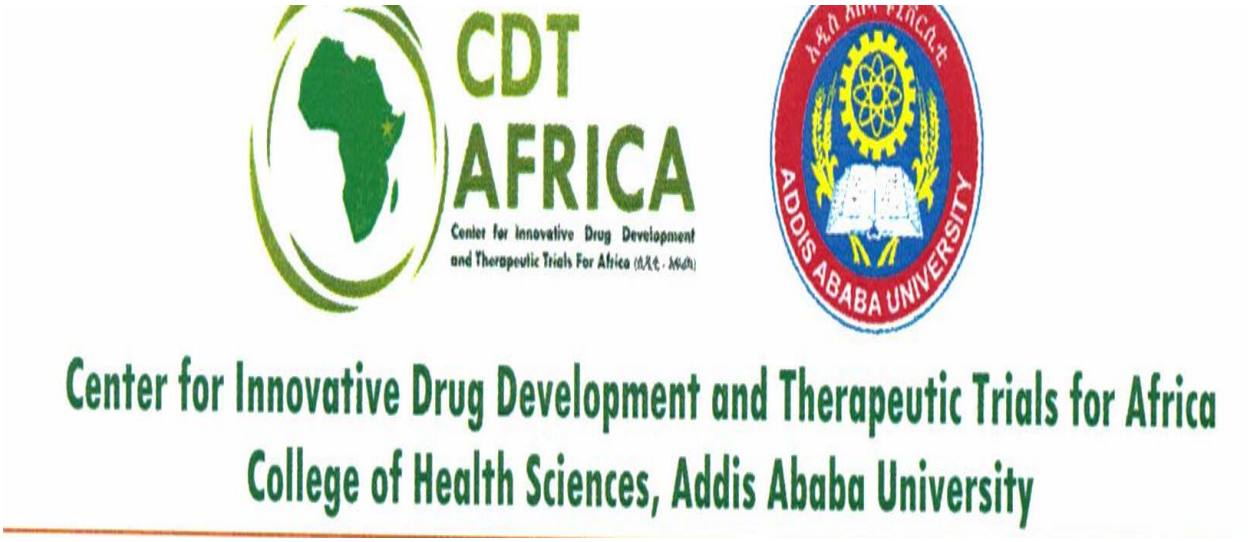

Efficacy and safety of vaccine trials conducted in Africa: a systematic review and Meta-analysis.

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2021

Addis Ababa, Ethiopia

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Acknowledgments

I would like to express my gratitude to the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, for their support. I would also like to thank my advisors Prof. Asrat Hailu and Dr. Anteneh Belete and to all who supported me in this study.

Acronyms/Abbreviations

AE	Adverse event
CRP	C-reactive protein
GAVI	Global Alliance for Vaccines and Immunization
IPD	Invasive Pneumococcal disease
LAIV	live-attenuated Influenza vaccine
MA	Meta-analysis
NGOs	Non-governmental organizations
OPVs	Oral Polio Vaccines
PCT	Procalcitonin
PCV	Pneumococcal conjugate vaccine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized control trial
RSV	Respiratory syncytial virus
RVGE	Rotavirus Gastroenteritis
SAE	Serious adverse events
SR	Systematic review
SSA	Sub-Saharan Africa
TIV	Trivalent Influenza vaccine
UNICEF	United Nations Children's Fund
VE	Vaccine Efficacy
VPD	Vaccine preventable diseases
WHO	World Health Organization

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Abstract

Background: vaccine preventable diseases have been of global concern. Vaccines are the best way for prevention. Studies are showing that there is disparity in efficacy of vaccines, in industrialized and in low-middle income countries. Additionally, vaccine related diseases are said to be occurring in recent decades. Africa produces less than one percent of vaccines and depends on imports. It is important to check how many of these imported vaccines have been subjected to clinical trials, to assess efficacy and safety before they are made available to mass consumption. This study is aimed to evaluate the vaccine trials conducted up to the end of 2020 with no start up period limit to inventory the type of trials undertaken in comparison with the vaccines that are in routine use in African countries and to assess vaccine effectiveness in African settings.

Methodology: A systematic review and meta-analysis was carried out to assess the vaccine trials conducted in the 54 African countries. Eighteen WHO approved registries, 2 immunization schedule sites and databases were searched. Data were exported to MS excel and RevMan version 5.4 for analysis.

Result: The largest vaccine trial for disease prevention purpose was seen for malaria with 119 (21.2%) whereas the lowest was for tetanus with 1 (0.2%) trial. Out of these vaccines, BCG and OPV are given in all African countries, whereas vaccines for; Hepatitis A Influenza (for both pediatric and adult), MenAC, bOPV, deworming, cholera, DTaP, TdIPV and dtaPHibIP are given only in one country each. From the 26 single disease specific vaccine 17 and from 13 combination vaccines 4 multi-disease vaccines was found to have gone through clinical trial which ranges from the lower 1 (Tetanus) vaccine trial per disease of interest to the highest of 119 (Malaria) vaccine trials in the single disease specific trials. BCG and OPV given in all African countries (100%) attributed to only 55 (15.5 %) and 2 (0.5%) of the trials, respectively, whereas Malaria vaccine which is given only in 3 (5.5%) of African countries attributed to 119 (33.6%) of the trials. In the malaria vaccine trial review, highest efficacy [30%, 95% CI (0.59, 0.84)] was seen against severe malaria in both children and infants. Whereas, the lowest efficacy [20%, 95% CI (0.75, 0.86)] was found to be in 1st episode of malaria in infants. The highest efficacy [67%, 95% CI (0.16, 0.66)] was seen in HIV positive adults and the lowest efficacy [21%, 95% CI (0.44, 1.42)] was seen in HIV positive infants. The highest efficacy [52%, 95% CI

(0.37, 0.61)] of the PCV vaccine was seen against 1st episode of IPD, and the lowest efficacy [13%, 95% CI (0.80, 0.96)] was seen against severe Pneumonia in HIV negative individuals.

Conclusion: The overall efficacy of the three types of vaccines that are included in this review was found to be low, and no significant SAEs were found across the vaccines. We found no vaccines terminated for futility. Safety data of these studies were mainly acquired from phase 3 trials not phase 4, we couldn't assess the safety issues identified from outside of a controlled environment i.e., for a long term effect and the issues seen in general populations.

Key words

Vaccine trials, Infectious diseases, Malaria, Influenza, Pneumonia, Phase 3, Phase 4, Efficacy, Safety, Serious adverse events, Africa

Research Questions

The systematic review was guided by the following key questions (KQ) and sub-questions:

KQ1: What vaccine trials have been conducted in Africa so far?

KQ2: How does the distribution look like across phases?

KQ 3: What vaccines are used for routine immunization program in Africa region?

KQ 4: How many of these vaccines have undergone through clinical trial?

KQ4a. Are there any vaccines that are terminated for futility?

KQ 5: What are the top 3 vaccine trials carried out across African countries?

KQ5a. What efficacious score is collected in the vaccine clinical studies conducted in African countries (Phases III–IV)?

1. Of each efficacy associated with a particular vaccine, what is the pooled effect?
2. Of each efficacy associated with a particular vaccine, what is the level of vaccine efficacy disparity depending on factors (including; study design, age, sex, race/ethnicity, underlying medical condition, whether the vaccine is administered individually or in a combination vaccine product, the schedule of vaccine administration, and medications administered concomitantly)?

KQ5b. What AEs or SAEs are reported in the clinical studies conducted in African countries (Phases III–IV)? Based on availability of data;

3. For each SAE associated with a particular vaccine, what is the pooled effect?
4. For SAEs what is the level of statistically significant associations with a particular vaccine and what is the level of certainty?
5. For each SAE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, underlying medical condition, the schedule of vaccine administration, and medications administered concomitantly)?

Introduction

1.1 Background

1.1.1: Description of infectious diseases

Infectious agents are one of the disease causatives that affect immune system and can result in acute, mild or fatal disease in susceptible individuals and may cause an autoimmune response through various mechanisms such as molecular mimicry, epitope spreading and polyclonal activation (1).These infectious diseases are attributed to, at least 12% of the human pathogens (2). Infectious diseases affect both health and economy of the industrialized and non-industrialized countries through their emerging and re-emerging behavior (3). When infectious diseases are pandemic, it may be of a national and international concern of policy makers (4). Examples are; outbreaks like, 2019 Novel Coronavirus (2019-nCoV) and Ebola (2). Globally the rate of mortality from infectious diseases has declined considerably (5). Given the substantial across and within-country i.e. by region and capital, disparities in sanitation and water access (6). Furthermore in recent decades the rate of outbreaks is increasing and diseases, such as measles and polio are recurring globally due to climate change, vaccination refusal and waning of immunity(5, 7). In Africa and Asia, it remains the leading cause of mortality mainly in children < 5years which is 34-folds higher than that of high-income countries. In 2016, high death rates in South Asia (24.8%) and sub-Saharan Africa (SSA, 44.4%) death was recorded (8). In low- and middle-income countries the burden of infectious diseases is intensifying (8, 9). Disease like influenza and rotavirus, especially in the tropic are endemic(3). In Africa, health had been an important aspect of the Millennium Development Goals (MDGs) (10). And, starting from 2015, Sustainable Development Goals (SDGs) (11). In the WHO regions, the highest epidemics, disasters and public health emergencies are seen in Africa (3).

1.1.2: Description of vaccine

Vaccines are suspension of different forms , could be; viral (live or inactivated), viral vector, subunit (protein or polysaccharide), nucleic acid (DNA or RNA) or Combination (inactivated, protein-based and/or protein-conjugated polysaccharide vaccine components)(12, 13). They produce an innate immune response (first line of defense against pathogens that have entered the body, within a few hours mostly), which in turn activates an antigen-specific adaptive immune response (provides a second line of defense, generally at a later stage of infection). It is characterized by an extremely diverse set of lymphocytes and antibodies which recognize and eliminate nearly all known pathogens. Each vaccine contains antigens that induce cell-mediated immunity by activating highly specific subsets of T lymphocytes and humoral immunity by stimulating B lymphocytes to produce specific antibodies. Adaptive immune system establishes immunological memory once pathogens are removed. This immunological memory enables long-term protection by antibodies generated from memory cells that can rapidly reactivate upon subsequent exposure to the same pathogen (14). Vaccine usage and demand differs from one to another region depending on several criteria; such as age, location, job, lifestyle, travel schedule, health condition and previous vaccinations. In the USA, there are 17 vaccines for routine use and 9 are used for travel purpose (15). In Europe; there are about 20 vaccines which are regularly used (16). Currently, according to WHO there are 47 vaccines. These are either accessible for routine use (Available vaccines) to protect from vaccine preventable diseases or pathogens, or they are under study (Pipeline vaccines) being supervised by WHO's Product Development for Vaccines Advisory Committee (PDVAC) (17). (See Annex 1 for type of vaccines for VPD)

As such safe and efficacious vaccines are one of the most important and effective public health interventions available for combating and containing the spread of infectious diseases (5, 18). Vaccines have become a part of multiple national health programs (1). Immunization is one of the most impactful and cost-effective public health interventions available (19-21), preventing six million deaths each year globally (22). Vaccines are also important, to advance life expectancy and achieve economic growth (8, 22). Apart from disease prevention, vaccination is at the center of universal health coverage (UHS) initiatives through introduction of communities to health system, infrastructural advancement and primary health care establishment. It also; brings improvements in health system and efficiency, provide wider economic and social benefit with expected profit of US $44, i.e., 44 times for every dollar spent (19, 21) lessening medical

expenses at individual and country levels (19, 20). Safety and efficacy of vaccines when assisted by religious value can help building trust in vaccines (23) and when vaccines work alongside sanitation and clean water health outcomes get enriched (22).

In limited time, vaccination has enabled several infectious diseases such as, smallpox, poliomyelitis, rabies, diphtheria, tetanus, pertussis, Haemophilus influenzae type b disease, measles, mumps, and rubella to be contained in many parts of the world (24). Routine immunization against diphtheria-pertussis-tetanus (DPT), measles and polio have prevented about 2.5 million deaths globally (25). Annually, 2-3 million children are protected by vaccination (19, 20, 26). Globally, child mortality has decreased from 65 to 29 per 100,000 in1990 and 2018 (20). Vaccines are fundamental to avoid child mortality from preventable diseases (26). In the United States of America and most part of Europe, 90-99% reduction is recorded (25). Vaccination programs in Africa have also made great progress in maintaining health and reducing death (19, 27). The launch of the Expanded Program on Immunization (EPI) in 1974 has strengthened it (27). Routine childhood vaccination coverage: such as diphtheria-tetanus-pertussis (DTP3) increased to 74% in 2016, Measles mortality declined by 85% in 2015, Polio and Tetanus are at the brink of eradication. By the end of 2016 more than 260 million people in the African Meningitis Belt had been vaccinated with MenAfriVac and new vaccines like: hepatitis B, Hemophilus influenzae type b, rotavirus, pneumococcal conjugate, and human papillomavirus vaccines among others were introduced (19, 27).

Vaccine development and distribution is supported by the World Health Organization's (WHO) Expanded Program on Immunization (EPI), Global Alliance for Vaccines and Immunization (GAVI), United Nations Children's Fund (UNICEF), the US National Institute of Allergy and Infectious Diseases (NIAID), The Bill & Melinda Gates Foundation (BMGF), and the Coalition for Epidemic Preparedness Initiative (CEPI) (20, 22, 28). Local manufacturing, could boost economy and assure availability of reasonably priced medicines (10). However low income countries mainly depend on the GAVI assistance for their vaccines (8). Every year, 1.5 million people lose their lives to vaccine preventable diseases globally. In 2019, it was reported about 14 million children didn't receive vaccine (26) signifying the deterioration of immunization in many countries (19). Furthermore, in Africa even when compared to other developing regions, little is

done in pharmaceutical manufactures, especially in vaccines (development and production) and biopharmaceuticals leading to higher trade deficit and poor access for the underprivileged (10). Approximately 1 in 5 African children do not receive all the necessary and basic vaccines. As a result, more than 30 million children under five still suffer from vaccine-preventable diseases (VPDs) each year. Over half a million children die from VPDs annually accounting for 58% of global VPD-related deaths (19). Globally, 45–50% of severe morbidity and mortalities from leading vaccine-preventable diseases are experienced by the 25% of the annual global births of sub-Saharan Africa (29).

Vaccines are usually administered to healthy individuals to prevent their target diseases so they undergo extensive safety and efficacy studies pre licensing. Naturally, higher standard of safety are taken, than medicinal products used to treat ill patients because inadequacy of vaccines capacity can result in luck of trust in communities which could lead to outbreaks (18). Safe and efficacious vaccine production is the leading innovation of this century to fight against morbidity and mortality from infectious diseases (8, 22, 23). Efficacy and safety of new entities is produced through clinical researches so the appropriateness of participants is crucial (30). On the other hand, there is growing indication that efficacious results of randomized clinical trials (RCT) may not be applicable to all health settings, because treatment outcomes may not be similar to all subjects across the globe (31).

1.1.3: Importance of study design for vaccine trials

Design and the outcome of the study to be measured affect the strength of the evidence (32). As such, outcome of a trial is greatly dependent on the trial design used. Hence, an in-depth designing is vital in order to address the hypothesis made properly with the intended power (33).Appropriate designing enables to address issues such as bias, confounders and chance through; proper sample size estimation, pre specified hypothesis, concealed randomization, equitable treatment or blinding and analysis plan (the use of intention to treat i.e. including all

participants that were enrolled for the study or per protocol analysis i.e. including only those who have finished the study) (34).

A trial may be unbiased but could deliver significance only to those who participated in the study, lacking generalizability (35). RCTs inapplicability could be minimized through a collaborative research design called multicenter trial. It renders higher sample recruitment capability (of different ethnicity or country) and outcome comparison to assess generalizability when compared to single center studies because it enables recruitment of participant with different background. It also enables sharing of ideas, resources and new knowledge, peer reviewed publication for learning purpose and funding opportunity so that health care could be enhanced (36-38). Presence of well and variety understanding of network members through continuous and planned communication also helps with protocol design and implementation allowing for groups to develop consensus-derived, well-informed, timely, and relevant research agendas to guide network projects (38).

Stimulated response of an individual upon drug (vaccine) administration may be determined by several factors, for immune arbitrated diseases is a result of diverse foundations. These include; environmental, genetic, hormonal and immune which is termed as the mosaic of autoimmunity as a whole (1). According to a review of 167 new molecular entities approved by the Food and Drug Administration (FDA) between 2008 and 2013, about 1 in 5 showed disparity in exposure response across races (30). The overall vaccine efficacies have also happened to vary upon the burden of rate of infectious diseases(39).

1.1.4: Global level of response towards vaccine

Clinical trials have demonstrated different levels of efficacy in countries with different income and mortality levels. Among other factors, these national level differences may be explained by variability in exposure to other environmental enteric pathogens. Studies have shown that there is inconsistency in vaccine responses in different regions (among developed regions vs. Africa and also other developing regions vs. Africa) (18). it is possible that there would also be disparities in

vaccine efficacy at the country level mainly affecting minorities (6).Oral vaccines such as polio and cholera are found to be less effective in low-income countries which could be attributed to different factors such as; co infection, concomitant administration and several other unknown factors (39).

Vaccines have reduced the burden of infectious diseases in the past, leading to the eradication of small pox and significantly limiting diseases such as polio, tetanus, diphtheria, and measles. However, established methods may not always be suitable. Live attenuated vaccines generally bear the risk of reversion, rendering this approach unfavorable for highly pathogenic agents. On the other hand inactivation may not induce protective responses, as is the case for Ebola or can even lead to undesired effects, like formalin-inactivated RSV (respiratory syncytial virus) that induced exacerbated disease upon wild type RSV infection in clinical trials in the 1960s (40). Many oral vaccines are less effective in developing countries(41) as a result of poor socio-economic factors, lack of sanitation and clean water(7) These include Sabin polio vaccine, rotavirus vaccines, CVD 103-HgR live cholera vaccine 4144, B subunit-inactivated Vibrio cholera whole cell combination vaccine and SC602 live Shigella flexneri 2a vaccine. Moreover, the phenomenon has been observed in all age groups, from young infants to adults. Early studies with OPV, RIT 4237 rotavirus vaccine, tetravalent rhesus reasserting rotavirus vaccine at the 10^4 plaque forming unit dosage level and other candidate rotavirus vaccine strains indicated a barrier to oral immunization. Two new rotavirus vaccines, Rotarix, the monovalent human G1P strain attenuated by multiple passages in tissue culture, and Rotateq, a pentavalent vaccine based on reassortant bovine rotavirus expressing human rotavirus surface proteins G1 to 4 and P, have been shown to be safe, immunogenic and highly protective against severe rotavirus gastroenteritis in large-scale, placebo-controlled efficacy trials in infants in North America, Europe and South America. However, when tested in efficacy trials in Africa and Asia, these two vaccines showed much lower efficacy (41). Rotarix and RotaTeq, rotavirus vaccines are found to be less efficacious which may be due to difference in strains that is seen in Africa. However ROTAVAC vaccine with similar effectiveness with that of Rotarix and RotaTeq used in India, for strain same as that of Africa showed less vaccine induced immunity especially in sub-Saharan countries (39). In a research reported based on different studies, one study showed a vaccine trial conducted in the slums of Dhaka (Bangladesh) results showed, introduction of

individual vaccines against enteric infections may not be sufficient. Another study on a rotavirus vaccine trial for infants conducted in urban Dhaka slums (31%) (i.e., two doses of the oral vaccine Rotarix at 10 and 17 weeks) and (28%) in local site which is so much lower than in industrialized settings. Another study of 2 years follow up oral cholera vaccine (OCV) trial (i.e., two doses of the bivalent whole-cell inactivated vaccine) was 53% effective against severely dehydrating cholera 2 years after vaccination, but the vaccine efficacy was only 16% for children under 5 years of age(42).

Similarly, immunogenicity and efficacy of oral vaccines was found to be impaired in low-income countries that have high prevalence of enteric disease (43). A Rotarix of 1-year protective efficacy >95% against severe rotavirus gastroenteritis (RVGE) in European infants showed < 50% efficacy in Malawi (44, 45). Live-attenuated oral cholera vaccines and oral poliovirus vaccine (OPV) showed similar effect. OPVs lack of sufficiency in efficacy has resulted in poliovirus transmission in several countries, delaying global eradication. A study on one live-attenuated Shigella vaccine candidate which was reactogenic and immunogenic in North-American adults, induced no adverse reactions or a serological response in Bangladesh (43). Poor immunogenicity was also seen in oral-killed cholera vaccine among children in Nicaragua (Central America) compared with Sweden (46). In a 2 year follow up study for severe RVGE lower efficacy of rotavirus vaccine was observed in Africa (Ghana, Kenya and Mali) Infants who were underweight (weight for age Z score < −2) when compared with infants who were not underweight. Also 1 year of follow-up study males had significantly higher vaccine efficacy when compared with females whereas in Asia (Bangladesh and Vietnam), this effect was reversed (47). In another double-blind, placebo-controlled trial in;, Ghana, Kenya, and Mali, the efficacy of the RotaTeq vaccine against severe RVGE was 39.3% (95% CI, 19.1 to 54.7) (48). In a similar trial in South Africa and Malawi, the efficacy of the Rotarix vaccine was 61.2% (95% CI, 44.0 to 73.2) (45). In Niger severe disease prevalent area, vaccine efficacy was 66.7% which was higher than the less prevalent countries but lower than rotavirus (80.5 to 90.4%) vaccines efficacy seen among Europe and Latin America children (49).

Cholera and live Shigella flexneri vaccine immunogenicity have shown disparity based on study population. Protection of live recombinant oral cholera vaccine CVD 103-HgR, Rotavirus

vaccines and OPVs were found to be low in children of developing countries and poor regions like Africa and India. Despite high immunization coverage OPV remained to have low efficacy in northern Indian states of Uttar Pradesh and Bihar. Similarly, the efficacy of oral rotavirus vaccines was almost 50% lower in some developing world countries. Trivalent OPV (50–90%) was also found to be less effective than IPV (>90%) in inducing systemic immunity in developing countries. The per-dose efficacy of trivalent OPV in Europe and North America was greater than 50%, but only 21% in most of India and only 9% in Uttar Pradesh (India). An evaluation of Rotarix demonstrated a wide degree of variation across the sites, with approximate protection against severe rotavirus diarrhea of 50% in Malawi, 77% in South Africa, 85% in Latin America and 96% in Europe (45). Rotavirus vaccine efficacy in Bangladesh, Ghana, India, Kenya and Mali was also lower. A similar phenomenon was seen when the efficacy of RotaTeq was examined in Nicaragua, with 58% full dose efficacy in severe Rota viral diarrhea but in Finland and the US, it was between 84% and 100% (50). Another study revealed that RV5 and RV1 were highly effective in industrialized countries with 90% minimum protection against severe RVGE and 74% minimum protection against rotavirus gastroenteritis of any severity. however, in Africa and Asia the efficacy of the 2 vaccines ranged from 56% to 64% in protecting against severe rotavirus gastroenteritis (51).

Like drugs, vaccines can also cause adverse events are also associated with adverse events. Usually the described adverse events are transient and acute, but may rarely present with hypersensitivity and induction of autoimmunity that may be severe and fatal (1). Vaccines in use of controlling and eradicating infectious diseases that resulted in adverse event >1 per 10,000 in controlled environment is raising safety issues when used widely as a result of limited size and scope of pre-licensure studies So, extensive post- licensure monitoring and evaluation is also required to identify the safety concerns (18). And malaria, influenza and pneumococcal vaccines are some of vaccines that are under routine use in African health settings as part of routine immunization program.

Development of an effective malaria vaccine is one of public health priority and plays an important role in reducing morbidity and mortality (52-57). But the demand for highly efficacious malaria vaccines isn’t met (57). And after 100 years of research a new vaccine for

parasite has been developed (58) The RTS,S/AS01 is a malaria vaccine formulated either with AS01 or AS02 adjuvant system (AS) that targets the pre-erythrocytic stage of the Plasmodium falciparum parasite (52, 54, 55, 58-62). It is a hybrid molecule recombinant expressed in yeast, in which the central tandem repeat and carboxyl-terminal region of the circum-sporozoite protein are fused to the N-terminal of the Surface antigen of the Hepatitis B virus, creating a particle that also includes the unfused S-antigen (58, 60, 63). Vaccine is an efficient and feasible strategy to reduce the burden of malaria in endemic regions (63) and has proven efficacy in clinical trials against clinical and severe malaria morbidity and mortality in African children (62).

Vaccination against seasonal influenza is recommended routinely for individuals aged over 65 years in many countries (64). Antenatal maternal immunization with influenza vaccine can prevent influenza illness in the mother and her infant in the first few months of life reducing morbidity and mortality since there is no vaccine for infants less than 6 month of age, it can also provide benefits to the fetus (65, 66). Especially in low- and middle-income countries, vaccination of children could protect them and reduce the probability of infecting their contacts (67).

Prevention of pneumococcal disease is a major, international public health priority due to high coverage of morbidity and mortality especially in children in developing countries (68-71). Pneumococcal conjugate vaccines (PCVs) are key measures in preventing and reducing pneumococcal infections, including childhood pneumonia (72, 73). A pneumococcal conjugate vaccine (PCV) containing *S. pneumoniae serotypes*, is highly effective in preventing IPD in infants and young children (68, 74). Vaccine-type IPD have been reduced by more than 75% among young children in which Reduction has been seen in the unvaccinated children and adults due to transmission interruption (74-76).

1.2. Problem statement

The magnitude may differ from one to another but infectious diseases remain the main concern globally and now even more so, as we are battling the Covid-19 pandemic. Many of these vaccine preventable diseases are only seen in low-income countries. Africa is one of the regions which are at constant threat of communicable diseases. Especially in sub-Saharan countries the

highest morbidity and mortality is attributed to vaccine preventable infectious diseases. Efficacious and effective i.e., vaccines that work well in controlled conditions and in the real world are found to be the best approach to fight against these VPDs. However, low-income countries are dependent on NGOs like UNICEF, GAVI and WHO for their vaccine supplies which will continue up until graduation. Most of these vaccines are produced outside these countries. Different studies have shown that, only about one percent of the continent's requirement is produced locally. Furthermore, since vaccine development and production is not carried out locally, due to many known and unknown confounding factors vaccine efficacy is being undermined when they reach the highly infected region of Africa. Hence, vaccines are displaying the lowest efficacy in Africa. For instance, since the declaration of its eradication in 2015 and the stoppage of OPV2, resurgence has been reported in different countries which are vaccine-derived. In August 2020, WHO reports showed that thirteen new cases of vaccine-derived poliovirus type 2 (cVDPV2) have been confirmed in Cameron, Sudan and Chad posing a new threat (77). So, it is important to check how many of these vaccines are tested, how much protection is being brought about from these imported vaccines and what is the weight of SAEs, by conducting clinical trials locally.

1.3. Justification

Clinical trial plays a substantial role in assuring the health of human kind. Currently, there are many types of trial that are carried out or are under trial to safe-guard the human well-being and vaccine clinical trial is one of them. At present vaccine clinical trials conducted in Africa mainly revolves around evaluating the clinical aspects of the vaccine at setting level as the production capacity is almost negligible. Vaccines before being allowed to be used in communities with living condition below a poverty line and political unrest the following questions need to be asked; how many undergo clinical trials prior to usage?, how many of the imported vaccines pass through clinical trial before they are distributed for human use?, do the trials begin from early stage or not?, are there any vaccine trials terminated for futility?, are the trials inclusive, are the vaccines safe?, are they efficacious enough?, etc. If the preventive measure which is rarely prone to resistance becomes the cause of an illness it does trigger a question as to why it could have happened. The question is for how long is a region like Africa going to depend on pharmaceutical companies of industrialized countries which may or may not be able to address

all the issues. Solid evidence is required to determine what confounding factors, are affecting the efficacy and safety of the vaccines.

This study was carried out to assess, primarily; how many vaccine trials have been conducted for preventive purpose to see how many of the vaccines that are in use (for routine immunization), in African countries have been tasted in clinical trial. And secondly based on the finding from the clinical trial registries the top three vaccine types i.e. based on how many countries have tested these disease specific vaccines was included in extended SR/MA so that it could give us a more generalizable outcome. These vaccine clinical trials conducted across Africa were analyzed through meta-analysis to assess the efficacy of the vaccines and presence of serious adverse events (SAEs).

1.4. Objective

1.4.1. General objective

- To assess the vaccine trials conducted in Africa, identify top 3 disease specific vaccine types as per of routine vaccination and examine their efficacy and safety.

1.4.2. Specific objectives

- To examine and describe vaccine trials conducted in Africa;
- Identify the phases of vaccine trials conducted in Africa
- Identify vaccines that are in use for routine immunization in African countries;
- To estimate efficacy of vaccines and assess presence of SAEs; and
- To assess the potential determinants.

Method

2.1. Study design

A systematic review and meta-analysis design was employed as per the Cochrane guideline to scrutinize vaccine-clinical trials conducted in Africa until December 2020 with no start date limit. A protocol to undergo this study was registered in Prospero (CRD42020212282).

While reviewing the studies;

A systematic electronic search was carried out in studies published in English language until the end of 2020.

1. Vaccine clinical trials was searched on the database of the WHO approved registries of the International Clinical Trials Registry Platform (ICTRP) which comprises:- Australian New Zealand Clinical Trials Registry (ANZCTR), Brazilian Clinical Trials Registry (ReBec), Chinese Clinical Trial Register (ChiCTR), Clinical Research Information Service (CRiS), Republic of Korea, ClinicalTrials.gov, Clinical Trials Registry - India (CTRI), Cuban Public Registry of Clinical Trials (RPCEC), EU Clinical Trials Register (EU-CTR), German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), ISRCTN, Japan Primary Registries Network (JPRN), Pan African Clinical Trial Registry (PACTR), Peruvian Clinical Trials Registry (REPEC), Sri Lanka Clinical Trials Registry (SLCTR), Thai Clinical Trials Register (TCTR), The Netherlands National Trial Register (NTR) and network member Lebanese Clinical Trials Registry (LBCTR) in order to identify the type of vaccine trials carried out in African countries and to select the vaccine types which are included for further analysis.
2. WHO immunization schedule and the South African sites were used to get list of vaccines that are under routine use (78, 79).
3. After the selection of target vaccine types, for published papers databases like; PubMed, science open, BASE, and www.ct.gov were used as a source. Google Scholar, Medline Plus, Cochrane and others were used as a source for relevant articles. For completed unpublished papers request was made and only one study in the vaccine/disease of interest was acquired from other data base but was excluded due to outcome difference. Reference list of related studies also used additional data.

2.2. Search terms

Step one;

Search terms for vaccine trials conducted in Africa

(Preventive clinical trials or clinical trials or vaccine trials in;

Africa or Cape Verde or South Sudan or Sao Tome & Prince or Seychelles or Djibouti or Namibia or Equatorial guinea or Eritrea or Mauritania or Central African Republic or Chad or Togo or Libyan Arab Jamahiriya or Angola or Burundi or Lesotho or Liberia or Madagascar or

Somalia or Swaziland or Eswatini or Niger or Guinea or Sierra Leone or Mauritius or Congo or Benin or Guinea Bissau or Gabon or Côte d'Ivoire or Ivory Coast or Sudan or Senegal or Congo, the democratic of republic or Botswana or Mozambique or Rwanda or Gambia or Cameroon or Mali or Algeria or Morocco or Burkina Faso or Zimbabwe or Ethiopia or Ghana or Zambia or Malawi or Tanzania or Tunisia or Nigeria or Uganda or Kenya or Egypt or South Africa or Comoros).

Step two;

Search terms for vaccines that are part of the routine immunization program in Africa.

Immunization or immunization schedule or vaccination in;

(Africa or Cape Verde or South Sudan or Sao Tome & Prince or Seychelles or Djibouti or Namibia or Equatorial guinea or Eritrea or Mauritania or Central African Republic or Chad or Togo or Libyan; Arab Jamahiriya or Angola or Burundi or Lesotho or Liberia or Madagascar or Somalia or Swaziland or Eswatini or Niger or Guinea or Sierra Leone or Mauritius or Congo or Benin or Guinea Bissau or Gabon or Côte d'Ivoire or Ivory Coast or Sudan or Senegal or Congo, the democratic of republic or Botswana or Mozambique or Rwanda or Gambia or Cameroon or Mali or Algeria or Morocco or Burkina Faso or Zimbabwe or Ethiopia or Ghana or Zambia or Malawi or Tanzania or Tunisia or Nigeria or Uganda or Kenya or Egypt or South Africa or Comoros).

Step three;

Further search terms added based on the preliminary results are Malaria, Influenza and Pneumonia.

These three disease specific vaccines were selected not based on the highest number of trials but, the number of countries that have conducted the specific vaccine irrespective of the phase of the vaccine trial or the type of vaccine (whether it is part of the routine immunization program or not). 1st, Malaria vaccine was found to have been conducted across 14 counties (Tanzania, Mozambique, Malawi, Ghana, Kenya, Guinea, Gabon, Nigeria, Gambia, Burkina Faso, Uganda, Senegal, Mali and Benin), 2nd Influenza vaccine was found to have been conducted in 11 countries (Cameroon, Kenya, Mozambique, Nigeria, Sudan, Uganda, Zambia, Mali, South Africa, Senegal and Gambia) and 3rd was Pneumonia vaccine which was conducted in 10 countries (Gambia, Kenia, Burkina Faso, Malawi, Mali, Nigeria, South Africa, Egypt, Uganda

and Cote devour), So these three vaccines were selected and included in this SR/MA and assessed individually.

("Malaria vaccines"[Mesh]) AND ("Congo"[Mesh] OR "Guinea-Bissau"[Mesh] OR "Democratic Republic of the Congo"[Mesh] OR "Cote d'Ivoire"[Mesh] OR "Equatorial Guinea"[Mesh] OR "Eritrea"[Mesh] OR "Comoros"[Mesh] OR "Guinea"[Mesh] OR "Djibouti"[Mesh] OR "Zimbabwe"[Mesh] OR "Zambia"[Mesh] OR "Uganda"[Mesh] OR "Tunisia"[Mesh] OR "Togo"[Mesh] OR "Tanzania"[Mesh] OR "Sudan"[Mesh] OR "South Africa"[Mesh] OR "Somalia"[Mesh] OR "Sierra Leone"[Mesh] OR "Seychelles"[Mesh] OR "Senegal"[Mesh] OR "Rwanda"[Mesh] OR "Nigeria"[Mesh] OR "Niger"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh] OR "Morocco"[Mesh] OR "Mauritius"[Mesh] OR "Mauritania"[Mesh] OR "Mali"[Mesh] OR "Malawi"[Mesh] OR "Madagascar"[Mesh] OR "Liberia"[Mesh] OR "Lesotho"[Mesh] OR "Kenya"[Mesh] OR "Ghana"[Mesh] OR "Gambia"[Mesh] OR "Gabon"[Mesh] OR "Ethiopia"[Mesh] OR "Egypt"[Mesh] OR "Chad"[Mesh] OR "Central African Republic"[Mesh] OR "Cameroon"[Mesh] OR "Burundi"[Mesh] OR "Burkina Faso"[Mesh] OR "Botswana"[Mesh] OR "Benin"[Mesh] OR "Angola"[Mesh] OR "Algeria"[Mesh] OR "Eswatini"[Mesh] OR "Libya"[Mesh] OR "Egypt, Ancient"[Mesh] OR "South Sudan"[Mesh])

((((malaria vaccines [Mesh Terms]) OR (RTS, S [Mesh Terms])) OR (malaria vaccine efficacy [Mesh Terms])) OR (malaria vaccines safety [Mesh Terms])) OR ("malaria Vaccines/adverse effects"[Mesh] OR "malaria Vaccines/therapeutic use"[Mesh]))AND (Africa or Cape Verde or South Sudan or Sao Tome & Prince or Seychelles or Djibouti or Namibia or Equatorial guinea or Eritrea or Mauritania or Central African Republic or Chad or Togo or Libyan Arab Jamahiriya or Angola or Burundi or Lesotho or Liberia or Madagascar or Somalia or Swaziland or Eswatini or Niger or Guinea or Sierra Leone or Mauritius or Congo or Benin or Guinea Bissau or Gabon or Côte d'Ivoire or Ivory Coast or Sudan or Senegal or Congo, the democratic of republic or Botswana or Mozambique or Rwanda or Gambia or Cameroon or Mali or Algeria or Morocco or Burkina Faso or Zimbabwe or Ethiopia or Ghana or Zambia or Malawi or Tanzania or Tunisia or Nigeria or Uganda or Kenya or Egypt or South Africa or Comoros [Mesh Terms])

("Influenza vaccines"[Mesh]) AND ("Congo"[Mesh] OR "Guinea-Bissau"[Mesh] OR "Democratic Republic of the Congo"[Mesh] OR "Cote d'Ivoire"[Mesh] OR "Equatorial

Guinea"[Mesh] OR "Eritrea"[Mesh] OR "Comoros"[Mesh] OR "Guinea"[Mesh] OR "Djibouti"[Mesh] OR "Zimbabwe"[Mesh] OR "Zambia"[Mesh] OR "Uganda"[Mesh] OR "Tunisia"[Mesh] OR "Togo"[Mesh] OR "Tanzania"[Mesh] OR "Sudan"[Mesh] OR "South Africa"[Mesh] OR "Somalia"[Mesh] OR "Sierra Leone"[Mesh] OR "Seychelles"[Mesh] OR "Senegal"[Mesh] OR "Rwanda"[Mesh] OR "Nigeria"[Mesh] OR "Niger"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh] OR "Morocco"[Mesh] OR "Mauritius"[Mesh] OR "Mauritania"[Mesh] OR "Mali"[Mesh] OR "Malawi"[Mesh] OR "Madagascar"[Mesh] OR "Liberia"[Mesh] OR "Lesotho"[Mesh] OR "Kenya"[Mesh] OR "Ghana"[Mesh] OR "Gambia"[Mesh] OR "Gabon"[Mesh] OR "Ethiopia"[Mesh] OR "Egypt"[Mesh] OR "Chad"[Mesh] OR "Central African Republic"[Mesh] OR "Cameroon"[Mesh] OR "Burundi"[Mesh] OR "Burkina Faso"[Mesh] OR "Botswana"[Mesh] OR "Benin"[Mesh] OR "Angola"[Mesh] OR "Algeria"[Mesh] OR "Eswatini"[Mesh] OR "Libya"[Mesh] OR "Egypt, Ancient"[Mesh] OR "South Sudan"[Mesh])

((((Influenza vaccines [Mesh Terms]) OR (Influenza [Mesh Terms])) OR (Influenza vaccine efficacy [Mesh Terms])) OR (Influenza vaccines safety [Mesh Terms])) OR (" Influenza Vaccines/adverse effects"[Mesh] OR " Influenza Vaccines/therapeutic use"[Mesh]))AND (Africa or Cape Verde or South Sudan or Sao Tome & Prince or Seychelles or Djibouti or Namibia or Equatorial guinea or Eritrea or Mauritania or Central African Republic or Chad or Togo or Libyan Arab Jamahiriya or Angola or Burundi or Lesotho or Liberia or Madagascar or Somalia or Swaziland or Eswatini or Niger or Guinea or Sierra Leone or Mauritius or Congo or Benin or Guinea Bissau or Gabon or Côte d'Ivoire or Ivory Coast or Sudan or Senegal or Congo, the democratic of republic or Botswana or Mozambique or Rwanda or Gambia or Cameroon or Mali or Algeria or Morocco or Burkina Faso or Zimbabwe or Ethiopia or Ghana or Zambia or Malawi or Tanzania or Tunisia or Nigeria or Uganda or Kenya or Egypt or South Africa or Comoros [Mesh Terms])

("Pneumococcal vaccines"[Mesh]) AND ("Congo"[Mesh] OR "Guinea-Bissau"[Mesh] OR "Democratic Republic of the Congo"[Mesh] OR "Cote d'Ivoire"[Mesh] OR "Equatorial Guinea"[Mesh] OR "Eritrea"[Mesh] OR "Comoros"[Mesh] OR "Guinea"[Mesh] OR "Djibouti"[Mesh] OR "Zimbabwe"[Mesh] OR "Zambia"[Mesh] OR "Uganda"[Mesh] OR "Tunisia"[Mesh] OR "Togo"[Mesh] OR "Tanzania"[Mesh] OR "Sudan"[Mesh] OR "South

Africa"[Mesh] OR "Somalia"[Mesh] OR "Sierra Leone"[Mesh] OR "Seychelles"[Mesh] OR "Senegal"[Mesh] OR "Rwanda"[Mesh] OR "Nigeria"[Mesh] OR "Niger"[Mesh] OR "Namibia"[Mesh] OR "Mozambique"[Mesh] OR "Morocco"[Mesh] OR "Mauritius"[Mesh] OR "Mauritania"[Mesh] OR "Mali"[Mesh] OR "Malawi"[Mesh] OR "Madagascar"[Mesh] OR "Liberia"[Mesh] OR "Lesotho"[Mesh] OR "Kenya"[Mesh] OR "Ghana"[Mesh] OR "Gambia"[Mesh] OR "Gabon"[Mesh] OR "Ethiopia"[Mesh] OR "Egypt"[Mesh] OR "Chad"[Mesh] OR "Central African Republic"[Mesh] OR "Cameroon"[Mesh] OR "Burundi"[Mesh] OR "Burkina Faso"[Mesh] OR "Botswana"[Mesh] OR "Benin"[Mesh] OR "Angola"[Mesh] OR "Algeria"[Mesh] OR "Eswatini"[Mesh] OR "Libya"[Mesh] OR "Egypt, Ancient"[Mesh] OR "South Sudan"[Mesh])

((((Pneumococcal vaccines [Mesh Terms]) OR (PCV [Mesh Terms])) OR (Pneumococcal vaccine efficacy [Mesh Terms])) OR (Pneumococcal vaccines safety [Mesh Terms])) OR (" Pneumococcal Vaccines/adverse effects"[Mesh] OR "Pneumococcal Vaccines/therapeutic use"[Mesh]))AND (Africa or Cape Verde or South Sudan or Sao Tome & Prince or Seychelles or Djibouti or Namibia or Equatorial guinea or Eritrea or Mauritania or Central African Republic or Chad or Togo or Libyan Arab Jamahiriya or Angola or Burundi or Lesotho or Liberia or Madagascar or Somalia or Swaziland or Eswatini or Niger or Guinea or Sierra Leone or Mauritius or Congo or Benin or Guinea Bissau or Gabon or Côte d'Ivoire or Ivory Coast or Sudan or Senegal or Congo, the democratic of republic or Botswana or Mozambique or Rwanda or Gambia or Cameroon or Mali or Algeria or Morocco or Burkina Faso or Zimbabwe or Ethiopia or Ghana or Zambia or Malawi or Tanzania or Tunisia or Nigeria or Uganda or Kenya or Egypt or South Africa or Comoros [Mesh Terms])

2.3. Data extraction (selection and coding)

ENDNOTE software version X9 and Zotero was used for citation and importing of the research articles from the electronic databases. Two authors independently selected studies based on the inclusion and exclusion criteria. Data extraction form was developed which comprises:-

1. Detail of search: title, year of publication, study design, study period, country where trial was conducted and any differences among reviewers was resolved by discussion.
2. Characteristics of the trial for descriptive analysis: vaccine trials conducted in Africa.
3. Characteristics of the trial for SR/MA: completed or terminated due to an early success, available result.

4. Target conditions: vaccine trials conducted in Africa to address infectious disease.

Studies of the top 3 vaccine type trials, conducted across African countries for vaccine prevention of infectious diseases were selected for final analysis based on; intervention vs. placebo or other approved vaccine. Disagreements were solved through discussion and third person view. The screening and selection process is reported in a PRISMA flow chart (80).

2.4. Study population

All vaccine trials conducted for prevention purpose in African countries were included.

2.5. Study period

This Thesis was undertaken from 20th of April to 7th of August of 2021.

2.6. Inclusion and exclusion criteria

2.6.1. Inclusion criteria

- Articles published in English language on vaccine trials carried out for prevention purpose in Africa
- Articles on both qualitative and quantitative studies of human vaccine trials conducted in Africa were included, i.e., the top three vaccine types, completed or terminated due to an early success, phase three and phase four trials with placebo or other standard care comparator vaccine trials

2.6.2. Exclusion criteria

- Articles on vaccine trials not part of routine immunization;
- Articles on single arm studies;
- Articles on Comparative studies; and
- Articles on trials done for other indications

2.7. Outcome(s)

Primary outcome: Estimate efficacy of Vaccine trials shown in terms of protection

Secondary outcome: Assess serious adverse events **(**SAEs) of the vaccines

2.8. Risk of bias (quality) assessment

Data were extracted by two independent reviewers; with an inter-rater agreement, discrepancies were determined through discussion and also third reviewer's opinion. Extracted data included the type of trial, phase of the trial, vaccines as per disease of interest, year of undertaking and country where it was done. The methodological quality (sequence generation; allocation concealment; blinding, incomplete outcome data; selective outcome reporting and other bias of the included study) was assessed and graded using Cochrane risk of bias assessment tool (80).

2.9. Strategy for data synthesis

We searched the data bases of the registries and the registered record of the studies; i.e., .xml, .csv, .txt was downloaded and exported or entered manually to excel. Read-only data, snap-shot was taken as primary record and it was entered to excel manually. Trials and studies were checked for duplication and registered and published on more than one registry and data base were removed leaving only one study to be selected for analysis. To analyze how clinical trial registration was developed in Africa so far, we conducted analysis of developments in clinical trial at each of the 18 registries where clinical trials are registered; ;

1. Types of registered vaccine trials (by type of disease) in African countries compared to vaccines under use in countries of Africa;
2. Study phases of the targeted trials;
3. Assess Impact of these clinical trials, primary analysis was done using excels. Review Manager (RevMan version 5.4) was used for the extended review and the observed studies' significance was estimated in forest plots with 95% confidence intervals (CIs) using a fixed effect model. PRISMA 2020 Systematic Review and Meta-Analysis guidelines for Reporting Items was followed to design and report results. The overall heterogeneity between studies was measured using the I^2 statistic (25% - 49% low, 50% - 75% moderate and >75% high). Confidence in the evidence of the studies was assessed using GRADE pro (81). Due to lack of sufficient predictor no meta-regression was done.

Results

We conducted this research starting from 20th of April to 7th of August, we searched the WHO and South African immunization schedule site to identify and analyze which vaccines are being used (administered) for the routine immunization program in Africa, we searched the 18 WHO approved registries to analyze the vaccine trials conducted in Africa for prevention purpose and further breakdown which preventive vaccine trials are used for routine immunization program. Only the types of vaccines that are in use i.e., for Malaria; RTS, S vaccine for Influenza; Influenza vaccine and for Pneumonia; PCV vaccines were searched and included in the extended SR/MA in which766, 440, and 292 articles, respectively were acquired primarily. And for the review 6, 10, and 5 studies we included, respectively.

3.1: vaccines that are part of the routine immunization program in Africa

Table 1: single-vaccine, single-disease immunization distribution across African countries

Countries	Vaccines												
	BCG	Pneumo_conj	Rotavirus	TT	Vitamin A	YF	HPV	Measel	Typhoid_conj	deworming	HIB	RTS.S	Cholera
Algeria	Yes	Yes											
Angola	Yes	Yes	Yes	yes	Yes	Yes							
Benin	Yes	Yes	Yes	yes			Yes						
Botswana	Yes	Yes	Yes	yes	Yes	Yes	Yes						
Burkina Faso	Yes	Yes	Yes	yes	Yes	Yes							
Burundi	Yes	Yes	Yes		Yes	Yes							
Cape Verde	Yes			yes		Yes	Yes						
Cameroun	Yes	Yes	Yes		Yes	Yes	Yes						
Central African Republic	Yes	Yes	Yes		Yes	Yes	Yes	Yes					

Chad	Yes			yes		Yes		Yes	Yes				
Comoros	Yes	Yes			Yes			Yes		Yes			
Congo	Yes	Yes	Yes	yes	Yes	Yes							
Congo, Democratic Republic	Yes	Yes	Yes		Yes	Yes		yes					
Cote D'voir	Yes	Yes	Yes		Yes	Yes	yes						
Djibouti	Yes	Yes	Yes	yes	Yes			yes					
Egypt	Yes			yes	Yes	Yes					yes		
Equatorial Guinea	Yes				Yes	Yes	yes	yes					
Eritrea	Yes	Yes	Yes		Yes		yes						
Eswatini(Swaziland)	Yes	Yes	Yes	yes	Yes	Yes	yes						
Ethiopia	Yes	Yes	Yes	yes	Yes		yes	yes			yes		
Gabon	Yes	Yes	Yes		Yes	Yes		yes					
Gambia	Yes	Yes	Yes			Yes	yes	yes					
Ghana	Yes			yes		Yes		yes				yes	
Guinea	Yes	Yes	Yes	yes	Yes	Yes	yes						
Guinea Bisaw	Yes	Yes	Yes	yes		Yes		yes					
Kenya	Yes	Yes	Yes	yes	Yes		yes					yes	
Lesotho	Yes	Yes	Yes	yes	Yes	Yes							
Liberia	Yes	Yes	Yes	yes	Yes	Yes	yes	yes	Yes				
Libyan Arab Jemahirya	Yes	Yes	Yes			Yes	yes						
Madagascar	Yes	Yes	Yes	yes				yes					
Malawi	Yes	Yes	Yes		Yes		yes					yes	
Mali	Yes	Yes	Yes		Yes	Yes	yes	yes					
Mauritania	Yes	Yes	Yes				yes						
Mauritius	Yes	Yes	Yes	yes			yes		Yes				

Morocco	Yes	Yes	Yes	yes	Yes								
Mozambique	Yes	Yes	Yes	yes	Yes								
Namibia	Yes	Yes	Yes	yes	Yes								
Niger	Yes	Yes	Yes		Yes	Yes		yes					
Nigeria	Yes	Yes	Yes		Yes	Yes	yes	yes					
Rwanda	Yes	Yes	Yes	yes			yes						
Saotome & Principe	Yes	Yes	Yes		Yes	Yes							
Senegal	Yes	Yes	Yes		Yes	Yes	yes						
Seycheles	Yes	Yes	Yes	yes	Yes		yes						
Sierra Leone	Yes	Yes	Yes		Yes	Yes	yes	yes					
Somalia	Yes			yes	Yes			yes					
South Africa	Yes	Yes	Yes		Yes		yes	yes					
South Sudan	Yes			yes				yes					
Sudan	Yes	Yes	Yes					yes					
Tanzania	Yes	Yes	Yes	yes			yes						
Togo	Yes	Yes	Yes	yes	Yes	Yes	yes						
Tunisia	Yes	Yes											
Uganda	Yes	Yes	Yes	yes			yes	yes					
Zambia	Yes	Yes	Yes		Yes		yes						
Zimbabwe	Yes	Yes	Yes	yes	Yes		yes		yes				yes
Total:	54	47	44	30	37	29	30	22	4	1	2	3	1
Percentage:	100%	87%	81.5%	55.5 %	68.5%	53.7 %	55.5 %	40.7%	7.4%	1.9%	3.7 %	5.5%	1.9%

Source; [Immunization schedules by antigens (who.int)](#)/[Immunization Schedules - Africa | Vaccines for Africa (uct.ac.za)](#)

BCG = Bacille Calmette-Guerln vaccine Pneumo_conj = Pneumococcal conjugate vaccine

TT = Tetanus toxoid vaccine

HPV = Human Papillomavirus vaccine

HIB = Haemophilus Influenza type b vaccine

YF = Yellow fever vaccine

Typhoid_conj = Typhoid conjugate vaccine

Table 2: multi-vaccine, per disease immunization distribution across African countries

Countries	Hep-A Pediatric	Hep-A adult	Hep-B Pediatric	Heb-B Adult	Influenza	Influenza Pediatric	Influenza Adult	menAC	MENACWY_ 135 conju	Men A_Conju	bopv	IPV	opv
Algeria			Yes			Yes	Yes			Yes		yes	yes
Angola			Yes									yes	yes
Benin			Yes									yes	yes
Botswana			Yes									yes	yes
Burkina Faso										Yes		yes	yes
Burundi												yes	yes
Cape Verde			Yes									yes	yes
Cameroun			Yes							Yes		yes	yes
Central African Republic			Yes							Yes		yes	yes
Chad										Yes		yes	yes
Comoros												yes	yes
Congo												yes	yes
Congo, Democratic Republic												yes	yes
Cote D'voir					Yes					Yes		yes	yes

Djibouti			Yes									yes	Yes
Egypt			Yes	Yes		Yes	Yes	yes				yes	Yes
Equatorial Guinea			Yes							Yes		yes	Yes
Eritrea										Yes		yes	Yes
Eswatini(Swaziland)				Yes								yes	Yes
Ethiopia												Yes	Yes
Gabon										Yes		Yes	Yes
Gambia			Yes							Yes		Yes	Yes
Ghana												Yes	Yes
Guinea										Yes		Yes	Yes
Guinea Bisaw												Yes	Yes
Kenya				Yes		Yes	Yes					Yes	Yes
Lesotho												Yes	Yes
Liberia												Yes	Yes
Libyan Arab Jemahirya			Yes	Yes		Yes	Yes		Yes				Yes
Madagascar												Yes	Yes
Malawi												Yes	Yes
Mali										Yes		Yes	Yes
Mauritania			Yes									Yes	Yes
Mauritius		Yes		Yes		Yes	Yes		Yes				Yes
Morocco			Yes			Yes;	Yes					Yes	Yes
Mozambique												Yes	Yes
Namibia			Yes								Yes	Yes	Yes
Niger										Yes		Yes	Yes
Nigeria			Yes							Yes		Yes	Yes

Rwanda												Yes	Yes
Saotome & Principe			Yes									Yes	Yes
Senegal			Yes									Yes	Yes
Seychelles			Yes	yes								Yes	Yes
Sierra Leone												Yes	Yes
Somalia												Yes	Yes
South Africa						Yes	Yes						Yes
South Sudan												Yes	Yes
Sudan										Yes		Yes	Yes
Tanzania												Yes	Yes
Togo										Yes		Yes	Yes
Tunisia	Yes		Yes			Yes	Yes					Yes	Yes
Uganda			yes									Yes	yes
Zambia												Yes	yes
Zimbabwe												Yes	yes
Total:	1	1	21	6	1	7	8	1	2	16	1	51	54
Percentage:	1.9%	1.9%	38.9%	11.1%	1.9%	12.9%	14.8%	1.9%	3.7%	29.6%	1.9%	94.4%	100 %

Source; **Immunization schedules by antigens (who.int)/Immunization Schedules - Africa | Vaccines for Africa (uct.ac.za)**

Hep-A Pediatric = Hepatitis A pediatric dose vaccine

Hep-A Adult = Hepatitis A adult dose vaccine

Hep-B Pediatric = Hepatitis B pediatric dose vaccine

Heb-B Adult = Hepatitis B adult dose vaccine

MENACWY_135 conju = Meningococcal ACWY-135 conjugate vaccine

Men A_Conju = Meningococcal A conjugate vaccine

bopv = bivalent oral polio vaccine

IPV = inactivated polio vaccine

menAC = Meningococcal AC vaccine opv = oral polio vaccine

Table 3: Combination vaccines, immunization distribution across African countries

Countries	Vaccines												
	DT	DTapHibHepBIPV	DTwPHib	MMR	MR	DTwP	DTaP	Tdap	TdaPIPV	TD	DTwPHibHepB	TdIPV	DtaPHibIP
Algeria	Yes	Yes	Yes	Yes	Yes					Yes			
Angola					Yes					Yes	Yes		
Benin					yes					Yes	Yes		
Botswana					yes						Yes		
Burkina Faso					yes					Yes	Yes		
Burundi					yes	Yes				Yes	Yes		
Cape Verde				yes						Yes	Yes		
Cameroun					yes					Yes	Yes		
Central African Republic					yes					Yes	Yes		
Chad											Yes		
Comoros					yes						Yes		
Congo					yes					Yes	Yes		
Congo, Democratic, R										Yes	Yes		
Cote D'voir					yes						Yes		
Djibouti						Yes				Yes	Yes		
Egypt	Yes			yes		Yes				Yes	Yes		
Equatorial Guinea										Yes	Yes		
Eritrea					yes					Yes	Yes		
Eswatini(Swaziland)	Yes				yes		Yes			Yes	Yes		
Ethiopia										Yes	Yes		

Gabon					yes					Yes	Yes		
Gambia										Yes	Yes		
Ghana											Yes		
Guinea					yes	Yes					Yes		
Guinea Bisaw											Yes		
Kenya					yes					Yes	Yes		
Lesotho	Yes				yes						Yes		
Liberia											Yes		
Libyan Arab Jemahirya				Yes				Yes	Yes				Yes
Madagascar										Yes	Yes		
Malawi					yes					Yes	Yes		
Mali										Yes	Yes		
Mauritania					Yes					Yes	Yes		
Mauritius	Yes	Yes		yes									
Morocco					Yes	Yes					Yes		
Mozambique			Yes		Yes						Yes		
Namibia					Yes					Yes	Yes		
Niger										Yes	Yes		
Nigeria										Yes	Yes		
Rwanda					Yes						Yes		
Saotome & Principe					Yes					Yes	Yes		
Senegal					Yes					Yes	Yes		
Seycheles	Yes	yes		yes	Yes	Yes		Yes	yes	Yes	Yes	yes	
Sierra Leone					Yes					Yes	Yes		
Somalia										Yes	Yes		
South Africa		yes								Yes			

South Sudan										Yes	Yes		
Sudan											Yes		
Tanzania					Yes						Yes		
Togo					Yes					Yes	Yes		
Tunisia	Yes	yes			Yes	Yes				Yes	Yes		
Uganda					Yes					Yes	Yes		
Zambia					Yes					Yes	Yes		
Zimbabwe					Yes	Yes				Yes	Yes		
Total:	8	5	2	6	33	8	1	2	2	38	50	1	1
Percentage:	14.8%	9.3%%	3.7%	11.1%	61.1%	14.8%	1.9%	3.7%	3.7%	70.4%	92.6%%	1.9%	1.9%

Source; Immunization schedules by antigens (who.int)/Immunization Schedules - Africa | Vaccines for Africa (uct.ac.za)

DT = Tetanus & diphtheria toxoid chldrens' dose DTaP = Diphtheria & Tetanus toxoid with cellular pertussis vaccine

DTapHibHepBIPV = Hexavalent Diphtheria & Tetanus toxoid with cellular pertussis, HIB, Hepatitis B & IPV

DTwPHib = Diphtheria & Tetanus toxoid with whole cell pertussis & Hib vaccine Tdap = Tetanus & diphtheria toxoid acellular pertussis vaccine

MMR = measles mumps & rubella vaccine TD = Tetanus & diphtheria toxoid for older children/adult vaccine

MR = measles & rubella vaccine DTwPHibHepB = Diphtheria & Tetanus & pertussis & Haemophilus influenza & Hepatitis B vaccine

DTwP = Diphtheria & Tetanus toxoid with whole cell pertussis vaccine TdIPV = Tetanus & diphtheria toxoid for older children/adults with IPV vaccine

DTaPHibIPV = Diphtheria & Tetanus toxoid with cellular pertussis, Hib & IPV vaccine

TdaPIPV = Tetanus & diphtheria toxoid with acellular pertussis & IPV vaccine

Tables 1, 2, and 3, show the distribution of vaccines that are part of routine immunization program in Africa. All in all, there are 39 vaccines of which; 13 are single vaccines/disease, 13 are multiple vaccines/disease and 13 are combination vaccines. Out of these vaccines BCG and OPV are given in all African countries, whereas Hepatitis A pediatric and adult, Influenza, MenAC, bOPV, deworming, cholera, DTaP, TdIPV and dtaPHibIP are given only in one country each.

3.2: Distribution of vaccine trials conducted in African countries.

Figure 1: Diseases specific vaccine trials conducted in Africa and registered until the end of 2020.

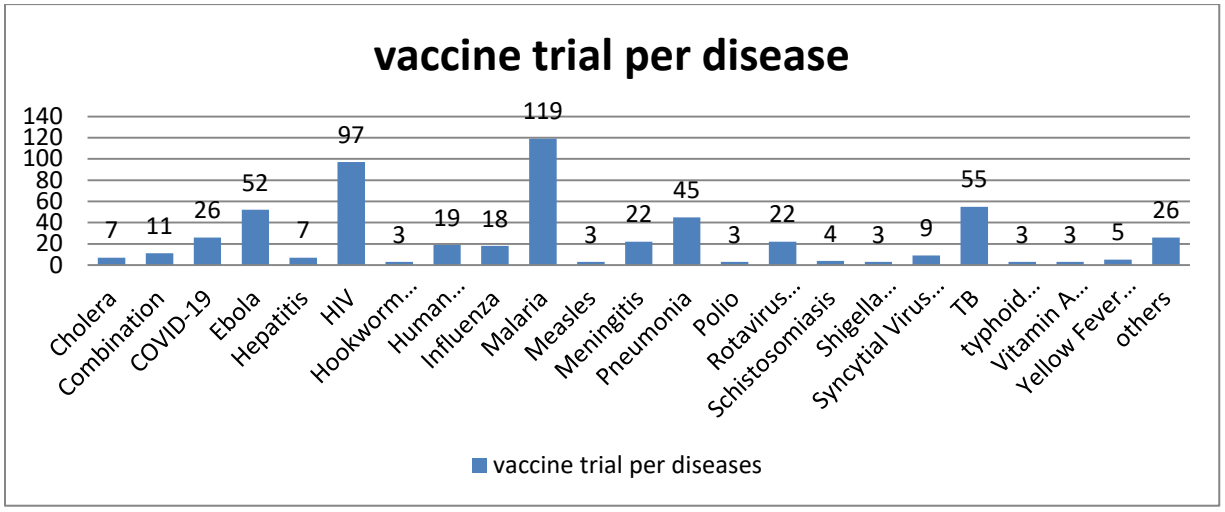

Figure 1, shows the general distribution and type of preventive vaccine trials per disease conducted in African countries until 2020. This figure shows that the number of trials on malaria and HIV vaccines is biggest with 119(21.2%), 97(17.2%), respectively. The smallest number of vaccine trial extended from 1(0.2) to 4(0.7) trials. Under other category, 14 diseases or implication are included (E.coli, Helminthic, Leishmanial, Tetanus, Monkey pox, Varicella Zoster, Rabies, Lassa fever, Clostridium difficile infection, trial for other indication, Herpes Zoster, Herpes Simplex, Hemophilia and gonorrhea).

Figure 2: Phases of the vaccine trials conducted in Africa and registered until the end of 2020.

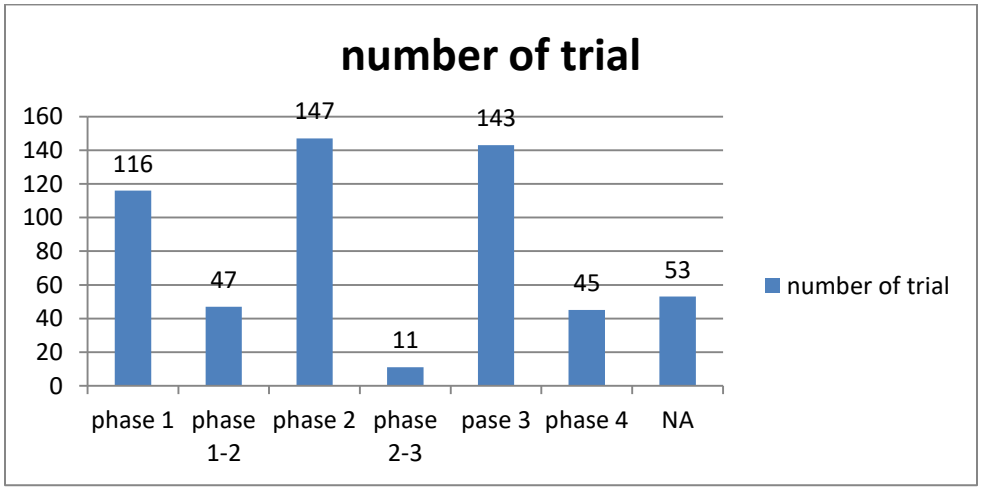

Figure 2, shows Distribution of vaccine trial conducted for preventive purpose in African countries across phases. There was almost an even distribution in phase 1, 2, and 3 with 116 (20.6%), 143(26.1%) and 143(25.4%), respectively.

Figure 3: Disease specific vaccine trials that are part of routine immunization program.

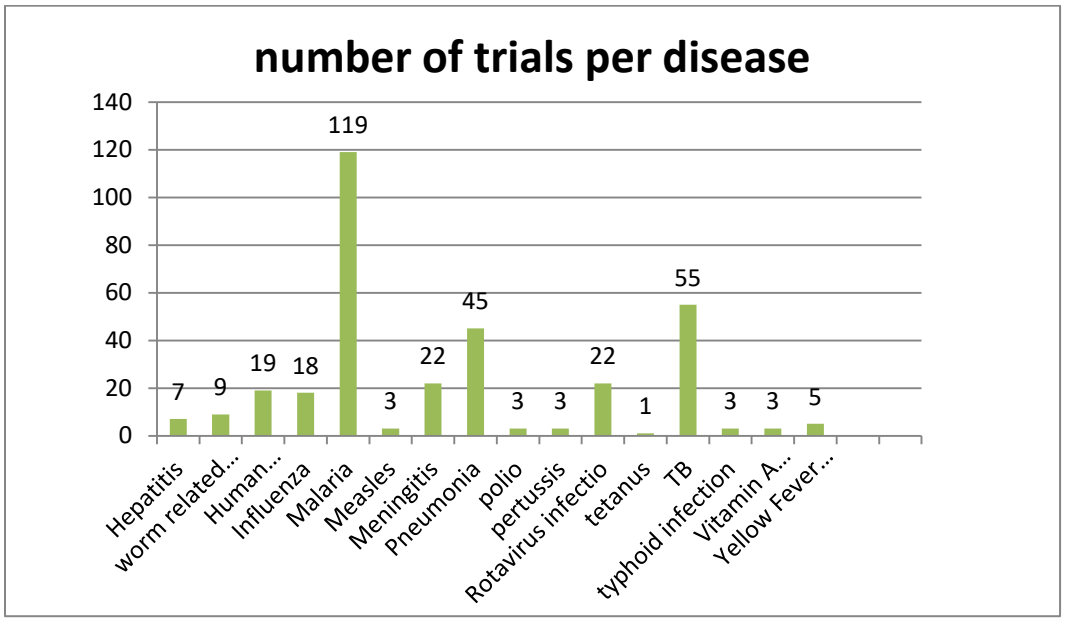

Figure 3, shows the distribution of vaccine trials that are part of the immunization program. This figure shows that the highest was for Malaria and the lowest for Tetanus with 119 (33.6%) and 1 (0.3%), respectively.

3.3 Treatment outcomes

3.3.1: Malaria Vaccine

Figure 4: PRISMA study flow diagram for Malaria vaccine.

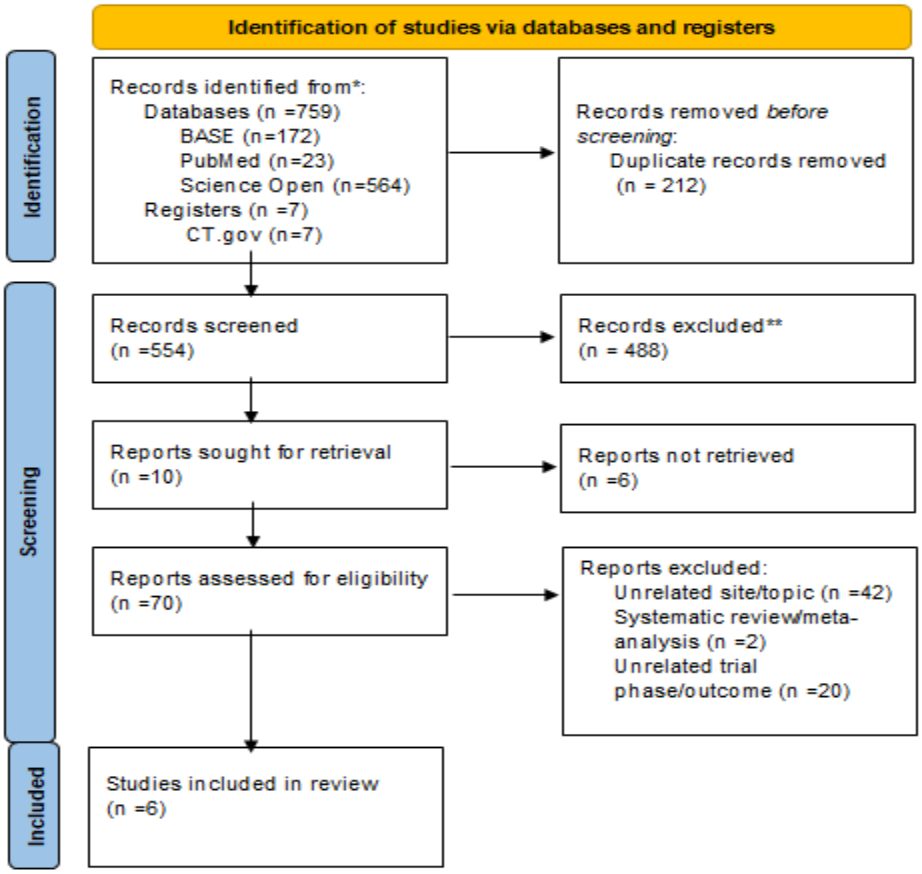

Figure 4, shows the number of studies included. A total of 6 studies were included in this malaria vaccine review which assess the efficacy and safety of RTS, S malaria vaccine trials that were conducted in African countries.

3.3.1.1: Included studies

A total of 6 studies were included in this malaria vaccine review (see figure 4) which assess the efficacy and safety of RTS, S vaccine trials that are conducted in African countries.

Table 4 : Characteristics of included studies

No	**Author name, Year of Publication**	**Study design**	**Study period**	**Subjects**			**subject outcome of interest**			vaccine	Control
				Number of participants	Age of participants	Follow-up					
1	Agnandji, S. T., 2012	randomized, controlled, double-blind trial, multi-center	December 2009 - January 2011	6537 infants	6 - 12 weeks	12 month for VE & 14 month for SAEs	Vaccine efficacy in-terms of protection against primary case definition after the three doses and SAEs after first dose			RTS,S/ AS01	meningococcal serogroup C conjugate vaccine
							>5000 parasites/mm3 and temperature ≥37.5°C	Clinical malaria/episode	1st /only	1161	714
									All	2301	1626
								Severe malaria		58	46
							SAEs	≥1 Serious adverse event		782	419
								≥1 Serious adverse event, excluding malaria		760	407
								≥1 Fatal serious adverse event*		66	28
								≥1 Serious adverse event related to vaccine		4	3
								≥1 Serious adverse event		192	96

								within 30 days after vaccination		
2	Guerra Mendoza, Y., 2019	block randomization, multi-center	December 2009 - January 2011	15,459 children & infants	5–17 months & 6–12 weeks	48 & 38 month	SAEs from first dose - four doses & after		RTS,S/ AS01	rabies vaccine & meningococcal serogroup C conjugate vaccine
							SAEs	≥1 Serious adverse event	1300	1465
								≥1 Serious adverse event, excluding malaria	1235	591
								≥1 Fatal serious adverse event	112	88
								≥1 Serious adverse event within 30 days after vaccination	285	312
3	Han, Larry, 2017	randomized, controlled, double-blind trial, multi-center	June 2009 - January 2011	760 children & 784 infants	5–17 months & 6–12 weeks	4-years	VE in-terms of protection against primary case definition after the three doses and SAEs after first dose		RTS,S/ AS01	rabies vaccine & meningococcal serogroup C conjugate vaccine
							>5000 parasites/mm3 and temperature ≥37.5°C	Clinical malaria/episode	1st /only	183	268
									All	406	720
4	Krishna, Sanjeev, 2014	randomized, controlled, double-blind	March 27, 2009 - January 31,	15,460 children & infants	5–17 months & 6–12 weeks	18 month	VE in-terms of protection against primary case definition after the three doses		RTS,S/ AS01	rabies vaccine & meningococcal serogroup C

		trial, multi-center	2011,								conjugate vaccine
							>5000 parasites/mm3 and temperature ≥37.5°C	Clinical malaria/episode	All	8105	6103
								Severe malaria		220	154
5	Otieno, L., 2016	randomized, controlled, double-blind trial, multi-center	December 2009 - January 2011	6537 infants	6 - 12 weeks	14 month for SAEs	SAEs after 1st and 3rd dose			RTS,S/AS01	Vero Rab rabies vaccine
							SAEs	At least 1 Serious adverse event		41	37
								Fatal serious adverse event*		5	4
								At least 1 Serious adverse event within 30 days after vaccination		20	12
6	Otieno, L., 2019	randomized, controlled, double-blind trial, multi-center	March 27, 2009 - January 31, 2014	153 HIV +ve children & infants	5–17 months & 6–12 weeks	39.3 month & 38.3 month	VE in-terms of protection against primary case definition after the three doses and SAEs after first dose			RTS,S/AS01	rabies vaccine & meningococcal serogroup C conjugate vaccine
								At least 1 Serious adverse event		47	42
								≥1 Serious adverse event, excluding HIV		43	40
								Fatal serious adverse event		15	15
								≥1 Serious adverse event within 3 doses 30 days after vaccination		14	12

							SAEs	≥1 Serious adverse event within 30 days after 4th vaccination	4	1

VE = vaccine efficacy ILI = influenza like illness

HIV = human Immunodeficiency virus positive SAE = serious adverse event

Table 4, shows the characteristics of the 6 included studies for this review which includes; the study ID, study design, study period, number and age of participant, the study follow up period, outcome of interest and the type of vaccine or control IP involved in the studies.

Figure 5: **Risk of bias summary for the studies included in the SR/MA of Malaria vaccine**.

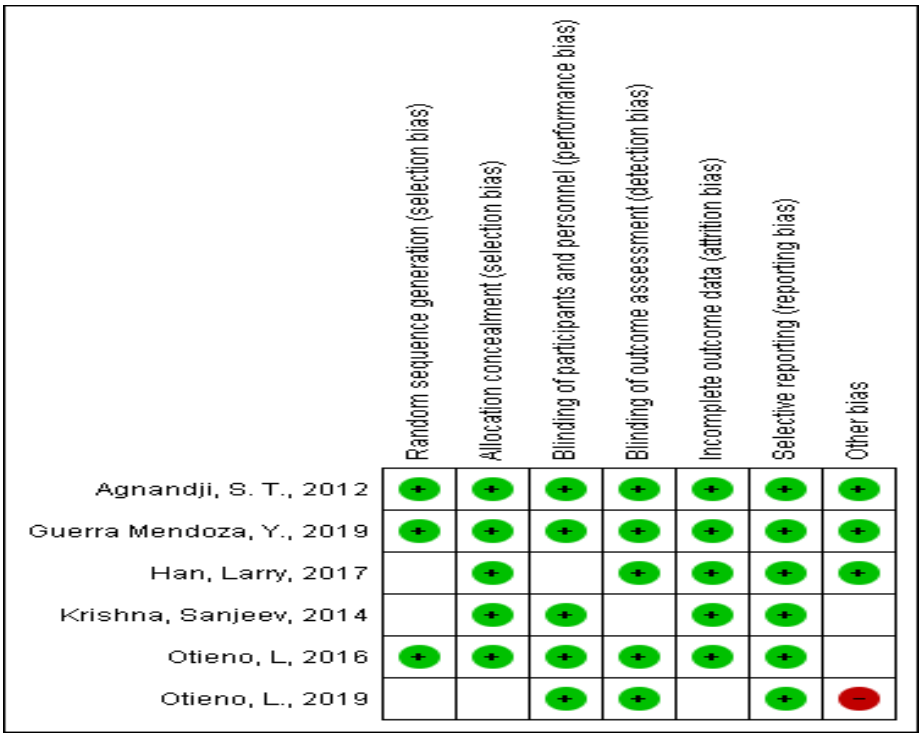

Figure 5, shows the summary of Risk of bias, which was assessed depending on whether the measures were strictly followed or not: for those studies that didn't clearly state how the measure was followed were marked as unclear, and high risk was assigned depending on the tendency of the risk to affect the outcome negatively i.e. in case of Otieno,L,2016 no formal sample size calculation was done and the IP was prepared by the study staffs though it is stated they were not part of the analysis.

Figure 6: Efficacy of RTS, S vaccine against all episode of malaria

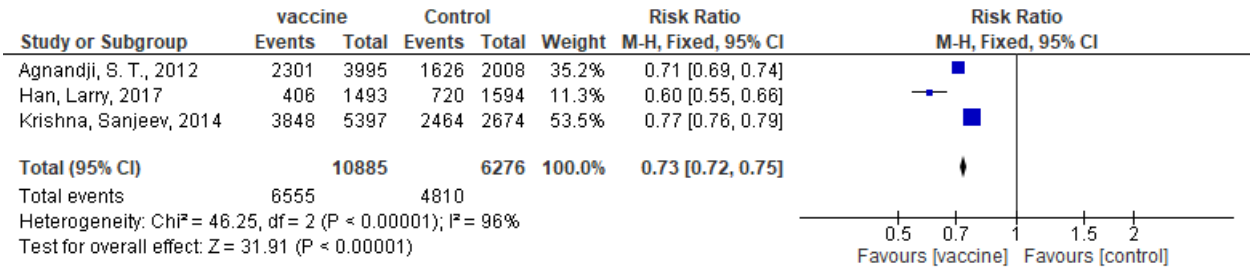

Figure 6, shows that, for all episodes of malaria in three studies (82-84) the RTS, S vaccine RR was found to be 0.73 with a significant p-value (p<00001), 95% CI (0.72, 0.75), and 17,161 participants were included and there was high heterogeneity across the studies= 96%. Number of event was acquired from the first episode with respect to total number of participants for study conducted by (83) whereas, for studies conducted by (82, 84) as recurrent event was used instead of total number of subjects persons year was taken, and the presence of high heterogeneity could have been as a result of that. The efficacy of pooled analysis of the malaria vaccine against all episodes of malaria was found to be 27%, i.e. the risk of developing malaria for those who received the vaccine was 73 % as high as developing malaria in those who didn't get the vaccine or RTS,s vaccine 27% effective in reducing the risk of acquiring malaria disease.

Figure 7: Efficacy of RTS, S vaccine against 1st episode of malaria

Figure 7, shows that, for 1st episodes of malaria in two studies (82, 83) the RTS, S vaccine RR was found to be 0.78 with a significant p-value (p<00001), 95% CI (0.72, 0.83) and 8326 participants were included and there was high heterogeneity across the studies= 85%. Number of event was acquired from the first episode with respect to total number of participants for study conducted by (83), whereas, for study conducted by (84) as recurrent event was used instead of total number of subjects persons year was taken, and the presence of high heterogeneity could have been as a result of that. The efficacy of pooled analysis of the malaria vaccine against all episodes of malaria was found to be 22%, i.e., the risk of developing malaria for those who received the vaccine was 78 % as high as developing malaria in those who didn't get the vaccine or RTS, S vaccine 22% effective in reducing the risk of acquiring malaria disease.

Figure 8: Efficacy of RTS, S vaccine against severe malaria

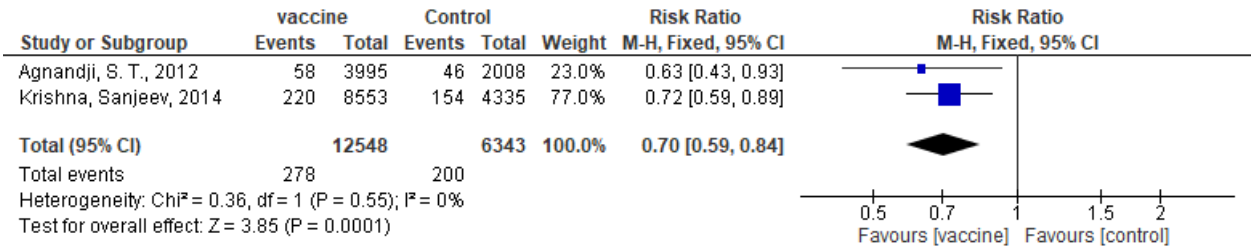

Figure 8, shows that, for severe malaria in two studies (83, 84) the RTS, S vaccine RR was found to be 0.70 with a significant p-value (p=0001), 95% CI (0.59, 0.84) and 18,891 participants were included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first episode with respect to total number of participants for study conducted by (83) for study conducted by (84) as recurrent event was used instead of total number of subjects persons year was taken The efficacy of pooled analysis of the malaria vaccine against severe malaria was found to be 30%, i.e. the risk of developing severe malaria for those who received the vaccine was 70 % as high as developing malaria in those who didn't get the vaccine or RTS, S vaccine 30% effective in reducing the risk of acquiring malaria disease.

Figure 9: Efficacy of RTS, S vaccine against all episode of malaria in infants.

Figure 9, shows that, for all episodes of malaria in infants in three studies (82-84) the RTS, S vaccine RR was found to be 0.75 with a significant p-value (p<00001), 95% CI (0.72, 0.75) and 15,510 participants were included and there was high heterogeneity across the studies= 91%. Number of event was acquired from the first episode with respect to total number of participants for study conducted by (83) whereas, for studies conducted by (82, 84) as recurrent event was used instead of total number of subjects persons year was taken, and the presence of high heterogeneity cold have been as a result of that. The efficacy of pooled analysis of the malaria

vaccine against all episodes of malaria was found to be 25%, i.e. the risk of developing malaria for those who received the vaccine was 75 % as high as developing malaria in those who didn't get the vaccine or RTS,s vaccine 25% effective in reducing the risk of acquiring malaria disease.

Figure 10: Efficacy of RTS, S vaccine against 1st episode of malaria in infants

Figure 10, shows that, for all episodes of malaria in two studies (82, 83) the RTS, S vaccine RR was found to be 0.80 with a significant p-value (p<00001), 95% CI (0.75, 0.86) and 7,081 participants were included and there was moderate heterogeneity across the studies= 42%. Number of event was acquired from the first episode with respect to total number of participants for study conducted by (83), whereas, for study conducted by (82)as recurrent event was used instead of total number of subjects persons year was taken, and the presence of high heterogeneity cold have been as a result of that. The efficacy of pooled analysis of malaria vaccine against all episodes of malaria was found to be 20%, i.e. the risk of developing malaria for those who received the vaccine was 80 % as high as developing malaria in those who didn't get the vaccine or RTS,s vaccine 20% effective in reducing the risk of acquiring malaria disease.

Figure 11: SAEs of RTS, S vaccine

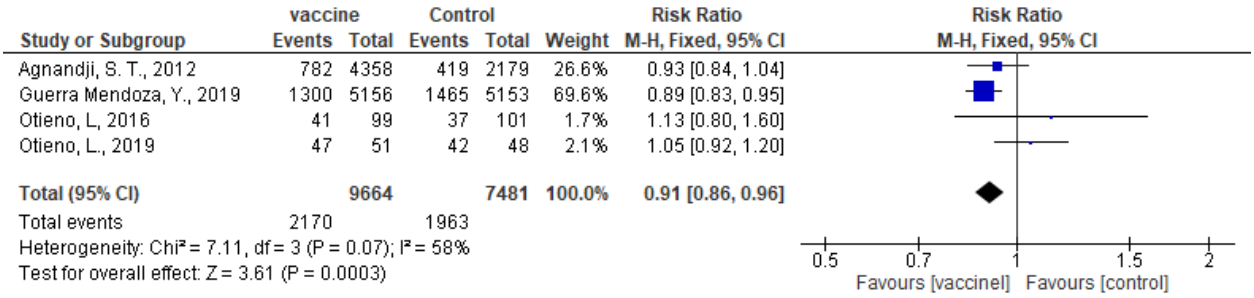

Figure 11, shows that, for all episodes of malaria in four studies (52, 55, 59, 83) the RTS, S vaccine RR was found to be 0.91 with a significant p-value (p=00003), 95% CI (0.86, 0.96) and 17,145 participants were included and there was moderate heterogeneity across the studies= 58%. Number of event was acquired from the first episode with respect to total number of participants. The SAEs of pooled analysis of the malaria vaccine was found to be 9%, i.e. the risk of developing SAEs for those who received the vaccine was 91 % as high as in those who didn't get the vaccine or RTS, S vaccine s 9% less likely to experience SAEs.

Figure 12: Fatal SAEs of RTS, S vaccine

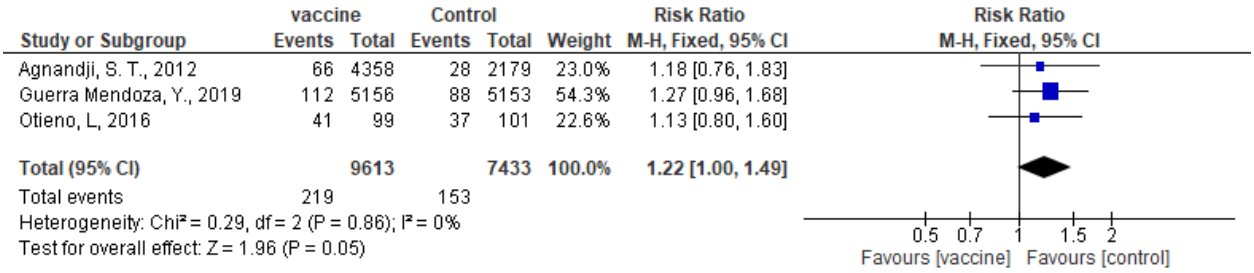

Figure 12, shows that, for all episodes of malaria in three studies (52, 55, 83) the RR was found to be 1.22 with a non-significant p-value (p=05), 95% CI (0.86, 0.96) and 17,046 participants were included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first episode with respect to total number of participants. The fatal SAEs of pooled analysis between the vaccine and control group was found to be non-significant.

Table 5: Summary of findings quality of included studies in the efficacy of malaria vaccine in SR/MA

Malaria vaccine compared to placebo or any other standard care for malaria disease prevention					
Patient or population: malaria disease prevention in African countries children and infants **Setting**: settings in African countries **Intervention**: malaria vaccine **Comparison**: placebo or any other standard care					
Outcomes	**Anticipated absolute effects***(95% CI)	Relative	№ of	Certainty of the	Comment

	Risk with placebo or any other standard care	Risk with malaria vakccine	effect (95% CI)	participants (studies)	evidence (GRADE)
malaria vaccine against all episodes of malaria disease	77 per 100	**56 per 100** (55 to 57)	**RR 0.73** (0.72 to 0.75)	17161 (3 RCTs)	⊕⊕⊕⊕ HIGH[a]
malaria vaccine against first episode of malaria	31 per 100	**24 per 100** (23 to 26)	**RR 0.78** (0.72 to 0.83)	8326 (2 RCTs)	⊕⊕⊕⊕ HIGH
malaria vaccine against severe malaria	3 per 100	**2 per 100** (2 to 3)	**RR 0.70** (0.59 to 0.84)	18891 (2 RCTs)	⊕⊕⊕⊕ HIGH
malaria vaccine against all episodes of malaria in infants	83 per 100	**62 per 100** (61 to 63)	**RR 0.75** (0.73 to 0.76)	15510 (3 RCTs)	⊕⊕⊕◯ MODERATE[b]
malaria vaccine against first episode of malaria in infants	34 per 100	**27 per 100** (25 to 29)	**RR 0.80** (0.75 to 0.86)	7081 (2 RCTs)	⊕⊕⊕⊕ HIGH

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. how the sequence was generated and blinding wasn't clearly stated in two of the studies

b. how the sequence was generated and blinding was not clearly stated in two of the studies

Table 6: Summary of findings quality of included studies in the safety of malaria vaccine in SR/MA:

Is Malaria vaccine compared to placebo or any other standard care safe in African countries children and infants

Patient or population: malaria disease prevention in African countries children and infants

Setting: settings n African countries

Intervention: malaria vaccine

Comparison: placebo or any other standard care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other standard care	**Risk with malaria vaccine**				
SAEs	26 per 100	**24 per 100** (23 to 25)	**RR 0.91** (0.86 to 0.96)	17145 (4 RCTs)	⊕⊕◯◯ LOW[a,b]	
fatal SAEs	2 per 100	**3 per 100** (2 to 3)	**RR 1.22** (1.00 to 1.49)	17046 (3 RCTs)	⊕⊕⊕◯ MODERATE[c]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. in 1 of the studies how sequence was generated and the concealment process isn't stated clearly and also the vaccine is prepared by the staff members which may affect outcome

b. in two of the studies there was very low sample size

c. The null effect is touched, so there is unclear evidence of favoring control or it's same for both comparisons

Table 5 and 6, show the summary of findings of the included 6 studies to assess the efficacy and safety of malaria vaccine trials conducted in African countries.

3.3.2: Influenza vaccine

Figure 13: PRISMA study flow diagram of studies included for the Influenza vaccine review.

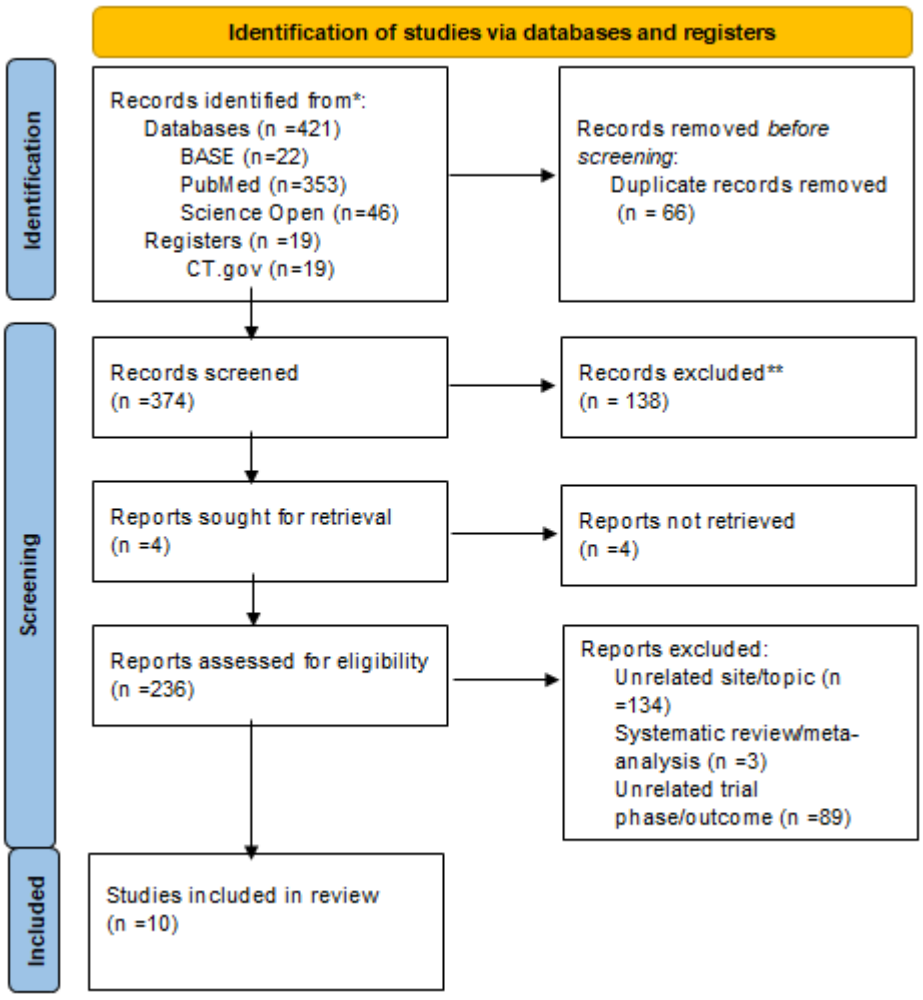

Figure 13, shows the number of studies included. A total of 10 studies were included in this influenza vaccine review which assess the efficacy and safety influenza vaccine trials that were conducted in African countries.

3.3.2.1: Included studies

A total of 10 studies were included in this Influenza vaccine review (see figure 13) which assess the efficacy and safety of Influenza vaccine trials that are conducted in African countries.

Table 7: Characteristics of included studies

No	**Author name, Year of Publication**	**Study design**	**Study period**	**Subjects**			**subject outcome of interest**		vaccine	Control
				Number of participant	Age of participants	Follow-up				
1	De Villiers, P. J., 2009	randomized, controlled, double-blind trial, multi-center	April 2, 2001, and November 30, 2001	3242 subject	≥60 years	15 days for VE & 28 days for SAEs	Vaccine efficacy in-terms of protection against primary case definition after the 1dose and SAEs after 1 dose		LAIV	placebo
							ILI positive viral culture of a wild-type virus subtype after ≥ 15 days after IP receipt symptoms; including feverishness, an oral temperature ≥37.2 C , sore throat, new or increased cough, tiredness, muscle aches	Any strain	1161	714
								Vaccine like strain	2301	1626

							SAEs	After 28 days	16	24
								After 8 month	163	139
2	Madhi, S.A, 2011	block randomization, single-center	11 April 2008 - 13 June 2008	506 HIV +ve adults	18-55 years	1 month	Vaccine efficacy in-terms of protection against primary case definition after the 1dose		TIV	Placebo
							Symptoms; including cough, history of fever, chills or rigor, sore throat, pharyngitis, or laryngitis, myalgia or headache	Influenza virus A or B	All	3	12
									ART	3	6
									Naïve	0	6
3	Madhi, S. A, 2013	randomized, controlled, double-blind trial, multi-center	February 27-22 may , 2009	403 children	6–59 months		Vaccine efficacy in-terms of protection against primary case definition after the 1 dose			TIV	Placebo
							Symptoms: <7 days fever more than 38.5C. Myalgia or irritability, sore throat or pharyngitis, rhinorrhea and/orCough of less than 14 days of duration.		Confirmed influenza	14	17
									ILI	19	37
4	Madhi, S. A., 2014	randomized, controlled, double-blind trial, multi-center	April 2, 2001, and December 2009 - January 2011	2116 HIV-ve & 194 HIV+ve pregnant women infected & their infant 24 weeks	18 - 38 years & an estimated gestation of 20 to 36 weeks & 24 weeks infants	10 month for mother 6 month infant for SAEs	Vaccine efficacy in-terms of protection against primary case definition after the 1dose and SAEs after 1 dose			IIV3	placebo
							Influenza virus by means of an RT-PCR assay	RT-PCR confirmed influenza	Mothers	26	54
									Infant	24	43
								ILI	Mother	199	108
									Infant	661	641

				after birth			SAEs	Mother		8	8
								Infant		5	11
5	Mutsaerts, E., 2016	randomized, controlled, double-blind trial, single-center	March – October 2012	477	18 - 38 years	1 year	Vaccine efficacy in-terms of protection against primary case definition after the 1 dose			IIV3	Placebo
							fever ≥38°C on oral measurement or chills/rigors, or feeling feverish in past for <7 days and any of cough/sore throat/pharyngitis, or any of muscle ache/joint ache/headache, or any of feeling shortness of breath/difficulty breathing/chest pain while breathing	PCR-confirmed influenza 2 years result		7	18
								PCR-confirmed influenza 2nd year result		406	720
6	Nunes, M. C., 2016	randomized, controlled, double-blind trial, multi-center	2011 & 2012	2049 infants	≤24 weeks	24 weeks	Vaccine efficacy in-terms of protection against primary case definition after the 1 dose/ born from vaccinated mother			IIV3	Placebo
							Influenza virus by means of an RT-PCR assay	PCR-Confirmed Influenza		19	37
7	Omer, S. B., 2016	randomized, controlled, double-blind trial, multi-center	April 25, 2011- April 24, 2013, in Nepal, Sep 12, 2011- April 18, 2013, in Mali, and March 3, 2011-	10, 002 women & 9,800 infant	18 - 38 years & an estimated gestation of 20 to 36 weeks & 24 weeks infants	6 month	Vaccine efficacy in-terms of protection against primary case definition after the 1 dose			IIV	Placebo & quadrivalent MCV
							Influenza virus by means of an RT-PCR	PCR-Confirmed Influenza	mother	To study end	19	36
										6 month follow-	53	103

			July 2, 2012, in South Africa				assay			up			
									Infant			24	54
8	Pepin, S., 2019	randomized, controlled, observer-blind trial, multi-center	2014/2015 and 2015/2016	5806	6–35 months	28 days	Vaccine efficacy in-terms of protection against primary case definition after the 2 doses and SAEs					IIV4	placebo
							a fever _38 _C lasting _24 h concurrently with cough, Nasal congestion, rhinorrhea, pharyngitis, otitis, vomiting, or diarrhea.		Laboratory-confirmed influenza			120	245
									SAEs	≤180 day after vaccination		43	40
										Of special interest		29	31
										Death		4	1
9	Tapia, M. D., 2016	randomized, controlled, double-blind trial, multi-center	Sept 12, 2011, to Jan 28, 2014. Between Sept 12, 2011, and April 18, 2013	4193 mother & 4105 infants	≥6 month	6 month	Vaccine efficacy in-terms of protection against primary case definition after 1 dose					TIV	quadrivalent MCV
							Influenza virus by means of an RT-PCR assay	Laboratory -confirmed influenza	Infant born to woman vaccinated any time/pregnancy	2 month		6	19
										5 month		52	77
									Different strains/woman			18	65
									Different strains/infant			42	106

10	Victor, J. C., 2016	randomized, controlled, double-blind trial, single-center	May 23, and July 1, 2013	1761 children	2–5 years	6 month	Vaccine efficacy in-terms of protection against primary case definition after the 1 dose			LAIV	placebo
							fever (>37·5ºC axillary) or feverishness and a cough or sore throat	Lab-confirmed influenza	All strains	210	105
									Vaccine strains	100	47

VE = vaccine efficacy

ILI = influenza like illness

HIV +ve = human Immunodeficiency virus positive

HIV -ve = human Immunodeficiency virus negative

RT-PRC = reverse transcription-polymerase chain reaction

LAIV = live attenuated influenza vaccine

CRP = C – reactive

SAE = serious adverse event

IIV3/IIV/TIV = trivalent influenza vaccine

IIV4 = quadrivalent influenza vaccine

MCV = meningococcal conjugate vaccine

Table 7, shows the characteristics of the 10 included studies for this review which includes; the study ID, study design, study period, number and age of participant, the study follow up period, outcome of interest and the type of vaccine or control IP involved in the studies.

Figure 14: Risk of bias summary.

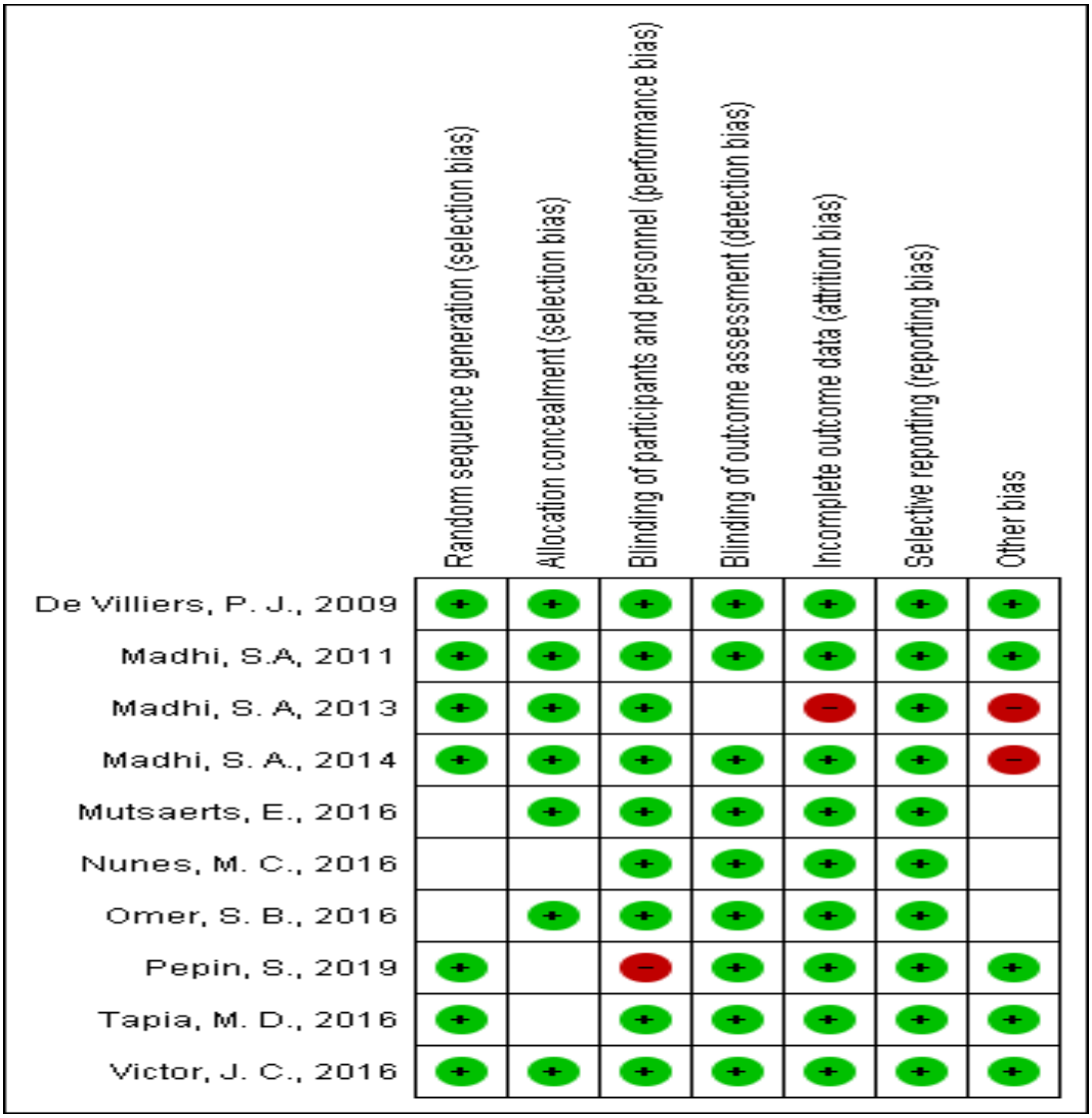

Figure 14, shows the summary of Risk of bias which was assessed depending on whether the measures were strictly followed or not: for those studies that didn't clearly state how the measure was followed were marked as unclear and high risk was assigned depending on the tendency of the risk to affect the outcome negatively, i.e., in case of Madhi,S.A, 2013 there was 20% loss of study participant due to withdrawal and loss to follow up, also small sample size was used and

during the peak of disease season required enrollment wasn't met, same with Madhi,S.A, 2014 and also Pharmacist and statisticians were aware of the IP. In Pepin, S, 2019 participants were not blinded.

Figure 15: Influenza vaccine efficacy.

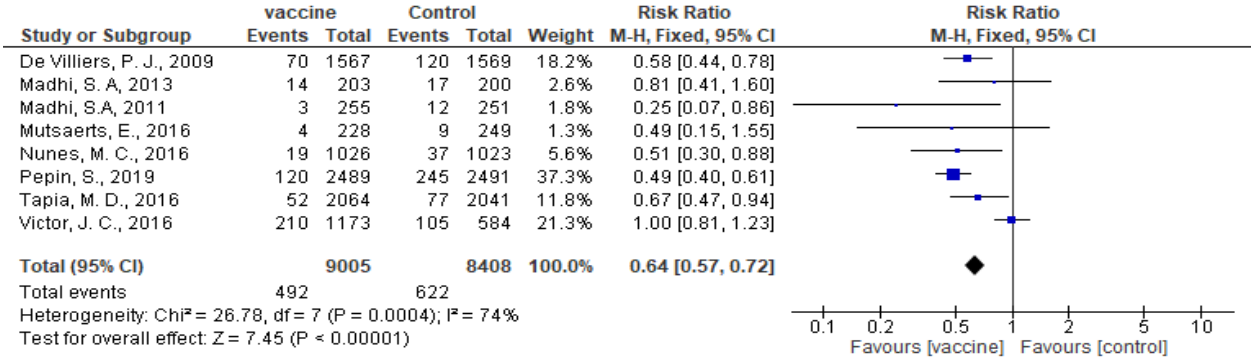

Figure 15, shows that, for Influenza in eight studies (85-92) the influenza vaccine RR was found to be 0.64 with a p-value (p<00001), 95% CI (0.57, 0.72) and 17,413 participants were included and there was high heterogeneity across the studies= 74%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the influenza vaccine against influenza disease was found to be 36%, i.e. the risk of developing Influenza for those who received the vaccine was 64 % as high as developing influenza in those who didn't get the vaccine or Influenza vaccine 36% effective in reducing the risk of acquiring Influenza disease.

Figure 16: Efficacy of influenza vaccine in multi-center vs single-center.

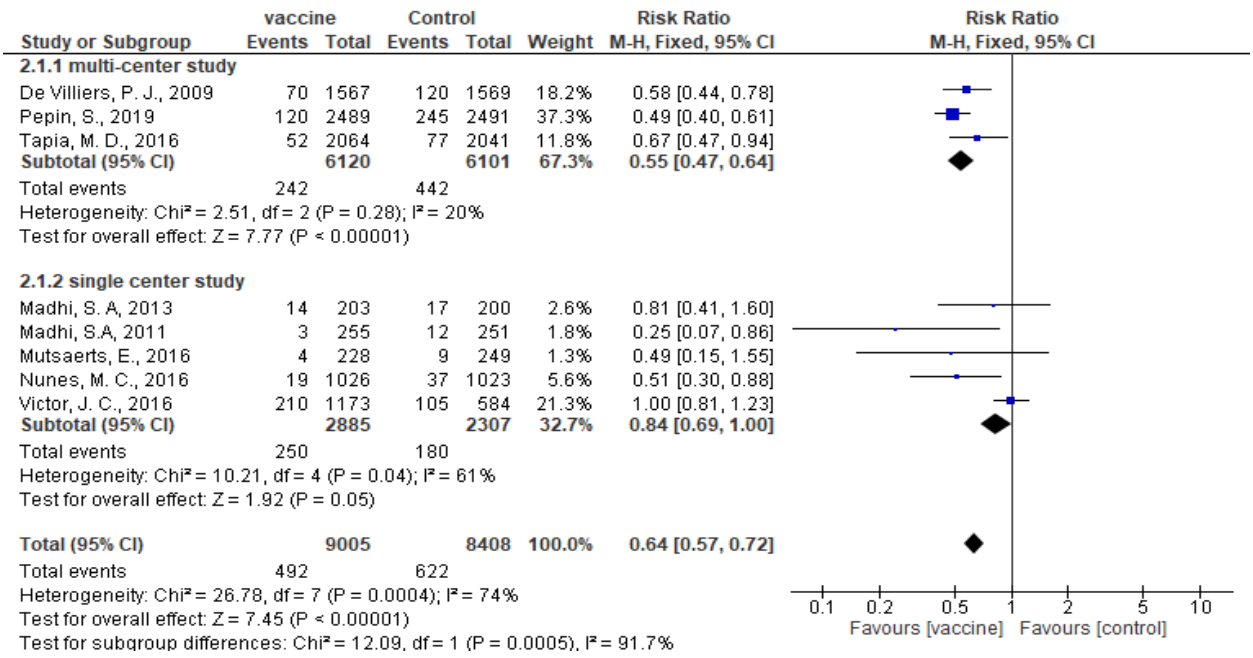

Figure 16, shows that, for Influenza in three multi-center studies (86, 88, 90) the influenza vaccine RR was found to be 0.55 with a significant p-value (p<00001), 95% CI (0.47, 0.64) , and 12,221 participants were included and there was no heterogeneity across the studies= 20%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza was found to be 45%, i.e. the risk of developing Influenza for those who received the vaccine was 55 % as high as developing Influenza in those who didn't get the vaccine or Influenza vaccine 45% effective in reducing the risk of acquiring Influenza disease.

Influenza, in five single-center studies (85, 87, 89, 91, 92) the influenza vaccine RR was found to be 0.84 with a non-significant p-value (p=0.05), 95% CI (0.84, 1.00) and 5,192 participants were included and there was a moderate heterogeneity across the studies= 61%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza was found to be non-significant.

The overall analysis of the difference between the two sub groups was found to be statistically significant with a p-value of (p=0.0005), I^2= 91.7%.

Figure 17: Efficacy of inactivated influenza vaccine vs live-attenuated influenza vaccine.

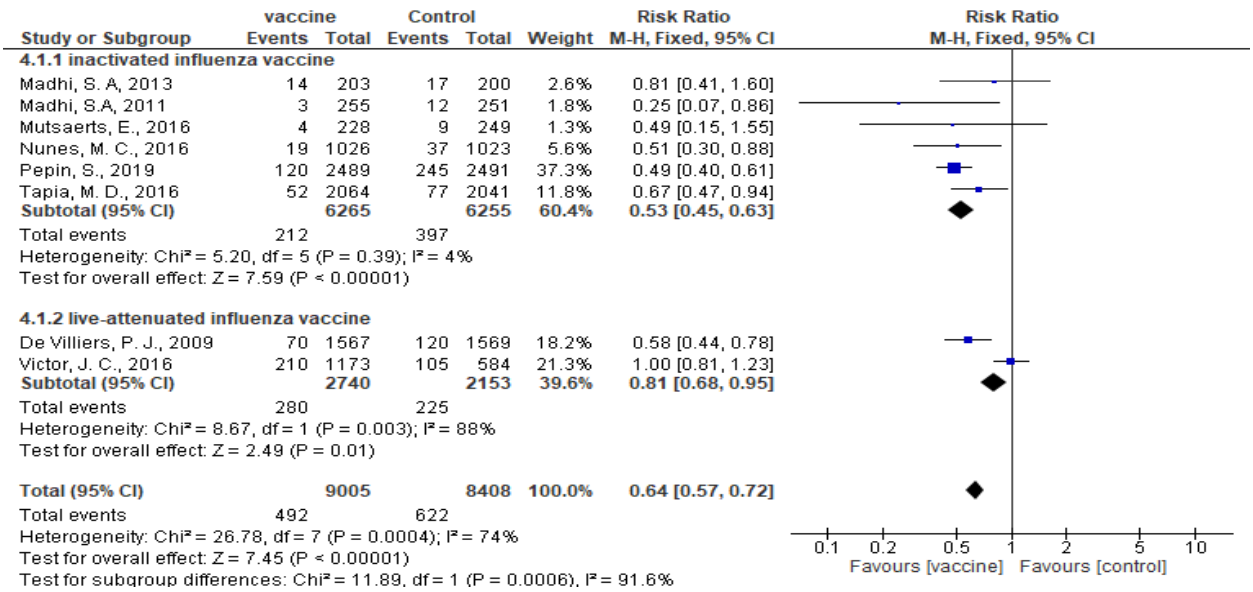

Figure 17, shows that, for Influenza in six inactivated Influenza vaccine studies (85-88, 91, 92) the RR was found to be 0.53 with a significant difference, p-value (p<000001), 95% CI (0.45, 0.63), and 12,520 participants were included and there was no heterogeneity across the studies= 4%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza was found to be 47%, i.e. the risk of developing Influenza for those who received the vaccine was 53% as high as developing Influenza in those who didn't get the vaccine or Influenza vaccine 47% effective in reducing the risk of acquiring Influenza disease.

Influenza, in two live attenuated studies (89, 90), the RR was found to be 0.81 with a non-significant p-value (p=0.003), 95% CI (0.68, 0.95) and 4,893 participants were included and there was a high heterogeneity across the studies= 88%%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza was found to be 19%, i.e. the risk of developing Influenza for those who received the vaccine was 81% as high as developing Influenza in those who didn't get the vaccine or Influenza vaccine 19% effective in reducing the risk of acquiring Influenza disease.

The overall analysis of the difference between the two sub groups was found to be statistically significant with a p-value of (p=0.0006), I^2= 91.6%

Figure 18: Efficacy of trivalent-inactivated influenza vaccine vs quadrivalent-inactivated influenza vaccine.

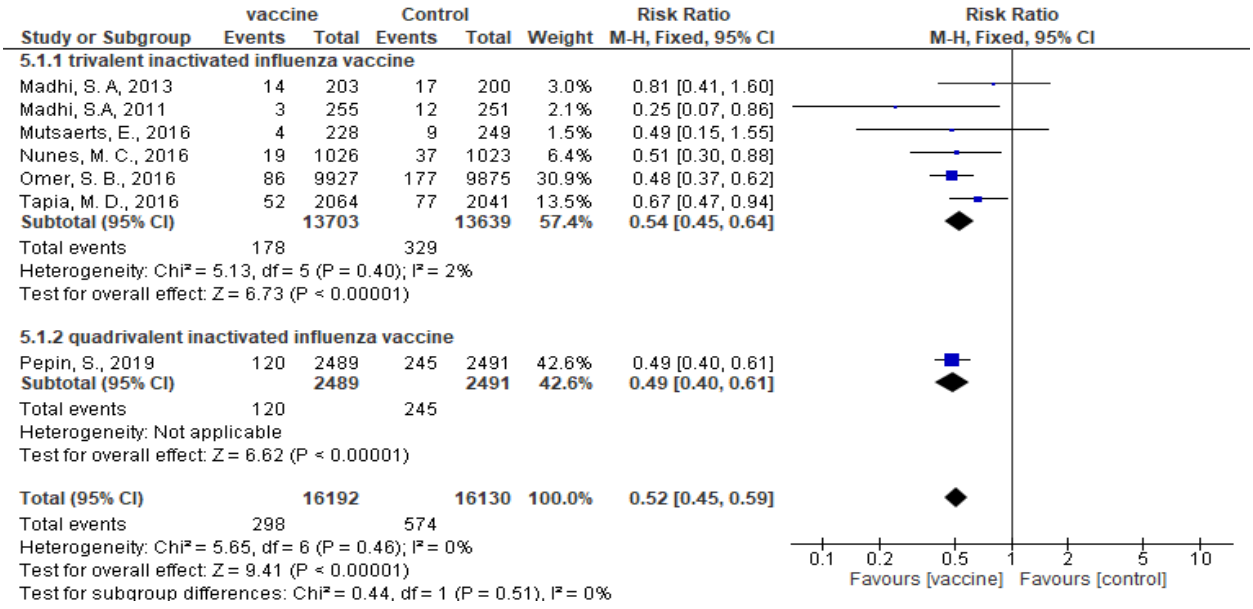

Figure 18, shows that, Influenza in six trivalent inactivated-influenza vaccine studies (66, 85-87, 91, 92) the RR was found to be 0.54 with a significant p-value (p<00001), 95% CI (0.45, 0.64), and 27,342 participants were included and there was no heterogeneity across the studies= 2%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine was found to be 46%, i.e., the risk of developing Influenza for those who received the vaccine was 54 % as high as developing Influenza in those who didn't get the vaccine or Influenza vaccine 46% effective in reducing the risk of acquiring Influenza disease.

Influenza, in one quadrivalent inactivated Influenza vaccine study (88) the RR was found to be 0.49 with a significant p-value (p<0.00001), 95% CI (0.40, 0.61) and 4,980 participants were included. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of single analysis of the Influenza vaccine against Influenza was found 51%, i.e. the risk of developing Influenza for those who received the vaccine was 49 % as high as developing Influenza in those who didn't get the vaccine or Influenza vaccine 51% effective in reducing the risk of acquiring Influenza disease. The overall analysis of the difference

between the two sub groups was found to be statistically non-significant with p value (p=0.51) and I^2=0.

Figure 19: Efficacy of Influenza vaccine in Adults.

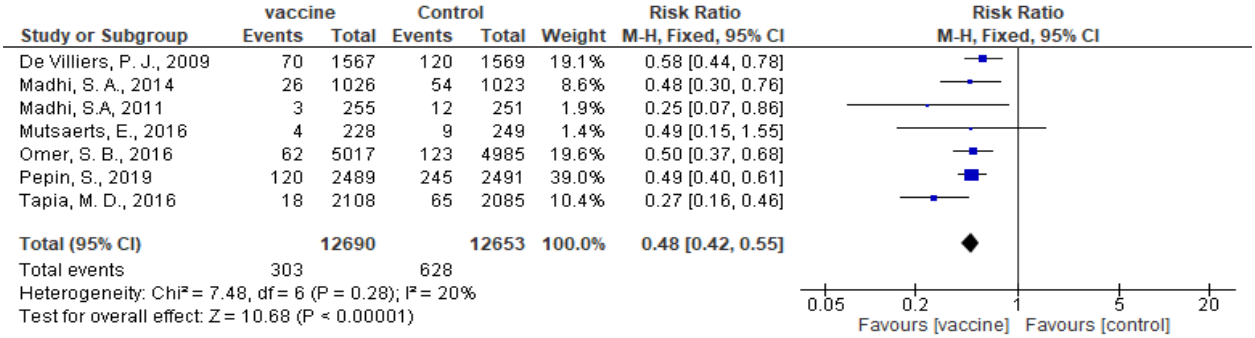

Figure 19, shows that, for Influenza in Adults in seven studies (66, 85-88, 90, 93) the influenza vaccine RR was found to be 0.48 with a p-value (p=0001), 95% CI (0.59, 0.84) and 25,343 participants were included and there was no heterogeneity across the studies= 20%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza disease was found to be 52%, i.e., the risk of developing Influenza for those who received the vaccine was 48 % as high as developing Influenza in those who didn't get the vaccine or Influenza vaccine 52% effective in reducing the risk of acquiring Influenza disease.

Figure 20: Efficacy of Influenza vaccine in children and infants.

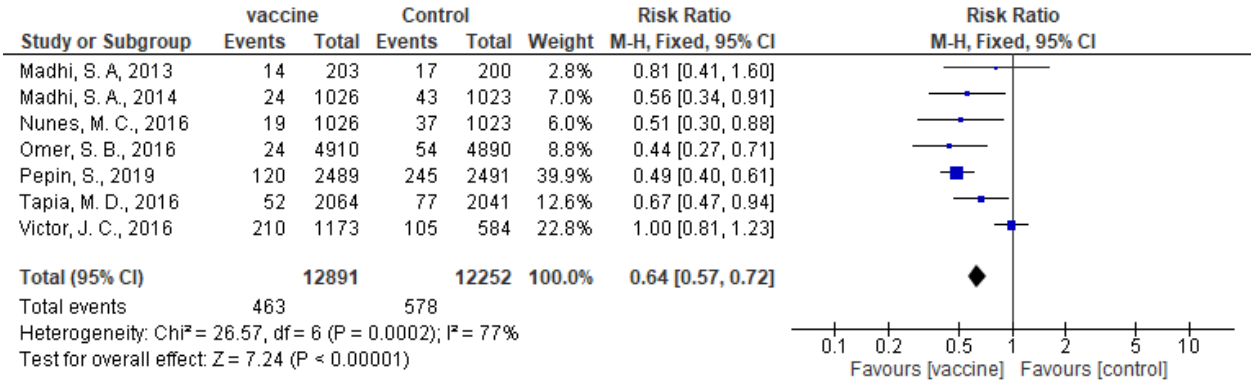

Figure 20, shows that, for Influenza in Children and Infants in seven studies (66, 86, 88, 89, 91-93) the influenza vaccine RR was found to be 0.64 with a p-value (p=0002), 95% CI (0.57, 0.72) and 25,143 participants were included and there was high heterogeneity across the studies = 77%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine was found to be 36%, i.e., the risk of developing Influenza for those who received the vaccine was 64 % as high as developing Influenza in those who didn't get the vaccine or Influenza vaccine 36% effective in reducing the risk of acquiring Influenza disease.

Figure 21: Efficacy of Influenza vaccine in HIV +ve Adults.

Figure 21, shows that, for Influenza in HIV +ve Adults in two studies (85, 93) the influenza vaccine RR was found to be 0.33 with a p-value (p=0.002), 95% CI (0.16, 0.66) and 694 participants were included and there was no heterogeneity across the studies = 0%. Number of event was acquired from the first episode with respect to total number of. The efficacy of pooled analysis of the Influenza vaccine against Influenza disease was found to be 67%, i.e., the risk of developing Influenza for those who received the vaccine was 33 % as high as developing malaria in those who didn't get the vaccine or Influenza vaccine 67% effective in reducing the risk of acquiring Influenza disease.

Figure 22: Efficacy of Influenza vaccine in HIV +ve infants.

Figure 22, shows that, for Influenza in HIV +ve Adults in two studies (91, 93) the influenza vaccine RR was found to be 0.79 with a p-value (p=0.43), 95% CI (0.44, 1.42) and 694 participants were included and there was no heterogeneity across the studies = 0%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza disease was found to be 21%. All in all there is no statistically significant difference between those who received the Influenza and the control vaccine.

Figure 23: Efficacy of Influenza vaccine in pregnant women ≤1 year follow-up.

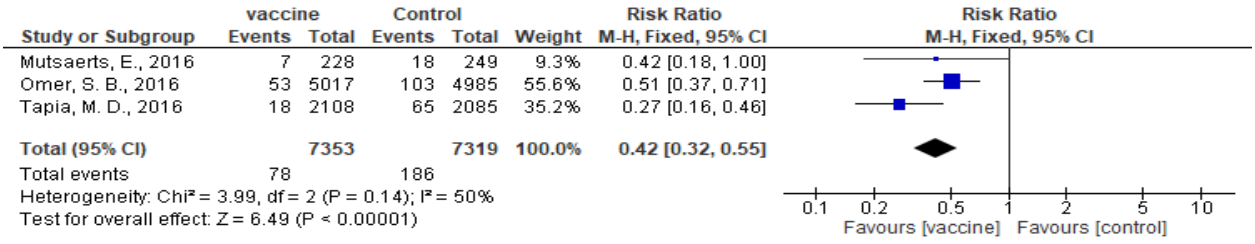

Figure 23 shows that, for Influenza in pregnant with ≤1 year follow-up in three studies (66, 86, 87) the influenza vaccine RR was found to be 0.42 with a p-value (p<0.00001), 95% CI (0.32, 0.55) and 14,672 participants were included and there was moderate heterogeneity across the studies = 50%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza disease was found to be 58%, i.e., the risk of developing Influenza for those who received the vaccine was 42 % as high as developing malaria in those who didn't get the vaccine or Influenza vaccine 58% effective in reducing the risk of acquiring Influenza disease.

Figure 24: Influenza vaccine efficacy for matched serotype.

Figure 24, shows that, for Influenza vaccine of matched serotype in two studies (89, 90) the RR was found to be 0.74 with a p-value (p=0.007), 95% CI (0.60, 0.92) and 4,893 participants were included and there was high heterogeneity across the studies = 86%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the Influenza vaccine against Influenza disease was found to be 26%, i.e., the risk of developing Influenza that are of similar strain as that of the vaccine, for those who received the vaccine was 74 % as high as developing influenza in those who didn't get the vaccine or Influenza vaccine 26% effective in reducing the risk of acquiring Influenza disease.

Figure 25: SAEs of vaccine vs control in Adult.

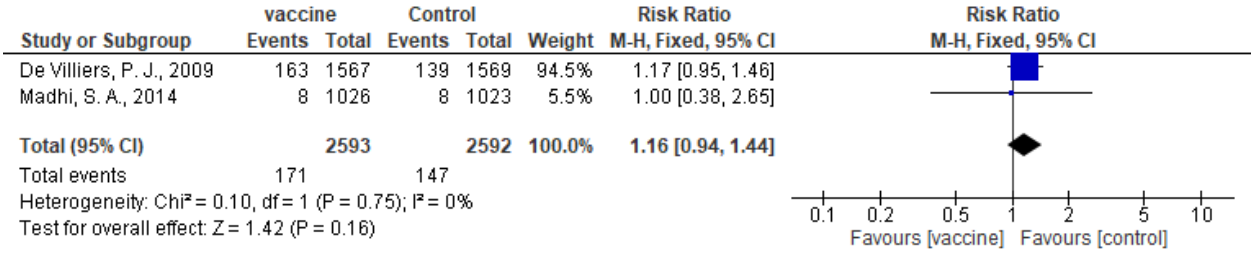

Figure 25, shows that, for all episodes of Influenza in two studies (90, 93) the influenza vaccine RR was found to be 1.16 with a non-significant p-value (p=0.16), 95% CI (0.94, 1.44) and 5,185 participants were included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first episode with respect to total number of participants. The SAEs of pooled analysis between the vaccine and control group was found to be non-significant.

Figure 26: SAEs of vaccine vs control in Children.

Figure 26, shows that, for all episodes of Influenza in two studies (88, 93) the influenza vaccine RR was found to be 0.82 with a non-significant p-value (p=0.20), 95% CI (0.60, 1.11) and 7,029

participants were included and there was low heterogeneity across the studies= 26%. Number of event was acquired from the first episode with respect to total number of participants. The SAEs of pooled analysis between the vaccine and control group was found to be non-significant.

Table 8: Summary findings of quality of included studies in the Influenza vaccine SR/MA:

Influenza vaccine compared to placebo or any other standard care for for Influenza diseases prevention in African countries population

Patient or population: for Influenza diseases prevention in African countries population

Setting: settings in African countries

Intervention: Influenza vaccine

Comparison: placebo or any other standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other standard care	**Risk with Influenza vaccine**				
Influenza vaccine against Influenza disease	7 per 100	**5 per 100** (4 to 5)	**RR 0.64** (0.57 to 0.72)	17413 (8 RCTs)	⊕⊕⊕◯ MODERATE [a]	
Influenza vaccine against Influenza disease in Adults	5 per 100	**2 per 100** (2 to 3)	**RR 0.48** (0.42 to 0.55)	25343 (7 RCTs)	⊕⊕⊕◯ MODERATE [b]	
Influenza vaccine against influenza disease in children and infants	5 per 100	**3 per 100** (3 to 3)	**RR 0.64** (0.57 to 0.72)	25143 (7 RCTs)	⊕⊕◯◯ LOW [c]	
Influenza vaccine against Influenza vaccine in HIV +ve Adults	8 per 100	**3 per 100** (1 to 5)	**RR 0.33** (0.16 to 0.66)	694 (2 RCTs)	⊕⊕◯◯ LOW [d,e]	
influenza vaccine against Influenza disease in HIV +ve infants	8 per 100	**6 per 100** (4 to 11)	**RR 0.79** (0.44 to 1.42)	591 (2 RCTs)	⊕◯◯◯ VERY LOW [f,g]	
Influenza vaccine against Influenza disease in pregnant woman with ≤ 1yr follow up	3 per 100	**1 per 100** (1 to 1)	**RR 0.42** (0.32 to 0.55)	14672 (3 RCTs)	⊕⊕⊕⊕ HIGH	

Table 8: Summary findings of quality of included studies in the Influenza vaccine SR/MA:

Influenza vaccine compared to placebo or any other standard care for for Influenza diseases prevention in African countries population

Patient or population: for Influenza diseases prevention in African countries population

Setting: settings in African countries

Intervention: Influenza vaccine

Comparison: placebo or any other standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other standard care	**Risk with Influenza vaccine**				
Influenza vaccine against Influenza disease of vaccine strains	8 per 100	**6 per 100** (5 to 7)	**RR 0.74** (0.60 to 0.92)	4893 (2 RCTs)	⊕⊕⊕◯ MODERATE [h]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. in 1 of the studies there was 20% study subject loss and in another study the participants were not blinded

b. in 1 of the studies statisticians and pharmacists were aware of the IP and allocation, and in another study participants were not blinded

c. in 1 study there were 20% study subject loss and there was small sample size, in one study statisticians and pharmacists were aware of the IP and allocation and in another study how sequence was generated and if allocation was concealed not stated clearly.

d. in one of the studies statistician and pharmacists were aware of the IP

e. sample size of the both studies included is low as a result of that the number of events is very low.

f. in one of the studies there is 20% loss of participants and the another study wasn't completely blinded.

g. both studies had a small sample size and there was no direct line to show whether the vaccine is favorable or the control and there is also a very wide CI

h. there is a significant of difference in the outcome of the 2 studies

Table 9: Summary findings of quality of included studies in the Influenza vaccine SR/MA:

Influenza vaccine compared to placebo or any other standard care for Influenza disease

Patient or population: safety
Setting: settings in African countries
Intervention: Influenza vaccine
Comparison: placebo or any other standard care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other standard care	**Risk with Influenza vaccine**				
SAEs in Adults	57 per 1,000	**66 per 1,000** (53 to 82)	**RR 1.16** (0.94 to 1.44)	5185 (2 RCTs)	⊕⊕◯◯ LOW[a,b]	
SAEs n children	25 per 1,000	**21 per 1,000** (15 to 28)	**RR 0.82** (0.60 to 1.11)	7029 (2 RCTs)	⊕⊕◯◯ LOW[c,d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. one of the studies is not completely blinded

b. the studies don't show whether vaccine is favored or control.

c. the studies aren't completely blinded .

d. the studies don't show whether the vaccine is safe or not, there is a wide CI and there is small number of event.

Table 8 and 9, show the summary of findings included studies to assess the efficacy and safety of influenza vaccine trials conducted in African countries.

3.3.3: Pneumonia Vaccine

Figure 27: PRISMA study flow diagram.

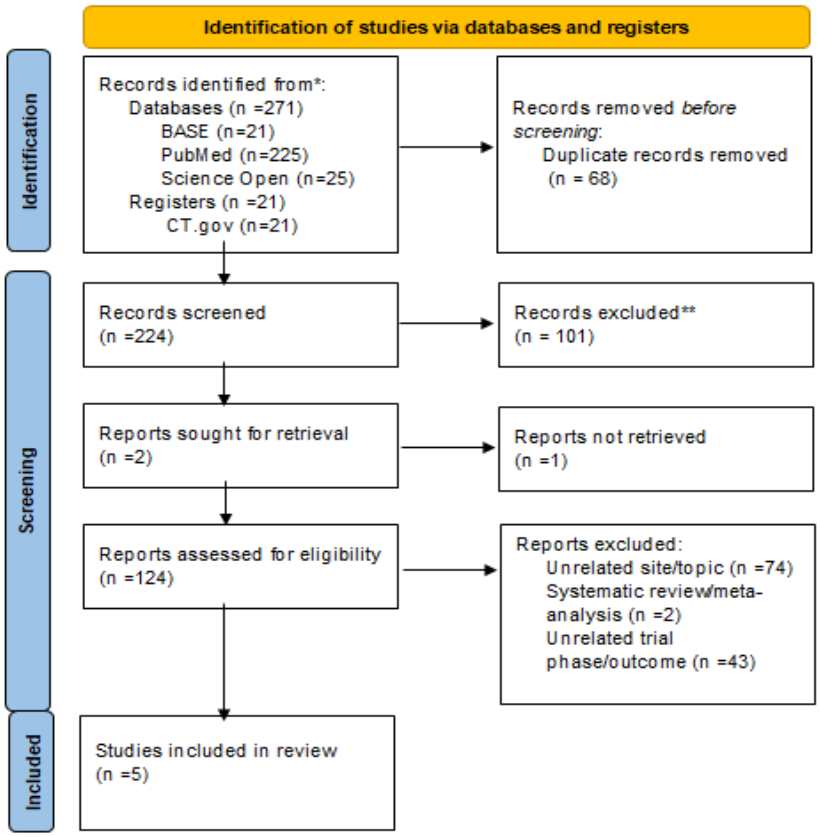

Figure 27, shows the number of studies included. A total of 5 studies were included in this Pneumonia vaccine review which assess the efficacy and safety of PCV vaccine trials that were conducted in African countries.

3.3.3.1: Included studies

A total of 5 studies were included in this Pneumonia vaccine review (see figure 27) which assess the efficacy and safety of PCV vaccine trials that are conducted in African countries.

Table 10: Characteristics of included studies

No	**Author name, Year of Publication**	**Study design**	**Study period**	**Subjects**			**subject outcome of interest**			vaccine	Control
				Number of participants	Age of participants	Follow-up					
1	Cutts, F. T., 2005	randomized, controlled, double-blind trial, multi-center	August, 2000, to February, 2003	17,437infants	6–51 weeks	2 month	Vaccine efficacy in-terms of protection against primary case definition after the three doses			9-PCV	placebo
							chest radiograph for patients with a raised respiratory rate for (≥50 breaths per min for children <1 year old and ≥40 per min for children ≥1 year old) or lower & cough or breathing difficulty < 14 day with a raised respiratory rate for age or lower Chest-wall in drawing.	Radiological/ 1st episode		1161	714
								IPD		2301	1626
								Severe Pneumonia		58	46
								Clinical		782	419
							SAEs	Serious adverse event	110		131
								Admission	110		119
								Death	12		19

2	Klugman, K. P., 2003	randomized, controlled, double-blind trial, single-center	March 2, 1998, and ended on October 30, 2000	39,836	28-84 days	1 year	VE in-terms of protection against primary case definition after the three doses				9-PCV	placebo
							radiologic evidence of pneumonia plus a positive immunofluorescence assay for a respiratory virus from a nasopharyngeal aspirate	IPD, 1st episode	HIV +ve		22	47
									HIV -ve		11	19
								Radiological, all episodes	HIV +ve		182	209
									HIV -ve		169	212
3	Madhi, S. A, 2005	randomized, controlled, double-blind trial, single-center	Throughout 2001	39,836 children	>24 months	2 years & 3 month	VE in-terms of protection against primary case definition after the three dose				9-PCV	placebo
							blood culture–confirmed	Radiological			251	303
								Severe			511	618
								radiological	HIV +ve		128	140
									HIV -ve		119	158
								Severe	HIV +ve		131	169
									HIV -ve		367	440
4	Madhi, S. A, 2006	randomized, controlled, double-blind trial, single-center	2011	39,836 children	42-112 days	12 hr.	VE in-terms of protection against primary case definition after the three doses				9-PCV	placebo
							Procalcitonin & CRP/ CXR-AC, chest radiographs demonstrated alveolar consolidation /severe pneumonia cough 14-day, lower chest wall in-drawing	HIV +ve	Pneumonia		124	139
									severe		247	285
								HIV -ve	Pneumonia		141	166

							and/or feeding difficulties, convulsions, central cyanosis or encephalopathy			severe	425	467
5	Madhi, S. A, 2007	randomized, controlled, double-blind trial, single-center	November 2001-October 2005	39,836 children	42–112 days	6.16 years	VE in-terms of protection against primary case definition after the three dose				9-PCV	placebo
							Serotype-specific antibody concentrations of ≥0.2 g/ml as a putative correlate of immunity against serotype-specific IPD	IPD/ all or any serotype	HIV +ve	All type	41	70
										1st episode	34	63
									HIV - ve	All type	13	20
										1st episode	13	20
								IPD/ all or any serotype	All type		54	90
									1st episode		47	83

VE = vaccine efficacy

IPD = invasive Pneumococcal disease

HIV +ve = human Immunodeficiency virus positive

HIV -ve = human Immunodeficiency virus negative

PRC = Procalcitonin

PCV = Pneumococcal conjugate vaccine

CRP = C – reactive

CXR-AC = Chest X-Ray

Table 10, shows that the characteristics of the 5 included studies for this review which includes; the study ID, study design, study period, number and age of participant, the study follow up period, outcome of interest and the type of vaccine or control IP involved in the studies.

Figure 28: PRISMA study flow diagram.

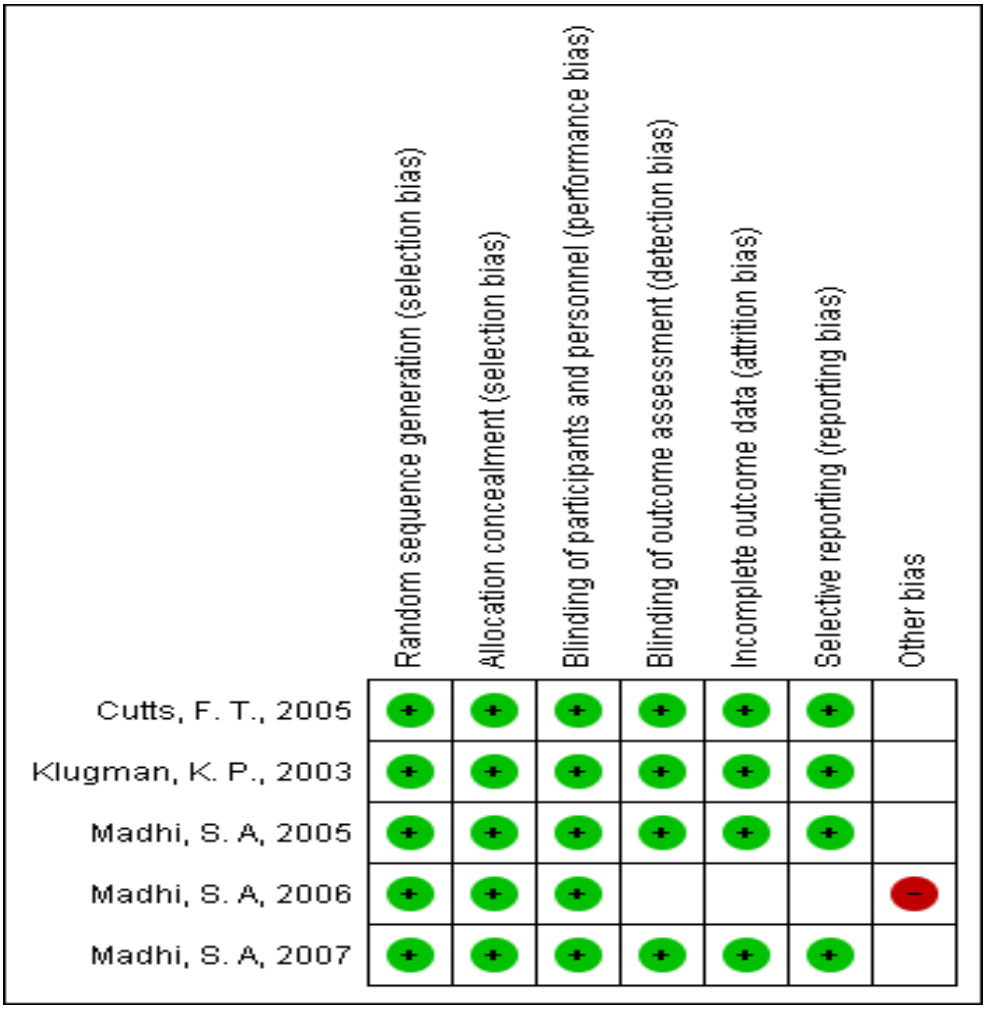

Figure 30, shows the summary of Risk of bias; which was assessed depending on whether the measures were strictly followed or not: for those studies that didn't clearly state how the measure was followed were marked as unclear and high risk was assigned depending on the tendency of the risk to affect the outcome negatively i.e. in case of Madhi, S.A, 2006 formal sample size calculation wasn't done and new outcome measure was used.

Figure 29: PCV efficacy against Pneumonia.

Figure 29, shows that, for Pneumonia in three studies (94-96) the PCV RR was found to be 0.75 with a p-value (p<0.0001), 95% CI (0.59, 0.84) and 92,689 participants were included and there was high heterogeneity across the studies= 76%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against Pneumonia disease was found to be 25%, i.e., the risk of developing Pneumonia for those who received the vaccine was 75 % as high as developing Pneumonia in those who didn't get the vaccine or PCV vaccine was 25% effective in reducing the risk of acquiring Pneumonia disease.

Figure 30: PCV efficacy against Pneumonia all episodes vs 1st.

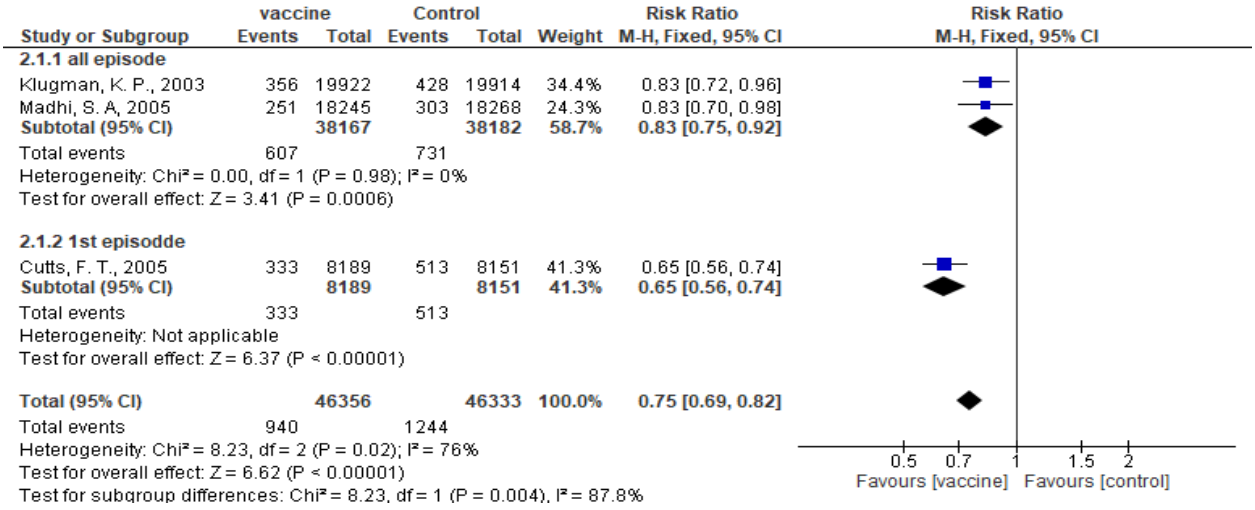

Figure 30, shows that, for all episodes of Pneumonia in two studies (94, 95) the PCV RR was found to be 0.83 with a p-value (p=0.0006), 95% CI (0.75, 0.92) and 76,349 participants were

included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against Pneumonia disease was found to be 17%, i.e., the risk of developing Pneumonia for those who received the vaccine was 83 % as high as developing Pneumonia in those who didn't get the vaccine or PCV vaccine was 17% effective in reducing the risk of acquiring Pneumonia disease.

For first episode of Pneumonia in one study (96) the PCV RR was found to be 0.65 with a p-value (p<0.00001), 95% CI (0.56, 0.74) and 16,340 participants were included. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of single analysis of the PCV vaccine against Pneumonia disease was found to be 35%.

The overall analysis of the difference between the two sub groups was found to be statistically significant with p value (p=0.004) and I^2=87.8%.

Figure 31: PCV efficacy against 1st episode of IPD.

Figure 31, shows that, for first episode of IPD in three studies (94, 96, 97) the PCV RR was found to be 0.48 with a p-value (p<0.00001), 95% CI (0.37, 0.61) and 96,012 participants were included and there was moderate heterogeneity across the studies= 56%. Number of event was acquired from the first or only episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against IPD was found to be 52%, i.e., the risk of developing IPD for those who received the vaccine was 48 % as high as developing IPD in those who didn't get the vaccine or PCV vaccine was 52% effective in reducing the risk of acquiring IPD.

Figure 32: PCV efficacy against severe Pneumonia.

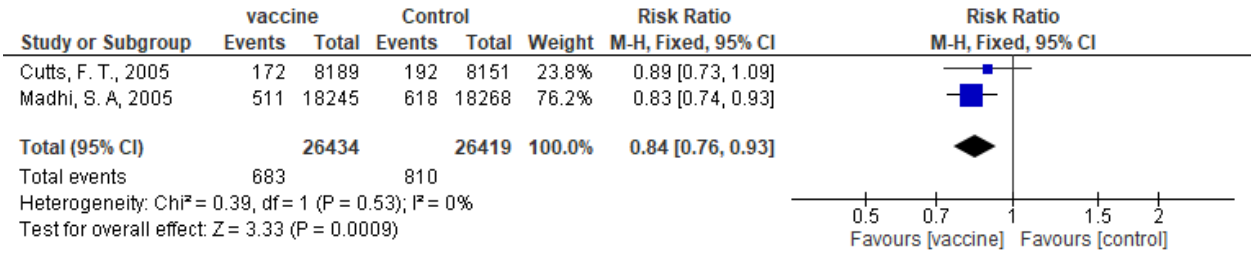

Figure 32, shows that, for severe Pneumonia in two studies (95, 96) the PCV RR was found to be 0.84 with a p-value (p=0.0009), 95% CI (0.76, 0.93) and 52,853 participants were included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against severe Pneumonia disease was found to be 16%, i.e., the risk of developing Pneumonia for those who received the vaccine was 84 % as high as developing Pneumonia in those who didn't get the vaccine or PCV vaccine was 16% effective in reducing the risk of acquiring Pneumonia disease.

Figure 33: PCV efficacy against Pneumonia in HIV negative individuals.

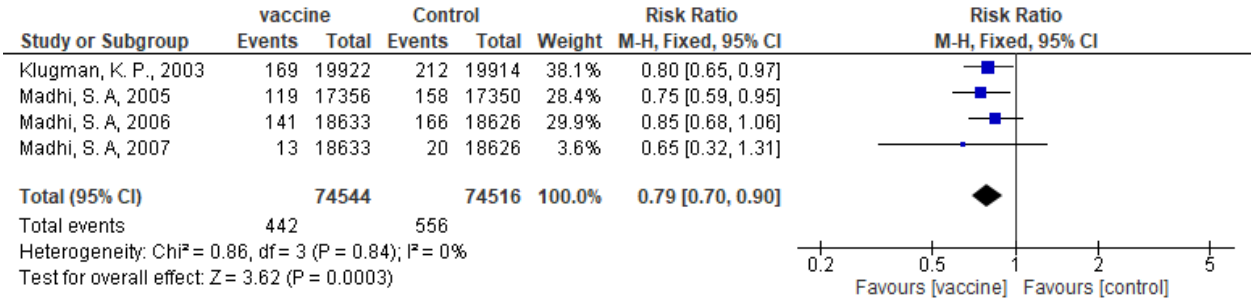

Figure 33, shows that, for Pneumonia n HIV –ve individuals in four studies (94, 95, 97, 98) the PCV RR was found to be 0.79 with a p-value (p=0.0003), 95% CI (0.70, 0.90) and 52,853 participants were included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first or only episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against Pneumonia disease in HIV –ve individuals was found to be 21%, i.e., the risk of developing Pneumonia for those who received the vaccine was 79 % as high as developing Pneumonia in those who didn't get the vaccine or PCV vaccine was 21% effective in reducing the risk of acquiring Pneumonia disease.

Figure 34: PCV efficacy against Pneumonia in HIV positive individuals.

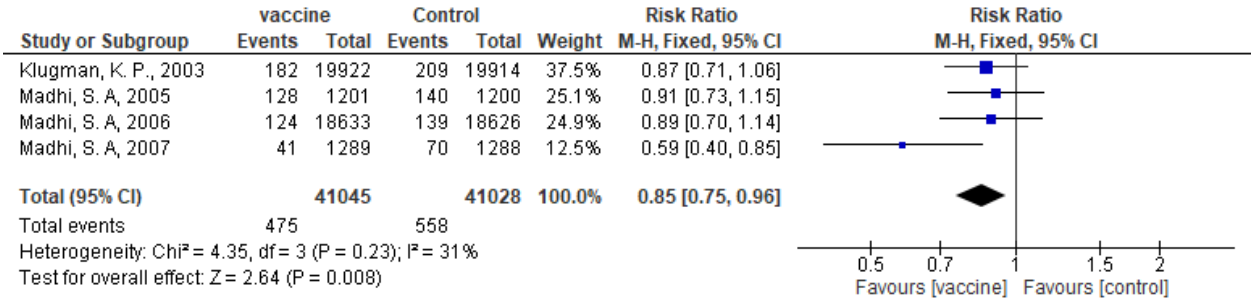

Figure 34, shows that, for Pneumonia in HIV +ve individuals four studies (94, 95, 97, 98) the PCV RR was found to be 0.85 with a p-value (p=0.008), 95% CI (0.75, 0.96) and 82,073 participants were included and there was low heterogeneity across the studies= 31%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against Pneumonia disease in HIV +ve individuals was found to be 15%, i.e., the risk of developing Pneumonia for those who received the vaccine was 85 % as high as developing Pneumonia in those who didn't get the vaccine or PCV vaccine was 15% effective in reducing the risk of acquiring Pneumonia disease.

Figure 35: PCV efficacy against severe Pneumonia in HIV negative individuals.

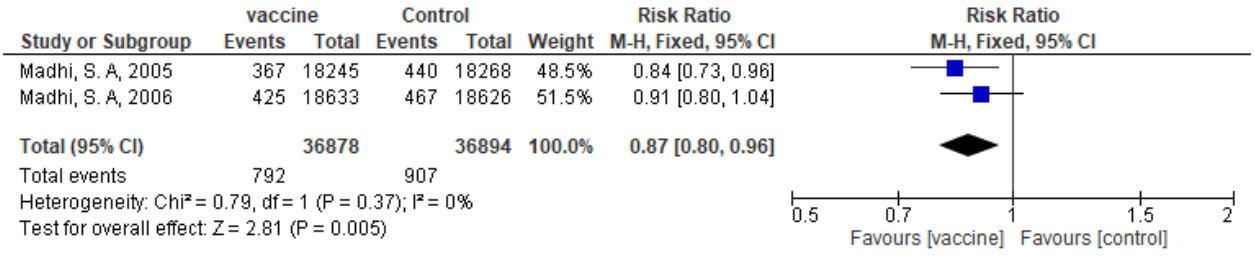

Figure 35, shows that, for severe Pneumonia in HIV -ve individuals two studies (95, 98) the PCV RR was found to be 0.87 with a p-value (p=0.005), 95% CI (0.80, 0.96) and 82,073 participants were included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against severe Pneumonia disease in HIV -ve individuals was found to be 13%, i.e., the risk of developing severe Pneumonia for those who received the

vaccine was 87 % as high as developing Pneumonia in those who didn't get the vaccine or PCV vaccine was 13% effective in reducing the risk of acquiring severe Pneumonia disease.

Figure 36: PCV efficacy against severe Pneumonia in HIV positive individuals.

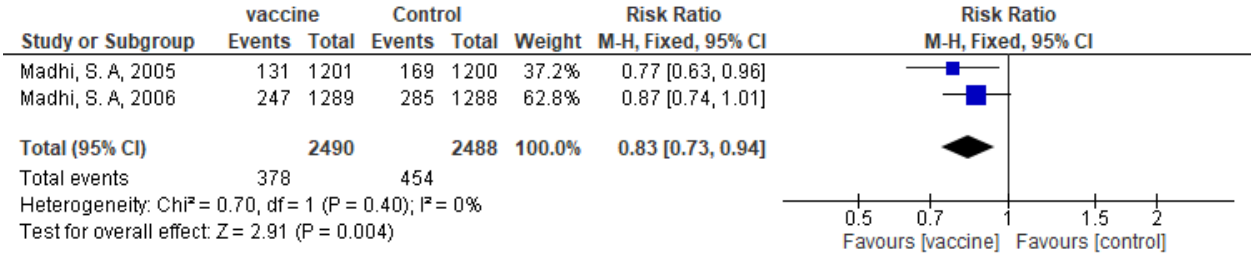

Figure 36, shows that, for severe Pneumonia in HIV +ve individuals two studies (95, 98) the PCV RR was found to be 0.83 with a p-value (p=0.005), 95% CI (0.80, 0.96) and 4,978 participants were included and there was no heterogeneity across the studies= 0%. Number of event was acquired from the first episode with respect to total number of participants. The efficacy of pooled analysis of the PCV vaccine against severe Pneumonia disease in HIV +ve individuals was found to be 17%, i.e., the risk of developing severe Pneumonia for those who received the vaccine was 83 % as high as developing Pneumonia in those who didn't get the vaccine or PCV vaccine was 17% effective in reducing the risk of acquiring severe Pneumonia disease.

Table 11: Summary of findings of included studies in the Pneumonia vaccine SR/MA:

Pneumonia vaccine compared to any other standard care for Pneumonia disease prevention

Patient or population: Pneumonia disease prevention

Setting: settings in African countries

Intervention: Pneumonia vaccine

Comparison: any other standard care

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with any other standard care	**Risk with Pneumonia vaccine**				
Pneumonia vaccine against Pneumonia disease	27 per 1,000	**20 per 1,000** (19 to 22)	**RR 0.75** (0.69 to 0.82)	92689 (3 RCTs)	⊕⊕⊕⊕ HIGH	

Table 11: Summary of findings of included studies in the Pneumonia vaccine SR/MA:

Pneumonia vaccine compared to any other standard care for Pneumonia disease prevention

Patient or population: Pneumonia disease prevention
Setting: settings in African countries
Intervention: Pneumonia vaccine
Comparison: any other standard care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with any other standard care	**Risk with Pneumonia vaccine**				
Pneumonia vaccine against 1st episode of IPD	4 per 1,000	**2 per 1,000** (1 to 2)	**RR 0.48** (0.37 to 0.61)	96012 (3 RCTs)	⊕⊕⊕⊕ HIGH	
Pneumonia vaccine against Severe Pneumonia	31 per 1,000	**26 per 1,000** (23 to 29)	**RR 0.84** (0.76 to 0.93)	52853 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Pneumonia vaccine against Pneumonia disease in HIV -ve individuals	7 per 1,000	**6 per 1,000** (5 to 7)	**RR 0.79** (0.70 to 0.90)	149060 (4 RCTs)	⊕⊕⊕◯ MODERATE[a]	
Pneumonia vaccine against Pneumonia disease in HIV +ve individuals	14 per 1,000	**12 per 1,000** (10 to 13)	**RR 0.85** (0.75 to 0.96)	82073 (4 RCTs)	⊕⊕⊕◯ MODERATE[b]	
Pneumonia vaccine against severe Pneumonia disease in HIV -ve individuals	25 per 1,000	**21 per 1,000** (20 to 24)	**RR 0.87** (0.80 to 0.96)	73772 (2 RCTs)	⊕⊕⊕◯ MODERATE[c]	
Pneumonia vaccine against severe Pneumonia in HIV +ve individuals	182 per 1,000	**151 per 1,000** (133 to 172)	**RR 0.83** (0.73 to 0.94)	4978 (2 RCTs)	⊕⊕⊕◯ MODERATE[d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. in one of the studies convenient sampling as used and new outcome measure was implemented.

b. in one of the studies convenient sampling was used and new outcome measure was implemented

c. One study used convenient sampling and the outcome measure was new

d. convenient sampling and new outcome measure was used.

Table 11, shows the summary of findings included studies to assess the efficacy of PCV vaccine trials conducted in African countries.

Discussion

Based on the result of our assessment on the 18 registries; From the 26 single disease specific vaccine 17 and from 13 combination vaccines 4 multi-disease vaccines was found to have gone through trial which ranges from the lower 1 (Tetanus) vaccine trial per disease of interest to the highest of 119 (Malaria) vaccine trials in the single disease specific trials. Vaccine trials not found to be registered so far irrespective of age were; for hepatitis we found no hepatitis A registered trial, for Polio no bOPV registered trial, for meningitis we found no MenAC registered trial. And from the combination vaccines we found no registered trial for; DT, DTapHibHepBIPV, DTwPHib, MMR, DTwP, DTaP, Tdap, TdaPIPV and TD vaccines. Though BCG and OPV is administrated in all African countries (100%) attributed to only 55 (15.5 %) and 2 (0.5%) of the trials, respectively whereas, Malaria vaccine which is administrated in 3 (5.5%) of African countries attributed to 119 (33.6%) of the trials, and we found no vaccine trials terminated for futility. A narrative assessment done in ICTRP found 377 vaccine-related trials in Africa, with which malaria had the highest number, i.e., 20% (74) trials then HIV/AIDS with 14% (55) trials. There were also 7% (26) trials on Tuberculosis infections and 6% (23) trials on Ebola disease (99).

So far there is no evidence that combining antigens results in adverse reactions(100). But, the probability of a new safety issue from a combination vaccine is non-existent (101). So, it is important to undertake a trial to evaluate the potency of each antigenic component, the vaccines efficacious ability when it is combined to induce immunity, risk of possible reversion to toxicity, and also the presence of reaction with other vaccine components (100).

In the malaria review, 6 studies were included and a fixed effect was used to assess the effect size. For studies that followed both per protocol (PP) and intention to treat design (ITT), PP was used as the ITT was mostly measured after the first dose of the vaccine was administrated. For those who reported using only PP or ITT it was included in the analysis. The pooled result of our study showed that the highest efficacy was seen against severe malaria of both children and infants with 30% 95% CI (0.59, 0.84), whereas, the lowest was found to be in 1st episode of malaria in infants with 20% 95% CI (0.75, 0.86). We believe, the fact (82, 84) used a recurrent event as an outcome measure might have affected the true level of efficacy of the RTS, S vaccine. With regards to SAEs, it was found to be a bit lower in vaccine group (9%), whereas, with regards to fatal SAEs there was no significant difference between the vaccine group and the control.

The immunological mechanisms of protection against malaria aren't known thoroughly yet, such as; what immune responses are induced in people, who are protected and who are not (102). Vaccines that are in use mostly show an efficacy which ranges from 70-80% whereas for malaria vaccine that might not be possible due to the organism's complexity, i.e., its presence in the peripheral-blood compartment and its circulation alongside of immune cells and proteins26 , the antigenic variability of the parasite and the lack of reliable and predictive animal models (103). But as it's the first developed vaccine against parasite it is a big mile-stone by going hand in hand with the present preventive measures. Currently, preventive interventions in malaria revolves on reduction of malaria transmission by insect vectors (insecticide spraying and the use of insecticide-treated bed nets), or using prophylactic treatment of defined population groups such as pregnant women, infants or children (104). However with the attempt to make an effective vaccine against malaria has delivered a malaria vaccine called Mosquirix given at month 0, 1, and 2 in children aged 5-17 month for severe malaria was 28.3% efficacy in phase 3 (105). And this RTS,s vaccine has only about 30-50% an overall efficacy (106). With regards to safety issue of RTS,S vaccines, no serious adverse events were judged to be vaccine related (107). The 48-month follow-up period of the *RTS, S* vaccines in infants and young children showed an average protection rates of between 18–36% with 3–4 doses of the vaccine (108).

Researchers believe after the waning of the vaccine, children are becoming more vulnerable which might be as a result of early RTS,S/AS01 vaccination averting the normal development of

malaria immunity (109). In contrary to that, clinical trials also suggest that pre-existing immunity induced immune tolerance, result in lower immunogenicity and efficacy of the malaria vaccine in African adults and malaria-exposed children. An additional three years of follow-up showed that RTS,S/AS01 vaccination might lead to periods of increased risk to uncomplicated malaria when vaccine-induced protection has waned (102).As vaccines have been linked with disease transmission such as; the polio vaccine, side effects related to malaria vaccine is affecting how the vaccine is perceived so the safety issue should be stressed on (110).

In this influenza review, 10 studies were included and a fixed effect was used to assess the effect size. For studies that followed both per protocol (PP) and intention to treat analysis (ITT), PP was used. The pooled analysis for influenza vaccine efficacy the combined was found to be *36%* 95% CI (0.57, 0.72). The highest efficacy was seen in HIV positive adults with 67%, 95% CI (0.16, 0.66) and the lowest was seen in HIV positive infants with 21%, 95% CI (0.44, 1.42). There was a statistically significant difference between trials that were conducted in single-center and multi-center where studies conducted in single center were non-significant with 16%, 95% CI (0.84, 1.00) efficacy. LAIV were also found to have low efficacy with 19%, 95% CI (0.68, 0.95). With regards to SAEs there was no significant difference between the vaccine and control group in the exposure in both Adult and children. In one of the study where the SAEs were presented in detail (90), there were 7 SAEs possibly related to vaccine 2, (1, Asthma and 1, Bronchopneumonia) in vaccine group and 5, (4, Pneumonia and 1, Guillain Barre like) in control group.

A review which was done across different age intervals in the USA using a random effect model of RCTs had a higher pooled vaccine efficacy; in Adults aged 18-64 was 59% (95% CI 51–67) whereas in children aged 6 months to 7 years, the pooled vaccine efficacy was 83% (95% CI 69–91). And the overall vaccine efficacy was 59% (95% CI 4–82). The overall LAIV efficacy in healthy individuals also showed 42% (95% CI 21–57), in individuals aged 60–69 years 31%, in aged 70 years or older 57% whereas, in adults aged 18–49 years, it was found to be non-significant (111).In contrary to our study a pooled efficacy of RCTs against PRC or culture confirmed influenza done irrespective of setting was 60% for LAIV (95% CI, 44%, 71%) and 56% for TIV (95% CI, 43%, 66%) for all serotypes. Whereas for matched serotypes the VE for

LAIV was 77% (95% CI, 67%, 86%) and for TIV was 65% (95% CI, 57%, 72%) (112). A pooled efficacy of RCTs against lab confirmed influenza (LCI) irrespective of setting was 53%, (95% CI 29–69%) (113).

In contrary to our finding in another review of observational studies in developed countries the efficacy of LAIV was found to be (42%; 95% CI, 30–52). And when analyzed based on different time frame the pooled efficacy of Trivalent LAIV was ;2011–2012 68%, (95% CI, 48–80), 2012–2013 (43%; 95% CI, 27–56), 2013–2014 (83%; 95% CI, 25–96), 2015–2016 (48%; 95% CI, 29–61). And in comparison of trivalent and quadrivalent LAIV; the efficacy of trivalent formulation was (53%; 95% CI, 35–66) and a quadrivalent formulation was (33%; 95% CI, 17–46 (114).

In reviews done irrespective of design; in health workers irrespective of setting the overall pooled influenza efficacy was found to be 60% (95% CI; 0.23–0.69), and the efficacy of influenza vaccine against laboratory confirmed influenza was found to be 88% 95% CI; 0.04–0.41) which is higher than our finding (115)Similar to our finding in Adult individuals, in HIV positive individuals in developed counties, irrespective of age the pooled efficacy was found to be 66%, (95% CI 0.18–0.64) (116). The pooled efficacy of influenza vaccine against confirmed influenza in infants born from vaccinated mother was 48% (95%CI: 33% to 59%) and the pooled vaccine efficacy of RCTs was found to be 36% (95%CI: 22% to 48%) (117).

In low- and middle-income countries prevention of influenza could be challenging because circulation may not adapt to the traditional northern and southern hemisphere seasons for which the vaccine is formulated (67). It is known the immune response to vaccination in elderly is lower than young adults (64). Because trivalent influenza vaccines contain only a single B-lineage strain and because circulation varies between seasons and regions the effect of vaccines is different depending on the vaccine and the B-lineages that is circulating dominantly (88).So, especially in young children, quadrivalent influenza vaccines containing both B lineages may reduce the risk of influenza illness and its associated morbidity and mortality (88).

In the pneumonia review, 5 studies were included and a fixed effect was used to assess the effect size. For studies that followed both per protocol (PP) and intention to treat analysis (ITT), PP

was used. The pooled vaccine efficacy of PCV vaccine against Pneumonia was found to be 25%, 95% CI (0.59, 0.84). the highest efficacy of the PCV vaccine was seen in against 1st episode of IPD with 52%, 95% CI (0.37, 0.61) and the lowest was seen against severe Pneumonia in HIV negative individuals with 13%, 95% CI (0.80, 0.96). In efficacy acquired by assessing Pneumonia through Procalcitonin or C-reactive protein was found to be non-significant for both HIV positive and negative individuals with 11%, 95% CI (0.70, 1.14) and 15%, 95% CI (0.68, 1.06) respectively. And 241 SAEs were reported by 1 study (96), 110 admissions were seen in the vaccine group and 119 in control group, 3, 9 death in vaccine group and 7, 12 deaths in control group at site and home, respectively. 1 death was definitely correlated with the vaccine in vaccine group.

Similarly to our review, a review done from USA and south Africa irrespective of design, the pooled efficacy of PCV vaccine against IPD was found to be 45% , 95%CI (31.2, 56.1) in HIV infected individuals and 52.6%, CI (25.7, 69.8) in HIV negative individuals (118).In another review, done irrespective of study design, the PCV Vaccine efficacy against pneumonia was found to be 14% (95%CI, -199 to 76%). And the vaccine efficacy against IPD in elderly was found to be 32% (95%CI, 18-61%) which is lower finding than ours, but it could be as a result of difference in follow up time and age factor (119).

Generally the incidence of invasive pneumococcal disease has decreased with the introduction of Pneumonia vaccine in both HIV positive and negative individuals and also in those vaccinated and non-vaccinated. Some studies undertaken after the introduction of PCVs have shown an increase in the incidence and prevalence of invasive disease and carriage caused by serotypes not included in the vaccine (non-vaccine-serotypes or NVT), called serotype replacement in both vaccinated individuals and non-vaccinated elderly (74).

Conclusions and Recommendations

5.1: conclusions

The overall distribution of vaccine trials is found to be low based on the results found in the registries but since most of trials are still registered retrospectively, it may not be the true value

of the trials that are conducted in Africa to present. The overall efficacy of the three types of vaccines that are included in this review that were selected depending on the number of countries that conducted the diseases specific vaccine was found to be low. And in contrary to what we expected i.e. to have a lower efficacy in the presence of underlining comorbidities, the vaccine efficacy was found to be higher in those groups with adult population however in infants the presence of comorbidity did affect the efficacy of the vaccines. As the presence of underlining diseases weakens individuals' response to a vaccine based on studies. Even though due to lack of diversity we could only test it in the influenza vaccine review. Where trials done in a multicenter setting showed higher efficacy and with-in the multi-center the ones done in multi-center/multi-country showed higher efficacy than those in multi-center/single-country. No significant SAEs were found across the vaccines but we couldn't conclude the vaccines are safe because, safety data of these studies were mainly acquired from phase 3 trials not phase 4, we couldn't assess the safety issues identified from outside of a controlled environment i.e., for a long term effect and the issues seen in general populations.

5.2: Recommendations

From what we set out to assess, only the question with regards to age, study design and presence of medical condition were possible to be answered partially so in future it would be very helpful to researchers if the trials were to be designed in a way they could answer multiple questions. Also there were significant differences between trials conducted in multi and single center so our researchers should be encouraged to create an integrative work between countries because it can help us get a general view of the condition as it would have a holistic approach.

Limitation of the study

Due to the presence of a very limited number of reviews with the same outcome we couldn't compare and contrast our results with other findings sufficiently.

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Annex

Table of: Type of vaccine for vaccines preventable diseases.

No.	Available vaccines	Pipeline vaccines
1	Cholera	Campylobacter jejun
2	Dengue	Chagas Disease
3	Diphtheria	Chikungunya
4	Hepatitis	Dengue
5	*Haemophilus influenzae* type b (Hib)	Enterotoxigenic Escherichia col
6	Human papillomavirus (HPV)	Enterovirus 71 (EV71)
7	Influenza	Group B Streptococcus (GBS)
8	Japanese encephalitis	Herpes Simplex Virus
9	Malaria	HIV-1
10	Measles	Human Hookworm Disease
11	Meningococcal meningitis	Leishmaniasis Disease
12	Mumps	Malaria
13	Pertussis	Nipah Virus
14	Pneumococcal disease	Nontyphoidal Salmonella Disease
15	Poliomyelitis	Norovirus
16	Rabies	Paratyphoid fever
17	Rotavirus	Respiratory Syncytial Virus (RSV)
18	Tetanus	Schistosomiasis Disease
19	Tick-borne encephalitis	Shigella
20	Tuberculosis	Staphylococcus aureus
21	Typhoid	Streptococcus pneumonia
22	Varicella	Streptococcus pyrogenes
23	Yellow Fever	Tuberculosis
24		Universal Influenza Vaccine

Source: WHO 2021, Immunization, Vaccines and Biologicals (who.int)