REVIEW ARTICLE

Varicella infection in the Middle East: Prevalence, complications, and vaccination

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Varicella (chickenpox) is the primary infection of varicella-zoster virus (VZV), it is a mild self-limiting infection, but it is also highly contagious and can cause severe complications among high-risk group of individuals. It is usually a childhood infection providing lifelong immunity, but adults without varicella history are also susceptible to infection. High-risk group of individuals is more likely to develop serious complications. Varicella vaccine was introduced to protect this group of individuals and to prevent epidemic spread of VZV infection in a community. Thus, it was added to the recommended vaccination schedules for children in most developed countries. This review aimed to outline varicella status, seroprevalence, complications, and vaccination in the Middle East region. Based on our findings, children were the most affected age group, but there are also adult cases due to high number of expatriates, especially in Gulf Cooperation Council countries. Central nervous system involvements and skin diseases followed by varicella pneumonia were the most varicella-associated complications. Varicella vaccine was introduced in most Middle East countries, either mandatory by the Ministries of Health or optional in the private clinics. Few numbers of studies have reported an obvious reduction in varicella prevalence, hospitalizations, and deaths in the Middle East following varicella vaccination. A basic database about varicella infection before the initiation and implementation of a vaccination policy is essential to determine the target group of individuals. As far as our knowledge, this is the first review about varicella infection in the Middle East.

Key words: Chickenpox, genotypes, Middle East, prevalence, vaccination, varicella, varicella-zoster virus

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INTRODUCTION

Varicella-zoster virus (VZV) is one of the human herpes viruses (HHVs); its official name is known as HHV-3, a member of DNA-containing *Herpesviridae* family. VZV causes varicella (chickenpox) as a primary infection and herpes zoster (HZ) after the reactivation of a latent VZV. Varicella is a childhood illness with highest incidence between 1 and 9 years of age, characterized by fever and a generalized pruritic vesicular rash. It is usually a mild-to-moderate illness in immunocompetent individuals but sometimes can cause serious complications such as central nervous system (CNS) involvement, pneumonia, secondary bacterial infections, and death. The severity of varicella is highly associated with pregnancy, infancy, elderly, and among immunocompromised individuals.[1-3] Varicella is a worldwide infection, is more prevalent in temperate climates than tropical ones, and often occurs in late winter and spring seasons.[4,5] Furthermore, varicella is transmitted by the respiratory aerosols from infected individuals and by direct contact with skin lesions of individuals affected by VZV.[6,7]

Varicella infection usually results in lifetime immunity, and varicella reinfection is very rare; however, in immunocompromised individuals, the reactivation of latent VZV results in more serious painful illness, the HZ known also as shingles.[8,9] Universal vaccination against primary VZV infection was first introduced in the United States in 1995, a live-attenuated varicella vaccine, and then in the same year, the World Health Organization (WHO) adopted a mass vaccination against varicella in most developed countries.[10-12]

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In developing countries generally and in the Middle East particularly, the status of varicella infection and vaccination is unclear. The Middle East is a transcontinental region centered on Western Asia and Egypt and includes the Gulf Cooperation Council (GCC) countries (Saudi Arabia, Kuwait, Bahrain, Qatar, Oman, and United Arab Emirates [UAE]), in addition to Iraq, Yemen, Syria, Jordan, Lebanon, Palestine, Israel, Iran, Turkey, and Cyprus. Some Middle East countries have reported on varicella burden, seroprevalence, complications, and eventually the cost of medical care of hospitalization. To develop a vaccination protocol and appropriate preventive health care measures against a disease in different countries, it is very important to know the seroprevalence of any disease for an individual country.[13] Accordingly, this review will look over the seroprevalence of varicella infection among the general community, premarital women, pregnant women, medical students, and health-care workers (HCWs) in each country of the Middle East. The seasonality of varicella, complications, vaccination program, and VZV genotypes is outlined according to the availability of published data.

SAUDI ARABIA

The seroprevalence and the age of primary VZV infection were investigated early in Saudi Arabia in 1989 on 224 Saudi children aged from 1 to 15 years and on 452 healthy adult male blood donors and pregnant women.[14] The overall seroprevalence of VZV was 68%. The study also showed a progressive increase of immunoglobulin G (IgG) antibodies against VZV with age as 90% of adults showed the presence of antibodies.[14] Another study investigated the seroprevalence of VZV among Saudi National Guard soldiers to determine the cost saving of antibody tests before mass vaccination program.[15] The seropositivity rate for antibodies to VZV was 88.5%, and the cost saving for prevaccination screening was effective by 32%.[15] In addition, a study on 926 Saudi pregnant women has reported that 74.4% of Saudi pregnant women have IgG against VZV.[16]

A seroprevalence study of VZV was also carried out in Hai Al-Jamea Hospital, Jeddah, Saudi Arabia, among diabetic and nondiabetic patients with acute peripheral facial palsy, over a period of July 2000–December 2001.[17] The VZV seroprevalence was significantly higher in patients than in the healthy control group.[17] Another study aimed to evaluate retrospectively the trend of varicella at the Preventive Medicine Department of the Armed Forces Hospital of the Southern Region of Saudi Arabia from 2007 to 2012.[18] The study showed that most cases occurred in children <15 years of age. The number of varicella cases was slightly higher in males than females and that varicella peaked in spring season, between March and April.[18]

Furthermore, a study was initiated in 1999 to assess varicella status in multinational HCWs of Saudi Arabian Hospital.[19] The survey was confined to HCWs who had direct contact with patients. A total of 1303 (64%) HCWs reported previous history of chickenpox, 519 (25%) were unaware of their status, and 225 (11%) reported no contact history. Among those who have disclosed a negative or unknown history of chickenpox, 181 (83%) were immune to varicella IgG.[19] Another seroprevalence study conducted among HCWs in a hospital in Riyadh showed that 11.3% were susceptible to varicella.[20] It was also found that housekeeping staff was the most susceptible group for varicella, and the study recommended vaccination of susceptible HCWs to prevent VZV transmission.[20]

A prospective study conducted at the King Abdul-Aziz Medical City, Riyadh, on chickenpox cases from 2001 to 2003 has investigated the development of complications after VZV infection.[21] Of 3802 reported chickenpox cases, 2984 (78%) occurred in children <15 years of age and 818 (22%) occurred in adults. Among all chickenpox cases, 78 (2%) required hospitalization, and the complications were less common in children (36/2984, 1.2%) as compared to adults (14/818, 1.7%). The overall fatality rate was 0.05%. The authors recommended the introduction of varicella vaccine within the National Immunization Program.[21]

In terms of varicella vaccination, the childhood varicella vaccination was introduced in Saudi Arabia population in 1998 and become mandatory in January 2008.[22] The varicella vaccination program had significantly reduced the annual incidence rate of childhood disease between 1994 and 2011.[22] There was also a report showing a decreasing trend of chickenpox due to the introduction of varicella zoster vaccination in 2008.[18]

KUWAIT

Most of the clinical cases published in Kuwait described the complications after VZV infection; there were no data about VZV seroprevalence in Kuwait. A case study described the complications of VZV infection during pregnancy.[23] The case represented a congenital anomalies following varicella infection of a pregnant woman in the 8th week of gestation. Although the baby had VZV antibodies and characteristics of the congenital varicella syndrome, no vesicles or depigmented skin areas were seen.[23] Another case study conferred the serious complications following varicella infections by presenting a case of a child who developed idiopathic purpura fulminans and varicella gangrenosa of the both hands, toes, and integument, despite that varicella gangrenosa is a rare complication of the disease.[24]

Moreover, a case study on a 6-year-old boy highlighted the association of chickenpox with complications of purpura fulminans.[25] The child presented with purpura of the legs that rapidly progressed to other parts of the limbs and the buttocks. The authors suggested an early and aggressive treatment of postchickenpox purpura fulminans might reduce the mortality and morbidity associated with this condition.[25] Another study highlighted an outbreak of chickenpox among susceptible staff in an Intensive Care Unit (ICU).[26] A 4-year-old child diagnosed with chickenpox-associated encephalitis was admitted to the ICU and transferred 12 h later to Infectious Disease Hospital. Three unvaccinated ICU staff nurses developed chickenpox 16–21 days following exposure, and they were also transferred to Infectious Diseases Hospital. Authors suggested that some precautions should be taken during patient isolation, exclusion of susceptible staff from attending the affected patient, preemployment anti-VZV-IgG screening, and vaccine coverage of staff to prevent the occurrence of such outbreak.[26]

Furthermore, a case study reported morphologic changes in fibroadenoma of a 25-year-old woman breast recovering from chickenpox with suspicious cytology in fine needle aspiration smears.[27] It was concluded that VZV could produce morphologic alteration mimicking a malignancy, by which pathologists should be aware of these changes to avoid a false-positive diagnosis.[27] Additional case study reviewed postvaricella musculoskeletal complications in eight children who were treated between 2001 and 2009.[28] The observed complications were cellulitis, pyomyositis, osteomyelitis, and gangrene that usually started after 8.8 days of VZV infection. Thus, physicians were advised to be more aware of chickenpox complications and to refer those suffered of early stage complications to specialists.[28]

Regarding VZV genotyping, a study aimed to genotype VZV in samples collected from patients using restriction fragment length polymorphism (RFLP) technique.[29] The predominant genotype was B (86.6%), followed by A (11.7%) and C (1.7%).[29]

VZV vaccination was introduced and available in most private clinics and hospitals of Kuwait since 2008, and from January 2017, varicella vaccination became mandatory as part of the National Immunization Program. There are no reference data regarding the incidence of pediatric varicella in Kuwait before the introduction of varicella vaccine.

UNITED ARAB EMIRATES

A study published earlier in the UAE investigated the susceptibility of varicella among children and healthy adults.[30] The total number was 648 healthy individuals aged from 8 months to 47 years; 161 of them were UAE citizens while 487 were expatriates mainly from India and Philippines. Of 648 individuals, 126 (19.4%) were susceptible to VZV infection and had no detectable antibody, while the overall adult seroprevalence rate was 81.3%. Expatriate adults had variable prevalence rates, with Sri Lankans being the most susceptible (35%). Furthermore, it was found that the rate of nationals' seroprevalence increased by age from 45.8% in children <10 years of age to the highest 94.7% in adults of 31–40 years. The study strongly recommended the introduction of an early varicella vaccination program.[30]

In addition, a 5-year descriptive study investigated the seroprevalence of varicella and varicella-associated complications in Al-Ain from 2000 to 2004.[31] The annual number of reported cases varied from 373 to 790 per 100,000 population. Most cases (89%) occurred in children aged <15 years, and the overall mortality rate was 1.1% among hospitalized children. Authors highlighted how varicella and varicella-associated complications turn to be a public health issue in the UAE.[31]

Several studies investigated varicella complications in the UAE. One study detected the risk of developing varicella pneumonia among 607 hospitalized adults with chickenpox from 1985 to 1996 in Al-Ain Hospital.[32] There were 26 cases of varicella pneumonia, of whom three died with respiratory failure. The authors suggested an early aggressive therapy for those at risk of developing pneumonia.[32] Another study reported the serious clinical complications of the chickenpox in 102 adults admitted to Rashid Hospital from 2005 to 2008.[33] The majority of them developed varicella pneumonia (28.4%), while the remaining presented with skin infections (25.4%), septicemia (10.7%), encephalitis/meningitis (8.8%), acute respiratory distress syndrome (6.8%), renal failure (2.9%), and hepatic failure (1.9%). The mortality rate of primary VZV infection was high (4.9%), especially due to varicella pneumonia in the elderly, immunocompromised individuals, and smokers.[33]

A clinical study was also concerned with varicella complication on 45 renal allograft transplantations (27 UAE nationals and 18 non-UAE national), performed outside the UAE between 1993 and 2009 from living related and unrelated donors (LRDs and LURDs).[34] Major viral infections detected were due to cytomegalovirus (CMV) (27%), varicella (12%), zoster (9%), and Epstein–Barr virus (3%) associated with posttransplantation lymphoproliferative disease in the LURD group, compared to only two viral complications due to CMV (10%) and varicella (10%) in the LRD graft recipient. The study showed the association of VZV infection with the clinical complications in immunosuppressed patients.[34]

Varicella vaccine has been available in the UAE for more than 10 years, but it was introduced to the National Immunization Program in 2012.[35] A prospective cohort study was conducted in the UAE to determine the seroprevalence of vaccine-preventable viral infections including VZV among Emirati medical students from 2011 to 2012.[35] Of the 261 participated students, 182 (70%) were seropositive for VZV IgG. The high seropositive rate was attributed to a recent introduction of varicella vaccination into the National Immunization Program and to acquired immunity from natural infection in the childhood.

OMAN

Two case studies were reported about varicella complications, but no data were published about varicella seroprevalence in Oman. One case study has reported postvaricella lower limb deep venous thrombosis in two children in Oman.[36] The author highlighted the importance of varicella vaccination of children, especially those identified with protein S deficiency.[36] Another case study reported the serious complications resulted from primary VZV infection in a patient undergoing hemodialysis.[37] The patient was a 70-year-old male presented with end-stage renal disease on hemodialysis; he was diagnosed for VZV encephalitis and was treated with intravenous acyclovir and steroids with full recovery back to preadmission neurological status. The study emphasized the role of varicella complications especially in immunosuppressed patients and the need for zoster vaccination in dialysis patients.[37] In Oman, varicella vaccination was introduced into the compulsory vaccination schedule in 2010.[36]

QATAR

In Qatar, according to the 2007 Qatar Annual Health Report, the number of reported cases of chickenpox among non-Qatari individuals (82.5%) was higher than Qataris (17.5%), due to the fact that the majority of the population is expatriates. Number of reported male cases (71%) was also higher than female cases (29%) since males are predominant among the population of Qatar. The VZV seroprevalence was reported in 41% of children aged 1–14 years and in 47% of adults aged 20–39 years.[38]

Another clinical study was conducted to determine the seroprevalence of VZV infection among HCWs of a community hospital in Qatar between 2012 and 2015.[39] The seropositivity was 92.2%; the authors recommended the importance of immunization of susceptible HCWs against VZV due to their direct exposure to patients' blood, body fluids, and other contaminated environmental sources.[39]

Regarding varicella complications, a case study described an immunocompetent adult suffering rhabdomyolysis after a varicella primary infection. The patient status was only improved by aggressive fluid therapy with an antiviral agent.[40] Another case study highlighted the role of VZV in neurologic complications, not only in immunocompromised patients but also in immunocompetent individuals.[41] The case described a 15-year-old girl who developed aseptic meningitis in the absence of exanthema following reactivation of VZV. Accordingly, authors suggested that VZV should be taken into consideration in aseptic meningitis in immunocompetent individual even in the absence of exanthema.[41]

Qatar was the first in the Middle East region to introduce the chickenpox vaccine (marketed as Varilrix®) in 2002 by primary health centers and hospitals. In 2007, 92% of infants <1 year of age were given the varicella vaccine. The varicella vaccine is given in two doses: one at 12 months and one at 4–6 years of age. However, the incidence of VZV is still high in Qatar due to the large number of expatriates susceptible to VZV.[38]

IRAQ

A seroepidemiological study has been conducted to study the pattern of exposure and immunological responses to VZV infection among 92 children from hospitals and clinics between 2007 and 2008.[42] The overall VZV antibody prevalence was 53.3% for both serologic and cellular responses. It was also found that a difference in the immune responses to VZV infections between male and females and the rates of exposure to VZV infections was higher in urban areas than in rural areas.[42] Another study on chickenpox has been performed in Iraq from 2007 to 2011.[43] It has reported a rise in the number of clinically registered chickenpox cases between 2007 and 2011, around 22% in 2007, 60% in 2008, 39% in 2009, 43% in 2010, and 74% in 2011. Moreover, most cases were 15 years of age and less (65%). The number of infected males was slightly higher than the number of females, and the highest frequencies were reported in March, April, and May.[43]

SYRIA

The prevalence of VZV IgG was determined among unmarried female university students aged from 18 to 30 years.[44] The total number of participants was 316; the sera were collected from October 2009 to November 2010. A total of 287 participants (91%) were seropositive, and this high percentage of immunity was attributed to the introduction of varicella vaccination program.[44]

Regarding varicella complications, a clinical case study reported the association of VZV with varicella-induced

remission of steroid-nonresponsive nephrotic syndrome. The case represented a Syrian boy with a nephrotic syndrome aged 3 years, who showed nonresponse to steroid therapy and developed chickenpox few days later. The remission has been sustained even after his full recovery of chickenpox, suggesting varicella-induced remission of steroid-nonresponsive nephrotic syndrome.[45]

JORDAN

A study has been carried out for the detection of VZV in skin samples of 33 patients. A total of 11 patients were positive for VZV.[46] No data were found on varicella prevalence or vaccination in Jordan.

LEBANON

A brief report was published in 1986 reporting the susceptibility of Filipino nurses working at the American University of Beirut Medical Center to VZV following an outbreak of varicella.[47] A prevalence of 18% was found susceptible to VZV as compared to 3% in a matched group of Lebanese colleagues.[47] Another varicella seroprevalence study was carried out on school adolescents in Lebanon from 1999 to 2000.[48] The study showed that 96.6% were immune to varicella, especially those who came from big families, and suggested a similar large-scale epidemiological survey to establish an appropriate strategy toward implementing a National Immunization Program.[48] Moreover, the seroprevalence of varicella was investigated among medical and paramedical university students in Lebanon between November 2007 and April 2008. Of the 502 students, 93% were immune to varicella.[49]

Regarding varicella complications, a study has reported a case of Hughes syndrome 1 week after the occurrence of chickenpox.[50] Moreover, a case study described bullous chickenpox in a 9-year-old boy, which is rarely reported variant of chickenpox that can affect both children and adults. The authors recommended the dermatologists to consider bullous chickenpox in the differential diagnosis of vesiculobullous diseases.[51] Furthermore, a case study described a disseminated varicella infection in a patient with acute abdominal pain 9 days before the appearance of the hemorrhagic rash, to be diagnosed later as hemorrhagic varicella.[52] Another case report study described a 5-year-old girl who developed generalized granuloma annulare 2 months after previously healed lesions of varicella infection.[53]

EGYPT

The CNS complications of the exanthematous viral diseases were observed among 26 patients following varicella infection.[54] They presented with CNS manifestations including disturbed level of consciousness, coma, seizures, motor deficits, ataxia, and myoclonus, and the most common finding on CT scan was brain edema.[54] Another study aimed to evaluate the association of VZV infection with Bell's palsy and its outcome on children in Egypt from May 2012 to December 2013.[55] The VZV IgG and immunoglobulin M (IgM) antibodies were both detected among 30 children with Bell's palsy, and the prevalence of VZV IgM antibodies was significantly higher in Bell's palsy patients than controls (36.6% of patients vs. 10% of controls). It was concluded that VZV reactivation might be an important cause of acute peripheral facial paralysis in children.[55]

IRAN

Several varicella seroprevalence studies were conducted among Iranian population of different age groups according to the published data.[56] In Kerman Province in the southeast of Iran, of 723 premarital Iranian women, 89.35% had serological evidence of varicella immunity.[57] Another seroprevalence study aimed to compare the prevalence of anti-VZV antibody in children under 7 years old in Tehran. It was found that 4.6% of 7-month-old, 12.8% of 18-month-old, and 21.3% of 6-year-old children were seropositive and suggested the necessity of varicella immunization between 7 and 18 months of age to prevent viral infection.[58] A different study aimed to estimate the prevalence of age-specific VZV antibody in Iranian < 40 years during 2003 and 2011 and has found an increase in the VZV seropositivity with age: 1–5 years (21.9%), 6–10 years (42.1%), 11–15 years (59.4%), and 40 years (87%).[59] Similarly, a national seroprevalence study of varicella infection was conducted between 2009 and 2010 among adolescents in different provinces in Iran, Central, West, North-Northeast, and Southeast.[60] Of 2753 individuals aged 10–18 years, 87.4% were positive for VZV antibodies. The prevalence of VZV antibodies varies between 85.24% in West region (mostly mountainous areas with cold climate) to 94.59% in Southeast region (subtropical climate).[60]

A seroprevalence study investigated VZV antibody among 250 young women before marriage in Sanandaj and found that 71.2% of women were seropositive.[61] Moreover, the varicella immune status was investigated among 400 pregnant woman aged 16–43 years. A total of 361 (90.3%) women were VZV seropositive. It was highlighted the importance of VZV screening in pregnant woman to avoid life-threatening complications for the mother and fetus during pregnancy.[62]

In addition, several varicella seroprevalence studies were conducted among HCWs in Iran.[63] In Ayatollah Rouhani

Hospital, Babol, Northern Iran, the seroprevalence of 459 HCWs was investigated, and 278 (95.5%) were shown to be VZV seropositive.[64] Another study has also shown that considerable proportions of young medical students are susceptible to varicella infection and to consequent complications.[65] Similarly, a study of varicella infection in Iranian medical students from three different schools of Qazvin University of Medical Sciences was conducted in 2012, showing VZV seropositivity of 74.5%. The authors recommended that all medical science students should be tested for varicella immunity regardless of their previous history of varicella infection.[66]

VZV genotyping was also performed in Iran by RFLP method among 38 chickenpox patients from hospitals of Iran University of Medical Sciences in Tehran. The common VZV genotype among Iranian patients with chickenpox was BglI (+) PstI (+) (89.5%) and PstI (+) BglI$^-$ (10.5%).[67]

Varicella was further associated with many clinical complications in several reported cases where VZV was found in skin lesions in kidney transplant recipients.[68] An outbreak of chickenpox in adult renal transplant recipients was reported in Southern Iran, Khuzestan, and it was suggested to screen all renal transplant recipients for VZV before transplantation, irrespective of previous history of varicella infection, and to vaccinate those seronegative recipients.[69] A rare presentation of varicella endotheliitis was also reported in an 18-year-old patient.[70] Furthermore, a case study described a 17-year-old immunocompetent boy who experienced cervical transverse myelitis after chickenpox, with inability to walk and with urinary retention.[71] Another study reported the association of varicella infection with aseptic meningitis among children in Southern Iran, Shiraz.[72]

Furthermore, a study showed that HSV and VZV were the most common etiologies of acute infectious encephalitis in Sina University Hospital in Hamadan, Iran, from April 2004 to March 2012.[73] A seroprevalence study on varicella was also conducted among 187 hemodialysis patients from the hemodialysis unit of Hasheminejad Kidney Center, who were potential kidney transplant candidates. It was found that 183 patients (97.9%) were VZV seropositive, and because varicella can cause life-threatening disease in immunosuppressed patients, it was suggested to target this group in future for varicella immunization program.[74] Another case study described a frosted branch angiitis in an immunocompetent patient caused by VZV.[75] In addition, a study conducted in the west of Iran showed that VZV was the most common herpesvirus to cause aseptic meningitis, particularly in young and middle-aged people.[76] A case study also described the association of varicella infection with internal root resorption in a 38-year-old woman, as a maxillofacial complication.[77] Other studies showed that chickenpox increased the risk of multiple sclerosis.[78,79] Moreover, a study has reported that concomitant cortical blindness and deafness followed VZV encephalitis in a human immunodeficiency virus (HIV)-positive patient.[80]

TURKEY

The varicella seroprevalence was investigated in a random sample of the Turkish population under age 30 in nine provinces of Turkey.[13] Out of 4387, 77.8% were VZV seropositive, with no difference in the seroprevalence rate between rural (76.3%) and urban (79.0%) areas. In addition, the varicella seroprevalence was reported to increase with age, with 20% in those aged 1 year, 40% in those aged 4 years, 60% at age 6 years, 80% at age 8 years, 85% at age 10 years, and 85%–90% in those over 10 years.[13]

In a study aimed to determine the seroprevalence of VZV-IgG antibodies among 885 children aged between 0 and 15 years in Turkey, it was found that VZV seropositivity rates were low up to the end of the first year and then showed a gradual increase. The seropositivity rates were 41.2%, 80%, and 85% for 4–5 years old group, 10–11 years old group, and 13–15 years old group, respectively.[81] Another study aimed to determine the varicella seroprevalence under age 30 in Eastern Turkey to design a strategy for vaccination against varicella.[82] The varicella seropositivity was 78% increasing with age. Accordingly, authors highlighted the need of the introduction of varicella vaccine into the routine childhood vaccination program in Turkey since majority of varicella infections occur during the early childhood.[82]

Another study was designed to evaluate the age-specific VZV seroprevalence in children aged <5 years. Of 292 children, 65 (22.3%) were positive to VZV IgG, with no differences between the sexes; however, the varicella seroprevalence was highest at the 48th and 60th months.[83] Moreover, a seroprevalence study of varicella was conducted in Eastern Turkey among 803 unvaccinated children aged from 1 to 16 years.[84] It was found that the seropositivity rate of varicella was 26.8% in children aged 1–4 years and 90.3% in those aged 13–16 years. Authors suggested a vaccination policy before the age of 2 to avoid possible complications in the future.[84]

Many other studies investigated the varicella seroprevalence in different regions in Turkey.[85] One study aimed to determine the reliability of a history of varicella to detect susceptible children, adolescents, and adults in Izmir.[86] The overall VZV seronegativity among 590 participants was 28.5%, specifically 18.8% in adolescents and 11.7% in young adults, while VZV seropositivity in children was 25.5%. Thus, it was recommended a serological testing for

adolescents and adults with negative history of varicella before VZV immunization.[86] Another study in Izmir has investigated varicella seroprevalence among 2136 healthy aged 15 years and above.[87] It has shown that VZV seropositivity was high (94.3%), and there was significant difference between VZV seroprevalence in urban and rural. Furthermore, a large proportion of the population in Izmir was naturally immunized against varicella.[87]

Several screening studies among HCWs were also conducted in Turkey regarding immunity against varicella and other viruses, and most studies confirmed that screening and vaccination of susceptible HCWs are essential.[88-91] A total of 1255 of HCWs at the Erciyes University Hospital in Turkey were screened for the immunity to varicella in 2010 and 98% of them were immune to varicella.[89] The cost of vaccination without screening was shown to be expensive for varicella, and the authors advised a prevaccination screening of HCWs.[89]

Regarding varicella complications, a case study reported T-cell lymphoma in leukemic phase with skin infiltration of neoplastic cells in a previous site of VZV infection.[92] Another case study described a 21-month-old boy who had a multiorgan failure due to VZV infection.[93] The varicella infection complications in healthy children were investigated in Izmir from 1997 until 2001.[94] The total number of hospitalized children due to varicella complications was 178, with no gender difference. They occurred mostly in preschool age children (3 years), 44% of complications occurred in young children (2 years), while neurologic complications occurred at an older age (6 years).[94] Another case study reported a high rate of herpes viruses including VZV in middle ear fluids of children with otitis media with effusion.[95] Aplastic anemia was also reported as unexpected complication after varicella infection in Balcali Hospital in Turkey.[96]

Furthermore, a case study reported a very rare condition of varicella gastritis in an immunocompetent child. Although varicella gastritis is uncommon and most of reported cases were among immunocompromised adult individuals, it was reported in an immunocompetent girl with severe abdominal pain.[97] In addition, two case reports discussed a pediatric case of Ramsay Hunt Syndrome.[98-100] The cases described a pediatric age group with facial paralysis due to VZV reactivation. The authors suggested that early diagnosis and treatment would have a positive effect on disease prognosis.[98-100]

Moreover, a study aimed to assess the outcome of disseminated varicella infection among renal transplant recipients from January 2001 to January 2014.[101] Of 1614 renal transplant recipients, 41 patients (2.5%) were VZV positive and the mortality rate due to VZV was 2%. An active immunization was recommended for all seronegative patients before organ transplantation, and an early initiation of antiviral therapy would prevent further complication.[101] Another case study reported a rare but severe neurological complication of chickenpox, Guillain–Barre syndrome, in a 4-year-old child.[102] In addition, a rare case was reported of primary inoculation tuberculosis seen after varicella.[103] The case explained the possible mechanism of VZV-mediated transient cellular immune suppression that predisposed the patient to cutaneous tuberculosis.[103] Breakthrough varicella is a varicella in previously immunized individuals, it was detected in previously healthy children or children with an underlying condition. A study has reported that the time elapsed between vaccination and hospitalization was approximately 5 years, and neurological complications, mainly encephalitis and meningitis, were the most common reasons for hospitalization in previously healthy children.[104]

Immunization with a single dose of VZV vaccine (Varilrix, SmithKline Beecham) was shown to be safe and effective in children with steroid-sensitive nephrotic syndrome in remission.[105] The effectiveness of varicella vaccination during an outbreak was assessed in a children's day-care center in Istanbul, and they supported routine varicella vaccination especially if given after 15 months of age to prevent all forms of varicella, medium-severe disease, and serious complications.[106] Another study investigated varicella rates among unvaccinated and one-dose vaccinated healthy children in Izmir; the study highly recommended a two-dose varicella vaccine policy to provide improved protection against future complications as breakthrough varicella.[107] The varicella vaccine has been implemented as part of the National Immunization Program in Turkey in 2013.[104]

CYPRUS

A prospective seroepidemiological study of varicella was conducted in 2006 on Turkish population in Cyprus.[108] The study aimed to determine the age-specific seroprevalence of VZV infection in 1–30-year-old healthy unvaccinated individuals in the Turkish population who were born in Northern Cyprus. Of 587 individuals, 486 were seropositive for VZV antibodies (84.1%) with no difference between genders. VZV seroprevalence dramatically increased from 16% of the 1st year of age to 85% in 9th year of age; however, after that, it was slowly increased to reach 96% in the age group of 21–25 year olds. The majority of VZV infection occurred during the childhood, and more than 90% of individuals acquired immunity to VZV before reaching adulthood.[108] Another VZV surveillance study in Cyprus reported the VZV incidence to be about 20 per 100,000 inhabitants in 2009 and 9 per 100,000 in 2010.[109]

BAHRAIN, YEMEN, AND PALESTINE

No data were officially published about the VZV infection prevalence, immunization, or complications in these three countries to date.

DISCUSSION

Varicella (chickenpox) is a common infection worldwide and occurs mainly among children <10 years of age. It is a self-limiting illness that lasts few days and provides lifetime immunity against the infection. However, varicella causes serious complications among immunocompromised individuals and sometimes among immunocompetent as well. VZV vaccine was developed to prevent the spread of varicella infection in a community and to protect those with weak immune system of developing serious illnesses leading to death. After the introduction of VZV vaccine by the WHO, most developed countries and some developing countries include it in their national vaccination program. Nevertheless, some developing countries are still very far of reaching this goal. Respectively, a general survey of varicella infection among different populations is essential to control and to prevent epidemic occurrence.

VZV infection was reported as childhood infection in the Middle East. The most affected age group was children < 10 years of age and 90% of adults have already VZV antibodies.[13,42-44,48,60,81,108] Furthermore, number of males, i.e., varicella-reported cases, was slightly higher than females in GCC countries and Iraq, and the varicella incidence in urban regions was higher than rural ones.[14,18,30,38,43] However, in Turkey, most studies have reported that there were no differences of VZV seroprevalence rate between rural and urban regions and/or sexes of children.[13,81,83] However, a study in Izmir, Turkey, have shown a significant difference in VZV seroprevalence between urban and rural areas.[87] Further data about varicella seroprevalence should be collected among different groups in a population before the decision of any strategy, taking into consideration some factors such as gender, economic status, living regions, and population density.

The climate of most Middle East countries is temperate where most VZV cases occur, unlike tropical countries where fewer cases are reported.[4] Varicella infection in the Middle East peaks mostly during spring, i.e. March, April, and May, which is in parallel with most reports from other temperate regions.[4,5,18,43] The seasonality of VZV does not occur in tropical climates and people enter adulthood uninfected by VZV.[110,111] The number of expatriates in the Middle East is large especially in GCC countries, where most belongs to Southeast Asia (India, Pakistan, Bangladesh, and Philippine), putting them at risk of acquiring VZV infection and developing life-threatening complications. Accordingly, most studies in the Middle East supported varicella vaccination for HCWs from tropical and warmer area to protect hospitalized patients and to prevent the transmission to other staff and/or patients.[20,26,35,39]

Middle East includes also countries with high number of population such as Egypt (90,253,760), Iran (78,778,000), Turkey (78,214,000), and Iraq (36,575,000).[112] Those countries with high number of population also have high rate of birth, which increases the risk of acquiring varicella infection during pregnancy leading to congenital diseases. To overcome this problem, young children and pregnant woman with negative varicella history should be vaccinated. In addition, according to most published data of VZV seroprevalence in the Middle East, the self-reported history in different groups of population was not reliable, and the history given was not corresponding to most cases after immunity testing. For example, although the universal screening is more costly than the routine verbal screening, it was more effective in Iran.[62] Accordingly, it was suggested in several studies to screen high-risk group of individuals for VZV antibodies and vaccinate those with negative results regardless of their reported varicella history.

Further, immunocompromised individuals and some immunocompetent adults with varicella negative history were at high risk of developing serious clinical conditions. The most reported complications due to varicella infection in the Middle East was CNS involvements followed by skin diseases,[25,26,37,41,51,54,68,72,73,104] varicella pneumonia,[24,32,33,37,41] and gastric diseases.[97] Varicella infection is often more severe and has high complication rate in adults than in children, and childhood vaccination is the only way to protect those susceptible adults of developing serious illnesses after varicella exposure.

Regarding VZV genotyping, only two studies were published one in Kuwait and the other in Iran.[29,67] Both studies relied on an early method for VZV genotyping the RFLP analysis; however, sequencing is currently used for this purpose. The most prevalent VZV genotype in Kuwait was genotype B (PstI+/BglI+), in Iran was BglI (+) PstI (+) that could be M or J, while in Europe and North America was genotype A (PstI-/BglI+) predominates.[113,114] The latest universal data about VZV genotyping are not available currently in the Middle East, and these data are crucial in terms of initiating and evaluating a vaccination program.

The introduction and inclusion of varicella vaccine in the national vaccination program were reported in GCC countries and Turkey. In GCC countries, it was available by preference in Saudi Arabia in 1998, followed by Qatar and UAE in 2002 and then Kuwait in 2008. However, it became

part of the mandatory national vaccination program in 2007 in Qatar, 2008 in Saudi Arabia, 2010 in Oman, 2012 in the UAE, and 2017 in Kuwait.[22,36,38] Bahrain was the only GCC country without an official report of varicella infection, although the website of the Ministry of Health shows that varicella vaccine is now part of the childhood vaccination program and that the first dose must be taken at year one while the second dose at 3 years of age (https://www.moh.gov.bh/HealthInfo/Immunizations? lang = en).

In Turkey, VZV vaccination was mandatory in 2013.[104] Reports have shown a decline in varicella incidence and childhood-associated diseases due to VZV vaccination.[18,22,104,106,107] The knowledge of prevaccination seroepidemiology is crucial in terms of evaluating the efficacy of vaccination programs on the epidemiology of the disease.

The highest number of publications in the Middle East about VZV infection was from Iran and Turkey, followed by GCC countries, Lebanon and Egypt. All GCC countries, except Bahrain, had published several clinical studies about VZV infection of approximately 30 research articles. Data were missing for Yemen and Palestine, possibly due to the unstable economic and security conditions in those countries over the past few years.

CONCLUSION

The purpose of this review was to have a general overview about varicella infection in the Middle East, its prevalence, most affected age group, VZV seroprevalence according to males and females, rural and urban areas, seasonality, associated complications, and varicella immunization. Of course, this will provide a general view about varicella medical burden in the Middle East, and its influence on the socioeconomic status by work loss, hospitalization, and cost of treatments due to varicella infection. From this review, varicella in the Middle East as most areas in the world is a childhood disease and the seropositivity of VZV increased by age, with almost no significant differences between sexes and rural and urban areas. Most Middle East countries have included varicella vaccine in their routine immunization program for children, provided through the Ministries of Health. The screening was shown to be important to identify susceptible pregnant women who are at risk of developing varicella complication and to avoid congenital varicella. All HCWs should be tested for VZV immunity, and vaccine should be offered to those tested negative to protect hospitalized, immunocompromised, and ICUs patients. Further studies should be conducted to evaluate the safety, efficacy, and effectiveness of varicella vaccine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors have no conflicts of interest.

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