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Scenario analysis of the expected number of hospitalisations and deaths due to pandemic influenza in the Netherlands

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Abstract

Another influenza pandemic, following those of 1918, 1957, and 1968, is likely, if not inevitable. In a 'regular' influenza epidemic, 5%-20% of the population becomes clinically ill; during a pandemic, this percentage can mount to 30% or even 50%. A pandemic could cause substantial social disruption, insofar as it would involve a large proportion of the population contracting a serious or less serious form of the illness.

In order to minimise the effects of such a potential pandemic on the population, the Dutch Ministry on Health, Welfare and Sport has drawn up an influenza pandemic contingency plan to be prepared to cope with mass illness and the burden on the health care services. The objective of this study is to calculate the expected numbers of hospital admissions and deaths in case of an influenza pandemic.

As many uncertainties are involved in this type of studies, we have developed alternative scenarios and consulted experts for their opinions on these scenarios and on the underlying model and assumptions. The effects of the intervention scenarios are compared in terms of preventing hospitalisation and mortality. Possible intervention strategies are vaccinations against influenza or pneumococcal infections (one of the possible complications of influenza) of certain groups or the prescription of antiviral medicine (within 48 hours after the first symptoms) for each person with an influenza-like illness.

Describing and comparing the alternatives gives insight into the impact of the pandemic in terms of how many will become ill or be hospitalised or die, the impact of the various interventions in terms of preventable influenza-related hospitalisation and deaths, and the crucial model parameters. Therefore, our scenario analysis will be helpful in designing and planning on national, regional, and even local levels. If there is an acute pandemic threat, the availability of the underlying decision-support model provides an opportunity to update estimations of hospitalisation and mortality on the basis of foreign or inland surveillance data.

Preface

There is a threat of serious disruption of society during an influenza pandemic because a large part of the population becomes more or less seriously ill. The burden of disease is considerable in all age groups. Many die before their time due to secondary bacterial infections. It is almost inevitable that there will be no vaccine, or hardly any, available at the beginning of a pandemic because the development of a specific vaccine against the pandemic virus strain requires time. Furthermore, a shortage of hospital beds during a pandemic is likely – partly because there are indeed more patients and partly because of panic. There will also be more cases of bacterial pneumonia, causing the need for antibiotics to rise.

To limit the effects of an influenza pandemic on society as much as possible, the Ministry of Health, Welfare and Sport, in Cupertino with other experts, has written a *Dutch Influenza Pandemic Preparedness Plan*. One of the purposes of this plan is 'the preparation for a great many cases of illness'. In connection with this preparation, the Health Care Inspectorate has asked the National Institute for Public Health and the Environment (RIVM) to estimate the care resources required in the event of an influenza pandemic.

A scenario analysis is the indicated method for carrying out this task because the care required is a social problem with many uncertain factors. We are grateful for the expertise that the following people have offered us in constructing the scenarios: A.I.M. Bartelds (NIVEL), H.J.M. Cools (LUMC), G.D. van Dijk (VWS), G.A. van Essen (UMCU), J.L. Kool (RIVM), A.D.M.E. Osterhaus (EUR), J.E. van Steenbergen (LCI), P. van der Torn (NIvU), J.K. van Wijngaarden (IGZ), and H.L. Zaaijer (VU).

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Samenvatting

Iedere winter krijgen veel Nederlanders griep (influenza). Dit leidt tot aanzienlijk ziekteverzuim en zelfs tot ziekenhuisopnames (gemiddeld 1900 per winter) en sterfte (gemiddeld 800 per winter) ten gevolge van complicaties van de griep. Je kunt iedere winter griep krijgen omdat het griepvirus voortdurend een beetje verandert, waardoor je er geen blijvende immuniteit (afweer) tegen opbouwt. Af en toe is die verandering in het griepvirus zo groot, dat niemand er meer immuun voor is. Als zo'n 'nieuw' virus dan ook ernstig pathogeen (ziekmakend) is én goed overdraagbaar van mens tot mens, kan een wereldwijde epidemie ontstaan, oftewel een pandemie. Daarbij kan het aantal zieken en dodelijke slachtoffers veel groter zijn dan bij een 'normale' epidemie. Dit grote aantal slachtoffers wordt mede veroorzaakt door het feit dat er bij een pandemie meestal niet tijdig een vaccin beschikbaar is. In de twintigste eeuw hebben er drie griep-pandemieën plaatsgevonden: de Spaanse griep in 1918-20, de Aziatische griep in 1957-58 en de Hong Kong griep in 1968-69. Volgens schattingen is circa een kwart van de wereldbevolking besmet geweest met het griepvirus tijdens de Spaanse griep-pandemie. Zo'n 40 miljoen mensen zouden zijn overleden ten gevolge van ernstige complicaties van deze griep (ter vergelijking: er waren 8 miljoen doden in de Eerste Wereldoorlog). In 1997 werd voor het eerst aangetoond dat een vogelgriepvirus afkomstig van kippen een mens rechtstreeks kon besmetten. Omdat het betreffende virus niet van mens op mens overgedragen werd, is er toen geen pandemie ontstaan. Mede door deze gebeurtenis is het niet langer een vraag óf er een volgende pandemie komt maar wannéér.

De verwachting is dat tijdens een grieppandemie 30-50% van de bevolking griep zal doormaken. Dit kan tot maatschappelijke ontwrichting leiden. Om de effecten van een pandemie te minimaliseren, ontwikkelt het ministerie van VWS een draaiboek waarin wordt aangegeven wie welke taken, verantwoordelijkheden en beslisbevoegdheden heeft bij een pandemie. Het ministerie van VWS heeft het RIVM (in het kader van het draaiboek) gevraagd om het te verwachten aantal ziekenhuisopnames en sterfgevallen ten tijde van een pandemie te schatten.

Daartoe hebben we scenario's opgesteld die alternatieve beelden van het verloop van een pandemie weergeven – beelden die gerelateerd zijn aan de mate waarin en de manier waarop de overheid invloed wil uitoefenen (interventies plegen) op het natuurlijke verloop van een grieppandemie. Omdat niemand weet hoe een volgende pandemie zal verlopen, moeten we veel zaken aannemen. Door middel van scenario-analyse kunnen we aan de hand van zo'n set

van aannames, de effecten vergelijken van verschillende interventies in termen van voorkómen ziekenhuisopnames en sterfgevallen. Zowel de scenario's als de aannames hebben we besproken met een groep experts. Op basis van onze bevindingen en deze gesprekken zijn we gekomen tot de volgende inzichten.

De overheid kan besluiten helemaal niet in te grijpen in een pandemie. Wil de overheid wèl ingrijpen, dan is er de keuze om bepaalde groepen van de bevolking tegen griep te vaccineren (als er tijdig een vaccin beschikbaar zou zijn), risicogroepen voor griep te vaccineren tegen pneumokokkeninfecties (één van de mogelijke complicaties van griep) of iedere zieke binnen 48 uur na aanvang van de symptomen antivirale middelen voor te schrijven.

Vergelijking van deze scenario's biedt hulp bij het nemen van beleidsbeslissingen op nationaal of regionaal niveau. Een hulpmiddel hierbij is het rekenmodel dat we hebben ontwikkeld. De beschikbaarheid van een rekenmodel maakt het mogelijk om bij nieuwe inzichten of bij de opkomst van een nieuw griepvirus in het buitenland, gegevens uit dat land over de meest getroffen leeftijdsgroepen te gebruiken om verwachte aantallen ziekenhuisopnames en sterfgevallen in Nederland (en naar regio) opnieuw te schatten.

Summary

Many of the Dutch have the flu (influenza) every winter. This leads to considerable absence due to illness and even to hospital admissions (an average of 1900 per winter) and death (an average of 800 per winter) as a result of influenza complications. We can get the flu every winter because the flu virus continually changes a little, so that we cannot build up any permanent immunity to it. Now and then, the change in the flu virus is so great that nobody is immune to it any more. If a 'new' virus is seriously pathogenic and very communicable from person to person as well, a world-wide epidemic, or pandemic, results. Then there are many more cases and deaths than in a 'normal' epidemic. One of the causes of so many victims is the fact that a vaccine is usually not available in time when a pandemic occurs. There were three flu pandemics in the twentieth century: the Spanish flu in 1918-1920, the Asian flu in 1957-1958, and the Hong Kong flu in 1968-1969. It is estimated that a quarter of the world population was infected with the flu virus during the Spanish flu pandemic. About 40 million are said to have died due to serious complications of this flu (in comparison, there were 8 million deaths in the First World War). It was first shown in 1997 that an avian flu virus originating from chickens could infect humans directly. There was no pandemic then because this virus cannot be spread from person to person. Therefore the question is not *if* there will be a next pandemic, but *when*.

It is expected that 30%-50% of the population will have the flu during an influenza pandemic. This can lead to social disruption. To minimise the effects of a pandemic, the Ministry of Public Health, Welfare and Sport has developed a plan which indicates who has which tasks and responsibilities, and who is authorised to make decisions in the event of a pandemic. In connection with this plan, the Ministry has asked the RIVM to estimate the expected numbers of hospital admissions and deaths that would occur in a pandemic.

For this purpose, we have set up scenarios that reflect alternative pictures of the course of a pandemic – pictures that are relative to the degree to which and the manner in which the authorities want to intervene in the natural course of a flu pandemic. We have to make many assumptions because nobody knows what turns an ensuing pandemic will take. We can compare the effects of various interventions in terms of preventing hospitalisation and death by means of scenario analysis with such a set of assumptions. We have discussed both the scenarios and the assumptions with a group of experts. On the basis of these discussions and our findings, we have come to the following insight.

The authorities can decide not to intervene at all in a pandemic. If the authorities do intervene, then there is the choice of immunising certain groups of the population against flu (if a vaccine is available in time), immunising groups at risk of flu against pneumococcal infections (one of the possible complications of flu), or prescribing antiviral medicine for every patient within 48 hours after the symptoms appear.

Comparing these scenarios is helpful for making policy decisions at national and regional levels. One aid for this is the model that we have developed. The availability of a calculation model makes it possible, in the case of new insights or the appearance of a new flu virus in another country, to use data about the most affected age groups from that country to estimate anew the expected numbers of hospital admissions and deaths in the Netherlands (nationally and regionally).

1. Introduction

An influenza epidemic occurs in the northern hemisphere during the winter every year. The reason for this is that the influenza A virus continually changes its surface antigens bit by bit (antigen drift). Now and then, the influenza virus changes to such an extent that nobody is immune any more (antigen shift). If such a 'new' virus is seriously pathogenic and very communicable from person to person, then we have a pandemic (De Jong 2000).

There were three pandemics in the twentieth century: the Spanish flu of 1918-1920 (the largest; it caused approximately 40 million deaths), the Asian flu of 1957-1958, and the Hong Kong flu of 1968-1969 (Potter 1998). It was shown for the first time in 1997 that the avian flu virus in chickens could infect humans directly. Then 18 people in Hong Kong were infected by the influenza AH5N1 virus, and 6 of them died (Claas 1998, Yuen 1998). Five people in China were mildly ill at the beginning of 1999, and two girls became seriously ill in Hong Kong as a result of infection with an influenza A H9N2 virus (Peiris 1999, ProMed mail 1999). At that time, H9N2 was known only as a poultry influenza virus. No pandemic took place in 1997 and 1999 because the virus could not be spread from person to person. Because of these two events, many believe it is no longer a question of whether there will be another influenza pandemic, but when (Belshe 1998, De Jong 1998).

An influenza pandemic can occur at any time of the year, not only during the usual flu season. New or mutated influenza viruses often originate in Asia. It takes an average of 18 months for strains of 'ordinary' flu viruses to spread over whole world. The previous pandemic strains needed only 6 months (Potter 1998). The next pandemic virus can arrive in the Netherlands faster due to increased travelling and transport (especially by plane).

During a 'normal' influenza epidemic, an average of 5%-20% of the population becomes ill, but this percentage can be as high as 30% or even 50% of the population (Glezen 1996). The most manifest infections are those of children in 'normal' influenza epidemics. The course of the disease is most serious for the elderly who are suffering from other diseases. Death due to the influenza virus strikes mainly the elderly (Nicholson 1998, Nguyen-Van-Tam 1998).

It has become clear that this might be different in a pandemic (Potter 1998, Glezen 1996). In 1918-1920, especially young adults became seriously ill, in addition to the usual risk groups; many died. The attack rate was the greatest for children of 4 to 14 years of age (49%) during the pandemic of 1957-1958, while this was definitely not the case in 1968-1969. Absence due to illness during the pandemic of 1957-1958 in the United Kingdom was estimated at over

20% of the population; one-third of the personnel of a hospital was ill during the peak of the pandemic; more than 50% of the school children were ill (VWS 1999).

An important problem after a sudden great change of the antigen composition of the influenza virus is that a vaccine becomes available too late (Glezen 1996, WHO 1999). Thus, the population remains without protection against the virus too long. This has consequences such as many becoming mildly or seriously ill; there are greatly increased absence due to illness, GP consultations, use of medicine, hospitalisation, and deaths. In such a case, it could come to disruption of community life.

The Ministry of Health, Welfare and Sport has developed a *Dutch Influenza Pandemic Preparedness Plan* on the basis of recommendations of WHO (WHO 1999) and in collaboration with experts on all the relevant areas. This book forms a framework which indicates who has which tasks and responsibilities, and who is authorised to make decisions in the various phases that can be distinguished in a pandemic. The purpose of the book is to minimalise the effects of an influenza pandemic on the Dutch population and society. One part of this purpose is 'to prepare for a great many cases of illnesses and deaths'. In this connection, the Health Care Inspectorate has asked the RIVM to estimate the expected workload for the health services in case of an influenza pandemic.

In the plan for this project the following questions are asked:

1. How many people will be ill?
2. How many GP consultations will be required?
3. How many hospital admissions will be necessary?
4. How many people will die as a result of influenza?
5. What amounts of antibiotics will be required?
6. How much respiration equipment will be needed?
7. How much nursing personnel will be required?

Scenario analysis is the suitable method for answering these questions because they concern a social problem with many uncertainties (Genugten 1996).

For this purpose, first the health care services required by a 'normal' influenza epidemic are estimated on the basis of the registration of GP consultations for influenza-like illness (ILI), influenza-related hospital admissions and deaths. Then, with the help of the vaccine efficacy and the degree of vaccination described in the literature, we calculate backwards to a situation without vaccination (a nonintervention scenario; worst case). Then we investigate the effect of variation in the attack rates and complication rates in various age groups on the numbers of deaths and desired hospital admissions. Finally, scenarios are developed in which

we investigate the effects of immunising or not immunising against influenza and/or pneumococci, and the effects of using or not using neuraminidase inhibitors or antibiotics, on the need for health services in terms of the numbers of GP consultations, hospital admissions, and deaths.

At a Delphi-like meeting on 7 March 2001, seven experts (and a written contribution from one expert) on controlling influenza, epidemics, and disasters, and the two commissioners of this report (Appendix I) gave their opinions about the sense and nonsense of various assumptions and scenarios and the estimated value of some crucial parameters (Appendix II). At the expert meeting, the questions were refined and choices were made with respect to scenarios that were meaningful for further calculation. It was agreed that the need for health care services in a pandemic would be expressed in terms of serious complications that lead to hospitalisation and/or death. The number of expected GP consultations was considered less important because the first-line health services during a pandemic will likely be organised differently. For example, there will probably be one central place per urban area where the logistics for hospital admission and for the dead (and possibly for distributing neuraminidase inhibitors) will be arranged. The most important results of the scenario analysis are how many hospital admissions and deaths can be prevented by the use of neuraminidase inhibitors, antibiotics, influenza vaccination, or pneumococcal vaccination. The necessary quantities of doses or cures of neuraminidase inhibitors, antibiotics, and influenza and pneumococcal vaccines were also estimated.

The definite question became: ‘How many hospital admissions and deaths can be prevented by the use of antibiotics, neuraminidase inhibitors, pneumococcal vaccination, or influenza vaccination in an influenza pandemic?’ We chose a scenario analysis of the required health services to work this out. In Chapter 2, the method of scenario analysis is elucidated. Then in Chapter 3, the extent of health care needed in a ‘normal’ epidemic is described. In the Chapters 4 to 7, the nonintervention scenario and the alternative scenarios are described: no influenza vaccine but pneumococcal vaccination; no influenza vaccine, but the use of neuraminidase inhibitors, and available influenza vaccine. In Chapter 8 we use an example to discuss the problem of the hospital beds needed at that time. We close with our observations and conclusions in Chapter 9. The figures belonging to this report are collected in Appendix VII.

2. Method: model and scenarios

We chose a scenario analysis to estimate the need for health care services (calculated from the hospital admissions and deaths) because of the many uncertainties (nobody knows how the following pandemic will run its course). Alternative pictures of the development of the need for care during an influenza pandemic were constructed in the scenario analysis, and a model was developed. To achieve the best possible details for the model and the scenarios, the following questions were placed before a panel of experts:

1. To what extent are the assumptions realistic? These assumptions concern the age dependency of the attack rate, the age dependency of the complication rate, and the time course of the pandemic (Sects. 4.1– 4.3).
2. To what extent are the formulated scenarios realistic? These questions are relevant to the availability of an influenza vaccine and the use of antibiotics or antiviral medicines. (Sect. 2.2).
3. Can you estimate quantities for the questionnaires? The numbers to be estimated concern GP consultations, hospitalisation, antibiotics prescribed by the GP and in the hospital, extent of limitation in the usual daily activities, and absence due to illness.

The detailed working out of these questions, along with a summary of the answers given by the experts can be found in Appendix II. These tables were the guide for the discussion at the expert meeting on 7 March 2001. The scenarios described in Sect. 2.2 result from that discussion.

2.1 Model and data

The model of Figure 1 (Appendix VII) was used to estimate the consequences of an influenza pandemic in terms required health services. The numbers of GP consultations, hospital admissions, and deaths are the basic results from which the remaining outcome variables were deduced. To get the basic results, we first classify the population into age groups of 0-19 years, 20-64 years, and over 65 years [as the Centers for Disease Control (CDC) also does: Meltzer 1999]. Then we classify the population further by risk: high or low. The high-risk group includes asthma, chronic obstructive pulmonary diseases (COPD), heart, and diabetes patients. The composition of the population for the period 1990-1999 was obtained from the Central Bureau of Statistics (CBS); and the extent of the risk groups for the period 1990-

1994, from the GP registrations Continuous Morbidity Registrations (CMR) Nijmegen (Weel 1993), Registration Net GP Practices (RNH; Knottnerus 1992) and the Transition Project (Lamberts 1996). The sizes of the high and low-risk groups in the population are given in Table 1. In the age group of 0-64 years, the percentage of high-risk people is 5, and in the age group over 65, it is 35.

Table 1. Sizes of the high and low-risk groups in the Dutch population

Age in years	Low-risk population	High-risk population	Total population
0-19	3 713 882	88 114	3 801 996
20-64	9 122 528	597 988	9 720 516
65 and older	1 363 643	732 698	2 096 341
Total	14 200 053	1 418 800	15 618 853

The following step in the model (*A* in Figure 1) is to determine the population at risk, or that part of the population that is not protected against influenza. The size of this group depends on the degree of vaccination and the efficacy of the vaccine. We define the efficacy as the percentage of serious complications (leading to hospitalisation and/or death) that can be prevented. The formulas used are presented in Appendix III.

The size of the unprotected population differs per scenario (e.g., it depends on whether an influenza vaccine is available) and is further worked out in the scenario-specific sections.

How many people have influenza-like illness (ILI) is determined per scenario by choosing a value for parameter *B* (the attack rate).

The GP consultation rate *E*, the hospitalisation rate *F* (including excess hospitalisation), and the death rate *G* (including excess mortality) are estimated from the registrations. The GP consultations are deduced from the NIVEL registrations of ILI cases (Bartelds 2000) for the winters 1996/1997-1999/2000, the hospital admissions from the PRISMANT registrations (1990-1996), and the deaths from the CBS cause-of-death statistics (1990-1998). The estimation of the excess hospitalisation of the period 1984-1993 is based on the method of Baltussen et al. (1998), and the estimate of the excess deaths in the period 1967-1989 is based on the method of Sprenger et al. (1993). Tables 2 – 4 show the data used. Appendix IV gives further information about the origin of the data used to estimate the hospital admissions and deaths in a ‘normal’ epidemic.

Table 2. Registered GP consultations for influenza-like illness per 100 000 people in a 'normal' influenza epidemic

Age in years	Consultations per 100 000
0-19	2764
20-64	2162
65 and older	1973

Source: ILI reports of CMR survey stations, average for the winters 96/97–99/00, NIVEL

Table 3. Influenza-related hospital admissions per 100 000 people in a 'normal' influenza epidemic

	With influenza		With pneumonia as a result of influenza	
Age in years	**Low-risk population**	**High-risk population**	**Low-risk population**	**High-risk population**
0-64	0.1	28	0.3	72
65 and older	2	10	38	175

Source: Baltussen et al. (1998), period 1984-1993

Table 4. Influenza-related deaths per 100 000 people in a 'normal' influenza epidemic

Age in years	Low risk population	High risk population
0-64	0.61	29.75
65 and older	26.24	84.92

Source: Sprenger et al. (1993), period 1967-1989

Estimates of the use of antibiotics, the required respiration equipment, required hours of specialist and nursing help in the hospital, and the total patient hospital days are determined by multiplying the number of GP consultations and the number of hospital admissions by parameters *H* to *L* inclusive. The parameters *C, D*, and *H* to *N* inclusive are defined as follows. *C*: the number of days that an ILI patient is hindered in his usual activities; *D*: the number of days that an ILI patient spends more than half the time in bed; *H*: the percentage of ILI patients who consult a GP and are prescribed antibiotics; *I*: the percentage of people hospitalised as a result of influenza and who receive antibiotics; *J*: the percentage of people hospitalised as a result of influenza who need respiration equipment; *K*: the number of hours

of specialist help and nursing care for a patient hospitalised as a result of influenza; *L*: the number of days that a patient is hospitalised as a result of influenza; *M*: the number of doses of antibiotics prescribed by the GP; *N*: the number of doses of antibiotics administered in the hospital.

Estimates (according to the experts, Appendix I) of the amounts mentioned are presented in Appendix II. An example: the amount of necessary respiratory equipment is deduced by multiplying the number of hospital admissions by the percentage of hospitalised influenza patients who needed respiratory equipment.

2.2 Scenarios

Various scenarios are possible, depending on the attack rate and whether influenza vaccine, pneumococcal vaccine, antiviral medicines, and/or antibiotics are available. The nonintervention scenario is a worst-case scenario in which it is presumed that no intervention is possible in a pandemic of various extent. The choice of the alternative scenarios is based on the discussion in the expert meeting and on consideration of the answers to the previously prepared questions (Appendix II). Table 5 is a summary of the discussion on the subject of the choice of scenarios at the expert meeting. The filled-in blocks represent the scenarios that are considered in the remainder of the rapport.

Certainly, with the current method of influenza vaccine production using incubated chicken eggs, it is expected that there will be no vaccine available at the beginning of a pandemic. Quicker and more flexible methods of vaccine production are being developed (Palache 1997, Voeten 1999, 2000). Therefore, this report emphasises scenarios of the necessary health care in the absence of a vaccine. As soon as influenza vaccine becomes available, the whole Dutch population will probably be vaccinated step by step. The order in which that is done is still to be determined. The Health Council has published a recommendation about the prioritising of medical risk groups (Gezondheidsraad 2000) and interdepartmental deliberations about the prioritising of the so-called vital groups are taking place. The government has concluded an option contract with a vaccine producer for 4 million units of vaccine. That would be enough to vaccinate the medical risk groups and the caregivers. This scenario (scenario 5 in Table 5, Chapter 7) is included next to a scenario in which the whole population is vaccinated (scenario 6 in Table 5, Chapter 7). As mentioned, time will pass before a vaccine is available, but both these scenarios may still be realistic in a later phase of the pandemic.

Table 5. Scenarios described in Chapters 4 to 7 inclusive

	No influenza vaccine available	Influenza vaccine available
1. No use of neuraminidase inhibitors	Nonintervention scenario	
2. No use of neuraminidase inhibitors	Pneumococcal vaccination for groups at risk of influenza (including people over 65)	
3. Therapeutic use of neuraminidase inhibitors	For all ILI patients	
4. Therapeutic and prophylactic use of neuraminidase inhibitors	Therapeutic for all ILI patients and prophylactic for the institutional population (inhabitants of nursing and care homes)	
5. No use of neuraminidase inhibitors		For groups at risk of influenza (including people over 65) and for caregivers
6. No use of neuraminidase inhibitors		For everybody

The Health Council recommends, in the absence of an influenza vaccine, to provide influenza risk groups (including those over 65) with pneumococcal vaccination according to the prioritising indicated for influenza control (Gezondheidsraad 2000). The reasons for this are that many secondary bacterial pneumonias occurring after influenza virus infection are caused by *Streptococcus pneumoniae* and that a 23-valent vaccine is available. The reasoning is, thus, that since influenza cannot be prevented, then at least some of the complications can be prevented because there is a pneumococcal vaccine. The government has concluded an option contract with a vaccine producer for 1 million units of pneumococcal vaccine. The results of this scenario on the need for care have also been investigated (scenario 2 in Table 5, Chapter 5).

At the expert meeting, there was an comprehensive discussion about the usefulness, the necessity, and the feasibility of the use of antiviral medicines in a pandemic. The relatively new neuraminidase inhibitors [zanamivir (inhalation) and oseltamivir (oral)] that are now on the market (Gubareva 2000), can be considered for this. It must be noted that oseltamivir is not yet available on the Dutch market. The 'old' antiviral medicines, amantadine and rimantadine are not suitable because they generate too much resistance (they also have side effects), and they are only effective against influenza A (CDC 1999, Couch 2000, Osterhaus 2000). Furthermore, rimantadine is not registered in the Netherlands. Neuraminidase inhibitors are effective against influenza A and B and have not generated much resistance (Gubareva 1998 and 2000, McNichol 2001). Further, zanamivir and oseltamivir appear to be safe, and they have seldom caused serious side effects (MacDonald 2000, Williamson 2000, McNichol 2001). Although neuraminidase inhibitors have proven to be very effective prophylactically (Monto 1999, Hayden 1999, 2000, Welliver 2001), the experts were unanimous in their opinion that using neuraminidase inhibitors prophylactically in a pandemic is pointless and not feasible. Neuraminidase inhibitors should be taken as long as the threat of influenza virus infection lasts in order to work prophylactically. This means at least several weeks (Kaiser 2000a), but possibly several months in a pandemic. An enormous quantity of neuraminidase inhibitors would be required for the Dutch population, for which compliance, in the course of time, would diminish drastically. Furthermore, it is possible that the pandemic will merely be postponed, as it were, and only really burst out at the moment that the majority of the population stops the prophylaxis.

If the taking of neuraminidase inhibitors is started within 48 hours after the beginning of the ILI, the duration and the seriousness of the disease are reduced (by 1 to 2 days) for adults (Hayden 1997, MIST Study Group 1998, Mäkelä 2000, Nicholson 2000, Treanor 2000), children (Hedrick 2000, Mäkelä 2000, Whitley 2001), and high-risk people (Mäkelä 2000, Monto 2000, Murphy 2000, Lalezari 2001). This therapeutic use of neuraminidase inhibitors also has the advantage that the medicine only has to be taken for 5 days and that infection is not prevented. The latter is an advantage because antibodies are formed (Whitley 2001) so that protection against a possible following infection by the same virus is built up. The mechanism of neuraminidase inhibitors is based on preventing the release of virus particles from infected cells (CDC 1999, McNichol 2001). The experts were unanimously for calculating a scenario in which each ILI patient asked to be treated therapeutically with neuraminidase inhibitors (at present, only zanamivir is registered for therapeutic use in the Netherlands) (scenario 3 in Table 5, Chapter 6). Considering the unusual situation at the time

of a pandemic, the experts are in favour of the provision of neuraminidase inhibitors based on a practical set of clinical symptoms (e.g. fever and coughing), and not on the basis of laboratory diagnostics. The usual influenza diagnostics take far too long in any case, and at the moment, there are still no quick tests available that are sufficiently specific and sensitive. Further, prescription on the basis of a clinical diagnosis would require a whole organisation because the taking of neuraminidase inhibitors must start within 48 hours after the initial symptoms in order to be effective. Less than a quarter of the ILI patients (the percentage is age dependent) consults a GP within 48 hours after the initial symptoms in the United Kingdom (Ross 2000). It is likely that both the consultation behaviour of ILI patients and the organisation of the first-line health care in a pandemic will be different from those of the current situation.

The experts were also of the opinion that the prophylactic use of neuraminidase inhibitors in institutionalised populations during a pandemic can be considered. This concerns a well-described population that also consists of many or exclusively high-risk people. Furthermore, the duration of prophylaxis is finite in such situations. The neuraminidase inhibitor zanamivir has proven useful in a nursing home and was associated with ending an influenza outbreak which amantadine had failed to stop (Lee 2000). A scenario in which neuraminidase inhibitors were used prophylactically as well as therapeutically for each ILI patient in nursing and general care homes (scenario 4 in Table 5, Chapter 6) was calculated.

It is usual that the GP prescribes antibiotics for an ILI patient whom s/he surmises to have a secondary bacterial pneumonia. At the expert meeting, it was suggested that antibiotics could be prescribed for every ILI patient during a pandemic by way of precaution and accommodation of the unrest in the population.

On the basis of the experts' opinions and the literature, we conclude that it is pointless to calculate a scenario in which antibiotics are prescribed for every ILI patient in a pandemic. The reason is that this will not prevent hospitalisation or death with respect to the current situation. In this situation, the GP prescribes antibiotics to ILI patients when a secondary bacterial pneumonia is suspected. We assume that this action at least will continue in a pandemic. The considerations are:

1. A primary influenza-virus pneumonia exists. In a ‘normal’ epidemic, it is rare; in a pandemic it could possibly occur much more often. Antibiotics have no effect on virus pneumonias (Cox 1999).

2. Secondary bacterial pneumonias can occur after influenza-virus infection. If this seems to be the case for an ILI patient, antibiotics are prescribed. The starting point in the scenarios is that this procedure will not change in a pandemic. Antibiotics might possibly be prescribed more often in a pandemic than in a 'normal' epidemic because a secondary bacterial pneumonia will be suspected more often and/or because of pressure from the patient (due to panic/fear). The starting point is that 10%-50% (Appendix II) of the ILI patients who consult a GP will be prescribed antibiotics. There is some discussion about this percentage, but there are no data in the literature.

3. The outcomes in the scenario analysis are the number of hospital admissions and the number of people who die. Antibiotics do not prevent death resulting from secondary bacterial pneumonia (Nicholson 1998). A trial has been carried out with COPD patients who were given antibiotics for the exacerbation of their disease as a result of a viral respiratory tract infection (Sachs 1995). The course of the disease of the antibiotics group did not differ from that of the placebo group.

4. Antibiotics facilitate recovery from a bacterial pneumonia (Cox 1999). How effective that is depends on host factors (such as age and underlying suffering) and the adequacy and timeliness of the therapy. Nonetheless, the efficacy of antibiotics is not relevant here because we presume that the procedure of prescribing antibiotics in a pandemic will take place at least as often as in the current situation.

5. A mixed form of primary and secondary pneumonia after influenza-virus infection is possible. We assume that antibiotics will be prescribed for it, but that it will not affect hospitalisation or death (Cox 1999).

In short, it is meaningless to calculate a scenario in which every patient is prescribed antibiotics. We assume a situation that is comparable with the current one. This means that antibiotics will be prescribed for 10%-50% of the patients who consult a GP (we assume that one of every four ILI patients in the general population will consult a GP; see Appendix II) if bacterial pneumonia is suspected. During a 'normal' epidemic, 40 000 to 200 000 antibiotic cures are needed in the GP practices (Table 6). Depending on the percentage of people who are infected in a pandemic, as many as 976 000 antibiotic cures can be needed.

Table 6. Antibiotic cures needed in GP practices and in the hospital[a]

	Prescribed by GP for 10%	**Prescribed by GP for 50%**	**Prescribed in the hospital**
'Normal' epidemic	39 007	195 037	1 915
Pandemic 10%	39 047	195 236	3 395
Pandemic 30%	117 141	585 707	10 186
Pandemic 50%	195 236	976 178	16 977

[a]It is assumed that, if twice as many people are infected with influenza virus, then antibiotics will be prescribed twice as often on suspicion of secondary bacterial pneumonia

If panic breaks out, more ILI patients may go to a GP. In addition to that, the GPs in that situation may prescribe antibiotics more often because they suspect a secondary bacterial pneumonia more often and/or the patient exercises pressure on them and/or because of the GPs' own fears (better safe than sorry). This has no influence in terms of prevention or complications, but more cures will be desired.

Finally, we assume that each patient in the hospital who is admitted for influenza or serious complications will have antibiotics prescribed (Table 6 and Appendix II), and that during a 'normal' epidemic, approximately 2000 antibiotic cures will be needed, rising to almost 17000 in a pandemic that affects 50% of the population.

Appendix II contains an overview of the various types of antibiotics that could be prescribed by GPs or in hospitals during a pandemic, according to the experts.

3. The 'normal' epidemic

In this chapter, the size of the care services required for a 'normal' epidemic are estimated. We assume that there were 'normal' epidemics in the winters after 1996; that is, after the introduction of vaccination for everybody over 65 and the medical risk groups. Approximately 80% of the population over 65 and more than 75% of the high-risk people are vaccinated against influenza (Table 7).

The data about hospitalisation and death are partially valid for the period before 1996. Another population than that after 1996 was at risk before 1996 because of a more limited vaccination strategy (Postma 1999). The available data (for sources, see Sect. 2.1) must therefore be converted to data that are comparable to data for the period after 1996. This means a correction for the population at risk in most cases. Section 2.1 already indicates that information about the degree of vaccination in the population and the vaccine efficacy is necessary to determine the size of the unprotected part of the population. The degree of vaccination is known for the period after 1996 from the National Information Network for GP Care (LINH) data, and we use CBS data (summarised by Tacken 2000; Table 7) for the period before 1996.

Table 7. Degree of influenza vaccination of the Dutch population in percentages

	Before 1996	**1996**	**1997**	**1998**
	(percentages)			
Total population	13	12.7	15.4	16.6
High-risk population[a]	48	74	76	76
Population over 65[b]	50	76	79	81

[a]Any age

[b]With or without medical risk factor

For the group aged 65 years and older, we assume a vaccine efficacy of 56% (Gross 1995); for the group younger than 65 years we assume a vaccine efficacy of 80% (Cox 1999, Couch 2000).

The combination (see Appendix III for the formulas) of the degree of vaccination and the vaccine efficacy with the complication rates for GP consultation, hospitalisation, and deaths in the total population (Sect. 2.1) provide the GP consultation, hospitalisation, and death rates for the population at risk now. We apply these rates to the associated population at risk and

thus we arrive at an estimate of the numbers of GP consultations, hospital admissions, and deaths in a 'normal' epidemic.

The great unknown in the description of a 'normal' epidemic is how many people have influenza. We assume that approximately 10% of the population becomes ill in a normal epidemic. This corresponds with the assumption that one of every four people with ILI goes to a GP. When the attack rates are between 5% and 20% (Glezen 1996), 800 000 to 3 million people contract influenza (Table 8).

Table 8. Cases in a 'normal' epidemic with attack rates between 5% and 20%

Age in years	Attack rate of 5%	Attack rate of 10%	Attack rate of 20%
0-19	236 998	473 996	947 993
20-64	462 448	924 895	1 849 791
65 years and older	80 702	161 404	322 808
Total	780 148	1 560 296	3 120 591

During a 'normal' epidemic, there are approximately 400 000 GP consultations for ILI (assuming that one in four ILI patients consults a GP, which corresponds to the registered ILI consultations in Table 2), approximately 1900 people are admitted to hospital, and approximately 800 people die as a result of serious complications of influenza (Table 9).

Table 9. Extent of the need for care in a 'normal' epidemic (attack rate of 10%)

Age in years	GP consultations	Hospital admissions	Deaths
0-19	118 499	62	9
20-64	231 224	346	28
65 and older	40 351	1508	783
Total	390 074	1915	819

4. Scenario: nonintervention

The nonintervention scenario (scenario 1 in Table 5) considers a situation in which there are *no* possibilities for intervention. The whole population is thus at risk. We assume that the prescription behaviour with respect to antibiotics and the care services are the same as the prescription behaviour and the care services in a 'normal' epidemic. Later, we interpret the outcome variable of hospital admissions as the desired number of hospital admissions.

The GP consultation rate, the hospitalisation rate, and the death rate for the population at risk must be known to determine the nonintervention scenario. These rates are calculated by dividing the numbers of GP consultations, hospital admissions, and deaths in the case of a 'normal' epidemic by the number of people in the unprotected population in a 'normal' epidemic (Appendix III). Then the extent of a 'normal' epidemic (we assume that 10% of the population becomes ill) is translated to a pandemic situation. This is done by assuming that a pandemic is several times greater than a 'normal' epidemic. The 'several times' is equal to the relationship of the attack rate by age in a 'normal' epidemic to the supposed attack rate by age in a pandemic.

In the further working out of the scenarios, assumptions are made about the age dependency of the attack rate, the conversion of the GP consultation, hospitalisation, and death rates in the situation of a 'normal' epidemic to a pandemic situation, and about the spreading of the influenza in time.

We have asked the experts for their opinion about these assumptions because the course of an ensuing pandemic cannot be predicted. A summary of the experts' thoughts about these assumptions is presented in Appendix II. The assumptions are discussed and the effect of variations are given in the following sections. How the assumptions are dealt with in the further working out of the scenarios is given at the end of each section.

4.1 The assumption of age dependency of the attack rate

In this section, we look at what effects the various suppositions about the attack rate by age have on the hospital admissions and deaths. Table 10 presents various alternatives for the attack rate by age for a pandemic that strikes 10%, 30%, or even 50% of the population.

Table 10. Attack rate by age (in percentages) for various extents of the pandemic

Age in years	Pandemic 10%	Pandemic 30%	Pandemic 50%
Age groups hit as in 'normal' epidemic			
0-19	12.5	37.4	62.4
20-64	9.5	28.6	47.6
65 and more	7.7	23.1	38.5
Age groups equally hit			
0-19	10.0	30.0	50.0
20-64	10.0	30.0	50.0
65 and more	10.0	30.0	50.0
Age groups hit in proportion of 1:1:2			
0-19	8.8	26.4	44.1
20-64	8.8	26.4	44.1
65 and more	17.6	52.9	88.2
Age groups hit in proportion of 1:2:1			
0-19	6.2	18.5	30.8
20-64	12.3	37.0	61.6
65 and more	6.2	18.5	30.8
Age groups hit in proportion of alternative 2:1:1			
0-19	16.1	48.3	80.4
20-64	8.0	24.1	40.2
65 and more	8.0	24.1	40.2
Age groups hit according to alternative CDC[a]			
0-19	16.4	49.3	82.2
20-64	8.5	25.6	42.7
65 and more	5.1	15.0	25.7

[a]Meltzer et al. (2000) use two divisions of flu cases by age. These are based on attack rates of three earlier epidemics: those of 1918-1920, 1928-1929, and 1957-1958. In the case of a pandemic with an extent of 30%, the associated attack rates become: 49.3%-56.7% for 0-19 years, 25.6%-22.5% for 20-64 years, and 15.4%-16.3% for 65 years and older

The alternatives differ in the way the various age groups are hit. In a ‘normal’ epidemic, the age group of 0-19 years is most often hit (12.5%), while the age group over 65 is hit the least often (7.7%). These attack rates by age are valid for the unprotected population and are deduced from the ILI registration (Table 2) assuming that one in four ILI patients consults a GP (Chapter 3). Then we suppose a relationship in which the three age groups are hit. For

example, the age groups hit in the proportion of 1:1:2 means that the age group of 65 years and older is hit twice as often as the group of 0 to 64-year-olds. In a pandemic with an extent of 10%, this gives attack rates of 8.8% for the 0 to 64-year-olds and 17.6% for those over 65. In a pandemic with an extent of 50%, as many as 80% of the people in an age group can be hit. In the alternative of 1:1:2, a maximum of 88% of the group over 65 becomes ill, while in the CDC alternative, 82% of the 0 to 19-year-olds becomes ill.

If we assume that a pandemic differs from a 'normal' epidemic only in attack rates by age and in the size of the population at risk (there is no influenza vaccine available), then various estimates for the extent of the pandemic in terms of hospitalisation and deaths follow for various attack rates by age from Table 10.

In a pandemic that hits 30% of the population, the desired hospital admissions (Figure 2) vary from 7541 (CDC alternative) to 19 630 (1:1:2 alternative). The deaths (Figure 3) vary from 2746 (CDC alternative) to 9009 (1:1:2 alternative). Three times as many hospital admissions and deaths occur in alternative 1:1:2 as in a 'normal' epidemic. In a 'normal' epidemic and in each of the pandemic alternatives presented, most of hospital admissions and deaths are those of people over 65. Thus, particularly the supposed attack rates in the age group over 65 greatly influence the numbers of deaths and desired hospital admissions and. This is a result of the assumption that the same complication rates are valid in a pandemic as in a 'normal' epidemic (the complication rate is greatest for those over 65. See Tables 3 and 4). In Sect. 4.2 we look at the results of other complication rates in the case of a pandemic.

In Figures 4 and 5, the numbers of deaths and desired hospital admissions for various extents of a pandemic (range: 10% to 50%) are presented for various attack rates by age. Again we see that the age group over 65 puts the most weight on the scale: the alternative with the greatest attack rate in the age group over 65 corresponds to the most hospital admissions and deaths. If half the population becomes ill in a pandemic, the deaths and desired hospital admissions increase dramatically: in alternative 1:1:2, approximately 32 500 hospital admissions are desirable, and almost 15 000 people die (approximately 1900 and 800 in a 'normal' epidemic for which an influenza vaccine is available).

For the sequel, we assume that the attack rates by age in a pandemic situation are the same as those of a 'normal' epidemic (the optional age groups are as in a 'normal' epidemic in Table 10) because no reliable prediction can be made beforehand.

4.2 The assumption of age dependency on the complication rate

If we assume that a pandemic differs from a 'normal' epidemic only in complication rates by age and in the size of the unprotected population at risk, then various estimates follow for various complication rates, desired hospital admissions, and deaths.

With the supposition that the complication rates are the same as in a 'normal' epidemic, we are speaking about the complication rates for the population at risk. We cannot check whether this assumption is justifiable because nobody knows what the course of a following pandemic will be. We can check what the effect will be if the 0 to 64-year-olds are admitted to hospital twice as often as is registered now in a 'normal' epidemic. In a pandemic that hits 30% of the population, hospital admissions increase by 2644 (Figure 6) to more than 12 830. If 50% of the population is hit, there are approximately 4400 more hospital admissions, raising the total to more than 21 383. Hospital admissions for the age group 0 to 64 years are found in the high-risk groups. With the extreme assumption that low-risk people aged 0-64 years have the same risk of hospitalisation as the high-risk people, in the case of a pandemic that hits 30% of the population, the almost 45 000 more hospital admissions are desired, totalling more than 55 665 (Figure 7). If 50% of the population is hit, the hospital admissions will increase by 75000 to more than 92 000.

Assuming that twice as many hospital admissions for those 65 and older are needed than in a 'normal' epidemic, the 10 186 desired hospital admissions increase to more than 17 500 in a pandemic with an extent of 30%. The majority of the influenza-related hospital admissions – as in a 'normal' epidemic – is for this age group.

These examples show the effect of the complication rates on the desired hospital admissions. There is a similar effect on the deaths. In the remainder of this report, we choose the complication rates to be those of a 'normal' epidemic because we cannot predict what they will be in a pandemic. If a pandemic begins outside the Netherlands, good surveillance in the countries affected can give indications of the attack rates and the complication rates in the various age groups in due course.

4.3 The time course of the pandemic

It is impossible now to predict how a following pandemic will develop in time. Extrapolating from previous pandemics (Potter 1998), one can philosophise about a so-called first wave, which could possibly last 6 to 8 weeks, followed by a second wave, and possibly even a third.

The second wave has often been more serious than the first in the past. However, a gradual course in time, spread over months, is not discounted. Appendix II gives a summary of the experts' opinions.
In short, the estimated hospital admissions and deaths can take place in various patterns in time. The pattern of occurrence is, of course, very important for the relationship of care demand to care supply and the degree of disruption of society. In Chapter 8, an example is worked out in which it is assumed that the first wave of a pandemic lasts 3 months and the patients are normally distributed in time.
The period in which the estimated health care services is required is not fixed for the treatment of the various scenarios in the remainder of this report.

4.4 Summary of the nonintervention scenario

It is assumed that the attack rates for the unprotected population, the complication rates, the use of antibiotics, and the care provided are equal to those in a 'normal' epidemic for the nonintervention scenario summarised in Figures 8 and 9. The numbers of deaths and desired hospital admissions are given by age groups for both a 'normal' epidemic and a pandemic of various extents. The desired hospital admissions vary from approximately 1900 in a 'normal' epidemic (for which influenza vaccine is available) to approximately 17 000 in a pandemic that hits 50% of the population (for which no influenza vaccine is available). The deaths vary from approximately 800 in a 'normal' epidemic to more than 6700 in a pandemic that hits 50% of the population.

5. Scenario: no influenza vaccine, but pneumococcal vaccination of risk groups of influenza

It was assumed that the attack rates for the unprotected population, the complication rates, the use of antibiotics, and the care services were the same as those of a 'normal' epidemic for the calculation of a scenario in which the influenza risk groups (including all those over 65) receive pneumococcal vaccine in the absence of an influenza vaccine. The Health Council (Gezondheidsraad 2000) recommends that, in the case that influenza cannot be prevented because no influenza vaccine is available, the influenza risk groups at least be protected from that part of the complications caused by *Streptococcus pneumoniae* infection since a pneumococcal vaccine is available (Sect. 2.2).

Vaccination with the available 23-valent pneumococcal vaccine only prevents invasive pneumococcal infections. These are specifically pneumonias associated with bacteremia, meningitis, and sepsis. Various studies show a vaccine efficacy of approximately 80% for the serotypes present in the 23-valent vaccine. The vaccine 'covers' approximately 80% of the serotypes that cause invasive pneumococcal infections in the Netherlands. This is why we suppose that the vaccine has an efficacy of 64% (0.8 0.8) (Postma 2001). A comparison of the hospitalisation rate for invasive pneumococcal infections (Postma 2001) with the hospitalisation rate for pneumonia shows that approximately half of the hospital admissions for all types of pneumonia (Table 3) can be attributed to invasive pneumococcal infections. We suppose, then, that half of the excess hospitalisation for pneumonia that is attributed to influenza can be prevented by pneumococcal vaccination with a efficacy of 64%.

We make a comparable assumption for the deaths: half of the excess mortality for pneumonia that is attributed to influenza can be prevented by pneumococcal vaccination with an efficacy of 64%.

For a pandemic with an extent of 30% (Figures 10 and 11), 3179 hospital admissions and 137 deaths could be prevented, for which 2.78 million people (the size of the influenza risks groups) will have to receive pneumococcal vaccine. For a pandemic with an extent of 50%, 4360 hospital admissions and 230 deaths could be prevented , for which, again, 2.78 million people will have to be vaccinated.

Pneumococcal vaccination prevents few deaths relative to the hospital admissions prevented because relatively less excess mortality attributable to influenza can be prevented. Pneumonia

has a greater share in the excess hospitalisation than in the excess mortality, in which heart disease has a large share.

6. Scenario: no influenza vaccine, but use of neuraminidase inhibitors

It is assumed that the attack rates for the unprotected population, the complication rates, the use of antibiotics, and the care provided are the same as those for a 'normal' epidemic for the purpose of calculating the scenarios for which the use of neuraminidase inhibitors is assumed. The questions answered here are: (1) How many deaths and hospital admissions can be prevented when each patient [defined as a person with influenza-like illness (ILI)] takes therapeutic neuraminidase inhibitors before or soon after infection, and how many cures of neuraminidase inhibitors are necessary? (2) How many deaths and hospital admissions can be prevented when inhabitants of nursing and care homes begin using neuraminidase inhibitors prophylactically as soon as one inhabitant or staff member has ILI, and how many cures of neuraminidase inhibitors are necessary?

Before this scenario can be calculated, we need information about the efficacy of neuraminidase inhibitors with regard to preventing hospital admissions and death. There are indications that therapeutic use of neuraminidase inhibitors reduces the incidence of complications associated with the use of antibiotics (Hedrick 2000, Kaiser 2000b, Mäkelä 2000, MIST Study Group 2000, Treanor 2000, Lalezari 2001, Whitley 2001). However, there is nothing in the literature about the effect on hospitalisation and deaths. It will be difficult, if not impossible, ever to investigate the effect of neuraminidase inhibitors on hospitalisation and deaths, at least in the case of risk groups, because it is not ethical to withhold vaccination from those at risk. The effect of vaccination combined with therapeutic neuraminidase inhibitors on hospitalisation and deaths versus the effect of vaccination alone, however, can be investigated. The neuraminidase inhibitor oseltamivir reduced the duration of the illness by an average of 1.8 days for high-risk people who contract influenza infections despite influenza vaccination (Zaug 2000). The effect of the therapeutic use of neuraminidase inhibitors on hospitalisation and deaths for low-risk groups can also be investigated, but such serious influenza complications seldom occur in these low-risk groups in a 'normal' epidemic (Tables 3 and 4) (Sect. 2.1).

Therefore, we assume a range of 25% to 75% of therapeutic efficacy for neuraminidase inhibitors on hospitalisation and deaths.

Another important assumption is that the neuraminidase inhibitors will *also* be effective on the 'new' pandemic influenza virus. This seems to be a realistic assumption, seeing that the neuraminidase inhibitors have an effect on influenza A and B because the position on the influenza virus where the neuraminidase inhibitors attack is firmly preserved (Elden 2000, Gubareva 2000). Oseltamivir has also been shown to be effective against influenza AH5N1 and AH9N2 in mice (Leneva 2000).

In a pandemic that hits 30% of the population, administering neuraminidase inhibitors to every ILI patient can lead to a sharp reduction of hospital admissions and deaths (Figures 12 and 13) depending on its efficacy. The medication must start within 48 hours after symptoms begin. From 2547 to 7640 admissions and from 1010 to 3030 deaths can be prevented for an efficacy of 25% to 75%, respectively. In a pandemic that hits 50% of the population, these numbers can rise to more than 4000 prevented hospital admissions and approximately 1600 prevented deaths for an efficacy of 25%, and more than 12 500 prevented hospital admissions and approximately 5000 prevented deaths for a efficacy of 75%. In the case of a pandemic that hits 30% of the population, 4.7 million cures of neuraminidase inhibitors for 5 days (twice a day) are needed, and as the size of the pandemic increases, more cures are necessary (approximately 8 million if half of the Dutch population becomes ill).

The second part of this scenario is the prophylactic administration of neuraminidase inhibitors to the nursing home and care home populations as soon as an inhabitant or a staff member of a nursing or care contracts ILI. We assume here that someone in every nursing or care home will contract ILI in a pandemic, regardless of the size of the pandemic, because the subjects form a very vulnerable group. An estimate of the size of the populations in both institutions is necessary for this scenario. Of those older than 65, 5.3% live in a care home (Vademecum Gezondheidsstatistiek Nederland, 1999, Table 6.30). This is equivalent to 110 000 people in care homes. There are 27.1 beds available per 1000 inhabitants aged over 65 in nursing homes, and the occupation is 97.6% (Vademecum Gezondheidsstatistiek Nederland 1999, Table 6.30). This is equivalent to 56 000 people in nursing homes. In total, there are 166 000 people in nursing and care homes, all of whom we categorise in the high-risk group of 65 years and older; thus, 22.5% of the total high-risk group is eligible for prophylaxis.

Information about the efficacy of neuraminidase inhibitors for prophylactic use is also necessary. Various studies show that 60%-90% of the laboratory-confirmed symptomatic influenza can be prevented (Monto 1999, Hayden 1999, 2000, Van Elden 2000, Welliver 2001). The percentage is dependant on the definition of the outcome variable (e.g. ILI with or

without laboratory confirmation, ILI with or without fever) and of the setting (e.g. in households or in the general population). Monto et al. (1999) found that zanamivir prevented 43% of all cases of ILI with fever without regard to laboratory confirmation of influenza. Because we assume that only the prevention of 'real' influenza (thus not ILI) reduces hospitalisation and deaths, we assume that prophylactic use of neuraminidase inhibitors provides an efficacy of 70% for preventing hospitalisation and deaths in this scenario.

In a pandemic in which 30% of the population becomes ill, the prophylactic administration of neuraminidase inhibitors to those in nursing and care homes (Figures 14 and 15) – which would mean the use of over 166 000 cures – would prevent approximately 900 hospital admissions and 450 deaths relative to the nonintervention scenario. In a pandemic that hits 50% of the population, the use of over 166 000 cures would prevent approximately 1500 hospital admissions and approximately 750 deaths.

This scenario has some limitations. The nursing and care home populations are naturally not entirely closed: staff members do not live in and are thus in contact with the outside world; the inhabitants ordinarily receive visitors. This means that the influenza virus can be introduced into the home again after an epidemic. Therefore, the necessary duration of prophylaxis in such a setting is possibly unclear; it may be too long to maintain good therapy compliance. Furthermore, this scenario contains the implicit assumption that the prophylactic effects of neuraminidase inhibitors for the nursing home and care home populations are the same as those for the healthy adult population. Too little is known to make this assumption.

The added value of the prophylactic use of neuraminidase inhibitors in nursing homes and other care homes 'above' the therapeutic use of neuraminidase inhibitors for every ILI patient is dependant on the (presently unknown) efficacy of the therapeutic use of neuraminidase inhibitors on hospitalisation and deaths: the less this efficacy, the greater the gain from prophylactic use in the institutionalised population. In practice, it is probable that neuraminidase inhibitors are used prophylactically in nursing and other care homes because it is considered unethical to allow such a vulnerable group to become ill before any measures are taken.

7. Scenario: influenza vaccine available

Assuming that the attack rates for the unprotected population, the complication rates, the use of antibiotics, and the care services are the same as those for a 'normal' epidemic, we can now calculate scenarios in which we suppose that an influenza vaccine is available and that it is used for the influenza risk groups (including people over 65) and the caregivers.

We set the size of the risk groups (including people over 65) equal to that of the high-risk population that we described in Sect. 2.1 (2.78 million people). There are 800 000 people at work in the care sector (Zorgnota 2000). This sector includes hospitals, revalidation centres, regional health care, care of the handicapped, care of the elderly, home care, extramural care, and pharmaceutical help. We assume that these people belong to the group aged 20 to 64 years and to the low-risk population. This has the consequence that 8.8% of the 20 to 64-year-olds in the low-risk group should be vaccinated. In total, approximately 3.5 million doses of vaccine are necessary if a one-time vaccination is sufficient. For a pandemic virus, two vaccinations could be necessary for optimal protection. For this scenario, this means that complete vaccination is assumed for the high-risk group and those over 65 in the low-risk group. In the 20 to 64-year-old group at low risk, a vaccination degree of 8.8% is assumed. The efficacy of the vaccine is assumed to be the same as that in a 'normal' epidemic. In other words, it is 56% for people over 65 (Gross 1995) and 80% for the group aged 0 to 64 years (Couch 2000, Cox 2000).

Some 6218 hospital admissions and 2251 deaths can be prevented in a pandemic with an extent of 30% (Figures 16 and 17) by vaccinating the influenza risk groups (including those over 65) and the caregivers – thus, 3.5 million people. In a pandemic that hits 50% of the population, 10 363 hospital admissions and 3752 deaths can be prevented.

Consider the cases of pandemics with extents of 30% and 50% for which the whole population (approximately 16 million people) is vaccinated (Figures 18 and 19). Approximately as many hospital admissions (6339 and 10 565, respectively) and as many deaths (2302 and 3837, respectively) would be prevented. The reason is that hardly any extra hospital admissions or extra deaths are prevented by vaccinating the whole population with respect to vaccinating the risk groups against influenza (including people over 65) and the caregivers is shown in the registries: almost no hospitalisation and not many deaths as a result of influenza occur in this low-risk group of 0 to 64-year-olds who would receive the extra vaccinations (Sect. 2.1). This is indeed the group that is important from an economic point of view, so when work productivity is considered as an outcome variable, it makes a

considerable difference whether the whole Dutch population or only the influenza risk groups (including people over 65) and the caregivers are vaccinated.

8. Hospital beds required

It is impossible to predict how a following pandemic will develop in the course of time (Sect. 4.3), but for a comparison of the demand for hospital beds with the supply, the time course is a very relevant factor. To obtain some insight, we imagine a scenario in which the first wave of the pandemic lasts 3 months (90 days), the number of patients is distributed normally over time, and hospitalisation averages 8 days per patient (Appendix II). Assuming that the attack rates for the unprotected population, the complication rates, the use of antibiotics, and the care services are the same as those of a 'normal' epidemic, we estimate that the total desired hospital admissions would be 10 186 in a pandemic that hits 30% of the population (and in which no influenza vaccine is available) in the nonintervention scenario. Using these assumptions in the scenario with 'therapeutic use of neuraminidase inhibitors for every patient', we estimate the total desired hospital admissions as 5093 (assuming 50% efficacy in preventing hospitalisation) in a pandemic that hits 30% of the population.

The daily desired number of new hospital admissions will increase in time to 406 on day 46 (the peak day of the epidemic), and to 203 hospital admissions per day with therapeutic use of neuraminidase inhibitors (Figure 20). If the average stay in hospital is 8 days, then on day 46 in the nonintervention scenario, 3166 hospital beds will be needed, but only 1583 if neuraminidase inhibitors are used therapeutically (Figure 21). If the average stay is 14 days, then 5257 (nonintervention) and 2628 (therapeutic use of neuraminidase inhibitors) hospital beds will be wanted on the 53rd day of the pandemic. The peak in the number of beds wanted occurs later in time because hospitalisation of 14 days instead of 8 days is assumed.

In a pandemic lasting 6 weeks, over 5800 (2900) beds are needed after 28 days in the nonintervention scenario with therapeutic use of neuraminidase inhibitors. For hospitalisation lasting 14 days, more than 8400 (4200) beds are needed on day 31 (Table 11).

For developing a regional plan, it is important to gain insight into the demand for care in each Medical Help for Accidents and Disasters (MHAD) region. The regional division for the MHAD came about because an organisation above the community level is necessary to assign the tasks in the area of medical assistance for accidents and disasters. For each MHAD region, Table 12 gives information about the size of the population, the number of influenza-related hospital admissions in a 'normal' epidemic, the desired number of hospital admissions and the associated number of beds needed (at the peak of a pandemic with an extent of 30%) for the nonintervention scenario and the scenario with therapeutic use of neuraminidase inhibitors. The number of beds needed is determined with the assumption that the first wave

of the pandemic lasts 3 months and that the average hospital stay is 8 days. This concerns the situation on day 46 (peak), with the assumptions mentioned at the beginning of this chapter.

Table 11. Hospital admissions and beds needed in a pandemic with an extent of 30%

	Maximum number of admissions per day	Peak use of beds for hospitalisation lasting: 3 days	8 days	14 days
First wave lasts 6 weeks				
1. Nonintervention scenario	807	2390	5870	8541
2. Therapeutic use of neuraminidase inhibitors	404	1195	2935	4270
First wave lasts 3 months				
1. Nonintervention scenario	406	1213	3166	5257
2. Therapeutic use of neuraminidase inhibitors	203	607	1583	2628

To gain more insight into the supply of hospital beds in the Netherlands, we give a short overview of the relevant, available data. The general hospitals had an authorised capacity of 44 016 beds on 1 January 1999 (Zorgnota 2000, Table A7.1), which corresponds to 2.8 beds per 1000 inhabitants. In the university hospitals, there was an authorised capacity of 7121 beds on 1 January 1999 or 0.5 beds per 1000 inhabitants. In total, this is 3.3 beds per 1000 inhabitants. In the same Health Services Discussion Paper (Zorgnota, Table A7.2 gives the capacity per general hospital (103 in total on 1 January 1999), and Table A7.3, the capacity per university hospital (8 in total on 1 January 1999). The last column of Table 12 gives an indication of the available beds per MHAD region. In the *National atlas of public health: a three-dimensional picture of care and health in the Netherlands* (ZorgAtlas in Dutch), the RIVM gives this information in map form (vtv.rivm.nl/zorgatlas1.0_internet). Table 10.3 (hospitals; capacity and use) in the *Vademecum of health statistics in the Netherlands 1999* (also in Dutch) shows that the authorised number of beds is greater than the actually available number of beds, and that these also include cradles for healthy infants and beds in psychiatric wards of general hospitals. The degree of occupation in the hospitals is approximately 70% excluding day nursing, and approximately 75% including it. During a pandemic, the degree of occupation could be even lower due to a shortage of nursing personnel who are not sick themselves.

Table 12. Total hospital admissions desired, beds needed at peak in a pandemic with an extent of 30% (first wave lasts 3 months and hospitalisation lasts 8 days), and beds available per MHAD region

			'Normal' epidemic	Nonintervention scenario		Therapeutic use of neuraminidase inhibitors			
	MHAD region	Total size of population	Total admissions	Total admissions	Peak in number of beds	Total cures	Total admissions	Peak in number of beds	Beds available[a]
1	Groningen	558 017	73	388	121	167 405	194	60	2631
2	Friesland	618 115	79	418	130	185 435	209	65	2031
3	Drenthe	464 672	62	328	102	139 402	164	51	1315
4	IJssel-Vecht	406 715	49	257	80	122 015	128	40	1337
5	Twente	611 316	76	403	125	183 395	201	62	2135
6a	Stedendriehoek / Northwest Veluwe	558 315	72	385	120	167 495	192	60	1822
6b	Achterhoek	258 628	33	177	55	77 588	88	27	786
7	Arnhem / West Veluwe Vallei	596 560	73	388	121	178 968	194	60	1806
8	Nijmegen and Rivierenland	499 449	57	302	94	149 835	151	47	1979
9	Utrecht	1 126 268	129	688	214	337 880	344	107	4014
10	North Holland, North	583 224	65	344	107	174 967	172	33	1747
11/13	Greater Amsterdam	1 291 610	154	827	257	387 483	414	129	4917
12	South and Middle Kennemerland	387 057	56	299	93	116 117	150	47	1875
14	Gooi and Vechtstreek	241 478	35	188	58	72 443	94	29	945
15	Haaglanden	934 666	126	668	208	280 400	334	104	3590
16	Rijnland/ Middle Holland	732 042	81	432	135	219 613	216	67	2301
17	Rotterdam-Rijnmond	1 197 339	156	829	258	359 202	415	129	4821
18	South Holland, South	475 761	57	304	94	142 728	152	47	1485
19	Zeeland	369 949	52	277	86	110 985	139	43	1164
20a	Western North Brabant	648 337	79	420	131	194 501	210	65	2207
20b	Middle Brabant	404 975	46	244	76	121 493	122	38	1253
21	Northeast Brabant	566 018	63	335	104	169 805	167	52	2043
22	Eindhoven	699 932	81	433	135	209 980	217	67	2478
23	North and Middle Limburg	480 971	57	303	94	144 291	151	47	1441
24	South Limburg	649 492	88	468	145	194 848	234	73	2407
25	Flevoland	293 286	27	142	44	87 986	71	22	636

The MHAD regions and the numbers of available beds per MHAD region 2001 were provided by L. Zwakhals (Department of Public Health Forecasting, RIVM)

[a]The number of available beds given here is not a measure for the actual number of beds available during a pandemic, which will depend on the available (thus, not ill) nursing personnel

9. Discussion and conclusions

Several countries have set up a contingency plan for an influenza pandemic according to the WHO recommendations – the United Kingdom, for example (NHS 1997). However, as far as we know, with the exceptions of the USA (Meltzer 1999) and New Zealand (Jennings 2000), no other country has worked on scenario development for the demand for health care services in a pandemic. The approach can be comparable in various countries, but the results are very country-specific because of the differences in the organisation of the care. Meltzer et al. (1999) assumed that an influenza vaccine would be available when they investigated which groups of the population could best be vaccinated in the USA to achieve as few deaths as possible for the least possible costs (direct and indirect). The method of Meltzer et al. (1999) was also used to investigate the situation in New Zealand with the assumption that an influenza vaccine would be available to find the best vaccination strategy.

The nonintervention scenario and four alternative scenarios are discussed in Chapters 4 to 7 inclusive. The nonintervention scenario describes a situation in which intervention is impossible. If we assume that a pandemic hits 30% of the population and that the attack rates for the unprotected population, the complication rates, the use of antibiotics, and care services are all the same as those of a 'normal' epidemic, then in the nonintervention situation, 10 186 hospital admissions will be wanted and 4040 deaths can be expected. The majority of these events will involve those over 65 (Chapter 4). If half the population becomes ill, 17 000 hospital admissions will be wanted, and 6700 deaths will occur. In a 'normal' epidemic that hits 10% of the population, there will be almost 1900 hospital admissions and over 800 deaths (Chapter 3).

In the alternative scenarios, the effect of potential interventions (pneumococcal vaccination, neuraminidase inhibitors, influenza vaccination) can be calculated to find how many hospital admissions and deaths can be prevented. In the most favourable case, (Figures 22 and 23, Table 13) with the assumptions just mentioned, 6339 of the 10 186 (62%) hospital admissions and 2302 of the 4040 (57%) deaths can be prevented if the whole population (16 million) is vaccinated against influenza (if the vaccine efficacy is the same as it is now). In the case that not the whole population, but the influenza risk groups (including those over 65) and the caregivers (in total 3.6 million people) are vaccinated, 61% of the hospitalisation and 56% of the deaths can be prevented. Vaccination of the whole population with respect to vaccination of the groups named would add little in terms of preventing hospitalisation and death, but probably a lot in terms of work productivity (not a subject of this analysis). As

mentioned, it is very improbable that an influenza vaccine will be available in time. At the expert meeting, it was stated that it is to be expected that an influenza vaccine will be piecemeal when it becomes available. It is also to be expected that it will be used for the risk groups first [according to the priorities of the Health Council (Gezondheidsraad 2000)] or on the basis of surveillance information from abroad if the pandemic begins earlier there. At the expert meeting, there was also some philosophising about the option of screening people quickly and simply (e.g. with a finger prick and an ELISA still to be developed) for the presence of antibodies against the pandemic virus (or for having or not having taken neuraminidase inhibitors, or whether they have had fever) to determine a priority for vaccination. This does not seem realistic at the moment.

Table 13. Prevented complications versus the doses/cures of vaccine and neuraminidase inhibitors needed in a pandemic with an extent of 30%

	Necessary doses/cures in millions	Number (percentage) of hospital admissions prevented	Number (percentage) of deaths prevented
1. Nonintervention scenario	-	-	-
2. Pneumococcal vaccination for groups at risk for influenza	2.78	3179 (31.2)	137 (3.4)
3. Therapeutic use of neuraminidase inhibitors	4.69	5093 (50.0)	2020 (50.0)
4. Prophylactic use of neuraminidase inhibitors	0.17	897 (8.8)	450 (11.1)
5. Influenza vaccination of risk groups and caregivers	3.59	6218 (61.0)	2251 (55.7)
6. Influenza vaccination of total population	15.62	6339 (62.2)	2302 (57.0)

Influenza vaccination seems to be the best option, and the early taking of therapeutic neuraminidase inhibitors by every ILI patient (without laboratory diagnostics) seems to be the second best option to prevent deaths and the demand for care (Chapter 6), provided that the assumption that neuraminidase inhibitors are 50% effective in preventing hospital admissions and death is realistic. However, an extensive organisation would be needed because the administration of neuraminidase inhibitors must begin within 48 hours after the beginning of the symptoms in order for these medicine to be effective. Depending on the therapeutic efficacy of neuraminidase inhibitors, the prophylactic use of neuraminidase inhibitors by the institutionalised population adds more or less in terms of prevented hospitalisation and death (Chapter 6). Possibly, this will be done anyway because of ethics and emotional considerations.

As is described in Sect. 2.2, prescribing antibiotics for every ILI patient (except in the case of a realistic suspicion of bacterial pneumonia) is pointless. Administering pneumococcal vaccine to the influenza risk groups (2.78 million people) would prevent 31% of the hospitalisation and only 3.5% of the deaths. This is less than influenza vaccination or the therapeutic use of neuraminidase inhibitors (with the assumptions named) would prevent because pneumococcal vaccination prevents only one type of influenza complication.

In a whole series of assumptions, the demand for care is always the greatest in the group over 65. We have also shown (Sects. 4.1 and 4.2) that variations in the attack and complication rates per age group have a great impact on the final estimates of the desired number of hospital admissions and the extent of the deaths. The model developed for the scenario analysis makes it possible to analyse the various alternatives. If a pandemic does not begin in the Netherlands (which is the expectation), then good surveillance abroad can give a timely indication of the attack rates and the complication rates in the various age groups. This information can be added to the model, making possible a better estimate of the demand for care in a more acute threat of a pandemic.

The unpredictable course of a pandemic in time greatly influences the relationship of the demand for care to the supply and therefore, along with other factors, the degree of social disruption. The discrepancy between the demand and supply of care may differ per region (Chapter 8).

The assumption that the care services during a pandemic are of a quality comparable to those of a ‘normal’ epidemic is necessary to obtain comparable and interpretable scenarios. This is, in fact, not so realistic. In practice, the caregivers will also become ill with the pandemic influenza virus so that the care supply will be reduced. However, in a situation as exceptional

as an influenza pandemic, people will possibly work longer hours than usual, and on recovery from illness, they will possibly go back to work sooner, or keep working while ill. Further, it is possible that more people than usual will be recruited to work in the care sector. Medical students might be an example. Moreover, it can be imagined that demand for replacement will appear: nonemergency care will be scrapped to increase the care supply for influenza.

The same objections with respect to the prophylactic use of neuraminidase inhibitors are just as valid for the caregivers as for the general population [duration, compliance, possible postponement of the pandemic (Sect. 2.2)]. Thus, this group, essential to the care of other patients, probably has the most to gain from early therapeutic use of neuraminidase inhibitors because it will reduce the duration of the illness by 1 or 2 days at least, and also make the illness less serious so that people can get back to work again more quickly.

Looking back at the original questions (Sect. 1), we see the following. We have assumed the numbers of people who become ill (question 1) and used them as input variables, supposing them to be 10%, 30%, and 50% of the population. We have presented the extent of the demand for GP consultations (question 2) only for a 'normal' epidemic because it became clear at the expert meeting that hospitalisation and death were considered particularly important outcome variables, and that the first-line health care during a pandemic will likely be organised otherwise. For example, the logistics for both hospitalisation and death (and possibly the distribution of neuraminidase inhibitors) will be arranged in one central place in each urban area. By making assumptions about the percentage of ILI patients who consult a GP (Appendix II), the expected demand for GP consultations can be deduced simply from the assumed number of patients in a pandemic of a given extent. The extent of the demand for hospitalisation and antibiotics and the number of deaths (questions 3 - 5) have been broadly discussed. In practice, there is a great difference in hospital care for children (to approximately 12 years) and adults, which we have not considered in this scenario analysis. The extent of the demand for respiration equipment and nursing personnel (questions 6 and 7) is considered only in Appendix II in the presentation of the experts' opinions. These questions appeared to be less relevant at the expert meeting because the supply is expected to be insufficient and people will just do what is possible [maximum use of available means and people, also other things than the usual (e.g. hand pumps for artificial respiration)].

The following conclusions can be formulated, despite all the background assumptions. If an influenza vaccine is available, it should be administered as quickly as possible. Vaccinating everybody does not seem necessary in terms of results concerning hospitalisation and death. Vaccinating the influenza risk groups and the caregivers will do. However, vaccination of the

whole population may indeed be desirable and purposeful for ethical and/or economic reasons. It is not appropriate to use extra antibiotics for every ILI patient. It is, nonetheless, worthwhile to consider having enough neuraminidase inhibitors available for early therapeutic use for every ILI patient and at the same time, to investigate, as far as possible, their therapeutic efficacies in terms of hospitalisation and death. Depending on the therapeutic efficacy of neuraminidase inhibitors, their prophylactic use by the institutionalised population may or may not contribute much to preventing hospitalisation and death. They may be used anyway because of ethical and emotional considerations.

Pneumococcal vaccination of the influenza risk groups (including those over 65) may be less effective in terms of preventing hospitalisation and death than having every ILI patient use neuraminidase inhibitors therapeutically, depending on the efficacy of the latter. This is logical since pneumococcal vaccination would presumably prevent only one complication of influnza (invasive pneumococcal infections), while neuraminidase inhibitors would prevent all complications (hospitalisation and death). Note that pneumococcal vaccination can and must be done in advance.

Scenario analysis is very useful for supporting policy decisions and for supporting those who must prepare the actual control of a pandemic, or reduction of its effects to a minimum, both regionally and nationally. It gives insight into the order of magnitude of the demand for care (also by region). Further, by using a model, we can compare the effects of various interventions in the demand for care within a set of assumptions. Moreover, scenario analysis gives insight into which parameters have the most influence on the outcome variables.

Finally, if there are already outbreaks of a new influenza virus abroad (a concrete threat of a pandemic), and if it provides information about the real attack and complication rates by age group, we will be able to input the values into our model to see what demand for care can be expected in the Netherlands, nationally and regionally.

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Appendix I. Experts consulted

Dr. A.I.M. Bartelds, NIVEL (Coordinator of Continuous Morbidity Registration)

Prof. H.J.M. Cools, University of Leiden (Professor of Nursing Home Medicine)

Dr. G.A. van Essen, Julius Centre of GP Medicine and Clinical Research, UMCU

Prof. A.D.M.E. Osterhaus, Erasmus University of Rotterdam
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J.K. van Wijngaarden, MD, Inspectorate, Ministry of Public Health, Welfare and Sport

Dr. J.L. Kool, Head of the Department of Infectious Diseases Epidemiology, RIVM
(until summer 2001)

Appendix II. Questionnaires at the expert meeting

The following questionnaires were given to the ten experts (Appendix I). Seven of the experts have returned them. The qualitative questions were generally answered by every expert. For the quantitative questions, this is less so; mainly the opinions of one or two of the experts were given in the questionnaire.

To what extent were the assumptions realistic?

In the following questionnaires, the most important assumptions that we used were presented in the scenario analysis. The experts were asked to give their opinions about this.

Assumption: age dependency of the attack rate

We have assumed that the spread of the influenza cases over the age groups in a pandemic would be the same as in a 'normal' epidemic. Is this assumption justifiable? If not, what do you think it would be? Can you describe it?	The majority said that this assumption was not right, but an alternative was not given. Others said nothing was wrong with the assumption. Note: The 1918 pandemic was referred to. A classification by age of the cases in previous pandemics was asked for.

Assumption: age dependency on the complication rate

In our pandemic scenarios, 10%, 30% or 50% of the population get influenza. As an example, we assume that the numbers of hospital admissions and deaths increase by a factor of 2 if the number of influenza cases in the population increase by a factor of 2. Is this assumption correct? If not, what would you expect? Can you describe it?	Assumption is correct, or don't know, or seems unlikely. Note:. For example, depending on (1) the cause of secondary pneumonia (virulence and resistance) and (2) the admission capacity of hospitals

Assumption: time course of the pandemic

In the scenario development, we limit ourselves to the first wave of a pandemic that lasts for a period of 6 to 8 weeks. We assume that the influenza cases are distributed evenly over this period. Is this assumption correct? If not, what would you expect? Can you describe it?	Normal distribution. Note. Importance of regional differences

To what extent are the scenarios realistic?

The experts were asked to give their opinions about the following assumptions with respect to the availability of an influenza vaccine and the use of antiviral medicines.

Scenarios: availability and use of influenza vaccine and antiviral medicine

During the prelude to the first wave of a pandemic, no vaccine is available. Is this a meaningful scenario?	Yes, a meaningful scenario. Note: Some vaccine is always available.
During the prelude to the first wave of a pandemic, a vaccine is immediately available, but in limited quantities. Which groups of people should then be vaccinated?	Priorities of the Health Council (i.e., medical risk groups), professional groups, indispensable groups, priority list of the Ministry of Health, Welfare and Sport Note: interdepartmental workgroup. Question: how can the scenario study contribute to the discussion about which groups should have priority to be vaccinated?
During the prelude to the first wave of a pandemic, a vaccine is immediately available and the whole population can be vaccinated in the near future. Is this a meaningful scenario?	Half are for this scenario and half against. Note: Unlikely scenario in connection with the first wave. Realistic scenario in connection with the second wave? How much time is needed to vaccinate the whole population?
Should antiviral medicines be used in a pandemic? If so, should they be used prophylactically and/or therapeutically? If you like, you can differentiate by age groups and/or risk groups. Does it matter if a vaccine is available?	If a vaccine is available, then they should be used therapeutically or play a minor role or none at all. If no vaccine is available, then they should be used prophylactically. Note: If no vaccine is available, and antiviral medicines are in short supply, then they should be used therapeutically in general and prophylactically for key groups. If there is no shortage, then they should be used therapeutically for serious cases and prophylactically for risk groups.

Can you give a quantitative estimate of the variables mentioned?

The experts were asked to give quantitative estimates (with a minimum and a maximum if applicable) of the variables mentioned. These concern both a 'normal' epidemic and a pandemic.

Quantities: GP consultations

	'Normal' epidemic	Pandemic
What percentage of people with influenza-like illness consult a GP? If you like, you can differentiate by age groups and/or risk groups.	15%-33% *(n* = 2) Note: Young children most often; older children least often	20%-33% (*n* = 2)

Quantities: hospitalisation

	'Normal' epidemic	Pandemic
For how many days does an influenza patient remain in hospital? If you like, you can differentiate by age groups and/or risk groups.	3-14 days	3-14 days
What percentage of the influenza patients in hospital are given intensive care? For how many days? If you like, you can differentiate by age groups and/or risk groups.	10%-20% for 1 week Note: This depends on available capacity.	10%-40% for 1 week Note: This depends on the nature of the pandemic and is determined by the available capacity.
What percentage of the influenza patients in hospital need respiration equipment? For how many hours? If you like, you can differentiate by age groups and/or risk groups.	10% Note: This is determined by the availability of the equipment.	30% Note: This is determined by the availability of the equipment.
How many hours of specialist help are needed for an influenza patient in hospital? If you like, you can differentiate by age groups and/or risk groups.	30-60 min per person per day Note: Depending on the available personnel	30-60 min per person Note: Depending on the available personnel, but less than in a epidemic situation because of routine
How many hours of nursing and other care are needed for an influenza patient in hospital? If you like, you can differentiate by age groups and/or risk groups.	Depend on available personnel	Depends on available personnel

Quantities: behaviour in prescribing antibiotics

	'Normal' epidemic	Pandemic
What percentage of the patients with influenza-like illness who consult a GP are prescribed antibiotics? What dosage? If you like, you can differentiate by age groups and/or risk groups.	10% to 30%-40% Duration: 1 week	10%-50% Duration: 1 week
What percentage of the patients with influenza-like illness in hospital are given antibiotics? What dosage? If you like, you can differentiate by age groups and/or risk groups.	All: high	All: high

Summary of the answers

What type of antibiotics are prescribed by GPs and in the hospital? What are the alternatives? If you like, you can differentiate by age groups and/or risk groups.

What do GPs prescribe?

- Broad spectrum (unless an authoritative, strict and urgent, medically substantiated recommendation has been given)
- Broad spectrum, effective against pneumococcus and staphylococcus
- Amoxicillin (a penicillin, β-lactam)
  Augmentin (combination of amoxicillin and clavulanic acid)
  Macrolides [azithromycin, clarithromycin (narrow spectrum, derivates of erythromycin)]
  against cocci, M. pneumoniae and Legionella
  If supplies of the medicines just mentioned are exhausted, then co-trimoxazole, cephradine (staphylococcus*, H. influenzae*), ciprofloxacin (a quinolone), doxycycline (a tetracycline, broad spectrum)
- Recommendation: a β-lactam such as amoxicillin for empirical therapy
  Lately, more often macrolides (levofloxacin and clarithromycin) for atypical causal agents
  First-generation cephalosporins?
- Doxycycline and amoxicillin (90%) and macrolides (10%)

⇨ Amoxicillin (in about 90% of the cases) and macrolides (in about 10% of the cases).

What is prescribed in the hospital?

- It depends on the type of secondary bacterial pneumonia.
- Augmentin or ceftriaxone (cefotaxime is a cephalosporin, parenteral), possibly + gentamycin (an aminoglycoside, broad spectrum, parenteral, reserved for serious /life-threatening infections).
  Flucloxacillin for pneumonia caused by *Staphylococcus aureus* (on gram preparation).
  If supplies of the medicines just mentioned are exhausted, then co-trimoxazole, vancomycin (parenteral, only gram-positive micro-organisms) for *S. aureus* and many others.
- Depends on local situation, the hospital flora

⇨ Determining the type seemingly depends on diagnostics; are there sufficient possibilities for it in a pandemic?

Quantities: limitations and absenteeism

	'Normal' epidemic	Pandemic
How many days is an influenza patient limited in his usual daily activities? If you like, you can differentiate by age groups and/or risk groups.	1-3 weeks Older than 75 years: 4-5 weeks	1-3 weeks Older than 75 years: 4-5 weeks
How many days does an influenza patient spend more than half the time in bed? If you like, you can differentiate by age groups and/or risk groups.	3-7 days Older than 75 years: 10 days	3-7 days Older than 75 year: 10 days
How many days is an influenza patient absent from work or school? If you like, you can differentiate by age groups and/or risk groups.	5-14 days	5-14 days

Appendix III. Formulas

TotPop	Total population by risk and age
PopatRisk	Population at risk
VaccD	Current degree of vaccination
VaccE	Current vaccine efficacy
GPCcmr	ILI GP consultations per 100 000 people according to CMR sampling stations (NIVEL)
HAbaltussen	Hospital admissions per 100 000 according to Baltussen, 1998
Dsprenger	Deaths by influenza per 100 000 people according to Sprenger, 1996
GPCrate	GP consultation rate for ILI
HArate	Hospital admission rate for consequences of influenza
Drate	Death rate for consequences of influenza
AR_Pandemic/Normal Epidemic	Relation of attack rates of pandemic versus those of a 'normal' epidemic

Formulas for the nonintervention scenario

HCrate = GPCcmr/(1- VaccD * VaccE)
HArate = HAbaltussen/(1- VaccD * VaccE)
Srate = Dsprenger/(1- VaccD * VaccE)

PopatRisk = TotPop

Number of GP consultations = HCrate * PopatRisk * AR_Pandemic/Normal Epidemic
Number of hospital admissions = HArate * PopatRisk * AR_Pandemic/Normal Epidemic
Number of deaths = Srate * PopatRisk * AR_Pandemic/Normal Epidemic

In the *alternative scenarios*, the variable PopatRisk changes because part of the population is vaccinated or because HArate diminished because of pneumococcal vaccination, for example.

Appendix IV. Mailing list

1 J.K. van Wijngaarden, MD
2 G.D. van Dijk , Msc
3 BIS
4-28 EISS members
29 P.W. Achterberg, PhD
30 A.I.M. Bartelds, MD
31 S.L.A.M. Bronzwaer, Ph.D
32 N.J. Cox, Ph.D
33 G.A. van Essen, Ph.D
34 K. Fukuda, MD
35 M. Gyldmark, Ph.D
36 U.M. Kühnel
37 M.I. Meltzer, Ph.D
38 M.A. Miller, MD
39 A.D.M.E. Osterhaus, Ph.D
40 J. Piercy, Msc
41 B. Sander, RN,MA,MEcDev
42 J.E. van Steenbergen, Msc
43 P. van der Torn, Ph.D
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45 Directeur SVM
46 Directie RIVM
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48 D. Ruwaard, MD
49 M.A.E. Conyn-van Spaendonck, Ph.D
50-52 Auteurs
53 J.A.M. Lijdsman-Schijvenaars, Msc
54 Bureau Rapportenregistratie
55 Bibliotheek RIVM
56-65 Bureau Rapportenbeheer
66-99 Reserve-exemplaren
100 Depot Nederlandse Publicaties en Nederlandse Bibliografie

Appendix V. List of abbreviations

AZ-VU	University Hospital, Free University of Amsterdam
CBS	Statistics Netherlands
CDC	Centers for Disease Control and Prevention, Atlanta, USA
CIE	Department of Infectious Diseases Epidemiology, RIVM
CMR	Continuous Morbidity Registration
COPD	Chronic obstructive pulmonary diseases
CZO	Department for Health Services Research, RIVM
GZB	Public Health Department, Ministry of Public Health, Welfare and Sport
ILI	Influenza-like illness
IGZ	Health Care Inspectorate
LCI	National Coordination Structure for Control of Infectious Diseases
LINH	National Information Network for GP Care
LUMC	University of Leiden Medical Centre
EUR	Erasmus University, Rotterdam
MHAD	medical help for accidents and disasters
NIVEL	Netherlands Institute for Health Services Research
NIvU	Netherlands Institute of Emergency Medicine
ppd	per person per day
RNH	Registration Net GP Practices
WHO	World Health Organisation
UMCU	University of Utrecht Medical Centre

Appendix VI. Overview of the tables

Appendix VII. Figures

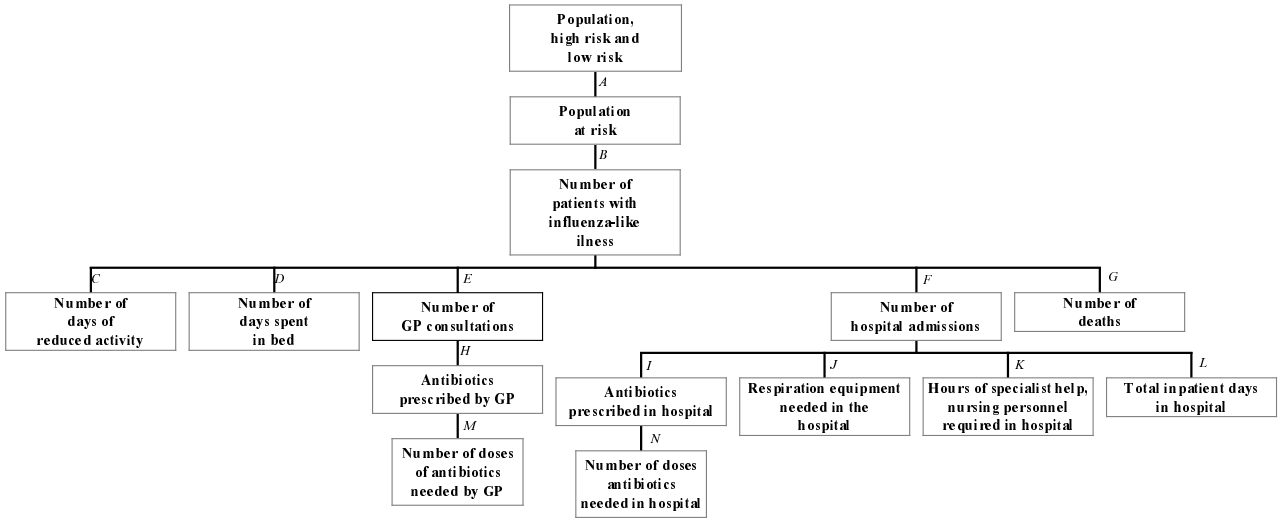

Figure 1. Schematic overview of the calculation model

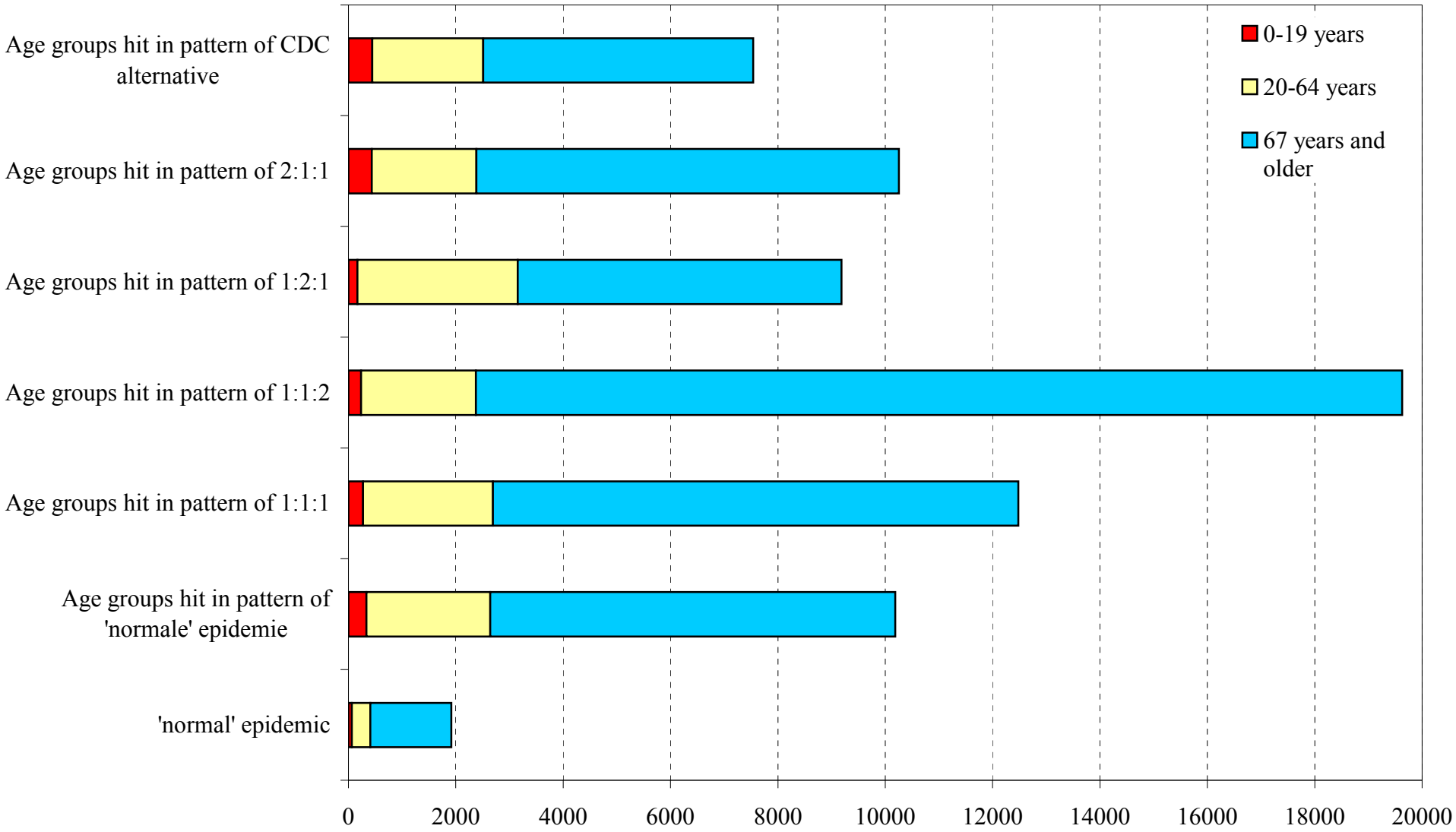

Figure 2. Desired hospitalisations by age, depending on attack rates in a pandemic with an extent of 30% no influenza vaccine available

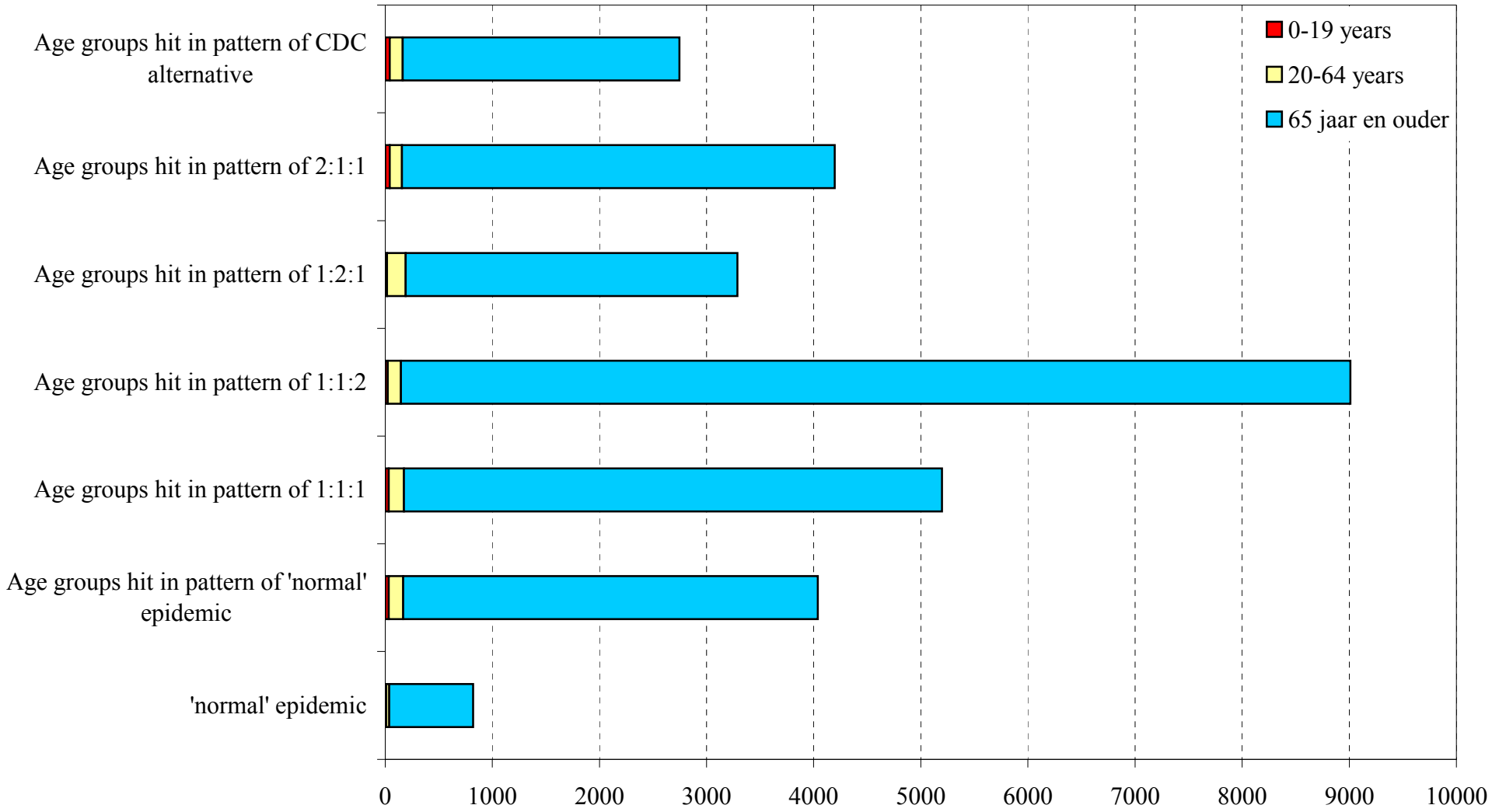

Figure 3. Deaths by age, depending on attack rates in a pandemic with an extent of 30% no influenza vaccine available

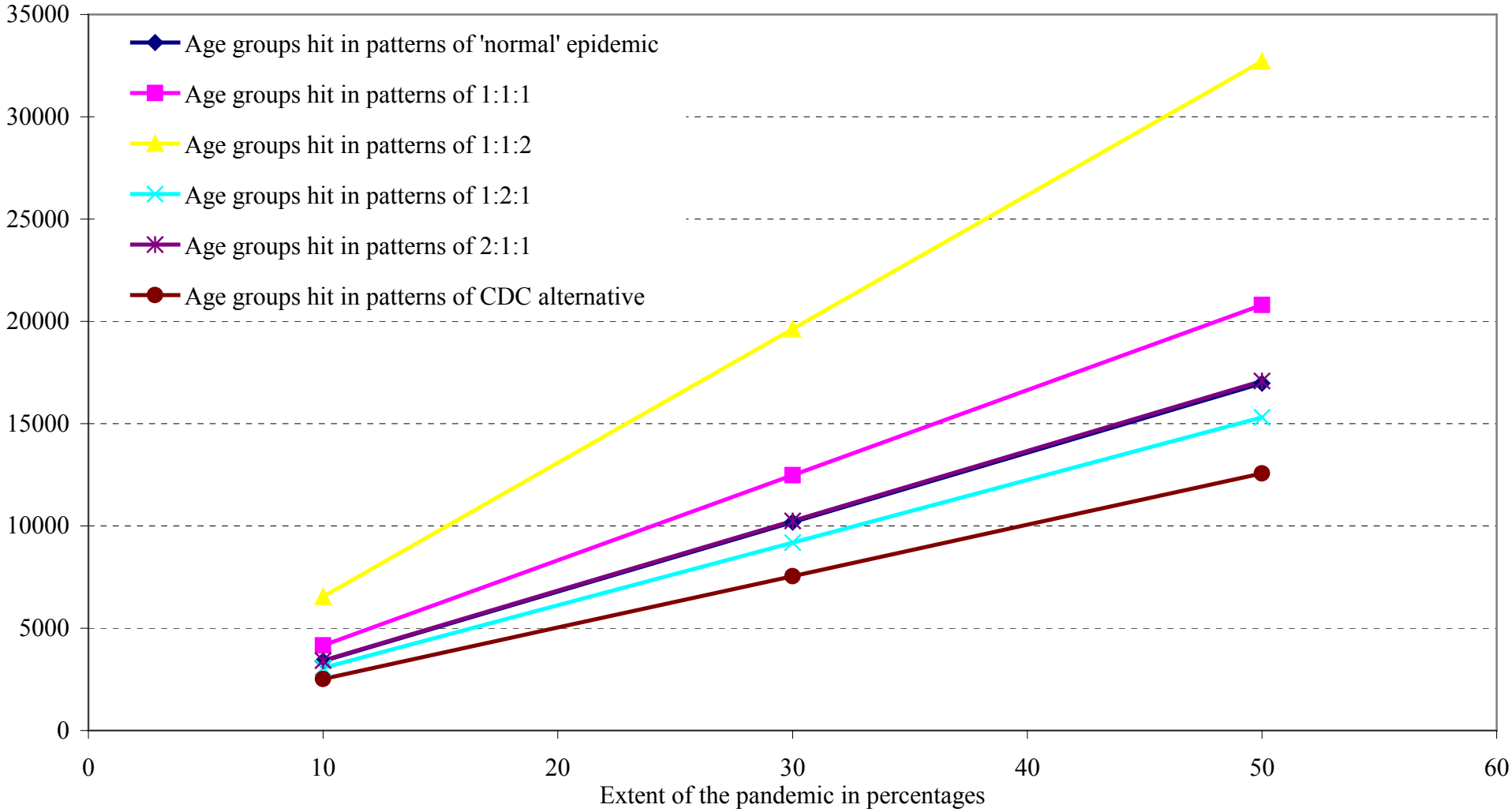

Figure 4. Desired hospital admissions for various extents of a pandemic by age, depending on attack rates no influenza vaccine available

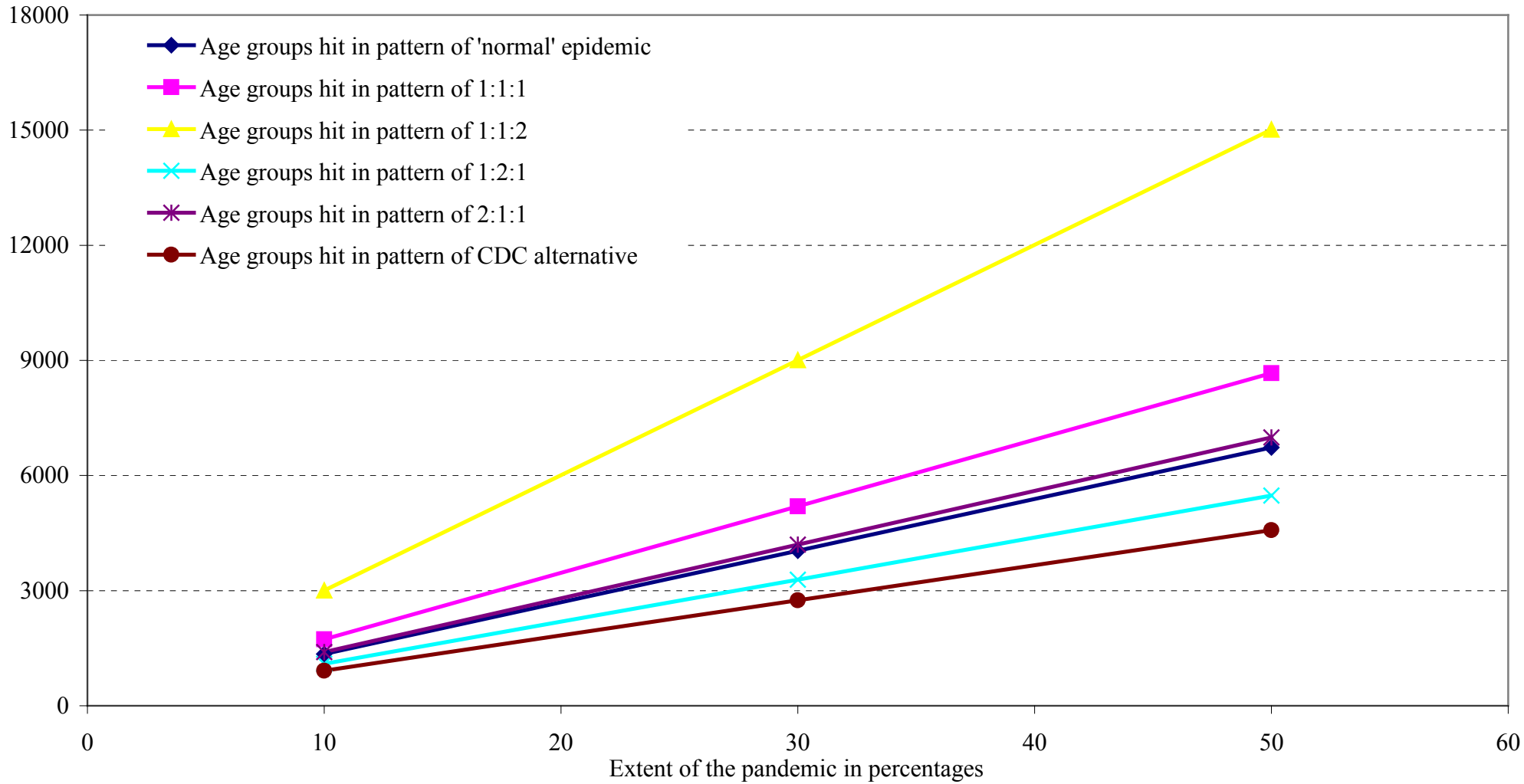

Figure 5. Deaths for various extents of a pandemic by age, depending on attack rates no influenza vaccine available

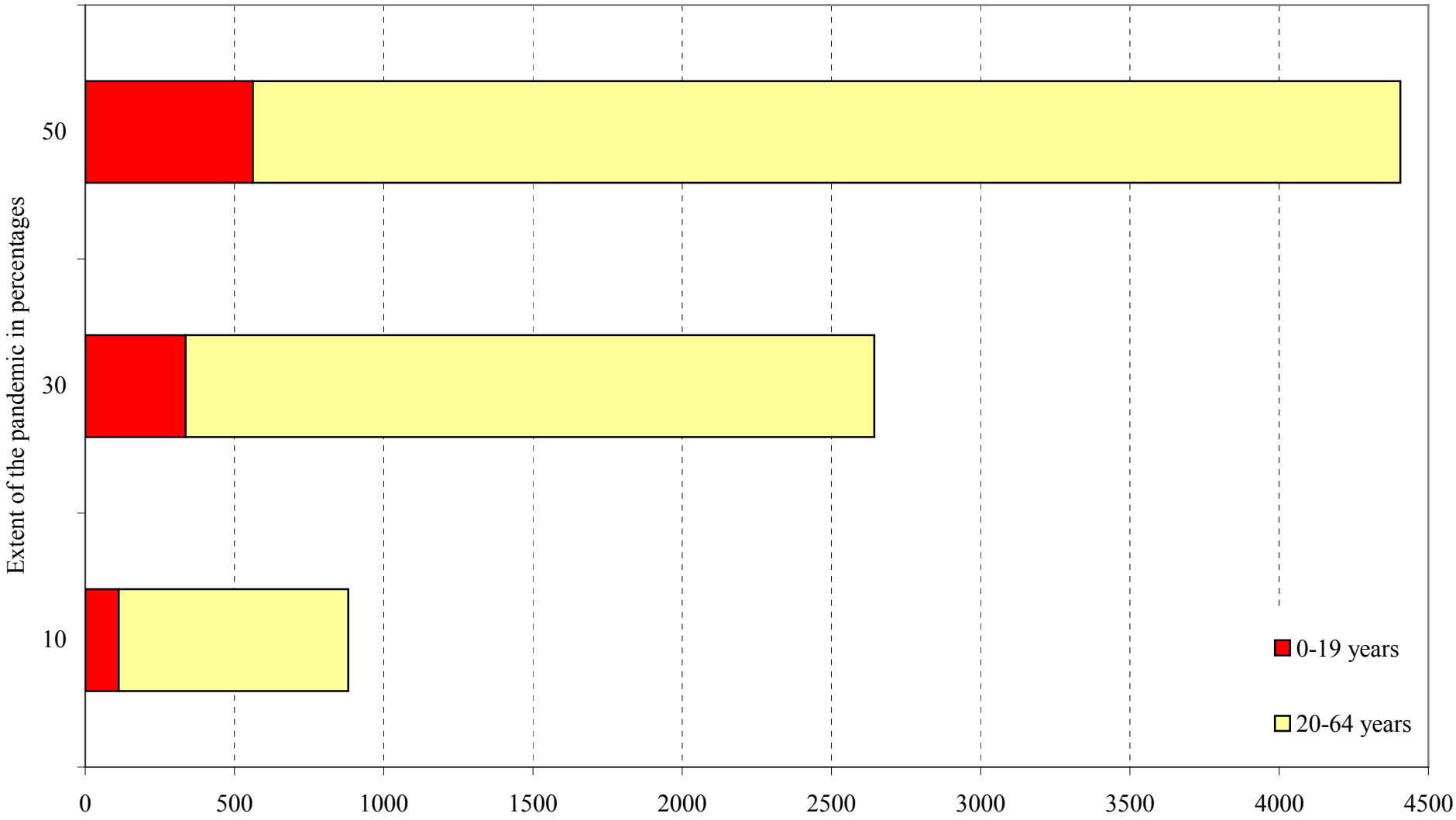

Figure 6. Increase of the desired number of hospital admissions if the hospitalisation rate for 0 to 64-year-olds is twice that of a 'normal' epidemic for 0 to 64-year-olds

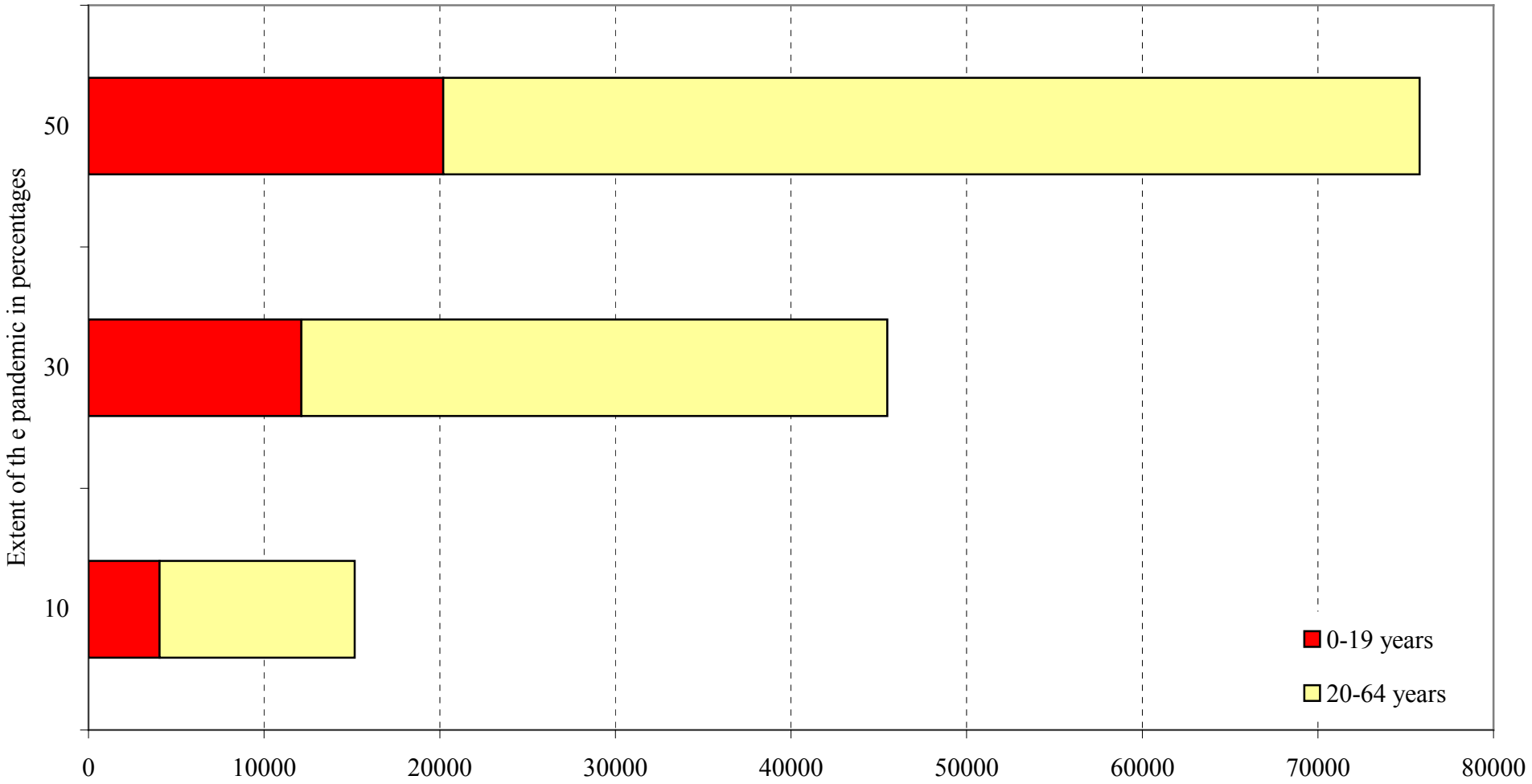

Figure 7. Increase of desired hospital admissions if the hospitalisation rate for the 0 to 64-year-old, low-risk group is the same as that for the 0 to 64-year old, high-risk group

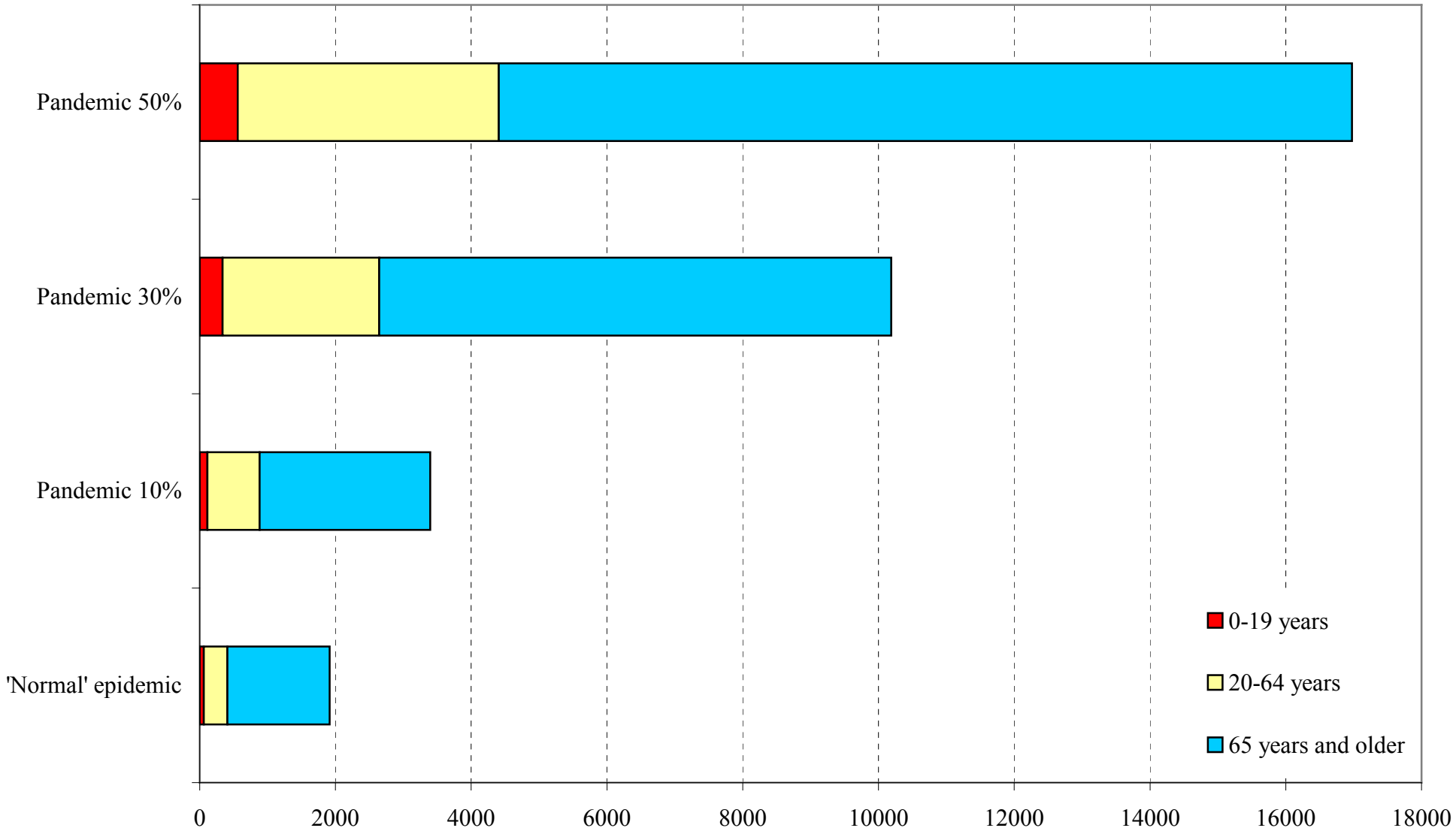

Figure 8. Desired number of hospital admissions in the nonintervention scenario

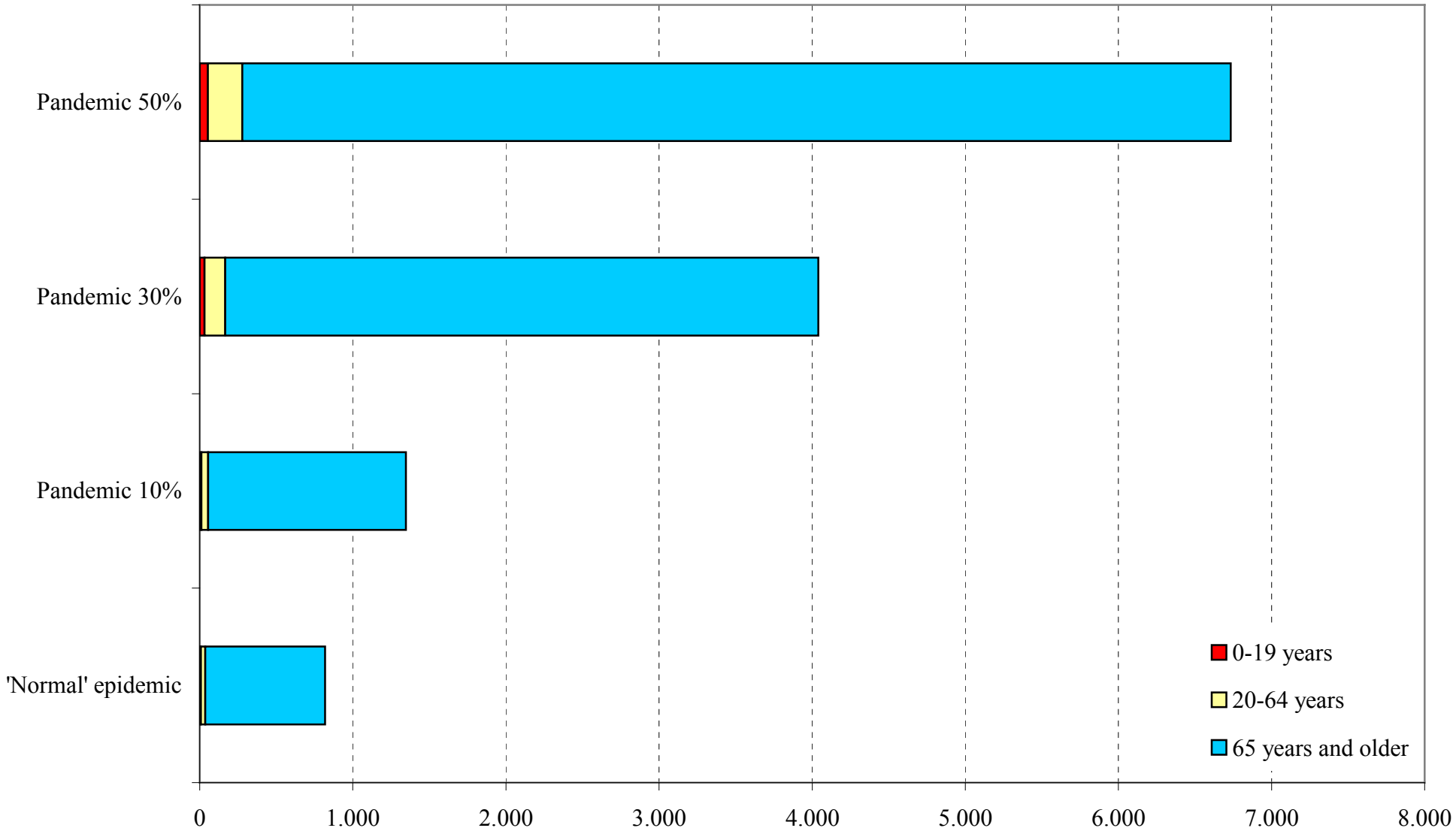

Figure 9. Number of deaths in the nonintervention scenario

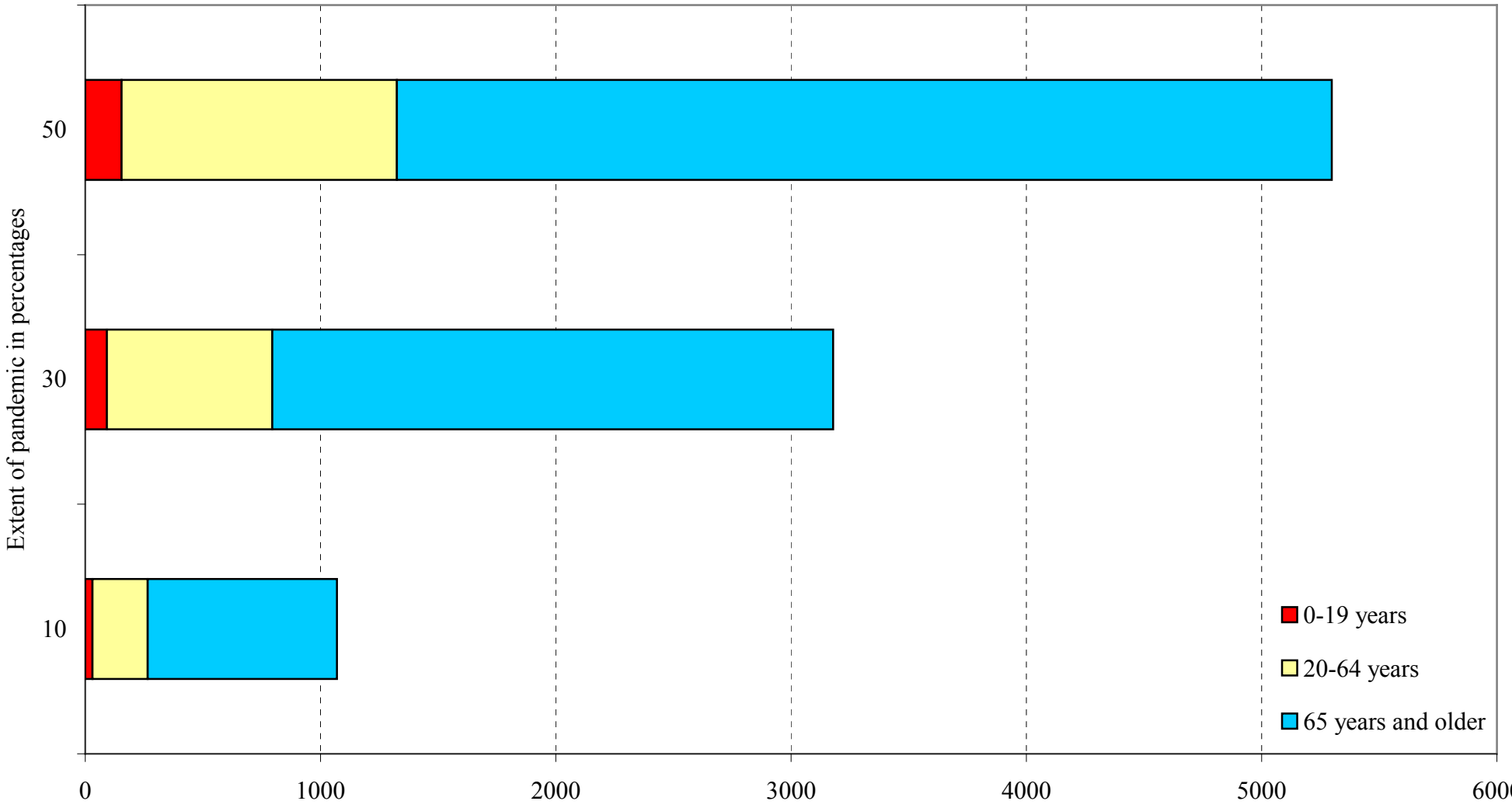

Figure 10. Hospital admissions prevented by pneumococcal vaccination of the influenza risk groups

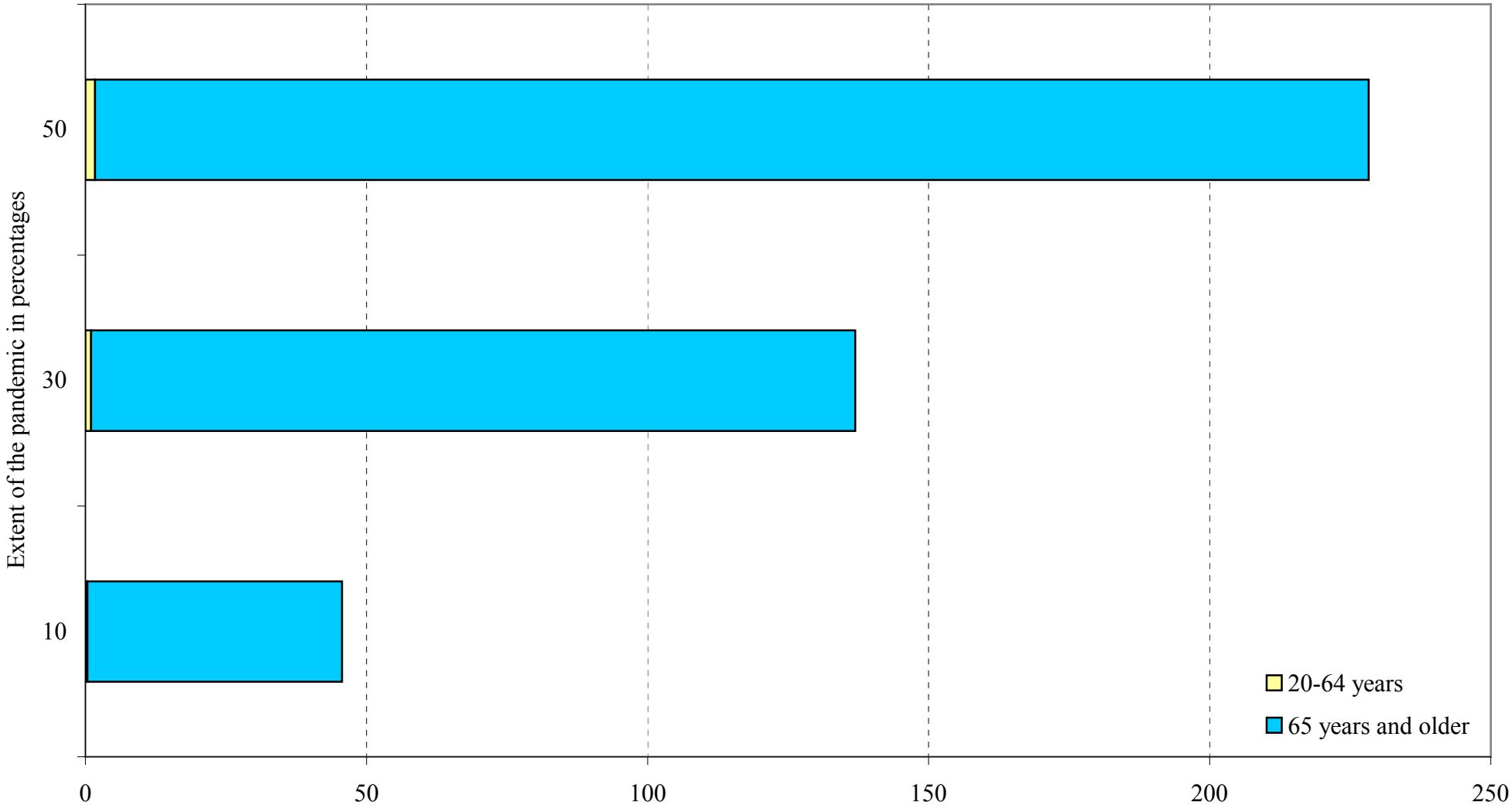

Figure 11. Deaths prevented by pneumococcal vaccination of the influenza risk groups

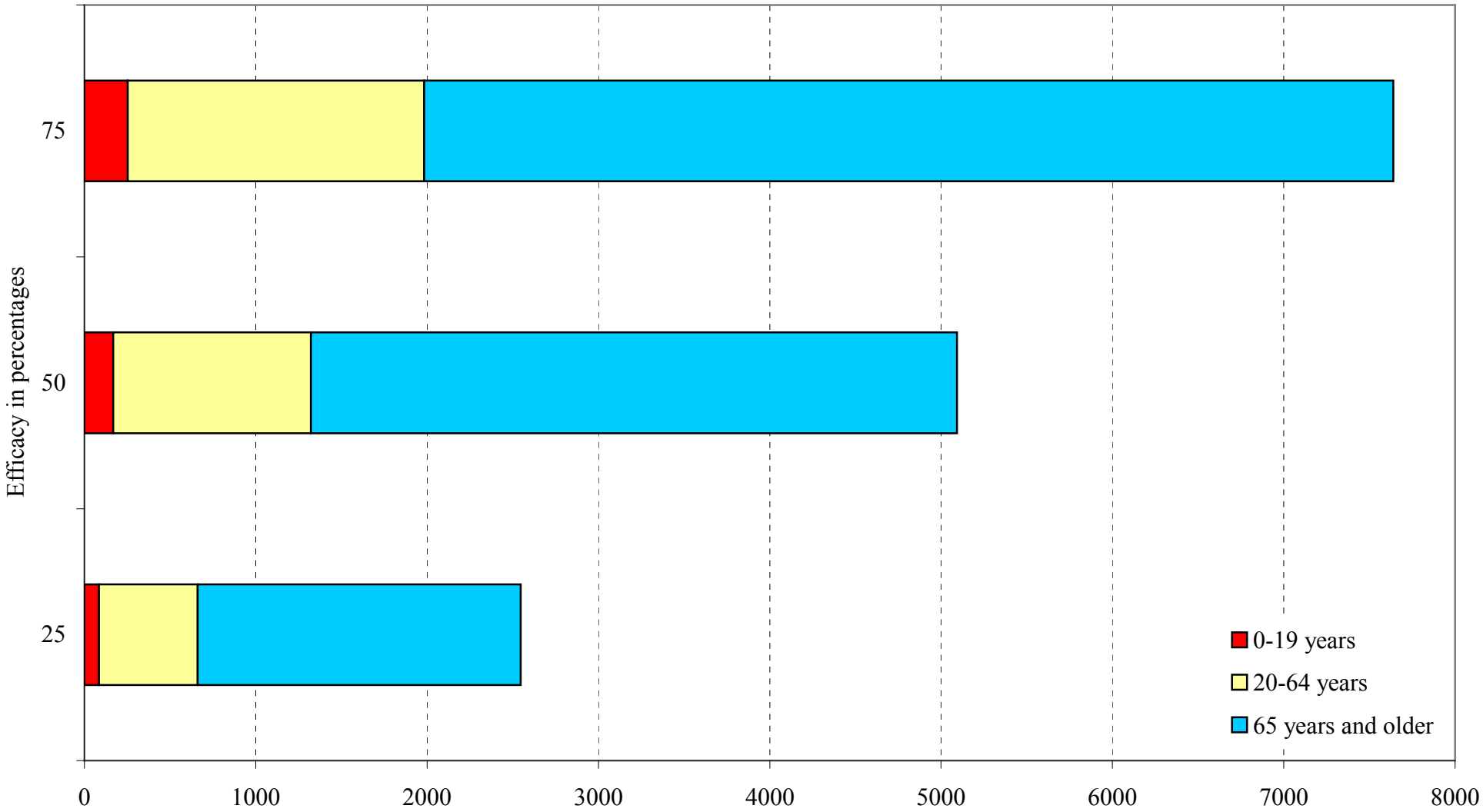

Figure 12. Hospital admissions prevented by therapeutic use of neuraminidase inhibitors for every ILI patient pandemic with an extent of 30%

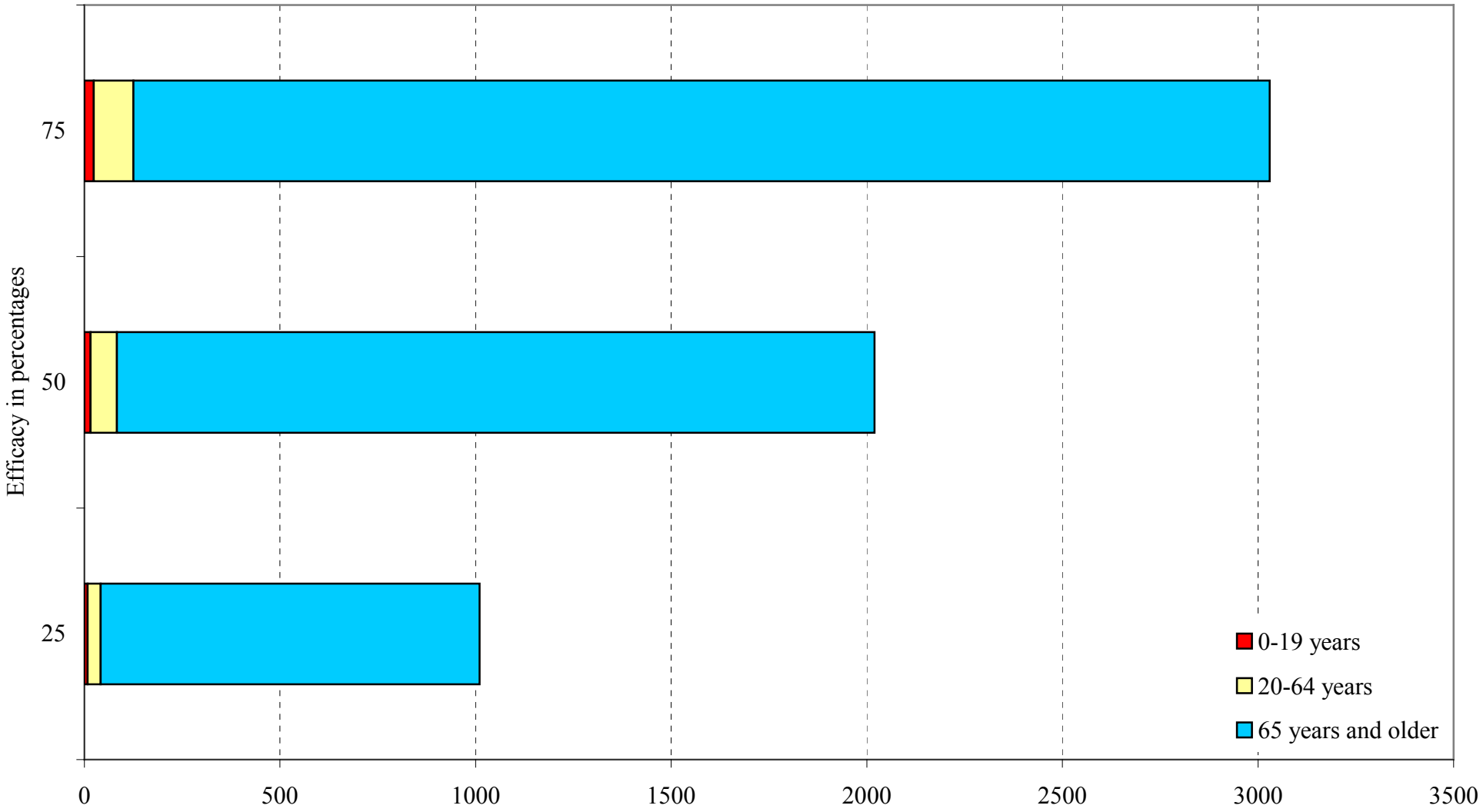

Figure 13. Deaths prevented by therapeutic use of neuraminidase inhibitors for every ILI patient pandemic with an extent of 30%

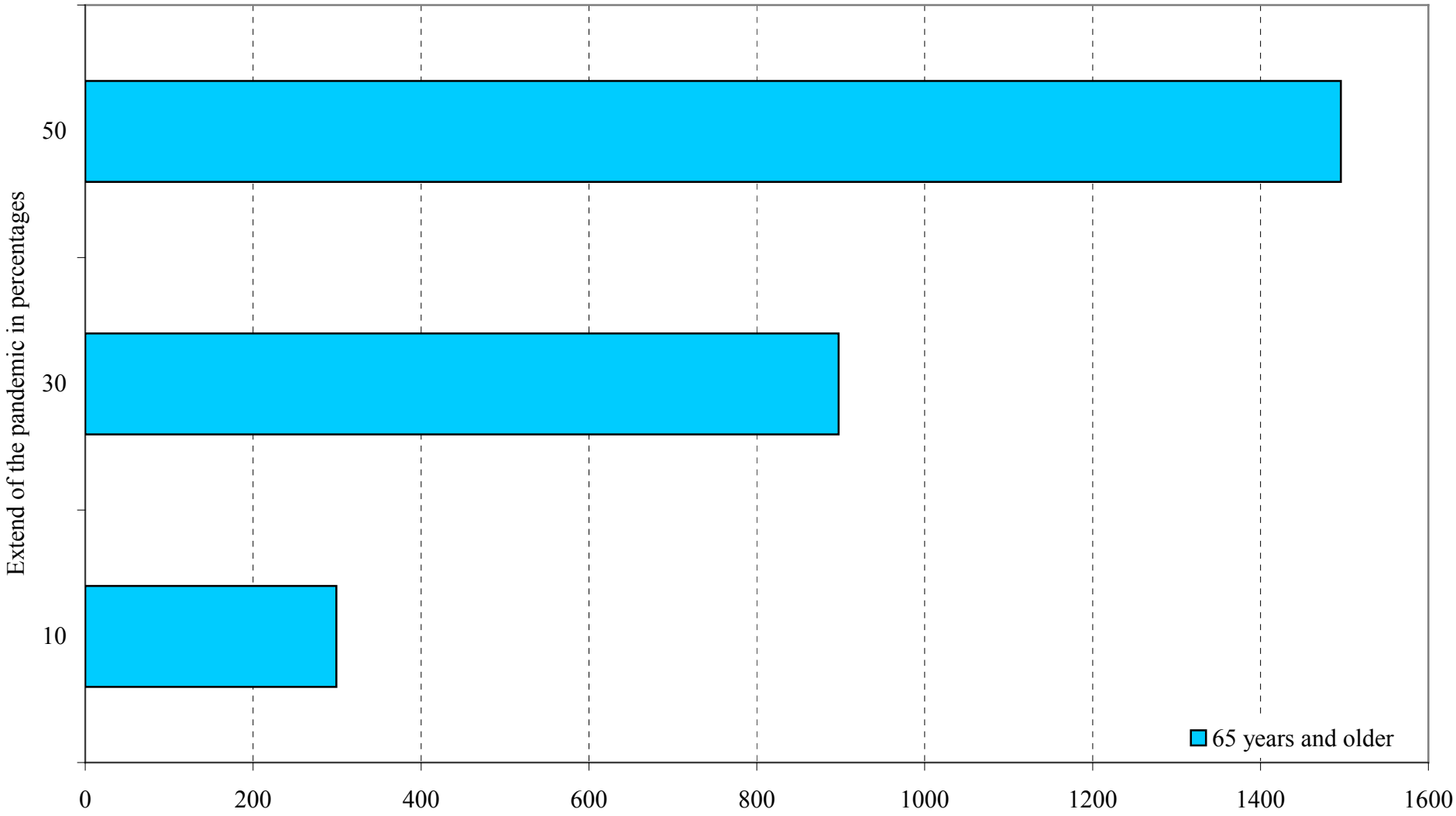

Figure 14. Hospital admissions prevented by prophylactic use of neuraminidase inhibitors in nursing and care homes

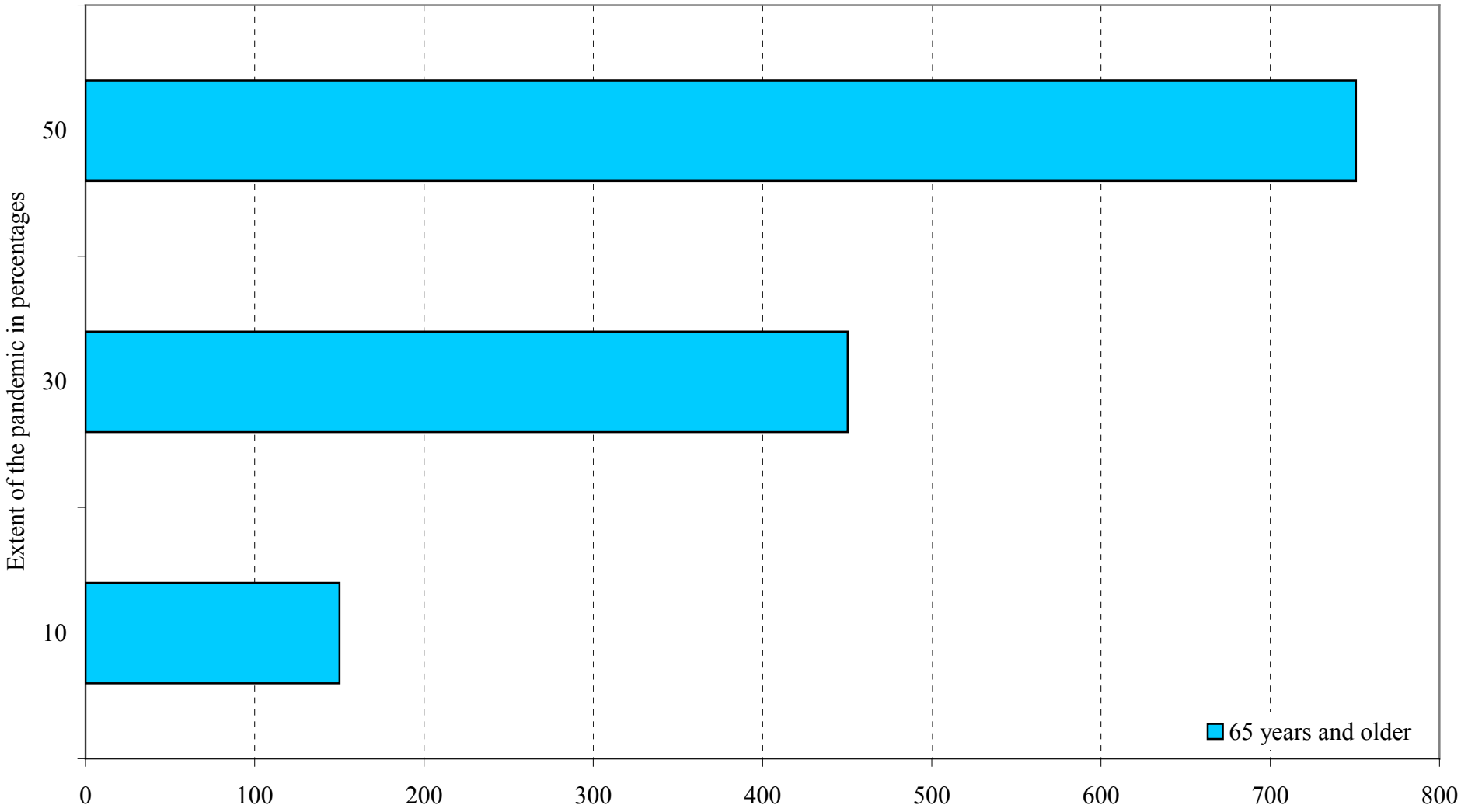

Figure 15. Deaths prevented by prophylactic use of neuraminidase inhibitors in nursing and care homes

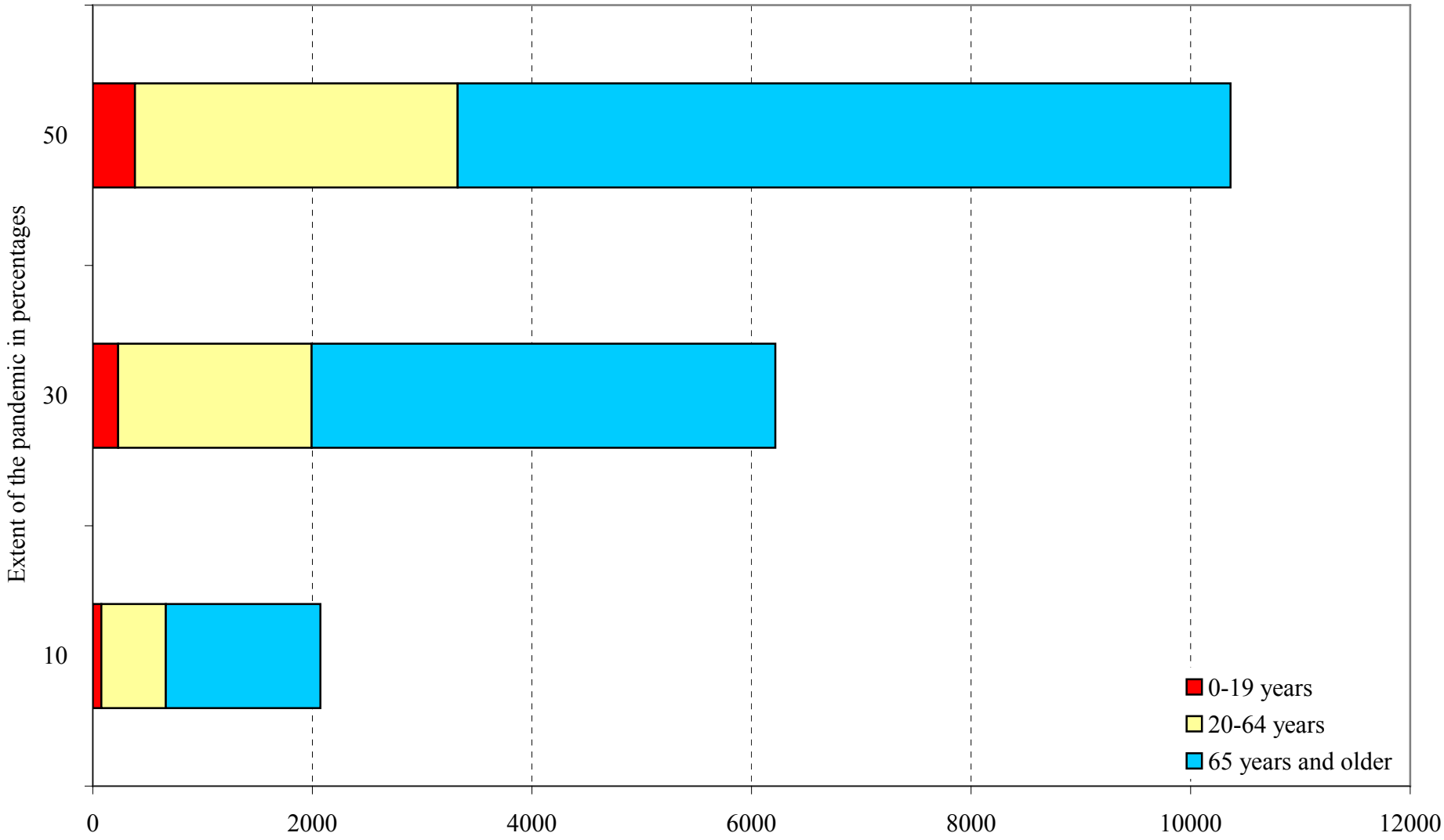

Figure 16. Hospital admissions prevented by influenza vaccination of influenza risk groups (including those over 65) and caregivers

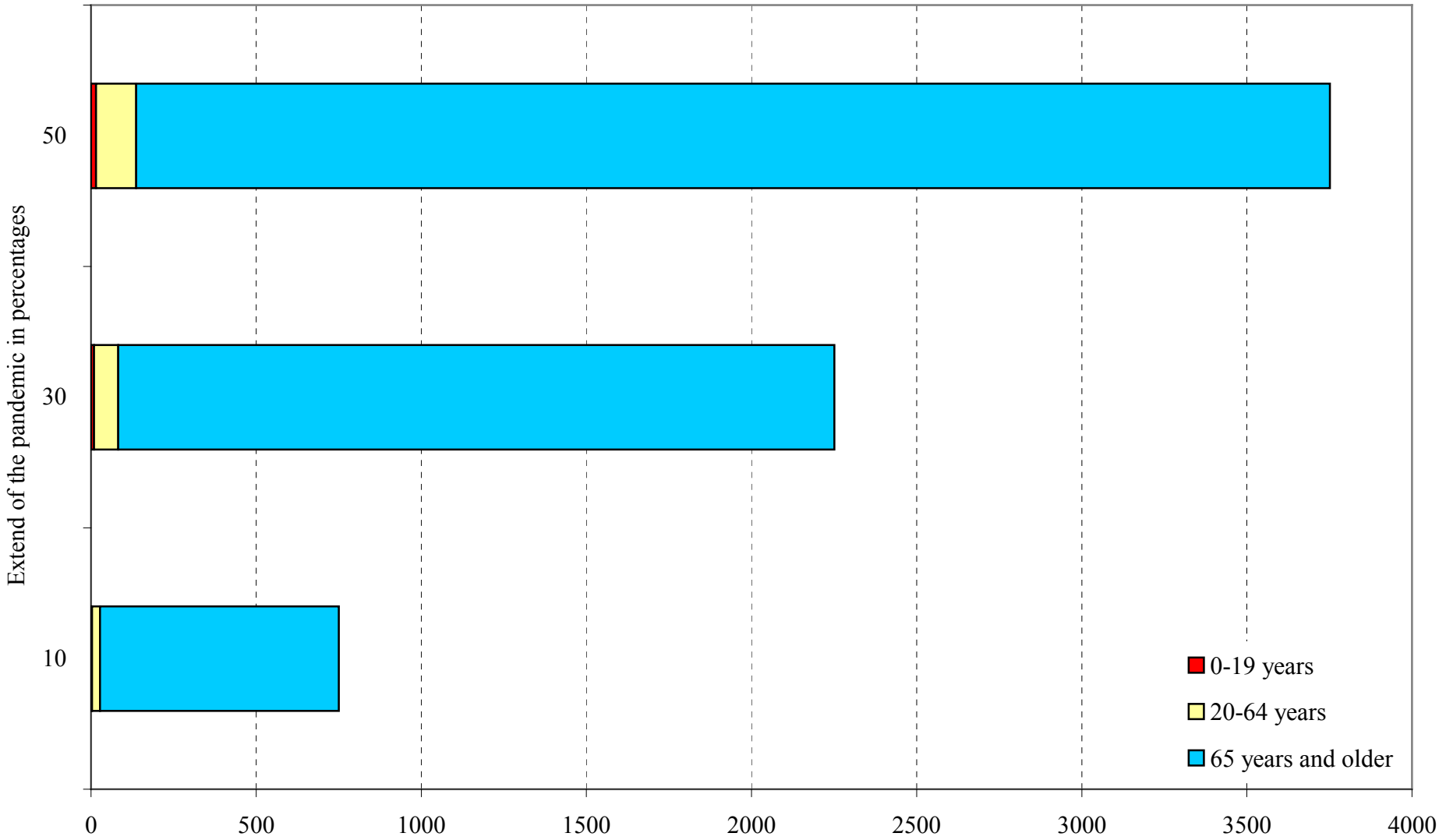

Figure 17. Deaths prevented by influenza vaccination of influenza risk groups (including those over 65) and caregivers

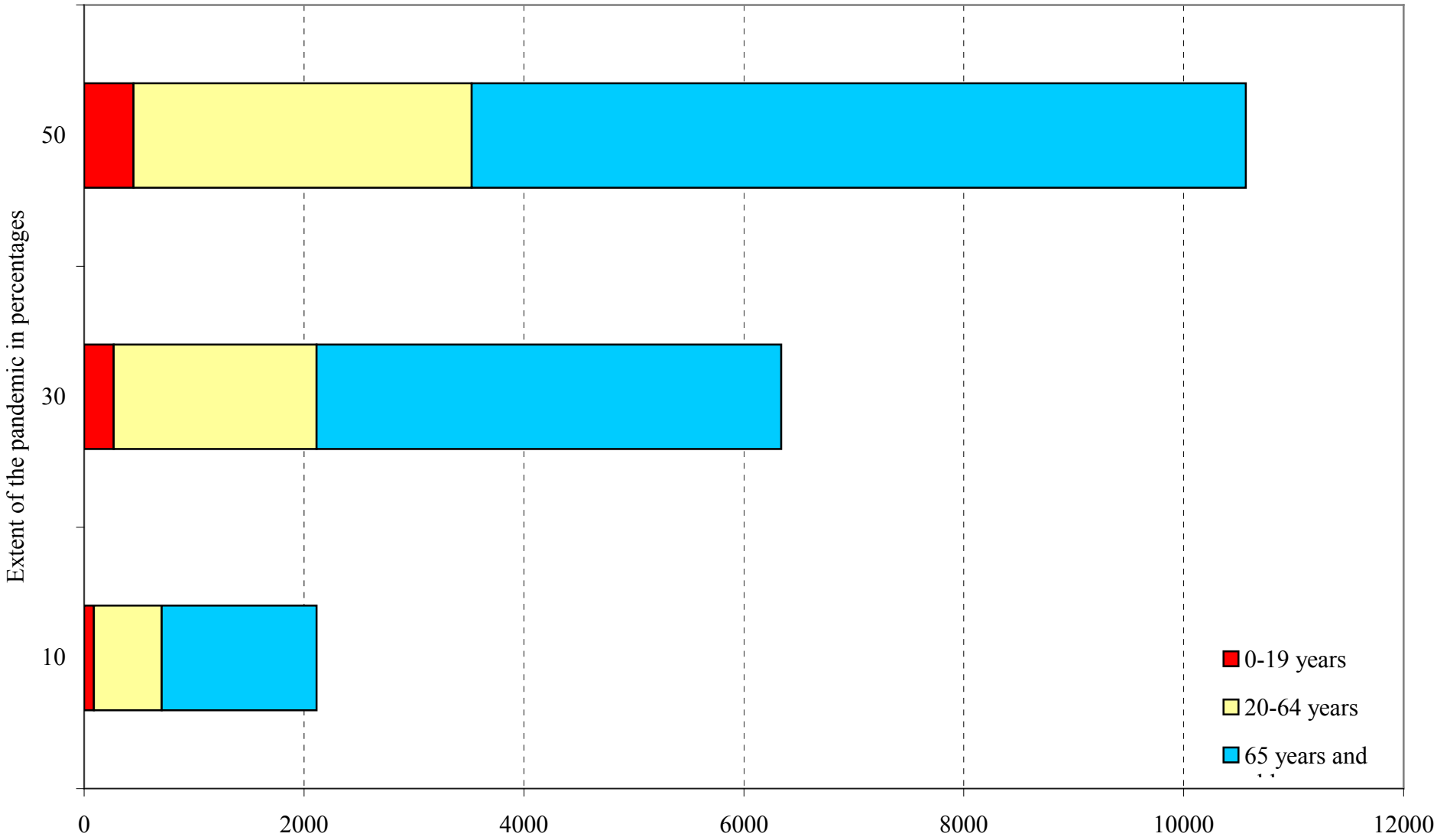

Figure 18. Hospital admissions prevented by influenza vaccination of the whole Dutch population pandemic with an extent of 30%

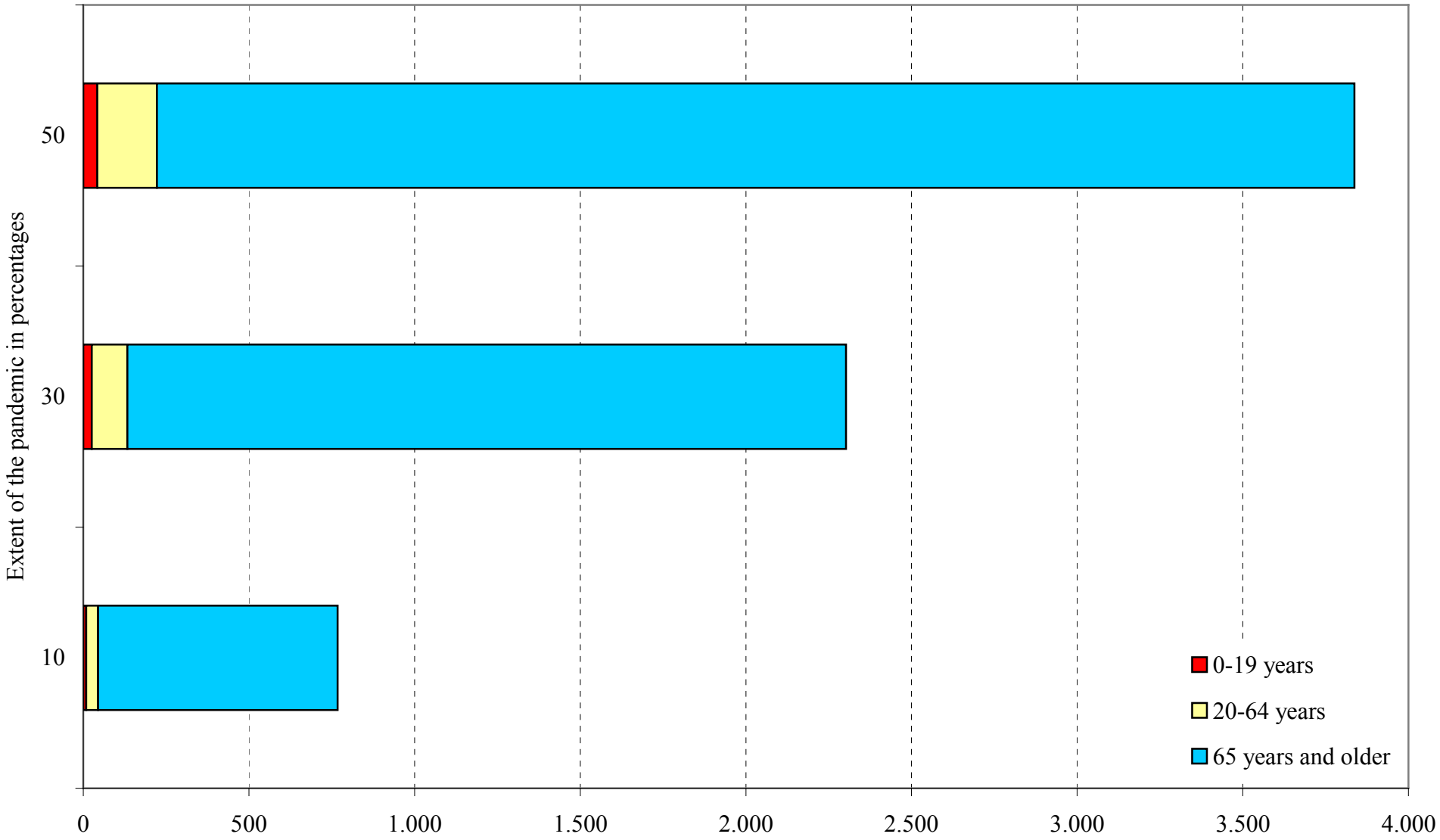

Figure 19. Deaths prevented by influenza vaccination of the whole Dutch population pandemic with an extent of 30%

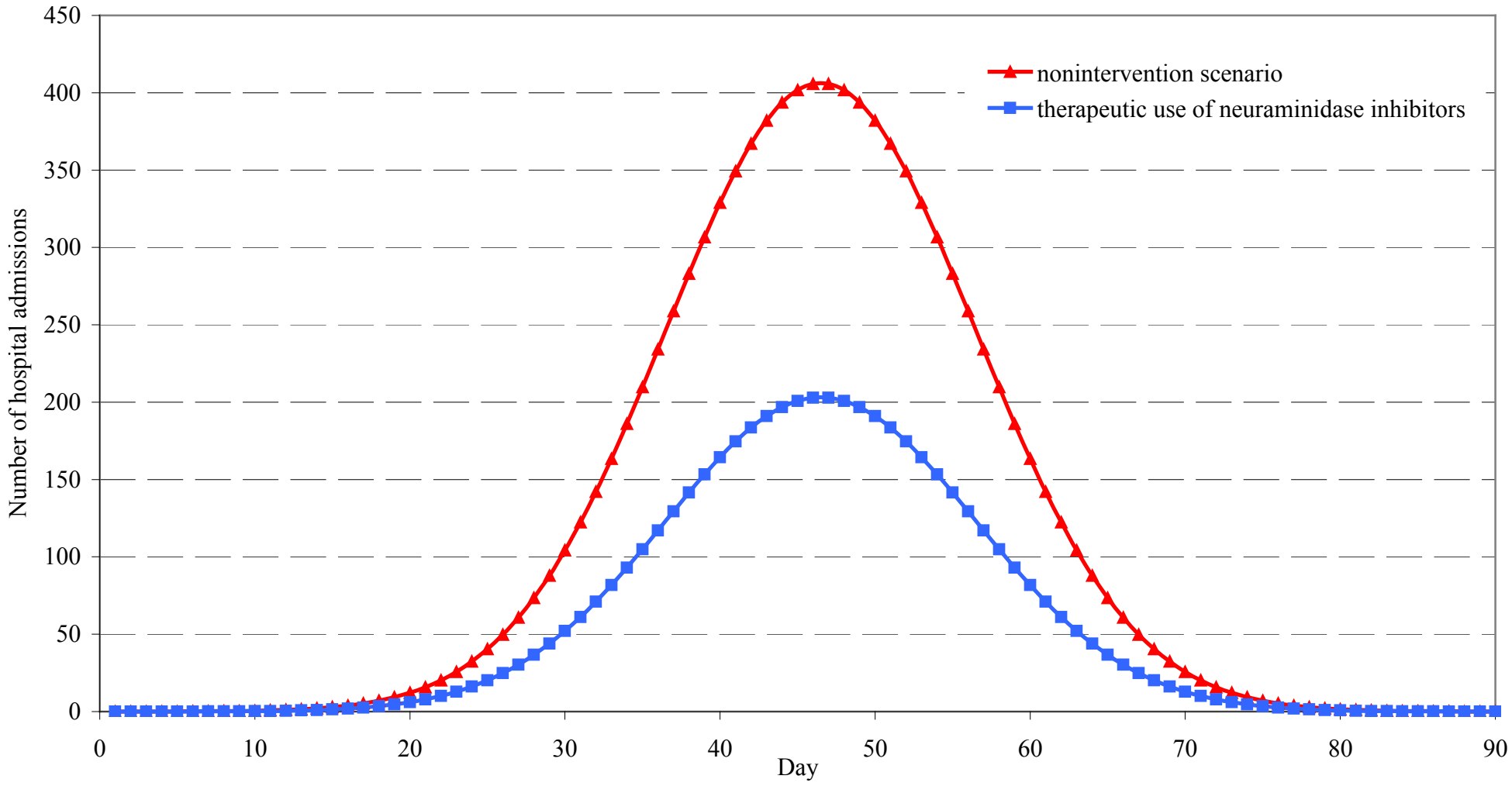

Figure 21. Hospital admissions desired per day, normally distributed over 3 months in a pandemic with an extent of 30%

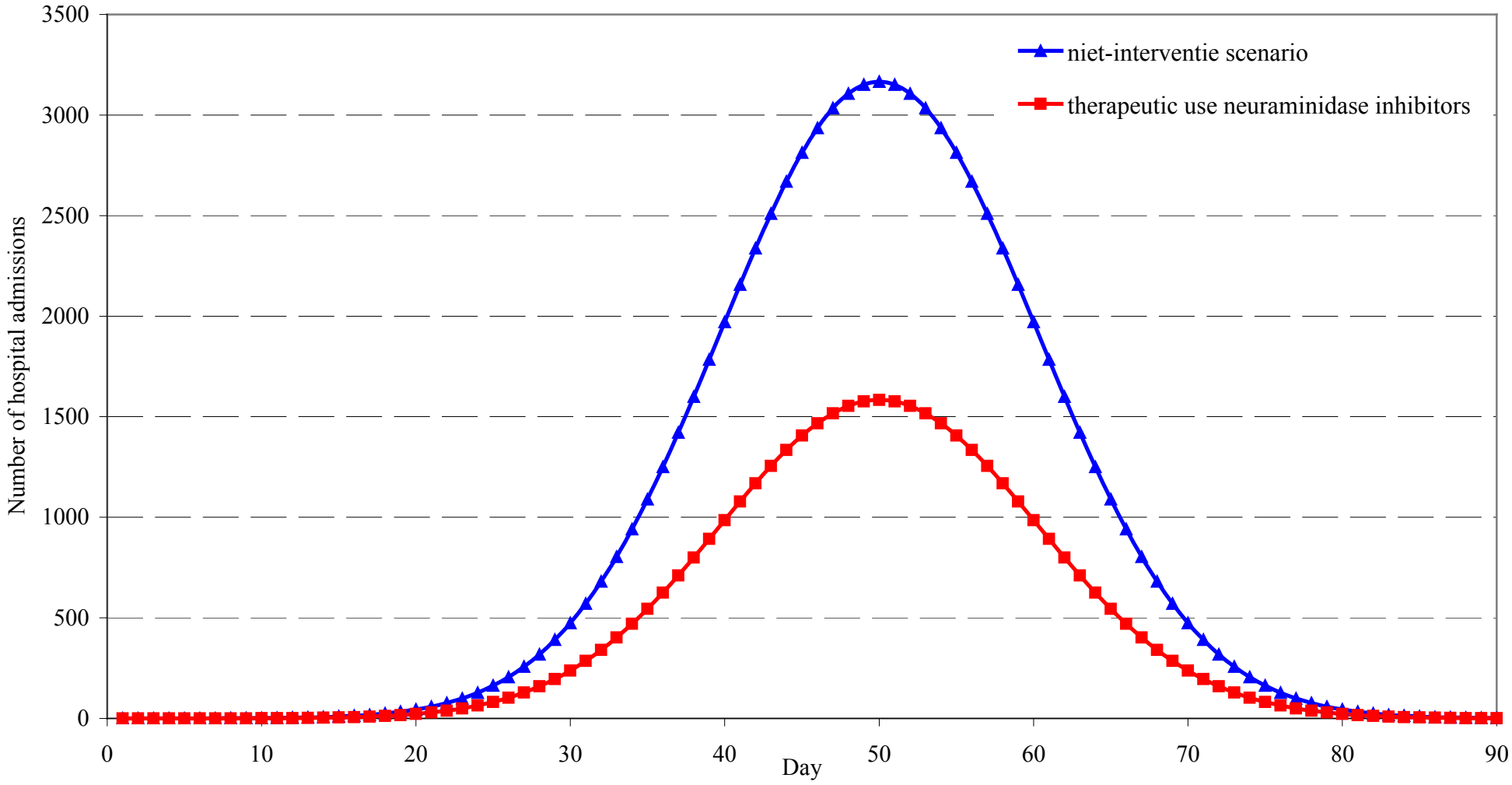

Figure 21. Hospital beds needed during 3 months in a pandemic with an extent of 30% and a stay of 8 days

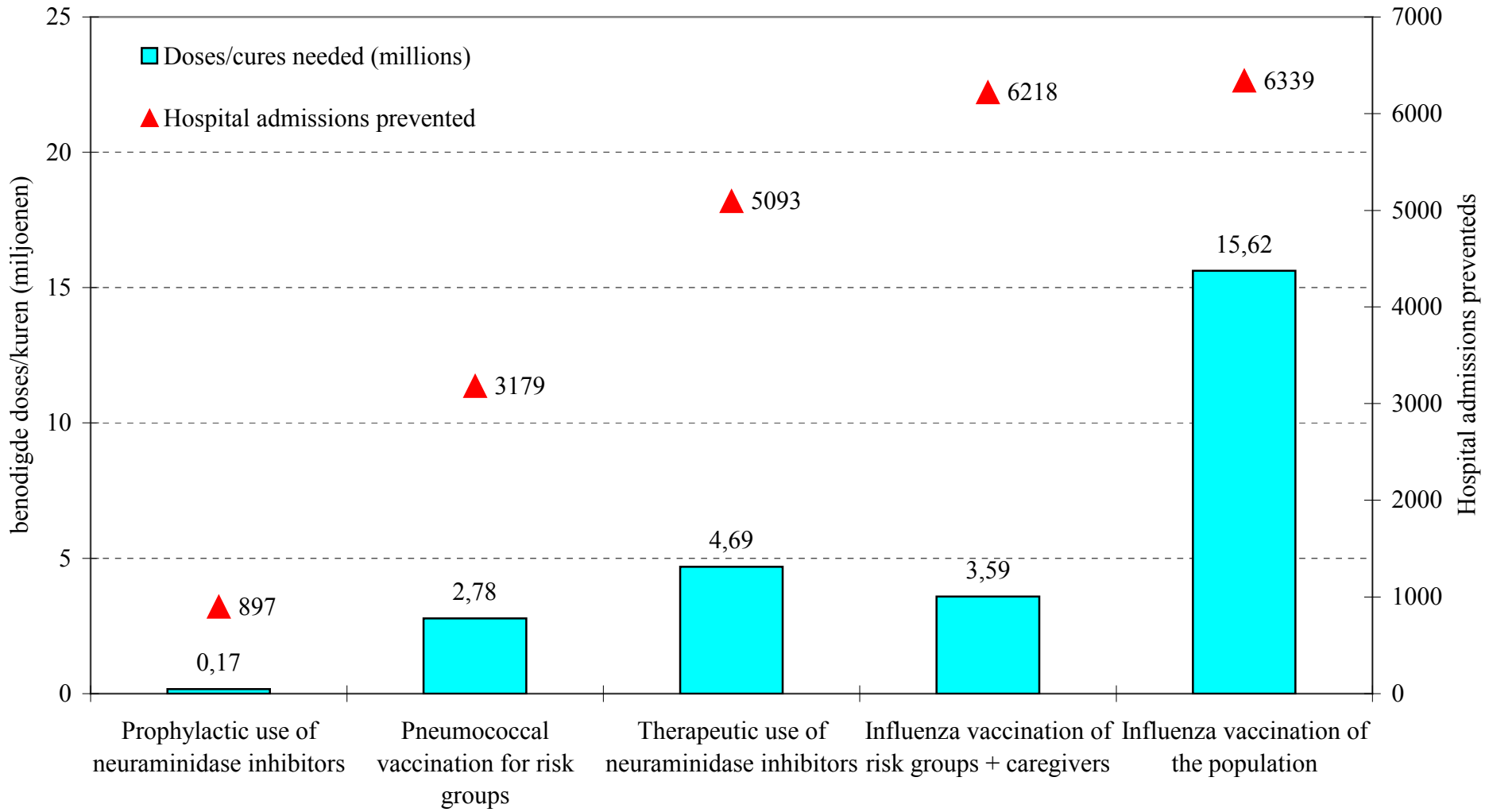

Figure 22. Hospital admissions prevented versus doses/cures of vaccines, neuraminidase inhibitors, or antibiotics needed

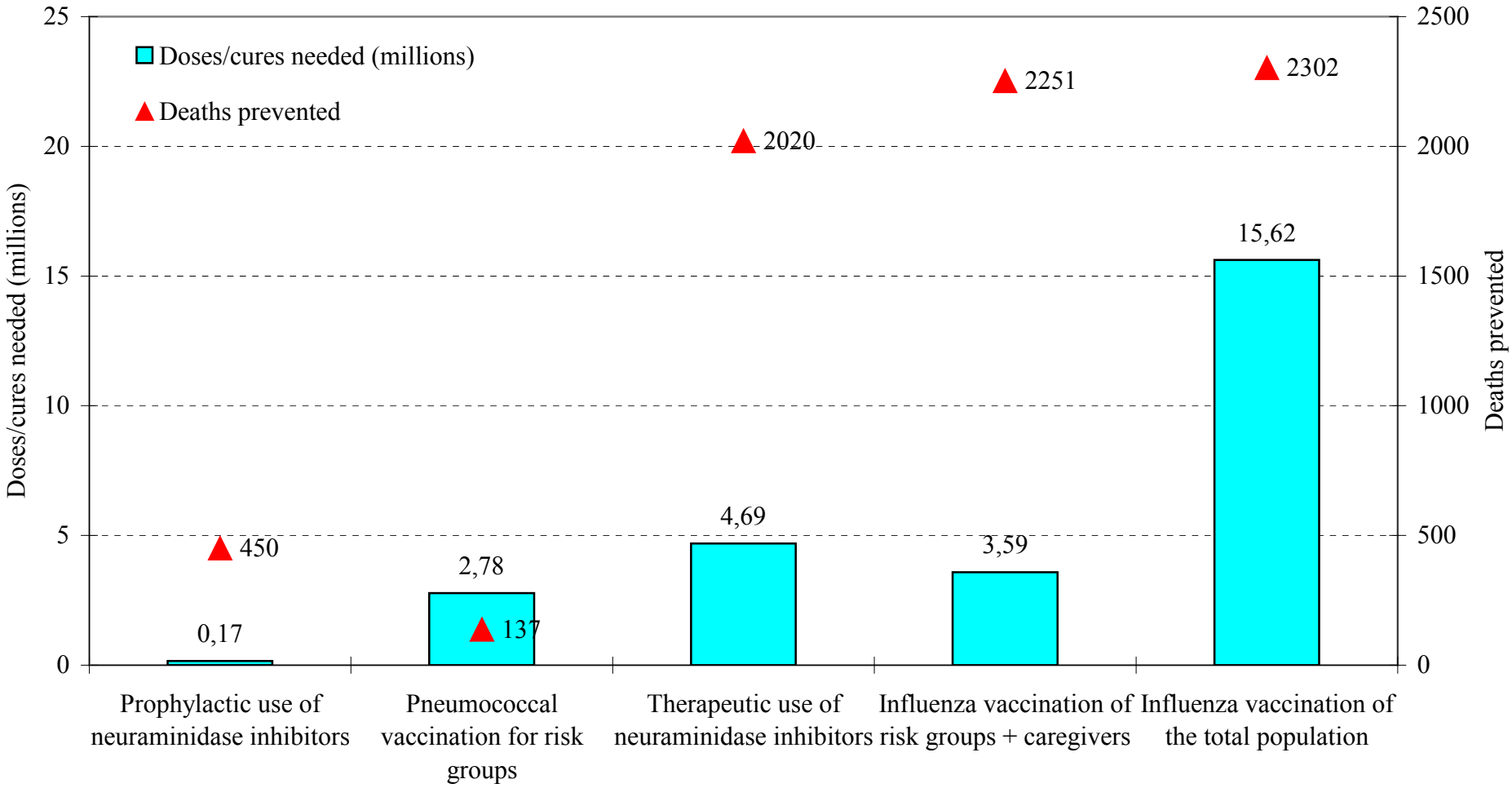

Figure 23. Deaths prevented versus doses/cures of vaccines, neuraminidase inhibitors, or antibiotics needed