


REVIEW

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## The clinical and economic burden of varicella in the Middle East: a systematic literature review

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### ABSTRACT

This systematic literature review was conducted to better understand the epidemiology and burden of varicella across the Middle East, gain insight into the evidence to support using universal varicella vaccination (UVV), and identify potential data gaps. Both epidemiology and economic data on the burden of varicella were limited and varied significantly. Most of the data focussed on varicella burden in the absence of a UVV program. In the absence of UVV, varicella incidence is increasing across this region with varicella infection associated with substantial morbidity. Although limited, data on the impact of vaccination at a population level indicated UVV programs reduce varicella incidence and hospitalizations, in line with global experience. Further research and action are needed to better understand varicella epidemiology in the Middle East, increase awareness and understanding in the region, and provide local data to support national public-health decisions regarding the implementation of UVV programs.

### ARTICLE HISTORY

Received 22 March 2019  
Revised 2 June 2019  
Accepted 26 June 2019

### KEYWORDS

Middle East; seroprevalence; systematic literature review; varicella; vaccination

### Introduction

Varicella is a common, highly contagious illness caused by the varicella-zoster virus.<sup>1</sup> The disease is characterized by an itchy, vesicular rash that usually starts on the scalp and face and is accompanied by fever and malaise. Typically, the disease is mild, with the vesicular rash disappearing over 7–10 days.<sup>2</sup> However, severe complications such as bacterial infections and encephalitis can arise.<sup>2</sup> Varicella can be transmitted through direct contact with individuals with rash, through aerosol droplets from an infected person sneezing or coughing, or by an individual coming in contact with the vesicular fluid of skin lesions. The global annual varicella disease burden is estimated to include 140 million cases, of which 4.2 million have severe complications that can lead to hospitalization and death; neonates and the immunocompromised are at particularly high risk.<sup>1</sup>

Vaccination can provide long-term protection against varicella. Varicella vaccines are based on live-attenuated varicella; most varicella vaccines available globally are based on the OKA virus strain, although some are based on the less well-studied MAV virus strain. Two different presentations are available: a single-component vaccine (either OKA or MAV) and a tetravalent vaccine that also protects against measles, mumps, and rubella (OKA only). Recommended vaccination schedules typically involve 1 (median prevention of 83%) or 2 (median prevention of 95%) doses.<sup>3</sup>

The World Health Organization recommends that routine childhood immunization is considered in countries where varicella has an important health impact.<sup>1</sup> Over the last decade, a number of countries in the Middle East have introduced varicella vaccination into their national immunization programs, and over 50% of the Middle Eastern population now lives in countries offering universal varicella vaccination (UVV).<sup>4</sup> However, this still leaves a substantial proportion of the region's population with only private and/or limited access to the vaccine.

Understanding the true local burden of disease and the potential impact of a UVV program is central to support varicella vaccination decision-making in the Middle East. In 2012 a working group on pediatric vaccine-preventable disease in low- to middle-income countries, which included experts from the Middle East, acknowledged that data on varicella epidemiology (specifically morbidity and mortality) and the use of varicella vaccine (as a single component or multicomponent vaccine) are lacking for these countries.<sup>5</sup> There are numerous global and regional reviews that discuss the epidemiology of varicella and the impact of vaccination programs on incidence, herd immunity, morbidity, and mortality.<sup>6–8</sup> However, very little has been published for the Middle East; a recent review by Al-Turab et al. provides a general overview of varicella infection in the Middle East with a specific focus on seroprevalence.<sup>9</sup> This review highlighted that, as in

most countries, varicella is a childhood disease with seropositivity to varicella increasing with age.

To the best of the authors' knowledge, this is the first systematic literature review (SLR) to assess the clinical and economic burden of varicella and the impact of varicella vaccination in the Middle East, addressing the need for a comprehensive review of varicella in the region. To gain a better understanding of burden of disease in the Middle East and to identify data gaps to be addressed in future research, this SLR was conducted to: (1) assess the epidemiology (incidence/prevalence) of varicella disease in the Middle East; (2) provide data on the status of vaccination programs, including coverage rates; and (3) examine the economic burden of varicella, including healthcare resource utilization.

## Results/findings

The SLR identified a total of 210 studies of which 35 were from the Middle East (Figure 1) specifically Iran, Iraq, the State of Palestine, Saudi Arabia, Turkey, and the United Arab Emirates (UAE). Of the studies identified, 34 reported epidemiology data; 13 were cross-sectional studies, 10 were retrospective studies, 10 were prospective studies, and 1 was a database/registry study. Studies varied greatly in terms of size, with samples ranging from 102 to 20,788 patients. Data were collected mainly through interviews and questionnaires/surveys. Seroprevalence was the most commonly reported outcome (21 studies), followed by incidence (9), complication (7), and mortality (3)

Studies identified in the SLR were supplemented with six pieces of gray data: four conference posters (one multinational, three in Turkey) and two publications (both Iran).

## Vaccination program and coverage

The SLR identified five studies that provided information on the inclusion of the varicella vaccine in national immunization programs (NIPs) in the Middle East; four in Turkey and one in Saudi Arabia. A single-dose universal schedule was mandated and government-funded in Turkey (2013), while a two-dose program was implemented (and supported by the government) in Saudi Arabia (2008) (Table 1).<sup>10,11</sup> Review of gray data also found that a single-dose schedule universal government-funded vaccination program has been implemented in Oman in 2010, and two-dose programs in the UAE (2009), Bahrain (2015), Kuwait (2017), and Qatar (2010).<sup>4,12,13</sup> Those countries in the Middle East where the vaccine is available privately only – particularly Lebanon and Egypt – tend to follow the US Centers for Disease Control and Prevention recommendations for target age and dosing.

Very limited data on vaccine coverage were identified in the SLR – only three studies reporting coverage data were found, all in Turkey. Before the introduction of the vaccination program in Turkey in 2013, varicella vaccine coverage varied substantially in the private sector. A 2002 survey of 3,405 subjects (aged 2–59 months) from the Umraniye Health District in Istanbul reported a varicella vaccination coverage rate of 2.7%.<sup>17</sup> In comparison, an evaluation of 144 children attending a nursery school during a varicella epidemic in 2006 reported a vaccination coverage of 50.6%, while a cross-sectional study of 2,802 children <2 y, conducted 2008–2009, reported a 60.1% vaccine coverage rate.<sup>14,18</sup> Since this SLR was conducted, data from Dubai in the UAE suggest that during the period of 2013–2018, following the

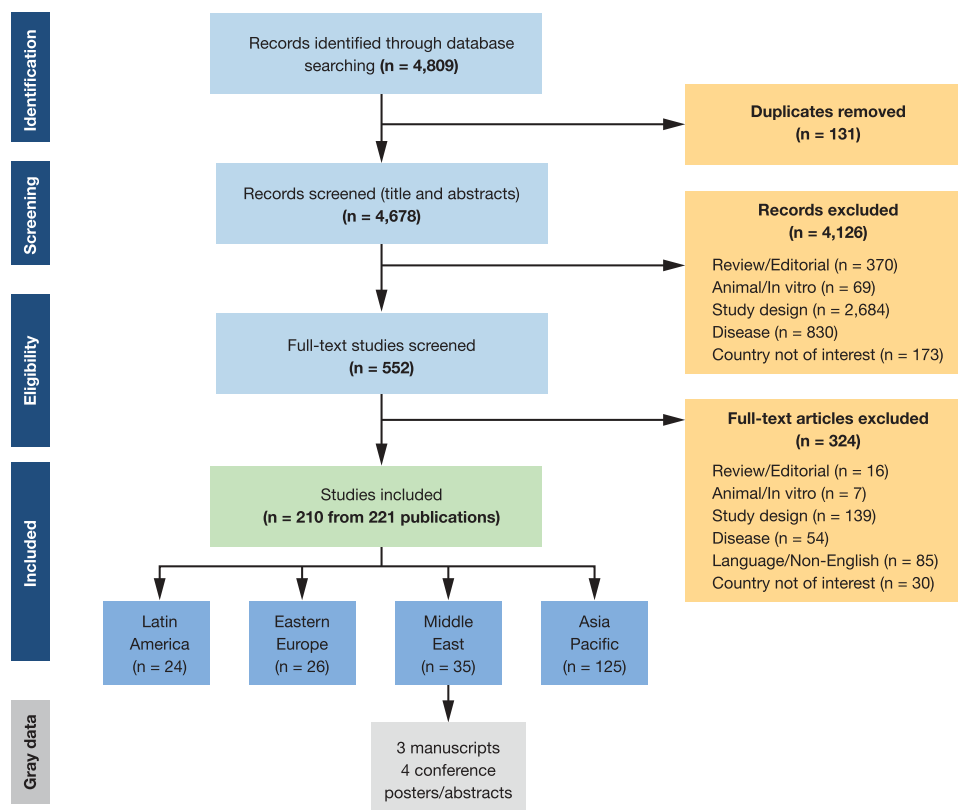


Figure 1. PRISMA flow chart for the global search with regional-level outcomes.

**Table 1.** Universal varicella vaccination programs in the Middle East.

Country	Dose	Schedule	Implementation date/approval date
Bahrain <sup>*4</sup>	2 doses	12 months; 3 y	2015
Kuwait <sup>*4</sup>	2 doses	12 and 24 months	2017
Oman <sup>*4</sup>	1 dose	12 months	2010
Qatar <sup>*4</sup>	2 doses	12 months; 4–6 y	2010
Turkey <sup>14,15</sup>	1 dose	12 months	2013
Saudi Arabia <sup>11</sup>	2 doses	12 months; 4–6 y	Childhood varicella vaccine introduced in 1998; made mandatory in 2008
UAE <sup>16</sup>	2 doses	12 months; 5–6 y	2009

UAE, the United Arab Emirates.

\*Identified via gray data review.

introduction of the vaccination program, the varicella vaccine coverage rate was 94 %. Based on the limited and varied coverage data found, this is an area that requires further research.

### Surveillance and incidence reporting

A total of 10 studies provided evidence on the incidence of varicella in the Middle East (Table 2).

There is substantial variation in reported varicella incidence in the Middle East. In the absence of the UVV in NIPs (pre-UVV) the reported annual incidence per 100,000 population ranged from 73.4 in Iraq (2007) to 759 in Saudi Arabia (2003).<sup>19,22</sup> Since varicella was not a notifiable disease in most of the countries where it was reported, very little is known about the exact case definitions use, or the reporting efficiency of these surveillance systems, which may partially explain the variation. Differences in climate may have contributed to the variation observed as incidence varied with the seasons, peaking in the spring; incidence was highest in April and May in Iraq, in March in Saudi Arabia, and in March and May in the UAE.<sup>19,23</sup> Differences in study design, in particular, study population, may also have contributed to the observed variation: in the UAE and Saudi Arabia the incidence of varicella varied according to gender (higher in men compared with women), and in Iraq and the UAE incidence varied with age (higher in patients aged <15 y compared with older patients).<sup>19,21,24</sup> As indicated by a quarterly summary report of communicable diseases, the annual incidence rate of varicella in Abu Dhabi was 486 per 100,000 population in 2011. Following the introduction of government-funded universal varicella vaccination in 2012, there was a decrease in the rates of varicella that ranged between 147 and 168 per 100,000 population starting from 2013.<sup>25</sup>

However, despite the variation in data, in the absence of a UVV program (pre-UVV era), an increase in varicella incidence over time was observed across the two studies that published longitudinal data (Table 2). In Iraq, a threefold increase in incidence was observed from 2007 to 2011.<sup>19</sup> Similarly, in Saudi Arabia incidence increased from 207/100,000 population in 1999 to 759/100,000 in 2003.<sup>22</sup>

Post-UVV incidence data were only found for Saudi Arabia, where a UVV was introduced in 2008. A study by Al-Tawfiq et al. in patients with varicella infection reported a 2011 post-UVV incidence of 88.1 per 100,000 population, which had fallen substantially from 739.8 per 100,000 population in 1994, prior to vaccine availability.<sup>11</sup> This finding was supported by Saleh et al., who reported a decline in the

number of cases recorded at an armed forces hospital from 754 in 2007 (pre-UVV era) to 227 in 2012 (post-UVV era).<sup>23</sup>

Comparison of varicella incidence data for vaccinated (breakthrough) and unvaccinated cases provides further insight into the potential impact of a UVV program. One study conducted in children (aged 2.0–15.5 y) in Turkey reported that the incidence of varicella was lower in vaccinated compared with unvaccinated children (4,550 per 100,000 patient-years vs 12,020 per 100,000 patient-years, respectively).<sup>14</sup> Similar findings were reported in a study of a varicella outbreak in preschool children (n = 124) in Turkey that was identified as part of the gray data.<sup>26</sup> Among vaccinated children (who had received one dose of vaccine before the outbreak), 23.4% had varicella compared with 34% among unvaccinated children.<sup>26</sup> It was also noted that the risk of disease increased with time since vaccination; the risk was 3.5 times higher in children vaccinated  $\geq 5$  y versus those vaccinated more recently.<sup>26</sup>

### Seroprevalence

A total of 35 studies from the SLR provided evidence on the seroprevalence of the varicella-zoster virus in the Middle East; most of the data were from Iran (12 studies) (Table 3). Based on the available SLR data, the seroprevalence of varicella in different age groups mentioned in Table 3 was shown to range from 27.6% to 94.6% in Iran, 74.4% to 88.5% in Saudi Arabia, 22.3% to 98.2% in Turkey, 91.0% in Syria, 80.6% to 88.0% in the UAE, and 92.2% in Qatar.<sup>28,29,35,36,39–45,48,49,53,54,56–60</sup> The large ranges in overall seroprevalence for Iran and Turkey are likely due to differences in the overall age of the study population as many studies from the Middle East suggest an increase in seroprevalence with increasing age (Iran, Turkey, and the UAE) (Figure 2). Based on gender distribution, a comparable seroprevalence was observed in men and women in Saudi Arabia and Turkey.<sup>40,47</sup>

A recent meta-analysis of 22 publications provides further information on seroprevalence. The overall seroprevalence of varicella-zoster infection in Iran was 78.5%.<sup>38</sup> When studies of high-risk populations (such as pregnant women and hemodialysis patients) were excluded, the overall seroprevalence rate of varicella-zoster virus in the general population was 67%. In agreement with other studies, seroprevalence in this analysis increased with age. In Lebanon, in adolescents and young adults aged 15–18 y, attending school and at high-risk, the rate of seroprevalence was 96.6%.<sup>61</sup>

**Table 2.** Incidence of varicella across the Middle East.

Country	Study	Design and vaccine availability status	Age group	Incidence	
				Minimum	Maximum
Iraq	Khaleel 2013 <sup>19</sup>	Retrospective study investigating trend of registered clinical cases 2007–2011 (pre-UUV era)	All ages	73.4 per 100,000 population in 2007	222.6 per 100,000 population in 2011
Jordan	World Health Association <sup>20</sup>	Surveillance report. Pre-vaccine incidence rate, 1991 (no UUV program)	All ages	458 per 100,000 population	
Lebanon	World Health Association <sup>20</sup>	Surveillance report. Pre-vaccine incidence rate, 1991 (no UUV program)	All ages	454 per 100,000 population	
Saudi Arabia	Almuneef 2006 <sup>21</sup> Jahan 2007 <sup>22</sup>	Retrospective study in an outpatient setting 2001–2003 (pre-UUV era) Retrospective study, 1999 and 2003 (pre-UUV era)	All ages All ages	4,121 patients reported with varicella, 60% of cases in age group 5–14 y 207 per 100,000 population in 1999	759 per 100,000 population in 2003
	Al-Tawfiq 2013 <sup>11</sup>	Retrospective study of 19,577 patients 1994–2011	All ages	88.1 per 100,000 population in 2011 (post-UUV era)	739.8 per 100,000 population in 1994 (pre-vaccine availability)
	Saleh 2014 <sup>23</sup>	Retrospective review of surveillance records and book registries from the Armed Forces Hospital of the Southern Region of Saudi Arabia 2007–2012.	All ages	227 cases in 2012 (post-UUV era)	754 cases in 2007 (pre-UUV era)
Syria	World Health Association <sup>20</sup>	Surveillance report. Pre-vaccine incidence rate, 1991 (no UUV program)	All ages	1,435 per 100,000 population	
Turkey	Dinleyici 2012, 2015 <sup>10,15</sup>	Retrospective study of 824 patients hospitalized due to varicella between October 2008 and September 2010 (pre-UUV era)	Ages < 1–15 y	Incidence of varicella-related hospitalization: 5.3 per 100,000 children (overall) 3.9 per 100,000 children aged 5–10 y	Incidence of varicella-related hospitalization: 6.9 per 100,000 children (overall) 13.8 per 100,000 children aged < 5 y
	Kurugol 2011 <sup>14</sup>	Cross-sectional study of 2,802 children from April 2008 to March 2009 (pre-UUV era)	Ages 2–15.5 y	4,550 per 100,000 person-years for vaccinated (breakthrough) children	12,020 per 100,000 person-year for unvaccinated (wild-type varicella) children
UAE	Uduman 2009 <sup>24</sup>	Retrospective study conducted between 2000–2004 (pre-UUV era)	All ages	373 per 100,000 population	790 per 100,000 population

UUV, universal varicella vaccine.

\*No gray data on incidence rates were identified.

**Table 3.** Seroprevalence data.

Country/Study	Population	Seroprevalence
<b>Iran</b>		
Allami 2014 <sup>27</sup>	Overall, n = 270	74.5%
Bayani 2013 <sup>28</sup>	Aged 18–49 y	94.6%
	Overall n = 459	
Ardakani 2013 <sup>29</sup>	Mean age 32.2 ± 1.1 y	95.5%
	History of varicella	27.6%
Talebi-Taher 2010 <sup>30</sup>	Overall population of patients aged	77.8% at ≤ 20 y
	Aged 1–15 y, n = 558	
Vojgani 2013 <sup>31</sup>	Pregnant women, according to age,	94.7% at ≥ 30 y
	Aged 16–43 y	
Hoseini 2016 <sup>32</sup>	n = 400; min–max values presented	6.6% at 7 months
	Children, by age, n = not available	
Motamedifar 2006 <sup>33</sup>	Aged 7 months to 6 y	21.3% at 6 y
	Min–max values presented	
Pourahmad 2010 <sup>34</sup>	Patients aged 10–18 y, n = 2,753	87.4%
	Children aged 0–10 y, n = 270	35.2%
Pourakbari 2012 <sup>35</sup>	Women aged 11–45 y, n = 334	72.7%
	Individuals aged between 10–25 y, n = 412	65.3%
Majidy 2016 <sup>36</sup>	Young women aged 13–40 y for pre-marital medical checkup, n = 250	71.2%
Sharif 2005 <sup>37</sup>	Overall, n = 635, aged 1–60 y	83.6%
Amjadi 2017 <sup>*38</sup>	Overall (meta-analysis), n = 7,867, aged ≤7–88 y	78.5%
<b>Iraq</b>		
Yassien 2012 <sup>39</sup>	Overall, children aged <1–15 y, n = 92	53.3%
<b>Saudi Arabia</b>		
Almuneef 2006 <sup>40</sup>	Overall, adults, n = 4,006	86.0%
Hossain 1989 <sup>41</sup>	Children aged 1–15 y, n = 224	68.0%
Memish 2001 <sup>42</sup>	Adults – healthy male blood donors and pregnant women, n = 452	90.0%
	Saudi Arabian National Guard soldiers, aged 15–40+ y, n = 1,350	88.5%
Ghazi 2002 <sup>43</sup>	Pregnant Saudi Arabian women, ages unspecified, n = 926	74.4%
Almuneef 2003 <sup>44</sup>	Healthcare workers, ages unspecified, n = 2,047	64.0%
Abbas 2007 <sup>45</sup>	Healthcare workers, ages unspecified	68.4%
<b>Turkey</b>		
Alp 2005 <sup>46</sup>	Subjects aged < 30 y, n = 568	78.0%
Alp 2012 <sup>47</sup>	Healthcare-worker population (pre-vaccination era), aged 19–60 y, n = 1,255	98.0%
Celikbas 2006 <sup>48</sup>	Healthcare-worker population, mean age 29 y, n = 363	98%
Gürgöze 2006 <sup>49</sup>	Unvaccinated children aged 1–16 y, n = 803	26.8% for 1–4 y
Karasahin 2014 <sup>50</sup>		90.3% for 13–16 y
	Healthcare-worker population, ages unspecified, n = 811	95.2%
Kanra 2002 <sup>51</sup>	Subjects aged < 30 y, n = 4,387	77.8%
Kose 2013 <sup>52</sup>	Subjects aged > 15 y, n = 2,136	94.3%
Aypak 2012 <sup>53</sup>	Healthcare workers, mean age 33.5 ± 11 y, n = 284	98.2%
Ozkan 2005 <sup>54</sup>	Children aged 9–60 months, n = 292	22.3%
Kurugol 2007 <sup>55</sup>	Overall (ages 1–30 y), n = 600	84.1%
Savas 2004 <sup>56</sup>	Children aged 0–15 y, n = 885	41.2% for 4–5 y
		80% for 10–11 y
		85% for 13–15 y
<b>Syria</b>		
Barah 2012 <sup>57</sup>	Females of childbearing age, n = 316	91.0%
<b>UAE</b>		
Sheek-Hussein 2012 <sup>58</sup>	Medical students, aged 16–33 y, post-vaccination era, n = 261	88.0%
Uduman 2001 <sup>59</sup>	Overall, aged <10–>41 y, n = 648	80.6%
<b>Qatar</b>		
Guanche Garcell, 2016 <sup>60</sup>	Healthcare workers, 84% aged 30–49 y, n = 705	92.2%

UAE, the United Arab Emirates.

\*Denotes identified gray data.

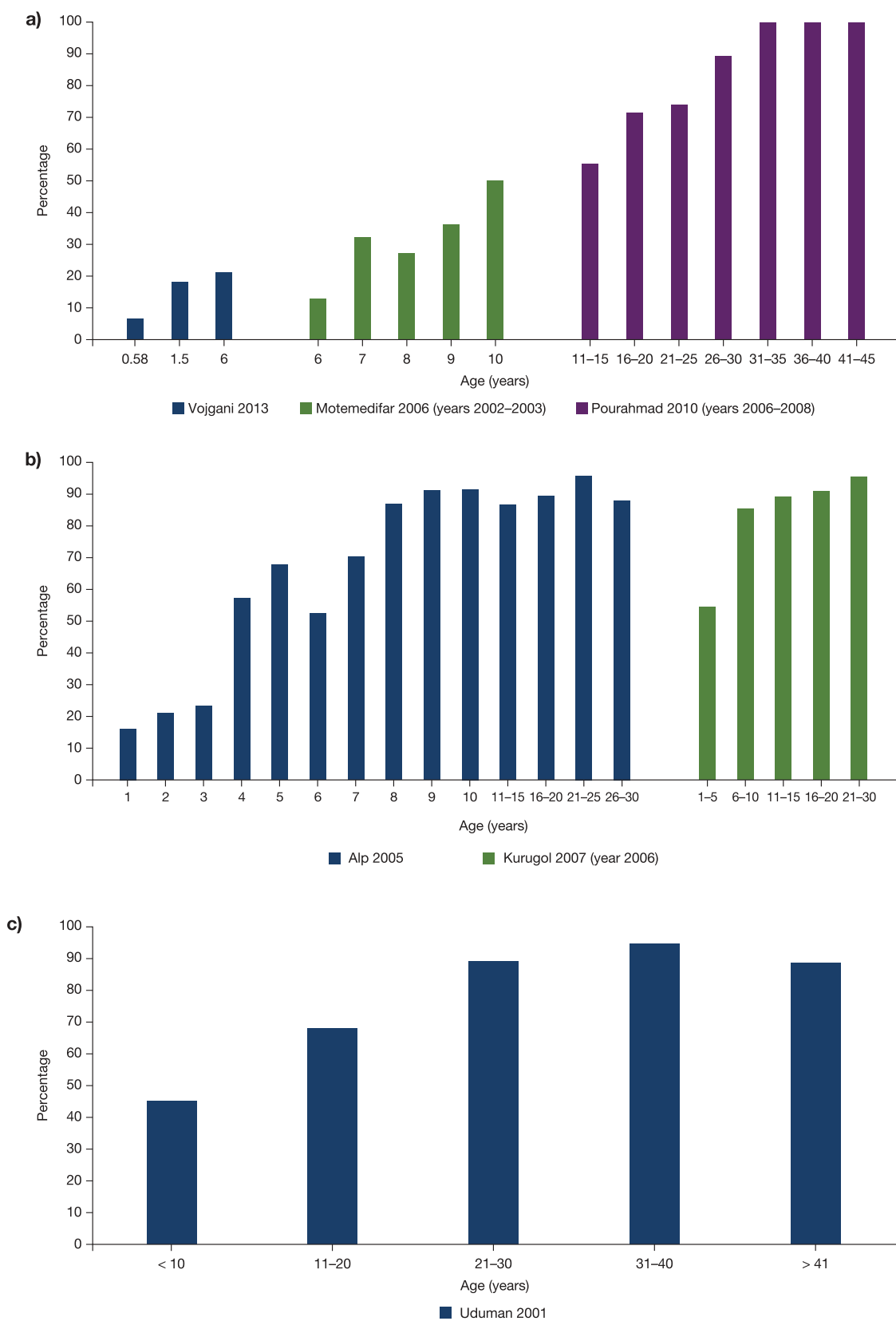
## Mortality

A limited number of publications (three studies) reported varicella-related fatality in the Middle East. In Saudi Arabia during 2001–2003 (pre-UVV era), there were two deaths in a cohort of 3,802 patients (0.05%); one adult died of pneumonia and one child died due to Group A beta-hemolytic *Streptococcus* septic shock.<sup>21</sup> A study of 102 hospitalized patients in the UAE from March 2005 to February 2008 (pre-UVV era) reported five deaths (4.9%) due to severe varicella pneumonia.<sup>62</sup> In a study of 36 children in Turkey, hospitalized with breakthrough varicella, one patient with hematological-oncological malignancy died due to varicella-related complications such as secondary bacterial infections and sepsis.<sup>10</sup>

## Complications

A total of seven studies (eight publications) provided data for the complications associated with varicella in the Middle East. Commonly reported varicella-associated complications in Saudi Arabia, Turkey and the UAE included bacterial infections, skin, and soft tissue infections, followed by neurologic complications and respiratory complications.<sup>10,15,18,21,24,62–64</sup> Two studies highlighted that bacterial infections often manifested as skin and soft tissue infections.<sup>10,24</sup> Bacterial infections have been long established as common complications associated with varicella.<sup>65</sup>

In Saudi Arabia, the incidence of varicella complications in a general cohort of 3,802 patients was 1.50% prior to the

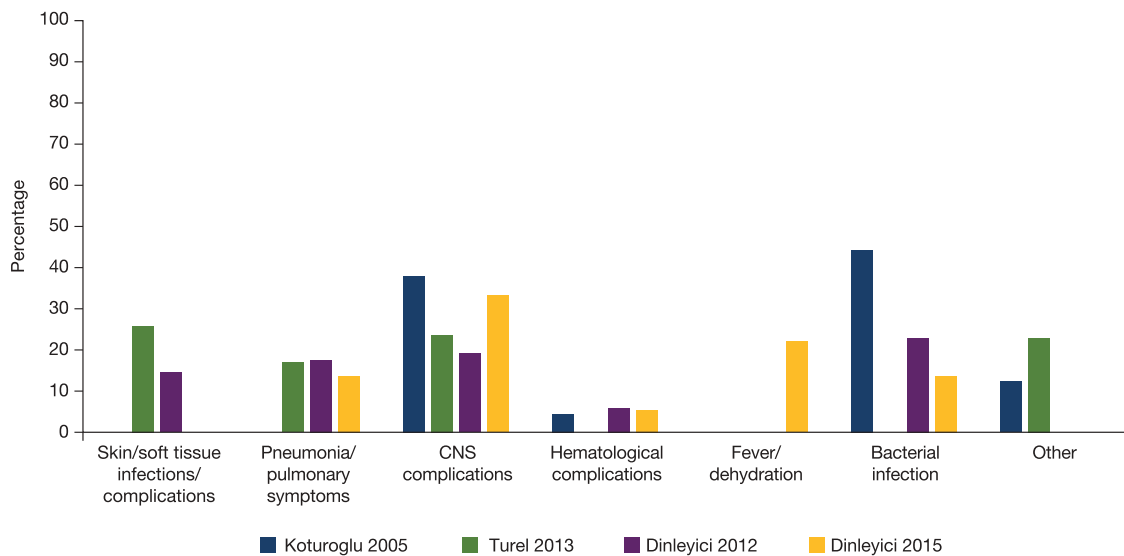


**Figure 2.** Seroprevalence by age in Iran (a), Turkey (b), and the UAE (c). References: Alp 2005,<sup>46</sup> Kurugol 2007,<sup>14</sup> Motemedifar 2006,<sup>33</sup> Pourahmad 2010,<sup>34</sup> Uduman 2001,<sup>21</sup> Vojgani 2013<sup>31</sup> UAE, the United Arab Emirates.

introduction of the UVV; the most commonly reported complications were skin and soft tissue infections (0.50%), pneu-

monia (0.42%), bacteremia (0.16%), encephalitis and cerebellitis (0.11%), and myositis and necrotizing fasciitis (0.11%).<sup>21</sup>





**Figure 3.** Common complications of varicella reported in hospitalized patients in Turkey. References: Koturoglu 2005,<sup>63</sup> Turel 2013,<sup>64</sup> Dinleyici 2012,<sup>15</sup> Dinleyici 2015<sup>10</sup>.

Four publications reported complications in patients hospitalized with varicella in Turkey: the most commonly reported were skin/soft tissue infection, pneumonia/pulmonary symptoms, central nervous system complications, hematological complications, and bacterial infection (Figure 3). In a study of varicella outbreak in children in Turkey (non-hospitalized), none of the vaccinated children experienced varicella-associated complications; however, in the unvaccinated group, 20.3% had secondary skin infections, 18.6% had vomiting, 11.8% diarrhea, 6.7% vertigo, and 5% pneumonia.<sup>18</sup> However, other studies have reported cases of hospitalization due to complications of breakthrough varicella, mainly neurological complications, fever and dehydration, respiratory complications, secondary bacterial infections, and hematological complications.<sup>10</sup>

Two studies reported varicella-associated complications in the UAE, both prior to the introduction of the UVV. Between 2000 and 2004, the most frequent varicella-associated complications in a group of 187 hospitalized children were bacterial infections (affecting 50.3% of cases; 25.1% of patients had secondary bacterial infection of the skin or soft tissue and 24.1% had respiratory tract infection including clinical pneumonia), fever (associated with respiratory tract infection in 20.3%, superficial skin infection in 19.3%, and dehydration in 15.5%), and cerebellar ataxia 12.3%.<sup>24</sup> In the other study, with 102 hospitalized patients, the most frequent were an increase of alanine aminotransferase (51.9%), thrombocytopenia (42.1%), varicella pneumonia (28.4%), leukocytosis (26.4%), and skin infection (25.4%).<sup>62</sup>

### Resource use and health economic aspects

Eight studies identified in the SLR evaluated the economic burden of varicella in the Middle East: five in Turkey, two in the UAE, and one in Saudi Arabia (five retrospective studies, one prospective study, one cross-sectional study, and one study that assessed economic evaluations). Sample size ranged from 102 to 137,310 patients.<sup>62,66</sup> In addition, four gray data sources were identified: two conference proceedings and one publication presenting data on the impact of varicella vaccination in Turkey and

one publication about the cost-effectiveness of varicella vaccination in Iran.<sup>67,68</sup> The majority of studies (11) provided evidence on resource use or hospitalization rates (Table 4). As seen for the epidemiology parameters, hospitalization data were predominantly prior to the introduction of the UVV into the NIP (pre-UVV era) and varied greatly between studies.

A study from Saudi Arabia conducted prior to introduction of the UVV, indicated that approximately 2% of varicella cases required hospitalization.<sup>21</sup> Only the VARICOMP study in Turkey provided population-level data on varicella-hospitalization rates. The overall estimated annual incidence of varicella-related hospitalization per 100,000 children (aged 0–15 y) was 5.3–6.9 in Turkey in the pre-UVV era.<sup>15</sup> Following the inclusion of varicella vaccine into the NIP in 2013, hospitalization in children aged 1–5 y fell significantly from 6.1 to 9.1 per 100,000 children per year (pre-UVV era) to 3.1–4.3 per 100,000 children per year (post-UVV era).<sup>67</sup> However, herd protection for other age groups was not observed. The VARICOMP study also indicated that in the post-UVV era, the mean age of hospitalized children was slightly older (52.8 vs 48.6 months  $p < .005$ ) and the hospitalization rate of children with underlying conditions was lower compared with the pre-UVV era.<sup>69</sup> Over a 7-y period from 2008 to 2015, neurological complications occurred in 17.7% of children hospitalized with varicella.<sup>70</sup> Authors highlighted that the proportion of children hospitalized with varicella and neurological complications was not significantly lower in the post-vaccine versus the pre-vaccine program era; however, the percentage of children with seizures (including febrile seizures) was significantly reduced (the VARICOMP study).<sup>70</sup>

In Turkey, most patients hospitalized were aged  $<3$  y, with the majority being  $\leq 1$  y.<sup>64</sup> The majority of hospitalized cases were reported in the spring and early summer months, and hospitalization peaked in May in Turkey, reflecting the seasonal incidence of varicella infection.

Hospital stays due to varicella ranged from 5–8 d (median) in Turkey to 7.5 d (mean) in the UAE. In Turkey, patients with central nervous system complications had the longest duration of hospital stay (9 d) (Table 4).<sup>15</sup> Other

**Table 4.** Hospitalization rate and duration of stay due to varicella.

Study	Study description/Population	Hospitalization rate	Average duration of stay
Turkey			
Dinleyici 2012 <sup>15</sup>	VARICOMP: Children between age 0–15 y hospitalized due to varicella, October 2008 to September 2010	Overall estimated incidence of varicella-related hospitalization: 5.3–6.9 per 100,000 children per year	6 d (median) 11 d in ICU (median)
Dinleyici 2015 <sup>10</sup>	VARICOMP: Children between age 0–15 y hospitalized due to breakthrough varicella, October 2008 to September 2013	NR	8 d (median)
Dinleyici 2016 <sup>*67</sup>	VARICOMP: Varicella-related hospitalization among children aged 1–5 y Pre-UUV era Post-UUV era	6.1–9.1 per 100,000 children per year 3.1–4.3 per 100,000 children per year	NR
Turel 2013 <sup>64</sup>	Study of 186 patients hospitalized with varicella, November 2006 to June 2011	74.2% of patients were aged < 3 y, of which 64.2% were ≤ 1 y	5 d (median)
Kurugol 2011 <sup>14</sup>	Study of 466 cases of breakthrough varicella in vaccinated children, and 723 cases of varicella in unvaccinated children	0.2% of children in the vaccinated group and 0.6% in the unvaccinated group	NR
Koturoglu 2005 <sup>63</sup>	Study of 178 cases in children between 2007 and 2011	NR	6.2 d (mean)
UAE			
Uduman <sup>24</sup>	187 hospitalized during 2000–2004 (pre-UUV era)	NR	7.5 d (mean)
Abro 2009 <sup>62</sup>	Study period March 2005 to February 2008 (pre-UUV era)	NR	7.45 d (mean)
Saudi Arabia			
Almuneef 2006 <sup>21</sup>	Data collection period June 1, 2001, to December 30, 2003 (Pre-UUV era)	Hospitalization rate due to varicella: 2,050 per 100,000 reported cases	NR

ICU, intensive care unit; NR, not reported; UUV, universal varicella vaccine.

\*Denotes gray data.

complications associated with long hospital stays were cerebellitis (8 d), hematologic complications (8 d), and respiratory complications (7 d). The most commonly reported treatments among hospitalized patients with varicella were acyclovir, antibiotics (intravenous and oral), and intravenous immunoglobulin.<sup>15</sup>

There are limited published data on the economic burden of varicella in the Middle East. The SLR identified two studies, conducted in Turkey, that provided evidence on economic burden prior to the implementation of the UUV in 2013. In a retrospective study, the estimated total cost to treat 824 patients hospitalized with varicella between October 2008 and September 2009 in Turkey was US\$ 422,102 (equivalent to US\$ 453,011 in 2017), with median cost of hospitalization of US\$ 338 per patient (equivalent to US\$ 363 in 2017).<sup>15</sup> In the second study of 186 patients hospitalized with varicella between November 2005 and June 2011, median cost of hospitalization was US\$ 283 per patient (US\$ 315 in 2017), and the annual cost for varicella hospitalizations in Turkey was estimated at US\$ 396,200 (equivalent to US\$ 440,369 in 2017).<sup>64</sup>

One study, conducted in Turkey, provided economic evaluations on screening and vaccination. The study concluded that the cost of vaccination without screening was significantly more expensive versus vaccination with screening (US\$ 43,566 [equivalent to US\$ 47,475 in 2017] and US\$ 10,159 [equivalent to US\$ 11,071 in 2017], respectively, for a cost difference of US\$ 33,407 [equivalent to US\$ 36,411 in 2017]).<sup>47</sup>

In a study published in 2017 in Iran, a decision-tree model was used to evaluate the cost-effectiveness of the varicella vaccination program in a cohort of 12-month-old children. The incremental cost-effectiveness ratios per disability-adjusted life years averted were US\$ 17,280 and US\$ 41,531 for one-dose and two-dose regimens, respectively.<sup>68</sup> Based on the assumptions used in the model, the authors concluded that neither the one-dose nor the two-dose vaccination

program would be cost-effective in Iran, although based on the sensitivity analysis, the one-dose vaccination may be cost-effective in a scenario of greater epidemiological burden.<sup>68</sup>

### **Rationale supporting varicella vaccination decision-making in the Middle East**

Currently, a substantial proportion of the population in the Middle East does not have access to varicella vaccination via UUV programs incorporated into NIPs.<sup>4</sup> Understanding the importance of varicella from a public health and economic perspective is critical in supporting UUV decision-making. To help address the data need, this review provides an insight into what is currently known about the clinical and economic burden of varicella in the Middle East.

Data identified in this review indicate that in the absence of a UUV program, the incidence of varicella is increasing over time across the Middle East; based on data from Iraq and Saudi Arabia, incidence increased at a rate of 3–3.7-fold over a 5-y period in the pre-UUV era.<sup>19,22</sup> Seroprevalence identified in the SLR showed a rapid increase in seropositivity in early childhood, tailing off in adolescence, and plateauing in adulthood, indicating that infection rates are highest in early childhood in the Middle East, consistent with the general understanding of varicella epidemiology.

Varicella is often perceived as a mild childhood disease of low severity; however, morbidity can be high, particularly in infants, adults, and immunocompromised people who are at risk of more severe disease and have a higher incidence of complications.<sup>71,72</sup> Consistent with this, the SLR identified studies reporting substantial varicella-related morbidity across the Middle East. Data from Turkey indicated that in the absence of a UUV program 5.3–6.9 children per 100,000 per year were hospitalized due to varicella.<sup>15</sup> Furthermore, general incidence data from Saudi Arabia indicated that



1.5% of patients with varicella experienced complications and approximately 2% of varicella cases required hospitalization.<sup>21</sup> Morbidity in hospitalized patients in the Middle East was high, with a substantial proportion of patients reporting soft tissue/skin infections, bacterial infections, and central nervous system and respiratory complications.<sup>10,15,18,24,62,63</sup> Fatality rates as high as 4.9% were also reported in varicella-hospitalized patients.<sup>62</sup>

In addition to clinical burden, varicella infection also carried a resource and economic burden in the Middle East. Patients hospitalized due to varicella had a median stay of duration of 5–8 d; those patients requiring intensive care had a median stay of 11 d.<sup>10,15,64</sup> In turn, hospitalization due to varicella carried a substantial economic burden – the annual cost of varicella hospitalization between 2005 and 2011 in Turkey was estimated at US\$ 396,200 (equivalent to US\$ 440,368.97 in 2017).<sup>64</sup> This substantial economic burden is not unique to countries in the Middle East and has been observed globally. Recent studies report a significant clinical, resource, and economic burden associated with varicella in countries where UVV programs have not been implemented, such as Poland, Argentina, and Hungary.<sup>73–75</sup> Occurrence of complications and the need for hospitalizations placed demand on health-care resources (e.g., need for medications, tests/diagnoses, health-professional consultations) as well as having an indirect economic impact (e.g., time taken off work to look after children).<sup>73–75</sup>

Although data on the impact of varicella vaccination in the Middle East are limited, the data that are available indicate that the UVV has the potential to substantially reduce the clinical burden of the disease. A Turkish study found that incidence rates were over 2.5-fold higher in unvaccinated compared with vaccinated populations.<sup>14</sup> Data from Saudi Arabia suggested that varicella incidence fell substantially, by approximately 88%, following the introduction of a two-dose UVV program.<sup>11</sup> This fall in incidence observed in the Saudi Arabia study is in a similar range to that reported with other two-dose regimens.<sup>6</sup>

Owing to a lack of published data from the Middle East in the post-UVV era, it is difficult to gain insight into the impact of UVV programs on hard outcomes such as mortality, complication rates, and hospitalization rates in this area. In Turkey, the proportion of children hospitalized with varicella was higher in unvaccinated compared with vaccinated children (0.6% vs 0.2%).<sup>14</sup> Data from Turkey (the VARICOMP study) suggested an approximate twofold reduction in varicella-related hospitalizations in children aged 1–5 y following the introduction of the UVV program.<sup>67</sup> The beneficial impact of vaccination on outcomes is also illustrated by data from other countries, highlighted by a reduction in varicella-hospitalization rate and death.<sup>6</sup> Collectively these data support the introduction of UVV programs from a clinical perspective.

The review only identified one study looking at the cost-effectiveness of a UVV program. This study concluded that neither a one- nor two-dose vaccination program in 12-month-old children would be cost-effective in Iran, based on the assumptions (including epidemiology assumptions) used in the model. However, the authors emphasized that the one-dose schedule may be cost-effective if there was a greater epidemiological burden than that captured in the primary

model; this emphasizes the need for accurate epidemiological data to enable realistic cost-effectiveness analyses and support varicella vaccination decision-making.<sup>68</sup>

Based on results from the SLR, published data on varicella epidemiology and economic burden are relatively sparse in the Middle East. Furthermore, most of the data focussed on pre-UVV data, therefore understanding of the potential impact of inclusion of the varicella vaccine into the NIP is limited in this region. This lack of data may be partially responsible for inhibiting or delaying the introduction of the UVV in the Middle East.

Those countries that do not have the resources to obtain local epidemiology and economic burden data may rely on data from neighboring countries. However, where available, the data are markedly different across the Middle East. For example, incidence in the general population in the pre-UVV era ranged from 73.4 per 100,000 population (Iran, 2007) to 7,590 per 100,000 population (Saudi Arabia, 2003).<sup>19,22</sup> This may in part be due to differences in study design (e.g. age of the study population) as well as variation in surveillance systems and reporting across the region. For example, in some countries such as Iran, Lebanon, and Turkey, varicella is not a reportable or notifiable disease,<sup>56,76,77</sup> therefore incidence rates associated with morbidity/mortality, and consequently burden of disease, may be underestimated. Furthermore, differences in climate and urbanization, which influence infection rates, may also contribute to the observed variation.

This variation in epidemiology is not unique to this review or to the Middle East. Standardized incidence rates for overall populations of 300 to 1,291 per 100,000 per year have been reported in Europe, which lies within the range observed in this review of epidemiology in the Middle East.<sup>6</sup> However, this variation in data, due to a variety of potential factors, makes it difficult to compare data from different countries and to extrapolate data between countries.

As demonstrated by the Iran cost-effectiveness analysis that highlights the need for accurate epidemiology data, lack of local-data makes varicella vaccination decision-making very challenging. A further potential challenge to the implementation of UVV programs is that varicella is currently perceived as being less important than other infectious diseases, which in part may be due to an underestimation of the disease burden, lack of awareness, and/or poor reporting. Therefore, progress on improving surveillance and reporting in the region should be sought if resources allow. Taken together, such improvements are likely to lead to a better understanding of the burden of disease, which will initially mean that an increase in cases will be noted. This is likely to be a positive outcome and lead to increased awareness and acceptance of varicella as a common, important, vaccine-preventable disease.

There are a number of limitations in our review relating to the interpretation of the burden of varicella in the Middle East: the limited-published data in the region, a high likelihood that the data available is an underestimate of the burden and costs of varicella, and the fact that many countries in the Middle East are not represented in the manuscript, as no data have been collected or analyzed.

In summary, the limited data identified for the Middle East indicate that in the absence of a UVV program the incidence of varicella infection is increasing across the region, which in turn will increase the already substantial varicella-associated morbidity, hospitalizations, and economic burden. Due to the large degree of variation in epidemiology data and the need for accurate data to determine the true cost-effectiveness of immunization programs, varicella needs to be better understood in the Middle East. In addition, there is a need for improved surveillance and reporting (where possible), changes in care-seeking behaviors, and increased public awareness. Hopefully, with such changes, decision-makers will recognize the importance of varicella and the need for inclusion of varicella vaccine in their NIPs.

## Methodology and data sources

A global SLR on varicella was conducted and publications with data from Middle East countries (including Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, the UAE, and Yemen) were identified and reviewed for this article.

In brief, key biomedical electronic literature databases were searched using a comprehensive search strategy to identify studies that provided relevant data on the epidemiology, economic burden, and coverage of vaccination programs associated with varicella. Databases used were: The Excerpta Medica Database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), Index Medicus for the WHO Eastern Mediterranean Region (IMEMR), Latin American and Caribbean Health Sciences Literature (LILACS), and Health Literature Libraries and Information Services (HELLIS). Studies that published data from database inception (pre-1966) up to the search date, February 1, 2016, were captured. The study was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.<sup>78</sup> Further details are given in the **Supplemental Online Material**.

Abstracts and subsequently full texts were screened based on the predefined eligibility criteria specified in the protocol. Studies evaluating individuals (of any age) with primary and/or breakthrough varicella infection were included as part of the review. The SLR was restricted to papers published in the English language.

Searches were also conducted on country-specific/global websites to address any data gaps. Gray data, such as country-specific health bulletins and locally published manuscripts, were also sourced.

## Acknowledgments

Medical writing assistance was provided by Anil Dandu, PhD, and Aruna Jeans, PhD, of Parexel and was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA. Project Management assistance was provided by Tracey Weiss of Merck & Co., Inc., Kenilworth, NJ, USA.

## Disclosure of potential conflicts of interest

N Al Kaabi, M Al-Qaseer, and FMAS Al-Olama have nothing to disclose. EC Dinleyici reports grants from GlaxoSmithKline Vaccines and Pfizer

Vaccines outside the submitted work. WA Hayajneh has nothing to disclose. M Loulou, T Ndao, and LJ Wolfson are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

## Funding

The study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The authors take full responsibility for the scope, direction, and content of the manuscript, and have approved the submitted manuscript.

## Author contributions

N Al-Kaabi, M Al-Qaseer, and LJ Wolfson have contributed to the conception, design or planning of the study. N Al-Kaabi, FMAS Al-Olama, EC Dinleyici, M Loulou, LJ Wolfson, and AR Bizri were involved in data acquisition. LJ Wolfson, EC Dinleyici and WA Hayajneh were responsible for analysis of the data. M Al-Qaseer, LJ Wolfson, and EC Dinleyici were involved in interpretation of the data. FMAS Al-Olama, EC Dinleyici, and WA Hayajneh contributed to writing the manuscript. All authors had full access to the data, were involved in critically reviewing or revising the manuscript and gave final approval before submission.

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