Pandemic (H1N1) influenza in Diyarbakir, 2009

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Abstract

Objective: This study was conducted to evaluate the pandemic (H1N1) influenza outbreak in 2009. **Method:** Influenza like illness (ILI) cases were reported between the 36th to 53rd weeks of the pandemic, from all health centres. 731 nasopharyngeal swabs were collected from ILI cases. **Results**: The first H1N1 confirmed case was reported at the 36th week and an increasing trend continued. At the 43rd week the outbreak reached its maximum level and at the 53rd week the level had decreased to the level at the start. During the outbreak 31117 cases were reported as ILI and 635 cases were hospitalized (hospitalization rate was 2.0%) and 17 H1N1 laboratory confirmed cases died (mortality rate 11.5/1.000.000). Symptoms of laboratory confirmed cases were similar to seasonal influenza. Coughing (90.9%), fever (84.5%), running nose (69.5%), headache (73.4%), diarrhoea (17.5%) were the some of the symptoms in laboratory confirmed cases. The median interval between the onset of symptoms and hospital admission was 3.5 days (min: 1, max: 11 days) and this was 7.5 days for the occurrence of death. **Conclusion**: During 36th to 53rd week an important outbreak of ILI was occurred. The mortality rate was not so high as expected but the infectivity was high. The delay for hospital admission may lead to higher mortality particularly for pregnant women.

Key Words: Pandemic influenza; H1N1; case fatality rate; hospitalization rate.

Diyarbakır'da pandemik (H1N1) influenza, 2009

Özet

Amaç: Bu çalışmada 2009 yılında -Türkiye'de pandemik influenza salgınını değerlendirmek amaçlanmıştır. **Yöntem:** Diyarbakır 'da 36 ve 53. haftalar arasında tüm sağlık kuruluşlarından influenza benzeri hastalık rapor edilmiştir. 731 nazofaringeal sürüntü alınmıştır. **Bulgular:** İlk H1N1 doğrulanmış vaka 36.haftada rapor edilmiştir ve vaka sayıları zaman içinde artış göstermiştir. 43. haftada salgın başlamış ve 53. haftada başlangıç düzeyine inmiştir.

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Salgın sırasında 31117 vaka grip benzeri hastalık olarak raporlanmış, 635 vaka hastaneye yatmış (hastaneye yatış hızı %2.0) ve laboratuvar olarak doğrulanmış 17 vaka ölmüştür (ölüm hızı milyonda 11.5). Laboratuvar olarak doğrulanmış vakaların semptomları mevsimsel influenza ile benzerlik göstermiştir. Laboratuvar olarak doğrulanmış vakaların bazı semptomları öksürük (%90.9), ateş (%84.5), burun akıntısı (%69.5), baş ağrısı (%73.4) ve ishal (%17.5) olmuştur. Semptomların başlaması ile hastaneye başvuru suresi ortancası 3.5 gün (en az:1, en çok:11 gün), ölüm süresi ortancası ise 7.5 gündür. **Sonuç:** Diyarbakır'da 36 ve 53. haftalar arasında önemli bir grip benzeri hastalık salgını yaşanmıştır. Mortalite hızı beklenildiği kadar fazla olmamakla birlikte, bulaştırıcılık hızı yüksektir. Hastane başvurularındaki gecikme özellikle gebe kadınlarda ölüme yol açmış olabilir.

Anahtar Kelimeler: Pandemik influenza; H1N1, vaka ölüm hızı, hastaneye yatma hızı

Introduction

In April 2009 an H1N1 Influenza pandemic was detected in the United States and Mexico, and in May 2009 the first cases were reported in the European region by WHO. Through rapid and frequent international travel, it had spread to over 208 countries around the world and over 12 thousand deaths have been reported up to December 30, 2009[1]. The first local case was detected 18th June 2009 in Turkey by sentinel surveillance. As of 22 December 2009 nearly 12 thousand confirmed H1N1 cases were detected in Turkey, and the first death was reported on 22 October 2009[2]. As in most of the European countries, the pandemic peak during the 42nd- 48th weeks in Turkey.[3] Almost all of Turkey was affected by the pandemic influenza but in some regions activity was higher. Preliminary H1N1 influenza cases in Turkey were reported in first week of September. The first case was recognized in the 36th week and in 43rd week the peak had appeared (Figure 1). In this study, we describe the demographic characteristics and clinical features of H1N1 cases reported by health centers in Diyarbakir.

In Turkey influenza is monitored by sentinel surveillance; and Diyarbakir is one of 14 cities where sentinel surveillance is being applied. The city is located in the south-eastern region of Turkey. The city's population was 1.482.000 in 2008; 60.0% of the population was living in the urban area.

The first confirmed H1N1 case was detected in the 36th week and by that time there were daily notifications of ILI. All of the primary health centers and hospitals (both private and government hospitals) were obliged to report ILI cases to the Health Directorate of Diyarbakir. Between 01September and 3 January, 2010 31,117 ILI cases were reported and 731 nasopharyngeal swab specimens had been collected. All specimens were sent to a referral laboratory of Refik Saydam Hıfzıssıhha Central Laboratory, in the capital city Ankara-Turkey. Specimens were daily transferred. In this descriptive study, 731 cases were presented to evaluate the demographic and clinical features of ILI and confirmed pandemic influenza (H1N1) cases.

The cases were evaluated according to their age, gender, their complaints at the time of applying to the health centers, the recovery period, working status, pregnancy, presence of chronic disease, hospitalization and duration of hospitalization. Patients who experienced acute onset of fever, cough, rhinorrhea, profuse sweating, sore throat, headache, myalgia, fatigue, general body pain, diarrhoea or respiratory distress were evaluated for the presence of ILI. Patients with fever and two of the above symptoms were defined as ILI. 731 patients were randomly selected and assessed for the presence of the H1N1 virus.

Laboratory diagnosis:

The Turkish Ministry of Health designated the Central Laboratory of Refik Saydam Hıfzıssıhha Institute/Ankara as the reference laboratory for isolation of the H1N1 virus. RNA extraction: the samples coming in the transport medium were gently mixed by vortex and 200 or 400 ml of the samples was transferred into a 1.5 ml microcentrifuge tube in a biological safety cabinet. Following the kits instructions, RNA extraction was done with a Total Nucleic Acid Isolation Kit in a Magnapure LC 2.0 isolation machine (Roche, Germany) or with an EZ1 virus Mini Kit and a Qiasymphony Virus/Bacteria Mini Kit in an EZ1 Advanced XL and Qiasymphony isolation machine (Qiagen Gmbh, Hilden, Germany).

After PCR amplification, viral RNA was searched by using either an "in-house" reverse transcriptase real-time PCR (rt RT-PCR) protocol provided by the Center for Disease Control or a Qiagen artus Infl/H1 LC/RC RT-PCR Commercial Kit (Qiagen artus GmbH, QIAGEN Strasse 1, D-40724 Hilden, Germany). A commercial rt RT-PCR kit provided an opportunity for directly searching an 80 base pair region of the pandemic influenza A virus (H1N1) by using the Rotor-Gene 6000 instruments. In the "in-house" rtRT-PCR method, the clinical samples were first analyzed for the influenza A matrix gene, pandemic influenza A (H1) and for RNaseP as external control in the same run. If any sample yielded a positive result for the influenza A virus but negative for pandemic influenza A (H1), those samples were tested for seasonal influenza A (H1) and influenza A (H3), with subtype-specific primers for the hemaglutinin gene segments. In house Real-time RT- PCR was performed on ABI 7500. The 25 ml PCR mixture contained 5 ml of extracted RNA, 1 ml each of forward and reverse primers, 1 ml probe, 0.5 ml SuperScript III RT/ Platinium Taq mix, 12.5 ml of 2X Master mix, and 4 ml nuclease-free water. RT-PCR amplification conditions were as follows: reverse transcription at 50 °C for 30 min, Taq inhibitor activation 95°C for 2 min and 45 cycles at 95°C for 15 sec, 55°C for 30 sec.

Analysis:

Demographic and clinical characteristics were analysed by using descriptive statistics. Categorical variables were described with the use of percentages. Comparisons between patient groups were made to assess symptoms associated with H1N1 positivity. We compared categorical variables using the χ^2 or Fisher exact test. Means or medians were used for description of attendance date after symptoms started or death date after symptoms started. A p value <0.05 was considered significant. Statistical analyses were performed with Epi Info 2000 (USA, Atlanta). Daily reported cases were shown by weekly incidence Figures.

In this study, all procedures were enrolled in accordance with the Helsinki Declaration Principle. Individuals who participated in this study provided informed consent.

Results

Figure 1 shows the epidemiologic curve of the weekly number of ILI cases reported to the Health Administration between 36th to 53rd weeks. The ILI outbreak was recorded during 1 September 2009 to 3 January 2010. The main peak was observed in 43rd week. It was stable by the 50th week, and decreased from that time.

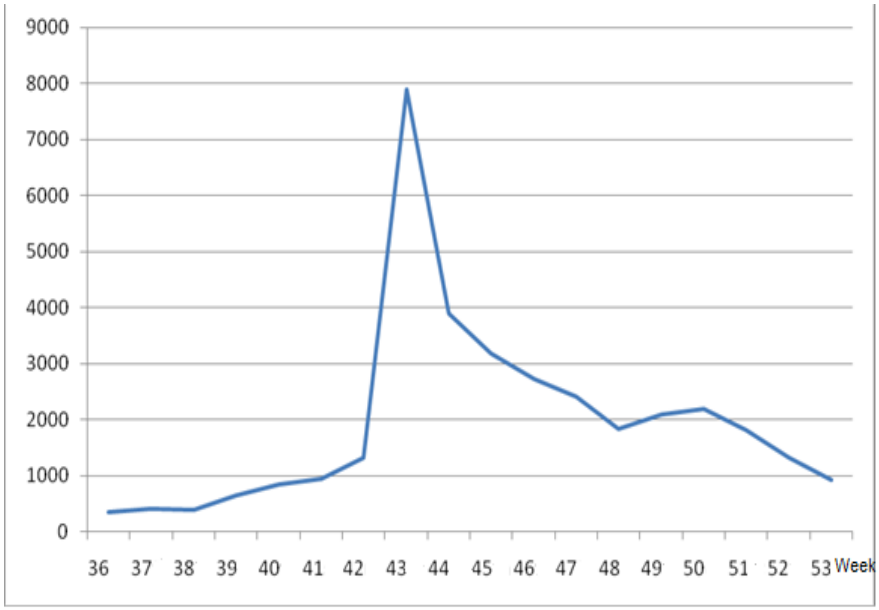

Figure 1: ILI Cases Reported by Health Centers (Diyarbakır, 2009)

In Figure 2, number of cases hospitalized and number of deaths during each week are presented. Hospitalized patients (635 cases) were admitted during epidemiologic weeks 42nd through 53th and 17 deaths were reported.

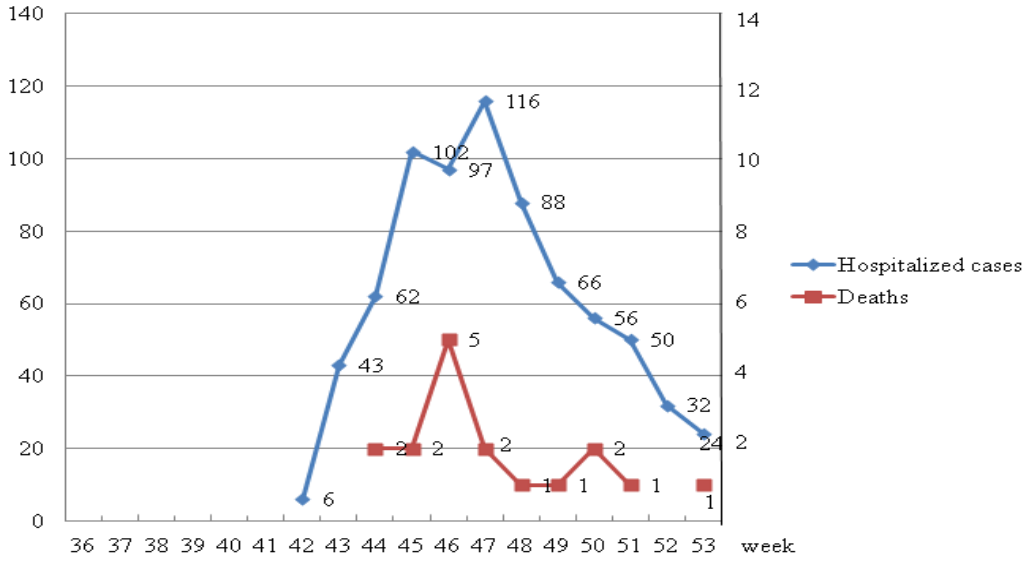

Figure 2: Number of cases hospitalized and number of deaths. (Diyarbakır, 2009)

The hospitalization peak occurred in the 47th week at a time 4 weeks after the peak of ILI cases. The first death was reported at the 44th week 2 weeks after the ILI peak. Totally 17 cases died during 36th to 53rd weeks of 2009. The Hospitalization rate per admission was %2.0 and the mortality rate per admission (case fatality rate) was ‰ 0.5. The hospitalization rate per 100.000 population was 42.8% and the mortality

rate per 1.000.000 population was 11.5. Nasopharyngeal swab specimens were collected from 731 patients from the 42nd week through the 50th week. In Table 1 summary of 731 cases is shown, according to week of attendance.

Table 1: Some characteristics of 731 specimen collected cases. (Diyarbakir, 2009)

		Attendance Weeks									
		42	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**Total**
Urban	n	14	104	231	103	56	40	32	15	9	604
	%	93.3	92.9	81.3	86.6	82.4	80.0	74.4	60.0	60.0	82.6
Rural	n	1	8	53	16	12	10	11	10	6	127
	%	6.7	7.1	18.7	13.4	17.6	20.0	25.6	40.0	40.0	17.4
Hospitalized cases	n	5	13	36	49	57	43	36	15	6	260
	%	33.3	11.6	12.7	41.2	83.8	86.0	83.7	60.0	40.0	35.6
Not hospitalized cases	n	10	99	248	70	11	7	7	10	9	471
	%	66.7	88.4	87.3	58.8	16.2	14.0	16.3	40.0	60.0	64.4
H1N1 (+) cases	n	12	82	176	52	26	19	12	14	13	406
	%	80.0	73.2	62.0	43.7	38.2	38.0	27.9	56.0	86.7	55.5
Ex cases	n	-	-	2	5	2	2	3	1	2	17
	%	-	-	0.7	4.2	2.9	4.0	7.0	4.0	13.3	2.3
Total	n	15	112	284	119	68	50	43	25	15	731
	%	2.1	15.2	38.9	16.3	9.3	6.8	5.9	3.4	2.1	100.0

Ninety three point three percent of the cases were from the urban region at the 42nd week but the illness skipped to rural region on the 50th week. Totally 35.6% of the 731 ILI cases were hospitalized. Between the 46th and 48th weeks the hospitalization rate was higher than during other weeks.

Fifty five point five percent (406 cases) of the 731 ILI cases were H1N1 positive. In the 42nd week 80.0% of the cases were H1N1 positive. H1N1 positive cases were compared with negative cases. Totally 406 patients (55.5% of 731 ILI patients) were H1N1 positive. Eighty three point three percent of positive cases were from urban areas. There was no statistically significant difference according to urban/rural residence or pregnancy.

Thirteen point one percent of positive cases were pregnant at the time specimens were collected (Table 2). Symptoms of patients are presented in Table 3.

Fever was present in 343 (84.5%) H1N1 positive cases, it was in 227 (69.8%) patients with negative cases ($p < 0.005$). The most frequent symptom was coughing (90.9%). Coughing was also significantly higher in H1N1positive cases ($p=0.005$). Running nose (69.5%), and myalgia (68.2%) were significantly higher in H1N1 positive cases than negative cases ($p<0.005$, $p=0.005$). Seventeen cases died but only data about 14 cases were reached.

Table 2: Sociodemographic characteristics and H1N1 confirmation status of 731 cases. (Diyarbakır, 2009)

		H1N1 confirmation			χ^2	p
Residence		**positive**	**negative**	**Total**		
Urban	n	338	266	604	0.015	0.903
	%	83.3	81.8	82.6		
Rural	n	68	59	127		
	%	16.7	18.2	17.4		
Age Groups*						
0-11 month	n	4	9	13	24.675	**0.001**
	%	1.0	3.0	1.9		
1-4	n	32	25	57		
	%	8.3	8.3	8.3		
5-9	n	76	32	108		
	%	19.6	10.6	15.7		
10-14	n	50	32	82		
	%	12.9	10.6	11.9		
15-24	n	117	77	194		
	%	30.2	25.5	28.2		
25-44	n	88	99	187		
	%	22.7	32.8	27.1		
45-64	n	18	18	36		
	%	4.7	6.0	5.2		
Over 65 years	n	2	10	12		
	%	0.5	3.3	1.7		
Sex						
Male	n	213	146	359	4.239	**0.040**
	%	52.5	44.9	49.1		
Female	n	193	179	372		
	%	47.5	55.1	50.9		
Pregnancy**						
Pregnant	n	25	19	44	0.031	0.860
	%	13.1	11.0	12.1		
Not pregnant	n	166	153	319		
	%	86.9	89.0	87.9		
Total	n	406	325	731		
	%	55.5	44.5	100.0		

* No age data for 42 cases

**No data on pregnancy for 9 women

Fisher exact test was used.

Table 3: Symptom of 731 cases and H1N1 confirmation status. (Diyarbakir, 2009)

Symptoms		H1N1 confirmation			χ^2	p
		positive	negative	Total		
Fever (+)	n	343	227	570	23.447	**<0.005**
	%	84.5	69.8	78.0		
Coughing	n	369	273	642	8.041	**0.005**
	%	90.9	84.0	87.8		
Running nose	n	282	183	465	13.471	**<0.005**
	%	69.5	56.3	63.6		
Sweat profusely	n	58	50	108	0.176	0.675
	%	14.3	15.4	14.8		
Sore throat	n	129	130	259	5.377	**0.020**
	%	31.8	40.0	35.4		
Headache	n	298	225	523	1.749	0.186
	%	73.4	69.2	71.5		
Myalgia	n	277	190	467	7.902	**0.005**
	%	68.2	58.5	63.9		
General body pain	n	104	105	209	3.638	0.056
	%	25.6	32.3	28.6		
Fatigue	n	108	99	207	1.339	0.247
	%	26.6	30.5	28.3		
Respiratory distress	n	26	23	49	0.293	0.588
	%	6.4	7.1	6.7		
Diarrhoea	n	71	56	127	0.065	0.799
	%	17.5	17.2	17.4		
Total	n	406	325	731		
	%	100.0	100.0	100.0		

In Table 4 the delay between the onset of symptoms and hospital admission was described for deaths of 14 H1N1 confirmed cases. The median age was 24 years (min: 1; max: 42 years). The median interval between the onset of symptoms and hospital admission was 3.5 days (min:1; max:11 days). Median interval between the onset of symptoms and occurrence of death was 7.5 days (min:2; max: 27days). Finally the median interval between death and hospital admission was 2.5 days (min:0; max:19 days). Ventilation was performed for all of the 14 death cases.

Discussion

Due to its increasing incidence in many countries and the occurrence of several large outbreaks in the present year, pandemic influenza (H1N1) is still an important and primary health issue. All 27 EU countries and 4 EFTA countries were reporting cases of pandemic (H1N1) during the 2009 influenza season. From week 41 to 51 the numbers of deaths each had shown a steady increase almost doubling every fortnight over six weeks.[4]

Table 4: Summary characteristics of deaths (n=14*) (Diyarbakır, 2009)

		Age	Interval between the onset of symptoms and hospital attendance (day)	Interval between the onset of symptoms and death (day)	Interval between death and hospital admission (day)	Ventilation duration (day)
Mean		21.85	4.6	8.7	3.9	3.6
Median		24.0	3.5	7.5	2.5	2.5
Minimum		1.00	1.0	2.0	.0	.0
Maximum		42.00	11.0	27.0	19.0	19.0
Sex: male/female	7/7					
Pregnancy rate (pregnant/all)	2/14					

* No data for 3 deaths

In the present study pandemic influenza (H1N1) experience in Diyarbakir city was presented. As in European countries, the outbreak in Diyarbakir was started on the 41st-42nd weeks and the case number fell to the baseline level by the 53th week. After 2 weeks death numbers began to increase and this trend was similar for EU countries.[5] In Diyarbakır, during the 17 weeks of outbreak totally 17 confirmed H1N1 cases died. The mortality rate was 11,5 per 1 billion persons. The mortality rate in our case was higher than in some of EU countries, but it was lower than Mexico (0.1%).[6] In present study case fatality rate 0.5‰ was lower than the rate of 4.0% reported from Mexico.[7] Case fatality rate was also smaller than in the United Kingdom (1.0-3.0 ‰).[8] However it was higher than New Zealand 0.05 ‰.[9]

The influenza hospitalisation rate changed from 11% in the 29th week to 5.0% in 31st week.[10] In England the hospitalization rate was 2.0%.[8] In our case, hospitalization rate was minimum in the 42nd week (0.4%); it increased to maximum level (4.8%) by the 47th to 48thweek and then decreased to 2.5% at the 50th week (overall hospitalization rate was 2.0%). Most of deaths were reported at the time hospitalization rates were increasing. In present study 731 ILI cases were investigated with detailed information about clinical and demographical features of the new virus infection. It was expected that influenza might be more prevalent in urban areas. Higher population density may cause higher morbidity in urban areas for communicable diseases like influenza. However it was reported that rural areas did not show a predictive value of protection against pandemic influenza in Kanagawa.[11] Lower morbidity in the towns and cities is likely explained by effective preventive measures in urban areas. Most of the cases at the beginning of the outbreak were from urban areas. At the later stage of the outbreak it was found that nearly 60% of the cases were from urban and 40% from rural. This result may indicate that influenza start in urban andspread throughout the rural.

In present study the proportion of laboratory confirmed cases were not different within subgroups, like sexes, pregnancy, and residency (urban/rural). But in the 25-44 years age group H1N1 positivity was higher than in other age groups. In Bolivia, it was found that the proportion of H1N1 laboratory confirmed cases was higher for men and there was no difference for age groups.[12] It was reported

that the median age of hospitalized infected cases was younger than common with seasonal influenza.[13] In present study 55.3% of the cases that were investigated detailed were young people, aged between 15-44 years old.

Clinically, pandemic influenza (H1N1) behaves similarly to seasonal influenza. It was reported that the only differentiating characteristics were vomiting and diarrhoea in a quarter of infected patients, which were rare in seasonal influenza.[7] Cough was the most common symptom, present in 82.0% of the cases, followed by fever (78.0%).[10] In another study most common symptoms were reported as fever (67.4%), cough (69.5%) and incidence of diarrhoea was 2.8%.[14] In present study like other studies coughing (90.9%), fever (84.5%), running nose (69.5%), and myalgia (68.2%) were the most common symptoms in laboratory confirmed H1N1 cases. Those symptoms were higher in laboratory confirmed H1N1 cases than H1N1 negative cases. However diarrhoea was determined 17.4% of the 731 ILI cases and 17.5% in laboratory confirmed H1N1 cases.

The average time interval between date of symptom onset and diagnosis was 3.6 days was reported from Germany.[10] In England death occurred a median of 12 days after influenza like symptoms began, in cases admitted to hospital with pandemic A/H1N1, symptoms started a median of three days before admisson.[15] In present study the results was similar to those in England and in Germany. Death occurred 7.5 (median) days, and hospital admission was 3.5 days after onset of symptoms started. Median interval between onset of symptoms and death occurrence was higher than SARS (20 days)[16] and in a review conducted by Bueving HJ et al there was no reported deaths due to seasonal influenza in 0-19 years old children.[17]

Like in many other regions intensive outbreak of pandemic (H1N1) influenza occurred from week 41 to 50. The hospitalization rates and case fatality rates in our case were similar to other regions of EU countries. The outbreak was started in urban region and spread out to rural region immediately. Although its progress was worse in children or in older aged people, age distribution of laboratory confirmed cases was more prevalent in young people and most of the deaths were younger aged people. Clinical symptoms of pandemic (H1N1) influenza were similar to seasonal influenza except from diarrhoea. An average time interval between date of symptoms onset and dying was short according to other communicable diseases. Although the pandemic (H1N1) influenza seems to be a mild disease clinically, it was causing deaths. The first wave might be completed, left major questions marks concerning its future.

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References

1.Pandemic (H1N1) 2009 - update 81, (2009)

http://www.who.int/csr/don/2009_12_30/en/index.html (accessed: 30.12.2009)

2. Grip, Turkish Ministry of Health, Dec.2009. http://www.grip.gov.tr/(accessed: 30.12.2009)

3. Main surveillance developments in week 51/2009 (from 14 Dec 2009 to 20 Dec 2009) ECDC, (2009).

http://ecdc.europa.eu/en/publications/Publications/091224_EISN_Weekly_Influenza_Surveillance_Overview.pdf (accessed: 04.01.2010)

4. Epicurve, 2009

http://www.ecdc.europa.eu/en/healthtopics/PublishingImages/EU_Epicurve.JPG (Accessed: 05.01.2010)

5. European Centre for Disease prevention and control 2009. Pandemic H1N1 2009 Risk Assesment Update-30 Dec 2009

6. Echevarria-Zuno S, Mejia-Arangure JM, Mar-Obeso AJ, Grajales-Muniz C, Roboles-Perez E, Gonzalez-Leon M, et al. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. Lancet 2009; Nov 11 epub ahead of print.

7. Luan-Yin Chang, Shin-Ru Shih, Pei-Lan Shao,Daniel Tsung-Ning Huang, Li-Min Huang. Novel Swine-origin Influenza Virus A (H1N1): The First Pandemic of the 21st Century. J Formos Med Assoc 2009; 108(7): 526-32.

8. Advice to businesses on helping minimise the spread of swine flu. Cabinet office UK, (2009). http://www.cabinetoffice.gov.uk/media/225195/20090716-planningassumptions.pdf (accessed : 24.12.2009)

9. Baker MG, Wilson N, Huang QS, Paine S, Lopez L, Bandaranayake D, et al. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. Euro Surveill 2009; 14(34):pii=19319.

10. Gilsdorf A, Poggensee G. On behalf of the working group pandemic influenza A(H1N1)v Influenza A(H1N1)v in Germany: the first 10,000 cases. Euro Surveill 2009; 14(34):pii=19318.

11. Nishiura H, Chowell G. Rurality and pandemic influenza: geographic heterogeneity in the risks of infection and death in Kanagawa, Japan (1918-1919) N Z Med J 2008; 121(1284):18-27.

12. Gianella A, Walter A, Revollo R, Loayza R, Vargas J, Roca Y. Epidemiological analysis of the influenza A(H1N1) outbreak in Bolivia, May-August 2009. Euro Surveill 2009; 14(35):pii=19323.

13. Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, et al. California Pandemic (H1N1) Working Group. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 2009; 302(17):1896-902.

14. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. National Influenza A Pandemic (H1N1) 2009 Clinical Investigation Group of China. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009;361(26):2507-17.

15. Donaldson LJ, Rutter PD, Ellis BM, Greaves FEC, Mytton OT, Pebody RG, et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 2009; 339: b5213 doi:10.1136/bmj.b5213 page: 1-8

16. Ofner-Agostini M, Wallington T, Henry B, Low D, McDonald LC, Berger L, et al. The SARS Investigative Team and T. Wong. Investigation of the second wave (phase 2) of severe acute respiratory syndrome (SARS) in Toronto, Canada. What happened? Canada Communicable Disease Report 2008; 34 (2):1-11.

17. Bueving HJ, Van der Wouden JC, Berger MY and Thomas S. Incidence of influenza and associated illness in children aged 0–19 years: a systematic review. Reviews in Medical Virology 2005; 15:383–391