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REVIEW

Use of antiviral agents and other measures in an influenza pandemic

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ABSTRACT

The Dutch Ministry of Health asked the Health Council for advice on how to prepare for a possible influenza pandemic. In two advisory reports the Committee responsible indicated the measures that it believes would need to be taken if such a pandemic were to reach the Netherlands. During a pandemic, the Committee recommends that every resident of the Netherlands with influenza-like illness should be treated with neuraminidase inhibitors such as antiviral agents. This approach serves to mitigate the course of the disease, to reduce infectivity and to allow patients to build up immunity to the virus. Since up to 30% of the population could become ill, the Committee anticipates that a stock of five million courses of the neuraminidase inhibitor oseltamivir is sufficient. If a pandemic were to occur at a time that the stock does not exceed the present 225,000 courses, the committee advises restricting treatment to three specified groups of patients. If the first few patients are traced shortly after they fall ill, the Committee recommends treatment of the patient and postexposure prophylaxis for his/her close contacts. The Committee does not advocate prophylaxis in general, but it can envisage prophylaxis for particular groups of patients or under particular circumstances. The Committee believes that in order to reduce rapid spread of the virus, schools should be closed and events where large numbers of people gather in a confined space should be cancelled. Because this recommendation would have major social and economic consequences, the Committee understands that its implication will depend on the anticipated severity and extent of the pandemic. The Committee regards vaccination against influenza as the best means of protecting the population. The development of a vaccine should be the absolute priority.

KEYWORDS

Antiviral agents, influenza, pandemic, risk groups, ring prophylaxis, treatment

INTRODUCTION

In the Netherlands, influenza viruses give rise to epidemics virtually every year. Epidemics recur 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 (H) and neuraminidase (N).[1] In patients, the antibodies formed in response to the infection protect against reinfection by the same virus strain and – by a process known as cross-protection – against a strain with a similar antigen composition. The more this antigen drift has occurred, 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 mutated 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.

Influenza viruses occasionally also lead to pandemics (i.e. epidemics on a global scale). Pandemics occur because of antigen shift, brought about by the transfer of genetic material from one virus strain to another (particularly

the genes for the H and N proteins).[1] Antigen shift leads to the development of a virus strain 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. Three such pandemics have 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 an infectious disease on record.[3] 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.[2] Furthermore, if a pandemic arises abroad it is difficult to predict how long it will take before it reaches our 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, after becoming ill, run a greater risk of complications. In contrast to the situation during an influenza epidemic, when fatalities are confined mainly to older people, during a pandemic higher levels of mortality can also occur amongst people who do not belong to the classic risk groups.[4] During the 'Spanish influenza' pandemic such a pandemic-specific risk group was formed by 20 to 40 year olds.[4,5]

The massive incidence of avian influenza in South-East Asia in the last few years appears to have increased the risk that a virus strain may emerge that is capable of triggering an influenza pandemic.[6,7]

The Dutch Ministry of Health asked the Health Council for advice on how to prepare for a possible pandemic. The Health Council published two advisory reports in which the Committee responsible indicated the measures that it believes would need to be taken if such a pandemic were to reach the Netherlands.[8,9] The objectives underlying the Committee's recommendations are: to level the pandemic over time by reducing the number of subclinical and clinical cases and to contain the impact of infection by means of antiviral therapy with neuraminidase inhibitors.

The Committee's recommendations are based on the current, limited, state of knowledge. This is due to both the unpredictability of a pandemic and the relative lack of scientific information on neuraminidase inhibitors.[10,11] The Committee is therefore at present only able to indicate what it believes would, in theory, be the best course of action. The Committee's 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, the recently established Centre for Infectious Diseases). 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.

NEURAMINIDASE INHIBITORS AS ANTIVIRAL AGENTS

In the preceding years, the Dutch government has stockpiled approximately 225,000 courses of the neuraminidase inhibitor oseltamivir (a second-generation antiviral agent). The Committee endorses the Dutch government's choice for neuraminidase inhibitors, since first-generation antiviral agents have relatively severe side effects on the central nervous system in particular and because of the relatively rapid emergence of strains resistant to the first-generation agents.[10] Research into new neuraminidase inhibitors is in progress,[12] 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.[13] In the event of there being a shortage of oseltamivir, the Committee considers that the neuraminidase inhibitor zanamivir could be purchased, but only for those patients who are unlikely to experience problems with the inhalations that are required with this remedy.

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. Postexposure prophylaxis for this period reduces the incidence of influenza in treated households and diminishes excretion of the virus by people who become ill in spite of such prophylaxis.[14]

Treatment

Oseltamivir (two daily doses of 75 mg for five days) or zanamivir (two inhalations of 5 mg twice a day for five days) should be used in patients 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.[15] When an influenza virus is in circulation, it is very likely that a patient displaying such symptoms has been infected with the virus.[16] The Committee emphasises the importance of starting treatment as soon as possible after the appearance of the first symptoms, and certainly within 48 hours. If treatment is started later, it may not be effective.[3,10]

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 treatment of the patient and postexposure prophylaxis for his/her family or household and other close contacts.[17] In a recent publication, the phrase 'ring prophylaxis' was coined to describe this type of strategy.[18] Mathematical analyses indicate that the recommended strategy could mitigate or even stop a pandemic.[19-21] The Committee's advice is that these measures should even be adopted when stocks of neuraminidase inhibitors are limited to the 225,000 courses mentioned earlier.

TREATMENT

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 advice 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% of the population could become ill during a pandemic,[22-25] the Committee anticipates that a total stock of five million courses of oseltamivir is sufficient.
If a pandemic were to occur at a time that the stock of neuraminidase inhibitors does not exceed the present 225,000 courses, the Committee recommends restricting treatment of the first clinical symptoms to patients from the following three groups:

- People from the risk group that was accorded the highest level of priority in the Health Council's advisory report on *Vaccination policies in case of an influenza pandemic*,[26] except for the patients with furunculosis. This risk group comprises patients with serious abnormalities or functional disorders affecting the airways, lungs or heart who, despite receiving medication, would be at great risk of lung or heart function decompensation if they were to be infected by the pandemic influenza virus. Patients with an insulin-dependent form of diabetes mellitus also belong in the category with the highest level of priority;
- People in the pandemic-specific risk group (if such a risk group exists);
- Professionals, that is to say all those responsible for the diagnosis, treatment and care of influenza patients and all those with logistical responsibility for the requisite medication.

During scarcity of neuraminidase inhibitors, otherwise healthy people should receive treatment only in the event of hospitalisation due to complications following influenza.

PROPHYLAXIS

The Committee does not advocate prophylaxis with neuraminidase inhibitors, even if there are adequate stocks, 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. Moreover, research findings from the United Kingdom suggest that the provision of prophylaxis 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.[27]
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.
Following influenza vaccination, one may not be fully resistant to infection for several weeks, since it takes some time to build up immunity. If sufficient stocks of neuraminidase inhibitors 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.
The Committee's recommendations regarding the use of neuraminidase inhibitors in an influenza pandemic are summarised in *table 1*.

GENERAL MEASURES

The Committee believes that, in order to reduce rapid spread of the virus, schools should be closed down and events where large numbers of people gather in a confined space should be cancelled for the duration of the pandemic. The Committee realises that this measure would have

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: post-exposure 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[b], professionals[c] and (where relevant) people in pandemic-specific risk group[a]; 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[d] and risk groups, professionals and (where relevant) people in pandemic-specific risk group[e]

[a]As soon as possible following the appearance of the first symptoms; if treatment is not started within 48 hours, it may not be effective. [b]Patients with serious respiratory, pulmonary or cardiovascular abnormalities or dysfunction, 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. [c]All persons responsible for the diagnosis, treatment and care of influenza patients, or for logistic management of the necessary resources. [d]Where considered appropriate by the doctor in charge of the individual patient. [e]Following vaccination and while the virus is circulating.

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. The development of a vaccine should be the absolute priority. However, 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. Should vaccine stocks prove inadequate, the Committee recommends that priority should be given to the particular groups defined earlier for preferential treatment during scarcity of neuraminidase inhibitors.

CONCLUSIONS

The Committee's recommendations are based on the current, limited, state of knowledge. In view of the paucity of the scientific data available, the Committee recommends 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 analysis. This recommendation especially concerns the monitoring for emergence of viral resistance to neuraminidase inhibitors. Until recently, influenza strains resistant to neuraminidase inhibitors were very rarely encountered. In a recently published study, however, virus strains resistant to oseltamivir were isolated in nine of 50 treated children.[28] 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.[29]

The Committee has not been in the 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 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.

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