Prevalence of human influenza virus in Iran: Evidence from a systematic review and meta-analysis

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ABSTRACT

This systematic review and meta-analysis was conducted to consolidate the information on the prevalence of the human influenza virus, including H1N1 and H3N2 as well as B-type influenza across Iran from 2000 to December 2016. The literature search was based on keywords including "influenza and Iran", "human influenza", "prevalence", "relative frequency", "incidence", and "drug" in MEDLINE (PubMed), Web of Science, Scopus, ScienceDirect, the Iranian Research Institute for Information Science and Technology (IranDoc), the Regional Information Centre for Science & Technology (RICeST), and the Scientific Information Database (SID). The literature search revealed 25 prevalence and seven drug resistance studies. In order to investigate the publication bias among studies, funnel plots and Egger's test were used. Additionally, the statistical tests of I^2, Chi^2, and Tau^2 were computed, and the results were visualized with forest plots. A high level of I^2 and Chi^2 were obtained among studies, which are representative of the high variation and remarkable heterogeneity between studies. This may be because of various methodologies applied in the studies such as study design, age groups, and different populations.

The prevalence of influenza H1N1, H3N2, and B in Iran have not yet been well evaluated. The heterogeneity among studies reveals that more attention should be paid to considering various factors, including gender, population size, and underlying conditions.

1. Introduction

The influenza virus is an epidemic infectious agent that belongs to the Orthomyxoviridae family [1]. Until now, three types of influenza viruses, including A, B, and C have been classified based on their immunological and biological properties [2,3]. The first two types, A and B, cause annual epidemics and affect people's lives and the economy while the type C virus has fewer effects [4].

The most frequent type of influenza virus that causes infections all over the world is type A [5]. Further classification of type A influenza viruses is based on the presence of two proteins on the virus surface, the hemagglutinin, or "H" protein, and the neuraminidase, or "N" protein. Therefore, H1N1 and H3N2 are known as the seasonal influenza A virus subtypes [6]. In April 2009, a new swine-origin H1N1 influenza A virus was detected in Mexico, which was called pandemic H1N1 (pH1N1). After that, the World Health Organization declared a pandemic phase due to pH1N1 propagation across different regions in Iran [7]. However, the H3N2 subtype has usually represented the predominant influenza A strain throughout the season [5]. Although there is limited information on the epidemiology and pattern of influenza B circulation in most countries, seasonal mortality due to influenza B-attributable respiratory illness was reported as 29% in the United States [8].

Influenza viruses have a more significant effect on communities than other common respiratory illnesses due to their capacity to be fatal and their highly contagious nature [9,10]. The economic aspects of the influenza burden are notable during both pandemics and seasonal epidemics. Hence, the influenza virus is considered a major global health threat [11,12].
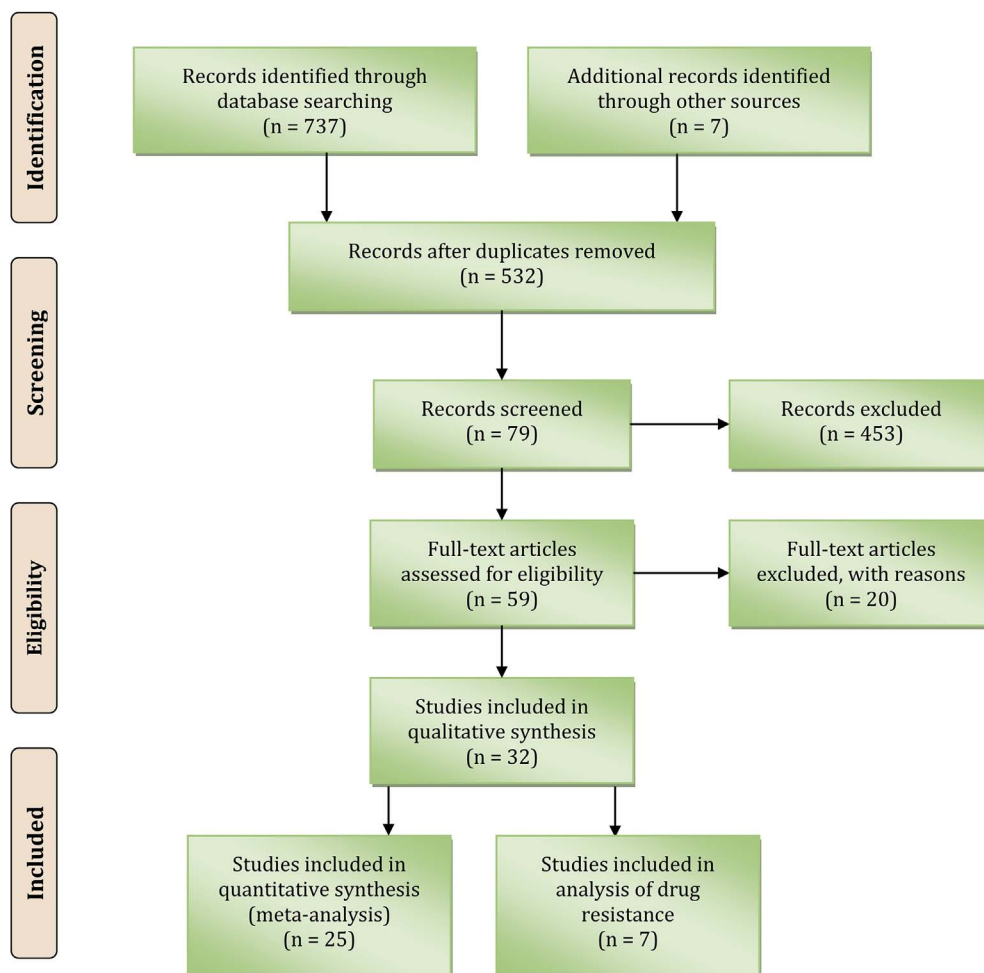
Information about the clinical features and epidemiological aspects of human influenza infection indicates variability in different geographical regions. Therefore, a systematic review and meta-analysis can provide a deeper understanding and a better perspective of influenza infection. The present data will assist in control, protection, and prevention of influenza prevalence events.

To the best of our knowledge, there is no overall estimation of human influenza infection prevalence among the Iranian population. This study was conducted to consolidate the information on the prevalence of the human influenza virus across Iran.

2. Material and methods

2.1. Study question

This study aims to survey the prevalence of three major human influenza viruses (A/H1N1, A/H3N2, and B) in Iran. Another objective is the investigation of drug resistance to common medications used for influenza treatment.

2.2. Search strategy

In our study, we review published articles from 2000 until December 2016, in both English and Persian. A comprehensive search on influenza prevalence in Iran was carried out in the main electronic databases, including MEDLINE (PubMed), Web of Science, Scopus, and ScienceDirect. The keywords and terms used in this study include "influenza and Iran", "human influenza", "prevalence", "relative frequency", "incidence", and "drug". Additionally, all of the relevant references cited in the original articles were explored manually to locate other articles that were not indexed by the mentioned databases. The reports were reviewed and managed with EndNote X7.1 (Thomson Reuters).

2.3. Gray literature search

Iranian databases, including the Regional Information Centre for Science & Technology (RICeST), the Scientific Information Database (SID), and the Iranian Research Institute for Information Science and Technology (IranDoc) were searched to find relevant research projects, dissertations, scientific reports of congresses, and organization reports.

2.4. Inclusion and exclusion criteria

To acquire reliable articles, the following criteria were considered: 1) studies must have reported data on flu-like syndromes; 2) the study reports the prevalence of influenza containing the influenza A/H1N1, A/H3N2, and B subtypes. Furthermore, reports including the assessment of resistance to human influenza medications were taken into account. The exclusion criteria were studies on individuals who were infected with avian influenza. The reports regarding the prevalence of animal influenza as well as reviews that did not contain original research data were also excluded.

2.5. Data extraction

In order to collect the data, two independent investigators screened articles at three levels: title, abstract, and main text. The following
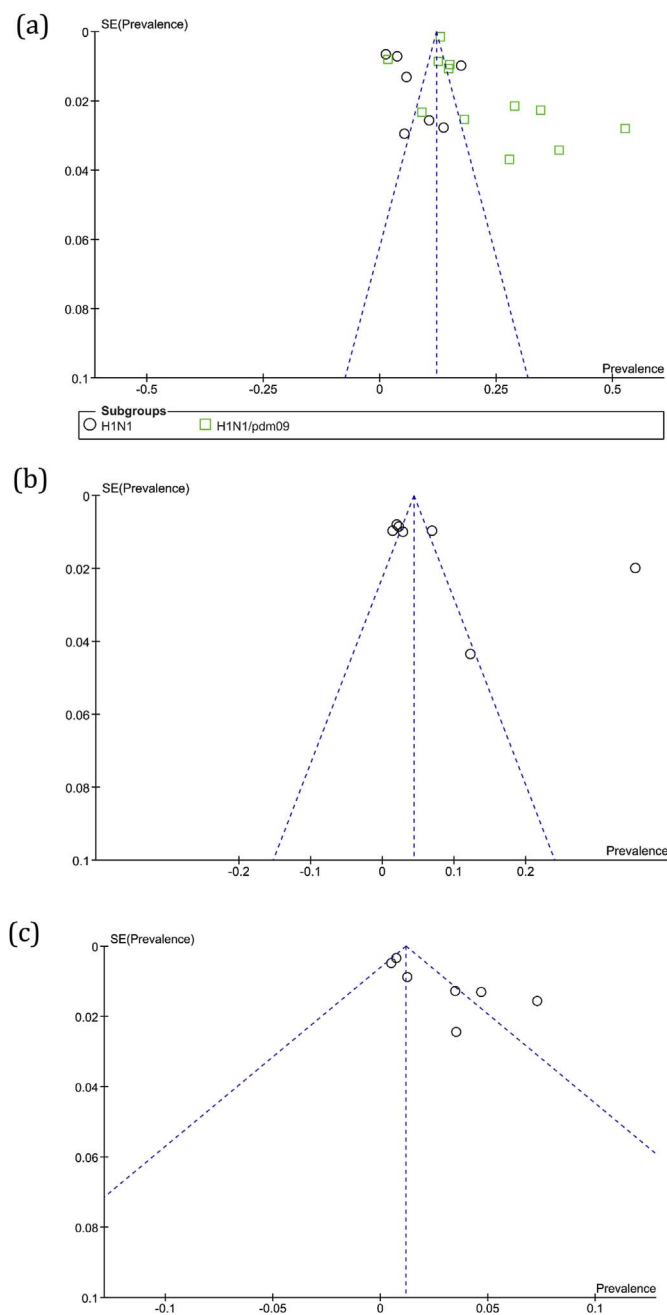
Fig. 2. Funnel plot of publication bias for the included studies related to (a) influenza H1N1, (b) influenza H3N2, and (c) influenza B.

information was extracted from each selected study: the first author, year of publication, province/city of the study, sample size, gender, number of confirmed cases of influenza A/H1N1, A/H3N2, and B subtypes, prevalence, age group, and mortality. The search was limited to human types of influenza. We also separately investigated H1N1/pdm09 as a subgroup of influenza A/H1N1. In sum, 32 papers were evaluated after rejection of duplicate or irrelevant reports. The complete process of the study selection and review is shown in Fig. 1.

2.6. Evaluation of study quality and risk of bias

In order to assess the quality of the included studies, a checklist adapted from Hoy et al. was used [13]. It comprises nine questions that evaluate the representativeness of the sample, the sampling method, the selection procedure, the data assemblage method, the uniformity of

data collection, the likelihood of non-response bias, the reliability of the study tool, case definitions, and statistical reporting. The response score for each question is "0" or "1," indicating "low risk of bias" and "high risk of bias," respectively. The overall risk of study bias is obtained from the sum of scores ranging from 0 to 9. It divides the studies into three groups: 1 to 3 are "low risk of bias," 4 to 6 are "moderate risk," and 0 to 3 are "high risk". Publication bias was assessed through funnel plots and Egger's test of asymmetry.

2.7. Statistical analysis

Primary data manipulation was carried out by Excel. The standard error of prevalence was computed as $\sqrt{(p(1-p)/n)}$, where p is the observed prevalence and n is the sample size [14]. The Cochrane review manager software (RevMan 5.3) was utilized for the meta-analysis. The heterogeneity among the studies was surveyed through these parameters: Chi^2, I^2, and Z-test. The I^2 test quantities were taken into account as 25%, 50%, and 75% to indicate low, moderate, and high heterogeneity, respectively. The random effects model was applied for a high level of heterogeneity across the studies. The kappa coefficient was used to assess the level of agreement between the two reviewers who evaluated the studies.

3. Results

3.1. Flow of studies through the selection process

The detailed descriptions of the search and the selection procedures are presented in Fig. 1. Overall, 532 articles were found after rejection of duplicate papers by exploring the databases of MEDLINE, Web of Science, Scopus, and ScienceDirect. Seven articles were detected through a search of the gray literature, including Irandoc, RICeST, and SID. Afterwards, 79, 59, and 32 papers were chosen by screening title, abstract, and full text, respectively. Finally, the selected papers were classified into two groups: 25 papers for the qualitative meta-analysis (kappa = 0.92; perfect agreement) and seven papers for analysis of drug resistance of influenza viruses (kappa = 0.95; perfect agreement).

3.2. Assessment of risk of bias and quality of the studies

The risk of bias of each study was assessed according to the checklist introduced by Hoy et al. [13]. All studies generally had a low risk of bias in spite of the high risk of bias in the representativeness of the sample. In order to check the bias of the average prevalence due to publication bias, funnel plots were created. Fig. 2 shows the symmetric funnel plots of influenza H1N1 and H3N2, which are confirmed by Egger's test (*p*-value = .6 and .12, respectively). Therefore, publication bias was not found among the studies related to these subtypes. However, the asymmetric funnel plot affirmed by Egger's test with a *p*-value of 0.02 reveals publication bias in studies related to the prevalence of influenza B.

3.3. Study characteristics

The collected data were from different regions of Iran and were focused on two major human influenza types, A (H1N1 and H3N2) and B. All 25 studies on the prevalence of human influenza infection were cross-sectional; six studies from Tehran, four studies from Mazandaran, and three studies from Khuzestan made up a majority of the studies (Table 1).

Table 2 includes information from seven reports related to H1N1 and H3N2 resistance to Oseltamivir and amantadine, respectively. The most extensive study was conducted by Khodadad et al., with a sample size of 77.

Table 1
Summary of the studies conducted on the influenza prevalence in Iran.

Row	Authors	Province	Sample. No	Confirmed Cases	Gender	Subtype	Prevalence (%)	Age Group	Mortality	Ref
1	Haghshenas (2015)	Mazandaran	571	201	F = 293, M = 278	H3N2	35.2	All	NA	[15]
2	Khodadad (2015)	Shiraz	200	77	NA	H1N1/pdm09	38.5	All	NA	[16]
3	Afrasiabian (2014)	Kurdistan	1059	157	F = 92, M = 65	H1N1/pdm09	14.8	All	NA	[17]
4	Alavi (2014)	Behbahan	318	167	F = 76, M = 91	H1N1/pdm09	52.5	Adults	10	[18]
5	Nandost (2014)	Mazandaran	2781	516	F = 281, M = 235	A	18.55	All	7	[19]
6	Ayatollahi (2013)	Yazd	1442	253	F = 111, M = 142	H1N1	17.5	All	20	[20]
7	Gorjipour (2013)	Tehran	330	29	NA	NA	8.7	Children	NA	[21]
8	Hajikhezri (2013)	Khuzestan	655	74	F = 39, M = 35	H1N1 (24), H3N2 (45), B (5)	3.7, 6.9, 0.7	All	NA	[22]
9	Makvandi (2013)	Khuzestan	232	42	F = 17, M = 25	H1N1/pdm09	18.1	2–17 yrs.	0	[23]
10	Alavi (2012)	Khuzestan	153	35	F = 15, M = 20	H1N1 (21) H1N1/pdm09 (14)	13.7, 9.2	Children	NA	[24]
11	Haghshenas (2012)	Mazandaran	1363	205	F = 111, M = 94	H1N1/pdm09	15.4	All	5	[25]
12	Moattari (2012)	Fars	275	33	NA	H1N1/pdm09 (5), H3N2 (8), B (20)	1.8, 2.9, 7.3	Adults	NA	[26]
13	Najafi (2012)	Sari	147	41	F = 19, M = 22	H1N1/pdm09	27.9	All	NA	[27]
14	Yavarian (2012)	All	40,169	5214	NA	H1N1/pdm09	12.9	All	156	[7]
15	Zarinfar (2012)	Markazi	1452	183	F = 89, M = 94	H1N1/pdm09	12.6	Adults	8	[9]
16	Mousavi (2011)	Tehran	142	17	NA	H1N1 (15), H3N2 (2)	10.6, 1.4	NA	NA	[28]
17	Dashti (2010)	Tehran	434	150	NA	H1N1/pdm09	34.5	All	9	[29]
18	Malekshahi (2010)	Tehran	202	11	NA	A (10), B (1)	4.9, 0.4	Children	NA	[30]
19	Moattari (2010)	South	450	130	NA	H1N1/pdm09	28.8	Children	NA	[31]
20	Alborzi (2009)	Shiraz	255	25	NA	A (13), B (12)	5.1, 4.7	All	NA	[32]
21	Soltani (2009)	Tehran	57	12	NA	H1N1 (3), H3N2 (7), B (2)	5.3, 12.3, 3.5	NA	NA	[33]
22	Barati (2008)	Tehran	160	7	NA	A (5), B (2)	3.1, 1.3	Children	NA	[34]
23	Naghshvar (2008)	Mazandaran	202	22	NA	A (15), B (7)	7.4, 3.5	Children	NA	[35]
24	Shahidi (2007)	Shiraz	300	24	NA	H1N1 (17), H3N2 (7)	5.7, 2.3	All	NA	[36]
25	Moattari (2006)	South	300	10	NA	H1N1 (4), H3N2 (6)	1.3, 2	1-15 yrs.	NA	[37]

Table 2
Summary of the studies reported on the drug resistance of influenza-infected patients in Iran.

Row	Authors	Region	Subtype	Segment	Drug	Sample Size	Drug Resistance	Mutation	Ref
1	Khodadad (2015)	Shiraz	H1N1	Neuraminidase	Oseltamivir	77	7 (9%), 8 (10.3%), 7 (9%), 7 (9%), 7 (9%)	V13G, V106I, V241I, N248D, N369K	[16]
2	Yavarian (2014)	Iran	H3N2	Neuraminidase, M2 protein	Oseltamivir, Amantadine	50	0.0 (0%), 4 (8%)	K292R, E119V, N294S, S31N	[38]
3	Karbalaie Niya (2014)	Iran	H3N2	Neuraminidase	Oseltamivir	50	0.0 (0%)	H274Y	[39]
4	Moradi (2011)	Tehran	H1N1	Neuraminidase	Oseltamivir	51	4 (7.8%)	H275Y	[40]
5	Yavarian (2010)	Iran	H3N2	M2 protein	Amantadine	14	10 (71.4%)	Ser31Asn	[41]
6	Ghaderi M (2010)	Iran	H1N1	M2 protein	Amantadine	21	7 (33.3%)	Ser31Asn	[42]
7	Yavarian (2009)	Six provinces	H3N2	M2 protein	Amantadine	15	11 (73.3%)	Ser31Asn	[43]

3.4. Prevalence of influenza infection and heterogeneity of studies

Three forest plots were drawn to explore heterogeneity among disparate reported prevalence of all influenza types (the H1N1 and H1N1/pdm09 subgroup H3N2 and type B) (Figs. 3–5). The high amounts of I^2 and Chi^2 represent the high variation and remarkable heterogeneity among the reports. The pooled prevalence of H1N1, H1N1/pdm09, H3N2, and B were obtained as 0.08 (95% CI = 0.03, 0.13), 0.22 (95% CI = 0.17, 0.26), 0.09 (95% CI = 0.03, 0.14), and 0.03 (95% CI = 0.01, 0.04), respectively. The most comprehensive study was carried out by Yavarian et al., who report on the prevalence of the pandemic influenza A (H1N1/pdm09) virus from 2009 to 2011.

3.5. Drug resistance of the influenza virus among the Iranian population

The studies indicate the highest drug resistance is to amantadine, with a value of 73.3% among patients who were infected by the H3N2 influenza virus. It resulted from a mutation in the Ser31Asp residue. On
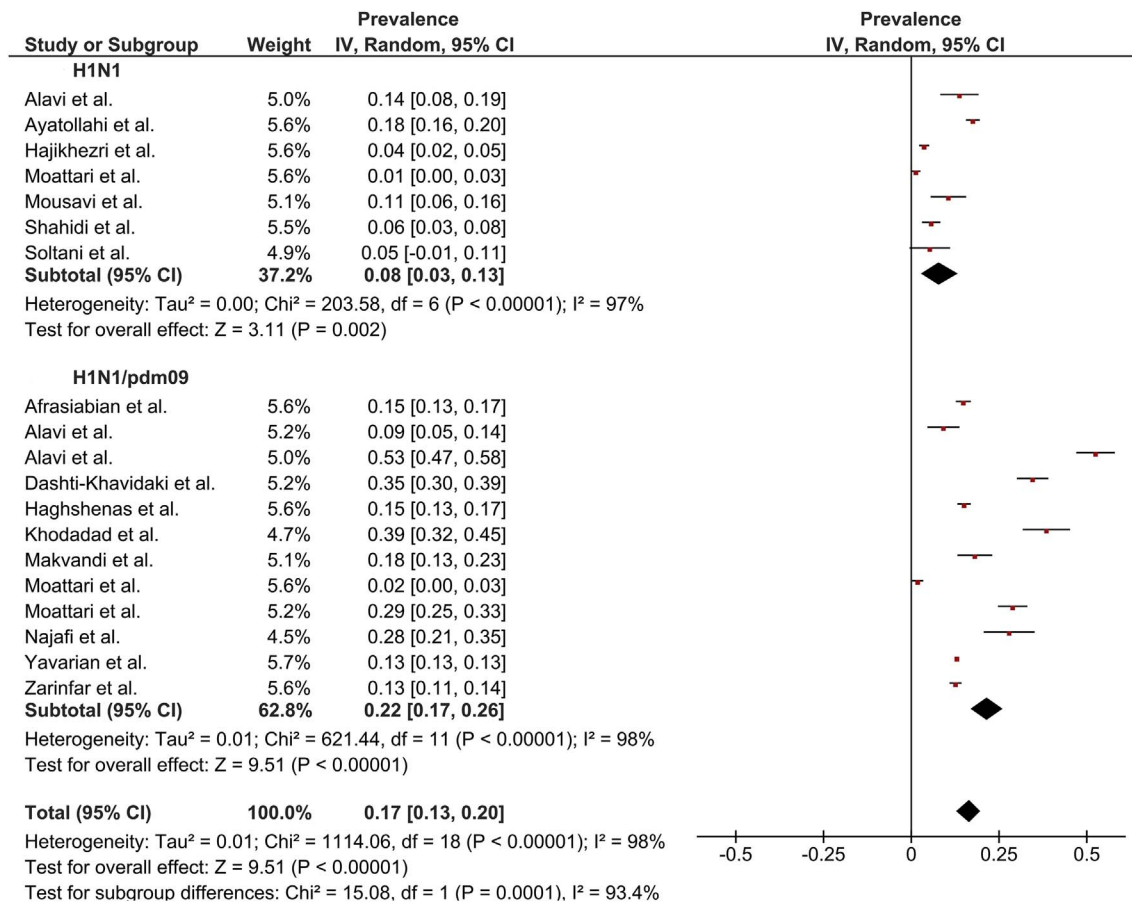
		Prevalence		
Study or Subgroup	Weight	IV, Random, 95% CI		IV, Random, 95% CI
H1N1				
Alavi et al.	5.0%	0.14 [0.08, 0.19]		
Ayatollahi et al.	5.6%	0.18 [0.16, 0.20]		
Hajikhezri et al.	5.6%	0.04 [0.02, 0.05]		
Moattari et al.	5.6%	0.01 [0.00, 0.03]		
Mousavi et al.	5.1%	0.11 [0.06, 0.16]		
Shahidi et al.	5.5%	0.06 [0.03, 0.08]		
Soltani et al.	4.9%	0.05 [-0.01, 0.11]		
Subtotal (95% CI)	**37.2%**	**0.08 [0.03, 0.13]**		

Heterogeneity: Tau² = 0.00; Chi² = 203.58, df = 6 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.11 (P = 0.002)

		Prevalence		
H1N1/pdm09				
Afrasiabian et al.	5.6%	0.15 [0.13, 0.17]		
Alavi et al.	5.2%	0.09 [0.05, 0.14]		
Alavi et al.	5.0%	0.53 [0.47, 0.58]		
Dashti-Khavidaki et al.	5.2%	0.35 [0.30, 0.39]		
Haghshenas et al.	5.6%	0.15 [0.13, 0.17]		
Khodadad et al.	4.7%	0.39 [0.32, 0.45]		
Makvandi et al.	5.1%	0.18 [0.13, 0.23]		
Moattari et al.	5.6%	0.02 [0.00, 0.03]		
Moattari et al.	5.2%	0.29 [0.25, 0.33]		
Najafi et al.	4.5%	0.28 [0.21, 0.35]		
Yavarian et al.	5.7%	0.13 [0.13, 0.13]		
Zarinfar et al.	5.6%	0.13 [0.11, 0.14]		
Subtotal (95% CI)	**62.8%**	**0.22 [0.17, 0.26]**		

Heterogeneity: Tau² = 0.01; Chi² = 621.44, df = 11 (P < 0.00001); I² = 98%
Test for overall effect: Z = 9.51 (P < 0.00001)

| **Total (95% CI)** | **100.0%** | **0.17 [0.13, 0.20]** | | |

Heterogeneity: Tau² = 0.01; Chi² = 1114.06, df = 18 (P < 0.00001); I² = 98%
Test for overall effect: Z = 9.51 (P < 0.00001)
Test for subgroup differences: Chi² = 15.08, df = 1 (P = 0.0001), I² = 93.4%

Fig. 3. Forest plot of the prevalence of influenza A (H1N1) among Iranian population.

		Prevalence			
Study or Subgroup	Weight	IV, Random, 95% CI	Year		IV, Random, 95% CI
Moattari et al .	15.0%	0.02 [0.00, 0.04]	2006		
Shahidi et al.	15.0%	0.02 [0.01, 0.04]	2007		
Soltani et al.	11.2%	0.12 [0.04, 0.21]	2009		
Mousavi et al.	14.9%	0.01 [-0.01, 0.03]	2011		
Moattari et al.	14.9%	0.03 [0.01, 0.05]	2012		
Hajikhezri et al.	14.9%	0.07 [0.05, 0.09]	2013		
Haghshenas et al.	14.1%	0.35 [0.31, 0.39]	2015		
Total (95% CI)	**100.0%**	**0.09 [0.03, 0.14]**			

Heterogeneity: Tau² = 0.01; Chi² = 272.77, df = 6 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.05 (P = 0.002)

Fig. 4. Forest plot of the prevalence of influenza A (H3N2) among Iranian population.

		Prevalence		
Study or Subgroup	Weight	IV, Random, 95% CI		IV, Random, 95% CI
Alborzi et al.	12.6%	0.05 [0.02, 0.07]		
Barati et al.	16.6%	0.01 [-0.00, 0.03]		
Hajikhezri et al.	20.9%	0.01 [0.00, 0.01]		
Moattari et al.	10.8%	0.07 [0.04, 0.10]		
Naghvar et al.	13.0%	0.03 [0.01, 0.06]		
Shatizadeh etal	19.8%	0.00 [-0.00, 0.01]		
Soltani et al.	6.3%	0.04 [-0.01, 0.08]		
Total (95% CI)	**100.0%**	**0.03 [0.01, 0.04]**		

Heterogeneity: Tau² = 0.00; Chi² = 29.71, df = 6 (P < 0.0001); I² = 80%
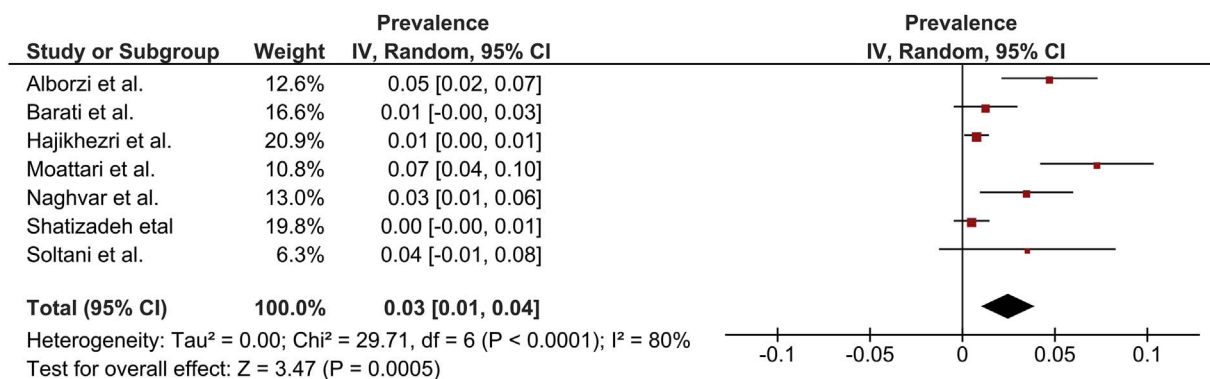Test for overall effect: Z = 3.47 (P = 0.0005)

Fig. 5. Forest plot of the prevalence of influenza B among Iranian population.

the other hand, drug resistance among H1N1-infected cases that received Oseltamivir was lower than that of the H3N2-infected patients.

4. Discussion

This study provides the first quantitative survey regarding the prevalence in Iranian reports of various types of influenza virus, including H1N1, H3N2, and B. This meta-analysis combines 25 studies published from 2000 until December 2016. The funnel plot analysis and Egger's test confirmed no significant publication bias in the related studies of influenza H1N1 and H3N2 while significant publication bias was observed in influenza B. Chi^2 and Tau^2 values, which are the estimate of between-study variance, could not correctly evaluate heterogeneity among the few studies (H3N2 and B) in the meta-analysis. On the other hand, far from the number of studies, I^2 illustrates the total variation percentage among studies due to heterogeneity. In the present study, the high amount of I^2 (97%, 98%, 98%, and 80% for H1N1, H1N1/pdm09, H3N2, and B, respectively) indicated high heterogeneity. This heterogeneity comes from using varying methodologies such as study design, age groups, and different populations. Moreover, there were few reports about the prevalence of H3N2 and B-type influenza, which are affected by the low pathogenicity of the related viruses.

Based on the isolation viruses from 1043 patients with acute respiratory illness in a 10-year study, type A influenza was found to be common during the winters of 1991–92, 1997–98, and 2000–01, and type B influenza was recognized as common during 1992–95 and 1996–97. Both type A and type B viruses circulated in 1995–96 and 1998–2000 [44].

The most prevalent influenza type is the H1N1 virus. This type of virus was studied more because mortality among the infected cases was higher than the other types. Therefore, more prevention and medical care were performed to treat the H1N1 influenza patients. However, according to a report in 2012, the mortality percentage among thousands of H1N1-infected cases was insignificant. This indicates that the Iranian health care organization was successful in controlling the disease until 2012 [45]. In this study, we surveyed the studies reporting the prevalence of H1N1/pdm09 individually because it was the first cause of the infectious pandemic disease in the 21st century. It spread out across all continents over the course of about six months [46]. The first study was carried out on the 2662 confirmed cases of H1N1/pdm09-infected people in the period time of between June 1st and November 11th, 2009. Two waves were observed for the virus incidence: exogenous and indigenous waves, which reached their maximum rate after educational centers were opened [47]. In another study, the deaths of 140 individuals due to the H1N1/pdm09 virus were reported between May and December 2009 in Iran. In contrast to the reports of other countries, mortality occurred among all age groups who had no underlying conditions or predisposing danger factors. Additionally, the blood serum of most Iranians showed a positive response to the polyclonal antibody for H1N1/pdm09 [48]. Underlying conditions such as pregnancy and neurological disorders may increase the influenza risk in those patients [49, 50]. Among the neurological disorders, cerebral palsy was one of the comorbidities that makes young children susceptible to developing severe H1N1 influenza. Therefore, the above-mentioned vulnerable groups should be considered in order to reduce prolonged hospitalization, ICU admission, and death [49].

Since the swine flu is commonly transmitted between individuals, human gatherings like Hajj can lead to a higher prevalence of disease. Hajj is a religious rite of Muslims, which is hold in Kingdom of Saudi Arabia (KSA). Annually, 3 million people attend in this holly event from more than 90 countries. It was predicted that Hajj pilgrim can increase prevalence of H1N1. So, the following preventive strategies were recommended: preventing the attendance of high risk people, vaccination for swine flu, consuming oseltamivir, giving awareness to hajjis for hand hygiene, and also using face masks for flu patients [46, 51].

The effectiveness of Oseltamivir in treating H1N1/pdm09 was

surveyed on 434 patients. The study revealed a variety of H1N1/pdm09 complications, especially secondary bacterial pneumonia. Furthermore, it was found that in 2009, influenza A (H1N1) infection-related critical illness and mortality affected younger patients more than elderly ones [29].

The commonly prescribed drugs used to treat influenza are amantadine, Zanamivir, and Oseltamivir. There were several studies regarding the mentioned drug resistance among Iranian patients. One of these reports showed a significant increase in amantadine resistance from 2005 to 2007. Additionally, a mutation was detected in the Ser31Asn amino acid in the M2 protein of all samples. Therefore, the authors suggest that amantadine consumption should be restricted in upcoming years to replace the refractory strains to the non-resistant IAVs [43]. In another report, the resistance of two drugs, including amantadine and rimantadine, against 14 H3N2 viruses was evaluated. The molecular analyses of the hemagglutinin, neuraminidase, and M genes disclosed the adaptability of resistance with the gradual evolution of H3N2 viruses. The study concluded that the medicinal effects of amantadine and rimantadine are low for influenza treatment [41].

The Oseltamivir-resistance of H1N1/pdm09 infection was detected in four patients from November 2009 through March 2010. The mutation analyses demonstrated the possibility of H275Y mutation in the absence or presence of an elective drug pressure. Therefore, drug resistance genotyping was proposed to prescribe suitable anti-viral medication [40].

In our systematic review, the results have been influenced by some limitations. Firstly, limited studies were performed regarding the prevalence of different influenza virus types in Iran. Secondly, there were substantial differences in the design of studies, including age groups and regions, which caused some heterogeneity between the studies. Therefore, future studies should be done on various age groups and the wider population. Additionally, the genotyping of the infecting virus and underlying conditions of influenza-infected patients must be carefully evaluated. Eventually, the drug resistance to common medications should also be assessed.

Ethics

This study is a systematic review and meta-analysis on the previous studies with no human or animal participants.

Conflicts of interest

The authors declare no conflicts of interests.

References

[1] J. Yavarian, T. Mokhtari-Azad, S.A. Nadji, H. Zeraati, M. Naseri, Analysis of the hemagglutinin and neuraminidase genes of human influenza A/H3N2 viruses circulating in Iran between 2005 and 2007: antigenic and phylogenetic relationships to vaccine strains, Intervirology 53 (2010) 133–140.
[2] S. Vatandour, M. Bozorgmehrifard, H. Shoushtari, S. Charkhkar, S. Bakhtiari, Molecular characterization and phylogenetic analysis of neuraminidase gene of avian influenza H9N2 viruses isolated from commercial broiler chicken in Iran during a period of 1998-2007, Afr. J. Microbiol. Res. 5 (2011) 4182–4189.
[3] A.L. Rack-Hoch, G. Laniado, J. Hubner, Comparison of influenza and RSV diagnostic from nasopharyngeal swabs by rapid fluorescent immunoassay (Sofia system) and rapid bedside testing (BinaxNOW) vs. conventional fluorescent immunoassay in a German university children's hospital, Infection 45 (2017) 529–532.
[4] R.G. Webster, E.A. Govorkova, Continuing challenges in influenza, Ann. N. Y. Acad. Sci. 1323 (2014) 115–139.
[5] Y.P. Lin, V. Gregory, M. Bennett, A. Hay, Recent changes among human influenza viruses, Virus Res. 103 (2004) 47–52.
[6] C. Kloth, S. Forler, S. Gatidis, R. Beck, D. Spira, K. Nikolaou, et al., Comparison of chest-CT findings of influenza virus-associated pneumonia in immunocompetent vs. immunocompromised patients, Eur. J. Radiol. 84 (2015) 1177–1183.
[7] J. Yavarian, M. Naseri, A. Shadab, N.Z. Shafiei Jandaghi, T. Mokhtari Azad, Epidemiological aspects of pandemic influenza A(H1N1) virus from 2009 to 2011 in Iran, Influenza Other Respir. Viruses 6 (2012) e74–e76.
[8] G. Matias, R. Taylor, F. Haguinet, C. Schuck-Paim, R. Lustig, V. Shinde, Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009

by influenza type or subtype, age, cause of death, and risk status, Influenza Other Respir. Viruses 8 (2014) 507–515.

[9] N. Zarinfar, A. Mohammadbeigi, Comparison of clinical-epidemiologic characteristics and consequence of flu-like and H1N1 influenza in Markazi Province, Iran, 2009-2010, HealthMed 6 (2012) 3114–3119.

[10] S. Hagel, K. Ludewig, A. Moeser, M. Baier, B. Loffler, B. Schleenvoigt, et al., Characteristics and management of patients with influenza in a German hospital during the 2014/2015 influenza season, Infection 44 (2016) 667–672.

[11] D. Sym, P.N. Patel, G.M. El-Chaar, Seasonal, avian, and novel H1N1 influenza: prevention and treatment modalities, Ann. Pharmacother. 43 (2009) 2001–2011.

[12] R. Heyd, A.M. Eis-Hubinger, A. Berger, S. Bierbaum, S. Pietzonka, J.J. Wenzel, et al., Retrospective analysis of clinical and virological parameters of influenza cases at four university hospitals in Germany, Infection 2017 (45) (2015) 349–354.

[13] D. Hoy, P. Brooks, A. Woolf, F. Blyth, L. March, C. Bain, et al., Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement, J. Clin. Epidemiol. 65 (2012) 934–939.

[14] A. Hackshaw, E. Paul, E.S. Davenport, Evidence-based Dentistry: an Introduction, John Wiley & Sons, 2006.

[15] M. Haghshenas, E. Jafarian, F. Babamahmoodi, A. Tabrizi, S. Nandoost, R. Alizadeh-Navaei, Prevalence of influenza A/H3N2 virus in northern Iran from 2011 to 2013, Caspian J. Intern. Med. 6 (2015) 116–119.

[16] N. Khodadad, A. Moattari, M. Shamsi Shahr Abadi, M.R. Kadivar, J. Sarvari, F. Tavakoli, et al., Prevalence of influenza A(H1N1)pdm09 virus resistant to oseltamivir in shiraz, Iran, during 2012-2013, Jundishapur J. Microbiol. 8 (2015) e23690.

[17] S. Afrasiabian, B. Mohsenpour, K.H. Bagheri, M. Barari, E. Ghaderi, R. Hashemi, et al., Epidemiological survey on pandemic influenza A (H1N1) virus infection in Kurdistan province, Islamic Republic of Iran, 2009, East. Mediterr. Health J. = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 20 (2014) 169–174.

[18] S.M. Alavi, R. Nashibi, F. Moradpoor, Prevalence and mortality of influenza A (H1N1) virus among patients with acute respiratory Infection in southwest Iran, Jundishapur J. Microbiol. 7 (2014) e9263.

[19] S. Nandost Kenari, M. Haghshenas, M. Mirzaei, M.S. Rezaee, A. Tabrizi, Prevalence of influenza A viruses in patients with flu symptoms attending mazandaran provinces health centers, 2009-2013, J. Mazandaran University of Medical Sciences 24 (2014) 1–10.

[20] J. Ayatollahi, M. Golestan, M.R. Sharifi, E. Esform, S.H. Shahcheraghi, Investigation of the relationship between demographic characteristics and frequency of mortality in certain cases of influenza A (H1N1) from yazd province (Iran), Jundishapur J. Microbiol. 6 (2013).

[21] H. Gorjipour, A. Karimi, A. Fahimzad, F. Shiva, F. Fallah, A.R. Shamshiri, The seasonal frequency of viruses associated with upper respiratory tract infections in children, Arch. Pediatr. Infect. Dis. 1 (2013) 9–13.

[22] Z. Hajikhezri, M. Makvndi, A.R. Samarbaf-Zadeh, N. Neisi, K. Ahmadi, Relative frequency of seasonal influenza A and B in khuzestan province by reverse transcription-polymerase chain reaction (RT-PCR) during 2009-2010, Jundishapur J. Microbiol. 6 (2013).

[23] M. Makvandi, A. Alvandi, E. Aryan, M.M. Gooya, M. Sorosh, M. Nabavi, et al., Clinical and epidemiological characteristics of children with influenza A H1N1 in khuzestan, Iran during july 2009-april 2010, Jundishapur J. Microbiol. 6 (2013).

[24] S.M. Alavi, M. Makvandi, S. Najafi-Fard, L. Alavi, Influenza A virus among the hospitalized young children with acute respiratory infection. Is influenza A co infected with respiratory syncytial virus? Caspian J. Intern. Med. 3 (2012) 530–534.

[25] M.R. Haghshenas, A. Asgari, F. Babamahmoodi, M.S. Rezai, A. Tabrizee, S. Nandoost, Prevalence of influenza A/H1N1 virus in north of Iran (mazandaran), 2009-2011, J. Mazandaran University of Medical Sciences 22 (2013) 50–57.

[26] A. Moattari, A. Emami, M. Moghadami, B. Honarvar, Influenza viral infections among the Iranian Hajj pilgrims returning to Shiraz, Fars province, Iran, Influenza Other Respir. Viruses 6 (2012) e77–e79.

[27] N. Najafi, A.R. Davoudi, F. Baba Mahmoodi, A. Tayebi, S. Alian, R. Ghassemian, et al., Epidemiological, clinical and laboratory features of patients hospitalized with 2009 pandemic influenza in north of Iran, Caspian J. Intern. Med. 3 (2012) 377–381.

[28] S.F. Mousavi, M.T. Kheiri, S.M. Hosseini, M. Taghizadeh, F. Fotouhi, B. Heydarchi, et al., Phylogenetic comparison of influenza virus isolates from three medical centers in Tehran with the vaccine strains during 2008-2009, Iran. J. Med. Sci. 36 (2011) 172–177.

[29] S. Dashti-Khavidaki, H. Khalili, F. Gholamalipour, A. Soudbakhsh, A.H. Talasaz, M. Hajabdolbaghi, et al., Approach to Pandemic 2009 influenza: first report from a main referral hospital for Pandemic H1N1 influenza care in Iran, J. Infect. Dev. Countries 4 (2010) 629–635.

[30] S.S. Malekshahi, T.M. Azad, J. Yavarian, S. Shahmahmoodi, M. Naseri, F. Rezaei, Molecular detection of respiratory viruses in clinical specimens from children with acute respiratory disease in Iran, Pediatr. Infect. Dis. J. 29 (2010) 931–933.

[31] A. Moattari, A. Emami, K.B. Lankarani, Pandemic influenza (H1n1) Infection in pediatric age group in southern Iran, Pediatr. Res. 68 (2010) 450.

[32] A. Alborzi, M.H. Aelami, M. Ziyaeyan, M. Jamalidoust, M. Moeini, B. Pourabbas, et al., Viral etiology of acute respiratory infections among Iranian Hajj pilgrims, J. Trav. Med. 2009 (16) (2006) 239–242.

[33] Z. Soltani, M. Hosseini, M. Shahidi, M. Hedayati, M.T. Kheiri, Molecular analysis of human influenza virus in Tehran, Iran, Intervirology 52 (2009) 63–67.

[34] M. Barati, S. Noorbakhsh, A. Tabatabaei, F.E. Taj, M. Talebi-Taher, Adenovirus, influenza virus A, B and respiratory syncitial virus Infection in children, Int. J. Infect. Dis. 12 (Supplement 1) (2008) e66.

[35] N. Farshad, M.J. Saffar, A.R. Khalilian, H. Saffar, Respiratory viruses in hospitalized children with acute lower respiratory tract infections, Mazandaran Province, Iran, Indian Pediatr. 45 (2008) 590–592.

[36] M. Shahidi, M.T. Kheiri, S. Amini-Bavil-Olyaee, M. Hosseini, A. Moattari, M. Tabatabaeian, et al., Molecular and phylogenetic analysis of human influenza virus among Iranian patients in Shiraz, Iran, J. Med. Virol. 79 (2007) 803–810.

[37] A. Moattari, M.R. Kadivar, T. Mokhtari Azad, Seasonal outbreak of influenza A virus infection in pediatric age groups during 2004-2005 in south of Iran, Iran. J. Med. Sci. 31 (2006) 131–134.

[38] J. Yavarian, N.Z. Shafiei Jandaghi, F. Rezeai, T.M. Azad, Adamantane and neuraminidase resistant influenza A/H3N2 isolated in Iran from 2005 to 2013, Tehran Univ. Med. J. 72 (2014) 40–45.

[39] K.-N. Mohammad Hadi, J. Yavarian, S. Shahmahmoodi, T.M. Azad, Comparison of real-time RTPCR assay with direct sequencing for detection of sensitivity or resistant to oseltamivir in Influenza A/H3N2 viruses, Virol. Antivir. Res. 2014 (2015).

[40] A. Moradi, S.A. Nadji, P. Tabarsi, S.M. Hashemian, M. Marjani, A. Sigaroodi, et al., Prevalence of oseltamivir-resistant 2009 H1N1 influenza virus among patients with pandemic 2009 H1N1 influenza infection in NRITLD, tehran, Iran, Tanaffos 10 (2011) 8–11.

[41] J. Yavarian, T.M. Azad, X. Zheng, V. Gregory, Y.P. Lin, A. Hay, Amantadine resistance in relation to the evolution of influenza A(H3N2) viruses in Iran, Antivir. Res. 88 (2010) 193–196.

[42] M. Ghaderi, T. Mokhtari-Azad, S. Shahmahmoodi, K. Samimi-Rad, J. Yavarian, M. Naseri, et al., Amantadine-resistant Among Seasonal H1N1 and 2009 Pandemic Isolated of Influenza A Viruses in Iran, (2010).

[43] J. Yavarian, T. Mokhtari Azad, N.Z. Shafiei Jandaghi, R. Nategh, Amantadine-resistant influenza A (H3N2) viruses in Iran, Acta Virol. 53 (2009) 135–138.

[44] T. Mokhtari-Azad, H. Mohammadi, I.A. Moosavi, Z. Saadatmand, R. Nategh, Influenza surveillance in the Islamic Republic of Iran from 1991 to 2001, East. Mediterr. Health J. = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 10 (2004) 315–321.

[45] J. Gholami, S.H. Hosseini, M. Ashoorkhani, R. Majdzadeh, Lessons learned from H1N1 epidemic: the role of mass media in Informing physicians, Int. J. Prev. Med. 2 (2011) 32–37.

[46] K. Lankarani, Hajj and swine flu pandemic (H1N1, 2009): what is ex-pected and what should be done? Iran. Red Crescent Med. J. 2010 (2016) 4–6.

[47] M.M. Gouya, M. Soroush, T. Mokhtari-Azad, A.A. Haghdoost, P. Hemati, M. Moghadami, et al., influenza A (H1N1) pandemic in Iran: report of first confirmed cases from June to November 2009, Arch. Iran. Med. 13 (2010) 91–98.

[48] M.M. Gouya, M. Nabavi, M. Soroush, A.A. Haghdoust, S. Ghalehee, P. Hemmati, et al., Mortality from pandemic influenza A (H1N1) in Iran, Iran. Red Crescent Med. J. 13 (2011) 698–701.

[49] A. Borhani-Haghighi, K.B. Lankarani, Swine flu (H1N1) infection among patients with neurologic disorders. A review of published evidence, Neurosci. (Riyadh, Saudi Arabia) 16 (2011) 213–216.

[50] G.S. Jahromi, F. Zand, A. Khosravi, Acute respiratory distress syndrome associated with H1N1 influenza during pregnancy, Int. J. Obstet. Anesth. 19 (2010) 465–466.

[51] R. Hamkar, M. RAZAVY, S. Jalilvand, A.H. ZIAEI, Z. Saadatmand, B.Z. NOUROUZ, et al., The study of viral respiratory Infections among Iranian Hajj pilgrims, 1383, Iranian J. Infect. Dis. Trop. Med. 10 (2005).