Review

Burden of acute respiratory disease of epidemic and pandemic potential in the WHO Eastern Mediterranean Region: A literature review

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عبء الأمراض التنفسية الحادة القادرة على إحداث أوبئة محلية وعالمية في إقليم شرق المتوسط: مراجعة أدبيات

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الخلاصة: توضح هذه المراجعة عبء الأمراض التنفسية الحادة القابلة لإحداث أوبئة محلية وعالمية في إقليم شرق المتوسط لمنظمة الصحة العالمية، وتهدف إلى المساعدة في تطوير سياسات وبرامج تستند إلى الأدلة للوقاية من هذه الأمراض ومكافحتها. تعرفنا على تقارير منشورة وغير منشورة ذات صلة بالموضوع من عمليات بحث في قواعد بيانات Medline و CAB و EMBASE. ولقد حقق معاييرَ البحث ما مجموعه 83 وثيقة. وحدِّدت أربع مجموعات رئيسية من الأمراض قادرة على إحداث أوبئة: الأمراض التنفسية الحادة، وإنفلونزا الطيور A(H5N1)، وإنفلونزا A(H1N1)pdm09، والمتلازمة التنفسية الشرق أوسطية لفيروس كورونا. الالتهاب الرئوي والأمراض التنفسية الحادة هي الأسباب الرئيسية للمرض والوفاة في الإقليم. خلال وباء عام 2009 كانت الإنفلونزا A(H1N1) أحد أهم أسباب المراضة. على الرغم من أن هذه المراجعة تقدم ملخصاً وصفياً لمعدلات المراضة والوفيات فإن الثغرات الموجودة في المعلومات المتعلقة بعبء المرض في الإقليم يجب أن تعالج من خلال تعزيز الترصد الروتيني.

ABSTRACT There are gaps in the knowledge about the burden of severe respiratory disease in the Eastern Mediterranean Region (EMR). This literature review was therefore conducted to describe the burden of epidemic- and pandemic-prone acute respiratory infections (ARI) in the Region which may help in the development of evidence-based disease prevention and control policies. Relevant published and unpublished reports were identified from searches of various databases; 83 documents fulfilled the search criteria. The infections identified included: ARI, avian influenza A(H5N1), influenza A(H1N1)pdm09 and Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Pneumonia and ARIs were leading causes of disease and death in the Region. Influenza A(H1N1) was an important cause of morbidity during the 2009 pandemic. This review provides a descriptive summary of the burden of acute respiratory diseases in the Region, but there still remains a lack of necessary data.

Charge des infections respiratoires aiguës à potentiel épidémique et pandémique dans la Région OMS de la Méditerranée orientale : analyse documentaire

RÉSUMÉ On observe des lacunes en matière de connaissances concernant la charge des maladies respiratoires sévères dans la Région de la Méditerranée orientale. La présente analyse documentaire détaille la charge des infections respiratoires aiguës (IRA) à potentiel épidémique et pandémique dans la Région, ce qui peut aider à l'élaboration de politiques et programmes de prévention et de lutte contre les maladies reposant sur des données factuelles. Des articles pertinents publiés et non publiés ont été identifiés grâce à des recherches dans différentes bases de données ; 83 documents satisfaisaient à nos critères de recherche. Les infections identifiées comprenaient les infections respiratoires aiguës (IRA), la grippe aviaire A(H5N1), la grippe A(H1N1)pdm09 et l'infection par le coronavirus du syndrome respiratoire du Moyen-Orient (MERS-CoV). La pneumonie et les IRA constituaient les principales causes de morbidité et de mortalité dans la Région. La grippe A(H1N1) était une cause importante de morbidité durant la pandémie de 2009. Cette analyse fournit un résumé descriptif de la charge des maladies respiratoires aiguës dans la Région mais il existe toujours une lacune concernant les donneés nécessaires à cet égard.

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Introduction

Acute respiratory infection (ARI) is consistently ranked among the top causes of morbidity and mortality worldwide. It has been referred to as a "forgotten pandemic", which kills more than 4 million people each year globally (*1*).

Acute respiratory illnesses can range from asymptomatic and mild infections, such as those often caused by rhinoviruses, to high case fatality diseases due to infections such as avian influenza and Middle East respiratory syndrome coronavirus (MERS-CoV). The burden of pneumonia as the primary cause of mortality among children under 5 years of age is well established (*2*). Worldwide, ARIs are the third most common cause of mortality in all ages, particularly in lower income settings (*1*).

Common bacterial and viral pathogens causing severe respiratory disease, such as pneumococcal disease and seasonal influenza, for which interventions exist, continue to be a threat. Emerging zoonoses causing respiratory disease, such as avian influenza and more recently MERS-CoV, in an immunologically naïve population are a concern for global health security. There are very real epidemiological and economic consequences in the event of uncontrolled transmission of these novel pathogens (*3*).

Recognizing gaps in the knowledge regarding the burden of severe respiratory disease in the Middle East, the World Health Organization (WHO) Regional Office for the Eastern Mediterranean Region is taking steps to improve surveillance for respiratory illness (*3*) in order to support evidence-based decision-making in policy development.

Therefore, to provide a baseline description of the burden of severe respiratory disease with epidemic and pandemic potential in the Eastern Mediterranean Region (EMR), we conducted a literature review of the published and unpublished literature.

Methods

The Cochrane Library database of systematic reviews was searched from 2000 to June 2015, initially to ensure that a similar literature review of the burden of acute respiratory diseases in the EMR was not already in existence. No such reviews were found.

For this review we included published and unpublished reports of the epidemiological burden of respiratory disease of epidemic and pandemic potential. The search included literature published or produced between 1995 and May 2015; 1995 was chosen as the lower limit based on an initial screening and assessment of the quality of studies prior to this date. In addition, limiting the results to the past 20 years provides a relevant time frame, given the emerging nature of some of the respiratory illnesses of importance.

The literature search was conducted from April to June 2015. We searched Medline, CAB and Embase databases using the OVID SP interface. The Index Medicus of the Eastern Mediterranean was searched using simple keyword searches. In addition, the websites of ministries of health and related ministries of all countries in the EMR were searched to find all potential reports on the burden of the diseases of interest. Websites of WHO and the Centers for Disease Control (CDC) in the United States of America (USA) were hand searched for relevant documents, and the Google search engine was used to search for unpublished documents for each country in the EMR. A range of search terms were used for severe acute respiratory illness (SARI) caused by common bacterial and viral pathogens, novel pathogens or those with the capacity to cause epidemics or pandemics that threaten international health security, together with EMR geographical terms.

This review concerns all ARIs with the potential to cause an excess burden of disease, whether caused by common pathogens or novel ones, and which may constitute public health emergencies of local and international concern, as defined by the International Health Regulations 2005 (*4*). These include:

- SARS;
- human influenza caused by a new subtype (i.e. avian influenza viruses including H5N1, H7N9, H7N2 and H9N2, swine flu/pandemic influenza H1N1);
- pneumonic plague;
- novel ARIs that can cause large-scale outbreaks or outbreaks with high morbidity and mortality (human cases of influenza A(H7N9) and MERS CoV) (*5*).

The 22 countries listed on the website of the WHO Region for the Eastern Mediterranean were used in this literature search (*6*).

The definition of disease burden used for this literature review is limited to the epidemiological indicators of morbidity and mortality attributed to the ARIs of concern. These indicators include: number of cases, incidence, prevalence, proportionate morbidity (i.e. the number of specific ARI cases either as a percentage of the total number of ARI cases or of all disease cases reported), proportionate mortality rates, case fatality rates (CFRs) and rates of hospitalization.

References were reviewed and relevant data were abstracted onto a standard proforma spreadsheet. Data abstracted were used to summarize the reported burden of ARIs in the EMR.

Incidence rates were normalized to 10 000-person years to allow comparisons where possible. Data obtained from weekly epidemiological bulletins, specifically from the Syrian Arab Republic for 2015 (*7*), were entered into a

separate data abstraction spreadsheet to obtain cumulative numbers of cases and proportional morbidities.

Results

Peer reviewed electronic database search resulted in the identification of 1789 articles. A further 2390 were retrieved from websites including WHO, CDC, Google, ministries of health and references of other articles. Of these, 3812 were duplicates or were excluded based on title and abstract screening. Full text was screened in 367 documents . Two-hundred and eighty-four documents were screened out due to lack of applicable data, an inability to obtain full text, or meeting at least one exclusion criteria. Eighty-three articles were retained that contained at least one indicator of burden. Figure 1 shows a flow diagram of the number of papers/documents identified and excluded at each step.

Overall, there is a general underrepresentation of reporting on the burden of disease in most countries of the EMR, with no specific trend seen related to country income classification (*8*) (Figure 2).

Human influenza A(H5N1)

Twenty-one papers were identified. Globally, and among the EMR countries with human influenza A(H5N1), Egypt has the highest total number of cases (*9*). As of 30 April 2015 the total number of cases in Egypt was 342, or 41% of the total number of cases recorded globally (*10*). The high number of cases is attributed to poultry outbreaks and contact with infected poultry, but there is no evidence so far of a change in human-human transmission (*9*).

The percentage of confirmed H5N1 cases in Egypt was highest in the 30–45 years age group; however, only two papers report this information (*11,12*). The only other report to cite a median age group was a report of Egypt's first 85 cases, for which the median age was 6 years (*13*).

Deaths attributed to influenza A(H5N1) in the EMR are mostly within Egypt (114 of the global 447 deaths to date) (*9*). Case fatality for influenza A(H5N1) has remained fairly stable over the last 10 years, with reports from 2006–2009 to 2015 all quoting 29% to 33% for country-specific rates (*9,10,11*). Iraq has the highest reported CFR at 67% (2 deaths out of 3 confirmed cases) (*11*).

Data on the age distribution of H5N1 deaths are only available from Egypt, where a median age of 25 years was reported (*13*), with the age-specific CFR reported to be highest among those aged 45 years and older at 47% (*10*). The only confirmed fatality reported in Pakistan was a 27-year-old family contact of the index case (*14*).

Human influenza A(H1N1)

Pandemic influenza A(H1N1), also known as swine flu, is currently in the post-pandemic phase and is behaving like seasonal influenza (*15*). All 26 articles in the Region reporting some measurement of morbidity and/or mortality are from the 2009/10 A(H1N1)pdm09 pandemic. Papers were identified from 8 countries and describe the morbidity and mortality in pandemic cases confirmed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR). More studies were from the Islamic Republic of Iran and Saudi Arabia than other countries of the Region.

Most of the papers reviewed were hospital- or health care-based studies documenting the proportion of suspected influenza cases that tested positive for A(H1N1)pdm09. One study, a suspected community outbreak of A(H1N1)pdm09 in a training institute in the Eastern Province in Saudi Arabia, resulted in community case finding and isolation of suspected cases in an attempt to control the epidemic (*16*). National surveillance data were reported and analysed in other studies (*17–22*).

A study in Morocco in 2009 used patients presenting with SARI and influenza-like illness (ILI) to hospitals and health centres as the study population. They were able to determine the percentage of cases that were positive for influenza in general (37%) and for pandemic influenza A(H1N1)pdm09 specifically (96% of influenza-positive cases), showing that A(H1N1)pdm09 was the dominant influenza strain (*19*).

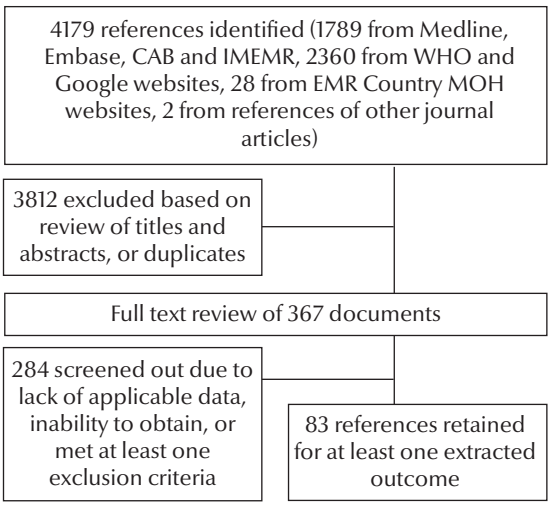

Figure 1 Summary of references identified and studies abstracted

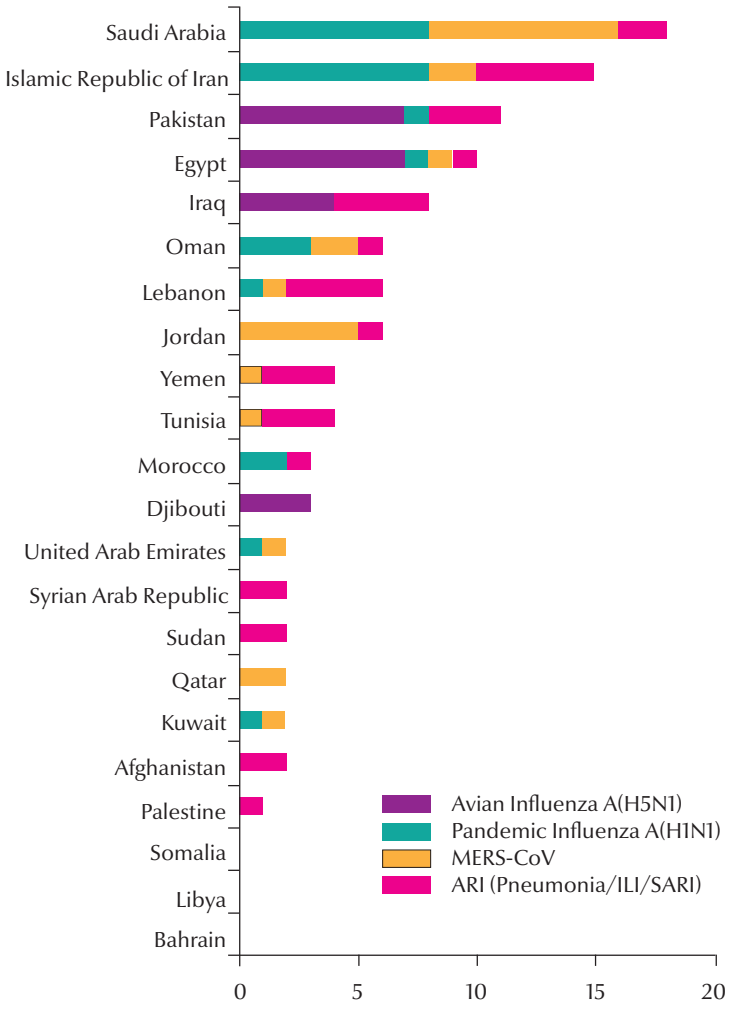

Figure 2 Countries in which burden information was extracted for this review, by disease and country

Disease due to A(H1N1)pdm09 appeared to affect mainly adults with mean and median ages in the 20–30-year age group; the highest proportionate morbidity was in the age group 20–50 years. A risk factor assessment from Hamedan Province, Islamic Republic of Iran found that pregnant women and those aged 20–39 years were at increased risk of A(H1N1)pdm09 infection (*23*). The absence of severe disease in children was likely a result of them being missed by surveillance systems detecting A(H1N1)pdm09. In papers that reported the sex distribution of confirmed A(H1N1)pdm09 cases, no significant gender differences were found.

The CFR for A(H1N1)pdm09 was 0% in Saudi Arabia in all studies reporting mortality (*16,18,24,25*). A CFR of 16.7% was observed in Rawalpindi, Pakistan among patients presenting to the pulmonary and critical care department (*26*). In Morocco, CFR was 19% in A(H1N1)pdm09 cases admitted to hospital with SARI (*19*).

Middle East respiratory syndrome (MERS-CoV) infection

Twenty-five papers were identified. Generally, the proportionate morbidity of MERS-CoV decreased in all countries affected from 2012 to 2015, except in Saudi Arabia and the United Arab Emirates where the contribution to the global case load continues to increase. These two countries are ranked 1st and 2nd respectively in numbers of cases among affected countries (*27*).

All documents describing the burden of MERS-CoV in countries of the EMR detail experiences in hospital inpatient settings, despite some acquisition in the community. Nosocomial transmission of MERS-CoV was first seen in an outbreak in Zarqa, Jordan in 2012 (*28*), which affected a high proportion of health care workers (*28,29*).

During an outbreak in Al-Ahssa, Saudi Arabia, in April and May 2013, 68% of cases were laboratory confirmed and 94% of those were acquired in hospitals (*30*). Another outbreak reported in Saudi Arabia, in Eastern Province in 2013, resulted in 17% of suspected cases confirmed for MERS-CoV (*31*). A study of inpatient data from hospitals that did not experience active outbreaks throughout Saudi Arabia found that only 2.1% of critically ill patients admitted with lower respiratory infection and fever tested positive for MERS-CoV infection (*32*).

No cases were detected in children under 2 years of age in Jordan (*33*). In Saudi Arabia, 8% of critically ill patients admitted for fever and lower respiratory tract infection were children under 17 years of age (*32*). The age of MERS-CoV patients ranged between a median of 33 years in Zarqa, Jordan (*28*) and 62 years in Riyadh, Saudi Arabia (*34*). A retrospective study of all patients diagnosed with laboratory-confirmed MERS-CoV infection in Saudi Arabia, both health-care-associated and community-acquired, reported age-specific morbidity and mortality rates at one centre over 20 months (*34*). In this study, 47.1% of lab confirmed MERS-CoV patients were aged ≥ 65 years. Mortality was high (60%) and age ≥ 65 years was the only independent risk factor for mortality (odds ratio 4.39; 95% confidence interval 2.13–9.05) (*34*).

Between 2012 and 2015, a CFR of 38% for MERS-CoV was reported to WHO from the EMR (*27*). For MERS-CoV in inpatient settings, the CFR initially reported after the Zarqa Jordan hospital outbreak in 2012 was 100% because both confirmed cases died; however, this was reduced to 15% when the total number of confirmed and probable cases was used as the denominator (*28*). The seroepidemiologically-confirmed CFR for the same outbreak was 22% for all cases and 16.7% in health care workers (*29*). In Saudi Arabia, a CFR of 76% was reported in cases of MERS-CoV confirmed by nasopharyngeal swabs or tracheal aspirates (*31*).

Acute respiratory infections

Respiratory infections caused by common bacterial and viral pathogens are included in the definition of epidemic- and pandemic-prone diseases. Thirty-five papers reporting ARI (including pneumonia, influenza-like illness and severe acute respiratory infection) were eligible for this review (Tables 1–3). While some studies reported sex distribution for ARI cases, no specific pattern or trend was apparent.

Incidence or prevalence of ARI (Table 1)

Point prevalence of community-acquired pneumonia in inpatients in Saudi Arabia was 30.3%, with the

Table 1 Incidence and prevalence of acute respiratory infection (ARI), by setting and type of infection

Disease	Population at risk (year) *(reference)*	Study design	Case definition as reported	Prevalence (%) or incidence per 10 000 person-years (age, if available)	Rank (relative importance)
Inpatient					
Pneumonia	Riyadh, Saudi Arabia All patients at King Fahad National Guard Hospital (2013) (*35*)	Point prevalence survey	Community acquired pneumonia	Overall 30.3%; (43.4% 50+ y, 17.1% 40–49 y, 3.9% 30–39 y, 6.6% 20–29 y, 6.6% 10–19 y, 14.5% 1–9 y, 7.9% < 1 y)	2nd of 5
Inpatient & Outpatient					
RSV infection	Damanhour, Egypt Population-based surveillance of ARI in 3 hospital and 3 outpatient settings (2009–2012) (*41*)	Descriptive cross-sectional	RSV associated hospitalization	2.4[a] (174.5[a] in children < 1 y)	
			RSV associated outpatient visits	60.8[b]	
Outpatient					
ALRI	Bam, Islamic Republic of Iran Post-earthquake assessment of disease (2004) (*36*)	Descriptive cross-sectional	Lower respiratory tract infection	312[c]	3rd
Surveillance					
ARI	Karachi, Pakistan Community surveillance in 4 peri-urban communities in Pakistan (2002/03) (*37*)	Cross sectional survey	Acute respiratory infection	4403[d]	
ALRI			Pneumonia and severe pneumonia	821[e]	
ARI	Sudan EWARS communicable disease weekly bulletin (2013/14) (38,39)		ARI	Range low to high: 239 to 848[f]	1st
	West Darfur (*38,39,69–72*) North Darfur (*38,39,69–72*) Population of Oman (2013) (*40*)		ARI ARI ARI in < 5 year olds	759 to 1149[g] 1206 to 1721[h] 11200[i]	1st 1st
Influenza	Syrian Arab republic All governates. (2013) (*73*)		Report	Cases influenza reported by health facilities	30482 cases/month
	Yemen, national data (2013) (74)		Annual statistical health report	Cases of influenza	40602 cases/year

ALRI = acute lower respiratory infection; EWARS = early warning and response system; RSV = respiratory syncytial virus; y = years.
[a]Reported as 24 per 100 000 person-years and 1745 per 100 000 person-years. [b]Reported as 608 per 100 000 person-years. [c]Reported as 26 per 10 000 person-months. [d]Reported as 440.3 per 1000 per year. [e]Reported as 82.1 per 1000 per year. [f]Reported as 4.6 to 16.3 per 10 000 per week. [g]Reported as 14.6 to 22.1 per 10 000 per week. [h]Reported as 23.2 to 33.1 per 10 000 per week. [i]Reported as 1120 episodes per 1000 per year.

Table 2 Proportionate morbidity of ARIs relative to all other diseases, by setting and type of ARI

Disease	Population at risk (year) (*reference*)	Study design	Case definition as reported	Proportionate morbidity (age, if available)	Rank
Inpatient					
ARI	Rasht, Islamic Republic of Iran Children (1 m–14 y) hospitalized with an infectious disease (2014) (*42*)	Descriptive cross sectional study	ARI in children hospitalized for infectious disorders	40.1% (1 m–14 y)	1st
	Kabul, Afghanistan Patients attending paediatric emergency service (2002/03) (*43*)	Retrospective cohort	ARI, bronchial asthma, pleural effusion, lung abscess	20% (paediatric)	2nd
	Oman, national population annual health statistics report (2013) (*40*)	Annual statistical report	ARI	13%	
Pneumonia	Zahedan, Islamic Republic of Iran Patients > 65y admitted to hospital (*75*)	Cross sectional study: retrospective medical record review	Pneumonia	14.9% (> 65 y)	2nd
	Tunis, Tunisia All children admitted to hospital (2004–05) (*44*)	Retrospective descriptive study	X-ray-confirmed CAP	3.6% (children)	
Outpatient and inpatient					
ARI	Population of the West Bank (1995) (*56*)	Assessment report of burden of disease	Respiratory disease (including ARI)	36%	1st
	Population of Gaza (1995) (*56*)	Assessment report of burden of disease	Respiratory disease (including ARI)	14%	1st
Outpatient					
ARI	Sousse, Tunisia Patients of primary health care centres (2002/03) (*76*)	Cross sectional survey	Respiratory diseases	43%	1st
	Bam, Islamic Republic of Iran Evaluation of morbidity reports post-earthquake (2004) (*77*)	Review of medical records	Upper respiratory Pneumonia	12.7% 2.2%	1st of 8 8th of 8
	Tikrit, Iraq Children attending outpatient clinics (2004/05) (*45*)	Prospective observational study	ARI	44% (2–11 m; 52.2%)	
	Peshawar, Pakistan Children <5y in a rural community (2005/06) (*78*)	Cross-sectional study	ARI	27% (< 5 y)	1st
	Oman, National population Annual health statistics report (2013) (*40*)	Annual statistical report	ARI	26.5%	
Community					
ARI	Iraq Children <5y (2000) (*46*)	Multiple indicator cluster survey	ARI	6.9% (< 5 y)	
Surveillance					
ARI	Darfur, Sudan IDPs (2005) (*79*)	Report	ARI consultations	18.7%	
	Iraq Populations of 16 reporting sites (7 refugee camps and 9 IDP camps) (2015) (*80*)	Report	ARI	49%	1st
SARI	Syrian Arab Republic, national population (2015) (7)	Report	SARI	1.3%	5th
ILI	Syrian Arab Republic Population of 448 sentinel reporting sites (2015) (*80*)		ILI[7]	54%	1st
			ILI	53%	1st

ARI = acute respiratory infection; CAP= community-acquired pneumonia; EWARS = early warning and response system; IDP = internally displaced person; ILI = influenza-like illness; SARI = severe acute respiratory infection.

Table 3 Proportionate morbidity of ARI in patients with respiratory symptoms

Disease	Population at risk (year) (*reference*)	Study design	Case definition as reported	Proportionate morbidity (age, if available)
Inpatient				
ARI	Erbil city, Iraq Patients attending the only specialized paediatric hospital (2012) (*48*)	Case control to investigate malnutrition as a risk factor for ARI	Acute URTI Acute LRTI: Mixed URTI & LRTI	27% 41% 16%
	Oman, national population (2013) (*40*)	Annual statistical health report	Severe ARI out of total ARI episodes	0.9%
Pneumonia	Amman, Jordan Children < 2 y admitted with respiratory symptoms or fever (2010–2012) (*33*)	Prospective descriptive study	Pneumonia diagnosed in ARI patients	11%(< 2 y)
	Ariana, Tunisia All patients with CAP admitted to ICU (1999–2008) (*47*)	Retrospective cohort study	Pneumococcal pneumonia (CAP in which Streptococcus pneumoniae was isolated)	48.3% (mean age: 49.5 y ±21.6)
RSV	Riyadh, Saudi Arabia Children aged 1m–3y hospitalized with suspected ARI (2007/08) (*49*)	Descriptive cross-sectional study	RSV-positive	35%(1 m–3 y)
Outpatient				
ARI	Tikrit, Iraq Children < 5y attending outpatient department for treatment of ARI (*45*)	Prospective observational study	Very severe disease Severe pneumonia Pneumonia Cough and cold	8.8% (20.8% < 2 m) 19.6% (22.2% 2–11 m) 48.2% (66% < 2 m) 23.4% (36.5% 12–60 m)
	Sousse, Tunisia Patients of primary health care centres (2002/03) (*76*)	Cross sectional survey	ARI	21.6%
RSV	Beirut, Lebanon Children presenting with ILI at hospital (2007/08) (*50*)	Descriptive cross-sectional study	RSV-positive ILI cases	26%
Surveillance				
Influenza	Morocco Patients presenting with ILI and SARI at clinics and hospitals across country (2007–2009) (*51*)	Descriptive study of routine influenza sentinel surveillance	Proportion positive for influenza among ILI and SARI cases Of those positive for influenza, proportion positive among ILI cases Of those positive for influenza, proportion positive among SARI cases	3% 87% 13%
Influenza A	Beirut, Lebanon Children presenting with ILI to the outpatient peadiatric clinic, American University Hospital (2008) (*50*)	Descriptive cross-sectional study	Proportion of ILI cases with influenza A	28%
Influenza B	As above		Proportion of ILI cases with influenza B	10%
SARI	Lebanon, Beirut population (up to week 52, 2013) (*81*)	ICU-based surveillance	URTI Influenza LRTI Acute respiratory distress	0% 7% 85% 7%
	Lebanon, north population (2013) (*82*)	ICU-based surveillance	URTI Influenza LRTI Acute respiratory distress	0% 18% 45% 9%
	Lebanon, Mount Lebanon population (up to week 24, 2014) (*53*)	ICU-based surveillance	URTI Influenza LRTI Acute respiratory distress	0% 0% 95% 3%
	Lebanon, Bekaa population (up to week 27, 2014) (up to wk 24, 2014) (*52*)	ICU-based surveillance	URTI Influenza LRTI LRTI	0% 0% 38% 8%

ARI = acute respiratory infection; CAP = community-acquired pneumonia; ILI = influenza-like illness; LRTI = lower respiratory tract infection; ; RSV = respiratory syncytial virus; ; SARI = severe acute respiratory infection; URTI = upper respiratory tract infection; m = month; y = year

Table 4 Acute respiratory infection (ARI)-attributable mortality, by type of infection

Disease	Place (year) (*reference*)	Case definition, as reported	Mortality burden data	Rank
ARI – proportionate mortality				
	Kabul, Afghanistan (2002/03) (*43*)	ARI as cause of child mortality	22%	2nd
	Herat province, Afghanistan (2004) (*54*)	ARI as cause of child mortality	30.5%	1st
	Karachi, Pakistan (2010) (*55*)	"Respiratory tract" as cause of child mortality	28.7%	1st
	Oman, annual health report (2013) (*40*)	Primary ARI deaths in children < 5 y	16 deaths out of 383, 272 ARI episodes	
Pneumonia – proportionate mortality				
	West Bank and Gaza (1997) (*56*)	Pneumonia/respiratory disease	All ages: 8.6%	4th of 15
			< 1 y: 22%;	1st of 10
			1–< 5 y: 19%;	1st of 10
			5–19 y:12%;	3rd of 10
			20–39 y: 4%;	6th of 10
			40–59 y: 3%;	7th of 10
			60+ y: 5%	6th of 10
	Ariana, Tunisia (1999–2008) (*47*)	Mortality in *Streptococcus pneumoniae*-confirmed pneumonia cases	25%	
	Islamic Republic of Iran (Tehran, Karaj, Savojbaolagh, Robatkarim, Shahriar) (2005/06) (*57*)	Pneumonia as cause of death in < 5 year-olds	< 5 y: 4.8%	3rd
			1–12 m: 27%	1st
			1–5y: 16.6%	1st
ARI – case fatality rate				
	Kabul, Afghanistan (2002/03) (*43*)	ARI as cause of child mortality	16%	8th of 9

m = month; y = year.

highest prevalence in those aged 50 years and older (*35*).

Lower respiratory tract infections after an earthquake in Bam, Islamic Republic of Iran had the 3rd highest incidence of all diseases measured after the earthquake, at 312 per 10 000 person-years (*36*).

Community surveillance in Karachi Pakistan showed that incidence of ARI was 4403 per 10 000 person-years, and that incidence of pneumonia and severe pneumonia was 821 per 10 000 person years (37). Weekly early warning and response system reports (EWARS) in Sudan for 9 weeks at the end of 2014/beginning of 2015 showed that ARI had the highest incidence for reportable disease in three regions of Darfur. The lowest weekly incidence seen in South Darfur was 239 per 10 000 person-years during week 52, 2014 (*38*), while the highest incidence in North Darfur was 1721 per 10 000 person-years during week 2, 2015 (*39*). National data from Oman in 2013 reported that children under 5 years of age experienced 11 200 episodes of ARI per 10 000 person-years, meaning each child experienced on average 1.12 episodes of ARI per year (*40*).

Only one paper reported pathogen-specific incidence of ARI. In Damanhour, Egypt, respiratory syncytial virus-associated hospitalization was 2.4 per 10 000 person-years, and the incidence of respiratory syncytial virus-associated outpatient visits was 608 per 10 000 person-years (*41*).

Proportionate morbidity of ARI (Table 2)

Proportionate morbidity of ARI is reported to determine the importance of ARI compared with other illnesses. Of the 13 papers in which ARI were ranked, 11 ranked them as having the highest or second highest proportionate morbidity.

In children aged 1 month to 14 years in the Islamic Republic of Iran and of "paediatric" age in Afghanistan, respiratory diseases accounted for 40% (*42*) and 20% (*43*) of inpatient visits respectively, and in Tunisia 3.6% of all children admitted to hospital had X-ray-confirmed pneumonia in those admitted to hospital (*44*). ARI accounted for 44% of morbidity in children attending outpatient clinics in Tikrit, Iraq (*45*). According to data analysed from UNICEF multiple indicator cluster survey in Iraq, 6.9% of childhood disease could be attributed to ARI (*46*). Morbidity due to ARI in all age groups ranged from 26.5% in Oman (*40*) to 49% in Syria (*7*).

Table 5 Rates of hospitalization and length of stay, by disease and country

Country	Location, year (*reference*)	Population at risk	Time at risk (length of study)	Rate of hospitalization of confirmed cases	ICU admission rate	Mean length of hospital stay	Pre-existing condition
H1N1							
Islamic Republic of Iran	Kurdistan, 2009/10 (*59*)	Suspected cases attending hospitals and health centres	1 yr	91.7%			
	Yazd, 2009/10 (*83*)	Patients registered at Yazd health centre	1 yr	60%	30%		
	Tabriz, 2009 (*61*)	Patients attending Sina Hospital	3 m		53%		
Saudi Arabia	Jeddah, 2009/10 (*25*)	Children presenting to hospital with ILI	4 m	73%		3.62 ± 2.05 d	
	Riyadh, 2009 (*58*)	Children attending King Khalid University Hospital with ILI	5 m	13%: median 3 y (1 m–12 y); 60% male, 40% female	10%		70% of hospitalized. 100% of those who died.
	Dhahran, 2009 (*84*)	Patients admitted with ILI	5 m	13.4 per 100 000		8.5 d	
Oman	Salalah, 2009 (*85*)	Patients >12 y presenting at hospital with ILI	2 m	24%: mean age 35.2 y, 60% males, 40% females			
	Muscat, 2009 (*62*)	H1N1 cases admitted to hospital	4 m			49.2% 1–3 d; 43% 4–78 d; 7.7% 7 d	70.8%
Kuwait	2009/10 (*60*)	Children admitted for influenza	5 m	255 patients	3%	4.5 ± 3.6 d	45%
Pakistan	Rawalpindi, 2009/10 (*26*)	Adult patients presenting to department of pulmonary and critical care	6 m		27.8	10.4 ± 7.52 d	
Pneumonia							
Tunisia	Ariana,1998–2008 (*47*)	All patients admitted to ICU with pneumococcal pneumonia	9 m				Median 9.5 d (range: 1–68 d)
MERS-CoV							
Saudi Arabia	Al-Ahsa & Riyadh, 2012/13 (*86*)	Outbreak of 12 critically ill patients in ICU	9 m				Median 41 d (8–96 d), ICU stay median 30 d (range: 7–104 d)

ICU = intensive care unit.
ILI – influenza-like illness.
d = day; m = month; y = year.

Disease- and pathogen-specific morbidity of ARI (Table 3)

Disease-specific ARI morbidity was also measured in an attempt to quantify the extent of severe disease among patients with respiratory illness. Children were the target population for all but one of the studies (*47*) set in inpatient and outpatient settings. Of children admitted to hospital for ARI, 11% under 2 years old in Amman, Jordan during 2010–2012 had pneumonia, while 41% in Erbil city, Iraq in 200–2007 had lower respiratory tract infections (*33,48*). In Tikrit, Iraq, 48.2% children < 5 years attending outpatient departments for ARI in 2004/05 had pneumonia (*45*).

Three studies report pathogen-specific morbidity. Of children aged between 1 month and 3 years with lower respiratory tract infection, 30% were confirmed to have respiratory syncytial virus (RSV) infections in a Saudi Arabian study (*49*). Similarly, 26% of children presenting with ILI at a hospital in Beirut, Lebanon in 2007/08 tested positive for RSV (*50*). Pneumococcal pneumonia accounted for 48.3% of patients admitted to the intensive care unit with community-acquired pneumonia in Ariana, Tunisia (*47*).

Surveillance of ILI and SARI in Morocco revealed that, of the influenza-positive cases, 87% had ILI (*51*). Of children in Lebanon presenting with ILI, influenza A was more common (28%) than influenza B (10%) (*50*). Annual statistical reports describing SARI in different areas within Lebanon in 2013/14 indicate that 38% of SARI cases in Bekaa (*52*) and 95% of SARI cases in Mount Lebanon (*53*) had lower respiratory tract infections.

ARI mortality (Table 4)

ARI accounted for 22% of child mortality in Kabul, Afghanistan in 2002/03 (*43*) and up to 30.5% of child mortality in Herat province, Afghanistan in 2004 (*54*). ARI was the primary cause of death among children in Herat and Pakistan, (*54,55*), and the second most common cause of mortality in Kabul (*43*).

Pneumonia accounted for 8.6% of deaths in all ages in the West Bank and Gaza in 1997 (*56*) and 4.8% of deaths in children aged under 5 years in the Islamic Republic of Iran in 2005/06 (*57*). Among laboratory-confirmed *Streptococcus pneumoniae* pneumonia cases in Ariana, Tunisia between 1999 and 2008 (all over 15 years), 25% died (*47*).

The age distribution of deaths due to ARI was described in the West Bank and Gaza and in several cities in the Islamic Republic of Iran (*56,57*). In both locations, ARI mortality was highest in the under 1-year-old age group, where it was the primary cause of death.

Hospitalization

The majority of papers reviewed describe morbidity and mortality in hospitalized patients, and specific rates of hospitalizations and lengths of stay were reported in some studies and are shown in Table 5.

By far the greatest amount of information available is for influenza A(H1N1)pdm09. Rates of hospitalization for confirmed cases ranged from 13% in a paediatric population in Saudi Arabia (*58*) to 91.7% in the Kurdistan province of the Islamic Republic of Iran (*59*). Admission to the intensive care unit for influenza A(H1N1)pdm09 ranged from 3% of 255 patients admitted for influenza in Kuwait (*60*) to 53% in Tabriz, Islamic Republic of Iran (*61*). The average length of hospital stay for influenza A(H1N1)pdm09 was lowest in Saudi Arabia (*25*), Kuwait (*60*) and Oman (*62*) and highest in Pakistan (*26*).

Only one paper each reported duration of hospitalization for pneumonia and MERS-CoV and there were none on duration of hospitalization for influenza A(H5N1).

Discussion

After searching the literature, a total of 83 studies were retained. The burden of severe respiratory disease in the EMR was summarized, including burden attributable to specific pathogens, where possible. ARIs of common bacterial and viral origin are important in children and also in the elderly. Global mortality due to pneumonia was estimated at 19% among < 5-year-olds and 14% of in children aged 1–59 months in 2008 (*63*). Data for the EMR extracted in this review suggest that pneumonia and acute respiratory disease are important contributors to child mortality in the Region, ranging between 22% and 30.5% (*54,55,56,57,58*). Novel pathogens and those capable of causing severe excess morbidity and mortality, namely influenza A(H1N1)pdm09, A(H5N1) and MERS-CoV, were found to mainly affect adults.

Influenza A(H5N1) was reported in four countries in the Middle East. Three of these, Djibouti, Iraq and Pakistan, have had a small number of cases and appear to have controlled the epidemic effectively with no new human cases reported in the last 5 years, according to WHO data (*11*). Nonetheless, multiple outbreaks of influenza A(H5N1) in poultry and wild birds have occurred in Pakistan and Iraq since 2006. Egypt continues to report human cases and has the highest number compared to the rest of the world, with the second highest number of fatalities (case fatality 33% overall and 47% in the 45+ years age group). Upsurges have largely been related to uncontrolled poultry farming practices (*9*), and while we remain in a pre-pandemic alert phase (*64*), with no change in transmission dynamics between humans at the present time, these findings are a concern. The EMR's contribution to the total global cases and deaths attributable to influenza A(H5N1) to date is 41.5% and 24.7% respectively (*11*). Further work is needed to understand the risk factors

for bird-to-human transmission in the EMR, and better prevention and control measures need to be implemented.

The 2009 A(H1N1) influenza pandemic was a good example of how a novel strain of transmissible influenza virus can affect an essentially susceptible population. This pandemic is estimated to have caused 201 200 deaths worldwide (*65*). Of the respiratory deaths attributed to A(H1N1)pdm09, 17 900 are estimated to be from the EMR, with a rate of 3.0 per 100 000 (*66*). Mortality rates per 100 000 were not cited in any of the papers included in this review. CFRs were reported, however, the highest being 19% from SARI cases confirmed to have influenza A(H1N1) pdm09 in Morocco (*19*).

Global data on MERS-CoV infection show that since its initial detection in 2012, Saudi Arabia and the United Arab Emirates continue to be the main contributors to incident cases, reflecting the distribution of the ostensible animal reservoir, the dromedary camel. CFRs were highest for MERS-CoV of all the ARIs discussed in this literature review. MERS -CoV infections in Saudi Arabia account for over 85% of the global cases (*67*). Cases continue to appear from either zoonotic exposure (primary cases) or exposure within health care settings (secondary cases) (*66*). Export of cases to other countries has not resulted in sustained community transmission, with the exception of the Republic of Korea, where extended onward transmission occurred in the health care sector (*66,67*).

Hospitalization rates and lengths of stay provide some insight into the clinical severity and economic burden of the disease. While this type of information was not plentiful, it is apparent that MERS-CoV infection resulted in severe disease with a median hospital stay of 41 days compared with 10 for pneumonia and pandemic A(H1N1)pdm09.

This review revealed a number of specific gaps in the available literature. Notably, there is a paucity of disease burden data that are statistically comparable between countries in the EMR. A number of countries had either no or very few reportable data. The target populations were mostly patients attending hospitals or health centres.

Thus, while every effort was made to find all publically available information fulfilling the inclusion criteria for this review, we were unable to perform statistical analysis and pooling of surveillance data to determine the incidence and prevalence of diseases. Such analysis would help improve baseline estimates of disease epidemiology but requires strengthened routine surveillance. Inclusion of burden indicators such as rates and duration of hospitalization will help assess burden in health economic terms as well.

The websites of ministries of health were searched for statistical health reports. Only Egypt, Lebanon, Oman, Syrian Arab Republic and Yemen provided this information publically. Efforts to liaise with ministries of health across the Region to gain access to annual statistical reports and other relevant data would be invaluable. Standardization of methods with respect to annual health reporting would also be beneficial to being able to compare data across countries. Standardization of laboratory methods and more rigorous epidemiological investigation and analysis are also needed.

There are several limitations to this review. Some are a result of the descriptive nature of the papers and the overall quality of the information available for review. Studies were not formally evaluated for their quality or representativeness, and the inconsistencies in research methodologies, case definitions and population denominators made data comparison across studies difficult. In an effort to obtain as much information as possible, wherever morbidity or mortality were reported, the data were summarized in descriptive tables.

This review was Internet-based, which may introduce bias related to the availability of electronic references for review. We believe, however, that all published/peer reviewed articles fitting the selection criteria were found but it is likely that some grey literature and material not openly accessible was missed.

We did not analyse information based on country characteristics. There is a wide disparity in terms of resources, health expenditures, states of crises and displaced populations across the Region and it would be useful to group similar countries with respect to national income, health care access and other pertinent characteristics allowing appropriate comparisons. It has been shown that ARIs are among the top causes of morbidity and mortality in conflict-affected populations (*68*) and taking this into account when comparing data might have provided another layer of analysis; however, more specific literature search terms and additional sources would have had to have been accessed.

This review looked at pathogen-specific illness and infection [A(H5N1), A(H1N1)pdm09, MERs-CoV, respiratory syncytial virus and *S. pneumoniae*] as well at diseases diagnosed such as pneumonia or upper respiratory tract infection. In an effort to describe as much respiratory-disease related burden as possible, no strict differentiation between disease and infection was made in this review.

Conclusion

There is a paucity of statistically comparable information regarding the burden of epidemic and pandemic respiratory diseases in the Region. The papers included in this review allow a descriptive picture of the situation. While it is suspected that the data abstracted for this review are not entirely representative of the whole Region, this summary provides an initial evidence base to support improved surveillance and reporting in the countries of the EMR.

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