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Meta-Analysis

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Correlations between History of Contact with Infected Person and Measles Vaccination Status on the Risk of Measles Incidence in Children: Meta-Analysis

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ABSTRACT

Background: Measles is a disease that can be prevented by immunization (VPD), which is highly contagious and often causes widespread outbreaks and can cause lifelong complications and death. Some evidence suggests that the risk of measles is due to contact history and vaccine status. This study aims to estimate the magnitude of the relationship between contact history and vaccine status with the incidence of measles in children, through a meta-analysis of primary studies conducted by previous authors.

Subjects and Method: This research is a systematic review and meta-analysis with PICO as follows, Population: children. Intervention: contact history, vaccine status. Comparison: no contact history, no vaccine. Outcome: measles. The articles used in this research were obtained from three databases, namely PubMed, Google Scholar, and Science Direct, using the keys "History contact" AND "Vaccine" OR "Vaccinated" OR "Immunization" AND "Measles" AND "Children. The included articles were full-text with a case-control study design from 2012 to 2023 and reported the adjusted Odds Ratio (aOR) in multivariate analysis. Article selection was carried out using the PRISMA flow diagram. Articles were analyzed using the Review Manager 5.3 application.

Results: A total of 8 case-control studies involving the African continent and the Asian continent were selected for meta-analysis. Children with a history of contact have an increased risk of developing measles 4.38 times compared with children without a history of contact, and this relationship is statistically significant (aOR=4.38; 95% CI=1.36 to 14.09; p= 0.010). Children who had been given the measles vaccine had a reduced risk of getting measles 0.30 times compared to children who had not been given the measles vaccine, and this result was statistically significant (aOR= 0.30; 95% CI= 0.22 to 0.40; p< 0.001).

Conclusion: Contact history statistically significantly increases the risk of getting measles in children, vaccine statistically significantly reduces the risk of getting measles in children.

Keywords: Contact history, vaccine status, measles, children.

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BACKGROUND

Measles is a disease that can be prevented by immunization (PD3I) which is highly contagious and often results in widespread outbreaks and can cause lifelong complications and death (Antona et al., 2013). Measles infects the respiratory tract and spreads throughout the body. Symptoms include high fever, cough, runny nose and rash all over the body (WHO, 2023a). The rash develops from the upper face and neck and gradually spreads downwards (WHO, 2020). In 2017 there were still around 110,000 deaths due to measles infection globally, mostly in children aged ≤ 5 years. Between January and July 2019, 182 states reported an estimated 364,808 cases of measles, exceeding the 129,239 cases reported during the same time in 2018 (CDC, 2019). The largest increases in measles cases between January and July 2019 were in Africa (186,675 cases), Europe (97,503 cases), the Eastern Mediterranean (17,717 cases), and the Western Pacific (56,055 cases). Between January and October 2019, there were 1248 measles cases and 22 measles outbreaks reported in the United States (Patel et al., 2020). Since 2022, Indonesia has recorded an increase in suspected and confirmed measles cases compared to previous years.

Between January 1 and April 3, 2023, a total of 2161 suspected cases of measles (848 laboratory confirmed and 1313 clinically compatible (suspected) have been reported in 18 of the 38 provinces in Indonesia, mainly from the provinces of West Java (796 cases), Central Papua (770 cases), and Banten (197 cases) (WHO, 2023[b]). Meanwhile, in 2021 there were 507 suspected measles cases in Central Java Province. The most suspected cases of measles are in Banyumas. The incidence rate of suspected measles in Central Java Province in 2021 is 1.4 per 100,000 population (Dinkes, 2021).

WHO estimates that between 2000 and 2017, measles vaccination could prevent 21.1 million deaths. Reducing 80% of deaths from measles worldwide (Dunn, 2020). Measles can be prevented with the Measles, Mumps, Rubella (MMR) vaccine (CDC, 2023). Measles, Mumps, Rubella (MMR) one is given at least nine months of age, while Measles, Mumps, Rubella (MMR) vaccine two is given at 15 months of age (WHO, 2023[a]).

Various host factors that influence the incidence of measles are child factors (vaccine status, age at vaccine, nutritional status, contact history, history of measles, administration of vitamin A), maternal factors (mother's education level, mother's level of knowledge, income) (Arianto, 2018). Measles is highly contagious through contact, travel history, and population density (WHO, 2014). As many as 90% of sufferers have a history of contact with other sufferers. History of easily infectious contact in the same air space, usually a closed area (e.g. living in the same house or being in the same room, school, health facility waiting room, office, or transportation) for a long time with the case during the case's infection period (Vemula et al., 2016). According to research conducted by Sitepu (2023), having a history of contact statistically significantly increases the risk of measles infection by 1.15 times (aOR= 3.44; 95% CI= 1.12 to 3.70). Also according to research conducted by Tang (2016), it was stated that when an Extraordinary Event (KLB) occurred in Guangxi (China), people who had contact with measles sufferers (visited the hospital) were 9.84 times more likely to get measles compared to other people.

Apart from that, some factors can cause measles infection, namely vaccination status, someone who is under one year old and has not received vaccination, and those who have incomplete vaccination are found to be at higher risk of infection (Mat, 2022). This theory is in line with research conducted by Rivedeneira et al. (2018), where measles vaccination reduces exposure to measles by 0.97 times compared to children who are not vaccinated (aOR= 0.97; 95% CI= 0.95 to 0.98). Measles vaccination increases immunity and high vaccination coverage reduces the risk of measles infection in the community (Zheng, 2015). Unvaccinated children are at highest risk of measles and its complications, including death.

Based on the description of the problem above, it is necessary to research the relationship between contact history and vaccine status and the incidence of measles in children to estimate the magnitude of the relationship between contact history and vaccine status and the incidence of measles in children. This study aims to estimate the magnitude of the relationship between contact history and vaccine status with the incidence of measles in children, through a meta-analysis of primary studies conducted by previous authors.

SUBJECTS AND METHOD

1. Study Design

This research used a systematic review method and meta-analysis was carried out using PRISMA guidelines and the PICO model. Population= children. Intervention= Contact history, vaccine status. Comparison= No contact history and No vaccine. Result= Measles. Articles were collected from databases such as Google Scholar, PubMed and Science Direct. Literature search using the keywords "Contact Hystory" OR "Contact" AND "Vaccination status" OR "Vaccinated" OR "Immunization" AND "Measles" OR "Measles Outbreaks" OR "Measles Infection" AND "Children".

2. Steps of Meta-Analysis

1) Create research questions using the PICO format, which involves defining the Population, Intervention, Comparison, and Outcome.
2) Search electronic and non-electronic databases such as PubMed, Science Direct, and Scopus for primary study articles.
3) Conduct a screening process to establish criteria for inclusion and exclusion, followed by a thorough critical assessment.
4) Gather data from the primary studies and compile effect estimates using the RevMan application.
5) Analyze the findings and formulate conclusions based on the interpreted results.

3. Inclusion Criteria

Research inclusion criteria were full text primary research articles from 2012 to 2022 with a case control research design, analysis using multivariate with Odds Ratio (OR), research subjects were children, and the outcome was measles.

4. Exclusion Criteria

Statistical results are reported in the form of bivariate analysis, articles published in languages other than English.

5. Operational Definition of Variables

Contact history: is a child who has had contact with a confirmed measles case.

Vaccine Status: is a child who has received at least 1 dose of the MMR vaccine.

Measles: is a clinical case accompanied by confirmed IgM+ Measles results.

6. Study Instruments

Quality assessment of primary studies used a critical assessment checklist from the Case control Study Design. In the context of a case control checklist, there are seven specific questions included. Each question can be answered with "Yes," "No," or "Unclear," and these responses are assigned scores of "2," "1," and "0," respectively. When the sum of all the scores for the questions equals or exceeds 14, it suggests that the primary studies exhibit a low level of bias. Whilst, if the cumulative score is less than 14, it indicates a higher risk of bias in the primary studies.

7. Data Analysis

The research in this study followed the PRISMA flowchart to gather articles and employed the Review Manager 5.3 software for analysis. The analysis involved determining the effect size and assessing the consistency of heterogeneity (I^2) within the chosen research findings.

RESULTS

The process of searching for articles in this meta analysis was carried out by searching through journal databases, namely PubMed, Science Direct, and Google Scholar with a time span between 2012-2023. Keywords History contact" AND "Vaccine" OR "Vaccinated" OR "Immunization" AND "Measles" AND "Children". Article searches are in accordance with the PRISMA flow diagram which can be seen as follows.

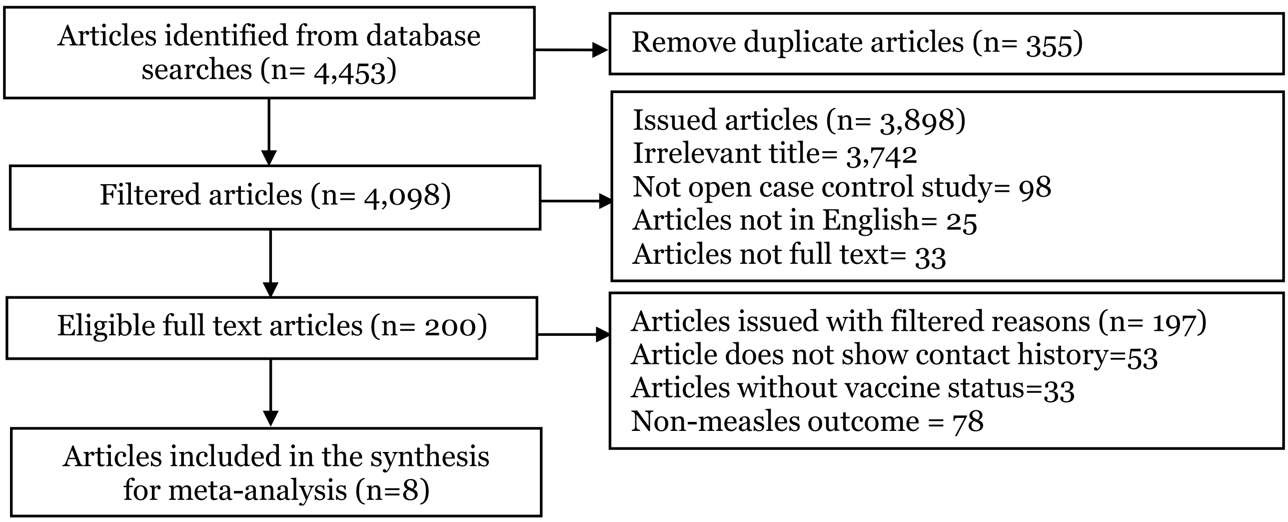

Figure 1. PRISMA flowchart

Figure 1 shows the results of the prism flow diagram, there were 4,453 main articles, after deleting duplicate articles there were 355 articles, after that the articles were selected taking into account the inclusion criteria, and 8 articles were included in the meta-analysis.

Figure 2 shows an overview of the study areas used in this meta-analysis which are spread across 2 continents, namely Asia and Africa. There were 8 articles at the end of the review process. All articles use a case control study design.

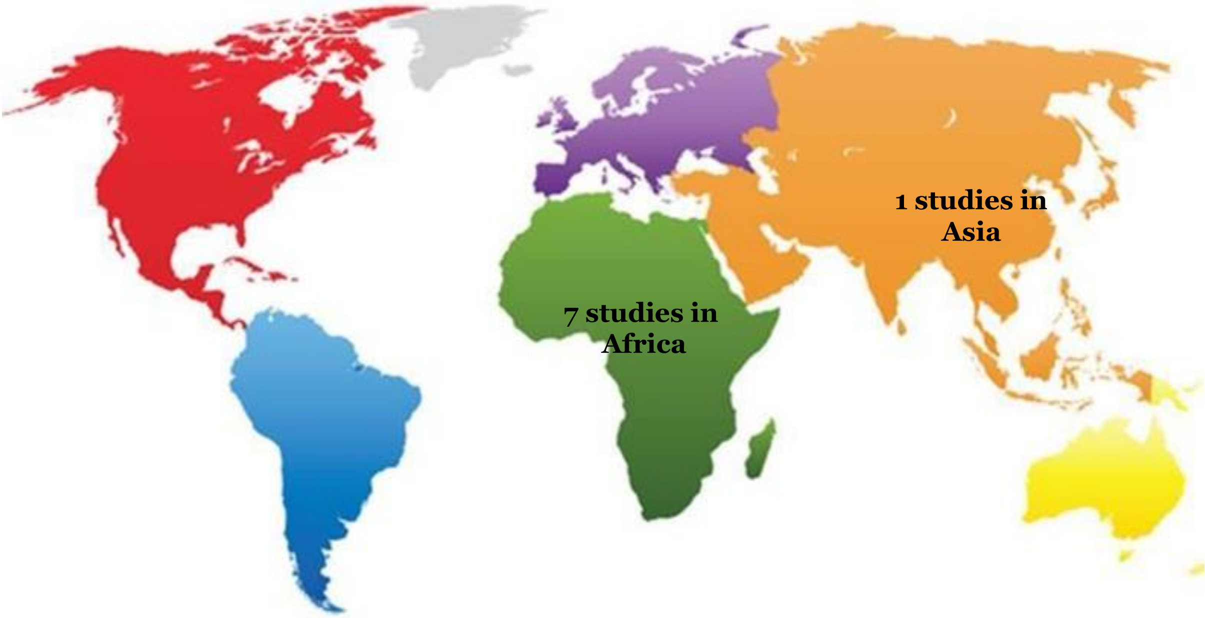

Figure 2. Map of the distribution of articles included in the meta-analysis

Table 1. Critical appraisal checklist for case control. Relationship between contact history and vaccine status with measles incidence in children

Author (Year)	Appraisal Criteria														Total
	1a	1b	1c	1d	2a	2b	3a	3b	4a	4b	5a	6a	6b	7	
Babalola et al (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Bukuno et al (2023)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Girmay et al (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Kidan et al (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Mebrate et al (2023)	2	2	2	2	2	2	1	2	2	2	2	2	2	2	27
Nassar et al (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Pomerai et al (2012)	2	2	2	2	2	2	2	2	2	1	2	2	2	2	27
Tsegaye et al (2022)	2	2	2	2	2	2	2	1	2	2	2	2	2	2	27

Note: Yes= 2, hesitant= 1, No= 0

Description of the question criteria:

1. **Formulation of research questions in the acronym PICO**

a. Is the population in the primary study the same as the population in the PICO meta-analysis?

b. Is the operational definition of intervention, namely the exposed status in the primary study, the same as the definition intended in the meta-analysis?

c. Is the comparison, namely the unexposed status used by the primary study, the same as the definition intended in the meta-analysis?

d. Are the outcome variables examined in the primary studies the same as the definitions intended in the meta-analysis?

2. **Method for selecting research subjects**

a. Does the selected accessible population represent the target population?

b. Was a case group and a control group selected at the start of the study?

3. **Methods for measuring contact history and vaccine status (intervention) and outcome variables**

a. Are the exposure and outcome variables measured with the same instruments (measuring tools) in all primary studies?

b. If the variable is measured on a categorical scale, are the cutoffs or categories used the same across primary studies?

4. Design related bias

a. Is there no "Recall Bias" in this primary study?

b. Have researchers made efforts to prevent or overcome such bias?

5. Methods for controlling confusion

a. Have primary study researchers made efforts to control the influence of confounding?

6. Statistical analysis methods

a. Did the researcher analyze the data in this primary study using a multivariate analysis model?

b. Does the primary study report effect sizes or relationships resulting from multivariate analysis (e.g., adjusted OR, adjusted regression coefficient)

7. Conflict of Interest

a. Is there no possibility of a conflict of interest with the research sponsor, which could cause bias in concluding the research results?

Assessment instructions

1. Total number of questions = 14 questions.
2. The answer "Yes" to each question is given a score of "2". The answer "Undecided" is given a score of "1". The answer "No" is given a score of "0".
3. Maximum total score = 14 questions x2 =28
4. Minimum total score = 14 questions x0 = 0. So, the range of total scores for a primary study is between 0 and 28.
5. If the total score of a primary study is >=24, then the study can be included in the meta-analysis. If the total score of a primary study is <24, then the study is removed from the meta-analysis (Munawaroh and Murti, 2023).

Table 2. Description of case-control studies on the relationship between contact history and the incidence of measles in children

Author (year)	Country	Sample	P	I	C	O
Babalola et al. (2019)	Nigeria	150	Children 0-59 months	Had Contact History, Vaccinated	Without Contact History, Unvaccinated	Measles outbreak
Bukuno et al. (2023)	Ethiopia	153	Children 0-14 years old	Had Contact History, Vaccinated	Without Contact History, Unvaccinated	Measles infection
Girmay et al. (2019)	Etiopia	87	Children 0-12 years	Had Contact History, Vaccinated	Without Contact History, Unvaccinated	Measles outbreak
Kidan et al. (2021)	Etiopia	120	Children <18 years	Had Contact History, Vaccinated	Without Contact History, Unvaccinated	Measles outbreak
Nassar et al. (2021)	Yaman	219	Children 6-60 months	Contact with Measles Case, Vaccinated	No Contact with Measles, Unvaccinated	Measles outbreak
Pomerai et al. (2012)	Zimbabwe	220	Children 0-10 years old	Had Contact History, Vaccinated	Without Contact History, Unvaccinated	Measles
Tsegaye et al. (2022)	Ethiopia	164	Children 0-59 months	Had Contact History, Vaccinated	Without Contact History, Unvaccinated	Measles infection

Table 2 explains that there are 8 articles with case control studies on the relationship between contact history and the incidence of measles in children with a sample size of 1,113. The research was conducted in four countries, namely Ethiopia, Nigeria, Yemen, Zimbabwe.

Table 3. Adjusted Odds Ratio (aOR) of the relationship between contact history and the incidence of measles in children

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Babalola et al. (2019)	7.50	2.90	19.7
Bukuno et al. (2023)	6.34	2.35	17.40
Girmay et al. (2019)	3.44	1.26	9.38
Kidan et al. (2021)	0.149	0.041	0.544
Nassar et al. (2021)	27.30	1.30	551.7
Pomerai et al. (2012)	41.14	7.47	226.54
Tsegaye et al. (2022)	3.243	1.034	10.175

Table 3 explains that there are 7 articles with case control studies on the relationship between contact history and the incidence of measles in children with the highest aOR in the study Pomerai et al. (2012), and the lowest aOR in the study Kidan et al. (2021).

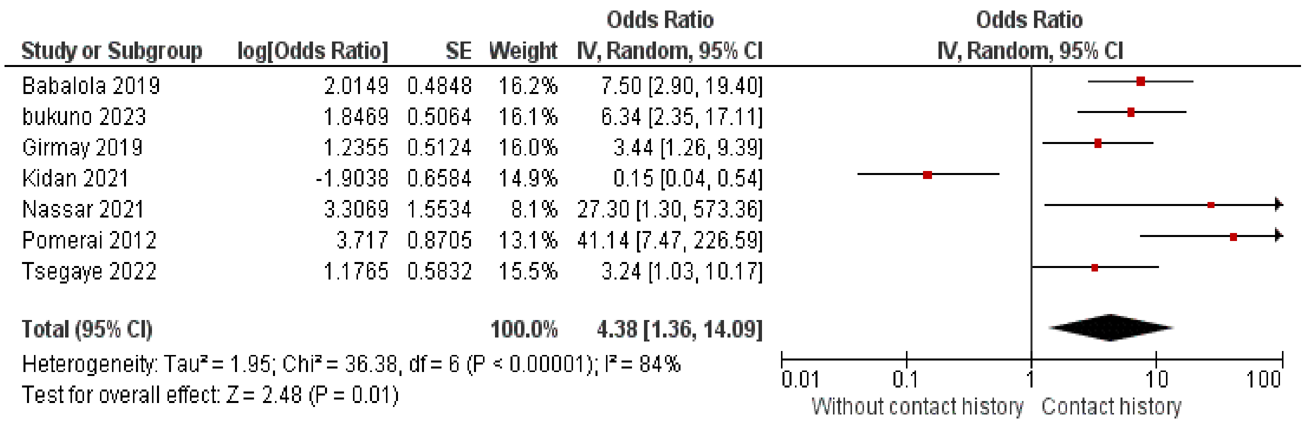

Figure 3. Forest plot of the relationship between contact history and the incidence of measles in children

The forest plot in Figure 3 shows that contact history is related to the incidence of measles in children. Children with a history of contact have an increased risk of developing measles 4.38 times compared with children without a history of contact, and this relationship is statistically significant (aOR= 4.38; 95%CI= 1.36 to 14.09; p= 0.010). The forest plot in Figure 3 shows the heterogeneity of effect estimates between studies is very large (I^2=84%; p<0.001). Thus, the calculation of the average effect estimate was carried out using a random effect model approach.

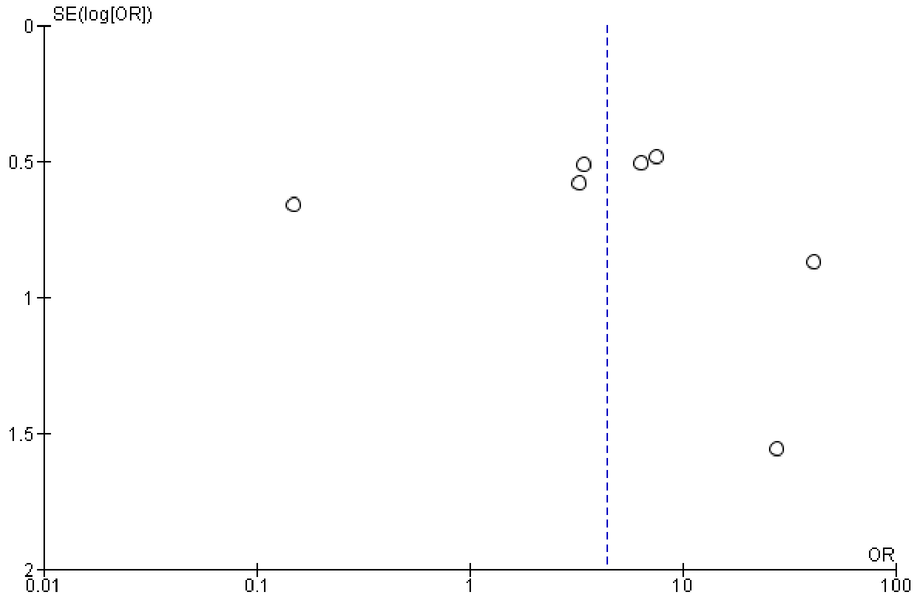

Figure 4. Funnel plot of the relationship between contact history and the incidence of measles in children

The funnel plot in Figure 4 shows that the distribution of effect estimates from the primary studies of this meta-analysis lies more to the right than to the left of the vertical line of mean estimates. The funnel plot shows publication bias. Because the distribution of effects is more to the right of the vertical line of the average estimate which is parallel to the location of the average estimate of the effect (the diamond shape which is located to the right of the vertical line of the null hypothesis in the funnel plot, the publication bias tends to exaggerate the effect of contact history with the actual incidence of measles (over estimation).

Table 4 explains that there are 8 articles with case control studies on the relationship between vaccine status and the incidence of measles in children with a sample size of 1,222.

Table 5. Adjusted Odds Ratio (aOR) of the relationship between vaccine status and the incidence of measles in children

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Babalola et al. (2019)	0.55	0.27	1.25
Bukuno et al. (2023)	0.35	0.13	0.90
Girmay et al(2019)	0.17	0.05	0.53
Kidan et al. (2021)	0.19	0.08	0.51
Mebrate et al. (2023)	0.52	0.11	2.35
Nassar et al. (2021)	0.05	0.01	0.34
Pomerai et al. (2012)	0.25	0.16	0.38
Tsegaye et al. (2022)	0.38	0.15	0.92

Table 5 explains that there are 8 articles with case control studies on the relationship between vaccine status and the incidence of measles in children with the highest aOR in the study by Babalola et al. (2019) and the lowest aOR in the study by Nassar et al. (2021).

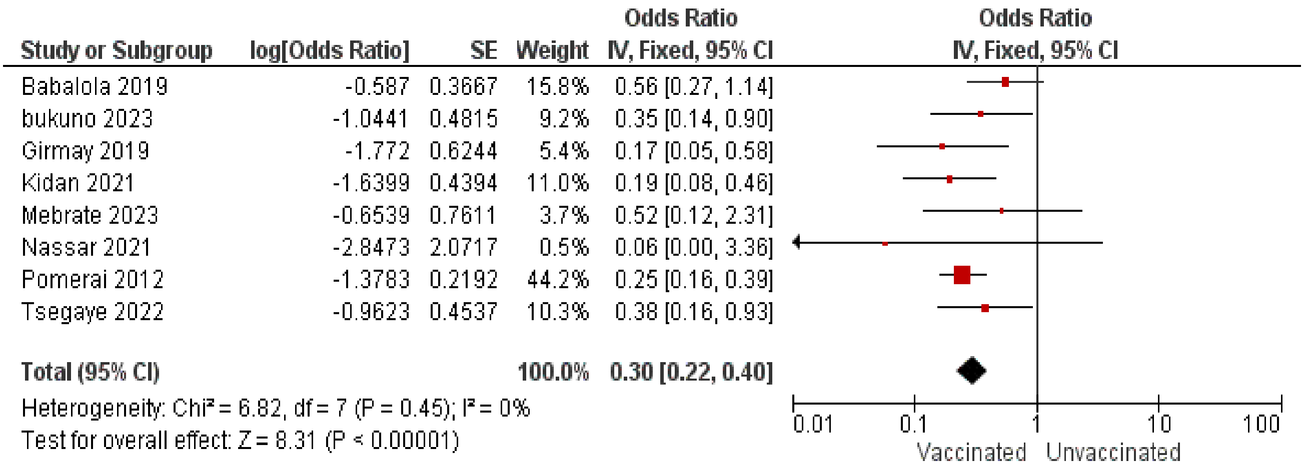

Figure 5. Forest plot of the relationship between vaccine status and the incidence of measles in children

The forest plot in Figure 5 shows that children who have been given the measles vaccine have a reduced risk of getting measles 0.30 times compared to children who have not been given the measles vaccine, and this result is statistically significant (aOR= 0.30; 95% CI= 0.22 to 0.40; p<0.001).

The Forest Plot in Figure 5 also shows high homogeneity of effect estimates between primary studies (I^2=0%; p= 0.450). Thus, the calculation of the average estimated effect is carried out using the fixed effect model approach.

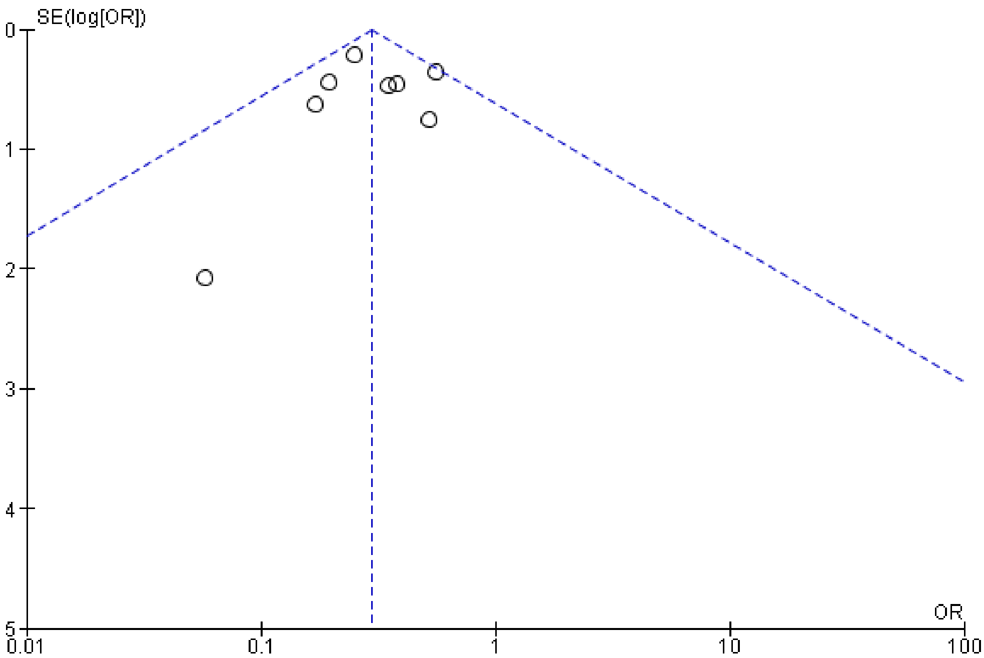

Figure 6. Funnel plot of the relationship between vaccine status and the incidence of measles in children

The funnel plot in Figure 6 shows that the distribution of effect estimates from meta-analysis primary studies is symmetrical. A symmetrical plot distribution indicates the absence of publication bias tends to reduce the true effect (under estimate).

DISCUSSION

1. Relationship between contact history and measles incidence

Measles is a highly contagious disease caused by a virus. The disease spreads easily when an infected person breathes, coughs, or sneezes. This can cause severity, complications, and even death. Measles can attack anyone but most often occurs in children (WHO, 2023a).

Primary research related to the relationship between contact history and the incidence of measles in children included in this meta-analysis synthesis was seven articles and then analyzed using Revman 5.3. The results of a meta-analysis of case control studies in seven articles showed that children with a history of contact had a statistically significant increase in the risk of measles 4.38 times compared to children with no history of contact (aOR= 4.38; 95% CI= 1.36 to 14.09; p=0.010). Because the measles virus is highly contagious, contact with any infected person increases the spread of measles transmission and infection (Tsegaye, 2022). The virus remains infectious in the air or on contaminated surfaces for up to two hours. A patient can spread the disease from four days after the rash appears to four days after the rash appears. There is no specific antiviral treatment for measles, but most people recover within two to three weeks (WHO, 2023[a]).

Based on the results of the synthesis of seven primary studies, it shows that there is high heterogeneity in effect estimates between primary studies (I^2= 84%; p<0.001) so the analysis uses the Random Effect Model (REM). High heterogeneity is based on sample sizes that vary between studies. The funnel plot shows publication bias. Because the distribution of effects is more to the right of the vertical line of the average estimate which is parallel to the location of the average estimate of the effect (the diamond shape which is located to the right of the vertical line of the null hypothesis in the funnel plot, the publication bias tends to exaggerate the effect of contact history with actual measles incidents.

The results of this study are in line with research (Mat, 2022) which shows that a history of high contact significantly has a risk of measles incidence of 14.03 times compared to no history of contact in children (aOR= 14.03, 95% CI= 8.23 to 23.90). These findings are consistent with other studies where individuals who had a history of contact with measles cases had a higher risk of infection compared with those who had no contact during the outbreak (Vemula et al., 2016). Measles has an incubation period of 7-18 days when a child is exposed to measles. Remembering that the peak period for measles transmission is 1-3 days after symptoms appear. So if there is contact between a child and a measles sufferer in the prodromal phase, the risk of measles transmission will be higher, especially if the contact is in the same household (Oktaviasari, 2018).

2. Relationship between vaccine status and measles incidence

A total of 13 experimental research articles Vaccine status measured as vaccinated or not vaccinated greatly influences contracting the measles virus (Kalil, 2020). According to the CDC (2022), about 9 out of 10 unprotected people will be infected with measles. Measles can be prevented with the measles, mumps, and rubella (MMR) vaccine. This vaccine protects against three diseases: measles, mumps, and rubella. This vaccine is a preventive measure to prevent measles and provide lifelong immunity (Ludlow et al., 2015). Before vaccination, deaths from measles significantly increased child mortality rates, especially for children under five. Approximately 95% of children who received the vaccine at 12 months of age and 98% who received it at 15 months of age produced anti-measles antibodies (Peart, 2022).

Primary research related to the relationship between vaccine status and the incidence of measles in children included in this meta-analysis synthesis was 8 articles and then analyzed using Revman 5.3. This research shows that the vaccine statistically significantly reduces exposure to measles in children by 0.30 times (aOR= 0.30; 95% CI= 0.22 to 0.40; p< 0.001). Vaccination is an effort to increase the body's immunity and is effective in reducing measles cases (Bose et al, 2022). Children who have received MMR vaccine have their immune systems formed so they become resistant to measles (Rosadi, 2019). This shows that measles vaccination increases immunity against measles and high vaccination coverage reduces the risk of measles infection in the community (Zheng et al., 2015).

Based on the results of the synthesis of eight primary studies, it shows that there is high homogeneity of effect estimates between primary studies (I^2= 0%; p= 0.450) so the analysis uses the Fix Effect Model (REM). The results of this study indicate that the distribution of effect estimates from meta-analysis primary studies is symmetrical, the symmetric distribution plot indicates the absence of publication bias. This is in line with research by Sitepu et al (2022) which stated that vaccinated children had a 0.432-fold reduction in the incidence of measles in children compared to unvaccinated children (aOR= 0.432, 95% CI= 1.22 to 4.27). Unvaccinated young children are at increased risk of measles and complications, including death (WHO, 2020). Vaccines for children, apart from their role as protection against disease, also provide great benefits for herd immunity (Anggreani, 2023).

Herd immunity is indirect protection against infectious diseases that occurs when a group has developed immunity either through vaccination or immunity obtained through previous infection. Therefore, children who are not vaccinated are at risk of having more vulnerable immune systems than children who are vaccinated (Henszel et al., 2020). This research is in accordance with meta-analysis research conducted by Morgan et. Al (2016), who stated that vaccination still carries a risk of measles. Vaccination affects immunoglobin G (IgG) (Ichimura et al., 2022). IgG antibodies are antiviral against the measles virus, and their titers are affected by the vaccine (Bose et al., 2022).

AUTHOR CONTRIBUTION

EFD is the main researcher who chooses the research topic, carries out data collection searches in the research. BM and HP carried out data analysis and reviewed research documents.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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