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Pandemic Flu in Islamic Republic of Iran; A Review of Health System Response From July to November

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A B S T R A C T

Background: Pandemic flu is a concerning problem with potentially high mortality and morbidity rates, so needs a proper health system response in each country.
Objectives: To evaluate the nationwide health system response in Iran after declaration of H1N1/Swine flu pandemic in June 2009.
Patients and Methods: A surveillance system in all regions of country was implemented upon declaration of pandemic flu by the World Health Organization; RT-PCR methods in National influenza reference laboratory in the capital were used to diagnose all types of circulating influenza viruses. Epidemiological data as well as laboratory response, performances of 40 medical universities all over the country concerning case detection and timing of admission were analyzed.
Results: 3847 confirmed cases of H1N1/Swine flu were detected up to November 2009, which 140 cases died (i.e.; 3.8% mortality rate), highest mortality rates were observed in infants (7.4%) and those older than 50 years (9%). For about 78% of confirmed cases of Swine flu, the result had been notified within 3 days after sample submission, despite the fact, most of mortalities had occurred in this group of "short result gap".
Conclusions: Although overall mortality rate in such a pandemic was comparable or better than other developing countries, it was shown that late hospital admission and late laboratory diagnosis were associated with higher mortality rates. Better case detection and earlier admission with more available and equipped laboratories seems necessary to improve the health system response for future pandemics in Iran.

Keywords: Pandemics; Iran; Influenza, Human

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Implication for health policy/practice/research/medical education:
Pandemic flu seems to be inevitable for all countries, so lessons from shortages as well as good experiences in each pandemic not only should be documented but also should prepare health system to respond more effectively in future epidemics and pandemics.

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1. Background

Shortly after detection of first case of H1N1/Swine flu as a novel reasserting virus of swine, human, and avian strains of influenza in June 2009 in Mexico, the world health organization raised its pandemic alert level in March 2009. Although the pandemic was stopped in August 2010, but more than 214 countries reported confirmed cases of this type of influenza (1).

Around 61 million cases of pandemic H1N1 influenza with more than 12000 deaths and 270,000 hospitalizations occurred in the US alone up to April 2010 (1); it was estimated that more than 30% of population in the UK got flu during the first wave of the pandemic in the UK, and hospitalization rate was more than 2% (2). The overall attack rate in Hong Kong, until December 2009 was 10.7 percent (3).

Mortality rate was also different in various countries; in the US it was 0.12 deaths per 100000 population (4), in surveillance study of 1088 cases in California in which around 11 percent of ICU admitted cases died, most cases died due to respiratory failure resulting from severe pneumonia and acute respiratory distress syndrome (5); in England, death rate was 0.6 per 100000 and was highest in infants under one year (6) and Bangladeshi or Pakistani origin children showed higher mortality rates. This was in contrast to a study in Mexico where highest mortality was observed in patients older than 70 years (7).

In Hong Kong case-fatality rates were 0.4 cases per 100,000 in children aged 5 to 14 years and 26.5 cases per 100,000 in adults aged 50 to 59 years (3). About 70% of admitted cases in the US, had at least one underlying problem which could potentially increase the severity of illness; chronic lung disease, immunosuppressive conditions, cardiac disease, pregnancy, diabetes mellitus and obesity were the most common underlying problems (1). Although race had affected not only the rate of acquiring the disease but also the fatality rate (1); indigenous population of Canada, Australia, and New Zealand as well as native Americans were more affected by disease and had higher fatality rates in several studies (8-10).

Although immediate virus sharing following virus isolation promoted rapid development and usage of diagnostic methods and many of the initial responses to the 2009 H1N1 pandemic, but there are many lessons to learn for future pandemic planning (2). An important challenge faced initially in this pandemic was temporary collecting and sharing clinical data to inform optimal management of critically ill patients worldwide. There is no doubt that establishing clinical research infrastructure prior to a pandemic and a central institutional review board preferably by expert teams of WHO would facilitate data collection and analyses not only for the next influenza pandemic, but also for other emerging or re-emerging pandemic problems (11).

In Islamic Republic of Iran, health system response was initiated early after declaration of the WHO in 2009 and efforts were made to contain the impacts of such a pandemic all around the country by harmonized national planning and close cooperation with the WHO programs. Given the importance of evaluation of such efforts, a review of national health system response during early phases of pandemic is important not only to detect shortages but also to understand the capabilities of Iranian health system to share with other countries and better assessment of pandemic preparedness plans for the future.

2. Objectives

The objective of this study was to evaluate the nationwide health system response in Iran after declaration of H1N1/Swine flu pandemic in June 2009.

3. Patients and Methods

This study was performed from June 1st until November 30th 2009 as a surveillance study; surveillance forms contained questions regarding demographic data and clinical information of suspected cases. At first special referral hospitals and clinics for all public health facilities were designated by each provincial university of medical sciences (PUMS) to cover all referrals. With more progression of pandemics, more centers were allocated for sampling; these centers were equipped with nasopharyngeal swabs and such samples were sent to regional and national influenza laboratories. On April 2nd, 2009 and after the official declaration of the first human cases of H1N1 by the WHO, the Ministry of health and medical education of Iran provided a new H1N1 nationwide manual for surveillance of disease in all public and private sections in the country, and all provincial universities of medical sciences (PUMS) were obligated to disseminate surveillance questionnaires to healthcare institutions in their provinces. Case definitions were as follows (12):

• A suspected case of H1N1 viral infection was defined as presenting with a high grade fever (> 38°C) or at least two acute respiratory symptoms including: nasal obstruction/rhino rhea, sore throat, cough, fever/feverishness and meets at least one of the following criteria:

1) Within the past seven days has returned from a country or region with an epidemic of H1N1

2) In close contact (within two meters) with a confirmed case of H1N1 within the past seven days

3) Has a moderate to severe respiratory illness requiring hospitalization.

• A probable case of H1N1 infection was defined as a suspected case which is confirmed with positive laboratory test results for influenza A but its subtype is unknown, or unexplained or unusual clinical patterns associated with serious or fatal cases of H1N1.

• A definite case of H1N1 infection was defined as a case with suspicious picture for whom the result of one of the

following laboratory tests becomes positive: a) reverse transcriptase PCR (RTPCR) b) viral culture c) 4 fold rising titer of neutralizing antibody against H1N1 influenza virus.

The designated centers were asked to take samples from patients who fulfilled the case definition criteria as well as those patients with severe pneumonia and respiratory distress who were hospitalized and send them for confirmation to the designated reference laboratories. Data of confirmed cases from each PUMS was sent to the Influenza surveillance center at center of diseases control of Ministry of health and medical education of Iran.

Nasal and throat swabs were taken for all patients who met the aforementioned criteria as suspected cases and samples examined by RT-PCR protocol distributed by the United States Centers for Disease Control and Prevention (US CDC) for the detection and characterization of pandemic H1N1 virus, as recommended by WHOM (13). Since declaration of the pandemic by WHO, sampling was started from June 1th, 2009 and the present study was over on November 30th, 2009. At the same time, national influenza committee, deputy of education in Ministry and other partners started to harmonize the activity of case prevention, diagnosis and management; i.e. education of public sector and updating all physicians about the plan, providing the drugs needed and better equipments and spaces for medical centers. Special attention was paid to foreign passengers and country borders especially at airports for case detection. Instructions regarding treating confirmed and in special settings for suspicious cases (including those with severe picture or with underlying disorder) with oseltamivir were also disseminated to hospitals all around the country. To exam the role of laboratory response in the prognosis during such a pandemic in our country we also defined three further definitions:

• Specimen gap: time elapsed from taking the sample until delivering to the laboratory.

• Response gap: time elapsed from the point the lab result become ready and was reported to the medical center.

• Result gap: from submission until getting the result by physicians, we classified it as short (less than 3 days), moderate (3-7 days) and long (more than 7 days).

• Delay admission: 3 days or more from onset of disease until admission.

• Late laboratory diagnosis: more than one day elapsed since receiving the sample by the laboratory until announcing the results to in charge physicians

Beside the aforementioned variables, we looked for distribution of all influenza cases, their fatalities, age and sex distribution, performances of PUMS, quality of specimens and underlying disorders. All data was analyzed by SPSS software (version 16) for frequencies as well as statistical analysis (appropriate Pearson chi-square or spearman correlation tests and ANOVA student t-test).All direct and indirect researchers' commands and interventions for treatment were according to the declaration of Helsinki, also all patients' names were kept secret.

4. Results

10026 samples from June 1st until November 30th,2009 were submitted and patients information were gathered in the national influenza laboratory and some other designated well equipped provincial university affiliated laboratories. Near 0.002 of samples were not suitable for analysis, so they were excluded. From 10005 samples, following results were obtained: H1N1/Swine flu: 3847, influenza A (not specified type): 257, influenza B virus:17 and influenza A/H3N2:9 cases; test results for 5875 samples were negative for any influenza virus (59% of total submitted samples); so, from 41% of positive samples, 93% had positive results for H1N1/Swine flu virus test. Mean age of cases was 27.8 years (SD = 18.78). Sex distribution and related mortality has been shown in *Table 1*. 140 deaths (i.e.; mortality rate of 3.8%) were attributed to influenza positive cases; all in H1N1/Swine flu, so no mortality from other types of influenza was noted; statistical analysis showed this difference as significant (P value = 0.003).

Table 1. Outcome Versus Sex Distribution Among 10005 Submitted Samples

Sex	Laboratory Results					Total
	A/H1N1/Swine Flu	A	B	Negative	A/H3N2	
Female						
Died	71	0	0	6	0	77
Alive	1917	125	12	2909	4	4967
Total	1988	125	12	2915	4	5044
Male						
Died	69	0	0	8	0	77
Alive	1790	132	5	2950	5	4882
Total	1859	132	5	2958	5	4959
Missed Data				2		2

Mortality rate in cases with A/H1N1/Swine flu was a bit higher in males (3.7% vs. 3.6%) but the difference was not significant (P value = 0.7). The highest mortality was observed in patients older than 50 years (9%) and then in infants (7.4%), but a large proportion of deaths (60 cases) occurred in 20-40 years old cases with a mortality rate of 4.1%;compared to other age groups, this age group also had the highest rate of submitted samples. Total mortality rate for patients under 20 years and above 40 years old were 2.7% and 5.8% respectively. Association between age groups and mortality rate was significant (P value < 0.0001). More information concerning mortalities and related risk factors has been published previously (14).

40 PUMS were participated in the surveillance, among them Tehran university of medical sciences and Shahid Beheshti university of medical sciences which survey the health issues in the capital, Tehran reported 1133 cases (out of 2765 samples) with A/H1N1/Swine flu and 77 cases with other influenza viruses (i.e. positivity rate of 41% for A/H1N1/Swine flu and 2.8% for other viruses). Other universities have submitted 7261 cases with positivity rate of 37.5% for A/H1N1/Swine flu and again 2.8% positivity rate for other types of influenza viruses.5 cases(2 cases with A/H1N1/Swine flu and 3 cases with influenza A, non A/H1N1/Swine flu and non A/H3n2) were imported cases from other countries. There was very different and meaningful performance variations both for quality (samples quality) and quantity points of view (P value = 0.001 by chi-square test) among universities rather than the capital; the number of submitted samples varied from just 1 to 669 samples; rate of positive samples for any type of influenza virus was below than 15% up to 77%. Quality of specimens were recognized as good, moderate and unacceptable in 83%, 16.9% and less than 0.1%, respectively; the difference between PUMS from quality point of view was significant (P value = 0.001).

Data for result gap is available for 3640 cases including 110 deaths. *Table 2* shows the association between result gap and outcome for various influenza infections with a significant difference (P value= 0 < 0.001); for H1N1 cases, around 78% of positive answers had been taken by physicians within 3 days of sample submission, unexpectedly however, it shows that mortality in the group with short result gap was higher (3.7%) than moderate result gap (0.7%) and long result group (no death).

Table 2. The Association Between Result Gap (RG) and Mortality

Groups	Outcome		Total	P value
	Died	Alive		
H1N1/Swine flu long RG No. (%)	0 (0)	80 (100)	80 (100)	0 <0.001
Moderate RG No. (%)	5 (0.7)	720 (99.3)	725 (100)	
Short RG No. (%)	105 (3.7)	2730 (99.3)	2835 (100)	
Other viruses long RG No. (%)	-	6 (100)	6 (100)	Not applicable
Moderate RG No. (%)	-	50 (100)	50 (100)	
Short RG No. (%)	-	227 (100)	227 (100)	

3619 of 3639 samples had been taken during first 24 hours of admission (99.5%); however, mean value of specimen gap for all specimens was more than 3 days (*Table 3*). The table shows the specimen and response gaps regarding death; the difference between dead and alive groups regarding specimen gap was not significant (P value = 0.7) but for response gap was significant (P value = 0.0001).

Table 3. Association Between Specimen Gap and Response Gap Concerning Mortality Among Submitted Samples

	Outcome	No.	Mean	Std.Deviation	Std.Error Mean	P value
Specimen gap						0.7
	Died	125	3.48	4.66	0.417	
	Alive	9840	3.34	4.98	0.050	
	Missed data	40				
Response gap						0.0001
	Died	124	0.97	1.58	0.142	
	Alive	9863	2.66	3.05	0.030	
	Missed data	18				

Considering the association between specimen gap among various viruses and negative samples for influenza, it was shown that mean times were 3.05,3.26,2.66,3.88 and 3.52 for A/H1N1/Swine flu, A, A/H3N2, B and negative groups respectively and the difference was statistically significant (P value = 0.0001). This was true again for response gap among above viruses (2.37,1.92,3.44,2.64,2.85 respectively, and statistically significant; P value = 0.0001); so there was difference for specimen submission and response of laboratory depending on the type of viruses.

Table 4 shows the mortality rates among early versus delayed admitted cases as well as the early versus late laboratory diagnosis in cases with A/H1N1/Swine flu; as it has been shown, here was a significant association between rapidity of admission and mortality rate (P value = 0.0001); there was also a significant association between rapidity of admission and rapidity of laboratory diagnosis regarding mortality rate (P value = 0.0001) (*Table 5*).

Table 4. Association Between Mortality Rate and Time of Admission in Cases With A/H1N1/Swine Flu

Time of Admission	Died	Alive	Total Mortality Rate	P value
Early admitted	69	2446	2.5%	0.0001
Late admitted	42	1057	3.8%	

Table 5. Association Between Mortality Rate and Rapidity of Laboratory Diagnosis

Time of Admission	Mortality Among Early Lab Diagnosed Group	Mortality Among Late Lab DiagnosedGroup	P value
Early admitted	(55/974) 5.6%	(13/1740) 0.007%	0.0001
Late admitted	(32/457) 7%	(10/642) 1.5%	

5. Discussion

According to the report of WHO regional office for eastern mediterranean region (EMRO) on November 22,2009 (a few days after termination of present study), more than 38359 cases of A/H1N1/Swine flu had been reported with almost 330 deaths; so apparently, the fatality rate of this region was 9/1000 cases (15). This rate is obviously under reported since the observed rate in north American was around 28/1000; still the reported rate of Iran (30/1000 cases) is acceptable given the limitations of health system response when comparing with developed countries, it shows acceptable case finding and registry. It also shows that many countries in this region need to improve their case finding during pandemics. On the other hand, the mortality rate was around 0.2 per 100000 people for Iran; this observed rate is higher than the US but much lower than the UK and Hong Kong rates. Although widespread and probably on time response of hospital settings, public education for timely admission as well as availability of oseltamivir in designated hospitals since the onset of pandemic could be effective, but some under reporting of cases, especially for those in remote areas of country as well as ethnic or genetic vulnerability for severe flu infection cannot be ruled out (1).

Performances of various medical universities were significantly different and cannot be explained just by the provincial population; positivity rate of samples were higher for Tehran universities; it could be due to better selection of samples, uneven distribution of cases especially during early phases of disease or sending samples with better quality to the national influenza reference laboratory which is located in Tehran. Still, the results shows that there might be a need for better supervision for sample submission from some universities as well as availability of more equipped laboratories in each province center for future pandemics.

Influenza viruses other than A/H1N1/Swine flu accounted for 3% of samples in this study; there was no mortality reported from them, this might be due to this reality that A/H1N1/Swine flu virus was the dominant virus for which there was no vaccination during early phases of disease in Iran; although the severity of this novel virus was shown to be similar to seasonal viruses (16) but other seasonal influenza viruses could be appropriately covered, especially in high risk groups by on time vaccination promoted via health system and mass media educational programs.

2288 of 3847 cases of A/H1N1/Swine flu in this study were younger than 25 years (around 60%), which this is compatible with the age group involvement in the US (1).

Looking gaps for specimens, it is evident that although mean time for specimen gap was 3 days and seems to be long (probably due to long distance of some provinces to the reference lab in the capital), but even for those with short response gap, no obvious decrease in mortality occurred. According to the Iranian national guideline for usage of antiviral drugs in countries committed to worldwide regulations (based on the WHO recommendations), all confirmed and suspicious cases of swine flu in

this study could be candidate for antiviral therapy and these gaps might not be as important to overall mortality or morbidity (17). Even for delayed admitted cases with underlying disorders, it was permitted to start antiviral therapy,although treatment is of greatest benefit when given within 48 hours of symptom onset (17, 18).

However, decisions to initiate antiviral therapy were varied during this pandemics; in Australia the decision to treat an individual patient, particularly before the results of confirmatory testing are available, depended on three factors: an assessment of the likelihood of influenza, based on the known prevalence of infection in the region, a history of contact and the characteristics of the illness, an assessment of the likely benefits of treatment, based on the presence of established complications, comorbidities and risk factors and the time from the onset of illness, the availability of antiviral drugs, and public health policies regarding distribution of the national stockpile (18). According to the revisable manual of antiviral therapy which was published in April 2009 by the ministry of health and medical education of Iran, all suspicious, probable and confirmed cases of A/H1N1/Swine flu were candidate for treatment with antiviral therapy (12), the strategy which remained unchanged during the whole period of present study. Such a strategy need to be revised as the potential likelihood of resistance to current drugs regarding their overuses (19).

In a study in admitted children in Poland, just 62% of cases received oseltamivir during their admission (20). Another study in Spain at the same time showed that just 14 cases of 127 did not receive the medication (21). In Islamic republic of Iran, this drug was distributed all over the country before pandemic and it was expected that all hospitals had accessibility to treat patients without delay.

Shorter result gap for higher mortality group in this study showed the maximal efforts of the reference laboratory to feedback the physicians, in interpandemic phases when case finding and selecting candidates for antiviral therapy is more important from cost-benefit point of view, it has been shown that early diagnosis especially in emergency departments could positively affect the admission rate of cases, shorter duration of antimicrobials and better selection of candidates for antiviral therapies (21). This may also help to avoid unnecessary interventions and drug interactions.

There was also a significant difference between various viruses for specimen and result gaps showing that probably most ill appearing cases were in A/H1N1/Swine flu group resulting in a more rapid laboratory testing.

Concerning delayed admission, it was shown that this factor could definitely affect the prognosis. In one study in a pediatric center, delaying the treatment more than 72 hours after the onset of symptoms and having a previously known disease were variables associated with PICU admission, so longer disease evolution before initiation of oseltamivir was found in patients who required admission to PICU (20). It is not surprising that in ill appearing late admitted group in our study, the highest mortality was seen in short result gap, again in spite of more rapid lab result and initiation of antiviral therapy. Interestingly, late admitted cases with long result gap had lower mortality probably due to milder courses of their diseases; this has been shown in other studies as well and almost all such milder cases did not need and antiviral therapy (21). Although overall performances of health system response for containment and mortality rate in such a catastrophic worldwide event seems reasonable, above results should prompt Iranian health system to set up more well equipped laboratories nationwide to change the strategy of antiviral usage during interpandemic phase toward a more cost benefit national program. There is also a need for study of private sector laboratories in pandemic and interpandemic phases.

Our study had some limitations; many questionnaires had not been appropriately filled out, probably due to emergency situation, no data is available for usage of antiviral drugs with the patient's general condition. Also economic impact of such a pandemic cannot be judged in such a large retrospective study, so future studies must concentrate on evaluating these factors as well and it is reasonable to conduct these studies under WHO supervision to achieve the best preventive strategies as well as action plans for both future pandemics and interpandemic phases.

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