Information for Physicians

Influenza

The “real flu” in humans is caused by both type A and type B of the influenza virus. This illness regularly occurs as an epidemic in the winter months and is typically characterised by an abrupt onset of high fever, head ache, throat ache, and muscle pain, a strong feeling of malaise, rhinitis, and dry cough. The acute illness lasts approx. one week, the cough and feeling of malaise may in some cases persist for several weeks.

In some patients, influenza may cause severe complications, with pneumonia caused by the virus itself or through bacterial superinfection as the primary symptom. The risk of developing such complications is elevated in all older patients (>60 years) and in patients with another primary disease. The annual influenza epidemics thus also entail significant excess mortality.

Influenza epidemic and pandemic

The influenza virus is a virus that undergoes major mutations. These changes primarily involve the two antigens located on the virus surface, hemagglutinin (HA) and neuraminidase (NA). These continuous changes result from what is called the **antigen drift** and occur both in type A and type B influenza viruses. This antigen drift also explains why influenza infections do not give rise to long-term immunity and frequent re-infections and epidemics occur year after year.

Sudden and drastic changes, known as ***antigen shifts***, are a hallmark of the type A influenza virus and occur at unpredictable intervals. Once such drastically changed virus variants have the ability to efficiently communicate from human to human, a widespread epidemic and as a result a pandemic may occur. In the documented history of influenza such pandemic viruses have emerged three times, with a new form of hemagglutinin and neuraminidase every time. In the most severe pandemic to date – what we know as the “Spanish flu” – a virus of the H1N1 sub-type emerged in 1918/1919. Other pandemics were prompted by viruses of the H2N2 and H3N2 sub-types in 1957 (“Hong Kong flu”) and 1968 (“Asian flu”) respectively.

The World Health Organisation (WHO) subdivides a pandemic into six phases, depending on which new influenza virus sub-types are detected in humans. Currently, the WHO sees an increased risk of a new aggressive influenza virus developing. All countries of the world are called on to take adequate measures to prepare for the occurrence of an influenza pandemic (also see Austrian "Influenza Pandemic Plan – Strategy for Austria" at www.bmgf.gv.at).

According to the experts, the current epidemiological situation corresponds to phase three. This phase is characterised by the appearance of infections in humans caused by a new sub-type without human-to-human transmission (except in rare cases due to close contact). The work to be performed as part of the public health strategy focuses on three key areas:

1. General measures, incl. the monitoring of infectious diseases in human and animals
2. Monitoring of free-range and domestic fowl
3. Provision of antiviral pharmaceuticals
4. Flu vaccination

Ad 1: Monitoring infectious diseases in humans and animals

Persons in contact with poultry and free-range fowl with suspected H5N1 infections

As several cases of the H5N1 virus in free-range fowl have been detected in Austrian territory, the following procedure is recommended for persons in contact with poultry and free-range fowl suspected of carrying the H5N1 virus:

1. The attending physician should provide a detailed case history and determine whether the patient actually had direct unprotected contact (= without protective clothing, gloves, mask) with the animal (poultry/wild fowl). Contact is defined to include the following: manipulation, touching, contact with blood, saliva, or faeces.

2. If such unprotected contact actually occurred, post-exposure prophylaxis should be started immediately by administering a neuraminidase inhibitor. If laboratory examinations determine that the animal was NOT INFECTED WITH H5N1, prophylactic treatment can be discontinued.

Furthermore, when determining the medical history of patients with flu-like symptoms who consult a physician, the medical practitioner should also determine whether the patient has been to any risk countries and had contact with living or dead waterfowl/poultry (also faeces) there.

Persons with suspected H5N1 infections

As the occurrence of H5N1 infections in poultry and free-range birds has increased in recent weeks and very many people have travelled from the affected areas to Austria, we cannot rule out intensive contact with infected fowl in individual cases possibly causing an infection of humans. Due to the circumstances, greater attention must be paid to persons coming from the affected areas, particularly if they are suffering from flu-like symptoms typical of a possible incubation period.

The criteria determining the clinical picture and epidemiological exposure are:

Clinical picture

Illness with all three of the following criteria

- fever (> 38° Celsius, irrespective of where measured)
- acute onset of illness and
- at least one of the two following symptoms
    - cough
    - dyspnoea

Epidemiological exposure

Exposure has occurred if **at least one of the following 3 events** applies within a 7-day period prior to the onset of the disease:

1. Stay in a zoonotically affected area (see http://www.oie.int)

AND in the following cases:

- direct contact with living or dead animals (poultry, wild birds, pigs) or their excrements, body fluids, or raw products (e.g. eggs that have not been heated)

- OR activities on a poultry or pig farm, at which infected animals or animals with suspected infections have been kept in the previous 6 weeks
- OR life in the same household or care of a human with all the aspects of the clinical picture

OR

2. direct contact with a human being or his/her secretions with an infection determined by way of laboratory diagnosis

OR

3. laboratory exposure (e.g. as lab staff in a laboratory, in which samples have been tested for A/H5)

All physicians confronted with these symptoms and a pertinent travel history are called on to prescribe Tamiflu (special pharmaceutical) – which according to the WHO, has proven to be effective in cases occurring in Turkey – to these patients. In Austria, ample stocks of Tamiflu are available (for details on the drug, see below).

Further procedure:

- Avoidance of contact between affected persons and other patients in the doctor's office
- Protection of medical staff against infection (protective mask for mouth and nose which meets the FFP1 standard, protective coat, protective glasses, gloves, disinfection of hands)
- Immediate contact with an infection ward and hospitalisation (patient transport with protection of staff against infection and preliminary report to the hospital).
- Compulsory registration! The responsible public health officer must be informed immediately so he/she can identify any possible further suspicious cases (e.g. travel companions) and close contact persons (family members and other persons living in the same household)
- If an infection with avian influenza is determined – post-exposure prophylaxis for persons who have had close contact to patient

Please note: Pursuant to the ordinance of the Federal Ministry of Health and Women to implement the Epidemic Act registration has been compulsory

for all diseases caused by infection with H5N1 viruses or other avian influenza viruses. In such cases, please contact your Provincial Health Department (Landessanitätsdirektion) immediately, refer the patient to an infection ward immediately and remember to start with post-exposure therapy with Tamiflu right away.

Ad 2.: Monitoring free-range and domestic fowl

When several wildfowl died of avian flu in Austria mid-February, the Federal Ministry of Health and Women stipulated certain measures to prevent the avian flu from spreading to Austrian poultry. Accordingly, the rule is now in effect nationwide that all poultry must be kept in closed coops or enclosures. Moreover, every wildfowl found dead must be reported to the official veterinarian of the competent district administration. Besides these rules applicable throughout Austria, special protection and monitoring areas have been set up in certain regions close to where the infected wildfowl were found. In those areas, additional special measures are applicable, such as rules of cleaning and disinfection, ban on the export of poultry and poultry products from those areas, etc. (for details on the specific rules and a current list of the affected areas, see www.bmgf.gv.at).

Ad 3.: General hygiene and organisational measures:

Observance of general hygiene standards, e.g. washing hands regularly and using throw-away paper handkerchiefs.

Ad 4.: Provision of antiviral pharmaceuticals

General information on virostatics effectively used against influenza

From today's perspective, two groups of suitable virostatics are currently available for prophylactic and therapeutic purposes: amantadine preparations and neuraminidase inhibitors.

1. Amantadine

Amantadine (and rimantidine, not approved in Austria), which has been used as a drug for influenza prophylaxis and therapy for the past 30 years, is a blocker of the M2 ion channel in the membrane of influenza A viruses that prevents the uncoating (inhibition of release of the viral genome) of the viral nucleic acid in the infected cell.
The following characteristics show that this preparation is not suitable for wide administration in the event of a pandemic:

- After only a brief treatment period (2-3 days), resistant variants of the viruses may begin to spread, propagate and render this therapy useless.
- Amantadine has only a narrow activity spectrum than the new, specific pharmaceuticals against influenza types A and B. Thus, it can only be used against type-A influenza. This appears to be sufficient, however, in the case of a pandemic flu, which the experts believe can be triggered by the influenza A virus only. It may be a disadvantage, however, that amantadine is not effective against certain infections caused by an Influenza B virus that may appear at the same time as the pandemic.
- In the current avian flu virus infections (H5N1) in poultry (commonly known as “bird flu”) the initial investigations of the WHO Global Influenza Laboratory Network have shown that these specific viruses appear to be resistant to amantadine. Since precisely those viruses are likely carriers of a human pathogen that could cause the outbreak of a pandemic, the possibility must be considered that amantadine would be completely inefficacious in such cases.
- The side effects and contraindications make amantadine appear in a more unfavourable light than the other available preparations for treatment of influenza A infection.

2. Neuraminidase inhibitor

Neuraminidase inhibitors are a group of recent drugs that specifically target influenza A and B. Zanamivir and Oseltamivir are available as active ingredients. Both substances block the neuraminidase of the flu virus and thus prevent release of the newly formed virus particles from already infected cells. Both Zanamivir and Oseltamivir are effective against all nine known neuraminidase (N) subtypes of influenza A virus and against the neuraminidase of the influenza B virus. Thus, according to our current state of knowledge, they should also be effect against human-pathogenic variations of the virus that could cause a pandemic based on the so-called “avian flu” germ (H5N1).

With both substances, in the case of an existing infection, therapy should be begun about 36 to 48 hours after the appearance of the first symptoms in order to ensure successful treatment. While Austria presently allows Zanamivir only for therapeutic purposes, Oseltamivir can be used both for prophylaxis and therapy.

Also the form of administration (Oseltamivir is taken orally, whereas Zanamivir is inhaled only) argues for the use of Oseltamivir in the case of a flu pandemic: administration by inhaling, as is required with Zanamivir, would not be impracticable in the case of a pandemic (Zanamivir is also unsuitable for infants and small children and, unlike Oseltamivir, is permitted only to those age 12 and up). In addition, it can seriously impair respiratory function in patients with severe asthma or chronic respiratory diseases and older patients with acute bronchial spasms.

With respect to the development of potential resistance, lab studies have shown that resistance against both neuraminidase inhibitors appears least common than with amantadine, although a new study (Kiso *et al.*, Lancet, 2004) shows that neuraminidase inhibitors have a somewhat higher than expected rate of occurrence of resistant mutations. At present, however, it is hard to evaluate with precision the ultimate significance of these findings in relation to the question of a clinically relevant development of resistance in the event of very wide-scale use of this group of substances, as in the case of a pandemic. From the current standpoint, however, the comparatively low potential for the emergence of resistant virus strains demonstrated by clinical tests on Oseltamivir gives reason to hope that the germ would continue to react to the substance for a sufficiently long time.

The possible side effects of treatment with Oseltamivir are predominantly of a gastrointestinal nature (nausea, vomiting) and similar or only slightly higher than values of the observed side effects in the placebo group.

Based on the available data, Oseltamivir currently appears to be the most suitable virostatic substance on the market for use in the event of a pandemic, especially because it can be used not only for therapy but also for preventive applications, i.e. prophylaxis (both seasonal and post-exposure) and is suitable for children of one year and up.

Summary: advantages of Oseltamivir:

- therapy and
- prophylaxis: seasonal and post-exposure
- Can be prescribed as therapy for children aged one and older.
- few side effects/safe use

Prophylaxis with Oseltamivir:

Sufficient early prophylaxis with Oseltamivir is especially necessary for highly exposed or vulnerable groups of individuals. In particular, wide-ranging prophylaxis should also be prescribed for individuals employed to maintain the infrastructure, as well as for hospital and nursing staff. In general, at least two different forms of prophylaxis:

- Post-exposure prophylaxis: in the case of unvaccinated individuals after contact with infected patients, treatment with chemoprophylaxis can be begun within 48 hours.
- Seasonal prophylaxis: In the case of unvaccinated individuals for the duration of the flu outbreak, regardless of whether or not they have had a demonstrated contact with infected patients, until immune protection is provided by vaccine.

During a pandemic, seasonal prophylaxis should be used, in particular. One advantage is that there are no interactions between prophylaxis with Oseltamivir and the formation of vaccine immune protection, so that it provides a transitional solution in the period between the time the vaccination is given and the time that the protective effects first appear. In any case, it must be mentioned that for successful prophylaxis, a high rate of compliance (i.e., regular and reliable administration of the drug) is decisive and that the population must be provided with an appropriate supply.

Oseltamivir has been approved for use in the prophylaxis for adults and adolescents aged 13 and older. The following **doses** apply for adults and adolescents aged 13 and older:

- 75 mg Oseltamivir once daily for at least 7 days in the event of post-exposition prophylaxis
- or up to 6 weeks when administered for seasonal prophylaxis
- adjustment of dosage in case of creatinine clearance 10-30 mL/min to 75 mg once every 2nd day or 30mg suspension once daily (see also technical information)

Therapy with Oseltamivir:

Oseltamivir can also be used as a causal therapy for individuals in whom the disease has already broken out. The drug must be used as early as possible (within 48 hours) after the appearance of the first symptoms, however. The effect of the treatment is to mitigate the symptoms of the disease and reduce the duration of the illness. Moreover, typical complications (e.g., bacterial infections of the lower respiratory tract, chiefly bronchitis) are reduced. Thanks to the reduced virus excretion rate that has been observed among the patients treated, the propagation rate might also have be positively affected.

Oseltamivir is permitted for therapeutic use on adults and children aged one year and older.. The **dosage** is:

- Adults and adolescents aged 13 and older:
  75 mg Oseltamivir twice daily for 5 days
  Adjustment of dose in case of creatinine clearance 10-30 ml/min to 75 mg once daily
  or 30mg of suspension twice daily (see also technical information)
- Children aged one and older: (use only suspension) -> dependent on weight of child:
  <15kg: 30 mg twice daily
  >15-23kg: 45 mg twice daily
  >23-40kg: 60 mg twice daily
  >40kg: 75 mg twice daily
  for 5 days each

Forms of administration

Tamiflu is available in bioequivalent forms: as a hard capsule or as a powder used to produce a suspension. In order to be able to include children, as well, the warehouses should concentrate on the form of a suspension, although the shelf life of the suspension is two years less than in the case of the hard capsules (5 years).

Ad 5.: Flu vaccination

Already in the current inter-pandemic phase, the broadest possible range of protective vaccinations with the seasonal flu vaccine is recommended, especially with respect to trades people involved in poultry keeping. This is intended to reduce the probability of co-infections (seasonal flu virus and avian flu virus).

WARNING: The season flu vaccination does not provide any protection against H5N1 Virus!

Excursus: Vaccines in the event of a pandemic

In the event of a pandemic, the most urgent objective is produce an effective drug with no side effects and to make it available as quickly as possible. As early as the inter-pandemic phase, this task requires preliminary work on the part of manufacturers and food and drug administrations with respect to manufacture, testing, and licensing procedures for such a vaccine. From the current point of view, it is not possible to give detailed information on the actual final formulation of a flu pandemic vaccine. It is very probable that such vaccines would have to be an inactivated, monovalent "whole-virus" vaccine formulated with adjuvant and preservative.

Based on the essentially higher number of units required in the case of a pandemic and the rapid availability required, after the inactivation no further preparation of the surface antigens will probably occur. The advantage of such a "whole-virus" vaccine is a lower loss of the required antigen, which would be required in large quantities in case of need. In order to provide sufficient immunogenicity and reduce the quantity of antigen necessary for an individual dose. it is to be assumed that the vaccine should be formulated with adjuvant.

Since a flu pandemic vaccine would presumably come in a multi-dose container to ensure faster production, better stability (cooling) and easier, more compact storage, the use of the preservative additive Thiomersal is unavoidable in the current state of the art, according to the vaccine manufacturers. When producing the vaccine strain, genetic engineering may also prove necessary and be deployed.

Production

The reproduction of the vaccine virus may– as with the flu vaccines currently on the market– may either be performed with embryonated chicken eggs or with the latest cell culture methods. According to the current state of the art, "Vero" or "MDCK" cells will be used in the latter case. These cells can be used for cell cultures for many years, have very good biological and genetic characteristics, and are free from germs. In all probability, the cell culture methods will make it possible to produce large quantities of the vaccine virus more quickly in the event of a pandemic. Experts also assume that cell culture technology will provide a higher degree of purity than is possible with embryonated chicken eggs.

Approval

The approval process is used to test the quality, safety and effectiveness of the vaccine. At the same time, it is necessary to avoid wasting time in the event of a pandemic. The approval procedure typically has a 2-stage process for marketing in case of need (mock up approval– pandemic version). This means that already BEFORE the outbreak of a pandemic – already in the inter-pandemic phase – a so-called "Core Pandemic" file is submitted and evaluated. Since there is no pandemic virus at this point in time, a “model virus” is used instead. The second phase of the approval procedure and authorisation to market the vaccine do not take place until an actual pandemic occurs, after the WHO has made available the necessary reference virus for the production of the actual pandemic virus. This second approval phase is carried out as a so-called "pandemic variation" (modification). In that variation, the model virus is replaced by the actual pandemic virus.

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For further information, please dial **050 555 666** to contact the **Info-Hotline** of the Austrian Agency for Health and Food Safety (AGES).

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Please not that this paper is in no way exhaustive and we assume no liability for its contents. Further information is available at www.ages.at and www.bmgf.gv.at. These websites also provide downloadable information on the Austrian Pandemic Plan and the "Crisis Plan for Classical Avian Flu and Newcastle Disease 2000".