- ACG Voordouw
  Committee for the Safety of Medicines, The Hague
- Dr K Groeneveld, *Secretary*
  Health Council, The Hague

Administrative support: TME Smith-Mets

Annex **C**

Arbitrary decisions underpinning efficiency analysis

In order for an efficiency analysis to be performed it would in the committee's view be necessary to make arbitrary decisions in four areas. These are considered in turn below.

Timescale

In a certain sense, the acquisition of a stock of neuraminidase inhibitors and the preparation of a national strategy for a pandemic may be regarded as a large-scale secondary prevention programme. Certain costs would be incurred every year for the prevention – or, to be more precise, for the control – of an emergency, the like of which only occurs very occasionally. It is therefore important to decide how long the measures are likely to be continued; would the programme continue for fifty years, a hundred years, or longer? There are parallels here with the debate concerning the appropriate height for the Netherlands' sea dykes. Cost calculations also require that a figure be placed on the likely incidence of pandemics. On the basis of their historical frequency, it is reasonable to expect a pandemic between every twenty-five and every fifty years. Furthermore, because the central measures are of a permanent, trans-generational nature, it is necessary to decide what approach should be taken with regard to writing off costs. Finally, one needs to ask whether the calculations should be based on a standard 'expected utility' approach when weighing up the low temporal likelihood of a pandemic against the very high cost and negative impact; there may be alternatives that are more appropriate in relation to the assessment of likelihood made by the government.

Alternatives

An efficiency analysis requires the definition of the alternative or alternatives with which the recommended strategy should be compared.

Costs and effects to be included

Under established accounting rules, the cost of maintaining a permanent stock of neuraminidase inhibitors would come under the heading of direct medical expenditure, as would the cost of distribution in a pandemic and particularly the ongoing need for logistic training and other preparatory activities. Such 'maintenance costs' easily exceed the cost of responding to any emergency that might arise (the situation being comparable to what one has with a fire brigade). In addition, of course, one has to take account of the cost of clinical response. However, the inclusion of costs arising out of the temporary closure of schools and the prohibition of gatherings is an arbitrary matter.

Where effects are concerned, one has to consider whether subclinical or brief complication-free cases of influenza should be included in the analysis. It is also necessary to decide whether the psychological effects of a (potential) pandemic are considered relevant, and, in particular, whether the possible benefits to the public of knowing that a national response strategy is in place should be taken into account.

Public health

In the context of policy formulation, it is necessary to address the question of whether the prevention of a disaster such as a pandemic should in principle be viewed purely from a public health perspective or in a wider context. The underlying interest is the prevention of social dislocation, rather than the reduction of mortality or morbidity. The answer to this question is important in relation to the choice of references, certainly where costs are concerned, and possibly also where policy responsibilities are concerned. This more general decision is outside the scope of the commission.