

Systematic Review of Respiratory Syncytial Virus Vaccine Efficacy

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Abstract. As the development of the vaccine against respiratory syncytial virus (VRS) has been rapid recently with the innovation of all sorts of gene engineering tools, it is necessary to analyse the efficacy of all kinds of relevant vaccines comprehensively to accelerate the massive usage of them. In order to achieve it, a systematic analysis was needed along with selecting all kinds of articles published from 2018 to 2020 in various databases (Pubmed, EMBASE and Cochrane library) to get the target data. The procedure was carried out by two independent examiners and supervised by another examiner. Five articles were picked, for a total of 12,719 observed people aged less than 3 months to about 26. The results of the RBM meta-analysis were that the estimated vaccine efficacy was 62% (95% CI: 36% to 78%) with high heterogeneity ($I^2 = 87\%$). The subgroup analysis showed that multiple factors contributed to the heterogeneity of the research and indicated that it is better to focus on modifying the vaccine on both infants and adults to prevent the spread of RSV. All in all, compared with other commercial vaccines, the efficacy of the RSV vaccine still needs to be improved and more trials on the safety and immunogenicity have to be operated in the future.

Keywords: Respiratory syncytial virus, Vaccine, Efficacy, Systematic review.

1. Introduction

As we are living in a period when Covid-19 is prevailing worldwide, RSV infections are always being veiled and maybe even increase the severity of Covid-19 infection. Thus, it is necessary to pay more attention to the prevention of RSV infections.

RSV is morphologically completely different from coronavirus, which is characterized by significant syncytia in single-ply cells, however, two are basically similar in symptomatology, so it is difficult to detect RSV infection alone [1]. Its genomic component is negative single-stranded RNA. It is stated that RSV has seasonal prevalence, normally between November and late January year after year [2]. RSV usually causes lower and upper respiratory system infection and develops bronchitis and pneumonia if the infection could not be controlled. Generally, classical symptoms, including fever, chest tightness and cough, will show up a week after being affected by RSV.

About 60,000 children under 5 years old died because of RSV infection annually in the whole world which has aroused researchers' interest to develop effective tools to halt these severe medical disasters [3]. Thus, RSV is the major factor that contributes to acute respiratory infection among children aged <5 years, causing substantial hospitalizations and huge economic burden [4]. Besides, RSV is also one of significant pathogens in adults or even older adults. During the pandemic of Covid-19, infection of the respiratory syncytial virus (RSV) had become more common in adults rather than infants, which has aroused worry that adults could be a subtle source of infection to children [5]. Based on the facts about epidemiology of RSV, it is necessary to look for effective methods to prevent the spread of RSV as there is no effective approved means for curing or preventing RSV infections.

It is well known that pregnant women play an important role in preventing infants from severe RSV Infections. Pregnant women often suffer from RSV infection which offers a chance to transfer maternal virus-neutralizing antibodies to fetus so that it can reduce the severity of RSV infection related illnesses among infants. Thus, immunization of pregnant women may be one of useful tactics of prevention of RSV infection because it was proved that it can prevent tetanus, diphtheria, pertussis and influenza safely and effectively [6].

As talking about the potential function of RSV vaccine targeted for pregnant women, however, the development of RSV vaccine had been suspended for decades due to its significant side-affect and there was not a review about the development of RSV vaccine until 2018 [7]. As we had a better understanding of RSV neutralizing epitopes, there are nine candidates being tested in phase 3 trials and it is said that mirsevimbab, would be introduced into markets within next 12 to 24 months as of July,2022 [8]. However, mirsevimbab does not account for real vaccine, as it is actually a neutralizing monoclonal antibody targeting RSV fusion glycoprotein (F). In addition, it is restricted by high production cost and short length of protection [9]. Thus, development of RSV vaccines still donot meet the medical need. However, there are many clinical trials for RSV being ongoing recently in order to satisfied the need for RSV infection protection.

Notably, there has been no recent systematic review about the efficacy of RSV vaccines. In order to fill in the gap, we conducted a systematic review about it and hoped to offer some useful perspectives which can be consulted by the governments and public health apartments.

In order to realize the goal, this research pooled the relevant studies and estimated the pooled efficacy of RSV vaccines which had undergone clinical trials or cohort study to reduce the infection of RSV. Besides, we used subgroup analysis to look for some factors which affect the efficacy of RSV vaccines significantly so that give some directions to works about RSV infections prevention.

2. Methods

2.1. Identification and selection of studies

A selection for optimal references was undergone through Pubmed, EMBASE and Cochrane library to locate any kinds of trials that explored the efficacy of the Respiratory syncytial virus vaccine. The search was performed from 2016 to 2023, which corresponds to the time that the efficacy, safety and immunogenicity of the vaccine had attracted researchers to look into it. This research only looks for experiments on humans and do not set limits on language. The following three sets of keywords were used to get relevant articles: (1) “Respiratory syncytial virus vaccine” or “RSV vaccine” or “RSV.” (2) “vaccination” or “vaccine” or “antibody.” (3) “efficacy” or “efficiency.”

The criteria of inclusion considered all stages of clinical trials that evaluated the efficacy of different kinds of vaccines against Respiratory syncytial virus, RCT or cohort with the placebo group and vaccine group, research without limitation on age and gender, and researches that takes vaccine efficacy against significant clinical infection of Respiratory syncytial virus or the number of participants in each group of being infected or healthy as an outcome.

All relevant articles were assessed by two authors. The third reviewer helped resolve arguments between the first two authors. The workers were blinded to the author’s name when selecting articles.

2.2. Quality of evidence assessment

The quality assessment of each selected article was finished by two examiners using the Cochrane Collaboration tool. This tool contains several criteria, each criterion has detailed explanation on the panel in the Review Manager 5.4.1 and certain items with high risk can be considered the potential source of heterogenicity among the overall analysis [10].

2.3. Data extraction

Targeted outcomes were related to the efficacy of the Respiratory syncytial virus vaccine in protecting against significant clinical infection. The following data would be chosen: (1) the identification of the studies (author, publication year, countries) (2) details of the trials (the study centers number of center/blinding, patients’ age range, sample size of each group, vaccine administration) (3) observed outcomes (the numbers of infected and healthy people in each group, vaccine efficacy).

2.4. Statistical analysis of the data

The effectiveness of intervention (vaccine or placebo) was estimated by the values of risk ratio (RR) and 95%CI which comes along with the estimated efficacy of RSV vaccine that was shown as (1- risk ratio). A meta-analysis and subgroup analysis were necessary to get the pooled results and look for the potential source of heterogeneity which was found in the research.

In order to get the pooled risk ratio, we use REM to realize the purpose. A forest diagram was chosen to displayed the final results of the whole analytic work. The heterogeneity between selected articles was detected by the inconsistency method. Above all the analyses were performed in the Review Manager 5.4.1.

3. Results

3.1. Study selection

A total of 1140 relevant articles were first selected in various databases. Of which 1020 were discarded due to irrelevant titles, 50 due to unsuitable abstracts and 65 due to improper full text. Finally, five articles were included in the analysis [11-15]. The filtering process can be seen in Fig.1.

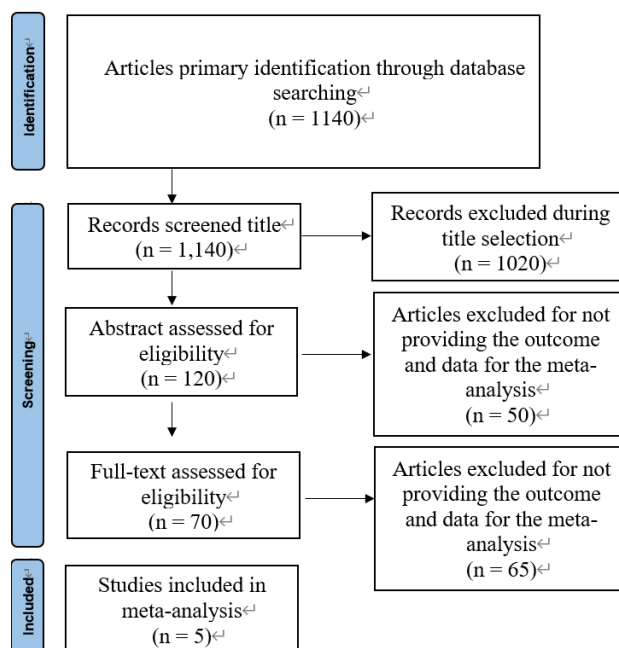


Fig 1. Flow diagram of filtering studies

The five selected kinds of literature provided six eligible studies and were published from 2020 to 2022. Of the 12,719 participants in the selected articles, 7,012 were distributed randomly to the vaccination group while 5,707 were allocated randomly to a placebo group. As for the number of research centers, four studies were multinational involving 5-23 or more countries in the world and only one study contained a single country. Otherwise, three articles were published in the USA, one in Germany and one in South Africa. Four studies included infants aged from 3-6 months or more, two studies included adults. The detailed contents of included articles are shown in table 1.

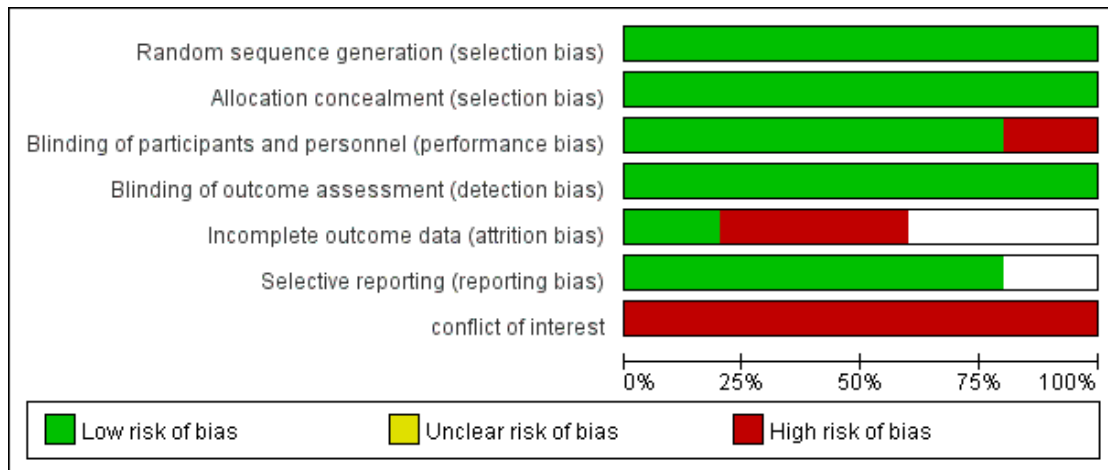
Overall, the selected articles included three kinds of vaccine which are RSV F vaccine, RSVpreF vaccine and Nirsevimab. All were administrated only once in the period of the prevalence of the virus each year and dosages were different from each other. All researches were funded by a commercial vaccine company.

Table 1. Detailed contents of included articles

Cou ntry	type of participa nts	No. of participants(vacci nation/control)	vacci ne	Administrati on (no. of doses,interva ls,dosage)	Study types (phase,n o. of centers,b linding)	Vaccina ted (infecte d/total)	Placebo(infe cted/total)
Sout h Afri ca	Pregnac y	3047/1582	RSV F vacci ne	1, -,120ug VP absorded to 0.4mg aluminium	III,11, observer -blind	97/2980	71/1547
Sout h Afri ca	infants	1562/3010	RSV F vacci ne	-	III,11, observer -blind	277/2980	174/1547
USA	infants	405/103	RSVp reF vacci ne	1, -,120ug/240u g (A/B antigen)	Cohort,5 , triple-blind	3/405	5/103
USA	infants	994/496	nirsev imab	1, -,50/100mg(<5kg/>5kg)	Cohort, multi-nation,do uble-blind	12/994	25/296
Ger man y	adult	35/35	RSVp reF vacci ne	1, -,50mg	Iia,1, double-blind	2/31	15/31
USA	infants(p reterm)	969/484	nirsev imab	1, -,50mg	Cohort,2 3, double-blind	25/969	46/484

3.2. Quality assessment

As for the bias risk analysis through the Cochrane Collaboration tool, all researches showed high bias in terms of conflict of interest (sponsor involved in the research). Two studies showed a high risk of coping with the missing samples and one for lacking efficient blinding methods [12-13, 15]. Apart from what have mentioned above, all articles demonstrated relatively good quality (Fig.2).



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	conflict of interest
Beate,2022	+	+	+	+		+	-
Griffin,2020	+	+	+	+	+	+	-
Hammitt,2022	+	+	+	+	-	+	-
Madhi,2020	+	+	-	+	-	+	-
Simões,2022	+	+	+	+			-

Fig 2. Risk of Bias

3.3. Efficacy of the Respiratory syncytial virus vaccine

The results of meta-analysis were shown in Fig.3. To sum up, a total of 12,729 participants were chosen ranged from 3 months to 50 years old. The REM showed a RR of 0.38 (CI 0.22-0.64) with an $I^2=87%$ ($p<0.00001$) which indicated high heterogeneity among the selected studies. In addition, the vaccine efficacy was pooled to be 62%, with a range from 36% to 78%. There was a significant discrepancy between studies with larger number of participants and that with a smaller number of samples.

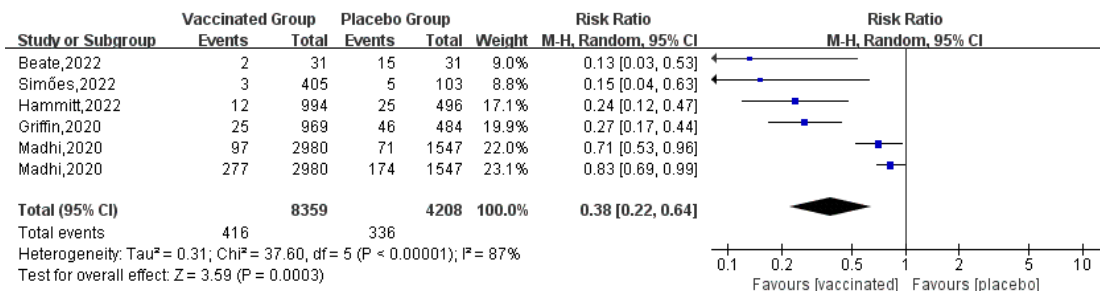


Fig 3. Forest diagram of meta-analysis of vaccine efficacy

The stratified meta-analysis (Fig.4-9), showed no heterogeneity for mirsevimeb, cohort study and double blinding research while with high heterogeneity for RSV F relevant vaccine (75%), clinical trials (72%) and non-double blinding (66%). Therefore, variations on the type of vaccine, study type and blinding method may have contributed to the heterogeneity found in the analysis which indicated the effect of the vaccine may not be unified by the designation of the study and more studies on the efficacy of RSV F relevant vaccine (RSV F/preF vaccine) are needed in the future to get unified results.

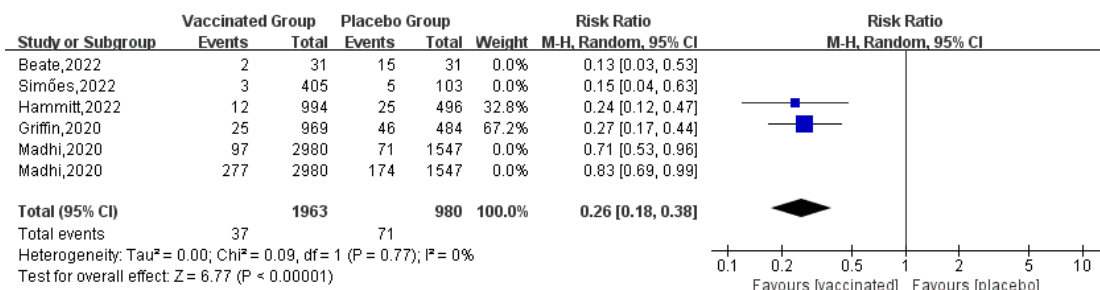


Fig 4. Efficacy for type of vaccine (mirsevimeb)

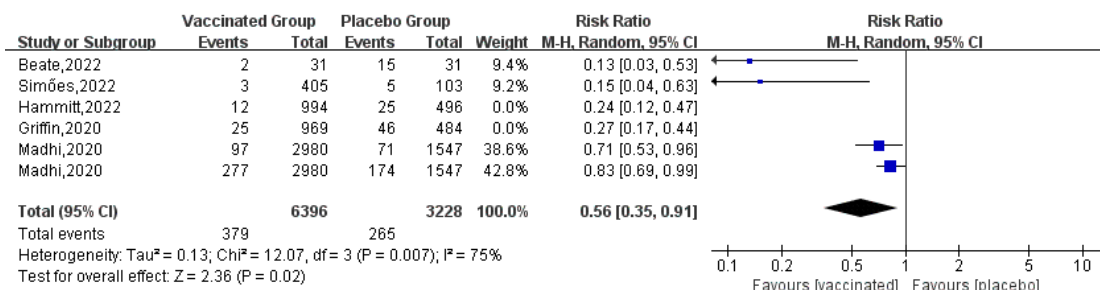


Fig 5. Efficacy for type of vaccine (RSV F relevant vaccine)

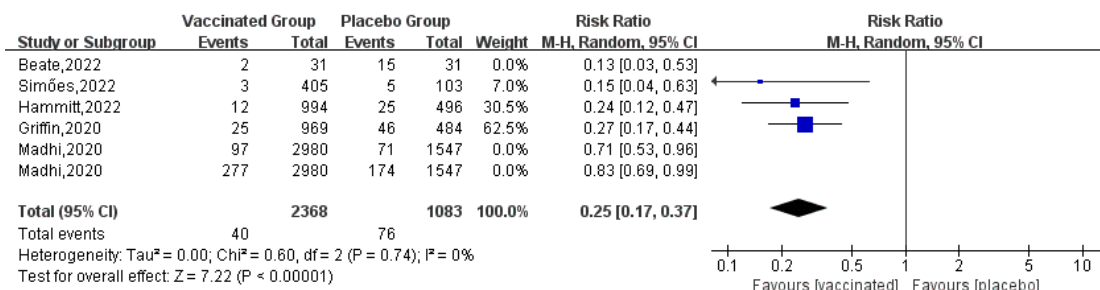


Fig 6. Efficacy for type of study (cohort)

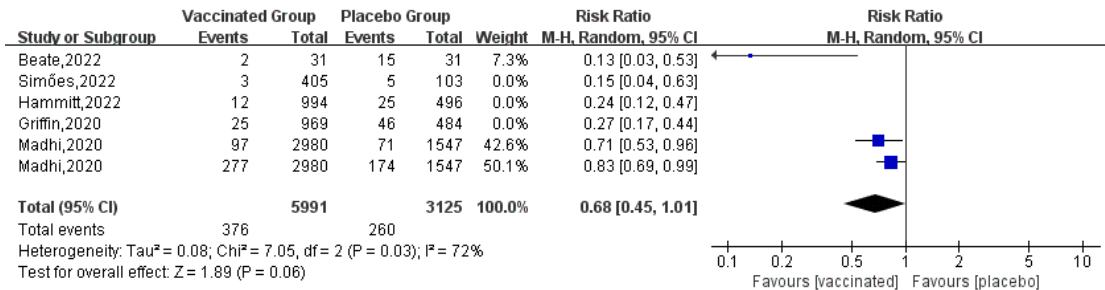


Fig 7. Efficacy for type of study (clinical trial)

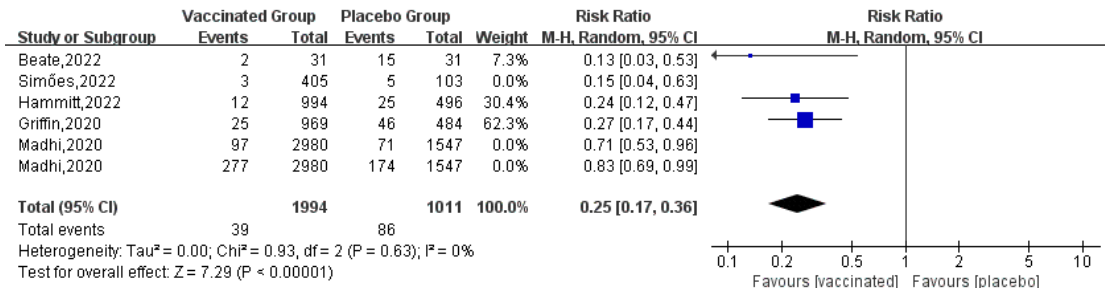


Fig 8. Efficacy for type of blinding (double blinding)

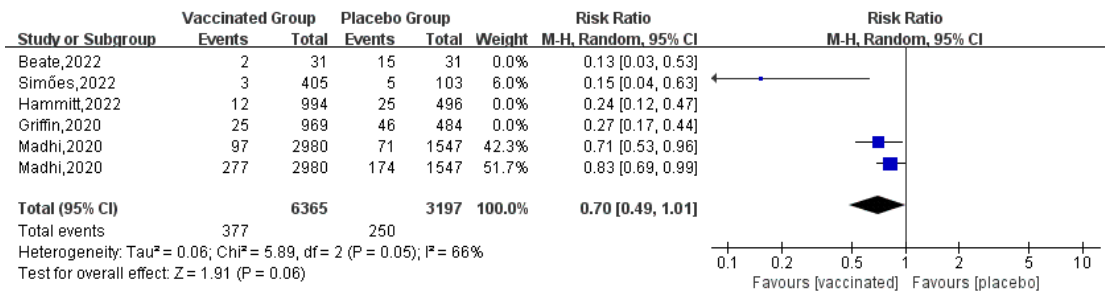


Fig 9. Efficacy for type of blinding (non-double blinding)

The meta-analysis also evaluates the effect of age on its efficacy (Fig.10-11). There was no significant difference in I² between infants and adults which indicated the divergence in groups of people was not the source of heterogeneity in the overall study. However, both showed high heterogeneity (91% and 81%), meaning that it is still demanding to put into more researches to get more data about the efficacy of the vaccine. It is noticeable that the results of subgroup analysis on infants or adults existed a significant gap between a specific study and any other studies which proved these studies may contributed the most of heterogeneity in this analytic work [11]. In addition, considering the RSV F vaccine only was used in the study and came out with the lowest vaccine efficacy, it is necessary to put more attention on modifying this kind of vaccine to get an ideal efficacy [11].

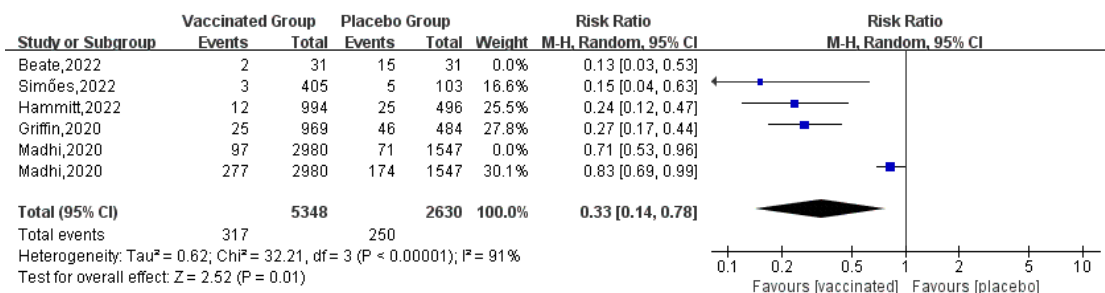


Fig 10. Efficacy in infants

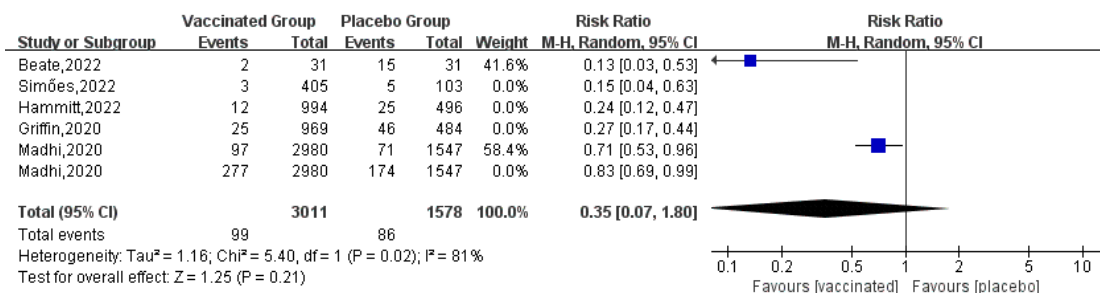


Fig 11. Efficacy in adults

4. Discussion

This meta-analysis allowed us to assess the first efficacy outcome of the Respiratory syncytial virus vaccine defend people away from significant clinical infections.

The data from phase IIa study and phase III study were included, being the most important data of this analytic work between vaccinated and placebo with random distribution of vaccination or not randomly [11, 14]. The results of IIa study provided minimum pre-requisites to conduct the phase III clinical trials.

In terms of the efficacy of the vaccine against significant clinical infection, the pooled index showed high protection (VE:62% (CI:36%-78%)) when all selected articles were analyzed together. However, results that indicate higher protection were noticed when studies were analyzed separately while we cannot use these data to get the final results that we hoped to.

Considering the value of efficacy on different kinds of vaccines. Articles using mirsevimeab showed high efficacy and much lower efficacy of RSV F vaccine and RSV preF vaccine. Because the former was an antibody product while the latter was a viral protein product, injecting antibodies would be effective faster than putting them into viral antigens. So, the difference in efficacy between the two kinds of vaccines may have been relevant to the length of observation time which indicates it is necessary to perform more studies with a longer duration of observation to ensure whether the RSV F vaccine and RSV preF vaccine are effective or not.

Cohort studies showed greater efficacy of the vaccine while clinical trials showed the opposite, which can be explained by the different diagnostic criteria of clinical RSV infection as relevant patients often show a mixed infection. Three cohort studies were conducted in the USA while the other two clinical trials were in South Africa and Germany respectively so it is possible to affect the efficacy of the vaccine by differences in diagnostic criteria. In addition, the same phenomenon was witnessed between studies with double-blinding and non-double-blinding which can be explained by the bias of blinding may infect the efficacy of the vaccine.

The efficacy in infants (67% (CI:22%-86%)) was higher and more stable than that in adults (65% (CI: -80%-93%)). This phenomenon can be explained by the greater activation level of immune systems in infants in order to adjust to the endemic areas. So only vaccination in infants may get a more ideal effect of preventing RSV infection than a conventional claim in which vaccinated adults (including a pregnant woman) immune infants through the internal exchange of antibodies during the pregnancy and herd immunity.

Moreover, whether a one-dose vaccination schedule is the best choice to get the ideal efficacy still need more research to verify as all five selected article only administrated one dose for each participant. The studies did not pick the hospitalization rates as an outcome due to the criteria for hospitalization differing from country to country, and these differences even vary due to the convenience of medical services in the same country. It was universally accepted that hospitalization means somebody have to stay in the hospital no matter how long it is. Almost in every country, the low class is not willing to go to the hospital due to the high cost of treatment but rather stay at home to let the body heal itself. Thus, the hospitalization rate is not considered in the study. The economic factors may make it difficult to get the real hospitalization rate [16].

The RSV vaccine has recently been developed and undergone different clinical trials in different countries. However, there are not enough studies to solve the questions mentioned above. Questions about the safety and immunogenicity of RSV vaccines must be solved, especially when large-scale of vaccination among infants who are the most sensitive to outer chemical products is put into effect. And the research on immunogenicity can be used to design a better vaccine administration schedule.

5. Conclusions

The results of this meta-analysis showed a relatively low efficacy of the vaccine against RSV infection, otherwise, the vaccine is more effective in infants compared with adults. As for the analysis of heterogeneity in the overall research, we found the type of vaccine, trials and the method of blinding all contributed to it with the proof of subgroup analysis. Notably, the efficacy of the RSV vaccine among infants was higher than that of adults which gives us new guidance on the development of the RSV vaccine.

Based on what we have got in the research, the result can show us the overall situation of the development of the RSV vaccine and shed new light on what should be focused on in the future. In addition, we noticed there are lacking studies about the safety and immunogenicity of the RSV vaccine right now which indicates another point that it is necessary to look into.

However, certain limitations were present in our study. First of all, there was a high level of heterogeneity in the pooled risk ratio estimate. A high I² value means there is a substantial proportion of observed variance attributed to real differences in effect size. Through subgroup analysis, the heterogeneity is likely attributable to the variances in the type of trials and method of blinding, and is especially notable in the type of vaccines. Second, the quality of selected studies was relatively high through the Cochrane Collaboration tool, however, we could not dismiss the effect of conflict of interest which sponsors somehow affect the results to the extent that they hope for. In addition, we did not take unmeasured confounders into consideration, such as health-seeking behavior could significantly affect the results of observational trials. Finally, the majority of data came from systematic review rather than laboratory confirmed, therefore the results from subgroup analysis may be useful for directing policy-making to counter the prevalence of RSV, but they do not necessarily represent the completed accurate efficacy of the RSV vaccine. In addition, there was lacking abundant data to conduct subgroup analysis based on more outcomes such as age, advert effect or immune response. Nevertheless, there are some systematic studies about safety of the RSV vaccine being published and the gap will be filled in in the nearly future.

As the pandemic of Covid-19 has brought some substantial changes to the prevalence of RSV, we hope there will be more attention on vaccination in infants to get the optimal effect of prevention while come out with more solutions to deal with the problem of infection among adults in the future.

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