Approaches on H5N1 Avian Influenza Spreading in Relation with Human Health Risk

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Abstract Recent experiences with highly pathogenic H5N1 avian influenza have given the world its first advance warning that another influenza pandemic may be imminent. Given the serious consequences of past pandemics, this advance warning has stimulated a search for ways to prevent such an event from occurring through preparedness, rapid response and containment. The rapid response and containment strategy aims to stop, or at least slow the spread of pandemic influenza at the source of its emergence in order to minimize global morbidity and mortality.

Keywords Epidemiological · H5N1 · Influenza

1 Introduction

Influenza is one of the most spread and studied disease in the world, mentioned by Hippocrate in 412 bc., the first attested epidemic being documented in 1580. Since then, 31 pandemics were counted, of which three in the last century: 1918 (Spanish flu), 1957 (Asian flu) and 1968 (Hong Kong flu). Spanish flu was the most virulent, decimating the population at the end of First World War. There are detailed descriptions of three centers of contagion: Brest (France), Boston (USA) and Freetown (Sierra Leone). If the number of deaths in the period 1918–1919 exceeded twenty millions, it is estimated that a new imminent pandemic will sick 30% of the world population, determining between 20 and 100 millions of deaths [1]. The concern to avoid this calamity is coordinated by international organizations as WHO, FAO, EIO. At European level this concern was emphasized by preparing national preventing plans for the potential pandemic in 18 of the 25 European Union countries. These plans consist of programs of rapid preparation for efficient vaccines and the

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assurance of safety stocks for anti-flu medicines. Totally, 24 European countries including Romania, have achieved such plans at the end of 2005, countering more than 30 measures, which fast implemented in case of pandemic, will minimize the its impact.

A flu pandemic starts in one country (usually in the South-East of Asia) and spreads rapidly worldwide (in 2–4 weeks) [2]. The pandemics of 20th century were developed 2–3 years with secondary/tertiary peaks till the immunization of the susceptible population, with notable differences between pandemic and inter-pandemic periods.

Flu is a problem of public health even in the inter-pandemic periods, each season of fall-winter determining an excess of hospitalization due to pneumonia and other acute respiratory infections. Although the flu etiology isn't always confirmed, its prevalence is considerable in extreme ages: children under 3 year old and people beyond 65 year old. During epidemic periods, happening once in 3–4 years due to antigenic shifting, the mortality in aged people increases 3–5 times. At present, the circulating human stems are A H1N1, A H3N2 and B. The pandemic stems appear due to recombining among human and aquatic birds stems. This recombining type appears frequently in the South-East of Asia due to the proximity of man-birds and density of population [3]. In this area there is no flu-seasonality and the surveillance must be extended the whole year. Other scenarios for the emergence of pandemic types confer a role to the direct human transmission of avian stems which acquire human tropism, leading to man to man transmission. This possibility is carefully investigated for avian types A H5N1, circulating from some years in the South-East of Asia. It was suggested also, the possibility of recycling old pandemic types, remained latent in an animal reservoir which could be transmitted to young generations, highly susceptible from the immunologic point of view [4]. This scenario explained the re-apparition of H1N1 type in 1977–1978 (Table 1).

Epidemiological signals are likely to be the most sensitive and reliable indicators of a transition from inefficient, non-sustained human-to-human transmission of the virus to efficient and sustained transmission [5]. The detection of clusters of cases, closely related in time and place, is likely to be the most important epidemiological signal of such transition [6]. An epidemiological signal may manifest itself as an

Table 1 The flu pandemics of 20th century

Period	Type	Attack rate	Mortality	Comments
1918–1919	H1N1	40%	20%	Mortality in all groups of age by haemorragic pneumonia
1957–1958	H2N2	< 10%	2%	Mortality in extreme ages
1967–1968	H3N2	< 10%	1%	Crossed immunity due to the maintain of NA
1977	H1N1 H3N2	20%	2%	Mortality only in persons born after 1956

increase in the number of persons with unexplained respiratory illness in a defined area over a short period of time. This pattern of unexplained respiratory illness should be different from that usually seen in the area. Observations with H5N1 infections to date suggest that a cluster of five closely related cases (including the index case) in which human-to-human transmission is suspected would constitute a signal [7].

To date, cases of human infection with the H5N1 virus have been sporadic and rare events, even in areas where the virus is widespread in poultry. Any transition in the behaviour and epidemiology of the virus indicating improved human-to-human transmissibility will most likely result in a visible event sufficiently "unusual" to be picked up by alert clinicians or the public health system.

2 The Surveillance of H5N1 Avian Influenza Virus Dissemination

The dates from the first half of 2005 resulted from the surveillance of H5N1 dissemination suggest that:

- The host spectrum of H5N1 was extended from chicken to other bird species;
- Recent epidemics in aquatic/terrestrial birds lead to a broad area of spreading for avian influenza;
- Different isolated H5N1 may be grouped in distinct genotypes with distinctive pathogenic and epidemic potential;
- The transmission of H5N1 from birds to man is certain and several control measures are imposed in subjects with professional risk;
- The early diagnose of human avian flu cases is difficult and this alternative must be carefully assessed;
- The experimental tests of anti-H5N1 vaccines in humans should be accelerated.

The flu virus H5N1 continues its evolution both as host spectrum and as virulence. In 2002, major epidemics in aquatic and terrestrial wild birds (*Ardeidae* sp, *Falcon* sp.) were noticed. Wild ducks and gooses (*Anatidae* sp, *Anser* sp) represent the natural reservoir and the source of flu viruses type A, for all the other mammalian and bird species. Usually, the virus H5N1 doesn't produce the illness in aquatic birds, but the high mortality in some Chinese lakes indicates the selection of some virulent types [8]. The study of H5N1 types emphasized the separation of two clusters corresponding to the geographic migration route of birds (Eurasiatic and American): highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI) (Table 2).

The pathogenity isn't determined by the geographical distribution, anywhere being possible the appearance of highly pathogenic types. Without exception, the very pathogenic types belong to sub-types H5 and H7, the neuraminidase not being essential for the virulence [9]. The highly pathogen viruses in some bird species may act as opportunistic in other species. Among domestic species, the chickens and the

Table 2 The morphological and clinical differences in avian flu infections

Type	Replication site	Infection	Simptomatology
LPAI	Respiratory/digestive tract	Local	Absent/moderate
HPAI	Respiratory/digestive tract; Vascular endothelium	Systemic	Severe/lethal

Table 3 Structural differences among HA of H5N1 types

Types	Cleavage sites HA	Cleavage enzymes	Aminoacides at cleavage sites
LPAI	Unique	Bacterial proteases	Arginine
HPAI	Multiple	Viral and ubiquitor proteases	Different basic amino acids

turkeys are highly susceptible to HPAI types, while the ducks and the gooses are resistant. The transmission route for all avian flu viruses is fecal-oral (especially in aquatic birds) and by air (especially in domestic birds living in high density).The post-proteolytic activation of H5N1 hemagglutinin (HA) is essential for the infective power, dissemination-excretion and virulence (Table 3). The viruses LPAI are activated by enzymes acting in blood coagulation, or by bacterial proteases present in normal conditions, in different bird species [10, 11]. The acquisition of new cleavage sites in flu HA sequences is determinant for the conversion of non-virulent stems in virulent ones and for the host spectrum change [12]. In last 5 years, 4 new types of flu viruses type A have appeared: H1N1 and H2N7 (in USA), H9N2 in Holland and H5N1 in South-East of Asia and even in Siberia and Kazahstan. It is difficult to predict the pandemic potential of these stems but it is obvious that H5N1 evolution imposes a high alert level.

The A viruses type H7N7 and H3N8 were isolated in Europe in horses. At present, three A viruses are circulating in Europe, being found in pigs: H1N1 (with an avian variant), H1N2 and H3N2 [13]. The H1 hemagglutinin from pigs is similar with the human H1 in proportion of 80%, and pigs represent a potential reservoir for the appearance of avian/human recombining.

3 The Possibility of Human Transmission for H5N1 Avian Influenza

Generally, the avian viruses aren't capable to be directly transferred in humans. The communicated cases starting from 1997, when an 3 year old boy died due a pneumonia complicated with a Reye syndrome and a H5N1 virus was isolated from him, resulted from infections with extremely concentrated doses of virus in immunodepresive persons. In 1997 in Hong-Kong 18 cases of H5N1 avian flu with 6 deaths were reported. These cases didn't confirm the possibility of inter-human transmission, but the fact that the avian viruses are not replicative in humans [14]. The extreme measure of bird sacrificing was selected as the only measure to avoid

Table 4 Significant events in the evolution of H5N1 types

Year	Clinical/epidemiological event
2002	The appearance of HPAI types in ducks and other aquatic birds in China
2003	Familial focus of human avian flu with two deaths in Hong Kong
2003–2004	Extended H5N1 epidemics in birds, HPAI types in domestic birds isolated in 9 countries from Asia[a]
2004	Isolation of virulent genotype Z+ in birds
2004	Notification of HPAI types dissemination through Siberia
2004	New human cases in Vietman (37 deaths at 76 cases), Thailand (12/17) and Cambodia (4/4)
2004	The first cases of inter-human transmission
2005	The cytokine balance – pathogenic element in human infection
2005	Other susceptible species (felines) possible vectors of avian flu
2005	Infections H5N1in pigs – hosts generating recombining with human tropism

[a]Vietnam, Thailand, Indonesia, Cambodia, Laos, Korea, Japan, Malaysia, China

Table 5 Genomic determinants of human tropism and virulence for H5N1 types

Involved gene	Molecular transformation	Result
HA	New cleavage sites	Enlargement of host spectrum
PB2	Glu 627→Lys 627	Human virulence
NS1	Only for HPAI types	IFN antagonist
NA	Depletion of 19 aminoacids	Higher pathogenesis, resistance to Oseltamivir

a pandemy. In the following years, the permanent circulation of H5N1 viruses has determined the extent of host spectrum and the increase of human pathogen potential (Table 4).

The possibility of man to man transmission of H5N1 avian influenza is the critical point in the initiation of a new pandemic. This viral characteristic becomes consistent in case of highly pathogenic viral isolates (HPAI) characterized during 2004–2005 (Table 5). The old isolates were less pathogenic in birds and mammalians. However, in rare cases (healthcare workers carrying for patients with avian flu) the H5N1 serum conversion was noticed, although the respiratory symptoms were missing.

4 Aspects of Public Health

Influenza is the most frequent infection of the upper respiratory airways. It is estimated that in every season, between November and March, 10–20% of the population get one flu episode, at least. Children are 2–3 times more susceptible than adults. In Romania, every year approx. 20,000 cases need hospitalization and more than 2,000 deaths are set down to flu, especially in ages upon 65 years. and chronic cardio-respiratory illnesses. The previous dates are 3–5 times multiplied during flu epidemics. The schoolchildren have a major contribution to the

disease dissemination. The families with schoolchildren aged 6–14 years are much more exposed, influenza affecting half or even more of their members. Influenza is transmitted not only by air, but through contaminated objects also, for example a door handle, a telephone receiver.

The simptomatology represents the most used criteria for diagnostic. The general symptoms (fever, chills, muscle pains, headache) prevail upon respiratory symptoms (dry cough, obstructed nose). The symptoms start in 1–2 days from the infective contact, last 4–5 days, followed by the convalescence with or without complications.

The incubation period is 1–3 days, the virus excretion precedes the disease beginning and continues more 3–5 days. The transmission route is by air or by contact. The children have a larger period of viral excretion and a higher attack rate (especially schoolchildren represents the main vector in flu dissemination in collectivities).

The acute debut consists of fever, muscle pain, nasal congestion, dry cough. The symptoms last 3–7 days, which make that flu not to differentiate from other acute respiratory infections (Table 6).

The most frequent complications are: pulmonary (primary viral/secondary bacterial pneumonia), renal and cardiac impairment, encephalitis, Reye syndrome (hepatic failure and encephalopathy).

Table 6 Clinical and laboratory data for a severe prognostic

Clinical data	Laboratory data
Respiratory frequency > 30/min	Urea > 7 mmol/l
Dyastolic blood pressure < 60 mmHg	Albumine < 35 g/l
Age > 65 years	Hipooxemie pO2 < 8 kPa
Atrial fibrillation	Leucocytes < 4,000
Associated severe chronic diseases	Leucocytes > 20,000
Drowsiness, confussion	Positive hemoculture

5 Risk Assessment

If this assessment based on relevant information concludes that the signal requires further investigation, several activities should follow immediately.

5.1 Diagnostic Confirmation

Laboratory specimens should be sent to a WHO H5 reference laboratory for identification, verification and confirmation of the causative agent, even when prior cases have been confirmed in the affected country.

5.2 Burden Assessment

The available data generated during the signal investigation will be used to characterize the disease pattern, determine the population at risk, and identify factors affecting transmission pattern and control activities (such as geographical location of outbreak, movements in an out of the area). Where feasible, modelling should be undertaken to help predict spread, and anthropological investigation should be undertaken to examine socio-cultural factors that may have implications for control interventions.

5.3 Needs Assessment

Based on the analysis of the burden and the available national resources for rapid response and containment, the need for additional support will be assessed, which may include personnel (such as epidemiologists, clinicians, logisticians, laboratory experts, experts in communications and social mobilization), supplies (such as personal protective equipment and antiviral drugs).

5.4 Request for Antiviral

Should the assessment establish a need to deploy a portion of the antiviral drug (Oseltamivir) from the global stockpile.

5.5 Outbreak Communications

A communication plan will be formulated to ensure that all information relevant to outbreak assessment and response is communicated to the general public, international community and partners. Risk communication, including key messages to the public, will be disseminated swiftly.

6 Immediate Control Measures

Routine control measures aimed at reducing opportunities for further transmission to occur should be initiated as soon as preliminary investigations of the detected clusters of cases confirm an existing epidemic. These measures should be strengthened and intensified concurrently as the risk assessment is being conducted in order not to loose time.

Recommended measures include traditional, standard interventions used during outbreak control. At present, many of these measures are being applied routinely in H5N1 outbreaks characterized by sporadic human cases with no evidence

of efficient human-to-human transmission. These measures should be introduced immediately and should not await laboratory confirmation of the causative agent.

Immediate measures include:

- Isolation of clinical cases of moderate-to-severe respiratory disease in respiratory isolation rooms or single rooms;
- Identification and voluntary home quarantine of persons who have had close contact with a case, and their daily monitoring for symptom onset;
- Antiviral drugs for the treatment of cases and for the targeted prophylaxis of close contacts;
- Strict infection control and the use of personal protective equipment during the delivery of health care in health care facilities.
- Intensive promotion of hand and cough hygiene.
- Domestic cleaning, using household cleaning products, to reduce transmission via fomites and from infectious respiratory secretions on surfaces.
- Appropriate waste management and disposal.
- Informing the public of the outbreak and initiating social mobilization measures.

7 A Two-Phased Containment Strategy

The rapid containment strategy is implemented in two phases:

1. Immediate implementation of standard measures aimed at reducing further transmission. In this phase, isolation of cases, active case finding and contact tracing are undertaken and antiviral drugs are administered, in a targeted way, to persons identified during these activities.
2. Implementation of exceptional measures, including wider prophylactic administration of antiviral drugs, quarantine, and the introduction of social distancing measures.

During both phases, surveillance activities should be intensified in the outbreak zone and the surrounding areas to guide the continued implementation of public health measures and monitor their impact. Geographically surrounding countries, or those that are linked through communication routes, may need to be on the alert for possible introduction of potential cases.

7.1 Phase One: Standard Measures to Reduce Transmission

Activities in this phase are based on the assumption that an emerging pandemic virus will not immediately cause the explosive increase in the number of cases seen during a full-fledged pandemic. Assuming that the number of new cases is still manageable,

activities should concentrate on investigation and laboratory confirmation of cases, appropriate management of cases in a safe environment, implementation of infection control measures within the health care setting, contact tracing and monitoring, use of antiviral drugs for the treatment of cases and targeted prophylaxis, intensified surveillance and the real-time reporting of data. The interventions at this phase aim to reduce opportunities for further transmission to occur and thus, ideally, prevent the virus from becoming well adapted to humans.

7.1.1 Case Management

In the initial phase, when a manageable number of cases is assumed, clinical cases should be hospitalized and managed in single rooms if possible. Once laboratory confirmation of infection is available, and the number of cases exceeds the available number of single rooms, patients may be hospitalized in group isolation rooms adapted to negative pressure facilities. Patients should be transported to these facilities by trained staff wearing appropriate personal protective equipment and using designated vehicles.

To minimize the risk of nosocomial transmission, persons showing signs of mild, moderate or severe respiratory illness must be assessed in premises separated from those where confirmed cases are being managed. Options for doing so include the establishment of fever clinics, home visits by medical staff, drive-through consultation services, and other methods of triage and diagnosis that limit opportunities for exposure.

7.1.2 Antiviral Treatment and Targeted Prophylaxis

In the containment zone, antiviral drugs should be administered to cases of moderate-to-severe respiratory illness to reduce morbidity and mortality, and to their contacts to reduce ongoing spread. Priority access to antiviral drugs and other medical interventions is expected to work as an incentive that increases the willingness of patients and their contacts to comply with recommended public health measures under what are likely to be stressful and demanding conditions.

Local and national authorities will define jointly (within the outbreak zone) the households, schools, workplaces, health facilities or other settings where the delivery of antiviral drugs, personal protective equipment, and other medical supplies should be targeted.

7.1.3 Intensified Surveillance

Once the reported signal is confirmed to be an influenza alert requiring immediate intervention, surveillance activities should be intensified immediately within the initial outbreak zone. The surrounding area, and the geographically “at risk” areas, should also intensify their surveillance and remain on alert for possible introduction of the virus. Within the outbreak zone, enhanced detection and reporting

of individual cases and clusters of human-to-human transmission can be achieved through institution of active surveillance to identify all potential cases, and increased diagnostic suspicion.

7.1.4 Contact Tracing

During investigation and response, contact tracing must be implemented to include the identification of extended social networks and the travel history of all cases and contacts during the preceding 14 days. Contacts of cases should be traced and followed up for evidence of respiratory illness for at least 7 days after last contact. If the number of contacts requiring investigation is large, follow up should be prioritized based on:

- Heightened probability of infection, such as contact with a laboratory-confirmed case
- Duration and closeness of this contact
- A high-risk exposure, such as unprotected patient care
- Exposure in settings that could accelerate spread to large numbers of contacts, such as when a confirmed case worked in a school or attended a large gathering. Whenever possible, cases should be isolated in health care facilities to maintain strict infection control. Contacts should be advised to remain at home (voluntary home quarantine) for at least 7 days after the last contact with a person under investigation.

7.1.5 Monitoring Contacts for Signs of Illness

The public should be informed of the most common symptoms which are fever and/or cough. They should receive instructions on how to self-monitor for fever post exposure, which should be performed for at least 7 days following the last contact with a possible case of influenza. People should immediately report the onset of fever and other symptoms to the health authorities and remain in voluntary home quarantine during the duration of self monitoring.

7.2 Phase Two: Exceptional Measures, Including Use of the Antiviral Stockpile

7.2.1 Voluntary Quarantine

Experience during the SARS outbreak suggests that quarantine, applied on a voluntary basis, may be as effective as enforced quarantine. However, for voluntary quarantine to succeed, the public will need to be informed and sensitized on benefits.

Local authorities should apply quarantine in the following situations:

– Exposure has occurred in a defined group of persons as, for example, in a household setting, at the workplace or school, or at a well-defined and circumscribed public gathering
– Exposure has occurred in a defined site or building (such as a hospital or an apartment building)

Quarantine may involve confinement at home or in a designed facility with appropriate equipment. Persons in home quarantine may need to be provided with food, access to communications, psychosocial support, and supplies of their usual medications, especially for chronic conditions.

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