Med Microbiol Immunol (2002) 191: 191–195
DOI 10.1007/s00430-002-0145-y

VIEWPOINT

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Conceptional considerations for a German influenza pandemic preparedness plan

Received: 12 July 2002 / Published online: 13 September 2002

Abstract A pandemic appearance of influenza A virus must be expected at any time. The limitations of health preserving and life-saving resources, which will inevitably be reached in the event of a pandemic, will be accompanied by ethical and possibly social conflicts, which can be lessened or resolved only through precautionary planning, clearly specified competencies and transparent decisions within a social consensus. In case of a shortage of vaccines and virostatic agents, decisions will have to be made with regard to the segment of the population that absolutely must be vaccinated. It is currently estimated that a (monovalent) vaccine developed for a new pandemic strain would only suffice for the single vaccination of approximately half of the German population after a year; only 10–14 million vaccine dosages would be available to provide basic immunization and single boosters to personnel required to maintain basic medical care and essential infrastructure after half a year. In the event of local influenza outbreaks, antiviral chemotherapeutic agents could be used to close the gap until a vaccine can become effective. Even if suitable influenza vaccines and virostatic agents are not sufficiently available at the start of a pandemic, it is still possible to at least prevent an outbreak of two of the most feared secondary infections that accompany influenza: pneumococcal pneumonia or meningitis and illnesses resulting from *Haemophilus influenzae*. Agreement still needs to be reached with manufacturers for guaranteeing the necessary vaccine production or ensuring that they have a sufficient stock to meet the minimum demand for antiviral agents and agents for symptomatic treatment.

Keywords Disaster prevention · Influenza · Pandemic · Preparedness plan · Public health

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Introduction

In general German usage, the term "flu" does not appear to be especially threatening; it is widely considered that this term includes all possible acute respiratory diseases. Today, the majority of the population and especially of the medical profession either have absolutely no knowledge of the extent of a "classic" influenza pandemic or they are unable to remember one ever occurring in their lifetime. The general awareness of the problem is low. This is not least mirrored in the comparatively low vaccination readiness in Germany.

The term pandemic refers to a massive accumulation of illnesses worldwide with a high rate of infections and mortality, this being triggered by a new subtype of the virus against which the majority of the population is not immune, i.e., most people are not protected by past infections or vaccinations. In the past century, influenza was the cause of three pandemics with serious consequences: 1918–1920 the "Spanish flu" (influenza A,

H1N1) with 20–50 million deaths around the world, 1957–1960 the "Asian flu" (influenza A, H2N2) and 1968–1970 the "Hong Kong flu" (influenza A, H3N2) with approximately 1 million deaths in each case. The course of the "Russian flu" (influenza A, H1N1) 1977–1978 was significantly milder. Nobody is currently able to reliably forecast whether an influenza pandemic will occur next year or in 2, 20 or 30 years, or the extent of the outbreak with regard to the morbidity and mortality rate. As has been proven by the "Avian influenza" virus (influenza A, H5N1) 1997 or some cases of influenza A (H9N2) infections in Hong Kong in 1998, new subtypes that are pathogenic to humans do not necessarily result in the occurrence of a pandemic. The World Health Organization (WHO) and the majority of experts suppose that a pandemic occurrence of the influenza is due within a foreseeable period of time [16]. It would be dangerous to rely merely on a talent for improvisation without planning in case of a pandemic. Rightly, various studies in mass psychoses and treatises from the civil defense field have pointed out that a majority of the population is primarily afraid of being completely at the mercy of harmful events that cannot be overcome. This is obviously especially valid as far as a contagious disease is concerned. Even before a pandemic occurs, all of the available options and actions that can be taken must be meticulously assessed, and all possibilities must be sought out to supplement them to avoid mass panic and prevent an expansion of the threat posed to public order. There is nothing worse than the citizens being convinced that the state is taking no action with regard to such a disastrous situation, which an influenza pandemic of the extent of those from 1918–1920 or 1968–1970 would represent even under present conditions. A practical social consensus with regard to damage prophylaxis and disaster preparedness plans is indispensable. The expected damage must be socially controlled to hold the effects to reasonably tolerable levels [2]. This is even more the case when one considers the fact that the population's expectations with regard to the performance of the public health care system in terms of prevention has clearly grown since the last pandemic in 1968–1970, this being proven by BSE, for example.

Scenarios and options for action

On the one hand, the course of a pandemic and the extent of its socio-economic effects are dependent on the percentage of people in the population who are already (partially) immune to a new virus. On the other hand, whether, when and to what extent a vaccine is available and whether and when a suitable virostatic agent is available for a pre- or post-exposure chemoprophylaxis or therapy will be decisive. The best measure that could be taken in order to influence the course of a pandemic would still be an early subtype-specific influenza vaccination of a maximum number of exposed individuals. New studies [9] have shown that supplying the population with newly developed virostatic agents could take on comparative importance in the future. They would also have to be provided for the segment of the vaccinated population that fall seriously ill even though they have been immunized.

The elaboration of a functional preparedness plan initially assumes a worst-case scenario. Proceeding from the key data from the pandemic of 1918–1920 [3], the following situation is given when based on the current population of Germany: 20 to 25 million cases, 200,000 hospital admittances with a total of 1.6 million days of hospitalization, 120,000 deaths from influenza and an annual excess mortality rate of 175,000. Approximately 1.2 million cases of pneumonia as a secondary infection should also be expected.

The Centers for Disease Control estimate that during a future pandemic up to 200 million people would be infected and 40–100 million would contract the disease in the USA alone. Between 18 and 45 million people would require outpatient medical treatment, between 300,000 and 800,000 would need to be hospitalized, and between 88,000 and 300,000 would die of influenza [1].

Objectives of the pandemic preparedness plan

The objective of the pandemic preparedness plan for Germany would be the structuring of the organizational actions, the analysis of actions that can be taken, and the ensuring of a good preparation and starting position in advance so that as few people as possible would have their health impaired and life threatened. Above all, the mortality and morbidity rates resulting from a viral influenza must be kept as low as possible by means of situation-related preventive medicine or hygienic, antiepidemic and therapeutic measures. In principle, this can be achieved:

a. By developing a satisfactory immunity among a large part of the population by means of preventive vaccinations
b. By means of epidemic-hygienic interventions in the sense of preventive protection against infection
c. By dispensing antiviral medication immediately after infection so that an outbreak of the disease is prevented
d. By providing suitable medical care for those individuals who are already ill to minimize deaths and late sequelae.

Depending on the extent of the morbidity resulting from a pandemic, these more or less direct health impairments are not the only consequences that should be expected. For example, most of the aforementioned measures cannot be implemented if there are too few trained personnel available or if those who are available are insufficiently trained. Furthermore, essential ser-

vices such as the supplying of water, energy, food, communication, public transportation and internal and external security that may be endangered by pandemic-related personnel losses must be guaranteed [6].

Vaccination

In the case of a pandemic, influenza vaccines provide the greatest chance, the highest incalculable risks and also the greatest dilemma. As it now stands, the time between the identification of a new influenza virus subtype and the release of the first vaccine dosages would not be less than 3 months. It is likely under current conditions that the period would be closer to 6–8 months. The chance that such a long warning time would be available is unlikely.

What is the maximum number of vaccination dosages that can be expected during the first pandemic occurrence, assuming a vaccine is available at all? Under the current premises, the two vaccine-producing companies in Germany would be able to manufacture a total of 3–4 million doses of a monovalent subunit vaccine (15 μg antigen/vaccine dosage) within the first 3 months after receiving a suitable seed virus, assuming that they dispense with clinical studies. The fact that both of the manufacturers are subsidiaries of foreign companies and regularly sell only around a quarter of their total vaccine production in Germany should also be taken into consideration. In the event of an actual pandemic, one would hardly expect that these companies would provide a greater share of their production for the German vaccination program. Therefore, a maximum of between 750,000 and 1 million doses would be available. For each additional week, an additional 3–4 million doses could be produced and between 750,000 and 1 million distributed in Germany so that one can expect 4–5 million doses after 4 months, 7–10 million after 5 months and not more than 10–14 million after 6 months. Even after a year, the number of available doses for a single vaccination would only be enough for approximately half of the German population. In addition, during the second wave, a variant of the subtype causing the pandemic can occur due to antigen drift, i.e., the vaccine would have to be modified. An improved situation (i.e., an increase in the number of available vaccine doses by a factor of 1.5) would result if a cleaned, inactivated full virus could be licensed and used as a vaccine as an alternative to the highly refined subunit vaccine [6].

It is therefore only logical for the WHO to demand in its pandemic preparedness plan from 1999 that each member state produce a national pandemic preparedness plan [16]. This plan should especially determine vaccination priorities, estimate the extent of the required vaccine doses and antiviral medication and should include agreements with pharmaceutical companies.

When there is a shortage of vaccines and antiviral medication, it is imperative that decisions be made with regard to that segment of the population that is to receive priority treatment. One can assume three different principles to serve as the basis for a list of priorities:

1. The socio-political aspect of the securing of medical care and public order as a priority (preferred vaccination and treatment of medical personnel, firemen, policemen, those employed by energy and water utility companies, etc.).
2. The specific individual medical aspects with regard to the priority treatment of risk groups (older and/or chronically ill people and, possibly, infants and very young children, i.e., that segment of the population which is deemed to be especially at risk with regard to mortality rates as a result of contracting an influenza infection).
3. The epidemiological aspect, i.e., the vaccination and medical treatment of those for whom infection is highly due to lifestyle or employment and those who are likely to pass this illness on (infants, students, persons working in institutions with a high exposure to the public).

Even when one considers the situation only with regard to the maintaining of medical treatment facilities and personnel and the most urgently required infrastructure, more than 7 million people in Germany would need to be given priority treatment and receive vaccines and chemotherapeutic agents. In accordance with the current recommendations made by the Standing Committee on Immunization (STIKO) at the Robert Koch-Institute in Germany, an additional 26 million older and/or chronically ill people would also need to be vaccinated. However, only approximately 12 million dosages of influenza vaccine are sold during inter-pandemic periods in Germany at present. This proves that the administering of influenza vaccination even among that segment of the population for which it is recommended as routine is not common. However, this figure fundamentally determines the production capacity of influenza vaccine during pandemic periods, as well. Therefore, an increase in the number of vaccinations provided during inter-pandemic periods could improve the availability of a vaccine should a pandemic occur.

What is currently not clear is whether a single dose of vaccine would provide sufficient protection against a new subtype or whether several applications are necessary. As a complete immunization of the entire population will not be possible during a pandemic, the decision must be made as to whether a majority of the population should be provided with limited protection by receiving a single vaccine dose or whether a booster should be administered to provide a smaller number of people with full protection.

An additional unsolved problem is the question of cost. Who will bear the expenses of the vaccine and the vaccination itself, and who will be held liable should a new vaccine have unexpected side effects.

Chemoprophylaxis and antiviral therapy

Initial clinical studies have shown that when compared with the M2 inhibitors (amantadin and rimantadin), the neuraminidase inhibitors (NIs) have increased effectiveness, lower side effects and reduced development of resistance. NI-resistant strains, which rarely manifested themselves in the past, were non-virulent, in contrast to amantadin-resistant strains. They also provide immediate protection to a local influenza outbreak and they are able to close the gap until an appropriate protective vaccination takes effect. According to past studies, the rate of prophylactic effectiveness for the two NIs that are currently on the market amounts to 60–90% [5, 7, 8, 10, 15]. However, the ready-to-use medication has a low stability of 2–3 years; when holding it in stockpile, appropriate preliminary production stages must be stored. These should be processed into the end product in case of a pandemic. According to the manufacturers' information, a maximum of 500,000 packages of the medication could be produced on a daily basis assuming that the basic substances are available [11]. In comparison, non-confirmed statements have been made in the pertinent literature to the effect that the M2 inhibitors are purported to have an extraordinary chemical and thermal stability of up to 25 years or longer [12]. The price advantage provided by amantadin would no longer be a valid argument if satisfactory effectiveness drops off due to resistance. We are of the opinion that when one considers the amount that would be required in a pandemic situation, a primary use of amantadin or rimantadin would still be an option that is not (yet) possible to ignore (see also [4]).

Protection from secondary infections (pneumonia)

If suitable influenza vaccines and virostatic agents are not sufficiently available at the time of a pandemic outbreak, it is still possible to at least prevent the outbreak of two of the most feared secondary infections which accompany influenza: pneumococcal pneumonia or meningitis and illnesses resulting from *Haemophilus influenzae*. Obviously, the objective here must be the full vaccination of the high-risk groups during the inter-pandemic phase. According to the recommendations concerning the vaccination against influenza, STIKO recommends that all persons over the age of 60 and those with an increased risk due to poor health should be vaccinated against pneumococcus [13]. This also raises the question of storing the vaccine before a pandemic occurs. This also applies to antibiotics and antipyretic agents and other medication for which there will be a much higher demand during a pandemic (see also [14]).

Protection from exposure and anti-epidemic measures

In the event of a commencing pandemic, information sheets will be used to inform the population about how to protect oneself against exposure, general roborant measures and simple hygienic rules, such as the following recommendations: rooms should be thoroughly ventilated, shaking of hands should be avoided, the use and proper disposal of tissues, etc. People who come into frequent and a relatively close contact with others can, for example, reduce the risk of infection by wearing a gauze mask. A prohibition of visits to medical and nursing facilities can also be considered. We believe that the early separation of patients with acute respiratory symptoms from those with other non-infectious illnesses in the admission and waiting areas of outpatient and in-patient facilities is of great importance. By means of a corresponding organization in private practices, it may also be possible to arrange separate treatment times for the two groups. This should be considered when elaborating hygiene plans.

The German Protection against Infections Act (Infektionsschutzgesetz, IfSG), which came into force on 1 January 2001, also stipulates measures such as the closing of schools and other communal facilities, a ban on public events or large crowds and the isolation of infected persons and suspected cases, where appropriate. As far as we are aware, the effectiveness of such measures have not been examined in detail with regard to influenza. Therefore, their application in special situations can only be ordered on trial. The same applies to the enforcing of border controls, restrictions of international traffic, immigration restrictions, etc., the practicability and socio-economical consequences of which are very difficult to calculate considering increased globalization.

Influenza pandemic working group of the federal government and states

Due to the possible effects of a future influenza pandemic on public life, an official influenza pandemic working group of the federal government and states (Bund-Länder-Arbeitsgruppe Influenza-Pandemieplan) has been set up at the Robert Koch-Institute in Berlin. This group has the task of drawing up a national pandemic preparedness plan taking into consideration the federal organization of Germany and the fundamental responsibilities of the states for the implementation of infection and disaster prevention measures. The working group will especially concern itself with the following aspects:

- Preventive measures are to be recommended and, together with the STIKO, a vaccination strategy is to be developed and concise recommendations have to be made with regard to the production of vaccines, use of antiviral medication and procedures for their distribution.
- An impending, commencing and spreading pandemic requires an – internationally agreed-upon – especially

intensive and extensive monitoring of the spread of the influenza and examination of the immunity situation of individual populations and the entire population.

- The inevitable limitation of health-preserving and – under these circumstances – potentially life-saving resources such as vaccines and therapeutic agents will be accompanied by ethical and possibly social conflicts that can only be solved or cushioned by making transparent decisions.
- The making of decisions pertaining to epidemic-hygienic aspects and measures such as those stated in Section 5 "Combating contagious diseases" of the German Protection against Infections Act, e.g., restriction or prohibition of public events and the gathering of crowds, the closing of communal facilities, etc., should be coordinated at the governmental level, although this is actually a responsibility of the communities or states, so as to avoid an undermining of the population's sense of security that might result from differing lines of action.
- A general social consensus and a wide acceptance of the rules and actions and the avoidance of general panic can only be achieved through transparent decisions and highly qualified public relations. The population has to be correctly, regularly and comprehensively informed about preventive measures based on the specific situation. The situation may require the request of specific behaviors by means of a public appeal. The early inclusion of the relevant media can help in avoiding reactions of panic and recklessness, and may very well be decisive when it comes to providing important and useful information.
- The working groups or crisis teams from the states concern themselves with the securing of health care, maintaining public order and providing basic services such as water supply, energy, basic food, etc. The specialized knowledge of the public health service (ÖGD) and the disaster prevention authorities together with the public utilities must also be taken into account.

With the formation of this official working group, the German Ministry of Health, the Robert Koch-Institute as the upper Federal authority responsible for infection prevention, and the states, which discussed this subject at their Health Minister conference in June 2001, have underlined their common aim of counteracting the potential threat to the health of the general population with foresight. This way, they are also responding to the recommendation of the WHO that all countries should develop a national pandemic preparedness plan.

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