ECDC **INTERIM GUIDANCE**

Use of specific pandemic influenza vaccines during the H1N1 2009 pandemic

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Contents

Executive summary

In April 2009, a new strain of human influenza A(H1N1) was identified and characterised. The attack rates for this A(H1N1) pandemic strain are expected to be higher than for seasonal strains because of the lower levels of pre-existing immunity in the population (except for older people, many of whom do seem to have a degree of immunity). Therefore the actual numbers of cases of influenza presenting to health services in a short period of time is likely to be higher than those of seasonal influenza.

Vaccination with a strain-specific pandemic vaccine is considered one of the most effective countermeasures for protecting individuals in the event of a pandemic. However, specific pandemic vaccines will not become available all at once, delivery from the manufacturers will necessarily be staggered, and there will also be difficulties in distribution. Ensuring vaccine supply will be difficult within a reasonable timeframe. Strategic use of vaccines, after careful prioritisation between different population groups, will be important to maximise the benefit of the available doses.

Overall objectives of vaccination should be specified before deciding who should be offered the vaccine and how to prioritise target populations. These may legitimately differ by country and/or region. They will particularly differ according to the resources, amounts of vaccine, numbers of syringes, etc. that are available and practical issues relating to distribution and delivery. These differences between countries will pose communication problems when they become apparent and these should be prepared for.

The objectives of a pandemic vaccination strategy can be considered in two broad categories which are by no means mutually exclusive: a) mitigation, to protect the individuals that may be at greatest risk of severe disease; and b) protecting essential services.

Influenza A(H1N1)v is a novel virus and pandemics in modern times have all differed one from another and from the current seasonal influenza. Hence, **risk groups** (those at higher risk of severe disease) may differ from those for seasonal influenza strains. Also, different strategies come into play with greater emphasis on the need to maintain essential services by immunisation. Hence **target groups** (groups that are offered vaccine who may or may not be in the risk groups) may also be different.

According to the current evidence on the A(H1N1) 2009 pandemic, the following population groups can be identified as risk groups:

- people aged less than 65 years with chronic underlying conditions, namely:
  - chronic respiratory diseases;
  - chronic cardiovascular diseases;
  - chronic metabolic disorders (notably diabetes);
  - chronic renal and hepatic diseases;
  - persons with deficient immunity (congenital or acquired);
  - chronic neurological or neuromuscular conditions;
  - any other condition that impairs a person's immunity or prejudices their respiratory function;
- young children (especially under the age of two years);
- pregnant women.

This list differs somewhat from the groups for whom many countries recommend seasonal influenza immunisation, especially with regard to people aged 65 years and over. Older people seem generally to be at lower risk of infection – possibly due to existing immunity – but there are indications that if they do become infected they suffer more severe disease than younger adults.

In addition, there are other groups to whom immunisation may be offered even though they are not at higher risk of severe disease (target groups). There are arguments for offering vaccination to children since they are experiencing high attack rates (albeit of mild disease) and may be particularly important in amplifying local outbreaks. There are also arguments for offering immunisation to all healthcare workers. This is both to prevent people in risk groups becoming infected from healthcare workers and to protect the healthcare worker from infected patients, thereby sustaining healthcare services. There are advantages to offering immunisation to people who care for those for whom immunisation may not be effective (e.g. people under treatment with immunosuppressive therapy). Babies under six months of age cannot at this stage be immunised because of lack of data on immunogenicity and safety and there are therefore arguments for offering vaccination to those that are in closest contact with them. Other potential target groups are workers essential for the response to the pandemic.

This guidance is based on the current scenario of the A(H1N1) 2009 pandemic. Particular areas of uncertainty are noted and discussed. As more data, evidence and opinions become available this document will be updated along with the ECDC risk assessment to which it is linked [1].

Based on the experience from previous pandemics, during which the pathogenicity and transmissibility of the virus increased over time, three other scenarios are presented. There are also annexes summarising the evidence for vaccination of particular risk groups for seasonal influenza and the current pandemic influenza and giving broad estimates of the size of the risk and target groups. The basis for the calculation is given in sufficient detail that people in the Member States can apply the methodology to their own population or compare the methods already used.

Comments on this interim guidance are welcomed and encouraged and should be sent to PHE.H1N1v@ecdc.europa.eu

Objectives of this document

The purpose of this document is to provide background information and guidance on pandemic vaccine use and options for prioritisation strategies that can be employed during any influenza pandemic affecting Europe. However, it especially focuses on the A(H1N1) 2009 pandemic.

Like other guidance issued by ECDC, and in accordance with its mandate, the document does not attempt to provide recommendations. Rather, it presents options based on the available scientific information and experience both within Europe and without.

The document is based on scientific evidence, public health principles and experience, expert opinions and on what is recommended in the various national pandemic preparedness plans [2] in EU countries, by WHO [3,4] and other national analyses. This document is intimately linked to the ECDC Risk Assessment which, in addition to the European data, also draws on the information becoming available to WHO and other partners, notably in countries that are already affected in North America and in countries in the southern hemisphere currently suffering from the regular winter influenza season and infections caused by the new virus [5].

This document will be updated at intervals as more data and analyses become available. Moreover, for a more precise development of vaccination strategies, the impact in combination with other interventions like the use of non-pharmaceutical public health measures and antiviral medications should also be considered [6,7,8].

Audience

The audience for this document is broad. The principal groups are those responsible for public health and policy development in the EU and EEA countries for which it is intended to act as a resource document. However, it is expected that elements of the paper will also be of interest to those responsible for clinical care and even to the general public.

Background

In April 2009, a new strain of human influenza A(H1N1) causing human disease was identified and characterised. Due to evidence of community transmission of the new strain from person to person in more than one of its regions, WHO declared pandemic Phase 6 on 11 June 2009. The morbidity and mortality associated with this, or indeed any other pandemic strain, may or may not be greater than recently circulating seasonal influenza A virus infections. This may also change (for better or worse) during the course of the pandemic [5]. However, the overall severity of this pandemic A(H1N1) influenza is so far considered by WHO to be moderate, meaning that most people recover from infection without the need for hospitalisation or medical care, but serious cases and deaths are also occurring [5]. 'Severity' is a complex concept influenced by properties of the circulating pandemic virus, and the specific and general overall vulnerability of the populations that are affected [5,9]. Pandemic strains have on at least one occasion (1918–19) become more pathogenic and/or more transmissible in the early stages of the pandemic. However, over time and after repeated waves of infection and disease, the pandemic virus generally adapts and becomes less pathogenic, albeit usually maintaining a higher level of pathogenicity than the preceding seasonal influenza A viruses.

However, the attack rates for the H1N1 2009 pandemic strain are expected to be higher than for seasonal strains because of the lower levels of pre-existing immunity in the population [5]. Population clinical (i.e. symptomatic) attack rates during pandemics have been estimated to be 20–35% [10]. These are higher than population attack rates observed for seasonal influenza, which usually range from 5 to 10% [11]. Attack rates in the general population for the influenza A(H1N1) 2009 virus cannot be easily estimated in this early stage of the pandemic but are expected to be high, especially in closed communities and in households [5]. Certainly, even if the clinical severity of the disease is comparable with that of seasonal influenza, the actual number of symptomatic cases will be higher than those of seasonal influenza.

It remains to be seen exactly which segments of the population will be most at risk of a) infection, and b) developing more severe infections, but already there are some useful indicators. So far, there is a marked underrepresentation of infections in people aged over 64 years in both the United States and Europe [5]. The risk of experiencing severe disease is somewhat less straightforward. Most of the deaths and cases of severe disease in the United States have occurred in people with chronic underlying conditions that would predispose them to complications of influenza, but also in pregnant women and very young children [12]. The numbers of these in previously healthy subjects is not clear. While older people (those 65 years and older), with or without underlying conditions, are less likely to be infected, if they do catch the virus they are more likely to suffer severe disease than a younger person without an underlying condition [5,13,14]. For a more detailed summary of known clinical features of the disease caused by influenza A(H1N1)v virus see the ECDC Risk Assessment [5].

Options for vaccination strategies

Vaccination with a strain-specific pandemic vaccine is considered to be one of the most effective countermeasures for protecting individuals in the event of a pandemic. However, achieving vaccination during a pandemic is a challenging task for the Member States. An essential first step for countries and communities is to decide what their objectives are.

Objectives of vaccination

Overall objectives of the vaccination should be specified before deciding who should be targeted for vaccination and how to prioritise target populations. These may differ by country and/or region and especially according to the amount of vaccine available, the particular epidemiology and practical considerations.

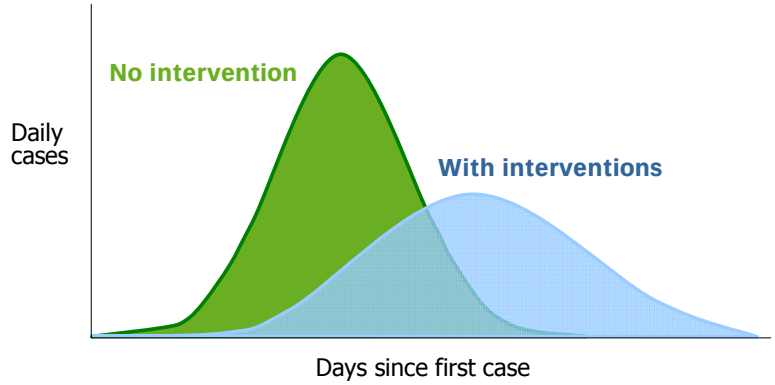
The objectives of a pandemic vaccination strategy can be considered in two broad categories which are by no means mutually exclusive:

Mitigation: to limit the impact of the pandemic by reducing morbidity and mortality, either:

- **directly**, usually by offering vaccination to those at higher risk of infection and/or severe disease, and those who provide healthcare for them; or
- **indirectly**, by offering vaccination to the wider population, thereby reducing transmission.

An important objective of mitigation, is to reduce the peak attack rates locally in order to take some pressure off the healthcare services (see Figure 1).

Figure 1. Illustration of the effect of vaccination as a mitigation strategy



Protecting essential services: to protect and ensure the general capacity to respond to the pandemic (over and above the healthcare sector) and to maintain essential services.

Mitigation

This objective aims at:

- reducing mortality,
- reducing the number of severe cases and hospitalisations,
- reducing transmission and the speed of spread of infection (particularly reducing peak attack rates),
- reducing the risk of transmission from healthcare staff to patients (especially vulnerable patients) and vice versa,
- ensuring as far as possible that healthcare services are delivered.

As already mentioned, decisions on who should be offered vaccination within the mitigation objective will be influenced by virus characteristics and the epidemiology of the pandemic (e.g., the intensity of transmission by age and setting, severity of the disease and risk factors for severity). For example, data from the United States suggest that influenza A(H1N1)v transmission is highest among school-age children and young adults, while hospitalisations and severe disease are highest among adults with pre-existing chronic conditions and pregnant women. However, other factors should be taken into account when developing a vaccination strategy. For example, in the experience of the pandemic preparedness self-assessments undertaken by Member States with ECDC, it emerged that European societies often place special emphasis on the value of children and will expect to prioritise the delivery of vaccine to them. This was also the experience in the United States when it went through a complex process of prioritisation [15].

Vaccinating groups at higher risk of complications or death will protect them from severe course of disease and fatal outcomes, whereas vaccinating groups which are effectively spreading the infection will hopefully reduce the overall disease incidence. As a consequence this should lessen the burden on the healthcare system and improve business continuity in the society at large by reducing work and school absenteeism.

Vaccinating groups that provide healthcare improves the likelihood of delivering care effectively and reduces the risk of infection being transmitted from carers to people at higher risk of severe disease.

Protecting essential services

This objective aims at protecting people who:

- are essential to the pandemic response apart from those who provide direct care for persons with possible pandemic illness (who are covered under 'mitigation', above), or
- provide other essential services.

These categories comprise occupational groups considered essential to the functioning of society in an emergency situation. This usually means only a small proportion of the population (see below). From the experience of ECDC pandemic preparedness self-assessment visits it is hard to imagine there being consensus between EU countries over what constitutes 'essential workers'. With regard to the current pandemic, it should be noted that, from early experience in Europe, one set of planning assumptions suggests that the proportion of the population that will be absent at the peak will be just over 10%, smaller than had been expected with a more pathogenic virus with more symptomatic cases [16].

Population groups to be considered at higher risk of severe disease from influenza A(H1N1)v infection

According to the current evidence on the A(H1N1) 2009 pandemic, the following population groups are considered at higher risk of severe influenza A(H1N1)v infection compared with the general population:

- people aged up to 64 years with chronic conditions (chronic respiratory diseases; chronic cardiovascular diseases, excluding isolated mild hypertension; chronic metabolic disorders, notably diabetes; chronic renal and hepatic diseases; persons with congenital or acquired immunodeficiency; chronic neurological or neuromuscular conditions);
- young children (especially those under two years old);
- pregnant women.

Another group deserving special consideration are people who care for those for whom immunisation may not be effective or cannot be given (e.g. people under treatment with immunosuppressive therapy). This includes all those in households with children younger than six months because influenza vaccines are not approved for those infants so far due to a lack of immunogenicity and safety data for this age group.

The objectives and target groups for vaccination against a pandemic strain may differ from those for seasonal influenza strains for different reasons, i.e. different attack rates by age, different severity, etc. Hence the groups targeted for seasonal flu vaccination may not be the same as for pandemic flu vaccination. However, in the early stages of a pandemic when precise epidemiological and virological information may be lacking, the groups at risk of severe seasonal influenza may be a reasonable approximation of risk groups to be included in the target groups for the pandemic vaccine. For A(H1N1)v that is the case, with the exception of older people (who are less affected than in some earlier pandemics (1918, 1968)), though even here there are other considerations which may mean countries will still wish to consider their immunisation (see below for areas of particular uncertainty).

Details of the evidence on the risk of people developing severe disease when infected with the A(H1N1)v virus are available in the ECDC risk assessment which is being updated at intervals [5]. As more epidemiological data become available the population groups considered vulnerable and at risk for severe infection may change.

For reference, a short review of the currently available evidence for vaccinating various groups at risk of developing a severe form of seasonal influenza, and whether immunisation is effective (where this is available), is shown in Annex 1.

Population groups who may be offered immunisation to reduce transmission

The size of these groups has yet to be determined but the data and analyses from North America and the UK would suggest that immunisation of children and young people may be especially effective in reducing transmission as they are the groups most commonly experiencing transmission [12,17].

Existing recommendations

The position of WHO is an important one and the WHO Strategic Advisory Group of Experts (SAGE) on Immunisation, which advises the Director-General met on 7 July 2009 and made the following recommendation [14]: 'All countries should immunise their healthcare workers (1–2% of the world's population) as a first priority to protect the essential health infrastructure.'

The SAGE Committee suggested the following groups for consideration for vaccination in the order shown, but noted that countries need to determine their order of priority based on country-specific conditions:

- Pregnant women.
- Individuals aged > 6 months with one of several chronic medical conditions. including asthma and morbid obesity, in order to reduce morbidity and mortality.
- Healthy young adults (aged > 15 years and < 49 years) to reduce morbidity and mortality.
- Healthy children, mainly to attempt to reduce transmission. However, there was uncertainty regarding the potential effectiveness of this approach.
- Healthy adults aged > 49 years and < 65 years to reduce morbidity and mortality.
- Healthy adults aged 65 years and older to reduce morbidity and mortality.

In addition, the position of some countries outside the European Union will be important to consider. The US Advisory Committee on Immunisation Practices (ACIP) met on 29 July 2009[i]. They identified five target groups for vaccination when the vaccine first becomes available, focusing on those who are at higher risk of the disease or developing complications, those most likely to come into contact with infected persons, and people who could infect the very young [18]:

- Pregnant women.
- People who live with or care for children younger than six months of age.
- Healthcare and emergency service personnel.
- People between the ages of six months and 24 years.
- People from ages 25 to 64 years who are at higher risk of A(H1N1)v influenza because of chronic health disorders or compromised immune systems.

The ACIP also considered which groups should be prioritised in the event of an initial shortage of A(H1N1)v vaccine and recommended that the following groups receive the vaccine before others [19]:

[i] As yet (31 July 2009) ECDC has not had an opportunity to evaluate all the data underpinning these recommendations.

- Pregnant women.
- People who live with, or care for, children younger than 6 months of age.
- Healthcare and emergency service personnel with direct patient contact.
- Children aged six months to four years of age.
- Children aged 5 to 18 years who have chronic medical conditions.

It should be noted already that the ACIP has generally recommended influenza immunisation to broader population groups than have European Union countries [20].

Further information needed for informing pandemic vaccination strategies – areas of particular uncertainty

At present, information about the behaviour of the virus is rapidly unfolding. In ECDC parlance a number of the 'known unknowns' are becoming known [21]. However, a number of uncertainties remain. These are discussed more fully in ECDC's risk assessment [5]. Those most pertinent to immunisation are discussed here.

Older people

People aged 60 or 65 years and older are usually considered at higher risk for severe seasonal influenza illness, and are therefore a usual risk group for offering seasonal influenza vaccination, not least because of the high percentage of elderly who have underlying chronic disease [22]. Preliminary findings from the US and Europe indicate that older people are the least affected age group at the moment. It is speculated that this is because they have some residual immunity.

However, seemingly not all older people are immune and those that do become infected fare less well than their younger counterparts, and experience a higher risk of severe disease, especially if they have other underlying conditions [13,14]. As a consequence, the median age of people infected, hospitalised, and dying rises steadily. Therefore, some older people are at increased risk of developing severe disease but they cannot be readily identified. It will be important to gather information on how much these men and women are requiring care in comparison with other groups to determine whether they should be another target group for vaccination, both for their own sake and to reduce stress on secondary care services.

Protecting the youngest children

Children under the age of six months cannot be immunised as so far no clinical trials are available for either seasonal or pandemic influenza vaccines in this age group. Where there are babies under six months old, there are therefore arguments for offering immunisation to all household members (in the United States this is referred to as the 'cocooning strategy'). Immunising pregnant women could probably afford some protection through maternal antibodies and make it less likely that babies will receive the infection from their mother. Further information is needed on the cocooning strategy concerning the many practicalities that arise (for example who should be considered a household member). In addition, it is hoped that more immunogenicity and safety data from planned trials in this age group will become available.

Immunising children generally

In the initiation phase in North America and Europe children have featured highly and some of the most intense outbreaks have been associated with schools [23,24,25,26]. Therefore, one suggestion is to offer immunisation to all children to dampen down the local outbreaks. The issue here is whether families will be willing for healthy children to be immunised against a disease that usually results in only a mild illness.

Clinical severity and clinical profile requiring care – taking pressure off the healthcare services

To identify target groups for vaccination, information on the clinical severity of cases is needed. This includes knowing the proportion of cases that experiences a severe acute respiratory illness (SARI), hospitalisation, and death, and what are the risk factors for severe disease and death. A distinct issue is what the characteristics are (notably age groups) of those requiring secondary care, as that may determine which groups should be offered immunisation in order to reduce the impact on the health services.

Transmission characteristics

In order to reduce the overall incidence of infection by targeting groups for vaccination in which transmission takes place, information on attack rates of disease by age group would be needed. In addition, in order to protect individuals living in at risk settings and to reduce overall transmission, attack rates in various community settings (nursing homes, schools, etc.) should be determined.

Virological and bacteriological factors

It is unclear at present to what extent there will be co-circulation of seasonal and pandemic strains in Europe this autumn though it is expected that B strains will continue to circulate. Currently the picture is mixed in the southern hemisphere, there being reports of both A(H1N1)v predominating in some areas and more mixed pictures in others. In addition, knowing the rate of bacterial complications, and the proportion of these caused by *S. pneumoniae*, would determine whether co-administration of the PPV-23 vaccine in younger individuals should be considered.

Vaccine safety

The lack of readily available risk and safety data for some specific groups (e.g. those with chronic diseases pregnant women, young children) may also play a role in the development of pandemic vaccination strategy.

Severity

The severity of a pandemic is a major determinant when deciding upon an effective vaccination strategy. However, severity of a pandemic is a complex concept and requires careful characterisation [27].

Some parameters to consider when determining the severity of a pandemic are:

- The case-fatality rate: the proportion of cases which are fatal.
- The risk of severe disease: the likelihood that an infected individual experiences severe disease (e.g. requiring hospitalisation).
- The pressure on the health services.
- The functioning of critical or essential services.
- Public and media perception of severity.

It is not yet possible to undertake such a comprehensive characterisation for the A(H1N1) 2009 pandemic influenza, though some information is emerging from North America, the first affected countries in Europe and from countries in the southern hemisphere, and will continue to do so in the coming weeks and months. It can be said with some confidence that at present the severity is less than that of the influenza A(H1N1) of 1918–19 and that most people infected only experience a mild illness.

In addition to the transmissibility and the virulence of the virus, the prevalence of underlying chronic conditions in the population will also be a major determinant of the disease burden and pandemic severity in Europe.

It also has to be taken into consideration that influenza pandemics can come in two or more waves and that the severity of the disease during the waves can vary, even worsening before the pandemic strain becomes a seasonal influenza. In 1918 the second wave was more severe than the first and this is a possibility that cannot be dismissed for Europe in 2009–10. However, that was not the case in 1957 which came as a single wave in Europe, while in 1968 the first transmissions were few in the summer of 1968, the first winter no different from the previous winter's seasonal flu but the second winter much more severe.

At present insufficient evidence is available to make a full risk assessment, let alone a credible forecast, of the evolution of the A(H1N1)v influenza virus [5, 28]. However, relevant information is becoming available from enhanced surveillance and investigations in North America and the temperate areas of the southern hemisphere. Features of the North American experience to date include:

- Most of those infected have mild self-limiting illnesses. However, hospitalisations occurred more frequently in the youngest age groups [29].
- The persons who are more likely to become severely ill and require hospitalisation and even die are those with underlying chronic illness, pregnant women and very young children; however, a few fatal cases have occurred among previously healthy persons [30].
- There is an under-representation of older people among those infected and hospitalised. This is consistent with some residual immunological memory in older people; nevertheless, according to first preliminary findings the risk of experiencing severe illness when actually infected with influenza A(H1N1)v increases with age.

- Transmission has occurred in healthcare settings in the US, despite recommendations on the use of personal protective equipment that were reinforced soon after identification of A(H1N1)v [31].
- The virus is currently almost entirely susceptible to the neuraminidase inhibitors (oseltamivir and zanamivir) but is resistant to the adamantanes.

However, this must be seen as a preliminary picture as of mid-July 2009. For more up to date information please consult later ECDC Risk Assessments on the ECDC website (www.ecdc.europa.eu/en/Health_topics/novel_influenza_virus/2009_Outbreak).

Prioritisation: which factors should be taken into consideration?

When a specific pandemic vaccine becomes available, ensuring vaccine supply sufficient to cover a high proportion of the population, or even just those most at risk, will be difficult or impossible within a reasonable timeframe. For this reason prioritisation exercises are needed at national, regional and European levels.

The prioritisation will be based on many considerations including the specific risk to individuals and groups. Those risks are known to vary from one pandemic to another, both in terms of risk of infection and severity of disease [32].

From the experience of the self-assessment exercises undertaken by ECDC and WHO with Member States, prioritising between and within each category depends on EU and an individual country's values and ethical considerations. Vaccine production capacity has been an important constraint but in the medium term may be less so as more production capacity becomes available. What is more important is timing (how soon a vaccine will be available and when vaccines become authorised for use [33]) and whether Member States can distribute the vaccine effectively.

Practical experience and logistics

Practical considerations are very important but it is difficult to generalise about them at the European level. One, for example, is the response to 'targeting'. It has been observed in the United States that offering vaccination to selected groups , such as those with chronic illnesses, can be relatively unsuccessful while broader approaches offering vaccination to everyone in particular age groups is more successful in achieving coverage.

Vaccination providers and immunisation programmes will need to balance the need to administer vaccine to as many persons and as quickly as possible with need to prioritise vaccination for smaller subgroups. Availability may vary greatly even at a local level and flexibility will be needed to adapt to changes in availability and demand.

It is likely that issues of seasonal immunisation and pandemic immunisation will become confused in the minds of both immunisers and those being offered immunisation. Hence there are arguments for pressing on with seasonal immunisation campaigns ahead of any pandemic vaccine becoming available, as has been recommended in the United States [20].

Potential target groups for vaccination outside the risk groups

There are other groups to whom consideration is given for offering immunisation. This is especially 'essential workers'. This is not an area that can be subject to scientific analysis and hence ECDC's contribution to the question of who should be included in these groups is necessarily limited. However, it may be worth noting that the current estimates are that at the peak of the pandemic only 12% of the adult population will be off work, which may be within the levels that can be coped with for larger essential worker groups by good business continuity planning [16].

Estimating the population size of potential target groups for pandemic vaccination

Table 1 shows a rough estimate of the distribution of the population of the 27 countries of the EU according to different target groups that may be taken into consideration for the prioritisation exercise. Numbers and percentages shown refer to a hypothetical European average population, therefore important variations from those figures can be observed in the different Member States. Further details on sources used and calculations are described in Annex 2.

Table 1. Rough estimates of population belonging to potential target groups for pandemic vaccination in the EU27

	Population	% of the whole population
Objective: maintain the essential services (~5%)		
Healthcare workers	10 000 000	2
Workers in essential services	20 000 000	4
Subtotal	**30 000 000**	**6**
Objective: protect the vulnerable (~30%)		
Very young children 0–24 months	10 500 000	2
Children 3–19 years with underlying chronic conditions	5 600 000	1
Pregnant women	6,600,000	1.5
Adults aged 20–64 with underlying chronic conditions		
20–44 years	13 000 000	3
45–64 years	21 000 000	4
65 years and over	84 000 000	17
Subtotal	**141 000 000**	**29**
Objective: limit the speed of spread of infection and the burden on the healthcare system (~65%)		
Healthy children 3–19 years		
Pre-schoolers 25–60 months	14 000 000	3
School-age children 5–19 years	73 000 000	15
Healthy adults not included in the previous groups	239 000 000	48
Subtotal	**326 000 000**	**66**
Total population (EU27)	**497 000 000**	**100**

Note these figures have been rounded to the nearest million or hundred thousand and so the totals do not appear to add up.

In conclusion, the list of potential target groups (i.e. those who should eventually be vaccinated) has to be agreed upon, taking into account a series of considerations both from scientific and ethical points of view. Building on that, a prioritisation exercise should drive the decision on which groups should receive the vaccine first, according to vaccine production capacity, logistics, etc. This will also depend on the severity of the pandemic. An advanced scenario analysis can support and facilitate the prioritisation exercise.

Possible pandemic scenarios

Several different possible scenarios can be described in order to inform the discussion on vaccination priorities once the pandemic vaccine becomes available. Some key epidemiological parameters, including those at risk of more severe disease, attack rates and case-fatality rate by age groups, will have to be monitored as closely as possible in order to determine which scenario is emerging as the reality. However, it needs to be remembered that case-fatality rate in particular is very difficult to determine in real time. Information to targeted groups and the general public about vaccination will also need to be developed.

The epidemiological information available to date is not sufficient to predict and describe the possible spread and evolution of the A(H1N1)v virus. However, evidence collected on the current virus from North America and past pandemic experience can support the scientific discussion. Three basic indicators can be used in order to characterise the severity of the pandemic: the gross attack rate, the experience of more severe illness and the case-fatality rate. These can lead to a rough estimate of the expected morbidity and mortality. Several possible scenarios can be described by those indicators, on the basis of the initial picture in North America and Europe and past experience. Here ECDC suggests four, but more are conceivable. Scenario A is the one that is now observed and should be seen as the default.

Scenario A. Initial North American experience (low attack rate; low case-fatality rate)

The initial experience suggests a low attack rate between 10% and 20% with seemingly little infection in older people but some people becoming very sick and dying, most of whom have underlying chronic conditions or are pregnant women or young children. Because of the under-representation of older people mortality will be less than for seasonal influenza[ii]. It is suggested by one EU country that there should be a planning assumption of a 30% attack rate [34].

Scenario B. Seasonal flu-like experience (moderate attack rate; low to moderate case-fatality rate)

ECDC and WHO consider that the attack rate of the seasonal flu usually ranges between 5% and 10%. According to surveillance in Europe the most affected age groups in terms of consulting their doctors [35] are the 0–4 and 5–14 year-olds. The overall case-fatality rate (i.e. for all ages) of seasonal flu is considered to be low on average (< 0.1%) [36], but it is higher in vulnerable populations like elderly people (perhaps approaching 1%) [37], and in patients with chronic underlying conditions.

Scenario C. Hong Kong flu-like experience (high attack rate; moderate case-fatality rate)

A further scenario of what could happen in the EU can be described as that similar to the Hong Kong flu in 1968 when the disease showed high attack rates in all age groups (as most of the population had not previously been exposed to the virus) but moderate case-fatality rate (comparable to that of seasonal flu) [38].

Scenario D. Spanish flu-like experience (high attack rate; high case-fatality rate)

As the worst case scenario, the Spanish flu in 1918 provides a good model. Attack rates were high (about 35% on average, comparable to those observed in the following pandemics) but the case-fatality rate was extremely high (3% in young adults and up to 6% in more vulnerable people) [39].

[ii] It should be recalled that even seasonal influenza accounts for a variable amount of mortality each year. For example, the last season seems to have seen higher mortality than usual with the circulation of A(H3N2) viruses. See Nogueira PJ, Nunes A, Machado E, Rodrigues E, Gómez V, Sousa L, Falcão JM. Early estimates of the excess mortality associated with the 2008-9 influenza season in Portugal http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19194.

Estimated impact

Table 2 summarises the estimated impact of a potential pandemic on the EU population (500 million resident people) according to the above-mentioned scenarios.

Table 2. Estimated number of cases and deaths from pandemic influenza in the EU27 population, under three different scenarios

	Number of cases (gross attack rate)		Deaths (case-fatality rate)	
Scenario A Initial North American 2009	50 million	(10%)	Unclear but considerably less than scenario B	(<0.1%)
Scenario B Seasonal flu-like	50 million	(10%)	40 000	(0.1%)
Scenario C Hong Kong flu-like	175 million	(35%)	175 000	(0.1%)
Scenario D Spanish flu-like	175 million	(35%)	3.5 million	(2.0%)

An important consideration under Scenario A is that if, as it appears from the preliminary data in the USA and Europe, older age groups are less affected because many have some immunity, then the case-fatality rate and thus the number of deaths, may be even lower than for seasonal influenza. Though there is also evidence that the few older people that lack immunity and are infected are more likely to be hospitalisd and have the highest observed case-fatality rate of any age group [12]. Deaths and severe disease in pregnant women, young children and those with chronic illnesses would make them priority groups for immunisation. Another consideration is that one scenario could change to another and plans need a degree of flexibility. For example, the A(H3N2) pandemic of 1968 initially would have seemed like Scenario A but then became like Scenario C while the A(H1N1) of 1918 was initially less severe in its impact than Scenario D.

Assessment of the current situation with the new A(H1N1)v virus

By analysing the outbreak in Mexico, the severity of the A(H1N1)v strain initially appeared to be comparable to that seen in 1957 (so called 'Asian flu') with attack rates around 30% among adults, 60% among children, and case-fatality rates ranging from 0.3% to 1.5% [40]. On the other hand, local observations not supported by serology, based on the virus spread in the US, suggest initial attack rates lower than in the preceding pandemics (about 10% overall) and an overall case-fatality rate of under 0.1%, less than what is commonly observed during seasonal flu epidemics [41].

Additional considerations

There are some special populations requiring more careful consideration with regards to the need for vaccination, even though they may constitute risk groups for severe disease. Currently, little information is available to support evidence-based suggestions for vaccination in these groups. They include:

- children < 6 months of age;
- pregnant women;
- immunocompromised people;
- people allergic to eggs;
- individuals with suspected or lab-confirmed influenza A(H1N1)v infection;
- non-residents of the country.

Conducting vaccination with the pandemic vaccines poses particular questions in relation to seasonal influenza vaccination. The key factors to consider are: (1) whether the population target groups for both vaccines will be similar or differ substantially; (2) what the timing of vaccination with both vaccines will be; (3) the recommended number of doses of the pandemic vaccine;(4) which channels of vaccination will be used for administering the pandemic vaccine: routine vaccination structures used for seasonal influenza or ad hoc solutions such as mass vaccination campaigns. If the pandemic vaccines are expected to become available late during the 2009–10 season it may be advisable to start vaccination against seasonal influenza early during autumn 2009.

This document is focused on the use of influenza vaccines but it is important to also consider that *S. pneumoniae* may be a cause of community-acquired pneumonia as a complication of influenza A. There is no information on this either way from the USA. However, inclusion of plans for pneumococcal vaccination could reduce the volume of complications in target high-risk groups if that is found to be an important complication.

Monitoring and evaluating pandemic vaccination programmes/campaigns

Monitoring and evaluation are essential for any vaccination programme. In the case of the new specific pandemic vaccines it becomes an especially high priority for several reasons related to effectiveness and safety of the newly produced vaccines. Due to the possible continuous mutation of the virus, effectiveness of the pandemic vaccines has to be measured in the field in the post-marketing phase, in order to assess the match between the vaccine strain and the circulating flu strain. Similarly, vaccine safety has to be assessed during the post-marketing phase, for the early detection and assessment of any credible adverse event. This will be especially important with a lower severity pandemic and one affecting groups where reported adverse reactions may be particularly difficult to assess because of higher incidence of background illness (young children, pregnant women and those with other conditions). ECDC can support such initiatives with the scientific and technical capacity already in place in this specific field (vaccine effectiveness) or being developed with EMEA and WHO (vaccine safety).

Vaccine effectiveness

Assessing and monitoring the effectiveness of pandemic vaccines is an essential activity after vaccines are marketed and distributed for administration. Though strain-specific pandemic vaccines are expected to be effective, early availability of vaccine effectiveness estimates would strongly contribute to the success of vaccination campaigns. When adverse events following immunisation are reported, the availability of data on vaccine effectiveness would allow the conduction of evidence-based risk management analyses. Similarly, it would facilitate better management of, and response to reports of vaccine failures. Moreover, should poor vaccine effectiveness be observed, complementary or alternative public health measures (e.g. antivirals) can be implemented and additional investigations conducted to improve vaccine use or vaccine composition. ECDC, through a project that is coordinated by the company Epiconcept[iii], has established a framework for routinely assessing seasonal influenza vaccine effectiveness, which has been running since the end of 2007. This project includes a network of 18 EU countries and it is known under the acronym I-MOVE. The first seven pilot studies were successfully conducted during the influenza season 2008–09 in six countries. All of them were based on sentinel GP networks. Although the methodology for assessing pandemic vaccine effectiveness is the same as for seasonal vaccines, the current pandemic situation has required an expansion of the project in terms of number of studies and their sample size. This is in order to obtain vaccine effectiveness estimates early after the first vaccines are distributed and to obtain estimates by vaccine type.

Vaccine safety

The unusual situation of possibly implementing mass vaccination in Member States of either vulnerable groups or the whole population during the coming autumn of 2009 emphasises the need for well developed and flexible vaccine safety monitoring. An established routine passive surveillance system is in place in most Member States, reporting to the EMEA *Eudravigilance* database and will be the basis for adverse event surveillance. In addition,

[iii] A company operating under contract to ECDC following a competitive tender http://www.epiconcept.fr/

establishing enhanced active surveillance for serious adverse events is an alternative for Member States to consider. Options for active surveillance could include using sentinel hospitals actively screening for adverse events following immunisation or asking vaccinating doctors or nurses to report to the National Authority on a weekly basis irrespective of whether they have seen any adverse event or not. Establishing protocols for assessing individual suspected cases of adverse events following immunisation to ensure best practice, and establishing background incidence rates of conditions from the list of adverse events of special interest before embarking on the vaccination campaigns, may be other important tools. To rapidly and energetically investigate plausible severe adverse events is of equal importance be they from vaccines or antivirals. To rule out associations is also of utmost importance for credibility of the vaccination programme. Joint efforts between the European Agencies EMEA and ECDC and the National Authorities are being planned. There will be limited data on safety available at the time of licensing but especially in certain groups like children < 6 months of age, pregnant women and the chronically ill, there will be no data available which is why post-marketing surveillance will be essential and a shared responsibility between manufacturers, National Authorities (Regulatory Agencies and Public Health Institutes), EMEA and ECDC [4].

Logistics

The aim should be to administer the vaccine to the target populations, or the general population, depending on the strategy, as soon as it arrives. One approach that could be taken by Member States is to establish Vaccination Centres that are able to provide vaccine, register vaccination on an individual basis, recall the patient for the second dose within 3–4 weeks (depending on which vaccine is to be used) and monitor and report adverse events. Breakthrough infections are considered adverse events in most Member States and should be reported using the forms for adverse events to the Public Health Institute or National Regulatory Agency that normally monitors adverse events and breakthrough infections. Expected capacity of a vaccinator is 50–100 individuals per day.

Annex 1 Selected evidence for vaccinating groups at risk of severe seasonal influenza

The following table is taken from a paper published in 2008 by A Nicoll, et al which summarised the evidence for vaccinating specific risk groups against seasonal influenza [22], and is complemented by available evidence for the current influenza A(H1N1) 2009 pandemic.

Risk groups	**Study type**	**Evidence for seasonal influenza vaccination**	**ECDC comment**	**Evidence for influenza A(H1N1)v vaccination**
Individuals aged 65 years and older	Guidelines [42]	Not applicable	US CDC updated recommendations for seasonal vaccination. Includes a comprehensive review of articles supporting vaccination of various risk groups. It is mainly based on evidence coming from the US.	The majority of influenza A(H1N1)v cases reported are children and young adults. In Europe 77% of cases are <30 years old [43]. In the US 60% of cases are <18 years [44]. It is currently unknown whether older individuals once infected are more likely to experience a severe influenza illness. Therefore, at this stage they should be considered as one of the risk groups for receiving the pandemic vaccine.
	Cohort [45]	VE against hospitalisation 21% (95% CI 17%-26%). VE against death 12% (95% CI 8%-16%).	Large cohort study conducted in the UK covering 10-year period. Provides robust data on the effectiveness of vaccination in the elderly (>64 years) against hospitalisation and death.	
	Cohort [46]	Incidence of hospitalisation for pneumonia/influenza or death: 8.2/1000 for healthy and 38.4/1000 high-risk individuals. VE against hospitalisation 48% (95% CI 42%-52%)	Large cohort study conducted in the US. Provides rates of death/hospitalisation for healthy and high-risk elderly as well as VE data.	
	Time Series Analysis [47]	Excess hospitalisations higher in persons >64 years (10 per 100 000).	Large study based on hospital discharge records from all public hospitals in Spain covering 4 influenza seasons. Excess hospitalisations attributable to influenza significantly higher in those >64 years old.	

Risk groups	Study type	Evidence for seasonal influenza vaccination	ECDC comment	Evidence for influenza A(H1N1)v vaccination
Chronic illness				The majority of A(H1N1)v cases experiencing a severe or fatal illness had one of the pre-existing conditions that are known to be risk factors for severe seasonal influenza illness [29,44]. However, there have been reports of severe clinical illness occurring in previously healthy individuals [48,30].
Chronic respiratory diseases	Review [49]	Influenza vaccination reduced the development of severe respiratory complications and hospitalisation by 50–80%, and death from both respiratory disease and all causes by 40–55%.		
	RCT [50]	VE against influenza confirmed ARI 76% among individuals with COPD.	VE was not influenced by the severity of COPD. None of the vaccinated patients required mechanical ventilation because of influenza-related ARI. By contrast, all the unvaccinated patients with moderate-to-severe COPD who were hospitalised because of influenza-related ARI needed assisted ventilation.	
Chronic cardiovascular disease	Cohort [51]	Vaccination reduced the risk of cardiovascular death - RR 0.34 (95% CI 0.17-0.71) in individuals with stable coronary heart disease.		
	Retrospective cohort [52,53,54]	Higher risk of acute myocardial infarction shortly after an acute respiratory infection (not necessarily influenza) RR 4.95 (95% CI 4.43 to 5.53).	The study was based on the United Kingdom General Practice Research Database, which contains computerised medical records of more than 5 million patients.	
Metabolic disorders (including diabetes mellitus)	Case control [55,56]	Influenza VE in diabetics was 79% (95% CI 19-95%)		

Risk groups	Study type	Evidence for seasonal influenza vaccination	ECDC comment	Evidence for influenza A(H1N1)v vaccination
	Cohort [51]	Higher risk of hospitalisations, OR: 2.19 (95% CI = 1.08–4.47); and of any complication, OR:1.74 (95% CI = 1.16–2.61), among non-elderly adults with diabetes.		
Chronic renal and hepatic diseases	Case-series analysis [57,58]	Excess influenza-attributable mortality in patients on dialysis.		
	Literature review [58]	Increased incidence of respiratory infections in patients with chronic kidney disease.		
Immunosuppressed	Review [59]	Higher incidence of complication among organ and haematopoietic stem cell recipients.		
HIV	Meta-analysis [60,61,62]	Pooled relative risk reduction of 66% (95% CI 36-82%).	The study of the highest quality, an RCT, yielded the most conservative estimate (RRR 41%; 95% CI 2-64%).	
	Cohort [61]	Influenza accounted for 42% of the ARI among HIV-infected individuals followed up in a single clinic	Probably high incidence of disease but no evidence of more severe disease than healthy population.	
Young people taking salicylates long term	Review [63]	Theoretical risk of developing severe disease (Reye syndrome) among people under age 20 taking salicylates	A causal association was never established.	

Risk groups	Study type	Evidence for seasonal influenza vaccination	ECDC comment	Evidence for influenza A(H1N1)v vaccination
Other groups Pregnant women	Review [64]	Not appropriate.	Evidence is contradictory on pregnancy as risk factor for more severe influenza disease in women who are otherwise healthy.	A number of reports from the US showed that among cases with severe or fatal A(H1N1)v infection there were previously healthy pregnant women [65,66]. Complications among pregnant women were severe including death and foetal loss. Based on the already existing evidence from seasonal influenza and on preliminary data on A(H1N1)v influenza, pregnant women should be included in the risk groups for receiving the pandemic vaccine.
Pregnant women with risk factors	Review [64]	Occurrence of acute respiratory illness was more likely than among healthy pregnant women [OR 3.2 95% CI (3-3.5)]. Influenza-attributable rate of hospital admission increasing with pregnancy trimester: 3.9 (−6.4 to 14.2), 6.7 (−4.1 to 17.5), and 35.6 (21.1 to 50·1) respectively/per 10 000 woman months		
Children	ECDC technical report [67]	Data for young children, particularly under two years of age, are scant from European countries. Routine immunisation of school-age children has an indirect beneficial effect for adults and the elderly in terms of reduced disease burden.	This report was developed by a panel of experts who reviewed the literature available up to January 2007.	Data from the US and Europe shows that children are at high risk of infection with the A(H1N1)v influenza virus. Little, however, is known on the risk of severe influenza illness in children. From seasonal influenza it is known that the rate of severe complications is highest among children less than 2 years old and those who have high-risk medical conditions.

Risk groups	Study type	Evidence for seasonal influenza vaccination	ECDC comment	Evidence for influenza A(H1N1)v vaccination
Obesity		No data available on obesity as a risk factor for severe seasonal influenza.		A relatively high frequency of obesity was observed among the severe A(H1N1)v cases [9,10]. At the moment it is unclear whether obesity is an independent risk factor for severe A(H1N1)v influenza disease. However, since obese patients have a higher prevalence of comorbid conditions, immunising people who are severely obese might be a useful strategy for capturing individuals with other chronic conditions of which they are unaware.

Annex 2 Sources and calculations used to estimate size of target groups

The numbers in Table 1 are average estimates for the total of the 27 European Union Member States, and do not consider the inter-country variations. They should be used as indicators rather than exact numbers; the aim is to assist the development of a pandemic vaccination strategy.

Table 3. Example of inter-country variation: proportion of population of the EU 27 by age group, 2007

Age group (years)	Average percentage of total population (EU 27 range)	Rounded average total number per age group in millions (EU 27 range)
0 – 14	15.8 (13.4;20.4)	78 (65;99)
15 – 24	12.6 (10.2;15.9)	61 (50;77)
25 – 49	36.3 (32.9;40.5)	180 (160;200)
50 – 64	18.3 (16.6;21.2)	89 (81;103)
≥ 65	16.9 (10.9;19.9)	82 (53;97)

Source: Eurostat. Population structure on 1 January 2007.

Total population and population by age group were retrieved from the Eurostat database [68]. 2007 is the most recent year for which the average population by five-year age groups is currently available. Therefore, this year was chosen for estimating the average number and proportion of possible target groups for pandemic vaccination.

Target group estimates

Healthcare workers

To estimate the proportion of healthcare workers in the EU 27 the WHO Health indicator database [69] was used which collects country data on medical, nursing, midwifery, laboratory and pharmaceutical personnel and a few other health-related professions. The data completeness varies from country to country and from year to year, therefore the decision was taken to use the most recent data from the years 2002–06. Four EU countries were randomly chosen to provide a rough estimate of the EU average, and the population of 2006 was retrieved from Eurostat as the denominator. The proportion of healthcare workers in the four countries lay between 1 and 2% of the whole population, and was rounded up to 2% to compensate for the incompleteness of the data.

Workers in essential services

In the US Guidance on allocating and targeting pandemic influenza vaccine the size of this group is estimated to be around 6.5% including healthcare personnel [15]. Essential services do not include the whole workforce but the part of the workforce that is considered critical to continue providing essential services in the event of a major event like a pandemic. These include security, fire and rescue services, and infrastructure (transport, communication, financial and community services). For this document an assumption was made that healthcare workers and other workers in essential services comprise an average of 6% in the EU. It is not possible to give more exact numbers as information is scarce. Not least, the definition of 'essential' is highly dependent on values and ethical considerations which will most probably differ from country to country, and also depend on the perceived severity of the pandemic and urgency of the situation.

Vulnerable groups

Pregnant women

The size of this group is not known. The number of live births during 2007 was used to calculate a rough estimate by multiplying with 1.25. This is of course an extremely simplified method not taking into account factors such as stillbirths and twins. According to Eurostat, 5 281 625 live births were registered in the EU 27 in 2007. The number of pregnant women was therefore estimated to be 6.6 million which is 1.5% of the total EU 27 population.

Very young children (0–24 months)

According to Eurostat, 5 187 609 children were under the age of one, and 5 129 842 children were one year old on the 1 January 2007. The two groups were simply added in order to estimate the size of the group of very young children between 0 and 24 months of age, which amounts to 2% of the total EU 27 population.

Persons with chronic medical conditions

One study by Fleming and Elliot (2006) specifically estimated the size of this risk group for England and Wales in relation to influenza vaccination. They estimated the number of people that have one or more of the chronic conditions that specifically place them at risk of severe outcome from influenza by collecting data from primary care in 2003 [70]. The data were later reviewed and updated by the UK Department of Health for 2007, which estimated the age-specific prevalence of people with 'one or more risk morbidities' (0–64 years of age) to be 8.3% of the UK population. This figure was used by Nicolls et al. to estimate the country-specific numbers of 0–64 year-olds in the EU that suffer from at least one risk morbidity [22].

The age range of the potential target groups identified in Table 1 does not correspond entirely to the age groups used by Fleming and Elliot in their paper. For the purpose of the exercise presented in Table 1 the prevalence given by Fleming and Elliot and the UK Department of Health for the age group 0–14 was applied to the target group of 3–19 year-olds, the prevalence estimates provided for the groups of 15–44 were used for the age group of 20–44 year-olds and the prevalence estimate given for the 45–64 year-olds was used for the same age group in the table. The results of this exercise do not intend to provide exact numbers on the size of specific population groups, but rather to give an idea of how these groups could be, at least, roughly estimated.

Table 4. Estimated size of risk groups for those with underlying chronic conditions by age group

Fleming and Elliot 2006; disease categories: respiratory, circulatory, diabetes & endocrine, renal, liver, malignant neoplasms, immune compromise		**Applied to EU 27 population in 2007**		
Age groups	Prevalence of risk group conditions	Age groups (see Table 1)	EU 27: total number in age group (in millions)	Number of affected EU 27 population (in millions)
0–14	6.04%	3–19	92.7	5.6
15–44	7.52%	20–44	176.2	13.3
45–64	16.59%	45–64	127.5	21.2
≥ 65	42.95%	≥ 65	84.3	36.2
Total				**76.3 (15.4% of the total EU 27 population)**

Estimating the number of persons with chronic medical conditions which put them at a higher risk for severe outcomes in case of an influenza infection irrespective of pandemic or seasonal influenza is a challenge. Data from the Member States are scarce, and show high variation, especially for some age groups and certain disease entities, e.g. asthma and respiratory symptoms [71,72].

An Italian survey performed in 2005 reported the percentage of persons with at least one chronic condition by age group. Included chronic conditions were diabetes, cardiovascular and cerebrovascular diseases, liver diseases, malignant neoplasms, neurodegenerative conditions like Parkinson, Alzheimer and dementia, and chronic respiratory conditions like chronic bronchitis but not asthma [73]. A comparison of the Italian estimates with the results of Fleming and Elliott shows almost identical numbers for the middle-aged and elderly, but a clear discrepancy in the younger age groups, especially children.

Table 5. Prevalence of risk group conditions by age group, according to two different studies

Age groups	Prevalence of risk group conditions, Italian survey (excluding asthma)	Prevalence of risk group conditions, Fleming and Elliot (including asthma)
0–14	1.2%	6.04%
15–44	2.95%	7.52%
45–64	14.6%	16.59%
≥ 65	42.00%	42.95%

People aged over 64

It was decided to keep the whole population of ≥ 65 as a potential target group for pandemic vaccination in Table 1, taking into consideration the high percentage of people with at least one chronic condition in this age group, being more than 40% of affected persons reported by both publications described above. In addition, preliminary epidemiological data from the US influenza A(H1N1)v outbreak so far show a significantly lower attack rate in the elderly, but a clear tendency towards a more severe infection course and outcome in comparison with younger age groups, although the absolute numbers are still too low to be able to draw final conclusions [13,14].

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