REVIEW

A Systematic Review of Influenza Epidemiology and Surveillance in the Eastern Mediterranean and North African Region

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ABSTRACT

Seasonal influenza represents a huge health burden, resulting in significant mortality and morbidity. Following the 2009 H1N1 pandemic, focus has been directed on the burden of influenza globally. Country and regional disease burden estimates play important roles in helping inform decisions on national influenza intervention programmes. Despite improvements in influenza surveillance following the 2009 pandemic, many opportunities remain unexplored in the Eastern Mediterranean and North African (EMNA) region, which has a high prevalence of patients with chronic disease and thus a population at high risk of influenza complications. We conducted a systematic literature review of Embase, Medline, Scopus and the Cochrane Database of Systematic Reviews from 1 January 1998 to 31 January 2020 covering the EMNA region with the aim to describe the epidemiology of influenza in the region and assess the influenza epidemiological surveillance research landscape. Relevant data on study characteristics, population, clinical/virology characteristics and epidemiology were extracted and summarised descriptively. Of the 112 studies identified for inclusion, 90 were conducted in the Eastern Mediterranean region, 19 in North Africa and three across the EMNA region. Data were reported on 314,058 laboratory-confirmed influenza cases, 96 of which were derived from surveillance systems. Amongst the surveillance studies, the percentage of positive cases reported ranged from 1% to 100%. The predominantly identified influenza strain was strain A; H1N1 was the most prominent circulating subtype. Typing was performed in approximately 75% and subtyping in 50% of studies, respectively. Data on those considered most at risk for influenza complications were collected in 21% of studies, highlighting a regional gap for these data. Our review reveals existing gaps in regional estimates of influenza health and economic burden, hospitalisation rates and duration, and highlights the need for robust and high-quality epidemiology data to help inform public health interventions.

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Key Summary Points

Why carry out this study?

The Eastern Mediterranean and North African (EMNA) region is geographically contiguous, making it an important region for influenza surveillance, yet the burden of disease is not well characterized in the region, and there are several countries with little to no data on influenza epidemiology

The region has a high prevalence of patients with chronic disease and thus a population at high risk of seasonal influenza complications; hence, these data are essential in helping to inform decisions on national and regional influenza intervention programmes

This study aimed to describe the epidemiology of influenza in the EMNA region and to assess the landscape for influenza surveillance and epidemiological research

What was learned from the study?

The study highlighted important gaps in regional estimates of influenza health and economic burden, hospitalisation rates and duration of hospital stay and a lack of surveillance standardization for influenza across countries

There is a high need for robust and high-quality epidemiology data and strengthening of surveillance systems to help inform public health interventions in the EMNA region

INTRODUCTION

Influenza represents a huge global health burden, with an estimated 1 billion cases occurring annually [1]. The World Health Organization (WHO) estimates that globally there are 3–5 million cases of severe illness, and 290,000–650,000 deaths annually due to influenza-related respiratory diseases alone [2, 3]. This estimate does not include influenza-related deaths in patients with chronic diseases such as cardiovascular disease or cardiovascular events and their complications.

Much of our understanding of seasonal influenza is derived from epidemiological data collected from western Europe and North America, whereas epidemiological data from the Eastern Mediterranean and North African (EMNA) region are less well characterised. The list of countries in this region can vary depending on the institution defining them. For the purposes of this review, the following countries were considered part of the EMNA region: Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iraq, Iran, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, Turkey, United Arab Emirates and Yemen. It has recently been shown that the seasonality of influenza epidemics for most countries in the EMNA region is in line with that reported for western Europe and North America [4]. With the exception of a few countries in the Arab peninsula, the influenza season primarily peaks in the winter between January and March in this region. Secondary peaks, with smaller amplitude, in general tend to occur in either spring or summer (May to July) or autumn (September to November) [4]. The notable exceptions are Bahrain and Qatar, where the primary peak is seen to occur earlier (November to December) and a secondary peak (of sizeable amplitude) occurs in March; Jordan, which has a secondary peak (only slightly smaller than the primary peak) in April; and Oman, where the primary and secondary peaks are of similar amplitude and take place in January and March, respectively [4].

Risk factors or risk groups for severe disease following seasonal influenza infection are well documented and include those with chronic medical conditions such as cardiovascular disease (or cardiovascular events), chronic pulmonary disease, metabolic disorders and immunodeficiency and young children, pregnant women, elderly or frail individuals and healthcare workers [5]. The EMNA region has a high prevalence of patients with chronic diseases and thus a population at high risk of seasonal influenza complications [2, 6, 7]. Influenza infections and their severe complications result in significant economic and societal burden, particularly among those in risk groups or with risk factors and/or whom are prone to severe complications [2, 3, 8].

In humans, the vast majority of influenza disease is caused by the influenza type A and B viruses, and infection is preventable by vaccination [9]. The relative proportion of influenza cases caused by each strain is subject to annual variation as a result of antigenic drift, and at any one time there will be a mix of strains circulating among the general population [9]. The A strain is further subdivided into a number of subtypes, the current most commonly circulating being H3N2 and H1N1 (also known as H1N1pdm09). The B strain is classified by lineage, the currently circulating lineages being Yamagata (B/Y) and Victoria (B/V) [2]. The emergence of the H1N1 pandemic in 2009 highlighted the importance of influenza surveillance to enable countries to better understand influenza epidemiology and help them implement appropriate preventive strategies. The pandemic also highlighted weaknesses of health systems in preparedness and response to the next pandemic.

Epidemiological and virological surveillance have been improved in the region since the formation of the Eastern Mediterranean Acute Respiratory Infection Surveillance (EMARIS) network, but is still far from well established, particularly as the network only collects data on severe respiratory infections, but not non-severe cases [10, 11]. In addition to improvement in virological laboratory assessments, the availability of data in the region has also increased as a result of the web-based influenza repository

FluNet, which was first launched in 1997 and provides a global tool for influenza virological surveillance [12]. The number of publications in this region relating to influenza epidemiology has grown since the 2009 pandemic, including a number of recent reports describing the epidemiology of influenza and disease burden in individual countries [13–15]. However, there is still a paucity of good-quality and consistent data looking at the region as a whole. Using a systematic literature review approach, we aimed to describe the epidemiology of influenza in the EMNA region and to assess the landscape for influenza surveillance epidemiological research.

METHODS

Literature Search

We conducted a comprehensive, systematic literature review of Embase, Medline, Scopus and the Cochrane Database of Systematic Reviews from 1 January 1998 to 31 January 2018 covering the EMNA region for the following countries: Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iraq, Iran, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, Turkey, United Arab Emirates and Yemen. As 'Arab world' and 'Middle East' are often used as acronyms for some of the countries in this region, we included these strings along with 'North Africa', 'Eastern Mediterranean Regional Office of WHO' (EMRO) and 'Eastern Mediterranean' amongst others in our search. A full list of search strings is given in Supplementary Table S1A. An updated search was conducted from 1 January 2018 through to 31 January 2020 for the same countries (Supplementary Table S1B). We did not evaluate the literature beyond this date in order to avoid potential implications on epidemiology as a consequence of the COVID-19 pandemic.

We also screened for laboratory-confirmed seasonal influenza infections, influenza-like illnesses (ILI) and severe acute respiratory infections (SARI) to identify any potential missed articles. Titles, abstracts, and full-text screening and selection were sequentially performed. This

article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Selection Criteria

Articles included were:

- Population-based studies with data of confirmed or suspected human influenza infections (including ILI and SARI)
- Studies of all age groups or for a specific age group or condition
- Studies reporting influenza incidence or mortality carried out for at least 1 year
- Studies reporting vaccine coverage for at least 1 year

   We excluded any articles:

- Reporting on influenza infection as a secondary co-infection in the study population
- Studies reporting data of avian influenza viruses
- Epidemiological data and mortality estimated through mathematical modelling
- Animal-only studies

No relevant studies were identified through the assessment of grey literature. In addition, we performed a manual search of the bibliography included in other systematic reviews and meta-analyses of influenza epidemiology and surveillance in the EMNA region.

Data Extraction

Relevant data on study characteristics, study population, clinical/virology characteristics and epidemiology from the included articles were summarised using a standardised data-extraction form (see Supplementary Table S2 for full list of variables extracted). Where age was not specified for the population, or if data were reported from adult and paediatric populations combined, the age group was defined as the general population. Data were extracted by two independent reviewers into an Excel file (Microsoft Office). Discrepancies were resolved by consensus through a common review by the two reviewers. All data are summarised descriptively. If not reported in the article, frequencies (such as influenza positivity rates and percentage breakdown of influenza A and B and their subtypes) were back calculated using the reported numbers of cases, the appropriate population size as denominators.

RESULTS

A total of 9408 studies were initially identified and, following article screening, 112 studies were retained. A diagram of the article selection process is shown in Fig. 1.

Of the countries in the EMNA region across which we conducted our search, data were available for 18 countries (Afghanistan, Algeria, Bahrain, Egypt, Iran, Jordan, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Tunisia, Turkey, United Arab Emirates and Yemen). The country of study setting and the number of studies retrieved are shown in Fig. 2. Ninety studies were conducted in the Eastern Mediterranean region and 19 in North Africa. Turkey, Iran and Saudi Arabia retrieved the highest number of articles (25, 24 and 15, respectively). The majority of studies (n = 89) were conducted during and/or after the 2009 pandemic.

Three studies were conducted across the EMNA region (Table 1) [4, 16, 17]. All three studies employed a surveillance study design and assessed the general population. The proportion of the 'at-risk' population was not reported in any of these studies. All three studies evaluated both influenza strains A and B; no other viruses were reported. Subtyping of the A strain was only performed in one of the studies, and only for the H1N1 and H3N2 strains which were reported to occur in 50.8% and 15.9% of the influenza positive cases; the remaining positive cases were identified as strain B (17.2%) or not subtyped (16.1%) [16].

The characteristics of all 112 studies conducted in the EMNA region are presented in Table 2. Eighty-four studies (75%) reported a study population size of at least 200 patients. The majority of studies did not look at any specific age group but evaluated across a range
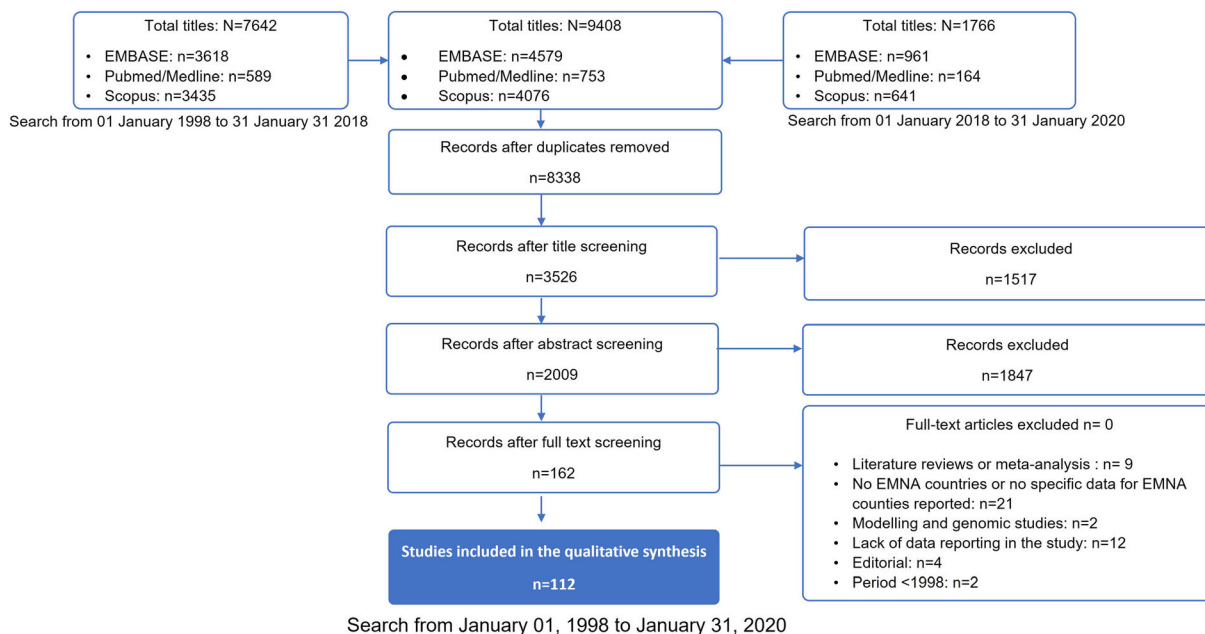
Fig. 1 Article selection procedure and number of studies included
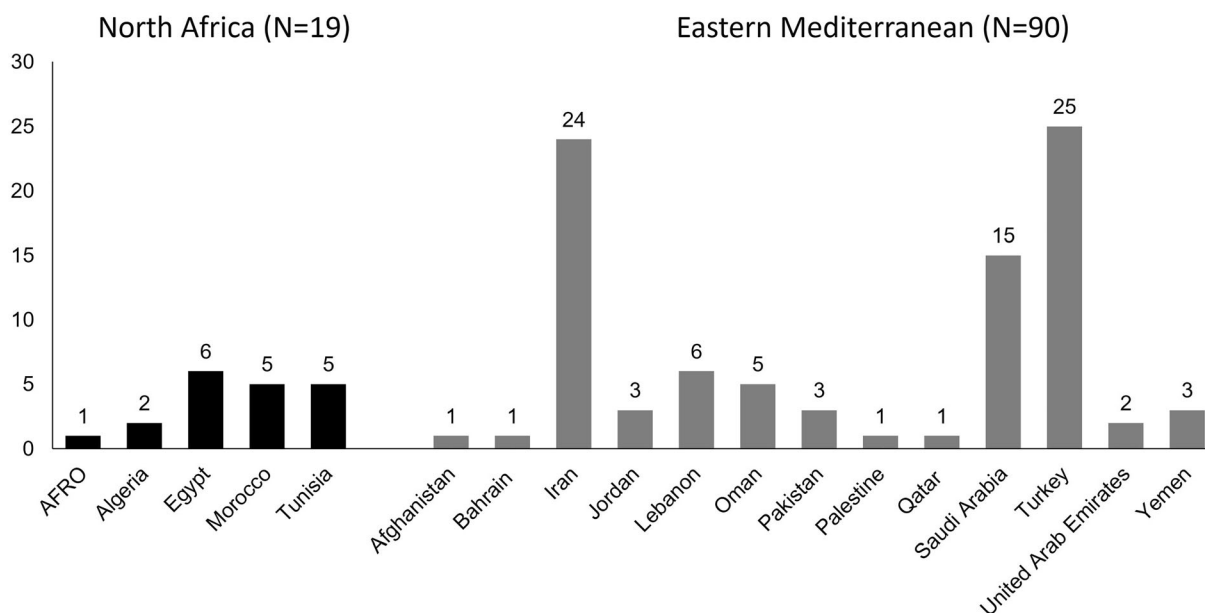
Fig. 2 Country of study setting and the number of studies retrieved

of ages or the general population (i.e. both paediatric and adult populations combined, across a range of ages or where all age groups were included, [n = 69, 62%]). Eighteen studies (16.1%) were conducted in adults only and 20 studies (17.9%) in patients aged less than

18 years old. Age was not reported in five (4%) of the studies. The average proportion of female individuals included in the studies was 46%. The percentage of patients with chronic medical conditions or risk factors predisposing them to an increased risk of complications from

Table 1 Characteristics of studies conducted in both the Middle Eastern and North African regions

Author and publication date	Region	Number of patients enrolled	Study setting	Duration (year)	Pre/post and during 2009 pandemic	Number of influenza seasons	Simplified case definition	Confirmed influenza cases, N (%)	Laboratory method for detection	A strain cases N, (%ᵃ)	B strain cases N, (%ᵃ)
Al Khatib et al. 2019 [16]	EMRO	563,087	Inpatient and outpatient	9	Pandemic and post	8	Laboratory-confirmed influenza	130,354 (3.6)	NR	869 (66.7)	224 (17.2)
Caini et al. 2018 [4]	EMNA	70,532	Inpatient and outpatient	6	Post	5	NR	70,532 (100.0)	NR	61,221 (86.8)	9310 (13.2)
Elhakim et al. 2019 [17]	EMNA	24,211	Inpatient	2	Post	2	SARI	3995 (17)	RT-PCR	2337 (58.5)	1146 (28.7)

EMRO Eastern Mediterranean region, *EMNA* Eastern Mediterranean and North African, *NR* not reported, *SARI* severe acute respiratory infection, *RT-PCR* reverse transcription polymerase chain reaction

ᵃ Percentage among positive cases

Table 2 Characteristics of all studies by region and county

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Eastern Mediterranean region							
Rasooly et al. 2016 [56]	Afghanistan	6900	Surveillance	Inpatient	7	Pre, pandemic and post	General population
Al Salman et al. 2018 [32]	Bahrain	26	Case series	Inpatient	0.6	Post	Adults
Caini et al. 2018 [4]	EMNA	70,532	Surveillance	Inpatient and outpatient	6	Post	General population
Al Khatib et al. 2019 [16]	EMRO	563,087	Surveillance	Inpatient and outpatient	9	Pandemic and post	General population
Farshad et al. 2008 [57]	Iran	202	Surveillance	Inpatient	2	Pre	< 5 years
Soltani et al. 2009 [58]	Iran	57	Surveillance	Inpatient	1.3	Pre	NR
Yavarian et al. 2009 [59]	Iran	400	Surveillance	Inpatient	3	Pre	General population
Moattari et al. 2010 [23]	Iran	300	Surveillance	Inpatient	2	Pre	General population
Moattari et al. 2012 [60]	Iran	275	Surveillance	Outpatient	0.4	Pandemic	Adults
Yavarian et al. 2012 [61]	Iran	40,169	Case series	Inpatient	2	Pandemic and post	General population
Makvandi et al. 2013 [33]	Iran	232	Surveillance	Inpatient	1	Post	< 18 years
Afrasiabian et al. 2014 [62]	Iran	1059	Surveillance	Inpatient	1	Pandemic	General population
Kenari et al. 2014 [63]	Iran	2781	Surveillance	Inpatient	4	Pandemic and post	General population

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Pourakbari et al. 2014 [64]	Iran	232	Surveillance	Inpatient	1	Post	< 5 years
Haghshenas et al. 2015 [65]	Iran	571	Surveillance	Inpatient	2	Post	General population
Khodadad et al. 2015 [66]	Iran	200	Surveillance	Inpatient	0.3	Post	General population
Faezi et al. 2016 [67]	Iran	143	Surveillance	Inpatient	0.8	Post	General population
Moasser et al. 2017 [68]	Iran	200	Surveillance	Inpatient	1	Post	General population
Hosseini et al. 2018 [69]	Iran	53,526	Surveillance	Inpatient	5	Post	General population
Javanian et al. 2018 [70]	Iran	123	Surveillance	Inpatient	0.5	Post	Adults
Yavarian et al. 2018 [71]	Iran	38,511	Surveillance	Inpatient	3	Post	General population
Haghshenas et al. 2019 [72]	Iran	3037	Surveillance	Inpatient	4	Post	General population
Hosssininasab et al. 2019 [73]	Iran	53	Case series	Inpatient	0.5	Post	< 15 years
Mohebbi et al. 2019 [74]	Iran	1836	Surveillance	Inpatient	1	Post	General population
Mood et al. 2019 [75]	Iran	240	Surveillance	Inpatient	0.5	Post	General population
Rahmanian et al. 2019 [76]	Iran	108	Surveillance	Inpatient	0.6	Post	General population

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Sharify Mood et al. 2019 [77]	Iran	240	Surveillance	Inpatient	0.5	Post	General population
Nateghian et al. 2020 [78]	Iran	11,080	Case series	Inpatient and outpatient	3	Post	General population
Nasrallah et al. 2000 [79]	Jordan	350	Surveillance	Inpatient	0.6	Pre	< 15 years
Al-Abdallat 2016 [14]	Jordan	2891	Surveillance	Inpatient	6	Pre, pandemic and post	General population
Altous et al. 2019 [80]	Jordan	170	Surveillance	Inpatient	5	Post	Adults
Zaraket et al. 2009 [81]	Lebanon	39	Surveillance	Outpatient	0.4	Pre	< 15 years
Zaraket et al. 2014 [82]	Lebanon	202	Surveillance	Inpatient	2	Post	General population
Saito et al. 2016 [83]	Lebanon	440	Surveillance	Inpatient	2	Post	NR
Saleh et al. 2018 [84]	Lebanon	742	Surveillance	Inpatient	1	Post	General population
Alibrahim et al. 2019 [85]	Lebanon	889	Surveillance	Inpatient	2	Post	General population
Tannous et al. 2019 [24]	Lebanon	100	Surveillance	Inpatient	0.1	Post	General population
Al-Lawati et al. 2010 [86]	Oman	131	Case series	Inpatient	1	Pandemic	General population
Al-Mahrezi et al. 2012 [87]	Oman	2318	Surveillance	Outpatient	1	Pandemic	Adults
Al-Awaidy et al. 2015 [28]	Oman	5147	Surveillance	Inpatient	6	Pandemic and post	General population

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Kharosi et al. 2017 [88]	Oman	231	Surveillance	Inpatient	1	Post	Adults
Abdel-Hady et al. 2018 [89]	Oman	19,405	Surveillance	Inpatient	3	Post	General population
Badar et al. 2013 [90]	Pakistan	6258	Surveillance	Inpatient	3	Pandemic	General population
Bashir et al. 2017 [91]	Pakistan	155	Surveillance	Inpatient	1	Post	< 5 years
Fatima et al. 2019 [92]	Pakistan	100	Case series	Inpatient	1	Post	< 15 years
Bakri et al. 2019 [93]	Palestine	200	Surveillance	Inpatient and outpatient	0.3	Post	General population
Al-Romaihi et al. 2019 [94]	Qatar	43,597	Surveillance	Inpatient and outpatient	6	Post	Adults
Bakir et al. 1998 [95]	Saudi Arabia	1429	Surveillance	Inpatient	3	Pre	< 5 years
Afifi et al. 2012 [22]	Saudi Arabia	21	Cohort study	Inpatient	2	Pandemic	General population
Mohamed et al. 2012 [25]	Saudi Arabia	160	Case series	Outpatient	0.1	Pandemic	General population
Al-Ayed et al. 2014 [96]	Saudi Arabia	135	Surveillance	Inpatient	0.8	Post	< 5 years
Ali et al. 2014 [97]	Saudi Arabia	80	Surveillance	Inpatient	1	Pandemic	NR
Amer et al. 2016 [98]	Saudi Arabia	174	Cohort study	Inpatient	1	Pre and pandemic	< 5 years
Tolah et al. 2016 [99]	Saudi Arabia	406	Surveillance	Inpatient	1	Post	NR
Al-Tawfiq et al. 2017 [100]	Saudi Arabia	1644	Surveillance	Inpatient	2	Post	Adults

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Altayep et al. 2017 [101]	Saudi Arabia	300	Surveillance	Inpatient	1	Post	General population
Fagbo et al. 2017 [102]	Saudi Arabia	2235	Surveillance	Inpatient	1	Post	< 15 years
Albogami et al. 2018 [18]	Saudi Arabia	4611	Surveillance	Inpatient	1	Post	< 15 years
Assiri et al. 2018 [103]	Saudi Arabia	909	Surveillance	Inpatient and outpatient	1	Post	Adults
Rabaan et al. 2018 [104]	Saudi Arabia	749	Surveillance	Inpatient	0.9	Post	General population
Al-Baadani et al. 2019 [105]	Saudi Arabia	448	cohort study	Inpatient	4	Post	Adults
Khan et al. 2019 [106]	Saudi Arabia	6492	Surveillance	Inpatient	2	Pandemic and post	General population
Kaygusuz et al. 2004 [107]	Turkey	211	Surveillance	Inpatient	2	Pre	General population
Yüksel et al. 2008 [108]	Turkey	151	Surveillance	Inpatient	2	Post	< 5 years
Çarhan et al. 2009 [109]	Turkey	1157	Surveillance	Outpatient	1	Pre	General population
Ceylan et al. 2012 [110]	Turkey	215	Surveillance	Outpatient	4	Pre	General population
Ciblak et al. 2012 [53]	Turkey	11,077	Surveillance	Inpatient and outpatient	9	Pre, pandemic and post	General population
Gülen et al. 2014 [111]	Turkey	1326	Surveillance	Inpatient	10	Pre, pandemic and post	< 18 years

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Karadag-Oncel et al. 2014 [112]	Turkey	200	Surveillance	Inpatient	0.4	Post	< 18 years
Çiçek et al. 2015 [113]	Turkey	5102	Surveillance	Inpatient	2	Post	General population
Cohen et al. 2015 [114]	Turkey	360	Surveillance	Outpatient	2	Post	General population
Puig-Barberà et al. 2015 [115]	Turkey	11,843	Surveillance	Inpatient	2	Post	General population
Altaş et al. 2016 [116]	Turkey	15,149	Surveillance	Inpatient and outpatient	5	Post	General population
Goktas et al. 2016 [117]	Turkey	845	Surveillance	Inpatient	1	Post	General population
Gülcen et al. 2016 [118]	Turkey	2041	Surveillance	Inpatient	3.5	Post	General population
Meşe et al. 2016 [119]	Turkey	1291	Surveillance	Inpatient	2	Post	General population
Puig-Barberà et al. 2016 [120]	Turkey	1409	Surveillance	Inpatient	1	Post	General population
Ersoy et al. 2017 [35]	Turkey	35	Case–control	Inpatient	1	Post	General population
Özişk et al. 2017 [121]	Turkey	106	Surveillance	Inpatient	0.4	Post	General population
Tanriover et al. 2017 [122]	Turkey	774	Surveillance	Inpatient	0.4	Post	General population
Aykaçet al. 2018 [123]	Turkey	1240	Surveillance	Inpatient	10	Pre, pandemic and post	< 18 years

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Erçen Diken et al. 2018 [124]	Turkey	197	Surveillance	Inpatient	1	Post	Adults
Meşe et al. 2018 [27]	Turkey	14,429	Surveillance	Inpatient	13	Pre, pandemic and post	General population
Ortac Ersoy et al. 2018 [125]	Turkey	99	Case series	Inpatient	0.5	Post	Adults
Ünver et al. 2018 [37]	Turkey	120	Surveillance	Inpatient	0.4	Post	General population
Aysert-Yildiz et al. 2019 [126]	Turkey	111	Surveillance	Inpatient	2	Post	Adults
Puig-Barberà et al. 2019 [127]	Turkey	704	Surveillance	Inpatient and outpatient	1	Post	General population
Alsuwaidi et al. 2017 [128]	United Arab Emirates	294	Cross-sectional	Inpatient	1	Post	< 15 years
Jeon et al. 2019 [129]	United Arab Emirates	1362	Surveillance	Inpatient	3	Post	Adults
Al Amad et al. 2016 [130]	Yemen	1665	Surveillance	Inpatient	4	Post	General population
Thabet et al. 2016 [131]	Yemen	1346	Surveillance	Inpatient	2	Post	General population
Al Amad et al. 2019 [132]	Yemen	1811	Surveillance	Inpatient	5	Post	General population
North Africa							
Radin et al. 2012 [133]	AFRO	113,480	Surveillance	Inpatient	4	Pre and pandemic	General population

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Ait-Aissa et al. 2018 [134]	Algeria	3447	Surveillance	Outpatient	5	Pandemic and post	General population
Derrar et al. 2019 [135]	Algeria	2766	Surveillance	Inpatient and outpatient	4	Pandemic and post	General population
Shafik et al. 2012 [136]	Egypt	450	Surveillance	Inpatient	1	Pre	< 5 years
Kandeel et al. 2016 [13]	Egypt	17,441	Surveillance	Inpatient	6	Pre, pandemic and post	General population
Reaves et al. 2016 [30]	Egypt	9992	Surveillance	Inpatient	6	Pandemic and post	General population
Refaey et al. 2016 [137]	Egypt	18,171 and 11,114	Surveillance	Inpatient/ outpatient	4	Post	General population
Elhakim et al. 2019 [138]	Egypt	1254	Surveillance	Inpatient	3	Post	General population
Rowlinson et al. 2017 [31]	Egypt	5768	Surveillance	Inpatient	4	Pandemic and post	General population
Barakat et al. 2011 [139]	Morocco	3102	Surveillance	Inpatient and outpatient	3	Pre	General population
Anga et al. 2012 [140]	Morocco	273	Surveillance	Outpatient	0.4	Post	NR
El Rhaffouli et al. 2013 [26]	Morocco	500	Cross-sectional	Inpatient	0.17	Post	Adults
Elfalki et al. 2016 [141]	Morocco	440	Surveillance	Inpatient	1	Post	General population
Tarek et al. 2018 [20]	Morocco	140	Surveillance	Inpatient	2	Post	Adults
El Moussi et al. 2013 [142]	Tunisia	8664	Surveillance	Inpatient and outpatient	3	Pandemic and post	General population

Table 2 continued

Author and publication date	Country	Number of patients enrolled	Study design	Study setting	Duration (year)	Pre/post and during 2009 pandemic	All ages
Chlif et al. 2016 [29]	Tunisia	2476	Surveillance	Outpatient	3	Post	General population
Bouneb et al. 2018 [34]	Tunisia	40	Case series	Inpatient	6	Post	Adults
Meddeb et al. 2018 [143]	Tunisia	25	Surveillance	Inpatient	1.3	Post	Adults
Tinsa et al. 2018 [36]	Tunisia	32	Case series	Inpatient	0.3	Pandemic	< 15 years

AFRO African region, *EMNA* Eastern Mediterranean and North African, *EMRO* Eastern Mediterranean region, *NR* not reported

influenza was reported in 24 studies; 18 studies reported a patient population (defined as ILI, lower respiratory tract infection [LRTI], SARI or laboratory-confirmed cases) of which more than 20% who had at least one risk factor.

Study Design and Data Sources

Surveillance data were the most common source for the selected 112 studies conducted in the EMNA region (n = 96; 86%). Other sources of data included case series (n = 10), cross-sectional (n = 2), cohort (n = 3) and case–control (n = 1) studies. The study duration ranged from 1 month to 13 years (median duration 24 months, interquartile range [IQR] 12–46.5 months).

Influenza Reporting

The data for influenza reporting for the studies conducted in the region are presented in Table 3. Overall, 314,058 laboratory-confirmed influenza cases were identified across all studies. Among surveillance studies, the percentage of positive cases reported ranged from 1% [18] through to 100% [4, 19, 20]. Case definitions for influenza surveillance varied across the studies. The most commonly used definition was that of the WHO for ILI (n = 45, 40.2%); other commonly used definitions included the WHO definition for SARI (n = 17, 15.2%) [21] (three case definitions [2.7%] included both ILI and SARI), laboratory-confirmed cases of influenza (n = 8, 7.2%), patients diagnosed with acute respiratory infections (ARI), and those presenting with upper and acute lower respiratory tract infections (URLI and ALRI) (n = 10, 8.9%).

The reverse transcription polymerase chain reaction (RT-PCR) was the most frequently used method to detect virus (n = 82, 73%). Other methods employed for identification included cell culture, the hemagglutination inhibition test (HIT) and immunofluorescence.

We identified 83 studies that reported the co-circulation of both influenza A and B strains, 26 reporting data on influenza A strain circulation only, and one study reporting on influenza B strain circulation alone. In studies

Table 3 Epidemiological data of all studies by region and county

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%ᵃ)	% H1N1	% H3N2	B strain cases N, (%ᵃ)
Eastern Mediterranean region													
Rasooly et al. 2016 [56]	Afghanistan	NR	NR	PCR	A + B	H1N1	No	7	248 (3.6)	156 (63.0)	NR	NR	NR
Al Salman et al. 2018 [32]	Bahrain	40.0	Laboratory-confirmed influenza	NR	A	H1N1	No	1	26 (100.0)	26 (100.0)	100.0	NR	NA
Caini et al. 2018 [4]	EMNA	NR	NR	NR	A + B	No	No	5	70,532 (100.0)	61,222 (86.8)	NR	NR	9310 (13.2)
Al Khatib et al. 2019 [16]	EMRO	NR	Laboratory-confirmed influenza	NA	A + B	H1N1, H3N2	No	8	130,354 (23.1)	869 (66.7)	50.8	15.9	224 (17.2)
Farshad et al. 2008 [57]	Iran	NR	LRTI	Indirect immunofluorescence	A + B	No	AdV, hPIV (1, 2, 3) and RSV	2	109 (10.9)	15 (68.2)	NR	NR	7 (31.8)
Soltani et al. 2009 [58]	Iran	NR	NR	RT-PCR	A + B	H1N1, H3N2	No	1.5	12 (21.0)	10 (83.3)	25.0	58.0	2 (16.6)
Yavarian et al. 2009 [59]	Iran	NR	ILI	RT-PCR	A + B	H1N1, H3N2	No	3.5	100 (25.0)	50 (50.0)	35.0	15.0	50 (50)
Moattari et al. 2010 [23]	Iran	NR	ILI	RT-PCR	A + B	No	No	2	26 (8.7)	26 (100.0)	NR	NR	0
Moattari et al. 2012 [60]	Iran	NR	ILI	RT-PCR and cell culture	A + B	H1N1, H3N2	No	1	58 (21.1)	26 (44.8)	17.2	27.6	37 (63.8)
Yavarian et al. 2012 [61]	Iran	NR	ILI	RT-PCR	A	No	No	2.5	5214 (12.9)	NR	NR	NR	NR
Makvandi et al. 2013 [33]	Iran	NR	ILI	RT-PCR	A	H1N1	No	1	45 (18.1)	45 (100.0)	100.0	NR	NR
Afrasiabian et al. 2014 [62]	Iran	NR	ULRTI	RT-PCR	A	H1N1	No	1	157 (14.8)	157 (100.0)	14.8	NR	NR

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%[a])	% H1N1	% H3N2	B strain cases N, (%[a])
Kenari et al. 2014 [63]	Iran	NR	NR	RT-PCR	A + B	No	No	4	517 (18.6)	517 (100.0)	NR	NR	NR
Pourakbari et al. 2014 [64]	Iran	NR	ILI	RT-PCR	A + B	No	AdV, hPIV and RSV	1	10 (4.3)	8 (80.0)	NR	NR	2 (20.0)
Haghshenas et al. 2015 [65]	Iran	NR	ILI	RT-PCR	A	H3N2	No	2	219 (38.4)	201 (91.8)	NR	35.2	NR
Khodadad et al. 2015 [66]	Iran	NR	ILI	RT-PCR	A	H1N1	No	1	77 (38.5)	77 (100.0)	100.0	NR	NR
Faezi et al. 2016 [67]	Iran	NR	ARI	RT-PCR	A + B	H1N1, H3N2	AdV, CoV and RSV	1	45 (31.5)	24 (53.3)	7.7	9.1	21 (46.7)
Moasser et al. 2017 [68]	Iran	NR	ILI	RT-PCR	A + B	H1N1, H3N2	No	1	98 (49.0)	80 (81.6)	44.9	36.7	18 (18.4)
Hosseini et al. 2018 [69]	Iran	NR	ILI	NR	A + B	No	No	5	7684 (14.4)	5456 (71.0)	NR	NR	2152 (28.0)
Javanian et al. 2018 [70]	Iran	11.4	ILI	RT-PCR	A	H1N1	No	1	58 (47.2)	58 (100.0)	100.0	NR	NR
Yavarian et al. 2018 [71]	Iran	NR	SARI	RT-PCR	A + B	No	MERS-CoV	3	4868 (12.6)	3866 (79.4)	46.7	32.7	981 (20.1)
Haghshenas et al. 2019 [72]	Iran	NR	ILI	RT-PCR	A	H1N1	No	4	442 (14.6)	442 (100.0)	100.0	NR	NA
Hosssininasab 2019 [73]	Iran	NR	Laboratory-confirmed influenza	rRT-PCR	A	H1N1	No	2	53 (100.0)	53 (100.0)	100.0	NA	NA

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%ᵃ)	% H1N1	% H3N2	B strain cases N, (%ᵃ)
Mohebbi et al. 2019 [74]	Iran	NR	SARI	RT-PCR	A + B	H1N1, H3N2	No	1	566 (30.8)	507 (89.6)	88.9	0.5	60 (10.6)
Mood et al. 2019 [75]	Iran	NR	ILI	RT-PCR	A + B	H1N1, H3N2	hPIV (1, 2, 3, 4) and RSV (A, B)	1	205 (85.4)	196 (95.6)	65.4	34.6	9 (4.4)
Rahmanian et al. 2019 [76]	Iran	NR	LRTI	RT-PCR	A	H1N1, H3N2	No	1	43 (39.8)	43 (100.0)	100.0	NA	NA
Sharify Mood et al. 2019 [77]	Iran	NR	ILI	RT-PCR	A + B	H1N1	hPIV (1, 2, 3) and RSV (A, B)	1	205 (85.4)	196 (95.6)	33.17	NR	9 (4.4)
Nateghian et al. 2020 [78]	Iran	31.1	SARI	RT-PCR	A + B	H1N1, H3N2	No	3	11,080 (100.0)	8403 (75.8)	35.7	30.6	2599 (23.5)
Nasrallah et al. 2000 [79]	Jordan	NR	ULRTI	Direct immunofluorescence	A + B	No	hPIV	1	22 (6.3)	15 (68.2)	NR	NR	7 (31.8)
Al-Abdallat et al. 2016 [14]	Jordan	16.0	SARI	rRT-PCR	A + B	H1N1, H3N2	No	1	257 (8.9)	192 (74.7)	39.6	47.0	65 (25.3)
Altous et al. 2019 [80]	Jordan	NR	LRTI	RT-PCR	A + B	No	AdV, CoV, hMPV, hPIV, RV and RSV	5	19 (11.2)	12 (63.2)	NR	NR	7 (36.8)
Zaraket et al. 2009 [81]	Lebanon	NR	ILI	PCR	A + B	No	hMPV and RSV	1	15 (38.5)	11 (73.3)	NR	NR	4 (26.6)
Zaraket et al. 2014 [82]	Lebanon	NR	ILI	RT-PCR	A + B	No	No	2	72 (35.6)	57 (79.2)	NR	NR	15 (20.8)
Saito et al. 2016 [83]	Lebanon	NR	ARTI	RT-PCR	A + B	No	No	2	119 (27.0)	82 (68.9)	NR	NR	37 (31.1)

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%ᵃ)	% H1N1	% H3N2	B strain cases N, (%ᵃ)
Saleh et al. 2018 [84]	Lebanon	NR	SARI	RT-PCR	A + B	No	No	1	100 (13.5)	57 (57.0)	NR	NR	43 (43.0)
Alibrahim et al. 2019 [85]	Lebanon	NR	ILI	RT-PCR	A + B	H1N1, H3N2	No	4	304 (34.2)	183 (60.2)	29.3	31.5	121 (39.8)
Tannous et al. 2019 [24]	Lebanon	100.0	ILI	RT-PCR	A	No	No	1	10 (10.0)	10 (100.0)	NR	NR	NR
Al-Lawati et al. 2010 [86]	Oman	NR	Laboratory-confirmed influenza	rRT-PCR	A	H1N1	No	1	131 (100.0)	131 (100.0)	100.0	0.0	NA
Al-Mahrezi et al. 2012 [87]	Oman	9.2	ILI	rRT-PCR	A	H1N1	No	1	626 (27.0)	626 (100.0)	27.0	0.0	NA
Al-Awaidy et al. 2015 [28, 144]	Oman	35.0	SARI	rRT-PCR	A + B	No	No	5	423 (8.2)	273 (64.5)	NR	NR	151 (35.7)
Kharosi et al. 2017 [88]	Oman	82.7	NR	RT-PCR	A + B	No	AdV, EV, hPIV, RV and RSV	1	84 (36.4)	62 (73.8)	NR	NR	22 (26.2)
Abdel-Hady et al. 2018 [89]	Oman	NR	SARI	RT-PCR	A	H1N1	No	3	3997 (20.6)	2390 (59.8)	59.8	NR	NA
Badar et al. 2013 [90]	Pakistan	NR	ILI	rRT-PCR	A + B	H1N1, H3N2	No	3	1489 (23.8)	1066 (71.6)	60.3	11.4	423 (28.4)
Bashir et al. 2017 [91]	Pakistan	NR	LRTI	rRT-PCR	A + B	No	AdV, influenza, hMPV and RSV	1.5	49 (31.6)	38 (77.6)	NR	NR	11 (22.4)
Fatima et al. 2019 [92]	Pakistan	NR	Laboratory-confirmed influenza	PCR	A	H1N1	No	1	12 (12.0)	12 (100.0)	12.0	NR	NA

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%a)	% H1N1	% H3N2	B strain cases N, (%a)
Bakri et al. 2019 [93]	Palestine	NR	URTI	RT-PCR	A	H1N1, H3N2	No	1	50 (25.0)	50 (100.0)	48.0	52.0	NR
Al-Romaihi et al. 2019 [94]	Qatar	NR	ILI	RT-PCR	A + B	No	hCoV, hMPV, hPIVs, hRV and RSV	3	9853 (22.6)	7602 (77.1)	NR	NR	2261 (22.9)
Bakir et al. 1998 [95]	Saudi Arabia	NR	ARTI	Immunofluorescence antibody and virus culture	A + B	No	AdV, hPIV (1, 2, 3) and RSV	3	45 (3.1)	32 (71.1)	NR	NR	13 (28.9)
Affifi et al. 2012 [22]	Saudi Arabia	NR	ILI	RT-PCR	A	H1N1	No	1	12 (57.1)	12 (100.0)	100.0	NR	NR
Mohamed et al. 2012 [25]	Saudi Arabia	NR	Laboratory-confirmed influenza	RT-PCR	A	H1N1	No	1	160 (100.0)	69 (43.1)	43.1	NR	NR
Al-Ayed et al. 2014 [96]	Saudi Arabia	NR	ULRTI	RT-PCR	A + B	No	AdV hBoV, hCoV, hMPV, influenza virus, hPIV, hRV and RSV	1	10 (7.4)	8 (80.0)	NR	NR	2 (20.0)
Ali et al. 2014 [97]	Saudi Arabia	NR	ILI	RT-PCR	B	B/Y, B/V	No	1	3 (3.8)	NA	NA	NA	3 (100.0)
Amer et al. 2016 [98]	Saudi Arabia	NR	ARTI	rRT-PCR	A	No	CoV, MPV, hPIV and RSV	1	34 (19.5)	34 (100.0)	NR	NR	NR
Tolah et al. 2016 [99]	Saudi Arabia	NR	ARTI	rRT-PCR	A + B	H1N1, H3N2	No	1	33 (8.1)	26 (78.8)	6.2	0.3	7 (21.2)
Al-Tawfiq et al. 2017 [100]	Saudi Arabia	NR	LRTI	RT-PCR	A + B	No	MERS-CoV	2	271 (16.5)	107 (39.5)	NR	NR	44 (16.2)
Altayep et al. 2017 [101]	Saudi Arabia	NR	ILI	RT-PCR	A	H1N1	No	1	54 (18.0)	54 (100.0)	100.0	NR	NR

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%a)	% H1N1	% H3N2	B strain cases N, (%a)
Fagbo et al. 2017 [102]	Saudi Arabia	NR	ARTI	Extracted nucleic acids	A + B	No	AdV, hBoV, hCoV (NL63, 229E, OC43), hEV, hMPV, hPIV (1,2,3,4), hRV and RSV (A, B)	1	1364 (61.0)	74 (5.4)	NR	NR	45 (3.3)
Albogami et al. 2018 [18]	Saudi Arabia	NR	ARTI	NR	A + B	No	No	2	65 (1.4)	55 (85.1)	NR	NR	9 (13.8)
Assiri et al. 2018 [103]	Saudi Arabia	NR	SARI	RT-PCR	A + B	No	No	1	289 (31.8)	NR	NR	NR	NR
Rabaan et al. 2018 [104]	Saudi Arabia	NR	LRTI	RT-PCR	A	H1N1	No	1	100 (13.4)	100 (100.0)	100.0	NR	NR
Al-Baadani et al. 2019 [105]	Saudi Arabia	52.3	LRTI	NR	A + B	H1N1, H3N2	MERS-CoV	3	366 (81.7)	150 (41.0)	41.0	NR	NA
Khan et al. 2019 [106]	Saudi Arabia	NR	ILI	RT-PCR	A	H1N1	No	1	1041 (16.0)	1041 (100.0)	100.0	NR	NA
Kaygusuz et al. 2004 [107]	Turkey	NR	ULRTI	Immunofluorescence	A + B	No	AdV, hPIV (1,2,3) and RSV	2	28 (13.3)	25 (89.3)	NR	NR	3 (10.7)
Yüksel et al. 2008 [108]	Turkey	NR	LRTI	Direct fluorescent antibody	NR	No	AdVs, hPIV and RSV	2	9 (6.0)	NR	NR	NR	NR
Çarhan et al. 2009 [109]	Turkey	NR	NR	RT-PCR and cell culture	A + B	H1N1, H3N2	AdV, hPIV and RSV	1	276 (23.9)	188 (68.1)	26.4	41.6	88 (31.9)
Ceylan et al. 2012 [110]	Turkey	NR	ILI	NR	A + B	H1N1, H3N2	AdV, hPIV and RSV	3	97 (45.1)	35 (36.1)	11.3	21.6	59 (60.8)
Ciblak et al. 2012 [53]	Turkey	NR	ILI	RT-PCR	A + B	No	No	9	4187 (37.8)	3596 (85.9)	NR	NR	585 (14.0)

Table 3 continued

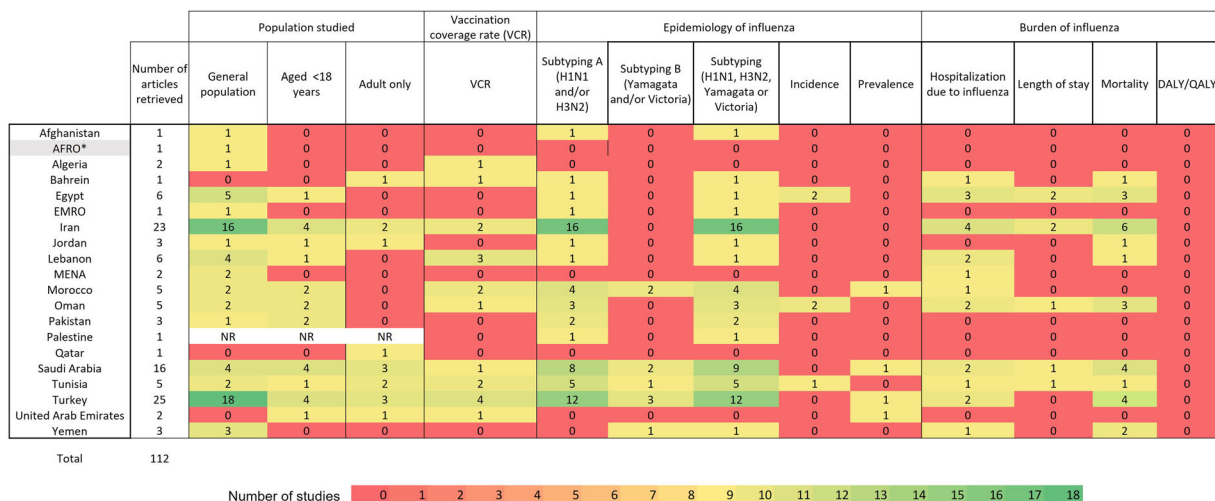| Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%ᵃ)	% H1N1	% H3N2	B strain cases N, (%ᵃ)
Gülen et al. 2014 [111]	Turkey	NR	ARTI	Cell culture, direct fluorescent antibody test and/or multiplex PCR	A + B	No	AdV, hPIV (1, 2,3) and RSV	10	503 (38.0)	395 (78.6)	NR	NR	24 (4.0)
Karadag-Oncel et al. 2014 [112]	Turkey	NR	ILI	RT-PCR	A + B	H3N2	BoV, CoV, MPV, RV and RSV	1	64 (32.0)	40 (62.5)	NR	40.0	24 (37.5)
Çiçek et al. 2015 [113]	Turkey	NR	ULRTI	Direct immunofluorescence antibody and cell culture	A + B	No	AdV, hBoV, hCoV, hPIV (1, 2, 3, 4), hRV, hMPV and RSV	3	1704 (33.4)	446 (26.2)	NR	NR	39 (2.3)
Cohen et al. 2015 [19]	Turkey	NR	ILI	rRT-PCR	A + B	H1N1, H3N2, B/Y, B/V	No	2	360 (100.0)	150 (41.7)	11.7	26.7	210 (58.3)
Puig-Barberà et al. 2015 [115]	Turkey	19.1	ILI	RT-PCR	A + B	H1N1, H3N2, B/Y, B/V	No	2	2713 (22.9)	1949 (71.8)	36.5	29.8	719 (26.5)
Altaş et al. 2016 [116]	Turkey	NR	NR	rRT-PCR cell culture inoculation, HIT	A + B	No	CoV, paramyxoviruses, RV and RSV	5	3810 (25.2)	2442 (64.1)	NR	NR	1363 (35.8)
Goktas et al. 2016 [117]	Turkey	NR	ARTI	RT-PCR	A + B	No	Adenovirus, hBoV, hCoV, RV/EV and RSV	1	376 (44.5)	213 (56.8)	NR	NR	153 (40.8)
Gülcen et al. 2016 [118]	Turkey	NR	ILI	PCR	A + B	No	No	3.5	257 (12.6)	97 (37.7)	NR	NR	161 (62.6)
Meşe et al. 2016 [119]	Turkey	NR	ILI	RT-PCR	A + B	H1NI, H3N2	No	2	491 (38.0)	303 (61.7)	NR	NR	188 (38.3)

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%[a])	% H1N1	% H3N2	B strain cases N, (%[a])
Puig-Barberà et al. 2016 [120]	Turkey	19.8	ILI	RT-PCR	A + B	H1N1, H3N2, B/Y, B/V	No	1	71 (5.0)	32 (45.1)	36.6	8.5	39 (54.9)
Ersoy et al. 2017 [35]	Turkey	NR	ILI	RT-PCR	A + B	No	No	1	35 (100.0)	12 (34.3)	NR	NR	10 (28.6)
Özişik et al. 2017 [121]	Turkey	65.1	ILI	RT-PCR	A + B	H3N2	AdV, BoV, CoV (NL63, 229E, OC43, HKU1), echovirus, EV, hMPV (A, B), hPIV (1, 2, 3, 4), RV and RSV (A, B)	1	19 (17.9)	17 (89.5)	NR	89.5	2 (10.5)
Tanriover et al. 2017 [122]	Turkey	85.7	ILI	RT-PCR	A + B	H1N1, H3N2	No	1	142 (18.3)	131 (92.3)	47.9	40.1	11 (7.7)
Aykaç et al. 2018 [123]	Turkey	NR	ULRTI	RT-PCR	A + B	No	AdV, CoV, hPIV (1, 2, 3) and RSV	9	37 (3.0)	NR	NR	NR	NR
Erçen Diken et al. 2018 [124]	Turkey	24.4	NR	NR	A + B	H1N1, H3N2	hMPV	1	91 (46.2)	88 (96.7)	30.0	14.7	3 (3.3)
Meşe et al. 2018 [27]	Turkey	NR	ILI	RT-PCR	A + B	H1N1, H3N2	No	13	3927 (38.0)	1603 (40.8)	16.4	24.4	752 (19.1)
Ortac Ersoy et al. 2018 [125]	Turkey	56.6	Laboratory-confirmed influenza	NR	A + B	No	RSV	1	99 (100.0)	65 (65.7)	NR	NR	30 (30.3)
Ünver et al. 2018 [37]	Turkey	NR	ARTI	PCR	A + B	No	CMV and RSV,	1	28 (23.3)	5 (17.9)	NR	NR	23 (82.1)

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%a)	% H1N1	% H3N2	B strain cases N, (%a)
Aysert-Yildiz et al. 2019 [126]	Turkey	42.6	ILI	RT-PCR	A + B	H1N1, H3N2	AdV, CoV, hPIV, hMPV RV and RSV	2	15 (13.5)	10 (66.7)	20.0	46.7	5 (33.3)
Puig-Barberà et al. 2019 [127]	Turkey	52.1	ILI	RT-PCR	A + B	H1N1, H3N2	No	1	143 (20.3)	124 (86.7)	47.6	39.2	11 (7.7)
Alsuwaidi et al. 2017 [128]	United Arab Emirates	NR	ARTI	Serology	A + B	No	No	1	188 (63.9)	44 (23.4)	NR	NR	77 (40.8)
Jeon et al. 2019 [129]	United Arab Emirates	NR	ARTI	rRT-PCR	A + B	No	AdV, hBoV, hCoV, hEV, hMPV, hPIV, hRV and RSV	3	273 (20.0)	176 (64.5)	NR	NR	79 (28.9)
Al Amad et al. 2016 [130]	Yemen	24.0	SARI	NR	A + B	No	AdV and RSV	3	83 (5.0)	41 (49.4)	NR	NR	27 (32.5)
Thabet et al. 2016 [131]	Yemen	NR	SARI	RT-PCR	A + B	No	AdV and RSV	1	733 (54.5)	44 (6.0)	3.0	5.0	22 (3.0)
Al Amad et al. 2019 [132]	Yemen	23.0	SARI	RT-PCR	A + B	No	AdV, hPIV and RSV	5	89 (4.9)	67 (75.3)	NR	NR	22 (24.7)
North Africa region													
Radin et al. 2012 [133]	AFRO	NR	ILI and SARI	RT-PCR	A + B	No	No	4	19,592 (17.4)	NR	NR	NR	NR
Aït-Aissa et al. 2018 [134]	Algeria	NR	ILI	rRT-PCR and HAI	A + B	No	No	5	1460 (42)	983 (67.3)	NR	NR	477 (32.7)
Derrar et al. 2019 [135]	Algeria	NR	ILI	RT-PCR	A + B	No	No	4	1272 (46.0)	760 (59.7)	NR	NR	840 (66.0)

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%[a])	% H1N1	% H3N2	B strain cases N, (%[a])
Shafik et al. 2012 [136]	Egypt	NR	LRTI	Direct fluorescence assay, rRT-PCR and shell vial culture	A + B	No	AdV, influenza (A, B), hMPV, hPIV (1, 2, 3) and RSV	1	21 (4.6)	16 (76.2)	NR	NR	5 (23.8)
Kandeel et al. 2016 [13]	Egypt	27	SARI	rRT-PCR	A + B	No	No	7	2965 (17.0)	2013 (67.9)	NR	NR	923 (31.1)
Reaves et al. 2016 [30]	Egypt	NR	SARI	PCR	A + B	No	AdV, CoV, hMPV, hPIV and RSV	6	1569 (15.7)	902 (57.5)	NR	NR	563 (35.9)
Refaey et al. 2016 [137]	Egypt	NR	ILI and SARI	RT-PCR	A + B	H1N1, H3N2	RSV	3	2367 (13.0)/ 1851 (16.7)	1211 (51.2)/ 1221 (66.0)	16.1/ 35.5	35.0/ 30.4	1156 (48.8)/ 630 (34.0)
Rowlinson et al. 2017 [31]	Egypt	19	ARTI	rRT-PCR	A + B	No	AdV, hMPV, hPIV (1, 2, 3), and RSV	3	1602 (27.8)	487 (30.4)	NR	NR	316 (19.7)
Elhakim et al. 2019 [138]	Egypt	4.9	SARI	NR	A + B	No	RSV	2	192 (15.3)	128 (10.2)	NR	NR	66 (25.0)
Barakat et al. 2011 [139]	Morocco	NR	ILI and SARI	Culture and rRT-PCR	A + B	H1N1, H3N2	AdV, hPIV and RSV	2	98 (3.0)	74 (75.5)	44.9	30.6	24 (24.5)
Anga et al. 2012 [140]	Morocco	NR	ILI	NR	A + B	H1N1, H3N2	RSV	0.5	84 (30.8)	49 (17.9)	10.6	7.3	32 (11.7)
El Rhaffouli et al. 2013 [26]	Morocco	21	NR	HIT	A	H1N1	No	0	307 (61.4)	307 (61.4)	NR	NR	NR
Elfalki et al. 2016 [141]	Morocco	NR	ILI and SARI	RT-PCR	A + B	H1N1, H3N2	No	1	201 (45.7)	63 (31.3)	18.9	12.4	135 (67.2)
Tarek et al. 2018 [20]	Morocco	NR	SARI	RT-PCR	A + B	No	No	2	140 (100.0)	12 (8.6)	NR	NR	3 (2.1)

Table 3 continued

Author and publication date	Country	Proportion of at-risk population (%)	Simplified case definition	Laboratory method	Strain	Subtyping	Other viruses	Number of influenza seasons	Confirmed influenza N, (%)	A strain cases N, (%[a])	% H1N1	% H3N2	B strain cases N, (%[a])
El Moussi et al. 2013 [142]	Tunisia	NR	ILI	rRT-PCR	A + B	H1N1, H3N2, B/Y, B/V	AdV, hPIV and RSV	3	4126 (47.6)	4075 (98.8)	97.2	1.6	52 (1.3)
Chlif et al. 2016 [29]	Tunisia	NR	ILI	NR	A + B	H1N1, H3N2	No	3	698 (28.2)	487 (69.8)	30.3	39.5	198 (28)
Bouneb et al. 2018 [34]	Tunisia	33.3	Laboratory-confirmed influenza	RT-PCR	A	H1N1	No	6.5	40 (100.0)	40 (100.0)	100.0	NR	NR
Meddeb et al. 2018 [143]	Tunisia	NR	SARI	PCR	A	H1N1	No	2	5 (20.0)	5 (100.0)	100.0	NR	NR
Tinsa et al. 2018 [36]	Tunisia	NR	NR	PCR	A	H1N1	No	0.5	32 (100.0)	32 (100.0)	100.0	NR	NA

AdV adenovirus, *AFRO* African region, *ARTI* acute respiratory tract infection, *BoV* bocavirus, *B/V* influenza B Victoria, *B/Y* influenza B Yamagata, *CMV* cytomegalovirus, *CoV* coronavirus, *EV* enterovirus, *HAI* hemagglutination inhibition test, *hBoV* human bocavirus, *hCoV* human coronavirus, *hEV* human enterovirus, *HIT* hemagglutinin inhibition test, *hMPV* human metapneumovirus, *hPIV* human parainfluenza virus, *hRV* human rhinovirus, *ILI* influenza-like illnesses, *LRTI* lower respiratory tract infection, *MERS-CoV* Middle East respiratory syndrome-related coronavirus, *MPV* metapneumovirus, *NA* not available, *NR* not reported, *PCR* polymerase chain reaction, *RSV* respiratory syncytial virus, *RV* rhinovirus, *SARI* severe acute respiratory infection, *RT-PCR* reverse transcription polymerase chain reaction, *rRT-PCR* real-time reverse transcription polymerase chain reaction, *ULRTI* unclassified lower respiratory tract infection, *URTI* upper respiratory tract infection

[a] Percentage among positive cases

	Number of articles retrieved	Population studied			Vaccination coverage rate (VCR)	Epidemiology of influenza					Burden of influenza			
		General population	Aged <18 years	Adult only	VCR	Subtyping A (H1N1 and/or H3N2)	Subtyping B (Yamagata and/or Victoria)	Subtyping (H1N1, H3N2, Yamagata or Victoria)	Incidence	Prevalence	Hospitalization due to influenza	Length of stay	Mortality	DALY/QALY
Afghanistan	1	1	0	0	0	1	0	1	0	0	0	0	0	0
AFRO*	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Algeria	2	1	0	0	1	0	0	0	0	0	0	0	0	0
Bahrein	1	0	0	1	1	1	0	1	0	0	1	0	1	0
Egypt	6	5	1	0	0	1	0	1	2	0	3	2	3	0
EMRO	1	1	0	0	0	1	0	1	0	0	0	0	0	0
Iran	23	16	4	2	2	16	0	16	0	0	4	2	6	0
Jordan	3	1	1	1	0	1	0	1	0	0	0	0	1	0
Lebanon	6	4	1	0	3	1	0	1	0	0	2	0	1	0
MENA	2	2	0	0	0	0	0	0	0	0	1	0	0	0
Morocco	5	2	2	0	2	4	2	4	0	1	1	0	0	0
Oman	5	2	2	0	1	3	0	3	2	0	2	1	3	0
Pakistan	3	1	2	0	0	2	0	2	0	0	0	0	0	0
Palestine	1	NR	NR	NR	0	1	0	1	0	0	0	0	0	0
Qatar	1	0	0	1	0	0	0	0	0	0	0	0	0	0
Saudi Arabia	16	4	4	3	1	8	2	9	0	1	2	1	4	0
Tunisia	5	2	1	2	2	5	1	5	1	0	1	1	1	0
Turkey	25	18	4	3	4	12	3	12	0	1	2	0	4	0
United Arab Emirates	2	0	1	1	1	0	0	0	0	1	0	0	0	0
Yemen	3	3	0	0	0	0	1	1	0	0	1	0	2	0
Total	112													

Number of studies   0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

*African countries: only data from Egypt and Morocco were extracted

Fig. 3 Heat map showing number of articles retrieved and availability of data for each country in the EMNA region. *Only data from Egypt and Morocco were extracted

eporting both influenza A and B co-circulation, strain A was the predominantly identified circulating strain. Influenza A and B accounted for a median 67.6% (IQR 42%–86%) and 27.0% (IQR 11%–36%) of positive cases, respectively. Classification of influenza strain A (H1N1, H3N2) and/or lineage B (Yamagata, Victoria) was performed in half of the studies (*n* = 58, 51.2%). Of these, 47 studies were conducted in the Eastern Mediterranean region, most commonly in Iran (*n* = 17), Turkey (*n* = 12) and Saudi Arabia (*n* = 8). Ten were conducted in North Africa:,most commonly in Tunisia (*n* = 5) and Morocco (*n* = 4) and one study was conducted in both regions. Subtyping of the A strains, H1N1 and H3N2, was undertaken in 57 studies, 21 studies reported data for the H1N1 subtype only and three studies for the H3N2 subtype alone. Only five studies reported data on influenza B lineages and all but one were conducted in the general population. Other viruses were assessed in 46 studies including respiratory syncytial. Other viruses were assessed in 48 studies including respiratory syncytial viruses (*n* = 34), adenoviruses (*n* = 25) and parainfluenza viruses (*n* = 20).

The number of articles reporting on available data for each country are shown in Fig. 3.

Epidemiology

The number of influenza seasons per study ranged from 0 [22–26] through to 13 [27]. Of those studies reporting zero seasons, four were conducted over the course of 1 month [22–25] and one over 2 months [26].

The median percentage of positive influenza cases reported across the studies was 23.3% (IQR 1.4–85.5%). The incidence of influenza was only reported in four studies, all assessing surveillance data in the general population: one study in Oman which evaluated data on inpatients (incidence range [95% CI] from 0.5 [0.1–2.2] to 15.4 [1.1–21.3] per 100,000 population) [28], one study in Tunisia looking at data in outpatients (incidence range across three seasons ranged from 5536 [5457–5615] in 2013/14, 12,602 [12,484–12,722] in 2014/15 and 18,735 [18,590–18,881] in 2012/13) per 100,000 population [29] and two studies in Egypt both evaluating data from inpatients (incidence range 96.9/100,000 person-years [30] and 265.2/100,000 population [31]).

Vaccination against influenza was reported in 23 studies, ranging from 0% [32–36] to 66% [24] (median 7%; IQR 2–18%). However, it should be noted that for four studies reporting 0% vaccination , one was conducted in

pregnant women [37], one in children during the 2009 pandemic [36] and one in severely ill patients who were admitted to intensive care [34]. In the general population, the calculated vaccine coverage rate among included suspected cases ranged from 0% [32] to 66% (median 7% [IQR 1–20%]) [24].

Data on the duration of hospitalisation due to influenza were reported in 11 studies (9.8%). Eight of these were conducted in the Eastern Mediterranean region and three in North Africa. Of these, two studies reported data in patients aged less than 15 years, three studies in adults and six studies in the general population. The mean length of stay in hospital ranged between 4 and 23 days (median stay 6 days; IQR 4.4–6.7) in standard and intensive care units.

Information on patients with comorbidities, chronic disorders or considered at high risk of complications as a result of influenza was only reported in 25 studies (22.3%). Similarly, mortality data as a result of influenza were reported in less than a quarter of the studies ($n = 26$; 23.2%) and most commonly in the Eastern Mediterranean region, with the highest number of studies reported in Iran ($n = 6$) and Turkey ($n = 4$).

Not all studies looked at specific age populations, some stratified by age group, whereas others looked at the general population ($n = 69$). Eight studies evaluated patients aged less than 5 years age (all laboratory-confirmed cases), eight evaluated patients aged less than 15 years (all but one were laboratory-confirmed cases), four evaluated patients aged less than 18 years (all laboratory-confirmed cases), 18 studies specified the population as adults (all but four were laboratory-confirmed cases) and five did not report the age groups evaluated (all but one were laboratory-confirmed cases).

No studies reported data on disability-adjusted life year (DALY) or quality-adjusted life year (QALY) measures.

CONCLUSION

We present here a comprehensive, systematic review of the published literature looking at the epidemiology of influenza in the EMNA region over the last 21 years (from 1998 through to 2020). We analysed data from 112 studies, 90 of which were conducted in the Eastern Mediterranean region, 19 in Africa and three across both regions.

Overall, data were reported on 314,058 laboratory-confirmed influenza cases, the majority (86%) of which were derived from surveillance systems. Over half the studies (62%) evaluated data from the general public (paediatric and adult populations combined, across a range of ages or where all age groups were included). Influenza A accounted for a median 67.9% (IQR 41%–89%) of all influenza cases in our study, slightly lower than that reported by Caini et al., who assessed influenza surveillance data from the 2010–2016 from the WHO FluNet database and reported a median of 76.5% (IQR 60.4–90.3%). Influenza B accounted for a similar proportion of positive cases in our study (23.8% [IQR 11–36%]) as that reported in Caini et al. [4] (23.5% [IQR 9.7%–39.6%]) of all influenza cases. In line with Caini et al. [4], we also observed the H1N1 to be the most prominent circulating subtype. Typing was performed in approximately three-quarters and subtyping in only half of the studies we identified, with influenza B strain lineage characterisation only being performed in less than 5% of the studies we assessed, highlighting a gap for these data in the region. Identifying the virus strain and subtype circulating is important, in order to identify any possible vaccine mismatch, for implementing measures to inform public health interventions to ensure optimal protection of populations.

The number of influenza seasons per study ranged from zero through to 13. Influenza incidence data were not widely reported, only being cited in five studies.

The results of our review also revealed existing gaps in regional estimates of influenza health and economic burden, hospitalisation rates and duration of hospital stay. The absence of influenza disease burden estimates has previously been cited as a reason for a lack of country-level influenza vaccine policies [38].

Given the high prevalence of patients with chronic disease in the EMNA region [2, 3], it is important to collect data on those considered

most at risk from complications of influenza. These data were reported in only 21% of the studies we identified. No studies reported measures of quality of life and overall disease burden (i.e. DALY and QALY). Furthermore, data on mortality were reported in less than 24% of the studies identified. Morbidity and mortality data are important to provide a complete overview of the health burden of disease, which, in turn, is critical to understanding the impact of influenza infections on public health [39]. A lack of knowledge on influenza and its impact with respect to morbidity and mortality has been cited as a major barrier to attaining higher vaccination coverage in the region [40]. Collecting these data in future epidemiological studies may be helpful in informing future public health policies and interventions and help to increase uptake of vaccines.

Strengths and Limitations

Strengths of our review include the large number of studies included which provide an epidemiological overview of influenza research over the last 21 years across the EMNA region. Furthermore, we systematically searched multiple databases, beyond those reported in the WHO's FluNet, to look for epidemiological data.

Our study also relies on peer-reviewed and published data which provides more reliability and confidence on the data and findings, in comparison to other databases such as FluNet. However, it is possible that we may have not captured some data with the search strategy we implemented. Such databases tend to focus on virological surveillance data in the Eastern Mediterranean and African region WHO regions (though some countries also report the burden of disease data), and the aim of this review was to provide an overview of the epidemiology and burden of influenza disease. In addition, differences in clinical assessment, application of case definitions and laboratory assessment of influenza testing (including sampling methods) make data comparisons across countries difficult to perform. Furthermore, FluNet is limited by the quality of the data submitted (as a consequence of adherence to and robustness of the

methods used by the reporting country or centre), underreporting and misclassification are not uncommon, and the large variability in reporting between years by some countries may mean influenza estimates are based on limited data. Mixed-season influenza activity may mean data are oversimplified in large and geographically diverse countries where influenza activity is summarised countrywide [41].

In recent years, the epidemiology of influenza and disease burden has been assessed in single countries in the EMNA region [13–15]; however, studies across the whole region are lacking. A previous literature review, looking at how influenza had changed in the region from 2012 through to 2016, identified a limited number of publications on epidemiology of the disease, concluding that, although virus surveillance had increased, data were still needed, particularly on burden of disease [42]. More recently, Moghoofei et al. [43] conducted a systematic literature review assessing influenza A prevalence across 17 countries within the region. In common with our results, the majority of studies assessed virus in the general population, rather than a specific age group, and the most frequently used method to detect virus was PCR-based, with the most commonly identified subtype being the H1N1 strain. The pooled estimation of the influenza prevalence was reported to be 10.2%, albeit with much variation across the populations studied. We did not undertake a meta-analysis to estimate prevalence rate in our study owing to the large heterogeneity in methodology across studies. Unlike Moghoofei et al., we did not restrict our searches to influenza A and thus our review provides a broader picture of the influenza landscape across the EMNA region, including reporting for the influenza B strain. A summary of the epidemiological and characterisation of H1N1 and H3N2 strains of the influenza virus circulating in the EMNA region from 2009 to 2017 was also recently published by Al Khatib et al. [16]. Using virological surveillance data available from the FluNet database, the authors assessed data from 16 countries within the region; Saudi Arabia, Yemen and Libya were not included as data were not available. In line with that reported by Moghoofei et al. [43] and our

own results, Al Khatib et al. also reported that the influenza strain A H1N1 was, in general, the dominant subtype reported across the region. The study also estimated the epidemiology of influenza type B in the region, which accounted for 20.5% of influenza cases, higher than the 17.2% reported in our study. This difference may have been a result of Al Khatib et al., assessing data from FluNet, whereas our study looked at data from published studies only.

In line with the results reported in our study for the EMNA region, analysis of data at both the global and regional levels shows a predominance of influenza A compared to influenza B [44–46]. For instance, reports from the Global Influenza Hospital Surveillance Network show a predominance of influenza A with a prevalence greater than 60% and influenza B accounting for 21–34% between 2014 and 2017 [46, 47]. A systematic review by Tokars et al. [45] estimated the incidence of influenza A and B from surveillance data of the general population in the USA and Canada between 2010 and 2017 to be 7.1% (95% CI 6.1–8.1), which is in broad agreement with the incidence data presented in this review.

A large epidemiological study conducted in 31 countries looking at epidemiological characteristics, pattern of circulation and geographical distribution of influenza B viruses using data from the Global Influenza B Study showed that they accounted for a median of 23.4% of total influenza cases between 2000 and 2018 [44], higher than that reported in our study. Again, this may be a result of our study looking at published data only, whereas the data from the Global Influenza B Study were database-derived. A systematic review looking at a global analysis of the epidemiology of influenza B virus found the frequency ranged from 0 to 40.6% across six studies from the USA and from 1.6% to 24.4% across four studies in Europe [48]. Variability in the way the data were collected makes it difficult to compare with the influenza B data reported in our review. A more in-depth comparison of the epidemiological patterns of influenza between the EMNA region and other geographical areas would be an interesting focus that will help tailor prevention and vaccination strategies.

Current Landscape

The EMNA region is geographically contiguous, making it an important region for influenza circulation surveillance. The availability of influenza data in the region has improved since the 2009 pandemic. The WHO has implemented a number of strategies across the EMNA region, including strengthening surveillance (with 15 countries reporting on ILI/SARI, or both) and improving knowledge of the burden of influenza [44]. Although the majority of countries in the region now have some form of influenza surveillance in place [45], they still face multiple challenges in introducing or expanding influenza surveillance, prevention and control programmes [46]. Encouragingly, laboratory detection, influenza disease burden estimation and use of seasonal influenza vaccines for influenza control are also increasing [45], although the approach to clinical and laboratory assessment and case definitions is not yet standardised.

A recent review, looking at seasonal influenza vaccination in 11 countries within the region, highlighted substantial research gaps and major disparities across countries [47]. Despite recommendations on influenza vaccination, attaining high vaccine coverage rates continues to be a challenge in the WHO Eastern Mediterranean region [40, 48].

The increase in the number of publications and research around influenza since the 2009 pandemic is encouraging and suggests an increase in awareness around influenza and the importance of reducing its burden. However, much work remains to be done. The heterogeneity in assessment and data collection across the region makes surveillance comparisons difficult. Implementation of regional standardisation would allow direct data comparisons and help in understanding the impact of influenza in the region. In addition to studying existing influenza virus strains, it is extremely important to be alert to any new emerging subtypes as well possible changes in virulence or transmission of new infections to the region; for instance, Egypt and Oman are the first countries outside of eastern and southern Asia to report human infection of H9N2 [49].

Finally, for the purposes of this review, we evaluated the literature up to and including January 2020 and did not evaluate the literature beyond this date in order to avoid potential implications on epidemiology as a consequence of the COVID-19 pandemic.

Current influenza surveillance data will be confounded, to varying extents, by the COVID-19 pandemic and the public health measures implemented by most countries to suppress COVID-19 transmission, including social distancing, hand hygiene and wearing of face masks, all of which may impact the circulation or transmission of influenza. The WHO reports that, in some countries, influenza activity is at lower than expected levels [50]. However, influenza data during the COVID-19 pandemic should be treated with caution and any subsequent analyses should account for resultant confounding.

Despite the improvement of influenza surveillance following the 2009 pandemic, many opportunities remain unexplored in the EMNA region. Data gaps are still substantial, including subtyping and vaccine coverage rates. Notable work is underway to fill these gaps, such as the initiatives being undertaken by the EMARIS network [11], but strengthening regional research is still needed for a better understanding of influenza epidemiology and to improve epidemic and pandemic response. Disease burden estimates, or studies evaluating the impact of vaccine data on reducing the risk or burden of influenza, play a crucial role in helping to address the threat of seasonal influenza and ensure adequate vaccination coverage. Our results highlight the need for robust and high-quality epidemiology data to inform policy and refine public health interventions. Although global and international efforts to collect virological data on influenza circulation are undertaken by the WHO and other health organisations, data reporting varies hugely across counties and sites.

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