Epidemics and pandemics: what health professionals need to know

WP3 Prototype Online Course for Primary Care Staff

DOSSIER 1

Responsible Partner: ZADIG
Contributing partners:

Dissemination level: PU

TELL ME - Transparent communication in Epidemics: Learning Lessons from experience, delivering effective Messages, providing Evidence.
Project co-funded by the European Commission within the 7th Framework Programme – HEALTH theme

Document Management

PROJECT FULL TITLE	Transparent communication in Epidemics: Learning Lessons from experience, delivering effective Messages, providing Evidence.
PROJECT ACRONYM	TELL ME
	Collaborative Project funded under Theme HEALTH.2011.2.3.3-3 "Development of an evidence-based behavioural and communication package to respond to major epidemics outbreaks"
GRANT AGREEMENT	278723
STARTING DATE	01/02/2012
DURATION	36 months

Dealing with human rights: a guide for healthcare workers

Task: 3.3

Leader: ZADIG – Other contributors: none

History of changes:

Vn	**Status**	**Date**	**Organisation / Person responsible**	**Reason for Change**
V1	Draft	30/1/2014	ZADIG	First draft
V2	Draft	14/5/2014	ZADIG	Second draft
Vf	Final	22/5/2014	ZADIG	Final draft

Table of contents

INTRODUCTION 4
1. Definitions 4
1.1. Epidemic 4
1.2. Pandemic 5
2. Main epidemics 8
2.1. Seasonal influenza 8
2.1.1. Clinical information 8
2.1.2. Categories at risk 9
2.1.3. Treatment 9
2.1.4. Epidemiology 10
2.2. Avian flu 12
2.2.1. Clinical information 12
2.2.2. Categories at risk 12
2.2.3. Chemoprophylaxis and Treatment 13
2.2.4. Epidemiology 13
2.3. A(H1N1) flu 14
2.3.1. Clinical information 14
2.3.2. Categories at risk 14
2.3.3. Treatment 15
2.3.4. Epidemiology 15
2.4. Middle East respiratory Syndrome (MERS) 16
2.4.1. Clinical information 16
2.4.2. Categories at risk 17
2.4.3. Treatment 17
2.4.4. Epidemiology 18
Bibliography 18

INTRODUCTION

Epidemics and pandemics represent serious threats to human life and health, and require great efforts in order to prevent them to inflict such damage. However, facing these problems is far from being easy, due to many factors, from their unpredictability to the high level of national and international cooperation that is necessary to establish when dealing with them.

Healthcare workers represent the first line of intervention and the first level of interaction between healthcare institutions and citizens. For these reasons, they should know as much information as possible – epidemiology, modes of transmission, symptoms, diagnosis, prevention, treatments and so on – about the infectious diseases that are circulating at the moment.

Prevention, in particular, is quite a relevant theme that also brings several issues, mainly because of the criticism that surrounds vaccines. Given this, a full dossier has been entirely dedicated to prevention. Such a dossier contains both technical information about preventive measures and advices about how to properly communicate them to the public. This is the reason why there is no reference to prevention in the following chapters.

1. Definitions

First, it is necessary to clarify a definition in order to avoid confusion and misunderstanding. The difference between epidemic and pandemic is highly important because of the different kinds of approach they require and the feelings they evoke in the citizens.

1.1. Epidemic

The term epidemic is often associated with outbreak and many epidemiologists use both terms interchangeably, sometime even together, that is “an epidemic outbreak”. A broad definition given by many epidemiologists for epidemic is “more disease than is anticipated by previous experience”, whilst a more precise one is “a number of cases (infectious or not) greater than the expected in a defined place and time of any dimension”, and is to be distinguished by an outbreak, which is “an epidemic confined to a defined short time and place”. Such a distinction, however, is less meaningful to the general public, since epidemic is more likely to imply a crisis (Green et al., 2002). According to the US Centers for Disease Control and Prevention (CDC), an epidemic (or an outbreak) exists when “there are more cases of a particular disease than expected in a given area, or among a specific group of people, over a particular period of time”. This may be due to the recurrence or emergence of a new microorganism within a given population or to the emergence of an agent with a genetic mutation.

At irregular intervals, an influenza A virus emerges which is different from the current human seasonal influenza viruses and can not only infect humans but can also cause disease in some of them and crucially is capable of efficient human to human transmission. The virus has to be novel enough to prevail over the seasonal A viruses, and because of its novelty there can be little specific immunity among humans, except for older people who may have met a similar virus in the past. This new virus can then spread rapidly from

human to human all over the world. Because of the lack of human immunity, the virus causes a variable amount of severe disease and deaths: this is an influenza pandemic (ECDC). As immunity increases among humans, and the pandemic virus changes, the pandemic strain becomes part of (and may dominate) the mix of seasonal influenza A viruses, perhaps changing some of the characteristics of seasonal influenza. Influenza pandemics vary, and in order to mitigate or even prevent some of their most concerning impacts there is a need for specific and general preparedness.

1.2. Pandemic

There have been controversies over the precise definition of what a pandemic is, especially following the 2009 H1N1 swine flu pandemic, with several experts claiming that there has been an excess of alarmism from healthcare authorities. A pandemic is said to occur when a new infectious agent, or a reemerging one, spreads across multiple continents, or even worldwide. This is the reason why, for instance, cancer, which is not infectious, is not considered pandemic even though is responsible for many deaths, nor is malaria, that spreads through continents but isn't new, nor are very severe diseases like those caused by Ebola virus, self-limiting because of their own lethality. According to the classical epidemiological definition, a pandemic is defined as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people" (Last JM, 2001).

This says nothing about population immunity, virology or disease severity. But by this definition, pandemics could be said to occur annually in each of the temperate Southern and Northern hemispheres, given that seasonal epidemics cross international boundaries and affect a large number of people. However, seasonal epidemics are not considered pandemics. A true influenza pandemic occurs when almost simultaneous transmission takes place worldwide. In the case of pandemic influenza A(H1N1), widespread transmission was documented in both hemispheres between April and September 2009, period that was out of season in the Northern hemisphere. (Kelly, 2011). Case fatality ratio ranged from 0.01 to 0.03% (Donaldson, 2009, Bandaranayake 2010, McVernon 2011), that is much lower than feared, similar to those normally seen in the case of seasonal influenza (Wilson 2009). However, the number of deaths was higher in younger people, as it happened in previous influenza pandemics (Kelly, 2011).

A debate is still ongoing whether H1N1 influenza should have been labelled a "pandemic" at all. The Council of Europe voiced serious concerns that the declaration of a pandemic became possible only after WHO changed its definition of pandemic influenza, few weeks before it also expressed misgivings over WHO's decision to withhold publication of the names of its H1N1 advisory Emergency Committee (Council of Europe, 2010). "At stake in this debate are the public trust in health officials and our collective capacity to respond effectively to future disease threats. Understanding this controversy entails acknowledging that both parties are partially correct, and to resolve it we must re-evaluate how emerging threats should be defined in a world where the simple act of labelling a disease has enormous social, economic and political implications", Peter Doshi wrote on the Bullettin of WHO (Doshi, 2011).

The controversy raised by the fact that since 2003, the top of the WHO Pandemic Preparedness homepage has contained the following statement: "An influenza pandemic occurs when a new influenza virus appears against which the human population has no immunity, resulting in several simultaneous epidemics worldwide with enormous numbers of deaths and illness". However, on 4 May 2009, scarcely one month before the H1N1 pandemic was declared, the web page was altered in response to a query

from a CNN reporter. The phrase “enormous numbers of deaths and illness” had been removed and the revised web page simply read as follows: “An influenza pandemic may occur when a new influenza virus appears against which the human population has no immunity.” Months later, the Council of Europe would cite this alteration as evidence that WHO changed its definition of pandemic influenza to enable it to declare a pandemic without having to demonstrate the intensity of the disease caused by the H1N1 virus. WHO, however, denied having changed any definitions (WHO press conference, 2010).

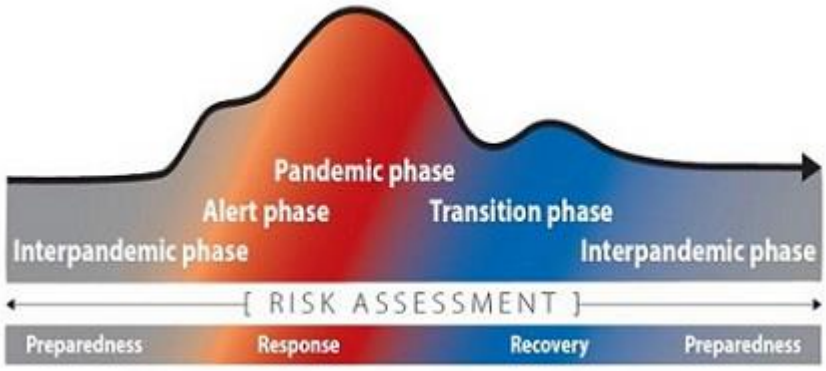
WHO argues that this phrase had little bearing on policy responses, it was “never part of the formal definition of a pandemic” and was never sent to Member States, but simply appeared in “a document on WHO’s website for some months”. In actuality, was displayed at the top of the WHO Pandemic Preparedness home page for over six years and is consistent with the descriptions of pandemic influenza put forth in various WHO policy documents over the years. While it unambiguously describes disease severity and certainly reflects general assumptions about pandemic influenza, it is unrelated to the criteria WHO applied to declare H1N1 influenza a pandemic. In fact, a formal definition of pandemic influenza has never been formulated. What we have from WHO’s pandemic preparedness guidelines are only “pandemic phase” definitions.

2009: WHO Pandemic influenza preparedness and response

WHO declared a pandemic on 11 June 2009, after determining that the novel reassortant H1N1 virus was causing community-level outbreaks in at least two WHO regions, in keeping with the definition of pandemic phase 6. The declaration of phase 6 reflected wider global dissemination of H1N1, not disease severity. This point has received widespread attention and criticism. A new WHO 2013 interim guidance document (WHO, 2013), taking account of lessons learnt from the influenza A(H1N1) 2009 pandemic and of other relevant developments, updates and replaces the previous WHO guidance document (WHO, 2009), but it does not give yet a clear and formal definition of pandemics.

It admits that in 2009 Member States “had prepared for a pandemic of high severity and appeared unable to adapt their national and subnational responses adequately to a more moderate event”. This document

aligns more closely with the disaster risk management structures already in place in many countries and underscores the need for appropriate and timely risk assessment for evidence-based decision-making at national, subnational and local levels. It introduces a risk-based approach to pandemic influenza risk management and encourages Member States to develop flexible plans, based on national risk assessment, taking account of the global risk assessment conducted by WHO.



2013: Pandemic Influenza Risk Management WHO Interim Guidance

Breaking this down further sensibly becomes an international, national, sub-national and local response to the outbreak at whatever level the pandemic presents itself. This approach is very similar to the latest thinking on what is seen as the best way to tackle climate change, which is a disaster risk management approach to climate change adaptation that is now further maturing into the convergence of "disaster risk reduction and climate change adaptation". There are some key principles in crisis management that may be relevant here:

- organizations are reluctant to take responsibility for the making of decisions for other organizations. In other words the WHO may declare a pandemic, but how governments respond is their own responsibility;
- "delegation of responsibility" is important in order to achieve a timely and an appropriate response (i.e. in relation to the local impact of the crisis);
- responsibility in a crisis lies where it does in 'peace time'. Of course there will be some aspects of that responsibility which will change because of the crisis but essentially responsibility rests where it is.

In response to lessons learnt from the influenza A(H1N1) 2009 pandemic, a revised approach to global phases is introduced in this guidance. The phases, which are based on virological, epidemiological and clinical data, are to be used for describing the spread of a new influenza subtype, taking account of the disease it causes, around the world. The global phases have been clearly uncoupled from risk management decisions and actions at the country level. Thus, Member States are encouraged as far as possible to use national risk assessments to inform management decisions for the benefit of their country's specific situation and needs.

Therefore, if the WHO identify an influenza outbreak and report the facts as known at the time, the responsibility for responding in an appropriate way lies with national governments. Of course, a

coordinated response between nations will help and the WHO should seek to facilitate this. The declaration that the influenza outbreak is a pandemic is almost academic at the beginning of the outbreak but may become more important and much clearer later as the influenza spreads. The fact is initially that an outbreak has occurred, is being monitored and governments and organizations need to take notice and respond appropriately. The WHO can of course give guidance on what is an appropriate response.

Anyway, a new definition of pandemic is needed, taking into account not only the spread of a new infection, but also its burden. This can depend on severity, in term of victims, but also on socio-economical costs, not to be undervalued in case of a widespread infection, even if less severe than expected.

2. Main epidemics

2.1. Seasonal influenza

2.1.1. Clinical information

Influenza is caused by RNA viruses from the *Orthomyxoviridae family*, which have a worldwide distribution and can infect birds and mammals, among which humans. They are usually classified into three broad types: A, B and C, according to differences in the antigenic properties of their external coat. Influenza A viruses, clinically the most threatening, are further divided into subtypes based on two proteins on the external coat, hemagglutinin (HA) (H1–H16) and neuraminidase(NA) (N1–N9). Type B viruses are usually responsible for less severe diseases, whereas type C viruses do not usually cause significant human disease. Each season, human influenza is caused by variable mixes of influenza A plus B viruses. Like other RNA viruses, the genome of influenza viruses is subject to a significant spontaneous mutation rate; in addition, their genome consists of eight separate segments. Thus, that re-assortment of the genome segments results in considerable antigenic variability, particularly of the HA and NA of the influenza A viruses.

Gradual changes in the level and type of human viruses in seasonal influenza is the result of what is known as *antigenic drift*, the continuous change of the viral HA and NA due to the high mutation rate of the genome and the fact that RNA viruses lack the proof-reading ability of DNA polymerases. This means also that influenza can quickly evolve to evade the human immune responses that follow natural infection or immunization. Pandemics are the result of larger changes sometime called *antigenic shift*. These are large genetic changes, for example through inclusion in the virus of HA and NA subtypes from avian or swine origin by reassortment. These reassortments are not rare but only very occasionally lead to a viable, transmissible influenza A virus for which many or most humans lack immune protection. That is then a pandemic strain.

Influenza is an acute infection that spreads easily from person to person. It is transmitted by droplets that get into the air when an infected person coughs or sneezes, but also through hand contact. For these reasons, the first line of defense is constituted by healthy habits such as covering their mouth and nose with a tissue when coughing, and washing their hands regularly. People could be able to pass the flu to someone else before they even know they are sick, as well as during the sickness. Some people can be infected with the flu virus but have no symptoms. During this time, those persons may still spread the virus to others.

Incubation usually lasts for 1-4 days, with an average of two. Symptoms are not specific and may be easily confused with those due to other respiratory affections, especially the common cold, which are not as severe as influenza and are called influenza-like illnesses. Typical of flu is the coexistence of sudden high fever (over

38°C), chills, cough (usually dry), headache, muscle and joint pain, weakness, sore throat, runny nose and malaise. In children, influenza may also produce gastrointestinal symptoms like nausea and vomiting. The presence of these symptoms in the season is usually enough to diagnosis influenza, but when a confirm is needed an antigen detection test, which is done by swabbing nose and throat, and then sending a sample to the laboratory for testing, can be done. The results of these tests can be available rapidly, and can help decide if specific treatment is appropriate.

2.1.2. Categories at risk

Influenza may cause some people to suffer from complications like pneumonia, bronchitis, sinus and ear infections, dehydration, and aggravation of pre-existent diseases. There are some categories that are more likely to incur into such complications, depending on age and health status. ECDC considers at risk people with:

- metabolic diseases (e.g. diabetes);
- chronic lung conditions (e.g. chronic bronchitis);
- cardiovascular disease (e.g. coronary artery disease);
- chronic kidney diseases (e.g. chronic renal failure);
- chronic neurological conditions and physical handicap (e.g. cerebral palsy);
- conditions and treatments that suppress the immune function (e.g. people receiving chemotherapy).

In some countries, it is considered that children and pregnant women are also in risk groups. While that was certainly the case in some countries in the 2009 pandemic, it is not clear if is the case in European Countries for seasonal influenza (ECDC, 2007b), although small children up to four years old were the most affected age group for mild disease during the 2011-2012 season (ECDC, 2013).

2.1.3. Treatment

NSAIDs and antipyretics can be used to keep fever under control and to mitigate the general discomfort that afflicts the patient. On the other hand, the use of antivirals in seasonal flu is controversial, since they could be useful in shortening the duration of the illness, but there are few evidences of their efficacy in reducing complications, hospitalization or death (Jefferson T et al, 2014a, b, c).

They can also have side effects, so they are not usually recommended in otherwise healthy adults with ordinary influenza. For people in a risk group, the most important way of preventing the serious complications of flu is to be vaccinated and take general precautions, but antivirals can also be considered, even if European countries have different policies about their use. Currently two drugs are mostly recommended for this use: oseltamivir (whose trade name is Tamiflu) and zanamivir (Relenza).

Amantadine and other drugs of the same class should not be used any more as all circulating influenza viruses are resistant to them. Zanamivir and oseltamivir belong to neuraminidase inhibitor family, drugs that attack the flu virus replication cycle and prevent its spreading within the body.

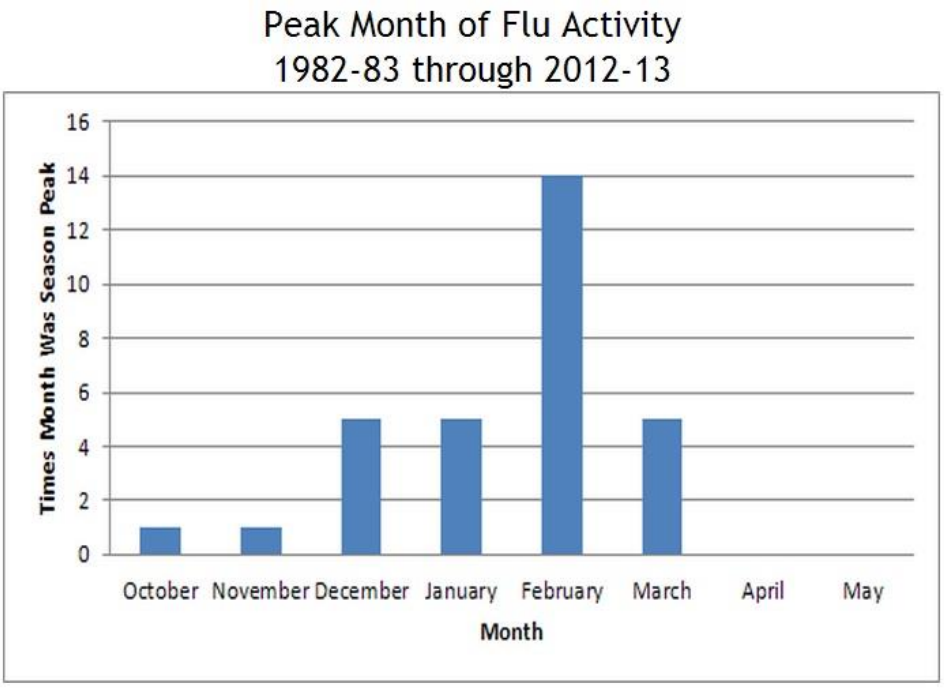
Oral oseltamivir or inhaled zanamivir (to be preferred in severely immunosuppressed patients) can so only be recommended when the flu is circulating or in laboratory-confirmed cases at high risk of complications, such as the elderly or those with underlying conditions like asthma or heart diseases, or in the general population when the illness gets complicated, requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

Anyway, it is important to stress that the efficacy of these drugs in reducing the risks of serious complications is still under scrutiny and in any case they can only be effective if they are taken early in the illness. The earlier the better. After 48 hours from the onset, drugs are not thought to help much at all: given within 12 hours of the illness starting the benefit seems to be greater than if they are not given for 24 hours, which in turn is better than 48 hours. For people at high risk of complicated influenza who have had contact with cases of the disease chemoprophylaxis could also be considered.

2.1.4. Epidemiology

Influenza spreads around the world in seasonal waves of epidemics and, despite being perceived as a soft disease, represents a serious public health problem that causes severe illnesses and deaths for higher risk populations. It is estimated that, in Europe, excess deaths due to influenza are from 8 deaths per 100,000 population in milder season to 44 per 100,000 in more severe, non-pandemic, ones. Applying figures from the US CDC to the EU population as a whole (around 500 million in 2010) would result in around 38,500 premature deaths each year, but with considerable season-to-season variation. The burden from influenza anyway is not only about its lethality. In addition, the socio-economic impact cannot be forgotten, since the disease produces large numbers of mild to moderate cases that result in time off work, losses to production and pressure and costs on the health and social care services.

In temperate regions, annual epidemics begin in autumn with peak during winter. Cold temperature facilitates the spread of influenza: cold air becomes drier and dehydrates mucus, thus preventing the body from effectively expelling virus particles. In addition, cold environments allow viruses to survive longer and to be more easily transmitted via aerosol. The annual recurrence of called flu seasons allows influenza activity to be sometimes predicted and tracked even if the exact timing and duration of flu seasons may vary. On the average, the peak flu activity in the Northern hemisphere in the last thirty years occurred in February, as shown in the following table from CDC website.



**During 2008-2009, flu activity peaked twice because of the 2009 H1N1 pandemic. Activity in the United States peaked once in in February due to seasonal influenza activity and then again in the Spring (June), with the first wave of 2009 H1N1 viruses A second, larger peak of 2009 H1N1 activity occurred in October, the peak of the 2009-2010 season.*

Usually, in almost all reporting countries, the most affected age group for mild disease is that of small children up to four years old, whilst the bigger group for hospitalized influenza cases is that of the elderly. (ECDC, 2013).

These data are collected each season through a constant monitoring of influenza and influenza-like illnesses conducted by several national and international institutions through extended networks of epidemiologic surveillance, which keep track of the number, localization and age distribution of new cases. In parallel, an intense activity of virological surveillance allows researchers to characterize the different virus strains circulating, thus updating the composition of the vaccine to be developed for the following flu season.

In Europe ECDC gathers and analyzes data coming from the European Influenza Surveillance Network (EISN) on a weekly basis and issues a weekly report, called Weekly Influenza Surveillance Overview (WISO). EISN consists of contact points for influenza surveillance (epidemiological and virological) nominated by the Competent Bodies for surveillance of the Member States.

The European Surveillance System (TESSy) aims to contribute to reducing the burden of disease associated with influenza in Europe, and include collection and exchange of timely information on influenza activity, contribution to the annual determination of the influenza vaccine content, provision of relevant information about influenza to health professionals and the general public and contribution to European influenza pandemic preparedness activities.

2.2. Avian flu

2.2.1. Clinical information

Among influenza viruses, type A are the most common in nature. They are generally hosted by wild aquatic birds, but can occasionally transmit to other animals, including humans. Avian influenza A viruses usually do not infect humans but rare cases of human infection with avian influenza A viruses have been reported, usually following direct or close contact with infected poultry.

Since 1996, a particular strain of bird flu known as A(H5N1) has emerged. First identified in Southern China and Hong Kong, it may have been around for longer than that elsewhere in the Far East. The A(H5N1) viruses kill a high proportion of poultry that they infect. They also infect a surprisingly wide range of birds and animals, have persisted over time, and spread to poultry in a number of countries with poor infection control in poultry flocks.

A(H5N1) occasionally infects humans in contact with infected poultry. Because it causes severe disease in humans, it has to be taken seriously by European public health and animal health authorities. Though occasionally present in European wild birds, A(H5N1) viruses have never become established in poultry in Europe because of high levels of biosafety. An outbreak of human infections with a new avian influenza A (H7N9) virus was reported in China by the World Health Organization on April 1, 2013. Chinese authorities promptly acted and closed live bird markets in order to control the spread of the disease. H7N9 influenza seems to be less deadly than H5N1, but its pandemic potential is considered concerning by experts.

Signs and symptoms may vary, depending on which avian influenza A virus is responsible for the infection. If the infection is low pathogenic the patient will show symptoms characteristic for influenza-like illness – thus including cough, fever, sore throat – and typically conjunctivitis, but in some cases also lower respiratory disease like pneumonia, which would require hospitalization. Symptoms associated with highly pathogenic avian flu virus are much wider and include all those reported for low pathogenic infections, but also severe respiratory illness, multi-organ disease, sometimes accompanied by nausea, abdominal pain, diarrhea, vomiting. Cases of neurologic changes, like altered mental status or seizures, have also been reported. Avian influenza A virus infection in humans can only be diagnosed through laboratory testing, usually by collecting a swab from the nose or throat of the sick person at the beginning of the illness and analyze it in a laboratory with a molecular approach or by trying to grow the virus.

Avian viruses do not transmit efficiently from person to person. Some cases of limited, non-sustained human-to-human transmission have been reported for H5N1 virus and some evidence points to limited person-to-person spread in rare circumstances also for the most recent H7N9 that spread in China. In any cases, healthcare personnel caring for patients with suspected or confirmed influenza A virus infection should wear recommended personal protective equipment and follow recommended infection control measures (standard, droplet, contact, and airborne precautions).

2.2.2. Categories at risk

Persons more at risk of being infected are those that work and/or live in close contact with poultry. In these circumstances, children may be at higher risk than adults and this could be due more to their rash behavior rather than their constitutional susceptibility. The European Centre for Disease Prevention and Control

(ECDC) included these persons in the “low but real risk” group. A second category is the one that comprehend those at theoretical risk of being exposed to the virus: healthcare workers, veterinarian, some ornithologists and hunters. Standard hygienic precaution to protect against other kinds of infections from birds – such as campylobacter and salmonella – should also be sufficient to protect against avian viruses such as H5N1 and H7N9. The majority of H5N1 cases have occurred among children and adults younger than 40 years old. Mortality has been highest in people aged 10-19 years old and young adults. As for H7N9, a prevalence of older males among infected patients was found by researchers but the reasons behind this unusual distribution are still unknown.

2.2.3. Chemoprophylaxis and Treatment

For avian flu, CDC and WHO currently recommend oseltamivir or zanamivir, two of four prescription antiviral medications currently licensed for use. Analysis on H5N1 circulating viruses suggested that most viruses are susceptible to these antivirals but also revealed some evidence of resistance to oseltamivir being identified in viruses isolated from some human cases.

The WHO reported that, according to laboratory tests, H7N9 viruses are sensitive to antiviral neuraminidase inhibitors (oseltamivir and zanamivir) but there is little experience with the use of these drugs for the treatment of H7N9 infection. Anyway, CDC recommended the use of oseltamivir or inhaled zanamivir chemoprophylaxis, especially for those considered at high-risk of exposure, which means household or close family member contacts of a confirmed or probable case. CDC also recommended treatments with a neuraminidase inhibitor medication for symptomatic close contacts. Healthcare workers that had close contacts with a confirmed or probable case, maybe during bronchoscopy or intubation, or handling inadequately screened/sealed body fluids without use of recommended personal protective equipment, are considered at a moderate risk of exposure, which correlates with an unknown risk of transmission; for these cases, antiviral chemoprophylaxis could be considered. Administration of chemoprophylaxis should begin as soon as possible after first exposure to the confirmed or probable case.

An adjuvanted vaccine against influenza A (H5N1) virus has been recently approved by the US Food and Drug Administration (FDA). It will be added to the US national stockpile as a second vaccine option but will not be available for commercial use or purchase. A vaccine against H7N9 is being tested in clinical trials.

2.2.4. Epidemiology

The most highly pathogenic strain known of avian influenza virus is H5N1, which spread throughout Asia and caused more than 600 sporadic cases of human infection in 15 countries since November 2003, with an estimated mortality rate of approximately 60%. The quick diffusion of H5N1 from Asia to Europe was probably due more to intense poultry trades than to bird migrations.

In 2012, no outbreak of highly pathogenic avian influenza (HPAI) in poultry or wild birds was reported in Europe while epidemics were reported in Africa, Australia, North America, the Middle East and especially in Asia, where the majority of outbreaks emerged, the subtype H5N1 being mainly responsible for these (ECDC, 2013).

H7N9 Chinese epidemic is being constantly monitored by the WHO in order to identify every possible sign of diffusion outside China or mutations that could provide the virus with the capability to spread from human to human. As far as February 2014, no cases of sustained human-to-human transmission have been confirmed, while many patients report a recent history of exposure to live poultry, which are suspected to be a main reservoir for the virus (Xian Qi, 2013).

H7N9 followed a similar seasonal pattern to H5N1 bird flu, with a second wave of infections in autumn and winter following its onset in spring 2013. As far as 20 February 2014 the total toll of infections was up to 361, with 112 deaths. At the same time, no cases of H7N9 infection have been reported, and the new H7N9 virus has not been detected, in people or birds outside of China and Taiwan. In January 2014, Canada has reported the first case of human infection with avian influenza A (H5N1) virus ever detected in the Americas, in a traveler who had recently returned from China. It is important to note that an avian flu pandemic may occur concurrently with the seasonal flu, thus increasing the chance of complications due to the combination of the two diseases.

2.3. A(H1N1) flu

2.3.1. Clinical information

In April 2009, a new strain of influenza A virus, belonging to the subtype H1N1, was identified. The virus was generated by a triple reassortment of bird, swine and human flu viruses, and showed a strict homology with swine flu viruses that, in the past, proved to be pathogenic for humans. It was unrelated to the human seasonal H1N1 viruses that have been in general circulation among people since 1977. Compared to seasonal influenza, H1N1 influenza had a higher frequency of pulmonary complications, including serious forms of viral pneumonia, which are harder to treat than bacterial pneumonias usually associated with seasonal influenza, often leading to ARDS.

Ways of contagion are pretty much the same as seasonal flu but there have been contrasting observations regarding contagiousness: the World Health Organization (WHO) reported that the H1N1 virus was probably more contagious compared to the seasonal one, while an article on the *New England Journal of Medicine* claimed the opposite about its transmissibility in households, compared to similar outbreaks in the past (Cauchemez S et al., 2009).

It is important to note that eating pork meat did not constitute a possible source of infection The name “swine flu” was due to the similarity between the combination of genes found in the new strain and that from some other swine-origin H1N1 influenza viruses, even if misconceptions were common on this point in populations at the time of pandemic. A correct diagnosis of H1N1 swine flu infection may only be obtained through testing of a nasopharyngeal, nasal or oropharyngeal tissue swab from the patient. Since 2010, a test based on molecular biology technique with 96% accuracy has been available.

2.3.2. Categories at risk

H1N1 influenza displayed a characteristic feature in terms of age sensitiveness, since adults, particularly those over 60, had some degree of immunity. According to CDC, 75% of patients were younger than 20, 10%

than 2 and only 10% were older than 40 years. In addition to chronic diseases, like for seasonal flu, pregnancy and obesity were considered strong risk factors for complications that required hospitalization.

2.3.3. Treatment

Antibodies to the seasonal H1N1 virus did not protect against the pandemic H1N1 swine flu virus circulating in 2009. The virus developed resistance to amantadine and rimantadine, while some rare variants also showed resistance to oseltamivir (Uyeki, 2014). Most patients recovered within one week, so antiviral treatments had to be used only when strictly necessary, as judged by the doctor, especially in case of hypoxia, hypotensive shock or sensory alterations. Also, prophylactic treatment with oseltamivir or zanamivir had to be considered for higher risk individuals that had been exposed to a patient with influenza (WHO, 2010).

Use of antivirals was supposed to significantly reduce the risk of pneumonia but some of these findings have been contested by an analysis carried out by the Cochrane Collaboration (Jefferson T, 2014a, b, c), which found no clear evidence that these drugs prevented lower respiratory tract infections or other complications of influenza. Antibiotics could become necessary in case of bacterial infections that may come together with H1N1 influenza. Vaccines for H1N1 swine flu are available.

2.3.4. Epidemiology

The initial warning of the 2009 pandemic came in the United States Centers for Disease Control and Prevention (CDC Atlanta) bulletin on 21 April 2009, with the description of two children in southern California (USA), who got a febrile respiratory illness provoked by a novel swine flu virus, without having had any known contact with pigs (ECDC, 2010, MMWR, 2009). Later, it emerged that the same virus had already caused epidemics in Mexico unusually late in their influenza season (in early March 2009), but only when cases of severe influenza appeared in seemingly healthy people in Mexico City, the virus was isolated.

Further studies in Canada and the USA showed that the Mexican and Californian viruses were indistinguishable: at this time, this virus already met the WHO criteria for a pandemic strain, well past WHO pandemic Phase 4 and probably beyond any possibility of successful containment.

On 25 April 2009, on the advice of an Emergency Committee convened under the International Health Regulations (IHR) 2005, the Director-General of WHO, Margaret Chan, declared that a Public Health Emergency of International Concern was underway. Within a few days, the same pandemic virus had been reported outside of the Americas and the transmission in New York City was increasing. The same Director General, again acting on the advice from the WHO Emergency Committee (IHR), declared then Pandemic Phase 5 on 29 April 2009. Since there are no qualitative differences between Phases 5 and 6, this implied that the pandemic was unstoppable and uncontainable, even though a number of more formally planned actions (such as switching to production of a pandemic strain vaccine) would not start until Phase 6. The initial reports on the new influenza A virus suggested that there were a significant number of severe respiratory illnesses and deaths in Mexico including among young, previously healthy, persons. This had prompted the Mexican authorities to take extreme measures early on, closing schools and banning public gatherings. Once more detailed reports from the USA were available it became clearer that the new virus was, in fact, not causing much severe disease as was reflected in ECDC's early risk assessment.

There was a considerable delay before pandemic Phase 6 was formally declared on 11 June 2009, as even though it was quite clear that the epidemiological criteria for this phase had been reached, there had been pleas by some countries at the World Health Assembly in May for delay and more reflection. This meant that by the time Phase 6 was actually declared, the ECDC estimated that 74 countries worldwide (26 of which were EU/EEA countries) had already reported over 27 000 cases of influenza A(H1N1), including 141 deaths. With the declaration of Phase 6, a number of actions were automatically triggered at the country level, so many authorities needed to rapidly adjust their pandemic plans designed to deal with a more severe pandemic.

WHO declaration of Phase 6 in June 2009 raised many criticisms as the organization was accused of having been influenced by vaccine manufacturers to create alarmism. These accuses did not come only from those groups that constantly fight against vaccines, but also from medical journals and government officials. This provoked a raise of mistrust and suspicions, which in turn led to a diffuse sense of false alarm and in a loss of trust towards public health institutions. WHO declared the formal end of the pandemic on 10 August 2010, with an estimated global number of victims of 18.500 deaths, not so many in comparison with a common flu season.

This figure anyway referred only to laboratory-confirmed cases, which were a minority, especially in developing countries. Further studies increased this burden. A paper published on the *Lancet Infectious Diseases* in 2012 raised the estimated number of deaths to more than 284.000 (Dawood F, 2012). About 25-30% of official deaths were in previously healthy people under 65 years of age, so even if milder than expected, the pandemic provoked a small but real risk of severe disease and death from in all healthy adults and children. As mentioned previously, there was a higher than expected rate of ARDS.

When the vaccines were made available, they were greeted with variable enthusiasm to vaccinate among the health professionals, with only some countries achieving high coverage among the whole population or targeted risk groups. The lack of widespread acceptance of this vaccine is partly due to the difficulty in transmitting the complex risk communication message that essentially told people that unless they were in a risk group (young children, people with chronic ill health and pregnant women), the chance of severe disease following infection was very low, but not irrelevant, given the peculiar characteristics of the disease.

2.4. Middle East respiratory Syndrome (MERS)

2.4.1. Clinical information

Coronaviruses are a large family of viruses that may cause a wide range of disease in humans, primarily infections at the upper respiratory and gastrointestinal tract. They are also held responsible for a significant percentage of all common colds in adults. Infections with coronaviruses are quite common among humans and they can spread from an infected person to others through the air, by coughing and sneezing, and close contact, such as shaking hands or touching contaminated objects then touching your mouth, nose, or eyes.

One of the most renown diseases caused by coronaviruses is the Severe acute respiratory syndrome (SARS), which spread initially in Asia and then in other parts of the world in 2003, infecting 8.096 persons and causing 774 deaths, with a case fatality ratio of 9.6%. However, since 2004, there have not been any known cases of SARS reported anywhere in the world.

In September 2012, a SARS-like virus was reported in Saudi Arabia. Further investigations identified it as the responsible of a new severe acute respiratory illness that has been called Middle East respiratory Syndrome (MERS). Retrospectively some infections have also been detected in humans with severe acute respiratory illness in Jordan in the spring of the same year. This new coronavirus (MERS-CoV) is different from the one that provokes SARS, even if they have been both found in bats (Memish et al., 2013) and camels (Haagmans et al., 2013).

Typical symptoms for MERS include fever, cough, shortness of breath and diarrhoea, but also more severe complications like renal failure and severe acute pneumonia, which may often lead to death. As reported by WHO, severely immunocompromised patients could also present with atypical signs and symptoms. Although the primary site of infection has been the respiratory tract, approximately one-third of patients have experienced gastrointestinal symptoms.

Even if MERS-CoV may spread from person to person in the same ways other coronaviruses do, the risk of sustained human-to-human transmission appears to be very low; this is due to the fact that MERS-CoV infects a lower number (about one fifth) of lung cells compared to other infectious diseases, which means that the number of virus particles needed to be inhaled to cause infection is larger than other cases. General hygiene measures for prevention of infections are still valid for MERS: washing hands with soap and water, cover nose and mouth with a tissue when coughing or sneezing, avoid touching eyes, nose and mouth with unwashed hands, avoid close contacts with sick people.

2.4.2. Categories at risk

To date, there is very limited information on transmission and other features of MERS-CoV due to the small number of cases reported so far globally. Overall, the median age of MERS-CoV patients is 50 years and the majority of them (64.5%) are males, while fatal cases were more likely to have an underlying medical condition. Only few cases have been reported in children less than 5 years of age.

So far, transmission has occurred in family or co-worker clusters, as well as in healthcare facilities. Even if the mechanism by which transmission occurred is still unknown, there is no evidence of a sustained community transmission. Since transmission has occurred in healthcare facilities, healthcare workers are considered a category at risk of being infected and should consistently apply appropriate infection prevention and control measures.

2.4.3. Treatment

Persons who develop fever and symptoms of lower respiratory illness, such as cough or shortness of breath, within 14 days after traveling from countries in the Arabian Peninsula or neighboring countries, should be seen by their doctor and mention their recent travel.

At the moment, treatments for MERS-CoV are supportive. No specific treatments recommended for illnesses caused by MERS-CoV, neither a vaccine, are available. Medical care is supportive and to

help relieve symptoms. Recent studies identified a MERS-CoV receptor – DPP4 – that could be involved in the virus-human interaction; the development of DPP4 inhibitors could thus represent an effective treatment against this pathogen. Treatments with systemic high-dose corticosteroids, which were intended to reverse the progression of respiratory distress and to prevent lung fibrosis, appeared to have been unsuccessful.

2.4.4. Epidemiology

As far as 28 April 2014, nine countries have reported cases of human infection with MERS-CoV. All the patients were diagnosed or had travelled in Middle East. Apart from Middle East countries, cases have been reported in France, Germany, Italy, Tunisia and the United Kingdom. In all these countries, Germany being the only exception, there has been the occurrence of limited local transmission due to close contact with laboratory-confirmed or probable cases.

The source of the virus, the types of exposure that may lead to infection, the mode of transmission and the clinical pattern of the disease are still unknown. MERS-CoV has been detected in bats and in camels linked to a human case in Saudi Arabia. However, these findings are not enough to understand the chain of transmission of the virus, neither to identify its animal origin. For these reasons, it is not possible to give specific advice on prevention of infection regarding contacts with animal or animal products.

Bibliography

Cauchemez S, Donnelly CA, Reed C, Ghani AC, Fraser C, Kent CK, Finelli L and Ferguson NM (2009). "Household Transmission of 2009 Pandemic Influenza A (H1N1) Virus in the United States". N Engl J Med; 361:2619-2627

Council of Europe (2010) "The handling of the H1N1 pandemic: more transparency needed". 2010 Jun 7. Available from: http://assembly.coe.int/Documents/WorkingDocs/Doc10/EDOC12283.pdf (accessed 7 April 2011).

CDC Resources for Pandemic Flu. http://www.cdc.gov/flu/pandemic-resources/

Dawood F (2012). "Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study". Lancet Infect Dis 12: 687-695

Doshi P (2011). "The elusive definition of pandemic influenza". Bull World Health Org; 89: 532-538

ECDC official website.
http://www.ecdc.europa.eu/en/healthtopics/pandemic_preparedness/basic_facts/Pages/definition_of_pandemic.aspx

ECDC scientific panel (2007b). "Childhood immunisation against influenza".

ECDC (2010). “The 2009 A(H1N1) pandemic in Europe. A review of the experience”. Special Report. http://www.ecdc.europa.eu/en/publications/Publications/101108_SPR_pandemic_experience.pdf

Green MS, Swartz T, Mayshar E, Lev B, Leventhal A, Slater PE, Shemer J (2002). “When is an epidemic an epidemic?” Isr Med Assoc J.4(1):3-6

Haagmans LB, Al Dhahiry SHS, Reusken CBEM, Raj VS, Galiano M, Myers R, Godeke GJ, Jonges M, et al. (2013). “Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation”. The Lancet Infectious Diseases

Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, McGeer AJ, Neuzil KM, Pavia AT, Tapper ML, Uyeki TM, Zimmerman RK, Expert Panel of the Infectious Diseases Society of America (2009). “Seasonal influenza in adults and children – Diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America”. Clinical Infectious Diseases; 48(8):1003-32

Jefferson T et al (2014a). “Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children”. The Cochrane Library DOI: 10.1002/14651858.CD008965.pub4

Jefferson T et al (2014b). “Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments” BMJ; 348:g2545

Jefferson T et al (2014c). “Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments” BMJ; 348:g2547

Kelly H (2011). “The classical definition of a pandemic is not elusive”. Bull World Health Org; 89:540-541

Last JM (2001). “A dictionary of epidemiology”. Oxford University Press, Inc., New York, New York

Memish ZA, Mishra N, Olival KJ, Fagbo SF, Kapoor V, Epstein JH, et al (2013). “Middle East respiratory syndrome coronavirus in bats”, Saudi Arabia. Emerg Infect Dis

MMWR (2009) Centers for Disease Control and Prevention (CDC). “Swine Influenza A (H1N1) Infection in Two Children---Southern California, March--April 2009. 58:400–2.

Xian Qi (2013). “Probable person to person transmission of novel avian influenza A (H7N9) virus in Eastern China, 2013: epidemiological investigation”. BMJ 347: f4730.

Uyeki TM 2014. “Preventing and Controlling Influenza with Available Interventions”.

WHO (2010). “Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses”

WHO (2009). Pandemic Influenza Preparedness and Response: a WHO guidance document.

WHO (2013). Pandemic Influenza Risk Management: interim guidance document.

WHO press conference (2010). Transcript of virtual press conference with Keiji Fukuda, Special Adviser to the Director-General on Pandemic Influenza. Geneva: World Health Organization; 2010. Available from: http://www.who.int/entity/mediacentre/vpc_transcript_14_january_10_fukuda.pdf [accessed 7 April 2011]).