DISTINCTIVE FEATURES IN THE EVOLUTION OF 2009 INFLUENZA PANDEMIC IN EAST EUROPEAN COUNTRIES

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During the influenza season 2009–2010, Member States of the WHO European Region have intensified influenza surveillance, due to the emergence of pandemic A/H1N1/2009 strain. In Eastern and Central Europe an unusually early start of the winter influenza season was signaled. Active circulation of the virus, with high proportions of sentinel respiratory samples testing positive for influenza A/H1N1, has been reported in all countries of the region. Nevertheless, Romania experienced an overall mild influenza season 2009–2010, while in neighbor countries (especially in Bulgaria and Ukraine) the intensity of influenza activity was high to very high and the impact on health services was evaluated as overcharged. In this review we assess the development of the 2009 A H1N1 outbreak in the region and identify the mitigation measures that have contributed to the limitation of the pandemic's impact. Romania has developed a reasonable and proportionate health response, adapted to the moderate severity of A/H1N1 outbreak evolution, while maintaining some attributes of the containment strategy envisaged for a very severe pandemic. Early antiviral treatment initiation for all patients with confirmed A/H1N1 infection and their contacts proved to be an effective strategy, reducing the incidence of serious complications, the mortality and the spread of the virus in the community.

Key words: 2009 A/H1N1 pandemic; Bulgaria; Romania; Ukraine; Mitigation measures.

INTRODUCTION

During the spring and summer of 2009, Member States in the WHO European Region have continued the influenza surveillance, due to the appearance of the pandemic A/H1N1/2009 virus[1]. The first European infections were reported in Spain, UK and France on April, 28 (week 17/2009). In Romania, the first case was confirmed on May, 27 (week 21/2009). As of October, 8 (week 40/2009, that, in terms of WHO reporting, marked the start of the new 2009/2010 influenza season) 49 out of 53 Member States had reported over 61 000 cases. Only a few countries in the European Region (*e.g.* Ireland, Malta and the United Kingdom) experienced clinical influenza activity due to pandemic A/H1N1/2009 during 2009 summer.

Novel influenza A virus infections in humans can always present a pandemic threat. In accordance with the historical precedents, during which several waves of disease occurred, with different morbidity and mortality and distinct epidemiologic profiles, WHO recommends that health departments in all countries must remain vigilant[2].

This overview of the situation in Romania and bordering countries during autumn–winter 2009 aims to facilitate the interpretation of influenza data and to improve the efficiency of control measures for the forthcoming seasons.

MATERIAL AND METHODS

WHO/Europe and the European Centre for Disease Prevention and Control (ECDC) conduct joint surveillance of seasonal influenza in the Region and publish weekly regional bulletins. We performed a systematic search from 2008 to 2010 (week 10) for epidemiological and virological data from

the countries in the Eastern European Region. Data were divided into four types: (1) weekly reports of EuroFlu, (2) data collected by clinicians' networks (consultations rate) and (3) laboratory networks (specimens positive for influenza viruses), consisting mainly of reports from WHO-recognized national influenza centers (NICs); and (4) published studies reporting population-based studies on influenza activity, both national and subnational. Mainly, in this report we have used the data posted on the following websites: http://www.who.int/csr/disease/swineflu; http://ecdc.europa.eu/en/; http://www.who.europa/influenza; http://www.euroflu.org; http://www.promedmail.org

All data concerning Romania presented in this review were from the National Influenza Center (NIC) – National Institute for Research and Development for Microbiology and Immunology "Cantacuzino" Bucharest (NIC-IC).

The intensity of influenza activity is reported in the range very high to low and the geographic spread of influenza-like illness (ILI) in the range widespread to sporadic or absent. The impact of influenza on health services is evaluated from overwhelming to moderate or low. Two kinds of data are reported concerning acute respiratory disease activity: ARI (acute respiratory infections) and ILI consultation rates. Both of them are typical for the beginning of the cold season in temperate region, when other respiratory infections, not necessarily influenza, could play an important role on the general morbidity. The case definitions[3] used by the EuroFlu surveillance network are:

ILI – every illness characterized by sudden onset, fever, myalgia and respiratory symptoms (cough, coryza). Sometimes the most restrictive "Pel criteria" were used "An acute onset (*i.e.* at most a prodromal stage of three to four days), accompanied by a rise in rectal temperature of >38°C, and at least 1 of the following symptoms: cough, coryza, sore throat, frontal headache, retrosternal pain, myalgia.

ARI – summarized the following diagnoses: common cold, rhinitis, rhino-pharyngitis, tonsilitis, sinusitis, otitis media, laryngitis, tracheitis, bronchitis, bronchiolotis, pneumonia and broncho-pneumonia.

RESULTS

Pandemic influenza activity in Central Europe

A substantial increase above baseline levels of influenza was observed in the WHO European Region after mid October 2009 (weeks 44–45)[4]. However, peaks for each individual country differ and are influenced by surveillance practices (enhanced versus monitoring)[5]. For a number of countries (*e.g.* Ukraine, Bulgaria) a marked increase in respiratory disease activity was observed as early as weeks 43–44 (Fig. 1). For the second week in a row, in week 44, in Bulgaria, Belarus and in Urals region of the Russian Federation, the intensity of clinical activity of influenza was described as very high, even if at the commencement, the large majority of the reported cases were mild. The clinical incidence of ILI and/or ARI was reported as widespread in Hungary and Serbia, while the impact was moderate in the Republic of Moldavia, indicating sustained circulation of influenza across the Eastern European Region. In week 44/2009, the level of clinical influenza activity in Ukraine was significantly higher than that reported in the same period during the six previous seasons. Active circulation of virus was marked by high proportions of sentinel respiratory samples testing positive for influenza. All analyzed countries tested at least 20 sentinel specimens and all reported at least 20% of these testing positive for influenza A/H1N1/2009: Bulgaria (26%), Hungary (30%), Serbia (20%), Ukraine (40%), the Republic of Moldavia (32%) and Romania (26%). Pandemic influenza A (H1N1) 2009 virus was the dominant virus in circulation, although influenza type B was also detected. At the beginning, all countries reported the impact of influenza on health care services as moderate.

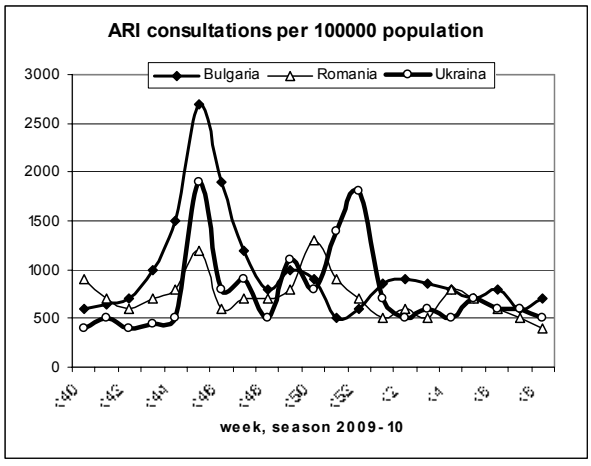

Fig. 1. The rate of ARI consultations by country. In Ukraine, after an earlier wave of mixed ARI cases, pandemic H1N1 influenza activity predominated and a second wave was registered after New Year Holydays. Information about pandemic influenza were derived from ECDC site. (http://www.ecdc.europa.eu/en/healthtopics/Pages/Pandemic_Influenza.aspxare).

The premature start of the winter influenza season in Eastern European Region was particularly evident in Bulgaria and Ukraina. Quantitative reported data on influenza-like illness (ILI)/acute respiratory infection (ARI) consultations showed persistent elevated rates in these countries over weeks 44 to 50 and stable rates in

the others countries. For Romania and Hungary, the ILI/ARI consultations rates were below the baseline, while for Serbia and the Republic of Moldavia they were approaching the baseline. Bulgaria and Ukraina reported a high intensity of influenza circulation until Christmas, when the consultation rate knock down by about 40%, reaching a medium intensity. Overall, in weeks 52–53, decreasing levels of influenza activity were observed throughout the European Region, with most countries reporting low levels during New Year Holydays. These data should be however interpreted with caution, as the seasonal holidays may have affected clinical consultation rates and testing of sentinel specimens[6]. The 2009–2010 season includes a week 53, which is unusual. The text, tables and the graphs do not include data for week 53 for technical reasons.

The pandemic H1N1 2009 virus remained the dominant virus in Europe in the first ten weeks of 2010[7]. The percentage of sentinel specimens testing positive for influenza in the Region was below 20% during week 10/2010, suggesting that influenza circulation continues at a low level. The other countries bordering Romania – the Republic of Moldova, Serbia and Hungary – reported low levels of hospitalizations for severe acute respiratory infection (SARI) comparable to those observed during the peak of the ordinary winter seasonal influenza wave. Continued surveillance remains essential to detect other viruses, patterns of resistance and any possible further pandemic waves[8]. From week 40/2009 to week 13/2010, 164 629 influenza virus detections were reported in all Europe: 163 281 were influenza A (99.2%) and 1348 (0.8%) were influenza B. Of the influenza A viruses, 148 610 (91.0%) were subtyped, with 146 920 being pandemic A(H1), 1060 A(H1) and 630 A(H3).

The evolution of A/H1N1/2009 pandemic in Ukraine

The highest rate of ARI/ILI was recorded initially in western Ukraine regions. Laboratory testing has confirmed pandemic H1N1 influenza virus in samples taken from the most affected western regions. As the pandemic virus has rapidly become the dominant influenza strain worldwide, it can be assumed that most cases of influenza in Ukraine were caused by the H1N1 virus.

Ukraine closed schools, banned public meetings including election rallies, and restricted travel for 3 weeks from week 43, after the confirmation of the first influenza A/H1N1/2009 death. The authorities reinforced hygiene measures and imported rapidly antivirals. During the following week a huge number of infections: 633 877 cases of ARI and 95 deaths related to ARI- representing a day to day significant increase (average +163 per cent for the number of cases and +10 per cent for the number of deaths) were reported by the Ministry of Health (MoH). A total of 1 347 538 people (2900 at 100 000) have contracted flu and acute respiratory viral infections in Ukraine during weeks 44-45, 2009. Out of these 73 373 (5.4%) patients have been hospitalized with influenza and acute respiratory viral infections and 39 380 (2.9%) patients have been discharged (Fig. 2). Recently, the World Health Organization has announced that, on a country by country basis, up to 15% of cases may require hospitalization, often including respiratory support. As of week 45, 2009, the Ukrainian MoH confirmed 265 deaths (0.0005%) of flu and acute respiratory viral infections, in 21 regions, including the Capital (Kiev) and Crimea (see: http://www.promedmail.org).

The initial analysis of information from Ukraine indicated that the numbers of severe cases (SARI) do not appear to be excessive when compared to the experience of other countries and do not suggest any change in the transmission pattern or in the virulence of the virus. Serious cases mounted because the sick people avoided hospitalization until their illness was dangerously advanced. Though the government had stockpiled Tamiflu in preparation for an outbreak, the drug was available only at the region's single infectious disease station, and only with laboratory confirmation of an influenza A/H1N/2009 infection, a 3-to-4-day process, that required that samples be sent to the capital city, Kiev. Stockpiles of Tamiflu were locked in centralized locations and the supply of ventilators in emergency wards fell short.

Ukraine called on the EU [European Union] for assistance, through the Community Civil Protection Mechanism on 31 Oct 2009 (week 44). The European Commission's Monitoring and Information Centre (MIC) sent a coordination and assessment team of experts. In addition, several countries offered aid to control this outbreak. The EU team confirmed that the rapidly evolving situation in Ukraine was mainly related to the pandemic. However, others causes for clusters of respiratory illness, specifically in the western regions could not have been ruled out.

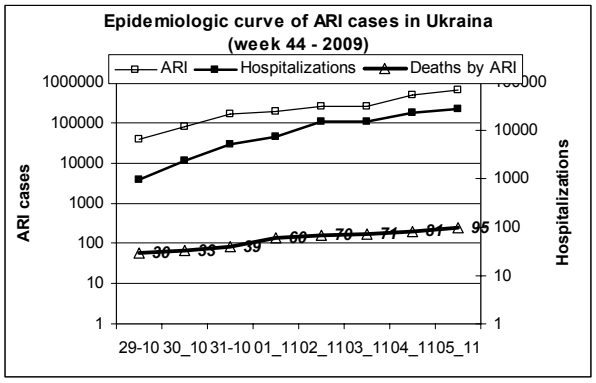

Fig. 2. Cumulative number of reported acute respiratory illness [ARI] cases in Ukraine, by day, since 29 Oct 2009 (data from Ukraine MoH posted on http://www.promedmail.org.

Two distinct peaks were observed in the Ukrainian ARI consultations' rates in weeks 45 and 47 and a distinct peak in sentinel SARI hospitalizations' in week 52. During the first four weeks of 2010, the reported numbers of severe acute respiratory infection (SARI) hospitalizations have declined to levels representing approximately half of the peaks observed in weeks 47–52/2009.

The development of A H1N1 pandemic in Bulgaria

The intensity of clinical influenza activity was described as very high in Bulgaria starting with week 43/2009. Like all EU Member States, Bulgaria had invested substantial time and effort into pandemic preparedness planning. The Bulgarian plan was tested in exercises, and Bulgaria participated in a review of national preparedness led by ECDC and the European Commission. An emergency operations centre was rapidly and efficiently set up in the capital city, Sofia and authoritative information about the pandemic virus was communicated to the public and health professionals. Clear clinical guidance has been disseminated and adapted to different levels of medical care. Medical authorities, however, have refrained from dispatching an all-out warning because the "threshold" needed for that to happen was considered to be 2000 people infected in every 100 000. In this regard, Bulgaria did not succeed to adapt the plan in timely manner to respond to the premature developing epidemiological situation at the beginning of fall. The advice from the World Health Organization (that whenever someone displays symptoms of flu, regardless if its seasonal flu, it should be regarded as swine flu and extreme precautionary measures must be implemented) was not followed in all its bearings.

The situation has slowly deteriorating across Bulgaria and the country was confronted with a nationwide H1N1 epidemic that affected as much as half the population. The worst affected were western regions in the country and big cities like Sofia, Plovdiv and Varna.

The ECDC team visited Bulgaria between 16 and 19 November (week 46) at the invitation of Minister of Health and visited healthcare facilities.

An emergency "holiday" was introduced in schools and people were advised to abstain from any unnecessary interaction at all cost. Ssimple measures such as regular hand washing, good respiratory hygiene and staying at home when ill were disseminated by media in order to limit the impact of the pandemic. The proactive measures taken by the authorities have adequately addressed the evolving situation and in four weeks the rate of ARI consultations has decreased below the epidemic level.

The occurrence of A H1N1 pandemic in Romania

The 2009 pandemic had a different course in Romania – it did very little for the first five months (summer – autumn 2009) and then took off early in the winter season. This is evident both in the number of ARI consultations (Fig. 3) and in the number of laboratory confirmed A/H1N1/2009 cases (Fig. 4).

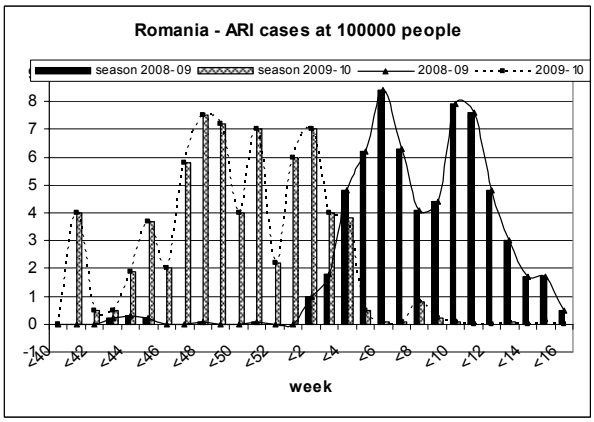

Fig 3. Sentinel data from Romania collected during the 2008/2009 and 2009/2010 influenza seasons. Rate of ARI consultations per 100,000 populations were similar for the seasonal (2008) and pandemic (2009) flu season.

In May – September 2009, most of the reported cases in Romania were imported from countries/zones with pandemic influenza outbreaks, without any further sustained local transmission. Starting with the second half of November 2009 (week 46), the H1N1 pandemic virus has circulated actively, as shown by the increase in the number of positive samples detected by RT-PCR and by the boost in the number of reported ARI, ILI, and SARI cases. In the following period the laboratory confirmed cases and clinical diagnoses continued to grow, with a maximum being registered during weeks 47, 48 and 49. At NIC-IC, 15.465 samples were tested by Real-Time RT-PCR[8] between April 2009 – March 2010 (week 11) out of which 5.554 (35,91%) were positive for the pandemic A/H1N1/2009 virus, 13(0,08%) for seasonal subtype A/H3 virus, 3 (0,01%) for seasonal subtype A/H1and 38 (0, 24 %) for type B influenza virus.

A decline was observed in weeks 1, 2 and 3 of 2010, with normal seasonal values being reached in week 4/2010. Even if Romania experienced a bad and long winter, no secondary waves of the outbreak were signaled until the end of the normal influenza season in April 2010. High absolute humidity and low temperatures influence the seasonal onset of influenza in the continental area[10] and may explain the mild course of outbreak.There was a lot of local variation. The national curve can overlook a series of short, sharp local epidemics. Higher peaks were registered in the Capital and in the extreme North East counties, close to the Ukrainian border.

An important point is that the authorities have done a lot in the autumn of 2009 in terms of social and pharmaceutical interventions. Interventions were started whenever three persons presented with influenza-like illness, with at least one testing positive for influenza A H1N1 2009 by real time PCR or by using rapid diagnostic test. The medical measures included oseltamivir (Tamiflu, Roche) treatment for patients and prophylaxis for contacts and staff. The use of alcohol-based hand sanitizer and daily disinfection of community equipment or shared spaces were implemented.

If the oseltamivir therapy was initiated the patient remained hospitalized until completion of five days of treatment and was symptom-free for 24 hours. To all contacts who shared the patient room or bathroom a 5-day prophylactic course of oseltamivir was also administered.

The health officials stated repeatedly that vaccination is the single best protection against H1N1 influenza virus[9] and authorities have recommended that all healthcare personnel (HCP) have to be vaccinated annually for influenza[10]. Since 2007, the overall influenza vaccination coverage among HCP has never exceeded 20% in any season. HCP was one of the five initial target groups to receive the influenza A (H1N1) 2009 monovalent vaccine when it first became available. This was associated with a greater probability of 2009 H1N1 vaccination[11]. Healthcare administrators considered influenza vaccination coverage among employees an important measure for maintaining patients safety and make appropriate efforts to increase coverage.

An effective public health response depends on strong health systems that are inclusive, offering universal coverage right down to the community level. It depends on adequate numbers of correctly trained, motivated, and compensated staff. It depends on fair access to affordable medical products and other interventions.

Antiviral medication was one of the key strategies deployed in Romania to contain the outbreak and to mitigate hospitalization and mortality rates. Although a vaccine well-matched to the pandemic viral strain is the most effective tool in responding to a pandemic, such a vaccine did not become available for several months after the pandemic beginning due to time needed to develop and produce the vaccine. The antivirals were a hoped-for bridge to availability of vaccine.

Supplies of H1N1 influenza vaccine produced in Romania were plentiful, the circulating virus closely matched the one in the vaccine, and the H1N1 vaccine has had an excellent safety record. But, ssubstantial amounts of vaccine against the pandemic virus became available only around the end of November and its value in containing the actual pandemic wave remains elusive.

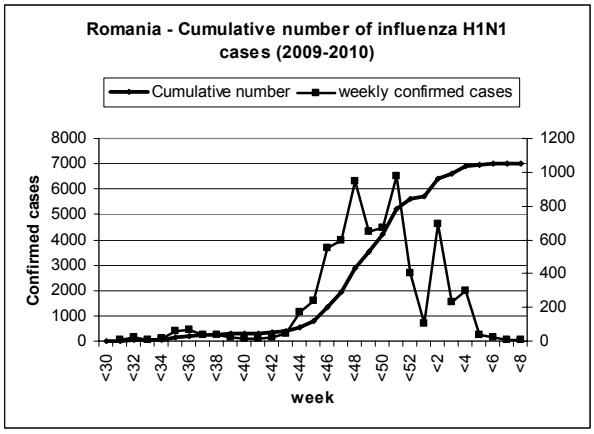

Fig 4. The national idealised epidemic curve for Romania showing the reduced number of A H1N1 confirmed cases (<5 for 100000) even in weeks with higher peaks.

DISCUSSION

Public health surveillance classically comprises six core activities (detection, registration, confirmation, reporting, analysis and feedback) that are made possible through three support activities (diagnostic, isolation, treatment). The epidemiologic characteristics of this outbreak underscore the importance of monitoring the effectiveness of community mitigation efforts: early detection, professional training and resource provision. Dissemination of significant health information (including clinical and virological characteristics, epidemiological and scientific information) was also essential[12]. Taking into account the less severe clinical characteristics of the current pandemic, Bulgaria and Ukraina changed from "containment" to "mitigation" strategy by the end of summer 2009. On the contrary, Romania elaborated a measured, reasonable and proportionate health response to the moderate severity of A H1N1 illness maintaining some attributes of the containment strategy envisaged for a very severe pandemic. Beside non-pharmaceutical interventions, and clinical management practices in anticipation of a possible pandemic, the key element was the identification and treatment of those with confirmed disease. As the pandemic evolved, laboratory testing of all potential cases was no longer required because the majority of cases were mild, but clinical judgment prevailed over epidemiological recommendations in individual case management. The six months setback in the production of influenza pandemic vaccine meant that it was not deployed in time to have any impact on the burst of influenza cases[13]. Also, school-based vaccine clinics for rapid distribution of the vaccine to a high proportion of children were not operating properly due to the delays in the availability of safety data for the pediatric population. H1N1 offered a stark reminder that current techniques for making a flu vaccine are taking much time – around six months from the identification of the new virus to production of any sizeable vaccine quantities. Substantial amounts of vaccine against the pandemic virus became available only around the end of November, after the first wave had already passed[14].

Key facts about Romania and its neighborhood were compiled in table 1 after data available at www.worldbank.org site for the year 2008. It is important to mention that the South-East Europe Region has been hit hard by the global financial and economic crisis in 2009–2010. The very forces of globalization that led to major progress since 1990 have transmitted the effects of the crisis to the region through international capital, product, and labor markets. Although there is differentiation across the region, all analyzed countries entered the crisis in a vulnerable position. Sharp drops in the commodity prices determined an abrupt economic fall for some countries in the eastern part of the Region – especially Moldova and Ukraine – which hit lower income economies hard through the slowing of exports and migrant remittances.

Our analysis of all the available data for influenza surveillance from 2008 to 2010 for 6 Central European countries has shown a substantial difference in respect to the impacts of 2009 pandemic on public health services. The general progress in reducing the impact of the pandemic should perhaps not be seen as surprising, because four powerful drivers of outbreak control are improving in most countries: the level of advance planning, capacity for response, available health care, and communication.

In order to understand the social and societal aspects which may affect populations vulnerability, in Tables 1 and 2 we put face to face basic demographic and economic data for each country with key facts about the A H1N1 pandemic.

Table 1

Romania and its adjacent countries – basic data and countries profile

Country	Population (million)	Population growth	Density per sq km	Primary School enrollmt	Life expectancy at birth	GNI per capita US $	Real GDP growth 2008/9; **Percent change y/y
Bulgaria	6.69	1.2	49.9	86.9	69	8613	–5.1
Hungary	10	–0.2	107.5	86.8	73	12810	–6.3
Moldavia	3.6	–0.9	105.8	87.6	69	1470	?
Romania	21.5	–0.2	90.3	93.9	73	7930	–7.1
Serbia	7.4	–0.4	84.9	95.1	73	5700	–5.7
Ukraina	46.3	–0.5	76.8	89.4	68	3210	–8.9
Average	95.49	0.166	85.9	89.95	70.83	6622	

Table 2

Romania and its neighborhood – key facts about 2009 H1N1 pandemic week 40 (2009) to week 10 (2010)

Country	Week of epidemic peak	The intensity of influenza activity	The geographic spread	The impact of influenza on health services
Bulgaria	Weeks 44–45	Very high	widespread	overwhelming
Hungary		Medium	regional	moderate
Moldavia	weeks 47–52/	High	widespread	high
Romania	weeks 49–50	Medium	regional	moderate
Serbia		Medium	regional	moderate-high
Ukraina	weeks 44–52 and	High	widespread	overwhelming

First, the GNI or income per head can affect susceptibility to infections through several channels from nutritional status to physical and financial access to health care. The GNI discrepancy explains differences in the intensity of influenza activity. Developing countries (Moldova, Ukraina) were more severely hit than privileged one (Hungary). Second, population density influences the transmissibility and the geographic spread, but in those Eastern Europe between countries differences were insignificant. However, in high dense urban collectivity, the airborne survival and transmission of the influenza virus increases greatly. Third, educational attainment level is another strong correlate of the intensity of influenza activity. In line with the critical impact of education we mention that CDC initiated a four-point travel health campaign: "Travel only if well; wash hands often with soap or sanitizer; cough and sneeze into a tissue or sleeve; and get vaccinated when possible, especially if you're in a target population". Fourth, it is now clear that healthy children and young adults were disproportionately affected, most unusually among those with severe respiratory disease without underlying conditions. One possible explanation for this case age distribution is the doctrine of Original Antigenic Sin, *i.e.*, novel H1N1 may be antigenically similar to H1N1 viruses that circulated at an earlier time, rendering older individuals less susceptible[12].

In our opinion an important fact to explain the mild evolution of 2009 pandemic in Romania was the strategy of early treatment for all who present to emergency care facilities. Early antiviral treatment for children and adults with influenza-like-illness reduced serious complications, reduced mortality and the spread of the virus in the community[13]. Further benefits were obtained by prophylaxing only contacts of those with H1N1 infection with underlying health conditions[14]. This strategy allowed controlling the spread of the virus while limiting those who took oseltamivir.

In addition to early treatment, aggressive management of patients in the hospital's intensive care unit, experience with ventilators and some other types of life support devices contributed to the improved patient outcomes.

In conclusion, the main implications of our study are that early antiviral treatment succeeded in flattening the epidemic peak, reduced the burden and threat on healthcare system, reduced total number of cases and offered a little extra time to vaccinate.

REFERENCES

1. Aguilera J.F., Paget W.J., Influenza pandemic planning in Europe. Euro Surveill. 2001;6(9):pii=320. available online: http://www.eurosurveillance.org.
2. WHO Weekly Epidemiological Report 2009, 84(21):185-90. available online: [http://www.who.int/wer/2009/wer8421/en/index.html].
3. Aguilera J.F. *et al.*, Heterogeneous case definitions used for the surveillance of influenza in Europe. *European Journal of Epidemiology* 2003: 18(8): 733-736.
4. Viboud, C., Miller, M., Olson, D., Osterholm, M. & Simonsen, L. *PLoS Curr. Influenza, RRN1153* (2010). Available at http://go.nature.com/DSfm6h.
5. Cernescu C., Lessons from the 2009 influenza pandemic. Proc. Rom. Academy serie B, 2010, 10, 181-185.
6. Miller M.A., Viboud C., Balinska M., Simonsen L., The signature features of influenza pandemics – implications for policy. N Engl J Med. 2009 Jun18;360(25):2595-8.
7. Nishiura H., Castillo-Chavez, Safan M., Chowell G., Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan. *Euro Surveill* 2009., 14(22).
8. Panning M., Eickmann M., Landt O., Monazahian M., Ölschläger S., Baumgarte S., Reischl U., Wenzel J.J., Niller H.H., Günther S., Hollmann B., Huzly D., Drexler J.F., Helmer A., Becker S., Matz B., Eis-Hübinger A.M., Drosten C., Detection of influenza A(H1N1)v virus by real-time RT-PCR. Euro Surveill. 2009;14(36):pii=19329. Available online: http://www.eurosurveillance.org.
9. Disease Control and Prevention. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009; 58(RR‐10):1–8.

10. Johansen K., Nicoll A., Ciancio B.C., Kramarz P., Pandemic influenza A(H1N1) 2009 vaccines in the European Union. Euro Surveill. 2009;14(41):pii=19361. Available online: http://www.eurosurveillance.
11. Shaman J., Pitzer V.E., Viboud C., Grenfell B.T., Lipsitch M., Absolute humidity and the seasonal onset of influenza in the continental United States. PLoS Biol. 2010 Feb 23;8:e1000316.
12. Reichert, T., Chowell, G., Nishiura, H., Christensen, R.A. & McCullers, J.A., Does Glycosylation as a modifier of Original Antigenic Sin explain the case age distribution and unusual toxicity in pandemic novel H1N1 influenza? *BMC Infect. Dis.* 10, 5 (2010).
13. Dawood F.S., Jain S., Finelli L. *et al.*, Emergence of a novel swine‐origin influenza A (H1N1) virus in humans. N Engl J Med 2009; 360:2605–2615.
14. Jain S., Kamimoto L., Bramley A.M., *et al.*, Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med 2009; 361:1935–1944.