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REVIEW

Epidemiology of Varicella Zoster Virus and Herpes Zoster Virus in Gulf Cooperation Council Countries: A Review of the Literature

Selim Badur · Onur Ozudogru · Mansour Khalaf · Serdar Ozturk · Sarah Albreiki · Salah Al Awaidy · Adriana Guzman-Holst

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ABSTRACT

Introduction: The reactivation of varicella zoster virus (VZV) in previously infected individuals can cause herpes zoster (HZ), which is characterized by a localized, painful dermatomal rash. While there is a global trend of increasing HZ cases, there is a lack of research examining the epidemiology of HZ within the Gulf Cooperation Council (GCC) countries. Therefore, we aimed to critically appraise evidence on VZV and HZ epidemiology in the GCC countries and identify gaps in the current literature.

Methods: A literature review was conducted via a comprehensive appraisal of the literature. PubMed and local-language journals were searched to identify articles related to HZ and VZV published up until 31 January 2022, with a sole focus on the GCC countries. Included studies reported on surveillance data, seroepidemiology, and patient outcomes for HZ and VZV, and comprised primary data reports, case series, case reports, narrative and systematic literature reviews, studies reporting HZ incidence or prevalence, and Ministry of Health reports.

Results: Thirteen studies were found that reported on VZV seroprevalence in Saudi Arabia, the United Arab Emirates (UAE), and Qatar, ranging from 15.0% to 92.2%, while no data were identified for Bahrain, Kuwait, or Oman. There was very limited country-wide information on the incidence of HZ in GCC countries, and three identified studies reported HZ prevalence as seen in a single clinic, ranging from 0.62% to 2.3%. A single study from Saudi Arabia and government surveillance data reported on the impact of VZV vaccination on VZV infection, though there was no evidence on the impact of VZV vaccination on HZ.

Conclusion: There is a clear gap in the literature regarding the incidence of HZ infection, and the impacts of HZ and VZV vaccinations in the GCC countries. Further research into the epidemiology of HZ is necessary to inform the implementation of vaccination programs in the GCC countries.

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S. Badur · S. Ozturk
GSK, Istanbul, Turkey

O. Ozudogru
GSK, Dubai, United Arab Emirates

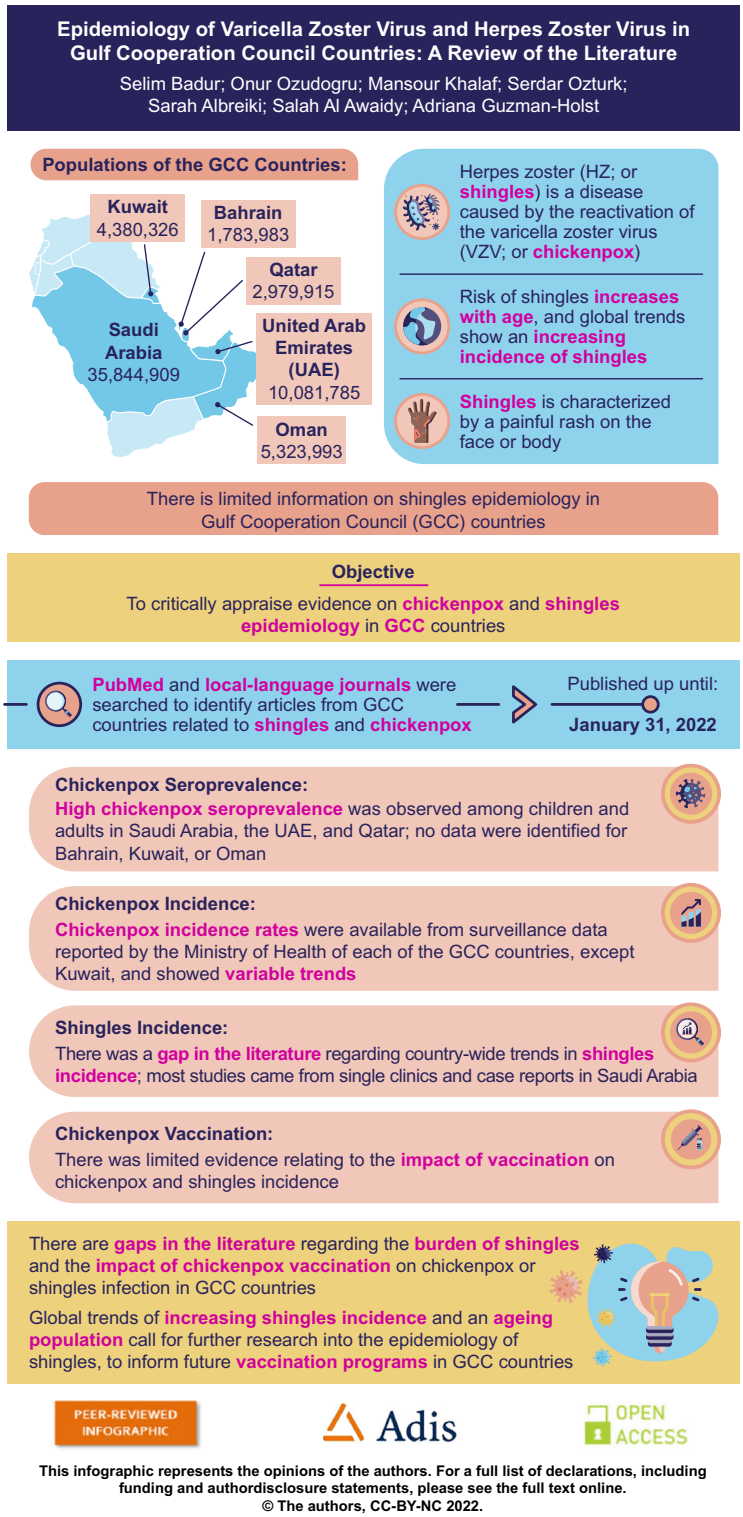
M. Khalaf
GSK, Jeddah, Saudi Arabia

S. Albreiki
King Fahd Hospital of the University, Dammam, Saudi Arabia

S. Al Awaidy
Ministry of Health, Muscat, Oman

A. Guzman-Holst (✉)
GSK Vaccines, 20 Avenue Fleming, 1300 Wavre, Belgium
e-mail: adriana.x.guzman@gsk.com

Graphical Abstract:



Keywords: Chicken pox; GCC countries; Herpes zoster; Shingles; Varicella; Varicella zoster virus

DIGITAL FEATURES

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Key Summary Points

In light of the lack of reviews examining the epidemiology and burden of herpes zoster (HZ) in the Gulf Cooperation Council (GCC) region, a literature review was conducted to critically appraise the evidence on varicella zoster virus (VZV) and HZ epidemiology in the GCC countries: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE).

Several studies reported an overall high seroprevalence of VZV in Saudi Arabia, the UAE, and Qatar; no data were identified from Bahrain, Kuwait, or Oman.

VZV incidence rates reported by surveillance data from governmental bodies showed variable trends.

There were notable gaps in the literature regarding country-wide trends in HZ incidence and the impact of VZV vaccination on VZV and HZ infection.

Further research into the burden of HZ in the GCC countries is needed to inform health policy and future HZ vaccination programs.

INTRODUCTION

Varicella, commonly known as chickenpox, is caused by varicella zoster virus (VZV) infection and characterized by fever, viremia, and scattered vesicular lesions of the skin. Following primary infection, which usually occurs in childhood, VZV becomes latent in ganglionic neurons and can reactivate to cause herpes zoster (HZ; shingles), which typically manifests as a localized, painful, dermatomal rash [1]. HZ can have a substantial negative impact on the physical and mental well-being of patients [2], and the acute presentation of HZ can markedly reduce health-related quality of life [3]. HZ is also associated with many complications, including postherpetic neuralgia (PHN), which results in persistent pain in the area previously affected by HZ for more than 90 days after rash onset [4]. Approximately 10% of people aged $\geq$ 50 years with HZ develop PHN [5], and the chronic pain that can occur as a result can lead to a considerable impairment of patients' quality of life and ability to function in their normal activities [6].

The risk of HZ increases as a result of declining cell-mediated immunity to VZV, which is associated with advancing age or an altered immune system [1, 3]. In the USA alone, it is estimated that approximately one million new cases of HZ are diagnosed each year, with the rate of incidence being significantly higher among individuals aged > 50 years [7]. Additionally, trends of increasing incidence of HZ have been observed across several countries over the past few decades, and as the global population ages due to increasing life expectancy, the global health burden of HZ is also likely to increase [8].

Strategies to alleviate the burden of VZV and HZ include vaccination. Currently, 36 countries and regions worldwide have introduced universal VZV vaccination, resulting in a reduction in incidence of the varicella disease and hospitalizations [9]. However, despite its established effectiveness, many higher socioeconomic status countries do not routinely vaccinate children against VZV [10], and some countries have only introduced VZV vaccination within high-

risk groups or at the regional level [11]. Comparatively, access to HZ vaccination is primarily limited to economically developed countries, and even among these countries that have licensed the HZ vaccine, few have implemented HZ vaccination into their national immunization programs [12].

The Gulf Cooperation Council (GCC) is a political and economic alliance of six Middle Eastern countries: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE), which was established in 1981. The total population of the GCC countries, as of 2022, is 58,862,475 [13]. Numerous GCC countries have introduced VZV vaccination into their national immunization programs over the last decade (Table 1), such that over 50% of the Middle Eastern population now reside in countries offering universal VZV vaccination [14]. However, vaccination against HZ is not currently included in the vaccination programs of any of the GCC countries, though it has recently been recommended in Saudi Arabia prior to official authorization [15].

It is essential for health policymakers to be informed on the HZ burden of disease, to facilitate the implementation of vaccination programs across the GCC countries. However, to our knowledge there have been no reviews of studies examining the epidemiology and burden of HZ in the GCC countries. As such, here we aim to summarize and critically appraise evidence on VZV and HZ infection and epidemiology in the GCC countries, and to identify gaps in the current literature.

METHODS

Literature Review

PubMed and local-language journals were searched to identify articles related to HZ and VZV, published up until 31 January 2022. The search strategy main string used the following terms: ("Herpes Zoster"[Mesh] OR "herpes zoster" OR "shingles" OR "zoster" OR "varicella zoster") AND ("Saudi Arabia" OR "Saudi" OR "Kingdom of Saudi Arabia" OR "Gulf" OR "Kuwait" OR "United Arab Emirates" OR "Bahrain" OR "Oman" OR "Qatar"). The geographical scope of the review focused solely on GCC countries and searches were conducted in English and Arabic. Information from relevant articles was extracted descriptively by two reviewers and references cited by the screened articles were manually reviewed for relevance using a "snowballing" approach [16]. The review was conducted via a comprehensive and critical appraisal of the literature.

Included studies comprised articles reporting surveillance data, seroepidemiology, patient outcomes for HZ and VZV, and impact of VZV vaccination on VZV and HZ infection. Primary data reports, case series, case reports, narrative and systematic literature reviews, and studies

Table 1 VZV national immunization programs in GCC countries

Country	Population [13]	Dose [14]	Schedule [14, 15]	Introduction to NIP [14]
Bahrain	1,472,233	Two doses	1 year; 3 years	2015
Kuwait	4,268,873	Two doses	1 year; 2 years	2017
Oman	4,576,298	One dose	1 year	2010
Qatar[a]	2,695,122	Two doses	1 year; 4–6 years	2010
Saudi Arabia	36,408,820	Two doses	1.5 years; 4–6 years	2008
UAE[a]	9,441,129	Two doses	1 year; 5–6 years	2009

GCC Gulf Cooperation Council, *NIP* national immunization program, *UAE* United Arab Emirates, *VZV* varicella zoster virus

[a]Countries in which VZV vaccination is available in the private sector

reporting percentage, proportion, incidence, or prevalence of patients with HZ (within healthy, at risk, and immunocompromised populations) were also included. Studies including patients of all ages were included, and adults were defined as those ≥ 18 years of age. Additionally, reports from the Ministry of Health (MoH) of the GCC countries were included, which reported data on VZV epidemiology.

Any studies that fell outside of the scope of the specified diseases and geographies were excluded. Any articles regarding VZV case definition and clinical management were also excluded, and only studies concerning HZ case definition and clinical management were considered for inclusion.

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.

RESULTS

Varicella Zoster Virus

VZV Seroprevalence

While there were no data found on VZV seroprevalence in Bahrain, Kuwait, or Oman, we found a number of studies reporting VZV seroprevalence for other countries within the GCC countries among different populations (Table S1). The majority of the studies were

Table 2 VZV surveillance data in GCC countries

Year	Incidence rates of VZV cases per 100,000 population				
	Bahrain[a]	Saudi Arabia[b]	Oman[c]	Qatar[d]	UAE (Abu Dhabi)[e]
2000	–	–	674.1	–	–
2005	–	–	700.5	–	–
2008	–	–	–	–	1902.1
2009	–	–	–	–	846.6
2010	–	–	633.7	–	–
2012	–	64.1	–	–	–
2013	304.5	36.5	–	–	425.4
2014	231.2	26.7	–	–	409.5
2015	127.1	19.0	501.6	234.8	–
2016	127.1	14.3	416.8	215.5	–
2017	53.1	13.9	417.6	179.4	391.1
2018	143.9	13.1	200.8	–	302.2
2019	88.9	–	220.3	–	–
2020	–	–	67.0	–	–

GCC Gulf Cooperation Council, *MoH* Ministry of Health, *UAE* United Arab Emirates, *VZV* varicella zoster virus

VZV surveillance data are not available for Kuwait. The VZV incidence rates for Oman, Qatar, and the UAE (Abu Dhabi) were originally reported as the number of VZV cases per year and were converted to incidence per 100,000 population using the population estimated for each year from the United Nations World Population Prospects [61] and World Population Review [62]. [a]Reported by the MoH in Bahrain [63]. [b]Reported by the MoH in Saudi Arabia [64, 65]. [c]Reported by the MoH in Oman [61, 66]. [d]Reported by the Qatar Planning and Statistics Authority [61, 67]. [e]Reported by the UAE Department of Health [62, 68–70]

from Saudi Arabia, which is the most populous of the GCC countries.

Five studies in Saudi Arabia have investigated the seroprevalence of VZV among children and adults, as well as among pregnant women [17–21]. For example, one study reported a VZV seroprevalence of 68% in children and 90% in adults in 1989 among 224 children aged 1–-15 years and a total of 452 healthy adult male blood donors and pregnant women [20]. Another study of 926 Saudi pregnant women, investigating seroprevalence rates of pathogens that cause infection in utero, reported that 74.4% had antibodies against VZV [19].

Four studies in Saudi Arabia have reported the seroprevalence of VZV among different professions, including soldiers and healthcare workers [22–25]. Saudi National Guard soldiers were found to have an 88.5% seropositivity rate for antibodies to VZV [25]. Moreover, in a study of the multinational healthcare workers of a Saudi Arabian Hospital in 1999, 1303 (64%) reported a previous history of VZV infection and 744 (36%) had a negative or unknown history of VZV infection; among those who disclosed a negative or unknown history of VZV infection and underwent antibody testing, 181 (83%) had antibodies to VZV [23]. Furthermore, in a hospital in Riyadh, 11.3% of healthcare workers were reported to be susceptible to VZV infections [22].

In the UAE, two studies have reported VZV seroprevalence among children, adults, and young adult students (defined as 16–33 years). One study found that 126 (19.4%) of 648 healthy individuals aged from 8 months to 47 years were susceptible to VZV infection and had no detectable antibodies, while the overall adult seroprevalence rate was 81.3% [26]. Another study of 182 Emirati students with a mean age of 21.2 years between 2011 and 2012 described a VZV seroprevalence of 88% (n = 161) [27].

Two studies were also found for Qatar reporting the seroprevalence of VZV among children and adults, as well as healthcare workers. The VZV seroprevalence was reported to be 41% in children aged 1–14 years and 47% in adults aged 20–39 years [28, 29]. Among healthcare workers in a community hospital in Dukhan between 2012 and 2015, the seropositivity for VZV was found to be 92.2% [30].

VZV Incidence

There are VZV surveillance data available for most of the countries in the GCC countries, which report the number of cases or incidence rates of VZV infection (Table 2). These data can be found from the MoH of Bahrain, Oman, and Saudi Arabia, the government data portals of Qatar, and the Department of Health of the UAE. However, no surveillance data on VZV infection were available for Kuwait.

We found few studies that reported the incidence of VZV at a national level (Table S2). A couple of articles described the incidence of VZV in Qatar. One reported 574 VZV cases in Qatar in 2014 with an incidence of 259.1 per 100,000, which was higher than that of 244.5 and 237.4 per 100,000 in 2012 and 2013, respectively [31]. Another review citing the 2007 Qatar Annual Health Report, also found that VZV cases among non-Qatari individuals (82.5%) and males (71%) was higher than that of Qataris (17.5%) and females (29%), respectively, as a result of non-Qatari and male individuals comprising the majority of the population [28, 29].

One other study was found that described the incidence of VZV in Al-Ain, a city within the UAE. The annual number of reported cases from 2000 to 2004, varied from 373 to 790 per 100,000 population. Of these cases, 89% occurred in children less than 15 years old, and the mortality rate among hospitalized children was 1.1% [32].

VZV Vaccination

There is little information in the literature regarding the effect of VZV vaccination on VZV infection in GCC countries (Table S2). One study conducted in Eastern Saudi Arabia reported that, following the introduction of the childhood VZV vaccine in 1998 and the vaccine being made mandatory in 2008, the total number of VZV cases decreased from 10,070 in the pre-vaccination period to 1577 cases in the mandatory vaccination period; with the incidence rate decreasing from 739.8 to 88.1 per

100,000 population between 1994 and 2011 [33].

However, trends relating to the potential effect of VZV vaccination can be observed in the surveillance data of some GCC countries where data are available prior to and after the implementation of VZV vaccination (Table 2). For instance, there is a sharp decrease in the incidence rates of VZV in Bahrain in 2015, and a decline in the number of cases of VZV in the UAE in 2009 and 2013, which coincide with the introduction of VZV national immunization programs within these countries. Nevertheless, a direct causation cannot necessarily be assumed as there is no clear trend observed for other countries, such as Oman where the number of cases of VZV seem to increase after 2010 despite the introduction of VZV vaccination in the national immunization program in this year. There were also no publicly available data on VZV vaccination and coverage, or further details on the methodology, population, and coverage of the surveillance data for each of these countries at the time of this review.

VZV Case Reports

There were no data identified on VZV seroprevalence or incidence in Kuwait and most clinical cases described the complications associated with VZV infection [29], while a single case study reported the congenital anomalies following VZV infection during pregnancy [34]. There were also several case reports of VZV found for Saudi Arabia, many of which described rare complications among immunosuppressed patients (Table S3). For example, one described a rare association of transverse myelitis and VZV infection in a 17-year old female with sickle cell disease, where transverse myelitis developed as a complication of VZV infection [35]. Another reported the occurrence of severe autoimmune hepatitis in a 23-year old male following VZV infection, where the liver damage was hypothesized to be caused by an immune cross-reaction to viral proteins [36].

Herpes Zoster

HZ Incidence and Prevalence

There is a scarcity of research examining the incidence and prevalence of HZ in the GCC countries. Of the identified studies, most were conducted in Saudi Arabia and reported the prevalence of HZ as seen in a single clinic (Table S4).

Three retrospective studies of different sizes and investigating different time periods came from dermatology clinics. One, which included 22,749 cases between 1988 and 2006, reported an HZ prevalence of 0.62% ($n = 141$) [37]. Another, which included 1244 patients from the city of Jeddah who attended the dermatology clinic in 2017, identified 81 (6.5%) viral infections, of which 29 (2.3%) were characterized as HZ [38]. Finally, a study of a dermatology clinic at a hospital in the Al-Baha region of Saudi Arabia between 2014 and 2018 reported a HZ prevalence of 0.99% ($n = 125$) from a total of 12,600 patients seen within the 4 year study period [39]. One retrospective analysis was also identified that was conducted in an adult hematology ward, and reported 4 HZ diagnoses, with one diagnosis confirmed by a skin biopsy [40].

Furthermore, little data on HZ incidence or prevalence were available for the other GCC countries. However, the Ministry of Public Health in Qatar did report a total of 2815 HZ cases between 2012 and 2017, and estimated the mean incidence of HZ to be 19/100,000 population. The incidence of HZ was also reported to have increased from 9.8/100,000 in 2012 to 36.2/100,000 in 2017 [41].

There were no studies found for the GCC countries on the impact of VZV vaccination on the incidence of HZ, and thus this remains a significant gap in the current literature.

HZ Case Reports

Although few studies were found that investigated HZ incidence, there were a few case reports of complications associated with HZ (Table S5). Two case reports from Saudi Arabia described uncommon complications that resulted from HZ infection. One described the cases

of a 63-year old diabetic male and a 58-year old male with type II non-insulin dependent diabetes who both presented with prominent motor weakness of the abdominal muscles following HZ disease, and suggested that muscle weakness is an often overlooked component of HZ disease [42]. Another reported a case of Ramsay Hunt syndrome that evolved to include multiple cranial neuropathies in an immune compromised 32-year old male diagnosed with HZ who had undergone a liver transplant 10 years prior [43].

A case report regarding a rare complication of HZ infection in a patient in Oman was also found, even though no incidence or prevalence data were available for this country. This report described the occurrence of multiple granuloma annulare lesions with simultaneous active HZ infection in a 54-year-old female with a history of breast cancer [44].

DISCUSSION

This study aimed to summarize and critically appraise literature on VZV and HZ infection epidemiology, as well as identify gaps in the literature for the GCC countries.

We found several studies in the literature examining the seroprevalence of VZV in the GCC countries, primarily in Saudi Arabia as well as the UAE and Qatar. Overall, substantial VZV seroprevalence was observed across the GCC countries among children, and seroprevalence was particularly high among healthcare workers in Saudi Arabia, even among those with no or unknown history of VZV infection. In comparison with VZV seroprevalence data available for the GCC countries, global trends in VZV infection show similar patterns. For instance, serological studies across Europe have found that VZV antibodies are rapidly acquired during early life and most individuals are seropositive by ages 15–19 years. In Italy, Ireland, Spain, England, and Wales, just over 5% of individuals aged 20–29 years were seronegative for VZV, and among healthcare workers and medical students, VZV seroprevalence was reported to range from 87.8% to 99.6% [45].

Comparatively, there were little VZV incidence data available for the GCC countries, and most came from the surveillance data reported by governmental bodies. The incidence rates of VZV reported from the surveillance data of Bahrain, Qatar, and the UAE (Al-Ain) fall mostly within the range of that reported across Europe (164–1291 per 100,000 population, with the majority of incident cases occurring in children) [45]. Surveillance data from the other GCC countries reported overall case numbers of VZV.

While there were sources available reporting the seroprevalence and incidence of VZV within the GCC countries, there is a clear lack of information available regarding HZ. Most of the identified studies relating to HZ in this review originated from Saudi Arabia and reported HZ prevalence from single clinics. Therefore, research examining country-wide trends in HZ infection represents a noticeable gap in the literature for the GCC countries.

The lack of studies identified in this review relating to HZ incidence and prevalence reflects the lack of evidence found in the Middle East by a recent meta-regression study examining trends in global HZ infection [46]. This may be because HZ is regarded as a low health priority in these countries. Global incidence rates of HZ have been reported to range from 3 to 5 cases per 1000 person-years, and 5.23–10.9 cases per 1000 person-years in individuals $\geq$ 50 years of age [8, 47]. With regional rates of HZ ranging from 6.6–9.03 per 1000 person-years in North America, 5.23–10.9 per 1000 person-years in Europe, and 10.9 per 1000 person-years in the Asia–Pacific region [47].

Furthermore, a trend of increasing HZ incidence has been observed over the last few decades, irrespective of region [8, 47]; incidence data in the $\geq$ 65 years age cohort from the USA, Japan, and Australia demonstrated an average annual increase in HZ of between 2.35% and 3.74% [48]. The global increase in HZ incidence is expected to be exacerbated by the world's ageing population and greater life expectancy, as older individuals are increasingly constituting a larger proportion of the total population of nearly every country. An estimated increase of between 83% and 376% by 2030 is expected in the number of annual incident cases of HZ

among those aged ≥ 65 years in the USA, Japan, and Australia, and similar trends in HZ infection are likely to reflect a rising humanistic and economic burden on patients and the healthcare systems of many countries [48].

While most GCC countries have introduced VZV vaccinations into their national immunization programs, there is limited evidence relating to the impact of vaccination on incidence rates of VZV, and an absence of research evaluating the impact of VZV vaccination on the incidence of HZ. There has been some debate on whether VZV vaccination confers protection against HZ, and several studies have reported inconclusive evidence on the effect of VZV vaccination on HZ. Studies conducted during the post-varicella vaccination era in the USA report inconsistent results [8], while multiple studies examining trends in HZ incidence over long periods found that incidence rates were increasing across all age groups, as well as in individuals older than 65 years, prior to and after the implementation of VZV vaccination programs [49, 50]. Similarly, increasing rates of HZ incidence have been reported in Taiwan, Spain, and Japan, often in the absence VZV vaccination programs [51–53].

On the other hand, effective HZ vaccines are available and are known to reduce the burden of disease and associated complications in older individuals, and have a positive impact on patients' quality of life [47]. There are currently two vaccines available for the prevention of HZ, including a zoster vaccine live (ZVL) and a recombinant zoster vaccine (RZV); the safety and efficacy of both vaccines has been demonstrated in clinical trials, as well as in several real-world effectiveness studies [54]. In particular, RZV has been shown to be effective in individuals aged ≥ 50 years and in selected immunocompromising conditions [54], and has been demonstrated to have a significant positive impact on quality of life [55]. Currently, RZV is preferentially recommended by the Advisory Committee on Immunization Practices (ACIP) for immunocompetent adults aged ≥ 50 years [56]. RZV is recommended in immunocompromised individuals aged ≥ 19 years in the USA, individuals aged ≥ 50 years in Canada, individuals aged ≥ 50 years as well as immunocompromised individuals aged 18–-49 years in Australia, and individuals aged ≥ 60 years in Germany [57–60] to protect against the clinical and economic burden of HZ. As such, the wider distribution of HZ vaccines may aid in combating the adverse impacts of HZ on the growing population of older individuals around the world [54].

CONCLUSIONS

There are multiple studies that report on VZV seroprevalence and incidence in the GCC countries, particularly in Saudi Arabia, though there are notable gaps in the literature regarding country-wide data on HZ incidence, and the impact of VZV vaccination on HZ in the GCC countries. In light of the global trends being observed of increasing HZ incidence, compounded by the world's ageing population, further research is essential in increasing understanding of the epidemiology of HZ in the GCC countries, to inform key health policy-makers and facilitate the implementation of HZ vaccination programs in this region.

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Compliance with ethics guidelines. 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.

Data availability. The authors confirm that the data supporting the findings of this study are available within the article. Most of the cited peer-reviewed publications of this study are available via PubMed, and the grey literature was derived from resources available in the public domain.

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