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REVIEW ARTICLE

Varicella immunity in Iran: an age-stratified systematic review and meta-analysis

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ABSTRACT

Objectives: To generate synthesized information on the epidemiology of VZV infection, as well as an estimation of prevalence of age-specific antibody in Iranian less than 40.

Material and Methods: After exclusion of irrelevant and overlapping reports, 15 papers were included (from nine major cities). Studies were pooled according to the heterogeneity test results. Random effect model methods were used for meta-analysis where significant heterogeneity was observed (age 1-16years).For other age groups, fixed model were used.

Results: Significant heterogeneity was observed in prevalence rates of all childhood age-groups. The seropositivity prevalence increased steeply from the age of 1-5 to 6-10 [from 21.9% (95% CI; 10.8-33.1) to 42.1 %(95% CI; 33.6-50.6)]. At the age of 11–15, 59.4% (95% CI; 46.1-72.8) of children showed to be infected. The rate of seropositivity was more than 87% in individuals of 40 and older.

Conclusion: The varicella seroeprevalence in Iran is in accordance with average tropical and temperate areas. Comparison of conducted studies during 2003 to 2011 didn't show any alteration in VZV seroprovalence in Iran.

Keywords: Varicella, meta-analysis, seroepidemiologic study, Iran

INTRODUCTION

Varicella-zoster virus (VZV) is a human –herpes virus that causes varicella (chicken pox) and zoster (zona). Primary VZV infection is a common and generally benign disease of childhood and occurs mostly during the first decade of life (1-2). Although mortality is uncommon, varicella causes considerable hospitalization (3). Symptomatic disease is more common in neonates, older ages, immunocompromised individuals, and pregnant women (1, 4). Following a primary infection, VZV may become latent in the dorsal root ganglia and reactivate later to cause zoster (shingles). Life time risk of zoster in infected individuals is estimated about 15%(1). Varicella during pregnancy is a serious condition. Congenital varicella syndrome which causes significant morbidity and mortality is occasionally associated with this condition (4). In the pre-antiviral era, mortality of pregnant women was as high as 20–45% and up to 10% were able to develop pneumonia (5). Also, a primary maternal infection may be responsible for severe neonatal varicella during perinatal period(1).

Iran (located in the Middle East, Asia) is the sixteenth in size among all countries of the world (Fig.1), and its climate ranges from sub polar to subtropical (7). Iran has a population of approximately 78 million of different ethnic groups and about 25% of population is 15 years old or younger (8). Although mass vaccination in the childhood is

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expected to result in a substantially lower incidence, hospitalization, and mortality of the disease(6), but vaccination against VZV is not a component of any immunization program in Iran (9). Despite a shortage of comprehensive data on epidemiologic patterns of varicella seroprevalence in Iran, there are some well-designed cross sectional studies to report local rates of varicella seroprevalence. Epidemiological studies of varicella seroprevalence in the country are constantly bound to numerous limitations: inadequate nationwide data sets, lack of standard population-based studies, flawed disease registries, and finally discontinuity of data maintenance between public and private health sectors as well as family physicians. Furthermore, papers are not able to easily find when they are published in the local or national Persian language journals. This systematic review aimed to: 1) generate synthesized information on the epidemiology of VZV infections (2), estimate the prevalence of age-specific antibody in Iranian population at different age groups (up to 40); and (3) compare the seroprevalence between different time periods. To our knowledge, there is no systematic review on varicella seroprevalence in Iran so far.

METHODS

We compared the standardized VZV antibody levels reported in the sub national serological surveys undertaken in 9 major cities of Iran in the different geographical region. The study was designed as an age-stratified systematic review of VZV seroprevalence in Iranian population between 0 to 40 years of age.

Data collection. The data was collected in four stages: **Stage 1)** Search on international database (Pub Med, Science Direct, and Scopus) Publications on varicella immunity prevalence in Iran were identified by searching on Pub Med, Science Direct and Scopus using these keywords: "varicella or chicken pox" in combination with "Iran, Iranian, Persian" and "seroprevalence or seroepidemiology".

Stage 2) search through national database ("IranMedex", the Scientific Information Database (SID), and Iran Doc) IranMedex (http://health.barakatkns.com/irmedex/query.asp) and SID (www.SID.ir) are databases for indexing Iranian medical scientific papers. The databases are using to index published papers in Persian or English, including articles in Iranian or International journals, scientific reports or medical thesis (only IranMedex). Iran Doc (http://thesis.irandoc.ac.ir) includes more than 650,000 records of which 220,000 are devoted to Iranian students' thesis and dissertations and other gray literature such as national, regional and international medical science congress and seminars' proceedings. Titles of all related articles and medical theses were reviewed.

We also reviewed related articles, hand-searched reference lists, and performed author contact.

Stage 3) Selection of relevant articles

1. Titles and abstracts were screened by authors separately to identify eligible studies according to agreed inclusion and exclusion criteria. Full papers of potentially eligible studies were retrieved for more

Fig. 1. Map of Iran and Coordinates.

City	Coordinates	City	Coordinates
Babol (North)	36.50°N, 52.58°E	Tehran (Center)	35.70°N, 51.42°E
Hamedan (West)	34.80°N, 48.52°E	Jahrom (South)	28.50°N, 53.56°E
Kermanshah (West)	34.31°N, 47.06°E	Shiraz (South)	29.62°N, 52.53°E
Qazvin (Center)	36.27°N, 50.00°E	Bushehr (South)	28.83°N, 50.89°E
Kashan (Center)	33.99°N, 51.48°E	Kerman (Southeast)	30.28°N, 57.08°E

S, South; W, West; http://www.daftlogic.com, http://www.infoplease.com/atlas/country/iran.html

detailed assessment. We selected papers for this systematic review if they could fulfill the following criteria:

1. Were conducted in Iran,
2. Contained data on frequency (prevalence) of VZV immunity,
3. Were published before 17thMarch 2014, and written in English or Persian, Studies on clinical pattern (types, risk factors and outcome) or mortality rate of varicella were excluded. We included studies on voluntary blood donors, pregnant women, and community studies. Analyses were done separately on studies from the following special groups (who were assumed to be at high risk for varicella): hospitalized patients, patients on haemodialysis, and hospital staff. Discrepancies were resolved by consensus.

Stage 4) Searching the references of the relevant papers. Each reference in relevant papers was checked for forward and backward citation of searched citations (to find more articles).

Data extraction. The following data were extracted from identified papers: authors' name, place of the study, year of the study, varicella seropositivity prevalence, gender, age, and job status.

Measurement of heterogeneity . Statistical heterogeneity of results was checked by using Cochrane Q-test with significance level at <0.1. Heterogeneity was calculated as the weighted sum of squared differences between prevalence in individual studies and the pooled prevalence across all studies, with the weights which were used in the pooling method. We assumed the same prevalence in all studies as the null hypothesis. To test the heterogeneity, we calculated the amount of Q and compared it with a table of standard critical values. If our calculated Q was lower than the standard, then we failed to reject the null hypothesis (the studies are similar). If the Cochran Q was statistically significant or Q/degree of freedom (df) was greater than 1, heterogeneity was explored or leastwise was clearly stated. If the Cochran Q was not statistically significant and Q/df was less than 1, important heterogeneity considered very unlikely. Also, we used I^2 statistic for quantifying inconsistency (I^2 = [(Q-df)/Q] x 100%, where Q is the chi-squared statistic and df is its degrees of freedom). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Negative values of I^2 are put equal to zero so that I^2 lies between 0 and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. A value greater than 50% was considered substantial heterogeneity. (10-11)

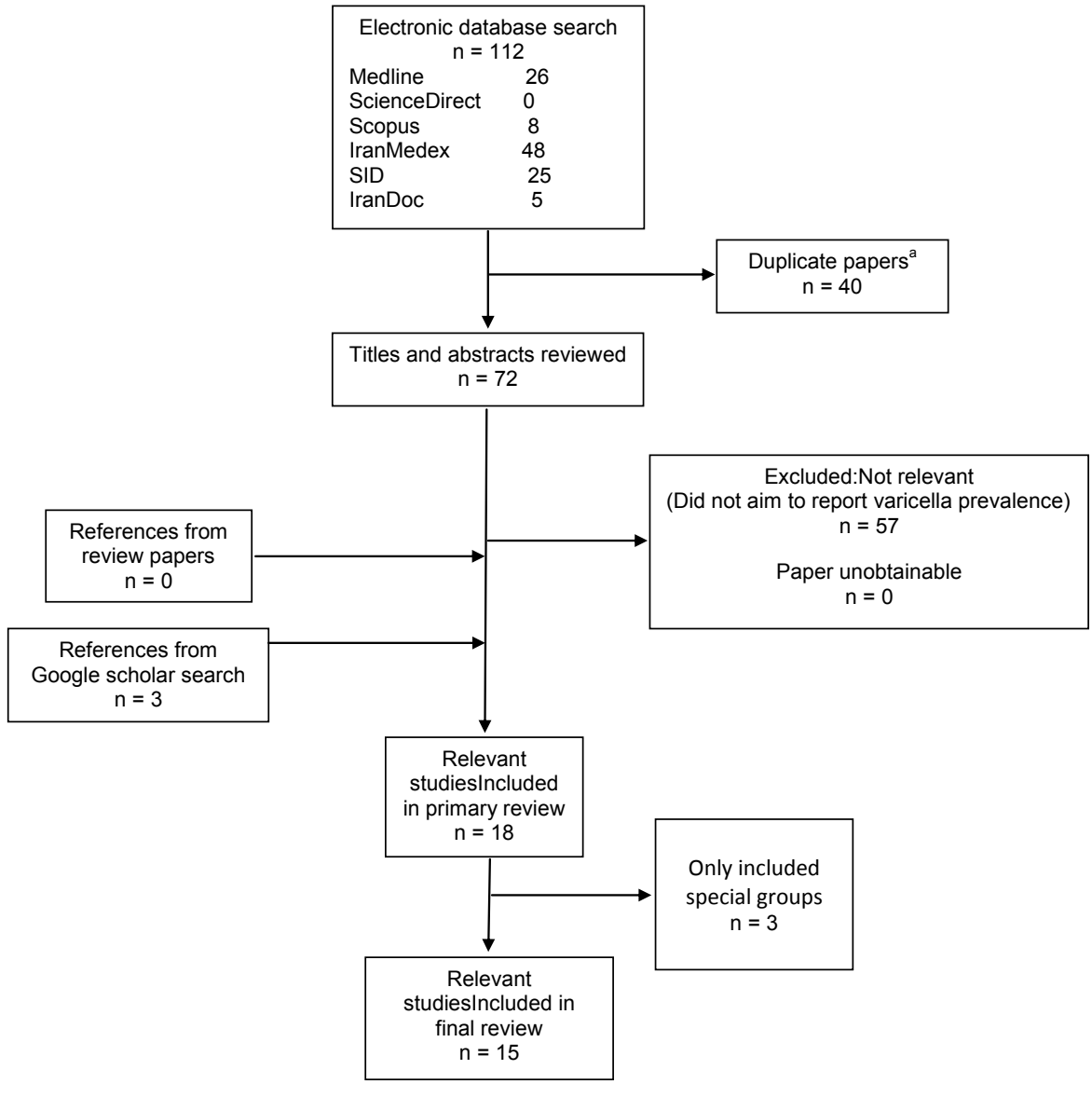
Pooling data and analysis. First Fix/random model meta-analysis was done using a Microsoft excel spreadsheet (10) and then studies were pooled according to the heterogeneity test results. In presence of significant heterogeneity, we used random model effect methods for meta-analysis. An overall prevalence with its 95% confidence intervals was calculated as a weighted average of individual summary statistics for eight age groups (1-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-40 and >40y). The results and forest plots were shown using Forest plot Viewer software (12). Since a large number of studies are included in the forest plots, the sample size and confidence intervals of pooled studies are listed in a separate table to reduce the clutter and to improve readability.

RESULTS

Search result. We found 72 relevant papers (after deletion of overlapping studies) out of all 112 searched citations in electronic search but failed to find more evidence during searching literature. Three new results were retrieved by backward and forward search of citations and Google scholar search. After exclusion of overlapping reports, we finally selected 15 studies. The detailed search process is demonstrated in Fig.2.

Studies. There were 18 relevant studies with satisfactory quality from 9 (out of 30) provinces (approximately 40% of the country's population). Five studies were from Tehran (the Capital) covering from 2003 to 2010 (13-17), two from Fars covering 2002-2003 and 2008 (18-19), and two from Kerman in 2008 and 2006 to 2008 (20-21). Other studies were from Bushehr 2009 (22), Hamadan (2009-2010) (23), Mazandaran (2010-2011) (24), Isfahan (2011) (25), Kermanshah (2012)(26), and Qazvin (2012) (27). All included papers were cross sectional studies conducted in Iran from 2002 to 2012 with sample sizes between 62 and 843. (Table 1) Age of the

Fig. 2. Selection of studies for inclusion in review: varicella seroprevalence in I.R. Iran.



a. Duplicated papers due to searching multiple databases.
b. Special groups: hospitalized patients, patients on haemodialysis, and hospital staff

subjects was between 1-70. Included studies have a female proportion between 100% (6 of 15) to 35%. Result of studies on the special groups (26, 28-30) who were assumed to be at groups with a higher risk for varicella (patients on hemodialysis, and health care workers) has been shown in Table 2. All studies had used ELISA methods, mainly Germany ELISAVZV IgG detection kits.

VZV immunity prevalence. Range of the reported VZV prevalence in childhood was wide and the studies showed heterogeneity (Table 3). The meta-analysis of point estimations and 95% confidence interval for VZV prevalence in different age groups were shown as a forest plot in Fig 3. The seropositivity prevalence steeply increased from the age of 1-5 to 6-10 [from 21.9% (95% CI; 10.8-33.1) to 42.1% (95% CI; 33.6-50.6)]. At the age of 11–15, 59.4% (95% CI; 46.1-72.8) of children showed to be infected. The rate of seropositivity was more than 87% in individuals of 40 and older. A gender difference in the prevalence of anti-VZV antibodies was reported in only one study(17). Trend of age-specific prevalence of VZV antibody in Iranian population during 2002 to 2012

Study's First Author (Year of collection*)	City	Target population	Prevalence of seropositivity in age groups [positive seroprevalence/ sample size (%)]											Reference
			1-5	6-10	11- 15	16- 20	21- 25	26- 30	31- 35	36- 40	41-45	46-50	51≥	Total	
Taghavi (2011)	Kashan	Referral pediatric hospital and public health centers	27/212 (12.7)	66/192 (34.4)	61/154 (39.6)									154/558 (27.6)	25
Farshchi (2012)	Kermanshah	Medical student					12/19 (63.1)	40/43 (93.0)						52/62 (83.9)	26
Allami (2012)	Qazvin	Medical science student				112/160 (70)	50/64 (78.1)	14/17 (82.4)	11/12 (91.7)					187/253 (74.0)	27

*: year of data collection / study

Table 2. Study characteristics of specific group, (varicella seropositivity prevalence in Iranian areas between 2002 and 2012 by regions)

Study's First Author (Year of collection*)	City	Target population	Prevalence of seropositivity in age groups [positive seroprevalence/ sample size (%)]									Reference
			16- 20	21- 25	26- 30	31- 35	36- 40	41-45	46-50	51-55	56-70	≥ 70	Total	
Talebi-Taher (2009)	Tehran	Health care workers		95/136 (69.8)	74/103 (71.8)	40/58 (68.9)	39/55 (71.0)	41/53 (77.4)					289/405 (71.4)	9
Talebi-Taher (2010)	Tehran	Patients on Hemodialysis			24/27 (88.8)			57/58 (98.2)			53/53 (100)	48/48 (100)	183/187 (97.9)	12
Bayani (2011-2012)	Babol	Healthcare workers			146/160 (91.2)		240/248 (96.8)		48/51 (94.1)				434/459 (94.6)	15
Farshchi (2012)	Kermanshah	Health care workers		10/16 (62.5)	30/39 (76.9)	80/88 (90.9)	39/45 (86.7)						159/188 (84.5)	26

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Table 1. Characteristics of included studies (varicella seropositivity prevalence in Iranian cities between 2002 and 2012 by regions)

Study's First Author (Year of collection*)	City	Target population	Prevalence of seropositivity in age groups [positive seroprevalence/ sample size (%)]											Reference
			1-5	6-10	11- 15	16- 20	21- 25	26- 30	31- 35	36- 40	41-45	46-50	51≥	Total	
Motamedifar (2002- 2003)	Shiraz	Primary school children		95/270 (35.2)										95/270 (35.2)	18
Sharifi (2003-2005)	Tehran	NA		46/77 (59.7)	31/51 (60.8)	91/104 (87.5)	133/151 (88)	42/47 (89.4)	51/58 (87.9)	43/49 (87.7)		64/74 (86.5)		511/611 (83.6)	13
Ehsanipour (2005)	Tehran	referred to hospital clinics	25/82 (30.6)	16/26 (61.5)	10/12 (83.3)									51/120 (42.5)	14
Pourahmad (2006-2008)	Jahrom	Premarital women			21/38 (55.3)	104/145 (71.7)	81/109 (74.3)	25/28 (89.3)	9/9 (100)	2/2 (100)	2/2 (100)			244/333 (73.3)	20
Ziyaeyan (2008)	Shiraz	referred to hospital clinics	39/154 (25.3)	60/139 (43.1)	78/106 (73.5)	84/101 (83.2)	41/49 (83.7)	41/48 (85.4)	37/42 (88.1)	31/35 (88.6)	81/92 (88)		67/77 (87)	559/843 (66.3)	19
Hosseininasab (2008)	Kerman	Premarital women					315/370 (85.1)	331/353 (93.8)						646/723 (89.3)	21
Pourakbari (2008)	Tehran	Children, adolescents and medical students			138/216 (63.9)	75/101 (74.2)	57/95 (60.0)							269/412 (65.3)	15
Talebi-Taher (2008)	Tehran	referred to hospital clinics					56/75 (74.7)	75/98 (76.5)	89/105 (84.8)	93/122 (76.2)				313/400 (78.2)	17
Barazesh (2009)	Bushehr	Premarital women				111/150 (74)	23/30 (76/67)							134/180 (74.5)	22
Mamani (2009-2010)	Hamedan	pregnant women				27/36 (75.0)	75/94 (79.8)	63/76 (82.9)	27/38 (71.1)	16/20 (80.0)	4/6 (66.7)			212/270 (78.4)	23
Talebi-Taher (2010)	Tehran	pregnant women				35/45 (77.8)	101/117 (86.3)	116/123 (94.3)	108/114 (94.7)					360/400 (90.3)	16
Bayani (2010-2011)	Babol	Pregnant women				40/47 (85.1)	90/101 (89.1)	137/150 (91.3)	109/117 (93.2)		9/12 (75)			385/427 (90.2)	24

Table 3. Heterogeneity for meta-analyses of prevalence

	Fixedeffects model				Heterogeneity	Randomeffects model			
Age group	Q	I^2(%)	Q/df	P value		Q_v	I^2_v	Q/df	P value
1-5	12.03	83.38	6.02	0.0024*	substantial	1.75	0	0.88	0.4160
6-10	10.54	62.06	2.64	0.032*	substantial	5.31	24.66	1.33	0.257
11-15	18.26	72.61	3.65	0.002*	substantial	3.57	0	0.71	0.613
16-20	3.99	0	0.50	0.8579	non-significant	10.97	27.06	1.37	0.2035
21-25	11.84	7.08	1.08	0.376	non-significant	10.77	0	0.98	0.463
26-30	3.85	0	0.43	0.921	non-significant	10.78	16.52	1.20	0.290
31-40	3.97	0	0.57	0.783	non-significant	-18.85	100	-2.69	1
>40	0.74	0	0.19	0.995	non-significant	1.31	0	0.33	0.859

df=degrees of freedom. *: significant P-value ≤ 0.10.

Age group	Estimate	95% CI (Lower CL-Upper CL)	N of studies	Total sample
1-5	21.96%	(10.83-33.09)	3	448
6-10	42.09%	(33.57-50.62)	5	704
11-15	59.44%	(46.07-72.81)	6	577
16-20	75.93%	(70.20-81.66)	9	889
21-25	80.23%	(75.31-85.15)	12	1274
26-30	89.54%	(83.62-95.45)	10	983
31-40	85.92%	(79.17-92.68)	8	723
>=40	87.17%	(75.89-98.45)	5	263

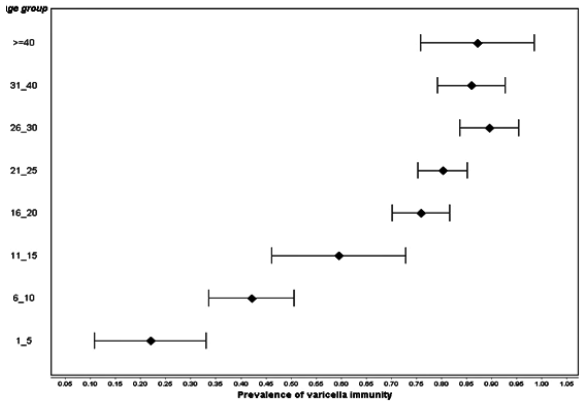

Fig. 3. Forest Plot of varicella immunity (prevalence estimation) by age group

is shown in Fig 4.

DISCUSSION

This study is an age-stratified systematic review and meta-analysis on VZV seroprevalence rates in Iran. Result of our study provides secondary (synthesized) epidemiological information on VZV infection based on results of seroprevalence studies in various regions of a climatically heterogeneous country. Also, it prepares the baseline information to design a more effective strategy for the national VZV control programs. We focused on published papers during 2002-2014 to estimate a more accurate estimation of VZV immunity prevalence rates. This meta-analysis indicates that varicella immunity tends to get higher in the older ages and VZV IgG antibodies remain detectable over a lifetime; while the rate of sero positivity is not decreased even among the individuals of 40s and more. This may be described by numerous re-exposures or endogenous

reactivation of VZV which preserve immunity (31). Seropositivity rates were low in the early childhood as the frequency of positive samples was 21.96% (95% CI; 10.83-33.09) during the first 1-5 years. By the age 6–10 years, 42.1% of the population had already been infected by VZV and at the age of 10–15 years, 59.4% of children were positive for anti-VZV antibodies. Finally, only a few individuals [12.83% (95% CI; 1.55-24.11)] were still susceptible to VZV infection by the age of 40 and more.

This study revealed that less than 60% of the populations have experienced infection before the age of 15. Also there is a relatively rapid rise in the seropositivity until the age of 25. This is important because varicella is considered as a benign and self-limiting disease of children, but it can be a potentially serious and life threatening condition in adults. (32)

Epidemiology of varicella shows different patterns in various climates. In tropical areas such as south Asian countries (e.g. Pakistan, Sri Lanka and India), the majority of varicella infections occur in young adults, while a few children (under 10 years old) are infected (33-35). A delayed onset of natural immunity (i.e. lower herd immunity and higher susceptibility to VZVin younger adults) happens in tropical regions while no apparent seasonal trend is observed. About one-fifth of the population remains at risk and VZV outbreaks can result complications such as pneumonia, hospitalization, and a greater burden of care especially in the middle-aged individuals (36-37). In temperate climates and in the absence of vaccination, varicella is relatively common in childhood with a high burden but low mortality rates. Many cases are presented before the age of 4, with a seasonal pattern (annual peak of late winter and early spring)(38-39).The majority of cases in temperate countries such as Germany, and Netherlands (before varicella vaccination), were found among young children and seroprevalence was increased steeply (40-41). Recent data from Switzerland showed that anti-VZV antibodies were detectable in 96.5% of 13–15-year old adolescents (42). Reasons for the different age distribution have remained unclear, although it could be a result of:1) different climates in these countries,2) a high degree of humidity and temperatures that inactivate the virus, thereby interrupting its transmission (43), and 3) the degree of childhood social interaction or population density in developed countries (44). As it is expected, the varicella seroepidemiology in Iran is compatible with

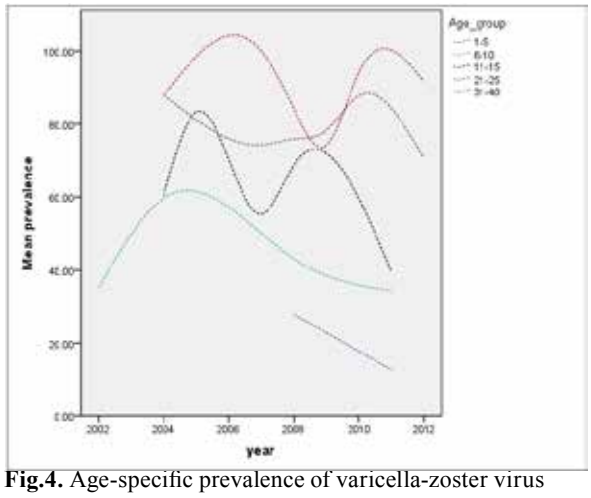

Fig.4. Age-specific prevalence of varicella-zoster virus (VZV) antibody in Iranian population (2002-2012)

average of both tropical and temperate regions. The results of the meta-analysis demonstrated a lower rate of varicella immunity in Iran than temperate countries and higher than tropical countries.

In our study, the comparison of prevalence rates in all childhood age-groups showed significant heterogeneity. Most of these studies were in Iranian temperate region. When there are only few studies, investigations of heterogeneity has a limited value (45). So, we performed a random effects model for meta-analysis instead of determining the causes of heterogeneity among results.

Considering overlap of VZV prevalence in two periods of time (2002-2005 and after 2005), we may conclude that prevalence rate of VZV in Iran has not changed significantly during those years. In Iran, absence of a mass vaccination program against VZV causes lack of significant changes in VZV immunity pattern. For example, in two studies from Tehran on the age group of11-15 (2003-2005 and 2008), positive seroprevalence rates were 60.78(95% C: 47.09-72.97) and 63.89 (95% CI: 57.29-70.00), respectively (13, 15). Also, studies conducted in adjacent countries to Iran have a similar finding. Comparison of conducted studies during 2002 to 2013 didn't show any alteration in VZV seroprevalence in Turkey (western adjacent) (46-49).

Result of this study could identify future potential research areas and help in medical service planning in Iran. The study provides baseline information to assess appropriateness of a mass vaccination program, design the most effective strategy, and evaluate national programs once in place. However, the main limitation of the study is limited generalizability of

the findings to whole Iranian population. The initial studies were conducted in nine major cities and did not cover rural population as well as people in other provinces and cities, so the results may not be easily generalized to whole Iranian population. This also could be a logical reason for more nationwide studies in this field.

CONCLUSION

The varicella seroepidemiology in Iran is in accordance with average tropical areas (south Asia) and temperate regions in the absence of vaccine (European countries). The seropositivity prevalence increased steeply from the age of 1-5 to 6-10 [from 21.9% (95% CI; 10.8-33.1) to 42.1 %(95% CI; 33.6-50.6)]. At the age of 11–15, 59.4% (95% CI; 46.1-72.8) of children showed to be infected. The rate of seropositivity was more than 87% in individuals of 40 and older. Comparison of conducted studies in Iran during 2003 to 2011 didn't show any alteration in VZV seroprevalence. In conclusion, our findings are consistent with prior information gathered in Iranian adjacent countries.

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