LESSONS FROM THE A H1N1 2009 INFLUENZA PANDEMIC

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The recent emergence of swine-origin H1N1 (swl) influenza virus that have transmitted to and spread among humans has fueled concerns that the outbreak is the start of a new pandemic. Many H1N1 swl influenza outbreaks have been registered internationally during the May–July 2009. In this paper, we investigate relations between the evolution of reported cases number and the effectiveness of **pandemic** control measures. Ten topics were considered representative from the first three months of pandemic spreading in Europe and the lessons were compared with the US response to the H1N1 (swine) flu outbreak. We analyze the latest developments and examine what things we can learn from the present situation and what might be done to combat the threat. The lessons may only be valid for a few months if major changes (*e.g.*, vaccine technology and availability, antiviral stockpile size, antiviral resistance) occur, but some of the parameters can still help guide pandemic planning measures and will continue to have relevance.

Key words: Human influenza; Swine influenza; Surveillance; Pandemic.

INTRODUCTION

On June 11, 2009, the World Health Organization raised the pandemic alert level from Phase 5 to Phase 6 indicating that an influenza pandemic is in progress. The novel influenza A (H1N1) virus will be referred in this paper as "pandemic H1N1 influenza virus of swine lineage" or H1N1 swl. After three months of surveillance is evident that the pandemic virus continues to disseminate, co-circulating with seasonal influenza strains, may be re-assorting with them or even mutating by giving origin to new pandemic influenza viruses. The number of new cases that were reported in past weeks was actually the largest number reported since the beginning of the outbreak, both in US and in Europe, in UK. W.H.O. is now reporting beyond 140,000 cases of this new virus in more than 100 countries and 732 associated deaths (July, 19th). It is very unusual for summer time of year in Northern Hemisphere to still be having so many countries reporting regional and widespread activity and that is just one feature that helps know that what we are seeing this year is quite different than what we usually see with seasonal influenza. In terms of the virologic testing the new H1N1 virus is now making up more than 90% of all the typed isolates. CDC is estimating that those reported cases are really just the tip of the iceberg. At least a million cases of these new H1N1 virus infections may occur in the United States so far this year and, in some metropolitan areas (New York), about 6% of their community members have had an illness that were consistent with the new virus.

MATERIAL AND METHODS

Search strategy and identification of studies. A literature search was carried out using the PubMed database with key words: human influenza, swine influenza, and surveillance pandemic. We included any study published on line in the following sites:

World Health Organization http://www.who.int/csr/disease/swineflu/updates/en/index.html

Pan American Health Organization, http://www.paho.org

US Center for Disease Control and Prevention (CDC), http://www.cdc.gov/h1n1flu/

European Center for Disease Control and Prevention, http://ecdc.europa.eu/

Ministry of Health, Romania, http://www.ms.ro

ProMED-mail <http://www.promedmail.org> ProMED-mail is a program of the International Society for Infectious Diseases <http://www.isid.org>

We identified additional articles by searching PubMed and the reference lists of articles. We also made a hand search in textbook of influenza and a bibliographic search of world-leading specialist's names. We limited our search to English language papers published between March–June 2009. Same documents that are available in draft form the US Department of Health and Human Services or from ECDC that were also referred.

THE CHRONOLOGY OF THE A H1N1 2009 PANDEMIC

In March and early April 2009, Mexico experienced outbreaks of respiratory illness and increased reports of patients with influenza-like illness (ILI) in several areas of the country. On April 12, the General Directorate of Epidemiology (Mexico DGE) reported an outbreak of ILI in a small community in the state of Veracruz to the Pan American Health Organization (PAHO) in accordance with International Health Regulations. On April 23, several cases of severe respiratory illness laboratory confirmed as swine-origin influenza A (H1N1) swl virus (swl stands for swine lineage) infection were communicated to the PAHO. Sequence analysis revealed that the patients were infected with the same influenza A (H1N1) swl strain detected in two children residing in California. Previous, few instances of human-to-human transmission of other swine influenza viruses have been reported. On the contrary, in spring 2009, several findings indicate that transmission in Mexico as well as in US involves person-to-person spread with multiple generations of transmission[1].

To accelerate confirmation of disease in additional patients, the World Health Organization (WHO) Influenza Collaborating Center in Atlanta, Georgia, has placed the genetic sequence of influenza A (H1N1) swl from California in GenBank. Specific primers have been developed and distributed through the WHO Global Influenza Surveillance Network (GISN) to reference laboratories throughout the world.

The epidemiologic characteristics of this outbreak underscore the importance of monitoring the effectiveness of community mitigation efforts, non-pharmaceutical interventions, and clinical management practices in anticipation of a possible pandemic.

Novel influenza A H1N1 swl is a new flu virus. The virus is infecting people and is spreading from person-to-person, generating a growing outbreak of illness internationally. This pandemic flu virus spreads in the same way that regular seasonal influenza viruses spread; mainly through the coughs and sneezes of people who are sick. It's uncertain at this time how severe this novel H1N1 outbreak will be in terms of illness and death compared with other influenza viruses. Because this is a new virus, most people not have immunity to it, and illness may be more widespread as a result. In addition, currently there is no vaccine to protect against this novel H1N1 virus. WHO anticipates that there will be more cases, more hospitalizations and more deaths associated with this new virus in the coming influenza seasons. As the human swine flu outbreak continues to grow the World Health Organization raised the worldwide pandemic alert level to Phases 4–5 and later to Phase 6 (Table 1). A Phase 4 alert is characterized by confirmed person-to-person spread of a new influenza virus able to cause "community-level outbreaks." Phase 5 is described by human-to-human spread of the virus into at least two countries in one WHO region. The declaration of Phase 5 is a strong signal that a pandemic is imminent. Phase 6, the pandemic phase, is proclaimed when community level outbreaks were pronounced in at least one other country in a different WHO region in addition to the criteria defined in Phase 5. Designation of this phase indicates that a global pandemic is under way. It is important to note that all of those phases are about how the virus is spreading – they're not about the severity of the disease.

Swine flu viruses do not normally infect humans. However, sporadic human infections with swine flu have occurred. Most commonly, these cases occur in persons with direct exposure to pigs (*e.g.* children near pigs at a fair or workers in the swine industry). On the contrary, human flu viruses infect pigs and pig to pig transmission of human, as well as avian flu viruses, can also occur. We like to make the point that control of an outbreak of influenza is a shared responsibility of public health and animal health autorities.

Table 1

Time table of 2009 swine flu pandemic start and development

Early March	Mexican authorities reported unusual severe cases of influenza-like illness in the Distrito Federal, which includes Mexico City.
April, 6th	Mexican health officials declare an alert because of respiratory disease outbreak in La Gloria, Veracruz state, Mexico. Residents believe it is caused by pig breeding farms in the area.
April, 23rd	Samples from Mexico arrive at CDC. CDC confirms some flu infections in California with the same A(H1N1) virus of swine origin as Mexican cases.
April, 25th	CDC publishes MMWR dispatch about six new U.S. cases with *increasing evidence of human-to-human transmission* and publicly links same strain of H1N1 to the Mexican outbreak.
April, 27th	Canada and Spain report confirmed cases to WHO. After an Emergency Committee meeting, WHO raises the pandemic threat level from *phase 3 to phase 4* indicating sustained human-to-human transmissions in community.
April, 29th	WHO raises the threat level from *phase 4 to 5*, indicating sustained community transmission in two countries (Mexico and the United States) in the same region. Other ten countries on 4 continents (Europe, Asia, Australia and South America) reported confirmed cases.
May, 2nd	Canada reports the first isolation of the new virus from pigs
May, 13th	A WHO project leader in the Global Influenza Programme acknowledges the limits of the phasing system, which give emphasis to transmission, not to severity.
May, 18th	At the opening of the World Health Assembly in Geneva, several countries urged WHO Director-General Margaret Chan to *revise the pandemic alert system*, as it reflects geographic spread but not the severity of disease
May, 20th	Confirmed world cases top 10,000
May, 27th	First imported case in Romania
June, 4th	Confirmed world cases top 20,000
June, 11th	Confirmed world cases top 30,000 WHO raises the threat level from phase 5 to 6, a full-scale pandemic.
June, 12th	Vaccine producer Novartis announces the first batch of vaccine against the novel H1N1 virus
June, 17th	Confirmed world cases top 40,000
June, 21st	Confirmed world cases top 50,000
June, 24th	Argentina reports that the novel H1N1 virus has infected a pig farm
June, 25th	CDC estimates the burden of H1N1 svl infections to about 1 million human cases
June, 29th	First detected strain of virus that has a resistance mutation for the drug Tamiflu (Denmark).
July, 7th	Confirmed world cases top 100,000

Phase 6 is the highest level of pandemic alert. It can be difficult to understand for non-experts why this is triggered in response to a disease that, at least in mid 2009, is mild. The confusion in the population may results from the comparison with the predicted severity of a pandemic associated with the emergence of mutant avian influenza. The term "pandemic" describes the geographic spread of the disease rather than its severity and is a means of coordinating world-wide preventive measures. In this paper, we investigate relations between the evolution of human reported cases and the effectiveness of pandemic control measures. The need to understand new pandemic is more compelling today in the modern global context in which societies are highly interconnected. Some lessons can be learned from the experience of more affected countries and their value evaluated in different geographic and economic context. The following ten aspects will be discussed:

1. The different geographical evolution of H1N1 outbreaks.
2. The interaction of influenza activity between the northern and southern hemisphere.
3. The relation between intra-country transmission *vs* imported cases.
4. The association between seasonal and pandemic influenza strains.
5. The public health importance of assessment transmissibility and severity of outbreaks.
6. The opportunity of implementing pandemic influenza containment versus mitigation strategies.
7. The need for research to improve understanding of the factors that determine viral pathogenicity and/or transmissibility.
8. The role of virologic surveillance in risk assessment of the pandemic.
9. The need for research into human diseases that originate in animals.
10. The striking differences between older pandemics and the current one.

1. THE DIFFERENT GEOGRAPHICAL EVOLUTION OF H1N1 OUTBREAKS

In May–June 2009 many countries experienced higher levels of influenza-like illness than is normal for this time of year. Numerous outbreaks were reported in schools, which was also very unusual for this summer time. Interesting, some geographic variation in the H1N1 flu activity was evident between continents, between countries in the same continent, as well as in different regions of the same country. The epidemiologic curve of influenza A H1N1 swl cases traced from WHO official case counts shows that recent pandemic originate in Mexico probable in March and peaked in US in June[3]. Mexico has been hard-hit, similarly to the United States. But, in June, the overall trend appears to be downward in Mexico with more sporadic cases rather than the larger earlier reports. In US, the seasonal influenza viruses are continuing to circulate and about half of all of the influenza viruses isolate recently were novel H1N1 swl virus. All American States confirmed H1N1 swl cases with activity appearing to be highest in the Pacific Northwest and the Southwest. For example, the grand total of cases from all Mexican Border States (Ar, Ca, Lu and NM) was inferior to a single Northern state like Wisconsin. This suggests that travel or transport in an aircraft were the main ways of dissemination. The US CDC agency estimates that over 1 million people in the U.S. have been infected. Even in the summer months, the New England and New York/New Jersey regions continue to experience higher than typical levels of health care visits for influenza-like illness. The case counts are always very incomplete. They are just the tip of the iceberg. Looking at influenza-like illness, more reports from outpatient visits than would be typical for this time of year were registered from New York area. In New York City, a community survey suggests that 6.9% of New Yorkers had experienced a flu-like illness during a three-week period in May when most of that influenza-like illness was caused by the new H1N1 strain. CDC estimated that swine flu has likely infected more than 1 million Americans, with many of those suffering mild cases never reported (without getting a test or necessarily seeking care). As July 24, after three months of outbreak evolution, there have been 302 deaths and nearly 44,000 reported cases (CFR – 6.86).

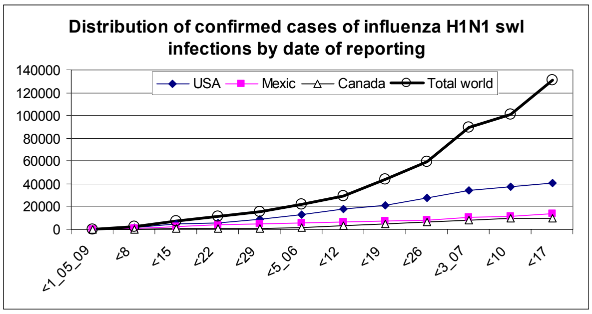

Fig. 1. Epidemiologic curve of confirmed influenza H1N1 cases by WHO shows that in mid July 2009 global burden of disease is no longer driven by US reported cases.

Graphics 1–3 cover data available until July 19th, 2009, when both WHO and ECDC suggested the surveillance activities to be re-oriented to a monitoring phase without daily data reporting.

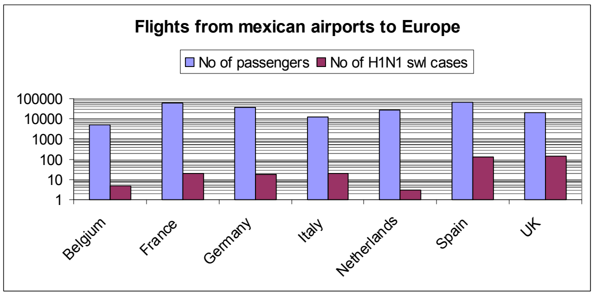

Fig. 2. Graphic shows the correlations between the flights from Mexican airports (March-April 2009) to different European countries and the number of confirmed H1N1 swl cases.

In EU, all countries have reported human infections, but the majority of cases (75%) have occurred in Germany, Spain and UK, first countries which detected imported cases[4]. It is the significant number of travel related cases concentrated in these countries that explain the widespread regional disease. Few cases have been reported in other countries where the virus has been repeatedly identified but the intra-country transmission was extremely low. Moreover, within countries, the distribution of cases has been markedly non-uniform. This might be related primarily to differences in the age distribution of imported cases but probably also reflects important differences in additional factors (*e.g.*, levels of surveillance and local behaviors). A related question is why does the extent of intra-country transmission was so different – from under 15% in France to 35% in UK and Germany. In part, the answer is that H1N1 remains an influenza virus that is not very adapted to human to human transmission.

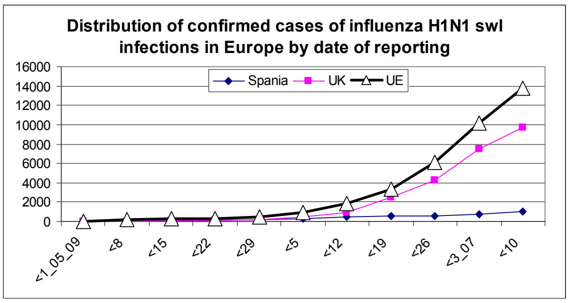

Fig. 3. Epidemiologic curve of confirmed influenza H1N1 cases by ECDC shows that in mid July 2009 near 70% of European cases and 88% of related deaths were in UK[5].

However, many other contributing factors are possible. One particularly important hypothesis is that cases are being missed because current surveillance primarily detects severe infections. It is clear that the reported numbers of laboratory confirmed human cases are conservative, but the extent to which these numbers are conservative is unknown.

In conclusion, as July 19th, all six WHO regions have confirmed cases. However, community transmission, defined as transmission chains spreading beyond close contacts into the community, has to date only occurred in a limited number of countries in Americas (Mexico, US, Chile, Argentina), in UK and Australia. EU countries are still experiencing limited chains of transmission to contacts of returning travellers from Mexico, US, Canada, and the UK.

2. THE INTERACTION OF INFLUENZA ACTIVITY BETWEEN THE NORTHERN AND SOUTHERN HEMISPHERE

Considering the interaction of seasonal influenza activity between the northern and southern hemisphere, we can expect the virus to behave similarly in terms of attack rates, clinical spectrum of illness and risk factors for severity. This gives an opportunity to countries in the northern hemisphere (which have encounter the pandemic at the end of influenza season) to learn from experiences in the southern hemisphere (where influenza season just started) and prepare accordingly. The seasonal as well as pandemic influenza virus situation in the winter period in the southern hemisphere is likely to reveal what can be expected in the winter in the northern hemisphere. The present situation (June–July 2009) in Chile[6] and Australia[7] at the beginning of winter season 2009–2010 shows the adaptability of public health response to the characteristics of H1N1 swl pandemic. Both countries are situated in southern hemisphere and have an established seasonal pattern of influenza activity and a good seasonal influenza surveillance system. Taking into account the less severe clinical characteristics of the current pandemic, Chile changed from a "containment" to a "mitigation" strategy by the end of May 2009 (two weeks after the first case report). Australia elaborated an original gradation of response in three stages: "contain", "sustain" and "protect". Protect is a measured, reasonable and proportionate health response to the moderate severity of H1N1 swl illness which replace the containment strategy envisaged for a very severe pandemic. The key element of protect phase is the identification and treatment of those with severe disease. Pathology testing of all potential cases (diagnostic, isolation, treatment) is not required or desirable because majority of cases are mild. Clinical judgement will prevail over epidemiological recommendations in case management.

In European Union (EU), influenza activity can be expected to remain on a low level during the summer months, whereas a steep increase, as seen currently in Australia and Chile, might be observed at the start of the influenza season, around September 2009. Another important thing is that the pandemic in Northern Hemisphere starts nearing the end of flu season when a decline in the number of cases is registered. It is expected that influenza activity come back again in the fall when the new flu season begins.

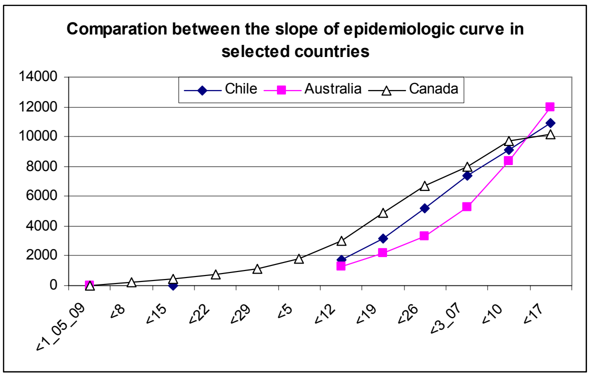

Fig. 4. In the Southern Hemisphere H1N1 swl influenza continues to circulate into winter season at the same pace as in Northern countries, together with seasonal strains.

The approach of the European Member States over the past few weeks has been to implement intense containment measures, including active case finding and tracing of contacts, isolation of cases and contacts, and antiviral treatment and prophylaxis. These measures were pertinent in reaction to the first appearance of the new virus in Europe. However, it is unclear if these efforts will still be sustainable in the coming winter season when the virus is likely to be widely circulating on the continent. It can be expected that countries will implement different measures depending on the national epidemiological and virological situation[8]. In Europe the number of cases reported by UK exceded two thirds of total cases. During weeks 27–29/2009, the UK (England) continued to report high and widespread pandemic influenza activity, especially among children. On July 21, the number of reported cases in England top 10000 (29 deaths). There is no data to suggest that there are better transmission properties of H1N1 swl virus in terms of heat and humidity British characteristic conditions. It is probable a susceptibility problem and some gaps in implementing mitigations measures. In any case, individual case reporting is not the most effective public health reporting tool. Recognizing the challenges of keeping up with it, WHO calls to be stopping the individual case counts, and laboratory confirmed case counts[9].

3. THE RELATION BETWEEN IN-COUNTRY TRANSMISSION VERSUS IMPORTED CASES

Public health autorities must to do everything possible to prevent the arrival of the virus or, once in a country, to delay its further spread and thus flatten the epidemiological peak. Based on the experience from Mexico and the US, it appears that seeding events established by travellers from affected areas are occurring in closed community settings such as schools, summer camps, chronic care facilities and nursing homes etc. The spread of the virus within these settings causes an amplification of the viral reservoir, ultimately leading to community spread. In the EU, some confirmed cases have been reported in children of school age and in close school contacts and monitoring of these events should continue to be done carefully. Half of the confirmed cases observed in the EU were between 20 and 29 years of age. This finding is influenced by the age structure of returning travellers among which most of the testing was carried out. It therefore does not indicate that this age group is at higher risk of disease. Most cases in young adults were mild. However, more severe clinical presentations may be expected when the infection will spread in the general population.

Transmissions of the disease from the imported cases to others (that is, the domestic cases with known infection source) were identified through clinical and virological observation. In EU the reproduction rate was rather low (less than 0.2) as compared with the data from North America. This should be one of the results of the strict control measures implemented so far. It is interesting that some imported case with little self-restriction in movement transmitted the disease to other many persons including members of family.

4. THE COMPARISON OF PANDEMIC H1N1 SWINE FLU TO SEASONAL FLU OUTBREAKS

At this time, there is not enough information to predict how severe novel H1N1 flu outbreak will be in terms of illness and death or how it will compare with seasonal influenza. From European data we know that influenza seasons vary in terms of timing, duration and severity. Seasonal influenza can cause mild to severe illness, and at times can lead to death. For example, each year in the United States millions influenza cases were registered. On average, 36,000 people die (case fatality ratio around 1‰) from flu-related complications and more than 200,000 people are hospitalized from flu-related causes (hospitalization rate <0.5%). Of those hospitalized, 20,000 are children younger than 5 years old. During influenza seasons over 90% of deaths and about 60% of hospitalizations occur in people older than 65[10].

So far in US, with novel H1N1 flu, the largest number of novel H1N1 flu confirmed and probable cases have occurred in people between the ages of 5 and 24-years-old (median age of hospitalized patients – 19 years). At this time, there are few cases reported in people older than 64 years old, which is unusual when compared with seasonal flu. However, pregnancy, obesity (BWI >40) and other previously recognized high risk medical conditions from seasonal influenza appear to be associated with increased risk of complications from this novel H1N1.

Table 2

The comparison between curent influenza H1N1 swl pandemic and seasonal outbreaks

Characteristic	2009 influenza H1N1 swl	Seasonal influenza
Incidence	sporadic	5–20% of population affected
Geographical distribution	worldwide	Different hemispheric pattern
*Reproductive number	1.2–1.6	1.3
Age with highest rate	Adolescents, young adults	Seniors and children
Hospitalisation rate (%)	– 9	<1
Case fatality rate (%)	1	<0.2
Complications, pneumonia (%)	2	<0.1

*Reproductive number = number of new cases attributable to a single established case

Spread of novel H1N1 virus is thought to be happening in the same way that seasonal flu spreads (mainly, person to person transmission). People may be contagious from one day before they develop symptoms to up to 7 days after they get sick. Children, especially younger children, might potentially be contagious for longer periods. Outside the tropics, influenza infections show seasonal patterns which depend on the latitude but appear not to be influenced by longitude[10]. The factors influencing this seasonality are not yet fully understood, but indoor crowding, lower temperatures, decreased humidity and reduced levels of sunlight are believed to influence both transmission and host susceptibility. In Romania, seasonal influenza typically occurs between November and March.

5. THE PUBLIC HEALTH IMPORTANCE OF ASSESSEMENT TRANSMISSIBILITY AND SEVERITY OF OUTBREAKS

The severity of an influenza pandemic can be measured by the number of cases of severe illness (hospitalisation rate) and death it causes (case fatality rate). The factors that determine the severity are: properties of the virus (contagiousness or reproductive number), population vulnerability (prevalence of immune subjects and frequency of people with underlying chronic conditions) and the quality of health services (supplies of medicines, including antibiotics, availability of uncrowded hospitals, equipment and staff quality, etc). The overall severity of a pandemic is further influenced by the tendency of pandemics to encircle the globe in at least two, sometimes three, waves. For many reasons, the severity of subsequent waves can differ dramatically in some countries[11].

The H1N1 swl virus tends to cause very mild illness in otherwise healthy people. Outside Mexico, nearly all cases of illness, and all deaths, have been detected in people with underlying chronic conditions. H1N1 appears to be more contagious than seasonal influenza. The secondary attack rate of seasonal influenza ranges from 5% to 15%. Current estimates of the secondary attack rate of H1N1 range from 22% to 33%. The case fatality ratio during the current pandemic varies between 6.47 $‰_0$ in US and 2.72 $‰_0$ in UK. Also in Southern Hemisphere the mortality is low (in Australia – 2.51 $‰_0$; in Chile – 3.66 $‰_0$ suggesting that additional virus adaptation does not happened by multiple cycles of transmission.

6. THE PROSPECT OF IMPLEMENTING PANDEMIC INFLUENZA CONTAINMENT VERSUS MITIGATION STRATEGIES

A pandemic of any level of severity greater than seasonal influenza would cause some level of social and economic disruption due to higher than usual hospitalization and death rates. As the public health threat posed by novel strains of swine influenza gaining transmissibility has been recognised as potentially devastating, two categories of interventions have been recommended: containment and mitigation.

Containment means the suppression of pandemic. The idea of containment (restraining influenza to one little place) in face of many seeding events of imported cases was not longer feasible even in US when earliest cases have been identified. Influenza spreads easily, person to person. The containment measures like border closing, international travel restrictions, quarantine, etc are social disturbing measures with significant economic burden. Also prophylactic use of antiviral medications is very expensive and must be reserved for initial containment efforts or other highly select circumstances. Stringent public health measures mitigated but not contained the spread of the virus.

Mitigation means to reduce the negative effect. The theoretical aims of community mitigation by public health measures are the delay and the limitation of pandemic impact. However it needs to be realized that the effectiveness of public health measures is by no means certain. The choice between containment and mitigation relies on knowledge of the Pandemic Severity Index (PSI). In each country the PSI evaluation (attack rate, hospitalisation rate, and case fatality rate) identify the recommendations for specific interventions that communities may use for a given level of severity. When these measures should be started and how long they should be used would involve making the most difficult decisions, and thus, present the greatest need for a pre-developed, widely understood planned framework. The severity of the pandemic is evaluated in US with a five point severity scale which corresponds to national scale for hurricanes. WHO proposed a simple three point scale corresponding to data available from past pandemics: mild (1957), moderate (1968) and severe (1918)[12].

For planning purposes there are four components of a pandemic wave – Initiation, Acceleration, Peak and Decline. After the decline there may be a second and even third wave before influenza settles back down to its seasonal pattern again. Coresponding to these stages ECDC proposed four action steps: early detection, early assessment, monitoring, and assessing intervention. A British innovation for early assessment was the introduction of FF 100 (first few hundreds) cases surveillance system.

Presently (July, 2009), Europe seems to be in a long-lasting initiation phase with occasional outbreaks and small peaks (in UK, for example). This could go on for months with the real first wave coming in the autumn or winter. As containment measures didn't succsed to control the import of pandemic viruses to Europe, ECDC published guidance on community mitigation strategies: 1. home isolation of ill person and hausehold contacts, 2. dismissal of students in schools with a confirmed or a suspected cases, 3. social distancing measures, public education etc.

An inappropriate and excessive response to the pandemic could be worse than the pandemic itself[4].

7. THE NEED FOR RESEARCH TO IMPROVE UNDERSTANDING OF THE FACTORS THAT DETERMINE VIRAL PATHOGENICITY AND/OR TRANSMISSIBILITY

Few experimental and fewer clinical studies have analysed the pathogenicity and transmit-ssibility characteristics of the influenza A (H1N1) swl virus. The results demonstrated significant but not lethal pathogenicity from the pandemic A(H1N1) swl – somewhat more than for seasonal A(H1N1) but considerably less than that seen for reconstructed 1918 pandemic H1N1 strain [13, 14].

Since the pandemic virus replicates in the same anatomical sites as seasonal A(H1N1) and A(H3N2) influenza viruses, the possibility of re-assortment of this virus with seasonal influenza viruses, and more importantly with avian A(H5N1) viruses, is a serious concern.

The relatively low number of cases detected in Europe, and insufficient epidemiologic and clinical data to estimate a PSI, present a notable challenge in terms of consider and weight up the threat posed by this novel influenza A virus[15]. The important point is that the pandemics varied a lot. They also varied in detail between European countries and even within countries. In the future there is an expectation that pandemics would be graded by severity. But severity can change over time and relevant information should be obtained according to each place and time. The key aspects would be:

1. epidemiological, clinical and virological characteristics;
2. social and societal aspects: vulnerability of populations; capacity for response;
3. available health care and communication infrastructure.

In each cluster of cases in actual pandemic, transmission has occurred through close physical contact; there is no evidence of pig-to-human transmission of swine influenza via meat consumption. Limited serologic surveys in New York area have found evidence of asymptomatic infections among contacts of active cases and nosocomial transmission to health care workers. Early reports indicate that no children and few adults younger than 60 years old have existing antibody to novel H1N1 flu virus; however, about one-third of adults older than 60 may have antibodies against this virus.

Among naturally-infected humans and experimentally-infected animals (ferrets, mice, pigs) the predominant features are respiratory disease with little evidence of extra-respiratory tissue tropism[13, 14]. However, there is evidence of extra-respiratory disease in humans (diarrhea and viral genomic sequences detected in the intestinal mucosa). The host immune response to H1N1 may contribute to the pathogenesis and expression of clinical disease. In severe human cases unusually high serum concentrations of various chemokines have been detected suggesting that the severity of human infection may be related to the induction of excessive proinflammatory responses that exacerbate tissue injury. The risk of pneumonia is increased in patients with comorbid conditions, such as chronic cardiac and pulmonary diseases or diabetes. The chronic underlying medical conditions, obesity, and pregnancy classically are associated with a greater risk for complications (and death also) for seasonal as well as for pandemic influenza. A significant component in estimating the potential impact of the influenza pandemic is the proportion of most vulnerable population in colectivity, because pre-existing medical conditions are at high risk of influenza-related adverse health outcomes[15].

Advanced age and presence of comorbidities are known to be associated with prolonged illness and poor outcomes in patients hospitalized with influenza infection. A recent study demonstrates that these patients may have higher initial viral loads and that active viral replication tends to continue beyond the first 2 days of illness, in contrast to that in healthier individuals. Unexpectedly, seniors were spared in this pandemic. It seems probable that seniors were protected by previous repeated infections with H1N1 viruses. An alternative explanation is that elderly persons have had previous exposure through vaccination, to an influenza A (H1N1) virus that is genetically and antigenically more closely related to the novel influenza A (H1N1) virus than are contemporary seasonal H1N1 strains. Serological studies in US suggest that vaccination with recent (2005–2009) seasonal influenza vaccines is unlikely to provide protection against the novel influenza A (H1N1) virus.

The best discussion on this area can be found through the ECDC PHM "Menu". http://ecdc.europa.eu/en/Health_Topics/Pandemic_Influenza/phm.aspx .

8. THE ROLE OF VIROLOGIC SURVEILLANCE IN RISK ASSESSMENT OF THE PANDEMIC

Close to 1000 pandemic H1N1 viruses have been evaluated by the laboratories in the Global Influenza Surveillance Network (GISN) for human adaptation markers in the PB2 protein and for antiviral resistance markers in the neuraminidase by direct sequencing.

Lam *et al.* (2008) postulated that a glutamic acid to glycine amino acid substitution at position 677 in PB2 could reflect adaptation to mammalian hosts of highly pathogenic avian influenza A (H5N1) viruses as it was found to be under positive selection based on phylogenetics of Indonesian viruses[16]. Based on the position of the mutation it might contribute to more efficient human-to-human transmission by enhanced replicative efficiency of the polymerase of the influenza A (H1N1) virus in humans [PB2 is a polymerase component]. This mutation was not observed in any of the A (H1N1) swl sequences submitted since April 2009 to GISN [16].

The analysis of resistance against neuraminidase inhibitors (oseltamivir and zanamivir) and M2-ion channel blockers (amantadine and rimantadine) is done by measuring IC50 values and/or by genotyping of viruses for detection of known drug resistance mutations. Influenza A viruses are fully cross resistant for amantadine and rimantadine. During the 2008/2009 influenza season in Europe antiviral resistance monitoring activities revealed:

– all analysed A(H3N2) influenza viruses were sensitive for oseltamivir and zanamivir but resistant against the M2-ion channnel blockers (amantadine and rimantadine);

– of the analysed seasonal A(H1N1) influenza viruses 98 per cent were resistant against oseltamivir but sensitive for zanamivir and [except one virus] all sensitive for the M2-ion channel blockers;

– of the analysed influenza B viruses all were sensitive for oseltamivir and zanamivir (M2-ion channel blockers do not act on influenza B viruses);

– the few instances of the oseltamivir resistant influenza virus A(H1N1) swl appear to represent sporadic cases of resistance. At this time, there is no evidence to indicate the development of widespread antiviral resistance among pandemic H1N1 viruses. Based on this risk assessment, there are no changes in WHO's clinical treatment guidance[12].

9. THE NEED FOR RESEARCH INTO HUMAN DISEASES THAT ORIGINATE IN ANIMALS

The influenza A H1N1 swl virus which is the etiologic agents of this pandemic easily crosses from humans to pigs (and birds?). If ordinary precautions are taken in facilities where infected pigs were found, the risk to humans does not increase significantly. In any cases thorough cooking ensures that meat is free of any virus. Is no need to change food consumption habits [17].

Temporary protection and surveillance zones must be established in areas where infected pigs are found. In these zones movement of live animals is restricted, desinfection measures are strictly applied and health of personel is closely monitored. Given the continued spread of this novel virus in the human population, the risk of it entering pig farms in Europe will, therefore, increase in the next months. From an animal health perspective, current evidence from the two field's outbreaks (Canada and Argentina) and findings from experimental studies (DEFRA, UK) suggest that this novel virus in its current form is unlikely to cause more significant health problems in pigs than those already seen by the swine influenza viruses circulating in pigs in Europe. In its natural host, swine influenza is a self-limiting infection of the respiratory tract with some morbidity but generally leading to uneventful recovery[18].

Recommendations issued by DEFRA and ECDC suggest that the measures to be taken on pig farms addressing human-to-pig transmission, pig-to-pig transmission and pig-to-human transmission should be proportionate to: 1) the risk posed by pigs in the transmission of the novel virus to humans compared to the role played by human-to-human transmission, 2) the severity of disease in animals and humans, and 3) risk factors in humans. The most important measure for reducing the risk of human-to-pig transmission is the implementation of bio-security measures on pig farms aimed in particular at reducing the risk that people infected with the novel influenza are in contact with pigs [19].

Absence of evidence of the pandemic virus in pig populations is not evidence of absence. It is now clear that the animal-and public-health communities underestimated the potential for pigs to generate a pandemic virus. Although pigs can be infected with many subtypes of flu, the three most common endemic strains are H1N1, H1N2 and H3N2 and we need to know more about interspecies transmission, reassortment, and human-to-human transmission[20].

Whereas flu surveillance has improved over the past six years in poultry and wild birds, pigs have been below reasonable and sensible level. In pigs, flu viruses, although common, tend to cause only mild disease, so there is no obligation to report cases of swine flu, much less take samples for genetic and antigenic analysis. Surveillance for swine flu was seen as a farming-industry problem [21]. Most flu surveillance in pigs was passive, relying on farmers or vets sending material to government labs. Active targeted surveillance with diagnostic tests must be a priority research topic.

10. THE STRIKING DIFFERENCES BETWEEN OLDER PANDEMICS AND THE CURRENT ONE

There have been three influenza pandemics during the past century and each has been caused by the emergence of a novel virus. The origin of the influenza virus responsible for the 1918 pandemic, which killed millions in a single year, appears to have been an adapted avian influenza strain. In the 1957 and 1968 pandemics, the new viruses contained components of previous human as well as avian influenza viruses. It has been proposed that genetic reassortment between avian and human viruses (human-avian reassortant viruses H2N2 in 1957 and H3N2 in 1968) leads to new viruses capable of pandemic spread. Reassortants may have been occured in coinfected persons or intermediate hosts, although the circumstances under which this happened remains unclear.

One study on the data from the 1918 pandemic from Copenhagen has created great concerns about the so-called "lethal 2nd wave" in the following pandemics. Such concerns may be totally irrelevant to the society in which we now live, with modern medicine, with influenza vaccination and antivirals. Also, rapid mitigation interventions can attenuate international travel which may disseminate the virus to multiple locations worldwide providing rapid herd immunity – as we are seeing now with the new H1N1/2009 virus[22].

The 1918 H1N1 influenza pandemic (Spanish flu) was the greatest outbreak of infectious disease in history. It has been estimated that if it happened again it would result in perhaps about a million additional deaths in the European Union area[23].

The 1957 pandemic was ten times milder than Spanish flu in terms of mortality (3 million deaths). There was a single sharp wave in the late autumn and the transmission was also especially among children. It tooks only three weeks to cover entirely China and three months to disseminate wholly world.

The 1968 pandemic was different again – it did very little in Europe for the first 16 months and had a quiet first winter of 1968/9 and then took off in its second winter. Hospital's capacity and preparedness was one of the important parts of pandemic planning. There were an increasing number of hospital-related incidents mainly caused by emergency department's overcrowdings, the lack of beds at ordinary wards and/or intensive care units and technical problems at the radiology departments. These incidents reduced the prehospital capacity as well as endangering the patient safety.

Swine flu viruses share at least 2 key features seen in all past pandemic flu viruses. They transmit well among people and are spreading quite efficiently. Two other characteristics must be monitored carefully: the patogenicity and the acquisition of resistance to antivirals.WHO has been informed by health authorities in Denmark, Japan and the Special Administrative Region of Hong Kong, China, of the appearance of H1N1 viruses which are resistant to the antiviral drug oseltamivir (known as Tamiflu) based on laboratory testing. These viruses were found in three patients who did not have severe disease and all have recovered. Investigations have not found the resistant virus in the close contacts of these three people. The viruses, while resistant to oseltamivir, remain sensitive to zanamivir.

Studies on the effectiveness of non-pharmaceutical public health measures from the southern hemisphere will be important, even though caution is recommended when comparing to countries with different healthcare systems, population density and social structures. In addition, the behavior of other seasonal influenza viruses in terms of co-circulation and predominance of one strain versus the other will be closely monitored. The predominance of the pandemic strain over other influenza strains is a phenomenon that has been observed in previous pandemics. If this will also become true for other southern countries, the same can be expected in the northern hemisphere, and public health measures, including vaccination and treatment, will need to be adapted accordingly.

DISCUSSION

In early June 2009, the Trust for America's Health (TFAH), the Center for Biosecurity, and the Robert Wood Johnson Foundation (RWJF) analyze the initial response to the H1N1 outbreak, Pandemic Flu: Lessons from the frontline. The published report reviews 10 early lessons learned from the response to the H1N1 (swine) flu outbreak [24]:

– Investments in pandemic planning and stockpiling antiviral medications paid off;

– Public health departments did not have enough resources to carry out plans;

– Response plans must be adaptable and science-driven;

– Providing clear, straightforward information to the public was essential for allaying fears and building trust;

– School closings have major ramifications for students, parents and employers;

– Sick leave and policies for limiting mass gatherings were also problematic;

– Even with a mild outbreak, the health care delivery system was overwhelmed;

Table 3

Comparison between previous three pandemics and the 2009 A H1N1 Swine Flu

Characteristic	1918 Spanish Flu	1957 Asian Flu	1968 HongKongFlu	2009 Swine Flu
Origin of virus strain	H1N1 (avian)	H2N2 recombinant)	H3N2 (recombinant)	H1N1 (swine)
Reproductive number	1.54–1.83	1.50	1.28–1.56	<1.2
Case mortality rate (%)	8–13	<2	<2	0.4–0.6
Death toll (million)	40	0.1	0.7	?
Rate of symptomatic infections (%)	25–40			9
Most affected age	Young adult	Children	All age groups	Young adult
Severity of the pandemics	severe	moderate	mild	Mild to moderate

– Communication between the public health system and health providers was not well coordinated;

– WHO pandemic alert phases caused confusion; and

– International coordination was more complicated than expected.

The report also identifies some surprises encountered during the H1N1 outbreak, including that much of the world's pandemic planning had revolved around the potential threat of the H5N1 (bird) flu virus, which had been circulating in Asia and elsewhere for nearly a decade.

In addition, according to the analysis in *Pandemic Flu: Lessons from the Frontlines*[24], there are a number of systemic gaps in the nation's ability to respond to a pandemic flu outbreak. We selected the following aspects that must be addressed in Romania too:

– maintaining the strategic reserve of antiviral medications, vaccinations, and medical equipment;

– enhancing the biomedical research and development abilities to rapidly develop and produce a vaccine;

– improving coordination among government and local autorithies to implement mitigation measures, vaccination programs, and education actions;

– providing enough funding for the on-the-ground response, including for the attraction of the next generation of public health professionals.

There are a lot of efforts around the vaccine development, testing, licensure and program planning. Assuming availability of a safe and effective vaccine, medical authorities have provided planning scenarios to identify venues for vaccination. Also will be discussion whether prioritiziation or tiering of potentially limited vaccine supply would be appropriate. Vaccination will be the most important tool to mitigate the pandemic evoloution. Additionally, it is obvious to take advantage of what we have learned so far about how pandemic behaves and the impact and effects of our intervention so that our next actions can be as practical as evidence based and useful as possible to all as we go forward into the fall.

REFERENCES

1. Outbreak of swine-origin influenza A (H1N1) virus infection - Mexico, March-April 2009. MMWR Morb Mortal Wkly Rep **2009**; *58*: 467-470.
2. CDC, Novel Influenza A (H1N1) Virus Infections - Worldwide, May 6, 2009. MMWR Morb Mortal Wkly Rep **2009**; *58*: 453-8.
3. Fraser C., Donnelly C.A., Cauchemez S., *et al.*, Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings. Science **2009**. Available from <http://www.sciencemag.org/cgi/rapidpdf/1176062v1.pdf
4. ECDC, Technical Emergency Team. Initial epidemiological findings in European Union following the declaration of pandemic alert level 5 due to influenza A/H1N1. Euro Surveill. **2009**, *14*, 1204.
5. PAHO (**2009**), influenza-like illness in the United States, Mexico. http://new.paho.org/hq/index
6. http://www.new.paho.org/chl
7. http://www.emergency.health.gov.au/swineflu/protect
8. Jakab Z., Pandemic 2009-2010. ECDC's future look and risk assessment. http://www.ecdc.europa.eu
9. Health Protection Agency (HPA), Weekly pandemic update. Accessed: July 23, 2009 http://www.hpo.org.uk
10. Finkelman B.S., Viboud C., Koelle K., Ferrari M.J., Bharti N., Grenfell B.T., Global patterns in seasonal activity of influenza A/H3N2, A/H1N1, and B from 1997 to 2005: viral coexistence and latitudinal gradients. PloS One. **2007**; *2*:e1296.
11. Lackenby A., Hungnes O., Dudman S.G., Meijer A., Paget W.J., Hay A.J. *et al.*, Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Euro Surveill. **2008**; *13*: 8026.
12. http://www.who.int
13. Maines T.R. *et al.*, Transmission and Pathogenesis of Swine-Origin 2009 A(H1N1) Influenza Viruses in Ferrets and Mice. Science **2009**. Published online July 2, 2009.
14. Munster V.J. *et al.*, Pathogenesis and Transmission of Swine-Origin 2009 A(H1N1) Influenza Virus in Ferrets. Science **2009**. Published online July 2 2009;
15. D.M. Morens *et al.*, The persistent legacy of the 1918 influenza virus. New England Journal of Medicine. DOI: 10.1056/NEJMp0904819 (2009) Genetic Relationships among Human and Swine Influenza Viruses, 1918-2009
16. Lam T.T., Hon C.C., Pybus O.G., Kosakovsky Pond S.L., Wong R.T., Yip C.W., Zeng F., Leung F.C., Evolutionary and transmission dynamics of reassortant H5N1 influenza virus in Indonesia, PLoS Pathog. **2008**; *4*, e1000130.
17. Canadian food inspection agency (2009): swine influenza - advice for veterinarians and swine producers. http://www.inspection.gc.ca/english/anima/disemala/swigri/swigrifse.shtml
18. CDC (**2009**): key facts about swine influenza (swine flu). <http://www.cdc.gov/swineflu/key_facts.htm
19. DEFRA (**2009**): swine influenza. <http://www.defra.gov.uk/animalh/diseases/vetsurveillance/az_index.htm#s
20. Garten RJ., *et al.*, Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans. *Science* **2009**, *325*, 197 – 201
21. Gray G.C., McCarthy T., Capuano A.W., Setterquist S.F., Olsen C.W., Alavanja M.C., Swine workers and swine influenza virus infections. Emerg Infect Dis. **2007**; *13*:1871-8.
22. Miller M.A., Viboud C., Olson D.R., Grais R.F., Rabaa M.A., Simonsen L., Prioritization of influenza pandemic vaccination to minimize years of life lost. J Infect Dis **2008**; *198*: 305-11.
23. Murray C.J.L., Lopez A.D., Chin B., Feehan D., Hill K.H., Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. Lancet **2006**; *368*:2211-2218
24. www.healthyamericans.org/assets/files/pandemic_flu_lessons.pdf