

Article

Prevalence of diabetes in the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus: a systematic review and meta-analysis

Alaa Badawi,¹ Seung Gwan Ryoo²¹Public Health Risk Sciences Division, Public Health Agency of Canada, Toronto, ON; ²Faculty of Arts and Science, University of Toronto, Toronto, ON, Canada

Significance for public health

Outbreaks of the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) have presented a considerable global public health threat over the past few years. Evidence suggest that infected subjects who are also diabetic are more likely to be susceptible to severe outcome of H1N1 and MERS-CoV. Systematic analysis of ~93,000 H1N1 cases and ~300 MERS-CoV cases indicated an overall prevalence of 14.6% and 54.4% for diabetes in H1N1 and MERS-CoV cases, respectively. This may suggest a possible etiological relationship between diabetes and each of the two infectious conditions. Introduction of effective public health vaccination intervention strategies against severe acute respiratory infections should be developed to target subjects with chronic disorders such as diabetes, obesity and cardiovascular conditions.

Abstract

Over the past two decades a number of severe acute respiratory infection outbreaks such as the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) have emerged and presented a considerable global public health threat. Epidemiologic evidence suggests that diabetic subjects are more susceptible to these conditions. However, the prevalence of diabetes in H1N1 and MERS-CoV has not been systematically described. The aim of this study is to conduct a systematic review and meta-analysis of published reports documenting the prevalence of diabetes in H1N1 and MERS-CoV and compare its frequency in the two viral conditions. Meta-analysis for the proportions of subjects with diabetes was carried out in 29 studies for H1N1 ($n=92,948$) and 9 for MERS-CoV ($n=308$). Average age of H1N1 patients (36.2 ± 6.0 years) was significantly younger than that of subjects with MERS-CoV (54.3 ± 7.4 years, $P<0.05$). Compared to MERS-CoV patients, subjects with H1N1 exhibited 3-fold lower frequency of cardiovascular diseases and 2- and 4-fold higher prevalence of obesity and immunosuppression, respectively. The overall prevalence of diabetes in H1N1 was 14.6% (95% CI: 12.3-17.0%; $P<0.001$), a 3.6-fold lower than in MERS-CoV (54.4%; 95% CI: 29.4-79.5; $P<0.001$). The prevalence of diabetes among H1N1 cases from Asia and North America was ~two-fold higher than those from South America and Europe. The prevalence of diabetes in MERS-CoV cases is higher than in H1N1. Regional comparisons suggest that an etiologic role of diabetes in MERS-CoV may exist distinctive from that in H1N1.

Introduction

For the past two decades, pandemics of severe acute respiratory infections (SARI) have been serious threats to global health, causing significant morbidity and mortality. Reassorted novel strains of influenza viruses and coronaviruses continue to arise, rendering vaccinations - if developed - less useful and posing increased risks to humans. Two prominent viruses - 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) - have markedly affected humans. H1N1, since the 2009 pandemic, has caused about 284,500 deaths, both directly via respiratory infections and indirectly from the cardiovascular diseases secondary to bacterial infections.¹ In addition, MERS-CoV, since its first emergence in 2012, has infected 1600 individuals, causing 574 deaths and was reported in 26 countries although the vast majority of reported cases originated from the Arabian Peninsula.²

H1N1 and MERS-CoV both target the respiratory tract, and share many similar clinical symptoms. The most common symptoms are fever, cough, shortness of breath, and sore throat³⁻⁸ followed always by gastrointestinal symptoms such as nausea, vomiting, and diarrhea.^{3,7-9} Both diseases often lead to complications such as pneumonia, acute respiratory distress syndrome, organ failure, and even death.^{4,6,9} Complications mostly lie within the respiratory system with organ failure commonly noted in the respiratory system, followed by renal and cardiovascular systems.⁵ Individuals infected with H1N1 usually belong to those aged between 21 and 50 years,^{4,5} and have a mean age in the early 40s.^{3,5} MERS-CoV, on the other hand, mostly infects older adults with a median age of 50 years.¹⁰ This difference was hypothesized to be related to the development of cross-reactive antibodies against influenza viruses from previous exposures to seasonal influenza in elder people.⁵ Another difference between H1N1 and MERS-CoV relates to the length of the incubation period. H1N1 has a short incubation period between 1 and 2 days,¹¹ whereas MERS-CoV has a much longer period of ~5 days.¹⁰

Many infected individuals exhibit comorbidities (*e.g.*, diabetes, hypertension, asthma, and obesity), rendering them more susceptible to complications.³⁻⁷ Diabetes is one of the known documented contributing host-related risk factor in both H1N1 and MERS-CoV severe cases, and is frequent in individuals developing fatal disease complications.^{4,7} This observation may suggest an etiological relationship between diabetes and acute viral respiratory infections. Diabetes and its related conditions downregulate the innate and humoral immune systems by reducing the function of T cells and neutrophils.¹² Hyperglycemia impairs critical components of innate immunity *in vitro*, such as chemotaxis, phagocytosis, and the bactericidal activity of neutrophils and macrophages and lead to secondary infections.¹³ The direct influence of diabetes, however, on acute respiratory infections

still needs more research to estimate the frequency of diabetes in severe viral conditions and to elucidate the etiologic role on diabetes in disease severity.¹⁴ The present study was undertaken to conduct a systematic review and meta-analysis of published literature to describe the prevalence of diabetes in two of the emerging severe acute respiratory infections such as H1N1 and MERS-CoV and to explore its possible contribution to the severity and complication of the two viral conditions.

Materials and Methods

Search strategy and selection criteria

A search was conducted in PubMed, Ovid MEDLINE, Embase and Embase Classic databases to the last week of July 2015 using the search terms (MeSH) H1N1 or MERS-CoV (Middle East respiratory syndrome coronavirus) and Diabetes. The search resulted in 123 articles selected for title and abstract review as they satisfied our selection criteria (see below). We limited the studies into those in humans and excluded reports published as review articles, letters, case studies, editorials, conference abstracts, vaccination trials or family-based studies. After eliminating duplicate listings and only considering articles in full text, a total of 44 peer-reviewed original studies were selected for full text review. Full article review resulted in the further exclusion of 8 reports that were not documenting the prevalence of diabetes in H1N1 or MERS-CoV (*i.e.*, no association studies), examining only a small number of travellers as a case report ($n=2$ subjects), reporting seasonal influenza alone, reviewing already reported cases (MERS-CoV), or simply documenting national surveys. A bibliography search of the remaining articles identified two additional studies. A total of 38 peer-reviewed articles (29 studies for H1N1^{3-5,14-39} and 9 for MERS-CoV^{6-9,40-44}) were identified for this article (Figure 1).

Inter-reviewer agreement

The abstracts of the identified studies were independently reviewed by two readers (AB and SJ). Differences were resolved through discussions for a consensus to be reached. Percentage agreement and Cohen's Kappa (κ) statistic⁴⁵ were calculated and interpreted in accordance with Landis and Koch's benchmarks⁴⁶ for assessing the agreement between reviewers as poor (<0), slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and excellent (0.81-1.0). The agreement on the inclusion between the two reviewers was 86%, with $\kappa=0.72$ (95% CI 0.58-0.85).

Quality score assessment

The methodological quality of each study was evaluated as previously described⁴⁷ with some modification. Quality of the study was based on four criteria: (a) the number of study subjects (n ; at least the median of 157 for H1N1 and 17 for MERS-CoV), (b) comprehensive reporting of patients' demographic information, (c) describing a minimum of 3 disease-associated symptoms and (d) reporting at least 2 comorbidities (in addition to diabetes). For each criterion, each study was given a score (0 or 1, with 1 fulfilling the criteria). The total score was calculated for each study (score range 0-4). Quality scores of 1, 2, 3, and 4 were considered poor, fair, good and very good, respectively.

Data extraction and analysis

Data extracted from the selected studies included the first author's name, publication date, country, dates of recruitment, ethnicity, total sample size (divided to males and females), age, prevalence of symptoms (including fever, shortness of breath, sore throat, cough and Acute Physiology and Chronic Health Evaluation II, APACHEII) and percentage of comorbidities at the time of presentation (including obesity, immunosuppression or HIV and heart conditions such as hypertension, cardiovascular diseases and/or coronary arterial diseases) (Tables 1 and

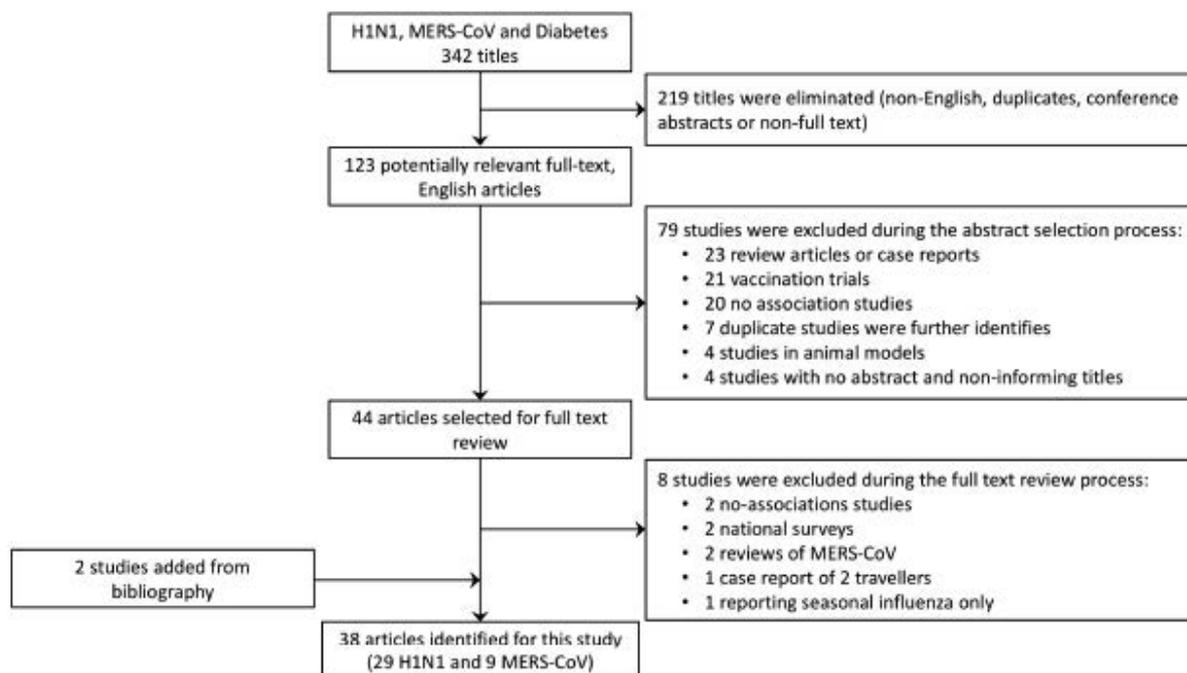


Figure 1. Systematic literature review process. The flow diagram describes the systematic review of literature on the contribution of diabetes to severe H1N1 and MERS-CoV. A total of 38 unique studies were identified (29 studies for H1N1 and 9 for MERS-CoV from an initial 342 examined titles).

2). Weighted average was used to calculate the average age and the overall prevalence of clinical symptoms and comorbidities. Publication bias was assessed both by the visual inspection of funnel plot (Figure 2) and by Egger's test. Egger's test is widely used to assess the tendency for the effects estimated in small sample size studies to differ from those estimated in larger studies. The results of Egger's test are presented in terms of bias coefficient. To measure the prevalence of diabetes in the two viral conditions, we extracted the proportion of the disease in the reported cases of severe respiratory infections. A subgroup analysis was carried out by region, only for the H1N1 studies (Table 3). Region subgroup analysis for MERS-CoV was not doable since all the identified studies were conducted on Saudi populations, with one study of pooled analysis where region/country designation was not possible. The primary outcome measure was to evaluate the prevalence of diabetes in H1N1 and MERS-CoV cases. The meta-analysis of proportions (and 95% CIs) was calculated for the identified studies (Figure 3) and in a subgroup analysis within each region (Table 3). Meta-analysis tests were conducted using the OpenMeta Analyst version 10.10, a free, cross-platform, open-source program.⁴⁸ We used binary random-effects model

since we assumed that the relationship between diabetes and severe respiratory infection is varied across populations. T-test was used to compare between average age in H1N1 and MERS-CoV since this factor was normally distributed in the two sets of studies. Mann-Whitney U-test was employed to compare the prevalence of clinical symptoms and comorbidities between the two diseases as these conditions were not normally distributed. To assess whether there is true heterogeneity among the selected studies and that all the studies are evaluating the same effect, we used the *Q* test.⁴⁹ *Q* test only informs about the presence versus the absence of heterogeneity and does not report on the extent of such heterogeneity. Therefore, we calculated the *I*² index to complement the *Q* test and quantify the degree of heterogeneity among studies.⁵⁰ Given the poor power of *Q* test to detect true heterogeneity among a small number of studies, we also quantified the true heterogeneity by estimating the between-study variance in the random-effects model (τ^2), as previously described.⁵¹ *P*<0.05 was considered to be statistically significant. Forest plots were used to illustrate the prevalence of diabetes in H1N1 and MERS-CoV severity from the selected studies and to inspect the heterogeneity of the individual findings.

Table 1. Characteristics of the H1N1 identified studies.

Study	Country	Dates, mm.yy	N			Age (yr)	Symptoms (%)					Comorbidities (%)		Quality Score	
			All (92,948)	M (46,181)	F (46,351)		APACHEII	Fever	Shortness of Breath	Sore Throat	Cough	Obesity	HT/ CAD/ CVD		Imm/ HIV
Al-Soub <i>et al.</i> , 2014 ³	Qatar	07.09-01.11	40	24	16	42.7	12	90	75	23	88	28	40	3	3
Allam <i>et al.</i> , 2013 ⁴	India	05.09-12.10	45	24	21			18	80	16		18	3	2	
Bagshaw <i>et al.</i> , 2013 ¹⁵	Canada	04.09-04.10	562	262	300	48	21					27		2	
Balaganesakumar <i>et al.</i> , 2013 ¹⁶	India	01.10-12.10	72	41	31	45.5		96	85	60	88	24		9	3
Chawla <i>et al.</i> , 2013 ⁵	India	10.09-12.10	77	44	33	40.9		97	77	33	87	25	8	3	
Jimenez-Garcia <i>et al.</i> , 2013 ¹⁷	Spain	01.09-12.09	11,499	5806	5693	39.6						9	2	2	3
Kusznierz <i>et al.</i> , 2013 ¹⁸	Argentina	05.09-07.09	242	121	121	33.7		72	71		88	16	33	3	4
Suryaprasad <i>et al.</i> , 2013 ¹⁹	USA-AB	05.09-07.09	88	31	57	37			9			71	8	4	2
Vallejos <i>et al.</i> , 2013 ²⁰	Argentina	05.09-08.09	44	25	19	49.5			91			25	34		2
Aziz-Baumgartner <i>et al.</i> , 2012 ²¹	Argentina	04.09-12.09	49	27	22	37						53			1
Chowell <i>et al.</i> , 2012 ²²	Mexico	08.09-12.09	3456	1482	1974	22		79.9	57	56	84	12		5	4
Delgada-Rodriguez <i>et al.</i> , 2012 ²³	Spain	07.09-02.11	813	403	410	38.5						9			2
Cortes-Garcia <i>et al.</i> , 2012 ¹⁴	Spain	06.09-12.09	2413	1246	1167	42.5						22	29	12	3
Marija Kojicic <i>et al.</i> , 2012 ²⁴	BAH	11.09-03.10	50	31	29	43	19		16			64	5	6	2
Miller <i>et al.</i> , 2012 ²⁵	USA	05.09-06.09	43	8	35	36.4		60	63	16	73			7	2
Wane <i>et al.</i> , 2012 ²⁶	Rwanda	10.09-05.10	532	257	275	42		85	33	58	88	2			3
Chudasama <i>et al.</i> , 2011 ²⁷	India	09.09-02.10	274	141	133	29.5		92	53	54	97	9	5		4
Gilca <i>et al.</i> , 2011 ²⁸	Canada	04.09-06.09	321	154	167	29						25	13	8	3
Ward <i>et al.</i> , 2011 ²⁹	Australia	07.09-08.09	302	125	177	45						35	14	10	3
Yokota <i>et al.</i> , 2011 ³⁰	Brazil	07.09	157	78	79	33		97	97	47	99	38	6	9	4
Van Kerkhove <i>et al.</i> , 2011 ³¹	Pooled	04.09-01.10	70,000	35,140	34,860	36						6	7	5	3
Allard <i>et al.</i> , 2010 ³²	Canada	05.09-07.09	162	73	89	28.6									2
Carcione <i>et al.</i> , 2010 ³³	Australia	05.09-08.09	871	427	444	26		88	33	56	85	9	5	3	4
Fajardo_Dolci <i>et al.</i> , 2010 ³⁴	Mexico	04.09-05.09	100	47	53	54.5		84	75		85	14	18	2	3
Koegelenberg <i>et al.</i> , 2010 ³⁵	S. Africa	08.09-09.09	19	4	15	39.5	18					21		32	2
Venkata <i>et al.</i> , 2010 ³⁶	USA	05.09-12.09	66	33	33	46.9		83	71	21	88	44	32	20	3
Xi <i>et al.</i> , 2010 ³⁷	China	10.09-12.09	155	90	65	43		94	47	30	92		38		2
CDC, 2009 ³⁸	USA-AB	04.09-12.09	416			44.5									1
Kwan-Gett <i>et al.</i> , 2009 ³⁹	USA	04.09-08.09	70	37	33	11						41	11	16	2
Total/Weighted Average (SD)	-	04.09-02.11	92,948	46,181	46,351	36.2(6.0)	20.2(4.5)	82.5(9.1)	53.3(7.3)	38.9(6.2)	85.9(9.3)	7.7(2.8)	7.2(2.7)	4.8(2.2)	-

APACHEII, Acute Physiology and Chronic Health Evaluation II; HT, CAD, CVD, hypertension, coronary artery diseases, cardiovascular diseases; Imm, immunodeficiency; AB, Aboriginal; BAH, Bosnia and Herzegovina.

Results

The present systematic review examines the relationship between diabetes and the H1N1 and MERS-CoV. A total of 38 studies that report the prevalence of diabetes in H1N1 ($n=92,948$ cases from 29 studies, Table 1) and MERS-CoV ($n=308$ cases from 9 studies, Table 2) were selected. The funnel plot (Figure 2) demonstrated a non-symmetrical distribution of the effect size of each study on either side of the pooled estimate. This seemingly non-symmetrical appearance of the plot suggested evidence of publication bias. Egger's test also supported this notion particularly in MERS-CoV studies where the bias coefficient was not statistically significant - given the assumption for evidence of small-study effects is based on $P < 0.1$ ($P=0.13$ for the H1N1 studies and $P=0.065$ for the MERS-CoV studies). These findings are supported by the significant heterogeneity ($P < 0.001$) among the selected studies (see below). According to our quality scoring criteria (see above), the majority of the studies were between fair (score 2; 12 reports) and good (score 3, 16 reports) quality with 7 studies that fulfilled all quality scoring criteria (score 4, very good). Within the selected studies, sex-ratio (male:female) in the majority of the H1N1 reports was 1:1 whereas it was ~2:1 in the MERS-CoV cases. The average age of H1N1 cases (36.2 ± 6.0 years, range: 11-54.5 years) was significantly younger than MERS-CoV cases (54.3 ± 7.4 years, range: 36-66 years, t -test $P=0.0004$). The prevalence of fever, shortness of breath, sore throat and cough was not statistically different between H1N1 and MERS-CoV cases from the two sets of studies (Mann-Whitney U test at $P < 0.05$). We observed a non-statistically significant ~2-fold higher frequency of obesity (>30 kg/m²) in the MERS-CoV patients compared to their H1N1 counterparts

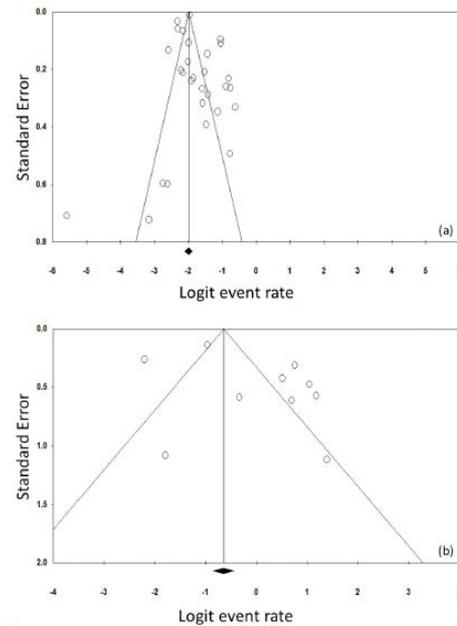


Figure 2. Funnel plot for systematic review on the prevalence of diabetes in H1N1 and MERS-CoV studies. The logit event rate for prevalence (horizontal axis) is presented against the standard error (SE) of the log of logit event rate (vertical axis) for H1N1 (a) and MERS-CoV (b) studies. The SE inversely corresponds to the study size. Asymmetry of the plot can indicate publication bias. Open circles indicate the individual studies.

Table 2. Characteristics of the MERS-CoV identified studies.

Study ID*	Dates, mm.yy	N			Age (yr)	Symptoms (%)					Comorbidities (%)		Quality Score	
		All (308)	M (199)	F (109)		APACHEII	Fever	Shortness of Breath	Sore of Breath	Cough Throat	Obesity	HT/ CAD/ CVD		Imm/ HIV
Shalhoub <i>et al.</i> , 2015 ⁴⁰	04.14-06.14	24	14	10	66		79		83	88		75		3
Al-Tawfiq <i>et al.</i> , 2014 ⁹	04.14-06.14	17	11	6	62		40	67	7	86		53		3
Al-Tawfiq <i>et al.</i> , 2014 ⁴¹	04.14-06.14	5	3	2	57.6							40		1
Arabi <i>et al.</i> , 2014 ⁶	12.12-08.13	12	8	4	59	28	67	92	8	83		93		3
Memish <i>et al.</i> , 2014 ⁴²	06.13-08.13	12	6	6	36		100	100	80	100	8	33		3
Assiri <i>et al.</i> , 2013 ⁷	09.12-06.13	47	36	11	64.5		87	72	21	83	17	62		4
Assiri <i>et al.</i> , 2013 ⁸	04.13-05.13	23	17	6	56		87	48		87	24	39	0	4
Memish <i>et al.</i> , 2013 ⁴³		7	0	7	43		57	57		29				2
WHO, 2013 ⁴⁴	09.12-10.13	161	104	57	50							7.5	5	3
Total/Weighted Average (SD)	09.12-06.14	308	199	109	54.3(7.4)	28	78.0(8.8)	70.6(8.4)	37.1(6.1)	83.6(9.1)	17.6(4.2)	31.3(5.9)	4.4	-

*All studies were from KSA, except WHO, 2013,44 examined samples pooled from France, Germany, Italy, Jordan, KSA, Qatar, Tunisia, UAE, UK. For abbreviation, see Table 1.

Table 3. Meta-Analyses for the prevalence of diabetes in severe H1N1 cases by region.

Region	Number of subjects	Percent prevalence of diabetes in H1N1 (95% CI)	Heterogeneity Analysis			
			τ^2	Cochran's Q	Statistic P	I^2
Europe ^{14,17,23,24}	14,775	10.1 (8.5-11.5)	0.0	11.5	0.009	73.9
Asia ^{3-5,16,27,29,33,37}	1,836	17.6 (12.1-23.1)	0.005	62.9	<0.001	88.9
Africa ^{26,35}	551	14.2 (-16.2-44.5)	0.043	8.6	0.003	88.3
North America ^{15,19,22,25,28,32,34,36,38,39}	5,294	19.7 (13.8-25.6)	0.008	166.7	<0.001	94.6
South America ^{18,20,21,30}	492	9.8 (4.4-15.3)	0.002	11.7	0.009	74.3

(17.6±4.2 vs. 7.7±2.8%). The combined frequencies of cardiovascular diseases, hypertension, and cardio-arterial diseases were ~3-fold higher in MERS-CoV cases than in H1N1 (31.3±5.9% vs. 7.2±2.7, P=0.0004).

Meta-analyses for the proportion of diabetes in H1N1 and MERS-CoV are shown in Figures 3 and 4, respectively. The overall proportion of diabetes in H1N1 is 15% (95% CI: 12-17%), 3.6-fold lower than its proportion in MERS-CoV (54%, 95%CI: 28-80%). The two sets of studies displayed a significant heterogeneity (P<0.001) among the selected studies (Q test: 1943 for H1N1 vs. 169.8 for MERS-CoV). Additionally, the degree of heterogeneity among studies was statistically significant (P<0.001) and comparable between the two sets of studies (I² index: 98.6 for H1N1 vs. 95.3 for MERS-CoV). The between-study variance in the random-effects model was markedly lower among the H1N1 studies (τ²=0.003) than the MERS-CoV reports (τ²=0.134).

Subgroup analysis by region for H1N1 studies (Table 3) showed that the frequency of diabetes in H1N1 from Asia and North America (~18-20%, P<0.001) is 2-fold higher than its prevalence in the cases recruited from Europe and South America (~10%, P<0.001). Cases from Africa (14%) showed a non-significant slightly lower diabetes prevalence compared to those from Asia and North America. It should be noted however, that the frequency estimate from Africa was developed only from two studies (compared to 8 and 10 studies from Asia and North America, respectively, and 4 studies from each of Europe and South America). The heterogeneity tests for the studies included in all regional sub-analyses exhibited significant overall heterogeneity (Q test, P≤0.009), degree of heterogeneity among studies (I² index) and between-study variance in the random-effects model (τ² test).

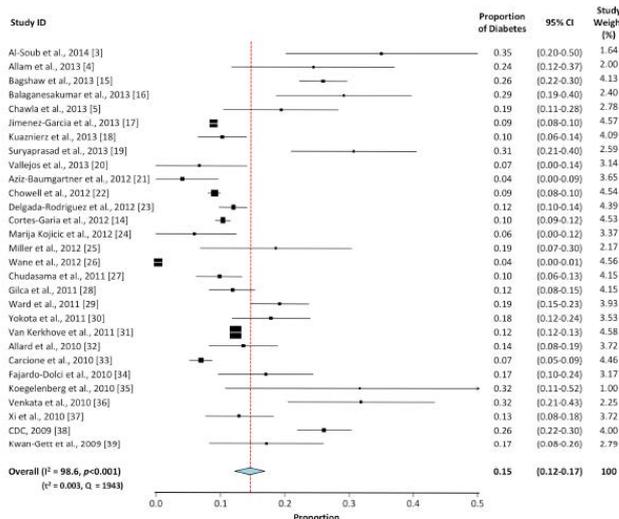


Figure 3. Meta-analysis for the proportion of diabetes in H1N1 cases. Weights are calculated from binary random-effects model analysis. Values represent proportion of diabetic cases in the H1N1 patients and 95% CI. Heterogeneity analysis was carried out using Q test, the among studies variation (I² index) and in between-study variance in the random-effects model (τ²).

Discussion

The present systematic review evaluates the frequency of diabetes in SARI conditions such as H1N1 and MERS-CoV. We observed a large difference between the volume of literature and total number of subjects evaluated for each condition and identified 29 studies for H1N1 (with 92,948 subjects) and 9 for MERS-CoV (with 308 patients). About 60% of the selected studies (23 out of 38) had a quality score between good and very good (Tables 1 and 2). This indicates that a large set of the studies had a sufficient enough number subjects to substantiate the outcome and have provided a comprehensive reporting of patients' demographic information. Furthermore, the majority of the selected studies reported a set of disease-associated symptoms and comorbidities that permitted developing a comprehensive profile of the infectious disease and its complication. This difference reflects the discrepancy between the two diseases in their global (H1N1) versus regional (MERS-CoV) spread, and the period during which they emerged. Immediately following its outbreak in 2009, the H1N1 triple reassortant swine influenza viruses contained genes from avian, swine, and human influenza A viruses^{53,54} and sustained a rapid between-human transmission to spread globally.⁵² On the other hand, in 2012, the emergence of MERS-CoV was to a great extent contained within the Arabian Peninsula⁵⁵ and dromedary camels were identified as the intermediate host⁵⁶ with a closely related virus sequences found in bats.⁵⁷ Apart from a number of nosocomial outbreaks involving healthcare workers caring for MERS-CoV patients; little evidence has been initially reported for sustained person-to-person transmission.⁵⁸ However, during the 2015 MERS-CoV outbreak in the Republic of Korea it was demonstrated that among 186 cases, 83.2% of the transmission events were linked to only 5 super-spreaders, all of whom had pneumonia at presentation and contacted hundreds of people, adding evidence to the person-to-person transmission in MERS-CoV.⁵⁹

The characteristic pattern of transmission and spread of H1N1 and MERS-CoV may have resulted in a distinctive sex-ratio for each condition. MERS-CoV cases exhibited a sex-ratio (male:female) of 2:1, twice that noted for H1N1 cases (Tables 1 and 2). The male predominance of MERS-CoV reflects the higher likelihood of exposure to the infectious agent in males than in females in Middle Eastern cultures. In addition,

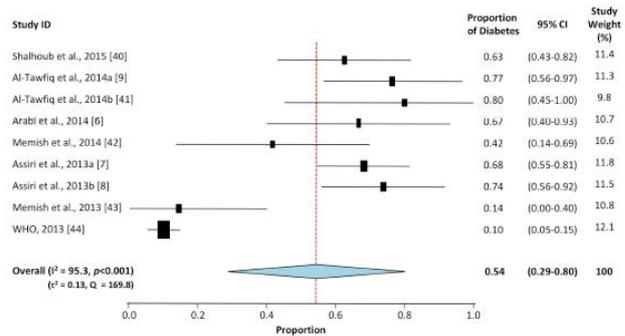


Figure 4. Meta-analysis for the proportion of diabetes in MERS-CoV cases. Weights are calculated from binary random-effects model analysis. Values represent proportion of diabetic cases in the MERS-CoV patients and 95% CI. Heterogeneity analysis was carried out using Q test, the among studies variation (I² index) and in between-study variance in the random-effects model (τ²).

most males who tested positive for the virus and died also had underlying medical conditions, which could explain the severity of cases in older males.⁶⁰ In agreement, MERS-CoV cases were significantly older (54.3 ± 7.4 years) than their H1N1 (36.2 ± 6.0 years) counterparts. The average age of H1N1 patients is similar to that in H5N1 cases where 90 percent of the subjects were 40 years or younger.⁶¹ As noted with H5N1 cases, it can be estimated that 15-20% of elder people may have residual immunity against this H1N1 flu strain following their life-time exposures to multiple influenza outbreaks.⁶¹⁻⁶⁴ This immunogenicity does not apply to coronaviruses and may explain the younger average age of H1N1 cases compared to MERS-CoV cases. Indeed, it was proposed over 60 years ago that repeated exposures to antigenic variants of influenza viruses may result in antibodies recognizing a large number of common flu antigens, and develop a reinforced immunity that lower the risk of infection with newly emerging variants.⁶⁵

The clinical presentations of SARI generally include respiratory symptoms, such as fever, new onset or exacerbation of cough, breathing difficulty and sore throat. Severe illnesses may vary from pneumonia, acute respiratory distress syndrome, encephalitis, myocarditis, or other severe and life-threatening complications.⁶⁶ The frequency of fever, shortness of breath, sore throat and cough was similar between H1N1 and MERS-CoV cases. In contrast, underlying medical conditions and comorbidities varied significantly between the two viral conditions. Patients with MERS-CoV had 2-fold higher rates of obesity ($P > 0.05$) and 3-fold higher combined frequencies of cardiovascular diseases, hypertension, and cardio-arterial diseases ($P < 0.05$) (Tables 1 and 2). The varying rates of comorbidities between H1N1 and MERS-CoV cases may relate to their different patterns of regional spread. Cardiovascular diseases are highly prevalent in the Middle East⁶⁷ than in many regions of the world.^{67,68} This observation also applies to obesity, although the lower prevalence of obesity in males from the Arabian Peninsula versus females⁶⁹ and their higher predominance in MERS-CoV patients (see above) together may have been combined to render the occurrence of obesity in MERS-CoV non-significantly different from that in H1N1. The increased risk of developing severe H1N1 and MERS-CoV complications in people with underlying chronic diseases was similarly reported in seasonal influenza. A recent study noted that, compared to subjects with no comorbidities, severe cases of influenza are more likely to manifest with obesity (OR for mortality 2.74, 95%CI: 1.56-4.80), cardiovascular diseases (2.92, 1.76-4.86), hypertension (1.49, 1.10-2.01) and neuromuscular disease (2.68, 1.91-3.75).⁷⁰ More studies examining the link between SARI and metabolic syndrome-related complications such as obesity and cardiovascular conditions are needed to evaluate their contribution to the severity of infectious diseases.

The overall proportion of diabetes was ~4-fold higher in MERS-CoV cases (54%) than in their H1N1 counterparts (15%) (Figures 3 and 4). In agreement, odds ratio for severe H1N1 in diabetic subjects (ranging from 2.2 to 4.4)^{16,19,23,30} was >3-fold lower than for severe MERS-CoV (OR ranging from 7.2 to 15.7).^{9,40} Although at varying extents, these findings implicate diabetes as a risk factor for severe MERS-CoV and H1N1. One reason for this difference may relate to the higher average age of MERS-CoV cases given that older age is a known risk factor for type 2 diabetes.⁷¹ Although in younger Middle Eastern populations rates of diabetes and its risk factors⁶⁷ are higher than those in older populations, the disease prevalence has increased across all age groups rather than just in older adults in the region.⁷² Another possible explanation can be attributed to the high prevalence of diabetes in the Middle East and the Arabian Peninsula⁶⁷ - where MERS-CoV originated and spread - compared to its prevalence in other world regions.⁶⁸ Similar increased rates of tuberculosis were noted in regions with high diabetes prevalence.⁷³ Additionally, subgroup analysis by region demonstrated that diabetes frequency in H1N1 cases from Asia and North America is ~2-fold higher than in those from Europe and South America (Table 3). This coincides with the high prevalence of diabetes

in Asia and North America (~12%) compared to Europe or South and Central America (~9%).⁷⁴ However, despite the lines of evidence suggesting an influence of the region of viral spread on diabetes proportion in the severe cases of SARI, the rate of diabetes in MERS-CoV was still ~3-fold higher than that in the H1N1 cases from Asia (17.6%, 95% CI: 12.1-23.1; $P < 0.001$; Table 3) - where diabetes rates are comparable to those in the regions of MERS-CoV. This observation suggests that the higher prevalence of diabetes in MERS-CoV cases than in H1N1, may not be simply related to the regional differences in the viral spread and that an etiologic role of diabetes in severe MERS-CoV cases may exist distinctive from that in H1N1.

Diabetes can impair the innate immune system⁷⁵ and render individuals more susceptible to a range of infectious diseases and severe illnesses.^{13,75,76} For example, during seasonal influenza outbreaks, compared to healthy subjects, diabetic patients were shown to have 6-fold higher risk of becoming critically ill and acquire hospitalization with 4-fold increased rates of pneumonia-related hospitalizations and a 3-fold elevated likelihood of dying of complications.⁷⁷ Diabetes share several common features with infectious disorders and its complication such as the endothelial dysfunction, the pro-inflammatory state and the attenuation of innate immune response.⁷⁵ The cytokine overload related to the Th1 (microbicidal action of IFN- γ) to Th2 (anti-inflammatory IL-4, -5, -10 and -13) shift in severe viral infection when accompanied by the increased cytokine levels arising from diabetes, both can be detrimental to the endothelium and lead to a range of subsequent complications.⁷⁸ Dampened innate immunity and the shift from Th1 to Th2 responses were implicated in linking the high prevalence of allergy observed in fatal viral infections, *e.g.*, Dengue fever.⁷⁹ Furthermore, diabetes can impair macrophage and lymphocyte functions with a subsequent status of reduced immune response⁷⁶ where individuals become at increased risk of severe infectious disease outcome. In support, diabetes-associated hyperglycemia and cellular insulinopenia are known to impair macrophage and lymphocyte functions with a subsequent status of reduced immune response.⁷⁶ Furthermore, levels of HbA1c $\geq 9\%$ were linked to a 60% increased risk of pneumonia-related complications and hospitalization due to a lower immune response.⁸⁰ Host defense to infection is largely mediated by cellular immunity and the synthesis of related cytokines, such as IFN- and interleukins, is downregulated in diabetes.^{75,81}

The present study has several limitations. Inspection of the funnel plot (Figure 2) and the Egger's test indicates that publication bias may have been derived from the small-study effect, *i.e.*, the possibility of including small studies with spuriously overstated estimates while ignoring those without statistically significant effects that may have a lower possibility of being published. Furthermore, the identified reports have shown 8-fold among-studies variance in the diabetes proportion for H1N1 (0.04-0.35; Figure 3) and MERS-CoV (0.1-0.8, Figure 4) cases. These inter-study differences may have contributed to the significant heterogeneity observed in our report. Additional sources of heterogeneity may relate to the large variation among studies in the sample size (19 to 70,000 H1N1 cases and 5 to 161 MERS-CoV patients) or the ethnic diversity of the study populations particularly within the H1N1 studies (collected from 14 counties). Furthermore, heterogeneous methodologies due to different study designs may have influenced the inter-study variation. This observation may levy some limitations on the estimated contribution of diabetes to severe H1N1 and MERS-CoV cases and render our results as a guide to generate more accurate estimates for national or international intervention strategies for severe SARI conditions in diabetic subjects. Furthermore, although the prevalence of diabetes is 15% in severe H1N1 cases and 54% in MERS-CoV, it may not implicate causality and warrants further studies to identify the nature and extent of the coexistence between diabetes and each of the two respiratory infections. Another limitation is the low number of MERS-CoV cases and the narrow geographic region from

which it was recruited, compared to the H1N1 cases that rendered subgroup analysis (by region) unattainable for MERS-CoV cases. This particular limitation may add more weight to the suggestion stipulating that the difference in diabetes prevalence between H1N1 and MERS-CoV can be attributable to the regional difference in spread. The small number of MERS-CoV studies highlights the need to develop international collaborations that include cases from countries other than those in the Arabian Peninsula, *e.g.*, from Korea where a few recent cases have been emerged recently. A single study⁴⁴ has examined MERS-CoV cases pooled from various countries but the findings were still limited by the small population size. The reports identified in the present study did not distinguish between the prevalence of type 1 and/or type 2 diabetes in H1N1 or MERS-CoV cases. With the exception of three studies (only in the H1N1 - but not MERS-CoV),^{14,17,35} all the identified reports have combined both types of diabetes despite their different characteristics, etiological factors and clinical features. Cortes Garcia et al.,¹⁴ and Koegelenberg et al.,³⁵ have clearly stated that the diabetic cases in their H1N1 series as type 2 cases. Jimenez-Garcia et al.,¹⁷ on the other hand, compared the demographic characteristics, underlying medical conditions and in-hospital case fatality risk (CFR) in the type 1 (prevalence 0.8%) and type 2 (prevalence 8.4%) diabetic patients and reported a ~2-fold higher CFR in type 2 cases than type 1.¹⁷ Given this paucity of information, it was challenging to distinguish between the two types of diabetes for their role in viral disease severity and complication.

Conclusions

In conclusion, the present study provides some evidence of a greater prevalence of diabetes to MERS-CoV severity compared to H1N1. If this relationship is causal, however, the substantial proportion of diabetes in each of the two infections suggests that introducing effective strategies for diabetes prevention may reduce the severity of a significant number of SARI conditions. Specific systematic vaccination intervention strategies against SARI diseases should be also considered for patients with metabolic syndrome and related disorders such as diabetes, obesity and cardiovascular conditions.⁸² This should be viewed as a key public health strategy in preventing SARI-associated morbidity and mortality.⁸³ During the 1957–58 pandemic and in response to substantial morbidity and mortality, the US Surgeon General recommended annual influenza vaccination for individuals with chronic debilitating disease, people aged ≥ 65 years and pregnant women.⁸⁴ For these high-risk groups, the first recommendation of national universal seasonal influenza vaccination was established in 2010 by the Advisory Committee on Immunization Practices (ACIP).⁸⁵ Recently, influenza vaccination was demonstrated to be associated with preventing all-cause hospitalization in infected subjects.⁸⁶ However, despite numerous recommendations from several public health organizations across the world (*e.g.*, CDC, WHO, etc.) to administer SARI vaccines (*e.g.*, influenza) annually to diabetic patients, vaccination rate in this vulnerable sub-population remains low.⁸⁷⁻⁸⁹ The current level of vaccination falls far short of the 2010 national health objectives call for a 90% rate to all elderly people (≥ 65 years of age) and 60% for younger people who have risk factors (*e.g.*, diabetes).⁸⁸ The prevalence of chronic diseases is rising in middle- and low-income countries as populations age and lifestyles and diets change. Further studies are being undertaken to evaluate the prevalence of other comorbidities in H1N1 and MERS-CoV. Subsequent introduction of effective public health vaccination intervention approaches and strategies is necessary to improve the protection against SARI in subjects with chronic disorders such as diabetes, obesity and cardiovascular conditions.

Correspondence: Alaa Badawi, Public Health Risk Sciences Division, Public Health Agency of Canada, 180 Queen Street West Toronto, ON M5V 3L7, Canada.

E-mail: alaa.badawi@phac-aspc.gc.ca

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