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Seroprevalence of Varicella Zoster Virus in the Eastern Province of Saudi Arabia in Post-vaccination Era

Reem Al Dossary

ABSTRACT

Background: Varicella zoster virus (VZV) is a highly contagious virus causing two types of skin infections known as varicella and herpes zoster. Due to its high burden, vaccination is available in almost 42 countries worldwide including Saudi Arabia. Since its introduction, data on the impact of the vaccine from local and neighboring countries is lacking. **Objective:** This study was done to determine the seroprevalence of anti VZV IgG and IgM antibodies in post-vaccination era fifteen years after varicella vaccine introduction in routine childhood vaccination schedules. **Methods:** retrospective observational study over seven years on all individual tested for anti VZV IgG and IgM in a tertiary university hospital in the eastern province of Saudi Arabia between Jan 2014 to Dec 2020. **Results:** 83.69% (6820/8149) of tested population were seropositive with significantly lower positivity in children less than ten years old (44%). Yet no significant difference was found between males and females or among different nationalities tested. **Conclusions:** varicella continuous to be prevalent in the eastern province of Saudi Arabia fifteen years after the introduction of the vaccine but the level of anti VZV IgG detection is significantly lower in children below ten years of age. Further large-scale studies are needed to assess the impact of universal vaccination on the epidemiology of VZV.

Keywords: varicella zoster virus (VZV), IgG, IgM, seroprevalence.

1. BACKGROUND

Varicella Zoster Virus (VZV) is the causative agent for a highly contagious common viral exanthematous disease. It is a member of the Herpesviridae viral family characterized by the ability to establish lifelong latent infections. Following primary infection, commonly seen in children, the virus causes Varicella (chickenpox) with fever, fatigue, anorexia and generalized itchy vesicular lesions. After recovery from varicella the virus travels retrograde neuronal axons to establish latency in peripheral autonomic ganglion (1). Upon reactivation, which usually occur many years following primary infection, the virus travel antegrade the neuron to reach the skin causing crops of vesicular lesion at a dermatomal distribution known as herpes zoster (shingles). Varicella zoster virus therefore causes two distinct clinical entity on primary infection and following reactivation of latent infection. Although it commonly causes a self-limiting disease, VZV infection can lead to serious complications especially in adults in the form of pneumonia, neurological complications, and secondary bacterial skin infections, among others. More recently, VZV has been linked to multiple sclerosis (2), yet solid evidence is still not available to support this (3) and metanalysis study showed association in Asian but not in European countries (4). Furthermore, history of chickenpox was found as predictor of multiple sclerosis in Alaseer region, Saudi Arabia (AOR= 0.045 95%CI (0.015-0.135)) (5, 6).

Varicella tends to be an endemic disease with high incidence affecting almost all children due to the high secondary attack rate reaching 61-100%, but with the development of an effective live attenuated vaccine, VZV infection tend to reduce dramatically with ~97% reduction in the United States (6). Two types of VZV vaccines are available, both are live attenuated. The first vaccine VARIVAX is a single antigen varicella vaccine and the other one is ProQuad which include varicella and measles, mumps, and rubella vaccine (MMR). VARIVAX and ProQuad were licensed in 1988 and 2005, respectively.

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gender	IgM Status				p value	IgG Status				p value
	negative	positive	% Positivity	Total		negative	positive	% Susceptible	Total	
Female	403	10	2	413	0.784	809	4086	17	4895	0.735
Male	233	8	3	241		520	2733	16	3253	
Unknown	1	0	0	1		0	1	0	1	
Total	637	18	3	655		1329	6820	16	8149	

Table 1. Distribution of anti VZV IgG And IgM positivity among different gender

nationality	IgM Status				p value	IgG Status				p value
	negative	positive	% Positivity	Total		negative	positive	% Susceptible	Total	
African	46	2	4	48	0.763	85	374	19	459	0.389
American	7	0	0	7		14	40	26	54	
Asian	572	15	3	586		1225	6375	16	7600	
Australian	0	0	0	0		0	1	0	1	
European	0	0	0	0		1	10	9	11	
unknown	12	1	8	13		4	20	17	24	
Total	637	18	3	655		1329	6820	16	8149	

Table 2. Distribution of anti VZV IgG and IgM positivity among different nationalities

The first country to introduce VZV vaccine in routine childhood vaccination was Canada in 2001, followed by Germany in 2003 and then UAE, Switzerland, and Uruguay in 2004. Nowadays a total of 42 countries have introduced varicella vaccination either in routine vaccination, outbreak management and for risk groups (7). In Saudi Arabia, VZV vaccine was introduced in 1998 and included in routine childhood vaccination in 2007-2008 (8) as two doses, first does at 12 months of age followed by a second dose at 4-6 years of age based on The Advisory Committee on Immunization Practices (ACIP) recommendations (7-9). Almost all children borne after vaccine introduction in the kingdom are vaccinated since it is a mandatory vaccine that need to be completed before joining school. The World Health Organization (WHO) recommend 80% vaccine coverage to control the transmission of varicella in the community and the burden of the disease and reduction of coverage below 80% might lead to shift in the age group of patients to older individuals with increased risk of morbidity and mortality (10)

Multiple studies were conducted in Saudi Arabia to assess the seroprevalence of varicella antibody in various specific study populations. One of the first studies in 1989 on 224 children (1-15) years old found that 68% were seropositive (11). Another study reported 74.4% seropositivity among pregnant Saudi women. Health care workers showed variable level of immunity demonstrated by positive IgG ranging from 67%-88.7% (12-14). In addition, introduction of varicella vaccine has led to reduction in varicella incidence from 739.8/100,000 in 1994 to 88.1/100,000 in 2011(8) and the trend of varicella tend to reduce in the southern parts of Saudi Arabia from 2007-2012(15).

2. OBJECTIVE

No recent local data are available to measure the impact of the vaccination program in the kingdom 15 years after introduction of the vaccine especially in the vaccinated population below 15 years of age (16), therefore this study is designed to measure the seroprevalence of VZV in the eastern province of Saudi Arabia in a wide range of ages groups over seven years and identify age related seroprevalence data.

3. MATERIAL AND METHODS

This is a 7-year retrospective observational study conducted in a tertiary teaching hospital in the eastern province of Saudi Arabia, from Jan 2014 to Dec 2020. All individuals tested for varicella zoster immunoglobulin IgG and/or IgM were included in the study. Indications for testing were clinically suspected varicella zoster virus infection and pre-employment check for VZV immunity to assess the need for vaccination in healthcare workers. Testing was done using DiaSorin Liaison indirect chemiluminescence immunoassay for quantitative determination of IgG and IgM immunoglobulin in serum samples. Results were retrieved from an electronic patient data system, duplicate results and multiple testing for the same patient were identified, and the first serological results were kept for analysis and the others were removed. Data were analyzed using frequency calculations and descriptive analysis using SPSS program.

4. RESULTS

Over the seven years study period, 8192 individuals were tested for anti VZV immunoglobulin. Age ranges from 0 to 88.8 years with mean age of 27.8 (SD=9.7) and 29.6 (SD=14.4) for IgG and IgM testing, respectively. Of those tested 5308 were females and 3494 were males (Table 1). Majority of individuals tested were Asian with

year	IgM Status				P value for linear trend	IgG Status				P value for linear trend
	negative	positive	% Positive	Total		negative	positive	% Susceptible	Total	
2014	60	2	3	62	0.519	51	439	10	490	0.000
2015	56	3	5	59		88	780	10	868	
2016	101	1	1	102		164	1169	12	1333	
2017	166	6	3	172		263	1162	18	1425	
2018	92	1	1	93		318	1185	21	1503	
2019	129	5	4	134		332	1570	17	1902	
2020	33	0	0	33		113	515	18	628	
Total	637	18	2.75	655		1329	6820	16	8149	

Table 3. Number of anti VZV IgG and IgM tests over seven years in a tertiary teaching hospital in the eastern province of Saudi Arabia

Age groups (years)	Status IgM				P value	Status IgG				P value
	negative	positive	Total	% Positivity		negative	positive	Total	% Susceptibility	
≤1.5	35	1	36	2.8	0.014	19	19	38	50	0.000
>1.5-10	33	0	33	0		33	22	55	60	
>10-20	36	0	36	0		117	487	604	19	
>20-30	265	6	271	2.2		738	4351	5089	15	
>30-40	163	5	168	3		263	1214	1477	18	
>40-50	56	0	56	0		87	443	530	16	
>50-60	33	4	37	10.8		54	215	269	20	
>60	16	2	18	11.1		18	69	87	21	
Total	637	18	655	2.7			1329	6820	8149	

Table 4. Distribution of anti VZV IgG and IgM positivity among different age groups

less African, American, European, and Australian (Table 2).

Testing for anti VZV IgG increased significantly in the year 2018, with a peak number of testing in 2019 with 1902 tests with no corresponding increase in IgM testing (Table 3).

For the 8192 patients, 8149 were tested for anti VZV IgG antibodies in sera and 655 were tested for anti VZV IgM.

Out of 8149 VZV IgG tests, 83.69% (6820/8149) were immune to varicella with positive anti VZV IgG, and 16.3% (1329/8149) were susceptible with negative anti VZV IgG. Seropositivity to anti VZV IgG was significantly lower in pediatric age group 0-10 years old reaching 44% (41/93) with p-value 0.000 (Table 4).

Regarding VZV IgM testing to detect acute infection, 97.25% (637/655) were negative and only 2.75% (18/655) showed immunological evidence of acute infection. seroprevalence of anti VZV IgM was not statistically different among different age groups (p-value=0.014) (Table 4).

Seroprevalence of anti VZV IgG and IgM was similar for both males and females tested with no significant difference (P-value 0.735, 0.784 respectively) (table.1). In addition, seroprevalence data were not significantly different among different nationalities tested (Table 2).

5. DISCUSSION

Varicella zoster virus is the causative agent of a highly contagious disease with significant global impact necessitating vigilant control measures in the form of varicella vaccination and continuous surveillances. Universal VZV vaccination has been shown to reduce the incidence of varicella disease, and hospitalization by more than 80% (17). In the kingdom of Saudi Arabia, varicella vaccine was included in routine childhood vaccination in 2007 and this has led to reduction in the incidence of varicella cases (8, 15), but the introduction of the vaccine might have other impact on VZV epidemiology by reducing the circulating virus in the community and therefore preventing natural boosting of immunity which could lead to unexpected rise in varicella cases in older age groups or increase in herpes zoster.

In Australia, introduction of VZV vaccine has been shown to reduce varicella hospitalization by 7% between 2000 and 2007 and increase zoster hospitalization by 5% from 1998 and 2007(18). Furthermore, the rate of varicella treatment was significantly reduced with a paradoxical increase in the rate of zoster treatment between 1998 and 2009 (19). In addition, a fourfold increase in the incidence of herpes zoster was observed over 60 years period between 1945 and 2007 questioning the association with VZV vaccine introduced less than 60 years (20). On the other hand, Gil-Prieto found no

significant difference in zoster hospitalization after VZV introduction (21). Although the increase in zoster is evident irrespective of the cause, a predictive study using mathematical models to measure the long-term effect of VZV vaccination over 100 years predicted a decline in varicella incidence and increase in zoster incidence by 20% for 50 years (22).

Studies on the impact of vaccination on varicella incidence is subject to bias since varicella is not notifiable in many parts of the world and many cases are mild self-limiting not requiring medical attention, leading to underreporting. Therefore, this study aims to assess the impact of varicella vaccination in the community fifteen years after the introduction of universal varicella vaccination by measuring anti VZV IgG and IgM antibodies.

During the 7 years study period, 655 were tested for anti VZV IgM and only 18 (2.75%) individuals showed serological evidence of acute varicella, with eleven cases in the age range between 20 and 40, six cases in individuals older than 50 years of age, and only one case in unvaccinated infant less than 1.5 years (table 4). This could be explained by the expected impact of universal varicella childhood vaccination but also by the fact that most cases in children are diagnosed clinically not requiring immunological testing for confirmation.

The overall VZV IgG seropositivity in the population tested was 83.69%, with no significant differences between males and females or between different nationalities tested, although the numbers of participant from different nationality was highly variable and sometimes small, preventing valid comparison between different nationalities. This level of anti-VZV IgG positivity indicate high level of protection in the population tested. This result is like other studies reporting 81.9% and 80.3% seropositivity among healthcare workers in Kuwait and China respectively (23, 24) and 71.2% in women before marriage in Iran (25). Yet, comparing seropositivity in different age groups is of particular importance since vaccination is relatively recently introduced in most parts of the world and therefore, IgG seroprevalence in adult population commonly reflect natural immunity secondary to varicella infections while that in pediatric age group commonly reflect vaccine induced immunity. In this study, a significantly lower level of anti VZV IgG was seen in children less than ten years old (44% (p value=0.000)), which is less than 80.3% seropositivity reported in German study on 13,433 children between 1 and 17 years of age in pre-vaccination era (26). In addition, pediatric populations were found to have 76.6% and 58.1% anti-VZV IgG seropositivity in unvaccinated children in Polish and Brazilian studies respectively (27, 28). No local data are available to compare pre-vaccination anti VZV IgG detection levels with results of this study, but comparison with the German, Polish and Brazilian data showed that unvaccinated children have higher level of varicella antibodies compared to our pediatric group.

Varicella vaccine has proven to be effective vaccine with a significant impact on varicella disease and complications and studies comparing immunogenicity

of varicella vaccines compared to tetravalent varicella-measles-mumps-rubella vaccine found that anti-VZV antibodies were detected in 89.7% in recipient of varicella vaccine compared to 99.4% in recipients of trivalent vaccine (29). Furthermore, since the duration of immunity induced by vaccine is not clearly defined compared to natural immunity, a study on 10,000 US air force recruits found that anti-VZV IgG seropositivity was higher in recruits with history of natural varicella infection (95.4%) compared to vaccine recipients (72.4%) and that the odds of seropositivity is 24% less in vaccinee compared to those with natural immunity. Furthermore, varicella vaccine-induced-seropositivity tend to reduce by 8% every year (30).

This study has a number of limitations including heterogeneity in the number of participants in different age groups with small number in the pediatric age group, yet it shed light on the low anti VZV IgG seropositivity in pediatric age group in the post vaccination era.

6. CONCLUSION

Varicella continues to be of high seroprevalence in the eastern province of Saudi Arabia with 83.69% with significantly low anti VZV IgG seropositivity in children less than ten years old (44%). This low level of antibodies might be explained by the high vaccination in pediatric population reducing circulating virus and therefore reducing natural boosting of immunity. Further large-scale studies must be done to better understand the impact of universal childhood vaccination on the epidemiology of varicella in the community and revise vaccination policies. Types of vaccine and vaccine coverage rate must be studied carefully as an important predictor of immunity and continuous surveillance must be set up to allow optimal control of the virus.

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- **Informed Consent Statement:** Patient consent was waived due to the retrospective nature of the study, large sample size and the fact that patient data privacy were maintained throughout the study and data were analyzed without reference to any identifiable personal information.
- **Data Availability Statement:** data analyzed in this study can be obtained by direct contact with the author.
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