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Author: Omolbanin Amjadi Alireza Rafiei Mohammadreza Haghshenas Reza Alizadeh Navaei Reza Valadan Zahra Hosseini-Khah Akbar Hedayatizadeh Omran Mohsen Arabi Reza Jafari Shakib Tahoora Mousavi G. Hossein Ashrafi

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A systematic review and meta-analysis of Seroprevalence of Varicella Zoster virus: a nationwide population-based study.

Omolbanin Amjadi[1], Alireza Rafiei[1*], Mohammadreza Haghshenas[2], Reza Alizadeh Navaei[1], Reza Valadan[1], Zahra Hosseini-Khah[3], Akbar Hedayatizadeh Omran[4], Mohsen Arabi[5], Reza Jafari Shakib[6], Tahoora Mousavi[1] and G. Hossein Ashrafi[7*]

[1] Molecular and Cell Biology Research Center, Department of Immunology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[2] Department of Microbiology and Virology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[3] Department of Molecular Medicine, School of Advanced Medical Technologies, Tehran University of Medical Science, Tehran, Iran.

[4] Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran

[5] Department of Social Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[6] Department of Immunology, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[7]SEC Faculty, Penrhyn Road, Kingston University London, Kingston upon Thames, UK KT1 2EE

[*] Corresponding Authors:

G. Hossein Ashrafi, School of Life science, Pharmacy and Chemistry, SEC Faculty, Kingston University London, Penrhyn Road, Kingston Upon Thames, KT1 2EE. Email: h.ashrafi@kingston.ac.uk

Alireza Rafiei, Faculty of Medicine, Molecular and Cell Biology Research Center, Department of Immunology, Mazandaran University of Medical Sciences, Sari, 48175-1665, Iran, E-mail: rafiei1710@gmail.com

Running title: Seroprevalence of Varicella Zoster virus

Abstract

Varicella zoster virus (VZV) causes chicken pox as a primary infection following which it becomes latent in neurons. It may then reactivate to cause shingles (herpes zoster). Severity of lesions and VZV pathogenicity are depended on the host's immune response and variant in VZV Dr Athina Myrto ChioniIdentification of VZV seroprevalance rate in general population may lead to develop new health strategic managements such as vaccination. Therefore, we aimed to provide a systematic review of the seroprevalence of VZV infection among Iranian population and estimate age- and gender- specific prevalence of VZV.

Keywords "seroprevalence", "varicella zoster virus", and "Iran" were searched in international electronic databases and also in national Persian databases. Twenty two pooled studies among 262 total studies containing (240 published articles, 18 dissertations, and 4 proceedings abstracts) from 1992 to 2014 with total sample size of 7867 individuals were included in the final review. Data was analyzed using random effect method. The heterogeneity was calculated using I-square statistics.

The overall IgG seroprevalence rate of VZV infection in general population of Iran was 78.50% (95% CI; 77.74% - 79.25%). There was significant heterogeneity among the studies ($P<0.0001$; $I^2=99.4\%$). Furthermore, the relative risk of VZV infection is high in females (80.47%, 95% CI; 79.40% - 81.54%) and older adults (95.30%, 95% CI; 94.11% - 96.48%).

Our results may represent a true background and estimation of VZV infection in Iran and generate the cost-benefits immunization program. Moreover, the ensuing data suggests further attention on disease seroprevalence in order to obtain efficient data for therapeutic intervention targeted against VZV.

Keywords: Varicella zoster virus, Seroprevalence, IgG, Immunity, Vaccination, Iran

Introduction:

Varicella Zoster Virus (VZV) is a double-stranded DNA genome from alpha-herpes virus family. VZV is a persistent human pathogen causing chicken pox in the early stages of infection. VZV establish a latent infection within the spinal cord ganglia (dorsal root/sensory ganglia) during the primary infection that can be reactivated and cause herpes zoster (shingles) followed by secondary viremia (Arvin, 1996), (Gilden *et al.*, 2011). Also clinical presentation of varicella is differed from chickenpox. In varicella, skin vesicles mostly distribute on the head but in chickenpox; vesicles, pustules, and scabs may be present at the same time on any part of skin (Gershon & Gershon, 2013). Although VZV has host specificity and shows less DNA-sequence diversity, but few *in vitro* and *in vivo* reports demonstrated differences in pathogenic potential of VZV (Gershon & Gershon, 2013).

The primary infection mostly manifested as macular rash, then formed papules and vesicular eruption, fever, while reactivation of dormant virus is involved in the severe form of the disease in adults (Mueller et al., 2008). Herpes zoster (HZ) is characterized by the painful blistering rash along the dermatomes (Sampathkumar et al., 2009). Although herpes zoster (HZ) is not limited to any age, the risk of HZ is increased by age and also with advanced immune-suppression (Liesegang, 2008).

The incidence of this highly contagious infection increases markedly by the age (Yawn *et al.*, 2007). There are some potential consequences of VZV infection; serious complications such as skin lesions, pneumonia, encephalitis, and hepatitis that threaten adolescents (Arvin, 1996). This may lead to mortality in some cases (Arbeter, 1996). Moreover, pregnant women are another group infected by varicella with high risk of transmission to fetus and newborns (Paryani & Arvin, 1986). Embryos suffer from congenital varicella syndrome and congenital malformation

due to transplacental infection of maternal varicella (Shrim *et al.*, 2012). Chorioretinitis, cerebral cortical atrophy, hydronephrosis, and cutaneous and bony leg defects, often presenting as a partial limb reduction are some examples of fetal deformations of varicella infection (Andrews, 2004).

Since different age groups of people are susceptible to HZ, the morbidity and mortality of zoster infection must be reduced by effective management and anti-viral therapy. Vaccination is one of the most appropriate protective ways used to increase immunity against varicella. As VZV vaccine is not a part of routine immunization schedule in Iran, data on the incidence of VZV are essential to schedule the effective vaccination programs. Seroprevalence studies can be counted as valuable approach to gain precise estimation of susceptible patients (Vandersmissen *et al.*, 2000). The most of the studies on prevalence rate of VZV infection in Iran have focused on high risk groups such as pregnant women, healthcare workers, and medical and paramedical students. On the other hand, there is no comprehensive information on the seroprevalence rate of VZV infection in overall population of Iran. To achieve this we employed a comprehensive systematic review on the seroprevalence of VZV and its risk factors association in general population in order to improve better health control policies. Here we highlight the necessity of vaccination program that may well lead to a faster resolution of VZV infection with obvious advantages for all VZV affected patients.

Methods:

Search strategy

Databases such as PubMed, Web of knowledge, Scopus, Science Direct, Google Scholar, DOAJ, Embase, and national Persian databases (Magiran, Scientific Information Database [SID], Iran

Medex, and Iran Doc), as well as conference proceedings were used to conduct comprehensive search of studies in the field of VZV infection. All studies from 1992 to 2014 were included using the search term of (Varicella zoster OR varicella zoster virus OR herpes zoster) AND (seroprevalence OR seroepidemiology OR epidemiological study OR immunity OR antibody) AND (Iran OR Islamic Republic of Iran).

Study selection

All cross sectional studies which aimed on IgG seroprevalence or seroepidemiology of VZV infection in the Iranian population were included. Of the total publications, duplicate and similar ones were identified and excluded. Since both English and Persian publications were included, publications with same data but different languages were removed in the next step. They were then reviewed by the two independent and blinded expert reviewers. The information was recorded on particularly designed sheets. Reviewers checked all potentially relevant studies and reached a consensus on all items. The evaluation was performed on the title and abstracts for the selection of studies. Any disagreement between the two reviewers was resolved after discussion and consultation with a third reviewer. Data were recorded on special designed forms containing general information about each article: author names, publication date, population size, regional target, age, and method of evaluation. The relevant studies were identified in to two stages: 1) all titles, abstracts and keywords were manually screened in order to find publications consistent with the main aim of the study; 2) full-text was downloaded and reviewed by the authors for further identification and confirmation of previous finding.

Inclusion and exclusion Criteria for determine Eligible studies

Inclusion criteria

The selection criteria included studies with all English and Persian articles that reported in the cross- sectional descriptive data from Iran with a focus on letters to the editors, abstracts, and dissertations studies on the Seroprevalence/Seroepidemiology of VZV in Iran, The inclusion criteria also concentrated on studies (a) with clear serological confirmation of IgG antibodies in sera of population using diagnostic methods (b) in high risk population group such as pregnant women and people of both genders and of all ages in every geographical region of Iran.

Exclusion criteria

We have excluded studies from Case reports, reviews, commentaries, author replies, animal studies, and non-accessible full-text articles. Insufficient raw data/ studies that have not been published in peer reviewed journals and studies with non-random sampling methods were also excluded.

Data Extraction

The data extraction form was used in order to provide a summary table containing necessary information of studies that were included in this review. Following data were extracted from each study: first author's name, date of publication, location of study, characteristic of population (age range, sample size, and population groups), diagnostic method, prevalence of VZV and calculated odd ratio (OR) and p-value. The extracted data were then checked by all authors for further verification.

Data Analysis

Point estimates and their 95% confidence intervals (CI) of seroprevalence of the studies were calculated. An overall seroprevalence rate and subgroup analysis based on gender- and age-

groups specific VZV seropositivity was calculated. A forest plot was used to visualize the heterogeneity among the studies. The heterogeneity was expected in advance, and statistical methods, I^2 statistics ($P<0.1$) were used to quantify the variations. For the purpose of meta-analysis, we assumed that the included studies were a random sample from a population of studies, and thus a random effects model was employed. Forest plots presented proportions of individual studies and overall seroprevalence. The meta-analysis was performed with the STATA software version 11.1 (StataCorp, College Station, TX, USA).

Results

Search Results

The study selection proceeded as described in the flow chart in Fig. 1. A total number of 262 publications were identified containing 240 databases-derived citations, 18 dissertations, and 4 abstracts of congress proceedings. 154 out of 240 articles with duplicate content were removed. 97 studies were considered for further screening following the exclusion of non-unique studies. The abstracts and full-text were then reviewed by the authors for screening irrelevant publications. Finally, 22 relevant reports with 7867 subjects were included in the systematic review and their information was summarized in Table 1. All eligible studies have used enzyme-linked immunosorbent assay (ELISA) as a diagnostic method to detect anti-VZV IgG antibodies.

Prevalence of VZV

22 articles reported VZV seroprevalence rate from 10 places among Iranian population; 9 studies from Tehran (Akhbari, 2012; Ehsanipour *et al.*, 2009; Pourakbari *et al.*, 2012; Sharifi & Emadi Ghanjin, 2005; Talebi-Taher *et al.*, 2013; Talebi-Taher *et al.*, 2014; Talebi-Taher *et al.*,

2010; Talebi-Taher & Rezaie, 2012; Vojgani *et al.*, 2014), 2 studies from Babol (Bayani M, 2013; Bayani *et al.*, 2013), 3 studies from shiraz (Moattari A, 2014; Motamedifar M, 2006; Ziyaeyan *et al.*, 2010), 1 study from Kashan (Taghavi Ardakani *et al.*, 2013), 2 studies from Hamedan (Mamani M, 2009; Mamani M, 2012), 1 study from Jahrom (Pourahmad *et al.*, 2010), 1 study from Kerman (Hosseininasab *et al.*, 2013), 1 study from Kermanshah (Farshchi & Niayesh, 2011), 1 study from Bushehr (Barazesh *et al.*, 2014), and 1 study from Qazvin (Allami *et al.*, 2014). The Talebi-Taher *et al*, study in Tehran reported highest seroprevalence of VZV, with incidence rate of 97.9% and the lowest VZV prevalence rate (15%) was found in Moattari *et al* (Moattari A, 2014). The results of heterogeneity test manifest extreme heterogeneity among reported studies (P=0.00; I^2=99.4%). Due to severe heterogeneity, random effect meta-analysis was performed. The overall seroprevalence of VZ infection among the Iranian population using the random-effects model meta-analysis was 78.50% (95% CI; 77.74% - 79.25%). It is found that 5565 individuals out of 7867 were VZV IgG seropositive. Fig 2 is shown forest plot. We observed high heterogeneity between studies; hence only data from "general" populations (excluding high risk population such as pregnant women and haemodialysis patients) were used in meta-analysis. As shown in Fig. 3 the overall seroprevalence rate of VZV infection in the general population was 67% (95% CI; 65.83 - 68.18%).

Subgroup analysis

Classification of participants according to gender presented high seroprevalence of VZV among females (80.47% vs. 75.62%, P=0.001, respectively) (Fig. 4). In the next step, we analyzed seroprevalence rate of VZV based on age distribution. Interestingly, all studies were distributed into three age groups. The seroprevalence rate increased with age: from 46.21% (95% CI; 44.53-

47.89%) in the age < 20 years to 88.97% (95% CI; 87.87-90.06%) in 20-40 years and then increased to 95.30% (95% CI; 94.11-96.48%) by age > 40 years. The peak prevalence was seen in the age >40 95.30% (95% CI; 94.11-96.48%) (Fig. 5).

Discussion:

In overall, VZV seropositivity rate is 78.50% in Iran. This is in consistent with studies from Turkish which reported 77.8% (Kanra *et al.*, 2002) and 78% (Alp *et al.*, 2005) VZV seropositivity increasing with age. Seroprevalence rate of VZV infection in Cyprus was reported 84.1% in an age-related pattern (Kurugol *et al.*, 2007). However, VZV prevalence was differed in other countries in Asia. In comparison to Iran, high VZV seroprevalence was reported from South Korea (92.7%) (Kang *et al.*, 2008) and Israel (90.2%) (Cohen *et al.*, 2006) while low VZV rate was reported from India (68.22%) (Lokeshwar *et al.*, 2000), Singapore (55.3%) (Fatha *et al.*, 2014), Thailand (61.4%) (Migasena *et al.*, 1997), and Pakistan (41.8%) (Akram *et al.*, 2000). In all reports, an age-dependent pattern was demonstrated in VZV seropositivity.

High seroprevalence of VZV IgG antibodies (94%) were found in adults in Amesterdam (95% CI; 92–96%) that is consistent with some European countries with more than 90% seropositivity (van Rijckevorsel *et al.*, 2012). A Polish study with VZV seropositivity rate 76.6% (95% CI: 74.6-78.7%) came to a same conclusion with Iranian's rate of VZV prevalence (Siennicka *et al.*, 2009). Results from that study demonstrated a close relationship between seroprevalence and age but no correlation with gender, rural/urban areas and geographical regions of Poland (Siennicka *et al.*, 2009).

Moreover, we found a linear relationship between seropositivity and age. Age-specific VZV seroprevalence increased significantly from 46.21% for individuals aged less than 20 years to

95.30% for individuals aged more than 40 years (Fig. 5). Similar age-increasing results were systematically reported in North America, Europe, and Asia-Pacific- based studies (Kawai *et al.*, 2014). Age-dependent VZV seropositivty was also demonstrated in European population (Pinchinat *et al.*, 2013). This systematic review also suggests that women have slightly high rates of VZV susceptibility than men (80.47% vs. 75.62%, P=0.001, respectively).

There is now revealed that women have an increased risk of developing varicella zoster. As the study population is unequally distributed on gender, high numbers of infected-women may lead to false seropositivity rates for women. While there are different results in seroprevalence level in different countries, even among neighboring countries, most studies were in agreements with age-related patterns of seroprevalence. Therefore, this finding provides a strong impetus to spur further research in an important global health imperative involving patients with VZV infection and emphasizes to focus on immunization programs capable of protecting elderly populations against VZV pathogenesis.

Findings from this systematic review revealed significant heterogeneity even after focus on stratification of study population on general population without consideration high risk people (Fig. 3). Variation in seroprevalence of varicella infection may depend on different risk factors. It is shown that risk factors such as age, gender, ethnicity, genetic susceptibility, exogenous boosting of immunity from varicella contacts, underlying cell-mediated immune disorders, mechanical trauma, psychological stress, and immunotoxin exposure could modulate the incidence of varicella (Thomas & Hall, 2004). There are other reasons to clarify heterogenic prevalence results. The prevalence of VZV may be affected by climatic factors (Kang *et al.*, 2011). It was found that Asian countries with temperate climates make a favor condition for varicella virus transmission (Lee, 1998). Temperate climates in Sri Lanka participate in high

VZV seroprevalence rates (Liyanage *et al.*, 2007). It was observed that VZV seroprevalence rate among young adults in temperate locations of Brazil was noticeably higher than that of the tropical regions (Reis *et al.*, 2003). High rates of VZV seropositivity in childhood in temperate climates and in adults in hot and tropical regions were reported in some studies (Schmid & Jumaan, 2010; Sengupta & Breuer, 2009). In addition to the influence of climatic differences in the incidence of VZV infection, seasonal pattern was also reported in the seroprevalence of VZV in temperate regions. On the other hand, its prevalence is higher in winter and spring (Rice, 2011). The rate of VZV seroprevalence is high, 90%, in North of Iran as a temperate region. This might be due to the fact that Northern region-derived studies focused on high-risk populations (pregnant women and healthcare workers), therefore high rates of seroprevalence was expected. This would have provided more useful information if seasonal pattern was also considered in these studies. In order to explore the effect of geographical region on this issue, more investigations are required in Northern provinces and other provinces of Iran with different climates. Comprehensive epidemiological data on general population in different regions is required to achieve further information on VZV prevalence. Fig. 6 demonstrates many unanalyzed regions and/or same regions with multiple results that should be further analyzed. Further research is needed to achieve more precisely and reliable results and facilitate the comparison of data from different region.

Differences in seroprevalence between natives and immigrants such as Afghan, may determine the effects of climate factors on the seroprevalence. Of the other possible explanation for heterogeneity could be the individuals participating in the study, as few investigations quoted in this analysis were based on vulnerable people such as pregnant women and/or healthcare workers with a great heterogeneity (Bayani M, 2013; Bayani *et al.*, 2013).

Insufficient number of studies on VZV seroprevalence restricted comprehensive searching, which is a problem in any systematic review. Therefore, we had to use all different studies and populations, thereby finding wide heterogeneity. Furthermore, there were some limitations in pooled publications. First, different populations in view of size, their occupation, location of birth and geographical state, age, and gender were surveyed in study design. Second, low number of populations restricted random sampling. Third, although same method was used in these studies; however, different types of kits might have influenced the sensitivity and specificity of results. Last, there are many unreported regions and also some places with more than one report in Iran (Fig. 6). Despite all limitations, significant heterogeneity was not unexpected.

Collectively, VZV is associated with establishment of two diseases following primary infection (chickenpox) and reactivation of latent infection (shingles). It may associate with pulmonary, neurologic, and cutaneous complications (Gnann, 2002). Since wide range of neurological manifestations such as aseptic meningitis, myelitis, peripheral motor neuropathy, encephalitis, Gullain-Barr syndrome, and stroke syndromes may occur in patients at any age, they are considered as the most important complications. Patients treated with immunosuppressive drugs due to cancer, HIV, transplants, and diabetes are more susceptible to be affected by HZ (Albrecht M, 2011). Moreover, VZV infection in pregnancy puts the expectant mothers at high risk for mortality and morbidity. Their pregnancy might lead to congenital varicella syndrome with destructive effects on fetus and newborns (Gardella & Brown, 2007). The airborne transmittance route of VZV made it as a highly contagious human disease (Schmid & Jumaan, 2010) and reactivation of latent virus may also affect people. Therefore, it needs more attention for cost-effective treatment and preventive strategies.

Obviously, accurate understanding of the epidemiology of disease is the perquisite step for obtaining effective health control program that could attenuate the destructive effect of disease/infection on human health. Varicella vaccination not only can reduce the rate and incidence of VZV but also decreases its severity (Schmid & Jumaan, 2010). It is renowned that varicella deaths are now preventable by vaccines (Meyer *et al.*, 2000). For example, a significant reduction in varicella deaths in US was observed after successful implementation of 1- dose vaccination program. The most severe outcomes of disease could be eliminated following the 2-dose program (Marin *et al.*, 2011). *"*The epidemiology of VZV has important implications for future vaccine strategies*"* (Kudesia *et al.*, 2002). Comprehensive population-based studies provide valuable data to planning immunization programs and evaluate the effect of vaccination as a cost-effective program (Brisson *et al.*, 2001). Serologic studies provide detailed information about varicella immunity and varicella-relating factors.

The present study was performed based on the importance of VZV specific antibody assay to evaluate immunity levels against the disease. The serologic data from 22 articles studying different ages, provinces, and at risk groups in Iran were collected. Although the most accurate results are dependent on participation of all geographical regions, systematic analysis of the current information may lead to effective monitoring in other regions.

Conclusion

Consequently our results demonstrated high VZV seroprevalence in Iran especially in North of Iran. Direct relationship has been found between age and prevalence of VZV. Our results show that women are more susceptible to varicella infection than men. Because of insufficient data from different climates, we cannot exactly direct a relationship between seroprevalence and

climate. Therefore, more screening and appropriate programs on disease prevention, treatment, and management planning are needed for virus eradication and reducing the social and economic burden of varicella infection in societies. Further investigations considering seroprevalence analysis, may provide a common condition for comparing prevalence rate and prioritizing treatment methods.

Authors' contributions:

AR and HA: conception and design, manuscript writing and final approval of the manuscript; RA-Nava and MA and RV: methodological and statistical advice and final approval of the manuscript; MH and AH-Omran: design study protocol; OA and TM and ZH-Khah: searching and collecting data and final approval of the manuscript; OA write the first draft. All authors have read and approved the final manuscript.

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Ethical approval:

This study is exempt from ethical approval because it will be collecting and synthesizing data from previous reports in which informed consent has already been obtained by their investigators

Competing interests:

The authors have no conflicting interests to declare.

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Figures

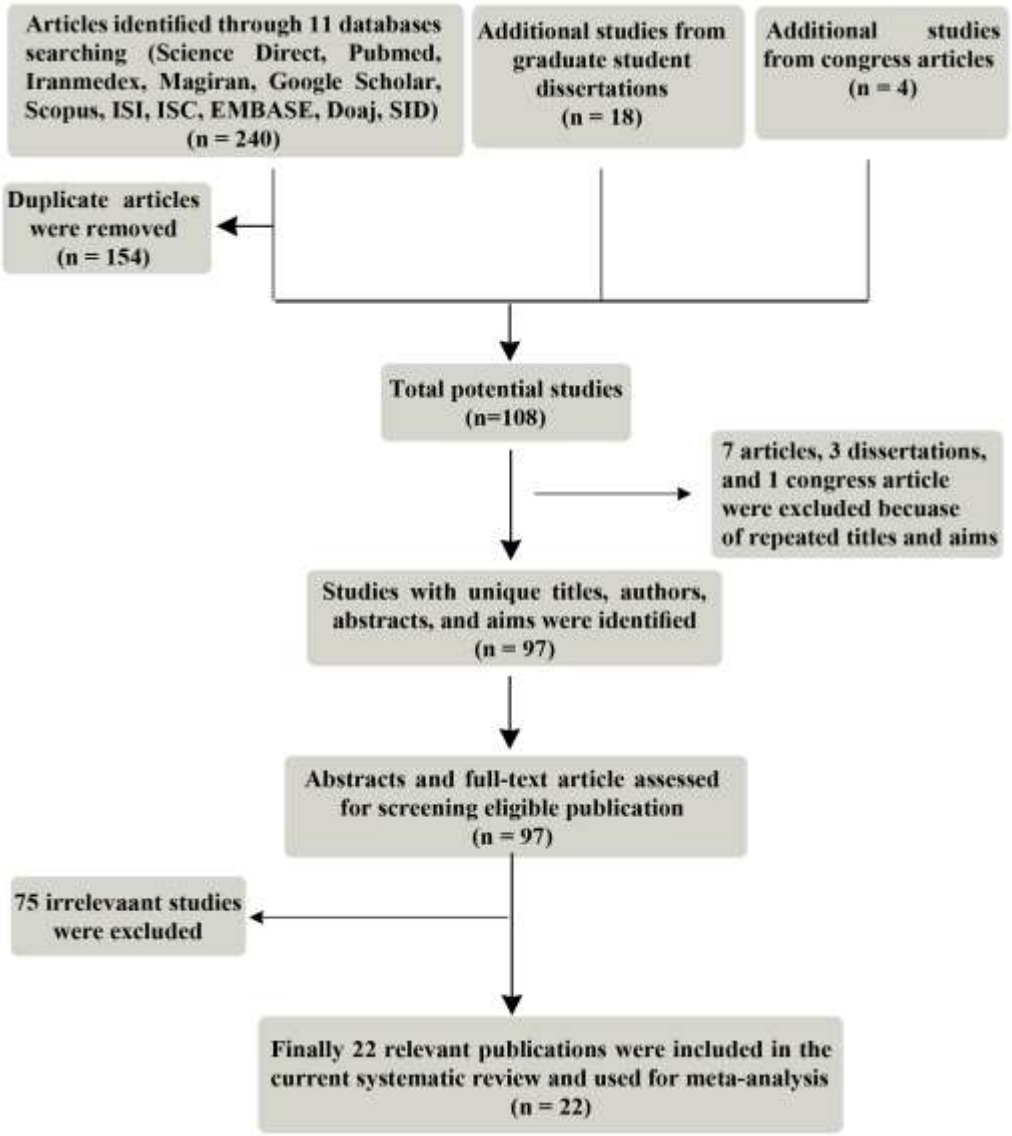

Figure 1: Flow diagram of selection strategies and including articles

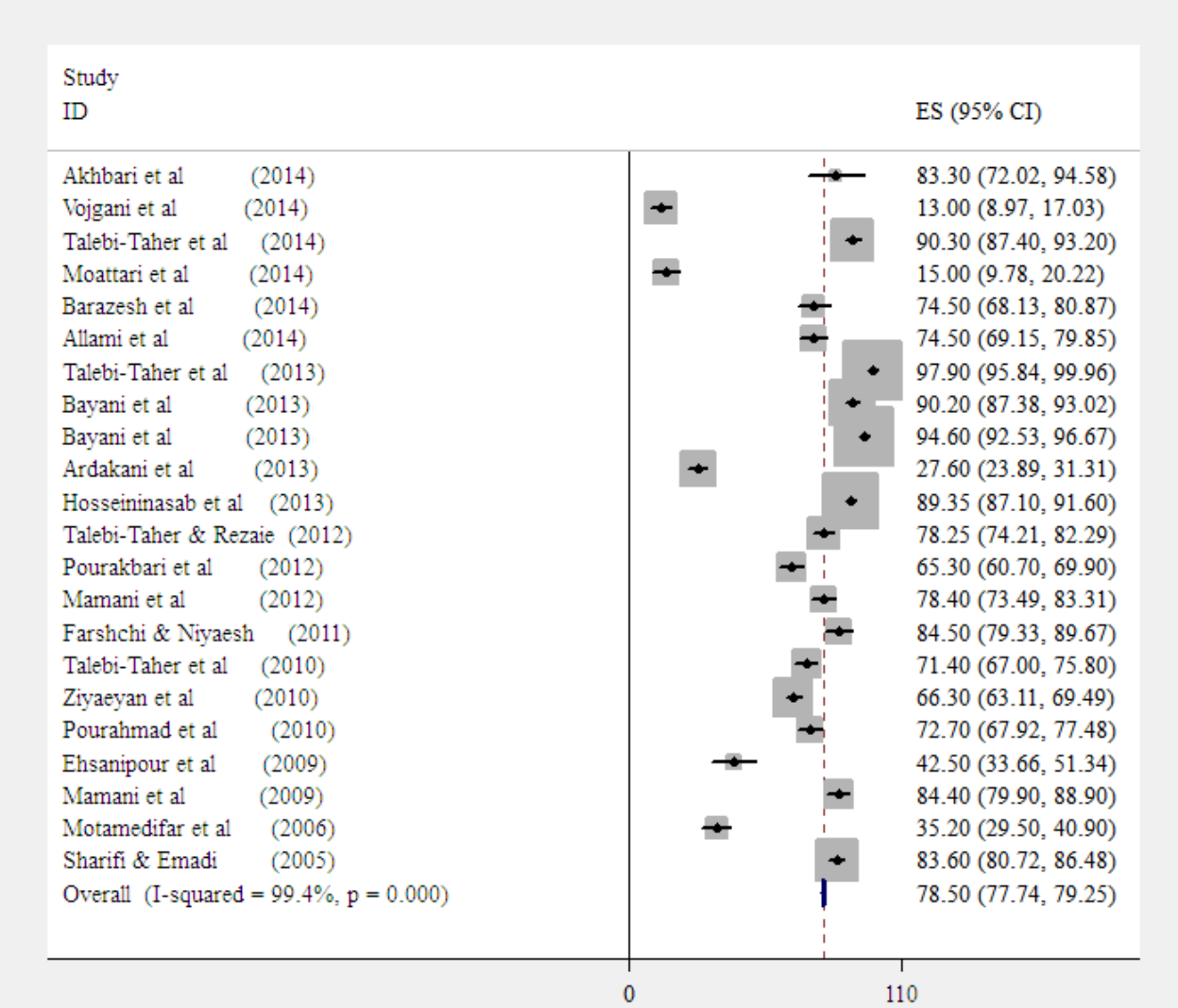

Figure 2: Forest plot diagram of 22 studies showing IgG seropositivity rates of *Varicella Zoster* infection in Iranian population (first author and year of publication)

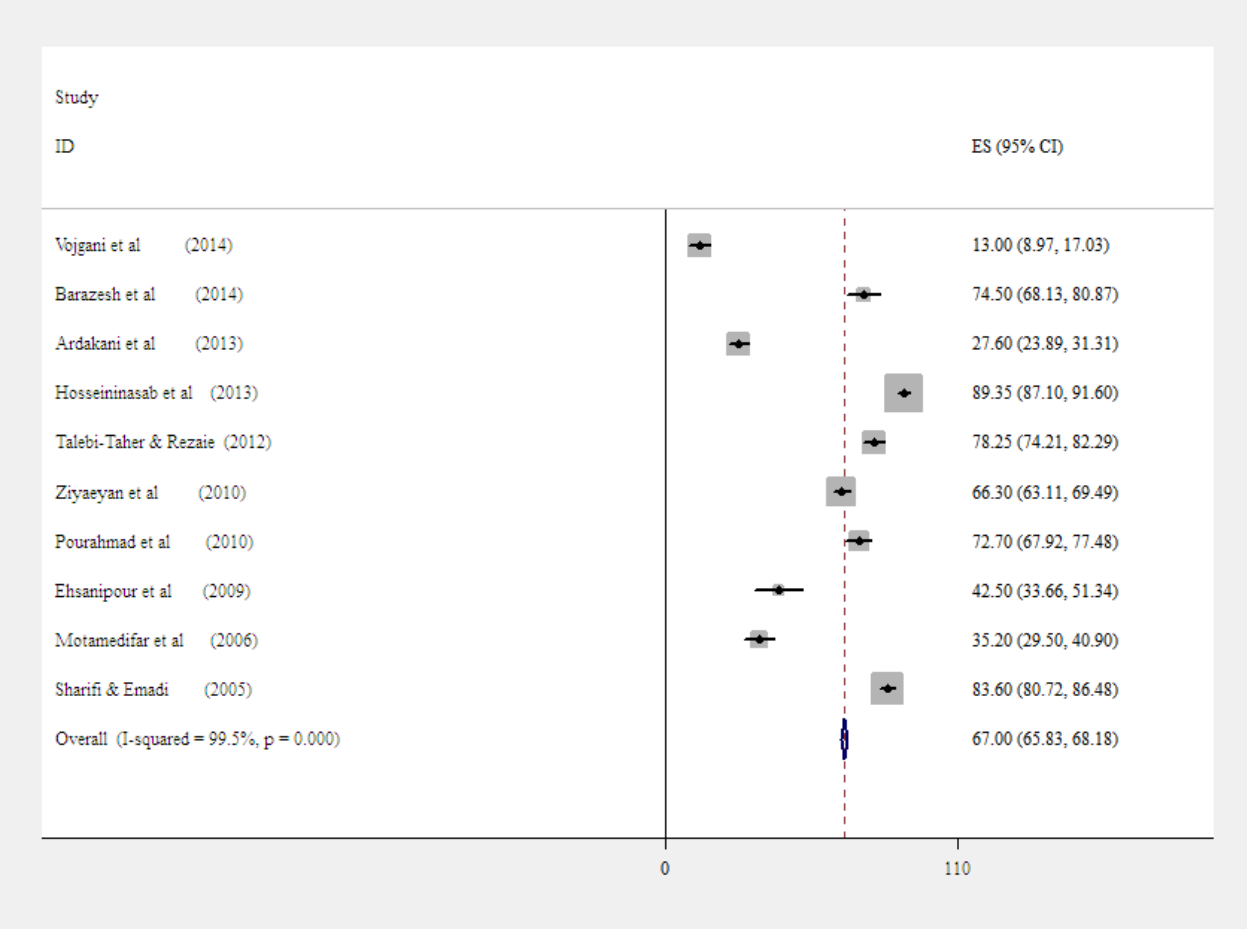

Figure 3: Forest plot diagram of 10 studies containing general populations showing IgG seropositivity rates of *Varicella Zoster* infection in Iranian population (first author and year of publication)

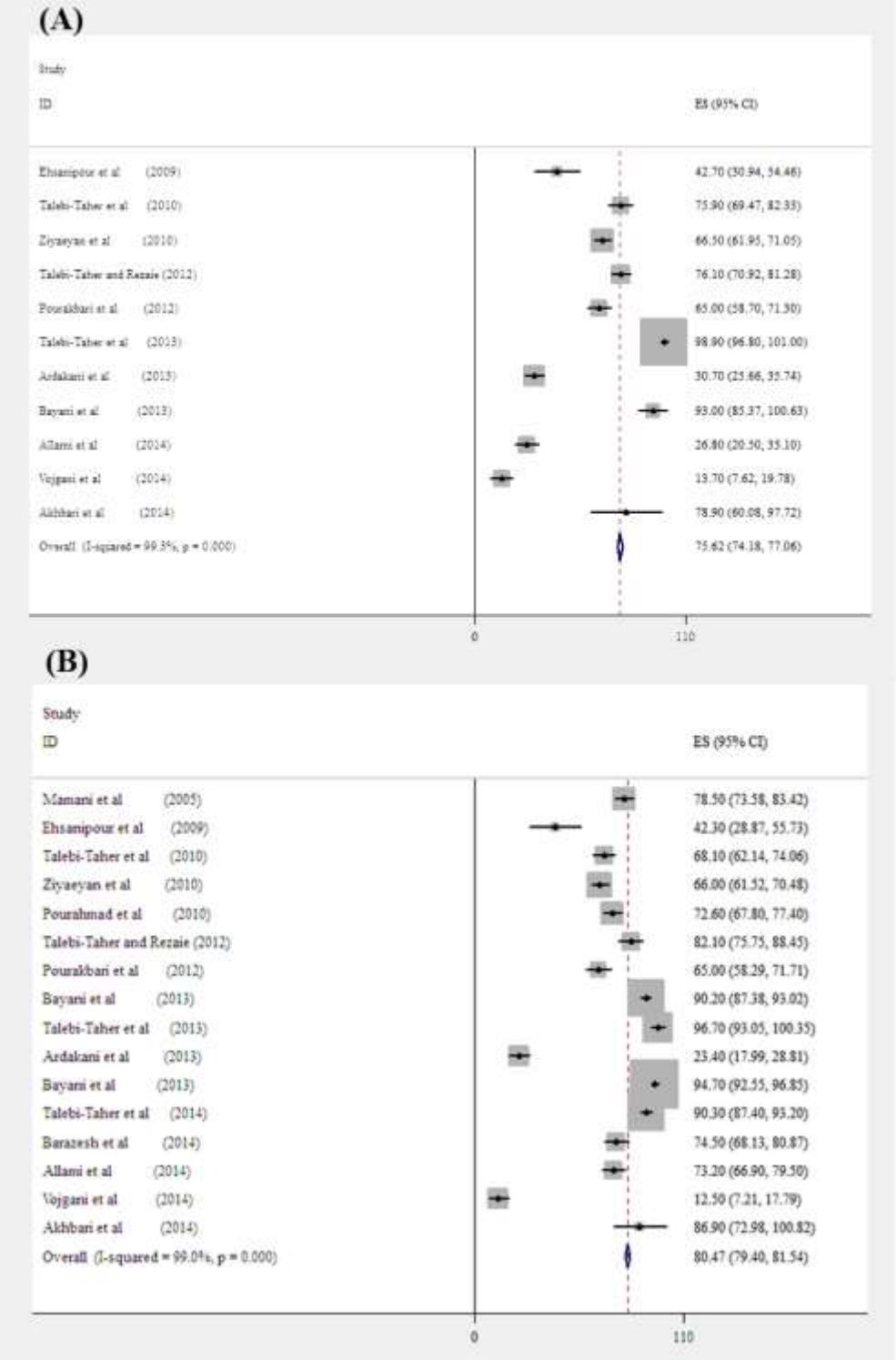

Figure 4: Forest plots of VZV seroprevalence in the males (A) and females population (B).

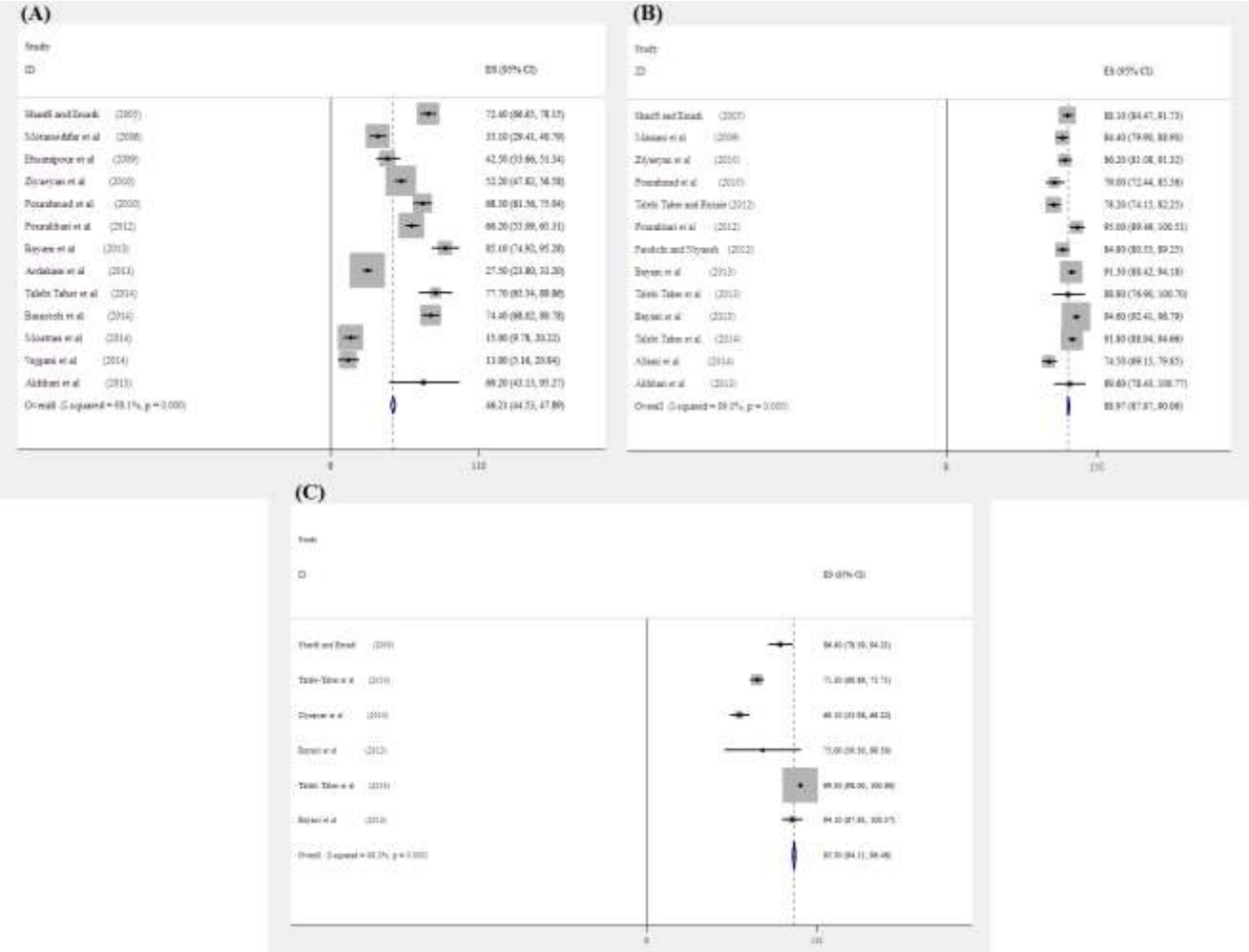

Figure 5: Forest plots of VZV seroprevalence in different age groups: (A) < 20; (B) 20-40; (C) >40

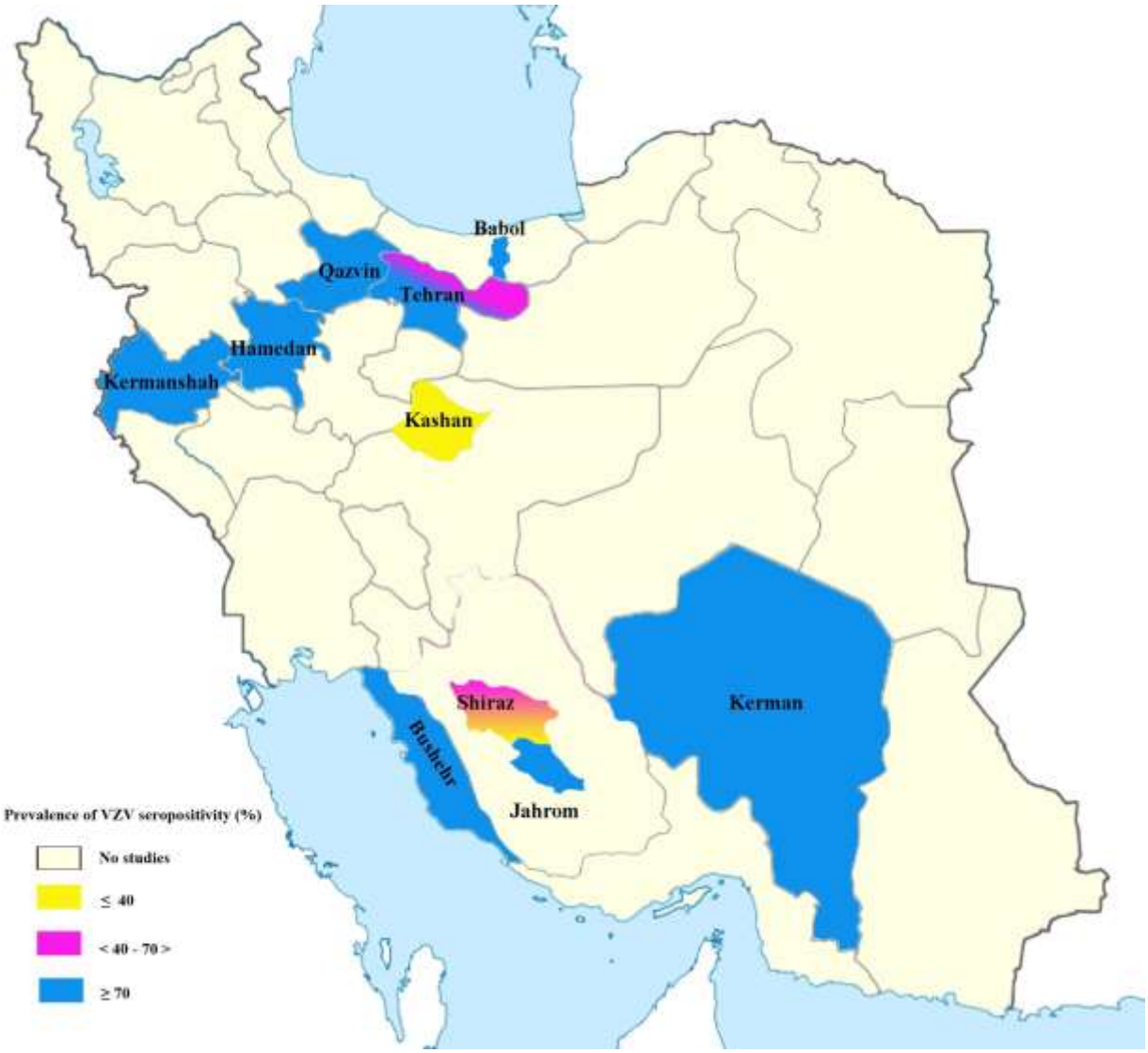

Figure 6: The seropositivity rate of varicella zoster infection in different regions of Iran.

Tables

Table 1: Characteristics of included studies

Reference	Study dates	Study region	Total individuals	Seroprevalence (%)	IgG positive (n)	Age range (Year)	Study population	Method
Akhbari *et al.* (Akhbari, 2012)	2012	Tehran	42	83.3	35	17-29	Medical students	ELISA
Vojgani *et al.* (Vojgani *et al.*, 2014)	2011-2012	Tehran	267	13	35	≤ 7	Healthy children	ELISA
Talebi-Taher *et al.* (2010) (Talebi-Taher *et al.*, 2010)	2009	Tehran	405	71.4	289	19 - 50	Healthcare workers	EIA
Talebi-Taher & Rezaie (2012) (Talebi-Taher & Rezaie, 2012)	2009	Tehran	400	78.25	313	20 - 40	Inpatients	ELISA
Talebi-Taher *et al.* (2013) (Talebi-Taher *et al.*, 2013)	2010	Tehran	187	97.9	183	18 - 88	Hemodialysis patients	EIA
Talebi-Taher *et al.* (2014) (Talebi-Taher *et al.*, 2014)	2010	Tehran	400	90.3	361	16 - 43	Pregnant women	EIA
Sharifi & Emadi (2005) (Sharifi & Emadi Ghanjin, 2005)	2003-2005	Tehran	635	83.6	531	1 - 60	Health volunteers	ELISA
Pourakbari *et al.* (2012) (Pourakbari *et al.*, 2012)	2008	Tehran	412	65.3	269	10 - 25	Children, adults, and medical students	ELISA

Ehsanipour *et al*. (2009)(Ehsanipour *et al.*, 2009)	2009	Tehran	120	42.5	51	1 - 16	Children	EIA
Bayani *et al*. (2013)	2010-2011	Babol, Mazandaran	427	90.2	385	16 - 50	Pregnant women	ELISA
Bayani *et al*. (2013)	2011-2012	Babol, Mazandaran	459	94.6	434	20 - >40	Healthcare workers	ELISA
Motamedifar *et al*. (2006)(Motamedifar M, 2006)	2002-2003	Shiraz	270	35.2	95	6-10	Young children	ELISA
Ziyaeyan *et al*. (2010) (Ziyaeyan *et al.*, 2010)	2008	Shiraz, southern Iran	843	66.3	559	1-70	Outpatients	ELISA
Moattari *et al*. (2014)(Moattari A, 2014)	2014	Shiraz	180	15	27	18- 21	Medical and dental students	ELISA
Ardakani *et al*. (2013) (Taghavi Ardakani *et al.*, 2013)	2011	Kashan	558	27.6	154	1-15	Primary health services	ELISA
Mamani *et al*. (2009)(Mamani M, 2009)	2009	Hamedan	250	84.4	211	32 ± 9.6*	Healthcare workers	ELISA
Mamani *et al*. (2012)(Mamani M, 2012)	2009-2010	Hamedan	270	78.4	210	24 - ≥34	Pregnant women	ELISA
Pourahmad *et al*. (2010) (Pourahmad *et al.*, 2010)	2006-2008	Jahrom (south of Iran)	334	72.7	242	12 – 45	Young women	ELISA
Hosseininasab *et al*. (2013)(Hosseininasab *et al.*, 2013)	2013	Kerman, southern Iran	723	89.35	646	24.1 ± 6.3*	Women on reproductive age	ELISA

Farshchi & Niyaesh (2011) (Farshchi & Niayesh, 2011)	2012	Kermanshah	188 62	84.5 84.5	159 52	23-40 18-25	Healthcare workers Students	ELISA
Barazesh *et al*. (2014)(Barazesh *et al.*, 2014)	2009-2010	Bushehr	180	74.5	134	17-24	Female students	ELISA
Allami *et al*. (2014) (Allami *et al.*, 2014)	2012	Qazvin	255	74.5	190	18-49	Medical, nursing, and obstetrics students	ELISA

* Mean age ± SD of these studies was accessible.