
13.1. Introduction

The scientific part of the German Influenza Pandemic Preparedness Plan (Part II) describes the current scientific knowledge on pandemic influenza preparedness planning and response to pandemic influenza and thus serves as a technical basis for decisions on measures to prepare for the event of a pandemic, as well as measures in the event of a pandemic. Recommendations for interventions or their implementation are not given in Part II; this remains reserved for Part I. The target audience for the scientific part is primarily the professional public, the public health service, staff at hospitals and in outpatient medical care, those involved in the supply of medicines to the general public and also the political institutions in the health sector.

The scientific part of the preparedness plan 2007 was updated under the direction of the Robert Koch Institute (RKI), supported by the RKI Expert Advisory Board on Influenza which was founded in November 2012. It advises the RKI prior to and during an influenza pandemic with regard to scientific questions concerning influenza. The experiences from the 2009 pandemic as well as the content of the Pandemic Influenza Risk Management - WHO Interim Guidance 2013 have been incorporated.

Essential changes compared to the 2007 scientific part were:

**Preparing a flexible response to different pandemic scenarios**

A fundamental lesson learned in the 2009 pandemic was that pandemics can greatly vary in their levels of severity. Neither the timing nor the impact of a pandemic triggered by an emerging influenza virus can be predicted and there may well be regional variations. Therefore, greater flexibility in planning is required to get national pandemic preparedness planning and management ready for different potential pandemic situations.

**National risk assessments as a basis for measures to be taken**

Assessments by the WHO and the global phases of a pandemic by definition describe the situation from a global perspective. The 2009 pandemic has shown that the epidemiological situation can differ greatly between countries and even within a large country such as Germany. It may be that some countries are already taking various measures in response to a pandemic, while other countries are still focussing on the preparation. Therefore, it is important that national measures are uncoupled from global pandemic phases. Based on risk and situation assessments at national and/or regional level, decisions can be made with regard to adapted measures whilst taking the proportionality of risks and benefits into account (risk-based approach).

**Dealing with unpredictable parameters of a pandemic**

Some characteristics are similar for all influenza viruses and it can be assumed that these are applicable to a pandemic situation. These characteristics, referred to by the ECDC, as the “known knowns” encompass the mode of transmission (droplet transmission, direct and indirect contact), the broad incubation period and serial interval, at what stage a person is infectious, the broad clinical presentation and the general effectiveness of personal hygiene measures. Many factors, however, are not known at the beginning of a pandemic (referred to as the “known unknowns” by the ECDC): the antigenic type and the phenotype of the virus, the susceptibility or resistance to antiviral medicines, existing susceptibility of the population, the effectiveness of influenza vaccines, the most affected age and clinical risk groups, the age groups with the greatest transmission levels, the clinical attack rate, the pathogenicity (infection rates and case fatality rates), the overall impact of the pandemic, the precise parameters for transmission (R0) and serial interval, the precise clinical presentation, the presentation of severe disease and complications, the
interaction with other infections, as well as the duration of the disease and virus shedding. A continuously updated and differentiated risk assessment at all levels (globally through WHO, nationally and regionally via by Member States) is of central importance for the response to a pandemic not only for the decision regarding measures to be taken but also for communicating any uncertainties that (still) exist.

Methodological approach to the revision
When the chapters of the scientific part were updated, a reproducible and (where applicable) an evidence-based methodology has been used. This includes systematic literature searches and the review of scientific evidence for the effectiveness of individual measures.

13.2. Epidemiology
In this chapter, the terms seasonal and pandemic influenza are defined and the epidemiological characteristics (similarities and differences) are described. Both seasonal and pandemic influenza have shown a very broad epidemiological spectrum regarding transmission and severity in the past. This heterogeneity manifests itself in different influenza seasons or pandemics. But also during a season or a pandemic, major differences may occur in the morbidity and mortality in different countries or regions of the world. The section on zoonotic influenza, the epidemiology of influenza viruses circulating endemically in animals is described for both the animal reservoir and humans.

13.3. Virological background and diagnostic methods
Acute febrile respiratory illness may be caused by a number of viral and (less frequently) bacterial pathogens before and also during an influenza pandemic. Hence the specific and sensitive laboratory detection method of a pandemic influenza virus is very important, particularly at the start of a pandemic. The virus detection allows for the isolation and medical treatment of patients and for the collection of epidemiological surveillance data to describe the pandemic waves. This information is crucial for the implementation and organisation of targeted management and intervention measures by the public health authorities and other public authorities. The genetic and antigenic characterisation, the pathogenicity and the transmission characteristics of the circulating pandemic influenza virus help to assess the potential of the virus to cause severe or fatal illness in humans.

13.4. Surveillance concepts and studies
Surveillance systems allow the systematic, ongoing collection, compilation, analysis and evaluation of data, as well as the real-time and continuous reporting of results. Important quality criteria when establishing influenza surveillance systems are the representative nature of the data sources, the collection of data for the various degrees of severity of the disease and the recording of denominators. Historical seasonal data for comparison is needed for the assessment of surveillance data in an influenza pandemic.

Studies are investigations focused on a specific issue for a limited time, the results of which are generally made available to the professional public in scientific publications. The results of surveillance and studies provide a significant portion of the information that is needed for continuous risk assessment before, during and after an influenza pandemic. The preparation of pandemic-relevant studies with regard to piloting and the clarification of ethical aspects and those related to data protection is essential prior to the onset of a pandemic. Both the applicability of study results onto the current situation and the research questions require critical examination.

Mathematical modelling can also contribute in the context of pandemic preparedness planning, however the quality of the results significantly depends on the available database and the stringent checking of modelling assumptions, as well as the accompanying intensive discussion with experts from various disciplines. Models may be used to examine specific aspects of the pandemic event.

13.5. Concept for risk assessment during a pandemic
The overall aim of a risk assessment during an influenza pandemic is the description and assessment of the pandemic situation. Three basic criteria can be used for the ongoing, differentiated in the risk assessment: The epidemic potential within the population, the epidemiological (severity) profile of influenza diseases and the impact on health care resources. This virological, epidemiological and clinical information is collected through surveillance systems and studies.

The primary purpose of a risk assessment is that appropriate measures can be recommended by decision-makers to respond to the pandemic. One particular challenge is that the virological, epidemiological and clinical information for the most part does not or does not reliably exist at the time when risk assessments are required and decisions on measures to be taken need to be made. Therefore, it is necessary that the risk assessment is continually updated with any available information and re-conducted.

This chapter describes the criteria and required information that allow for a risk assessment during a pandemic and delineates the international concepts for a pandemic influenza severity assessment.

13.6. Clinical presentation of influenza
The clinical presentation of influenza regarding symptoms as well as the frequency and type of complications is highly variable. Differences in the clinical presentation are determined by (a) the pathogenicity and virulence of influenza virus types and subtypes and (b) the age of the patient and whether the patient belongs to a risk group.

When a new influenza A subtype emerges (as in previous pandemics), many aspects of the influenza disease can differ from what is considered to be typical in seasonal epidemics where most influenza viruses are circulating on population level for years. In previous pandemics, younger age groups and a higher proportion of persons without underlying medical conditions were affected by severe illness than in seasonal epidemics. A higher proportion of primary viral pneumonia was also observed and new risk factors for severe illness were identified. Therefore, scientific knowledge needs to be rapidly gained, primarily at the start of a pandemic, in order to provide prophylaxis and treatment to persons with a high risk for severe course of illness.

13.7. Non-pharmacological interventions
Non-pharmacological interventions are implemented to reduce the probability of or inhibit transmission of the influenza virus. In general, non-pharmacological interventions can be implemented in the medical setting (ambulatory care or hospital) and in the general population. The latter can be differentiated in individual interventions or group interventions, where an intervention is decided by someone for a group of persons such as school closures or compulsory interventions in the occupational field.

This chapter aims to answer the following questions: (a) which non-pharmacological interventions are available in response to an influenza pandemic, (b) what evidence is available for specific interventions to reduce the transmission of influenza (or other less specific end points), (c) what aspects (in addition to the effectiveness) are important to consider in the recommendation process for certain interventions.

The literature research was carried out in two steps. First, a systematic literature search was performed primarily to identify randomised controlled trials.
hand hygiene. For intensified hand hygiene without additional intensification the effectiveness is even weaker. Moderate evidence exists that investigated the effectiveness of wearing a mask to prevent influenza transmission in the hospital setting. The identified studies showed that transmission of influenza is reduced when wearing a mask compared to not wearing a mask. There is limited evidence that wearing a FFP2 respirator is more effective than wearing a surgical mask. Case-control studies from the SARS epidemic reported the effectiveness of hand hygiene in preventing the transmission of SARS and suggest that this is also true for influenza. During a pandemic different factors for wearing a mask need to be considered: (1) the risk group of biological agent that is assigned to the pandemic influenza virus, (2) the occupational tasks performed i.e. performing aerosol producing procedures and if the patient wears a surgical mask and (3) the availability of different types of masks.

Studies in households with one influenza positive household member provide results regarding individual interventions in the general population. There is little evidence for the effectiveness of wearing a mask without additional intensified hand hygiene. For intensified hand hygiene without additionally wearing a mask the evidence for effectiveness is even weaker. Moderate evidence exists for the effectiveness of wearing a mask in combination with intensified hand hygiene (implemented by all household members) in reducing the transmission of influenza virus within the household. A prerequisite seems to be that the interventions need to be implemented soon after onset of symptoms of the index case and be implemented consistently.

Another study regarding individual interventions in the general population investigated whether surgical masks or intensified hand hygiene prevent the spread of influenza in situations with high population density. The study was performed in halls of residents for student in two consecutive winter seasons and showed little benefit of the interventions. In addition, there are many studies including different study types and different end points exploring the effect of intensified hand hygiene for respiratory illnesses. These studies in kinder gardens, primary and secondary schools showed a low but well documented effectiveness. Advantages of general recommendations for intensified hand hygiene in case of a pandemic are the low costs, the low rate of side effects and the potential of rapid implementation. The effect was higher if the study population did not wash their hands frequently prior to the start of the study, if the compliance was high or if influenza activity was high.

Recommendations regarding preventative interventions for the general population can only be successful and effective if there is a high compliance to the interventions. Hence the reported compliance and tolerance towards the interventions were systematically extracted from the identified household studies and studies in halls of residents for students. The compliance with interventions was generally higher during the 2009 pandemic than during seasonal influenza epidemics, which leads to the conclusion that compliant behaviour is associated with the perceived threat. It is known from household studies that even ill persons and children tolerated well wearing a mask. Other individual interventions are voluntary isolation of patients or voluntary quarantining of a patient’s contacts. The voluntary isolation of patients is an intervention that is frequently implemented in seasonal influenza epidemics and has few “side effects”; therefore the acceptance for this intervention is assumedly high. A Japanese study reported that the risk to acquire influenza-like illness increased if employees voluntarily stayed at home with a sick household member. On the other hand, the coworkers of those who stayed at home had a lower risk to acquire influenza-like illness. A range of possible interventions is available in the occupational setting but none was tested in studies whether it was effective.

Authorities often consider to avoid/cancel public mass gatherings or to close schools or kinder gardens in pandemics or severe seasonal epidemics. The most valuable data for the effectiveness of these interventions derive from the 1918 pandemic when public gatherings (in combination with school closures) were forbidden. Modelling studies suggest an effect of those interventions, but it is unclear whether this is applicable to the present day. School closure can be an active or reactive intervention. Active school closures aim to reduce the transmission of the influenza virus on population level, reactive school closures are implemented when a high number of children or staff of the school experience illness. The decision process to actively close schools is particularly complex. Active school closures may be considered if transmission rate among children is much higher than among adults and if the pandemic is severe. There are many reports that active school closures are epidemiologically effective. There but are also concerns such as the question when to start with closing schools, how long the duration should be and the provision of alternative care arrangements and continued education of children. Reactive school closures are probably only of benefit if the affected institution.

Lastly, interventions at borders are discussed on a regular basis. Theoretical considerations and practical experience showed that exit and entry screening is resource intense and ineffective. These conclusions need to be communicated to the public and authorities. Information about influenza and transmission of the influenza virus needs to be provided for travellers and physicians through a range of communication channels. Generally, closing borders is not regarded to be an effective intervention.

In summary, a gap of knowledge exists regarding the effectiveness of the non-pharmacological interventions presented here so there is an urgent need for more research including high quality studies. Nevertheless, for some interventions such as hand hygiene in the general population and exit and entry screening there are enough data available to come to a conclusion. In case of a severe pandemic, a combination of different non-pharmacological interventions can be an effective instrument to attenuate the pandemic impact.

13.8 Vaccine concepts

In Germany, the Standing Committee on Vaccination (STIKO) as a statutory commission gives recommendations with regard to immunisation. This applies also in a pandemic. Vaccines in sufficient quantities will probably only be available during the course of a pandemic. Therefore, it may be necessary to define those population groups who might especially benefit from vaccination or whose vaccination may result in a reduction of virus transmission in the pandemic situation while taking into account the specific vaccines and quantities thereof available.

The procedures for the licensing of seasonal influenza vaccines are anchored in national and European legislation. This involves the initial licensing of a defined seasonal vaccine composition; the annual adjustment of vaccine composition in line with the WHO recommendations («annual update») takes place within the framework of a so-called variation procedure. The vast majority of vaccines are formulated without adjuvants containing three strains of influenza virus in inactivated form. More recent developments are formulations with four inactivated influenza strains («tetravalent») and a live-attenuated vaccine.
In the case of pandemic vaccines, licensing is based on the concept of «mock-up» vaccines. In the inter-pandemic phase, a vaccine formulation with a potentially pandemic vaccine virus is licensed which can be very quickly adapted when an actual pandemic virus emerges using an amendment procedure.

Both the seasonal as well as the pandemic influenza vaccination 2009/2010 showed a moderate to high effectiveness against laboratory-confirmed influenza and its complications overall. Depending on the genetic match of the vaccine viruses with the circulating influenza viruses and on the studied population or risk groups, there may well be, however, significant differences in effectiveness.

Due to decades of application, the seasonal vaccines currently have a very extensive safety data base. The data show that the vaccines are very well tolerated and (apart from very rare exceptions) may cause only mild local or systemic adverse reactions. This also applies to the risk group of pregnant women.

New kinds of oil-in-water emulsions can be used as adjuvants in influenza vaccines, which may lead to a significant enhancement of the antibody response after vaccination. These emulsions permit the reduction of the amount of vaccine antigen required per vaccine dose thus facilitating the production of a number of vaccine doses as high as possible with the available production capacity - which is hugely important in the event of a pandemic. Vaccine concepts should therefore be flexible and take into account factors such as the severity of a pandemic and logistical requirements.

13.9. Medicines relevant in a pandemic

Currently three different antiviral agents for prophylaxis and treatment of influenza are available in Germany: amantadine, oseltamivir and zanamivir. Due to rapid development of resistance while being used, as well as the current resistance situation, amantadine has no longer been recommended in the past few years. In addition, amantadine has a narrow spectrum of activity (only influenza A) and is tolerated less well than neuraminidase inhibitors.

The protective efficacy of antivirals when used for the prophylaxis of influenza is approximately between 60% and 90%. The protective effect of antiviral medicines only persists as long as the drugs are being used. The safety of neuraminidase inhibitors has been demonstrated in long-term use of up to 16 weeks.

For the treatment of influenza, overall antivirals have shown a moderate effect with a reduction in the duration of illness of between 0.5 to 1.5 days in randomised controlled trials (RCTs). In some patient groups, the effectiveness was more pronounced; in other patient groups, the effectiveness was lower or not shown. In addition, the effects shown also vary in part for oseltamivir and zanamivir in different population groups.

Bronchitis in adults and otitis media in children tended to occur less frequently. In terms of pneumonia, positive effects were demonstrated in RCTs among adults. These are however not indisputable, since in most studies pneumonia was only reported by patients and not diagnosed by physicians. An influence on the occurrence of severe illness or mortality was not shown in RCTs. Clear indications of a positive effect of neuraminidase inhibitors on these can be seen in a variety of high-quality observational studies. This type of study has various advantages, such as the examination of medicines under real life conditions, the possibility of a follow-up of a higher number of patients for extended periods of time and the generation of data in situations in which control group appears ethically indefensible such as in severely ill patients. From a methodological point of view, it however remains unclear with regard to this type of study, to what extent results could have been distorted by unknown influencing factors that would consequently not be included in the analysis. In the absence of data from RCTs however, they may well provide valuable information for pandemic preparedness planning. A reduction in the virus shedding was observed when using antivirals; the clinical significance of which, i.e. whether disease transmission is actually reduced by this, still remains unclear. In the absence of other treatment options, the reported effects may well be relevant for individual patients as well as for the society in general during a pandemic.

The side effect profile for antiviral medicines, in particular for the neuraminidase inhibitors is well characterised due to the widespread therapeutic use during the influenza A(H1N1) 2009 pandemic. In general, the side effects of neuraminidase inhibitors are less pronounced than those of amantadine. For amantadine, particularly neuropsychiatric effects are described. For oseltamivir, particularly adverse effects on the gastrointestinal tract, the skin and neuropsychiatric effects are observed. For zanamivir, very frequently undesirable effects on the skin and the respiratory tract – such as bronchospasm – have been described.

Overall, the benefit-risk ratio, in particular for the neuraminidase inhibitors, is seen as positive. The indication to use antivirals must be determined considering the characteristics of the circulating viruses - such as transmissibility, virulence and resistance/sensitivity, as well as the individual risk of the patient determined for example by underlying medical conditions and comorbidities. The available recommendations of the respective medical professional societies must be taken into account. Current recommendations for the use of antiviral drugs during the seasonal influenza epidemics are available for Germany and can also be found, for example, on the European Centre for Disease Prevention and Control (ECDC) and Centres for Disease Prevention and Control (CDC) websites. Antibiotic therapy of influenza-associated pneumonia is carried out according to the S3 – guidelines regarding community-acquired pneumonia.