

Prevalence of HBsAg Amongst Healthy Children in Eastern Mediterranean and Middle Eastern Countries: A Systematic Review and Meta-Analysis

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Abstract

Context: Infections caused by the hepatitis B virus (HBV) pose a major challenge to the public health and also results in high mortality and morbidity rates in different parts of the world, especially in children. This study performed a systematic review and a meta-analysis of cross-sectional studies conducted during the years 2000-16 to clarify the prevalence of hepatitis B surface antigen (HBsAg) in children and adolescents younger than 16 years of age in EMRO and Middle Eastern (E and M) countries.

Evidence Acquisition: Scientific databases including PubMed, Ovid, Scopus, Google Scholar, and Persian databases were searched for relevant articles published from January 1, 2000 to October 31, 2016. Based on the results of homogeneity tests (a significant homogeneity test and a large I² value) a random effects model was used to aggregate the collected data and calculate the pooled prevalence estimates.

Results: We included 20 articles in our meta-analysis. The pooled HBsAg prevalence in children of E and M countries was 2.73% (95% CI: 1.73% - 3.72%). The prevalence rates in the EMRO and Middle Eastern countries were 1.85% (95% CI: 1.27% - 2.43%) and 2.66% (95% CI: 1.31% - 4.01%), respectively. The prevalence rates amongst children in nations considered in more than one study were 0.81% (95% CI: 0% - 1.74%) in Iran, 2.64% (95% CI: 1.63% - 3.64%) in Pakistan, and 5.83% (95% CI: 2.99% - 8.67%) in Turkey.

Conclusions: Based on the world health organization classification of HBV prevalence, intermediate HBsAg prevalence rates were detected in children of E and M countries during 2000 - 2016. Nevertheless, the prevalence rates were low in several included countries in mentioned regions.

Keywords: Prevalence, Hepatitis B, Eastern Mediterranean, Middle East, Meta-Analysis, Child

1. Context

Infections caused by the hepatitis B virus (HBV) pose a major challenge to the public health and also results in high mortality and morbidity rates in different parts of the world. Despite the availability of effective vaccines and antiviral drugs (1, 2), over 350 million individuals suffer from the HBV infection, with prevalence rates ranging from less than 0.5% in countries with low prevalence to more than 8% in high-prevalence countries (3).

Children have a particular risk of developing chronic hepatitis B (CHB) after viral exposure. HBV can be transmitted to children either vertically (mother-to-child transmission during pregnancy) or horizontally (through contact with other patients during preschool years) (4). About 90% of neonates with HBV infections and 25% - 50% of one-five-year-old children with acute HBV infections develop CHB.

However, this rate is much lower in adults and teenagers with HBV infections, i.e. less than 5% in symptomatic and 5% - 10% in asymptomatic cases (5). Several studies have revealed that about one out of every four individuals who are affected with HBV during infancy or early childhood develop either hepatocellular carcinoma or cirrhosis. Meanwhile, 15% of adolescents and young adults with HBV infections develop CHB (6).

According to the world health organization (WHO) recommendations in 1992, in order to reduce the overall prevalence of HBV infections, all children around the world should be vaccinated against hepatitis B. Serological surveys are required to monitor the reductions in HBV prevalence rates in children born after the initiation of the vaccination program and to validate the expected impact from coverage data. In 2006, the technical advisory group

for the expanded program on Immunization in the EMRO recommended that the prevalence of HBsAg should be reduced to < 1% among cohorts of children born after the introduction of the vaccine (7).

The Eastern Mediterranean regional office (EMRO) of the WHO has estimated the prevalence of HBV infection in the area at about 4.3 million (4, 5). The WHO classifies HBV infection prevalence rates as low (< 2%), moderate (2% - 8%), and high (> 8%) (8). A global study on the prevalence of HBsAg in children of the Eastern Mediterranean region office (EMRO) and some Middle Eastern countries showed that the prevalence rates were in low-intermediate and high levels (9).

Several studies have investigated the prevalence of HBsAg in children in the EMRO as well as the Middle Eastern (E and M) countries and have reported different rates. A study performed on a sample of over 10,000 Turkish children showed that about 8% of participants were HBsAg positive (10). Another study conducted by Qureshi et al. (2010) (11) showed that approximately 1.5% of children were HBsAg positive in Pakistan. The prevalence rates decreased in the children of Cyprus (12) and Iran (13) with prevalence rates of 0.28% and 0.35%, respectively.

The published studies on the prevalence of HBsAg in children of E and M countries have shown different rates. Moreover, due to the scarcity of large studies in these regions, there is a lack of comprehensive and reliable data regarding the exact prevalence of HBsAg in children of these countries. The most published review and meta-analysis studies in E and M countries have focused on HBV prevalence in patients, old people, high-risk groups or other hepatitis types (14-26). In addition, there is minimum information regarding the pattern of HBsAg prevalence in children of E and M countries in different years especially after the initiation of the vaccination program in these regions. Therefore, this study performed a systematic review and a meta-analysis of cross-sectional studies conducted during the years 2000 -16 to clarify the prevalence of HBsAg in children of E and M countries in these years.

2. Evidence Acquisition

2.1. Data Source

We searched the databases of Pubmed, Ovid, Scopus, and Google Scholar electronically for articles published from January 1, 2000 to October 31, 2016, with titles and/or abstracts related to the use of HBsAg to detect the total prevalence of HBsAg in children. We tried to search titles and/or abstracts of articles published in all mentioned databases, simultaneously. Next, the numbers of searched articles was recorded for each database to calculate the

total numbers of searched articles. We searched for different combinations of free keywords and mesh words including the following terms: "epidemiology," "prevalence," "HBV," "hepatitis b virus," "HBsAg," and "children," along with the names of the E and M countries, including: Afghanistan, Bahrain, Cyprus, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, Turkey, United Arab Emirates, and Yemen. We also searched relevant English and Persian key terms on the following Iranian databases: Scientific Information Database, Iran Medex, Magiran, and Medlib, as well as PakMediNet and Eastern Mediterranean journals from the WHO-EMRO indexing. We analyzed the search sensitivity by reviewing overlapping articles. We sent an e-mail to the authors if the full text of their articles was not available. If no response was received within one month, article abstracts were used for data extraction. Articles with inadequate information in their abstracts were excluded from the analysis.

2.2. Study Selection

Full-text articles in the English or Persian language were included if they had a cross-sectional design and provided clear information regarding the number of healthy HBsAg-positive children in E and M countries. Studies conducted on the general population were also included if they reported the HBsAg prevalence in the ≤ 15 years age group. The exclusion criteria were as follows: 1) studies that included high risk or infected children and 2) studies reporting unclear data or possible errors. The author's name or journal's name had no effect on the selection of articles.

2.3. Data Extraction

Two authors performed the quality assessment. The first author (M.B) performed the data extraction to find eligible studies. Another author (S.M.A), who did not participate in the literature search, critically evaluated the quality of the articles. The researchers discussed the research questions during a meeting before the critical evaluation. In addition, blinding and task separation were both used for study selection. The data were abstracted with standardized data-abstraction forms. After the final evaluation, researchers rechecked the selected papers and recorded the required data, i.e. first author's name, year of publication, country name, sample size, percentage of male participants, and HBsAg mean prevalence and standard error (SE), into Excel spreadsheets. SE was calculated using Cochran's test. One article from Iran was excluded because the prevalence of HBsAg was zero in those younger than 10 years of age (27). One reason for excluding the obtained article is that the value of 0.5% to zero prevalence should be

added, which may change the total prevalence of HBsAg in this study.

2.4. Statistical Analysis

Homogeneity was assessed based on the Cochran's Q-test results. However, since this test may fail to exactly identify the true homogeneity, it was complemented with Higgins and Thompson's I². The "Mitan" command was then used to apply a fixed or random effects model based on the results and significance of the Cochran's test results or a large I² value, respectively. Data aggregation and production of the pooled estimates were performed using the above-mentioned methods. Forest plots with descriptions of the findings were then developed to describe the results and calculate the point estimations along with 95% confidence intervals (CIs). Publication bias was assessed through the funnel plot. Funnel plot asymmetry was further tested using Begg and Egger's methods. Stata 11.0 was used for all statistical analyses.

3. Results

3.1. Study Selection

Primary data was collected from the titles and abstracts of 4,505 papers. Of these, 802 potentially relevant studies were selected. In the next step we removed the numbers of 470 duplicated studies and 332 articles related to prevalence of HBV in E and M countries, with a remaining 37 of them who were potentially related to HBV prevalence in children (Figure 1).

The total of 17 articles were excluded due to following reasons: 8 articles on HBsAg prevalence were rejected due to the fact that they contained participants who were not younger than 16 years of age (28-35), 4 were removed due to measuring the HbC/HBs antibodies (36-39), 1 was rejected because its samples were obtained from a family infected with HBV (40), and 1 was rejected because the prevalence of HBsAg in children was 0 (27). Three studies were excluded in the meta-analysis step due to inadequate data for calculating the standard error, unclear data, or for having a small sample size (41-43) (Figure 1).

3.2. Study Characteristics

The remaining 20 studies assessed 31,770 children for HBsAg prevalence in the E and M countries and were considered in the meta-analysis. Of these, 3 studies were conducted in Iran (13, 44, 45), 5 studies in Pakistan (11, 46-49), 4 studies in Turkey (10, 50-52), and 2 in Yemen (53, 54). Single studies were performed in the following nations: Afghanistan (55), Cyprus (12), Egypt (56), Iraq (57), Lebanon (58), and Palestine (8).

3.3. Total HBsAg Prevalence in Children of E and M Countries

Data could be retrieved regarding the prevalence of HBsAg in children of 10 countries. According to the obtained information, the pooled prevalence of HBsAg amongst the children of these 10 countries was 2.73% (95% CI: 1.73% - 3.72%) (Table 1). Furthermore, the prevalence rates in the EMRO and Middle Eastern countries were 1.85% (95% CI: 1.27% - 2.43%) and 2.66% (95% CI: 1.31% - 4.01%), respectively.

3.4. Total HBsAg Prevalence in Children of E and M by Country

The pooled HBsAg prevalence rates in nations with at least two studies conducted in them were 0.81% (95% CI: 0% - 1.74%) in Iran, 2.64% (95% CI: 1.63% - 3.64%) in Pakistan, 3.21% (95% CI: 2.02% - 4.4%) in Yemen, and 5.83% (95% CI: 2.99% - 8.67%) in Turkey (Figure 2). The prevalence rates in the other countries with 1 or 2 studies were shown in Table 1. In addition, the geographic distribution of HBsAg prevalence in children of EMRO and Middle East countries was shown in Figure 3.

3.5. Cumulative HBsAg Prevalence in Children of E and M Countries

The cumulative method indicates that the trends of HBsAg prevalence amongst children decreased from 2003 to 2010 and have remained relatively consistent since 2010 (Figure 4).

3.6. Review of Three Single Studies on HBsAg Prevalence in Children From Iran, Libya and Sudan

Studies from Iran (42) and Libya (41) showed that 3.2% and nearly 0.9% of children were HBsAg positive, respectively. In addition, one study from Sudan with a low sample size showed that 12.5% of participants were positive for HBsAg (43).

3.7. Risk of Publication Bias in Included Studies

To assess the publication bias, funnel plot, Begg's correlation and Egger's regression were used and indicated that there wasn't any publication bias in this study ($P > 0.05$) (Figure 5).

4. Conclusions

This review was sought to determine the prevalence of HBsAg in children of E and M countries during 2000 - 16. Based on our findings, the pooled mean prevalence of HBsAg in children and adolescents younger than 16 years, in the mentioned countries, was 2.73%, which is considered to be an intermediate prevalence rate by WHO. Moreover, the

Table 1. The Description of Studies in EMRO and Middle East Countries That Met Our Eligibility Criteria

Countries Authors' Names	Pub. Year	Samples Size	Min Age	Max Age	HBsAg Prevalence (%)
Afghanistan (E)					
Tanju, I.A	2014	330	1	15	3.6
Cyprus (M)					
Kurugol, Z	2009	352	1	15	0.28
Egypt (E & M)					
Reda, A. A	2003	1500	6	6	1.26
Iran (E & M)					
Farhat, A	2003	1064	2	10	1.97
Hashemi, S. A	2010	708	6	10	0.28
Fathimoghaddam, F	2011	284	1	11	0.35
Iraq (E & M)					
Tarky, A. M	2013	1641	1	10	0.91
Lebanon (E & M)					
Nabulsi, M. M	2001	841	1	6	0.11
Pakistan (E)					
Jafri, W	2006	3533	1	15	1.8
Quddus, A	2006	289	0	15	5.19
Aziz, S	2010	164	1	15	4.26
Qureshi, H	2010	4000	0	5	1.32
Sheikh, N	2011	1907	1	9	3.56
Palestine (E & M)					
Kuhail, S	2000	119	7	15	2.52
Turkey (M)					
Ertekin, V	2003	872	6	14	8.4
Dikici, B	2009	802	6	15	2.7
Kangin, M	2010	10391	0	14	8.1
Karatekin, G	2013	2148	0	14	4.23
Yemen (E & M)					
Al-Nassiri, K. A	2001	664	0	15	3.46
Sallam, T.A	2012	161	0	10	2.48
Pooled Estimate^a	-	31770	0	15	2.73 (1.73 - 3.72) ^b

Abbreviations: E, EMRO countries; M, Middle East countries; E & M, all countries from two regions.

^a Pooled estimate by random-effects Meta analyses.^b 95% confidence interval (in brackets).

mean prevalence rates were in the 1.85% in the EMRO countries and 2.66% in the Middle Eastern countries. Trends of HBsAg prevalence in children declined from 2003 to 2010 and have subsequently stayed relatively consistent.

Data regarding age-specific seroprevalence and endemicity of HBsAg in different E and M countries from 1980 to 2007 showed that there was a low to intermediate preva-

lence (2% - 4%) for HBsAg that is consistent with our results (9). Results of separate studies done on children in Nigeria showed that 4.3% (59), 12.4% (60), and 7.8% (61) of the participants were positive for HBsAg. In addition, prevalence rates of HBsAg in children were 2.3% in Equatorial Guinea (62), 2.9% in Tanzania (63), and 7.6% in Uganda (64), i.e. the HBsAg prevalence was higher in most African coun-

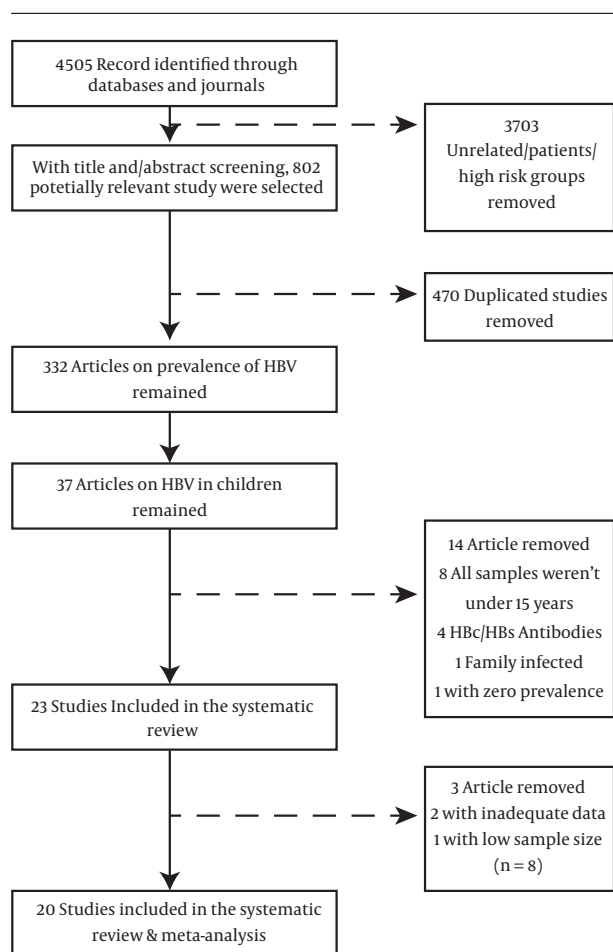


Figure 1. Follow Diagram of Systematic Review & Meta-Analysis of HbsAg Prevalence in Children of EMRO and Middle East Regions

tries compared to the E and M countries evaluated in this meta-analysis. HBsAg prevalence rates in children of some Southeast Asian countries show a different pattern. The prevalence rates were 0.4% in Malaysia (65), 3.1% in Indonesia (66), 0.3 to 3.45% in Cambodia (67), and 1.2% in Taiwan (68). These rates are close to the prevalence rates in the E and M countries studied in this meta-analysis. Global epidemiology of HBsAg prevalence in children shows that several developed countries such as the United States and Canada have low endemicity whereas low to intermediate prevalence was observed in European countries (9). Also, it seems that the rate of HBsAg in European children is similar to our results in E and M countries.

The current study indicated that HBsAg prevalence in the Middle Eastern countries was more than EMRO countries (2.66% vs. 1.85%) from 2000 to 2016. The prevalence of HBsAg in 4 studies amongst Turkish children, considered a Middle Eastern nation, was higher than 2%. It seems that

the higher HBsAg prevalence in Turkish children may influence the total prevalence in Middle Eastern countries. In addition, according to country-specific prevalence data and the region's 2014 birth cohort of 15.5 million, 1.2% of children < 5 years in the EMRO region had HBV infections (69). The lower prevalence of HBV in the mentioned study may be related to the higher HBV vaccine coverage in children. In addition, the published local or national studies in children ≤ 15 years in 10 countries was only studied, while the conducted study on < 5 year children have included national data from the ministry of health for all countries in the EMRO region, which can affect the estimated prevalence of HBsAg.

Trends of HBsAg prevalence in children were decreasing from 2003 to 2010 and were also relatively consistent. Prior to the WHO recommendation for universal HBV vaccinations in 1992, 6 (27%) out of 22 EMRO countries had already introduced programs to provide children with 3 doses of HBV vaccination, including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE). The number of countries increased to 17 countries (77%) in 2000 and to all EMRO countries in 2013. In general, vaccination coverage in these countries increased from only 3% in 1990 to 39% in 2000 and 83% in 2014. Nevertheless, the vaccination coverage in 2014 was below 80% in 6 countries (27%), which accounts for half of the EMRO birth cohort, i.e. Afghanistan, Djibouti, Iraq, Pakistan, Somalia, and Syria (69). Our results showed that the prevalence rates were higher than 2% in Afghanistan and Pakistan, which may be related to low vaccination rates. In addition, since the newest published data on the children indicates that the coverage of HBV vaccination within 24 hours of birth in the region was 24% in 2014, the intermediate prevalence of HBsAg is predictable (69).

The main limitations of this systematic review are related to the available data. First, because few published articles were found on children in E and M countries, we included articles conducted on the general population, which reported the age-specific prevalence of HBsAg in children ≤ 15 years old. Another limitation of this study was that data from different countries were different in terms of both the quantity and the quality. Moreover, this study did not evaluate university research projects and student theses that should be considered in future studies. The major strength of our study was including most relevant studies by adopting a highly sensitive search strategy, which covered all related keywords.

Based on the WHO classification of HBV prevalence, the prevalence of HBsAg in children of E and M countries (2.73%) and Middle Eastern countries (2.66%) was in the intermediate level during 2000 - 2016, while the individual prevalence rates in EMRO countries (1.88%) were cate-

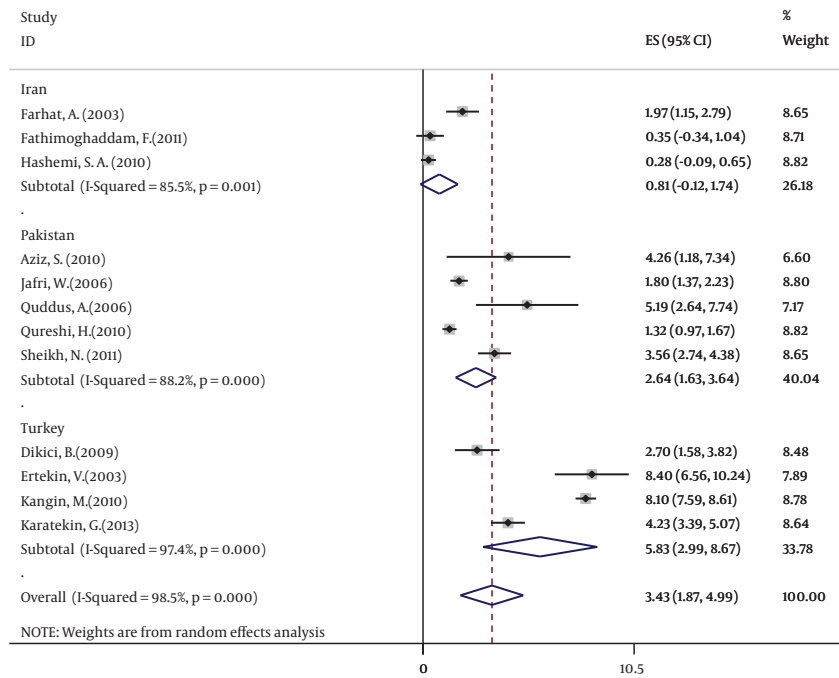


Figure 2. Forest Plot of HBsAg Prevalence in Children in Iran, Pakistan, and Turkey's Children

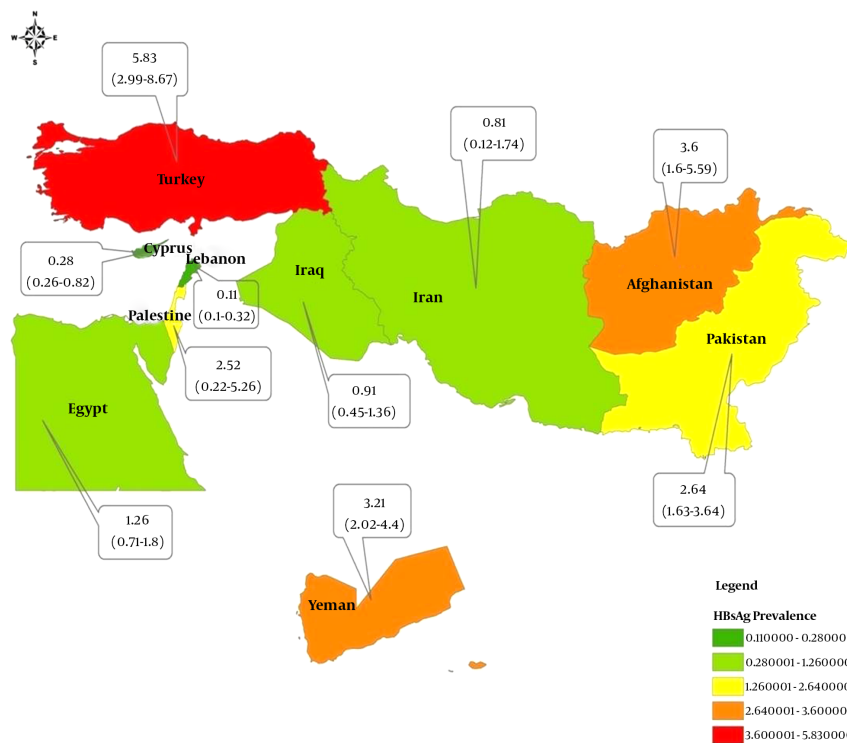


Figure 3. Geographical Distribution of HBsAg Prevalence in Children of EMRO and Middle East Countries

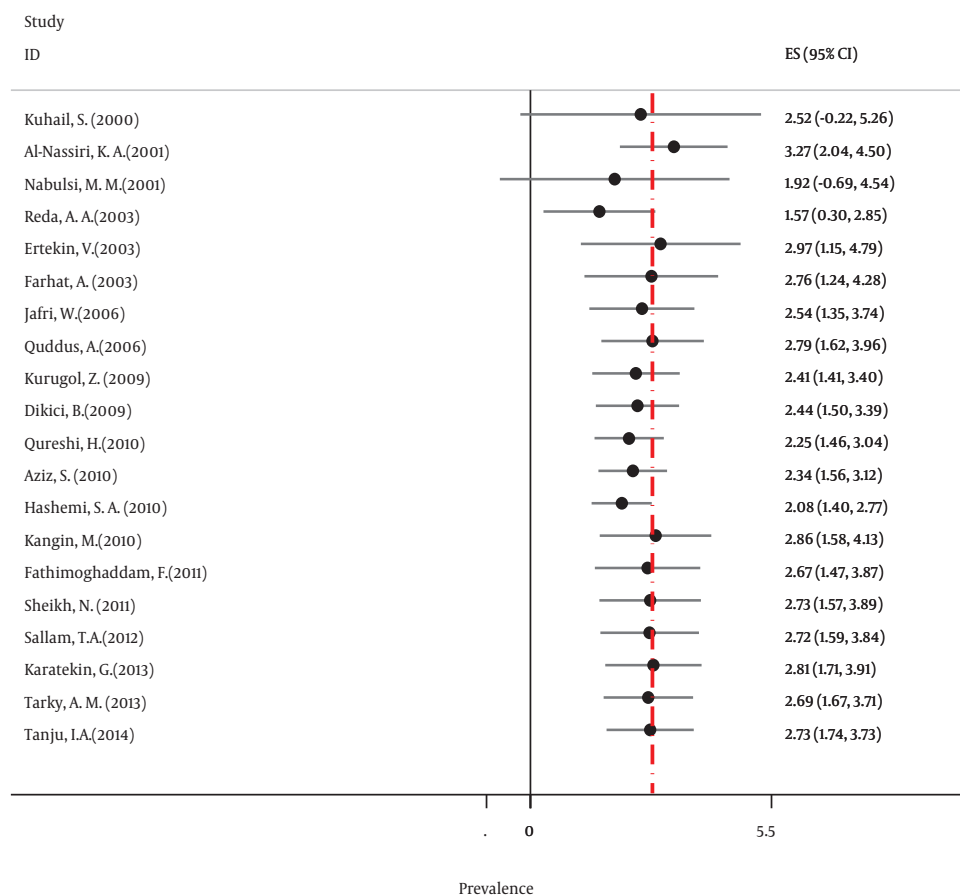


Figure 4. Forest Plot of Cumulative HBsAg Prevalence in Children of EMRO and Middle East Countries

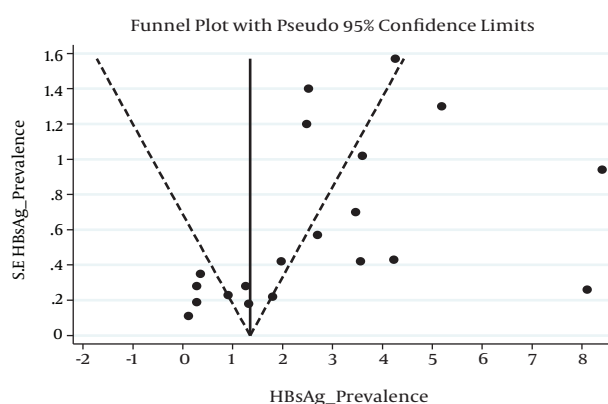


Figure 5. Funnel Plot of the Publication Bias in This Meta-Analysis

gorized as low level. The collected data indicated significant changes in HBsAg prevalence in children of E and M countries during the mentioned 17-year period. In fact, HBsAg prevalence amongst children and adolescents younger than 16 years of age generally decreased during this period and then remained almost constant. Tremendous efforts toward hepatitis B immunization can justify the observed reductions.

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