UNIVERSITY OF CAPE TOWN

School based versus supplemental vaccination strategies in the delivery of vaccines to 5-19 year olds in Africa – a systematic review

By

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DECLARATION

I, Haddison Eposi (HDDCHR002) hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

This dissertation is a systematic review comparing school based vaccination (SBV) strategies versus supplemental immunisation activities (SIAs) in the delivery of vaccines to 5-19 year olds in Africa.

The protocol (Part A) outlines the rationale for this review, the study aim and the methods. The aim of the review was to compare the effectiveness of SIAs to SBV for the delivery of vaccines to 5-19 year olds in Africa. Effectiveness was measured in terms of vaccination coverage, cost of the vaccination strategy and effect of the strategy on routine immunisation. The protocol follows the PRISMA guidelines.

The literature review (Part B) is a summary of the existing literature on the vaccination of school age children and adolescents in Africa. The literature review explores the burden of disease among school age children and adolescents and the challenges faced by existing structures in providing routine immunisation to this age group. It then ends by evaluating the use of complementary strategies to provide immunisation services to school aged children and adolescents.

The manuscript (Part C) is presented in a format suitable for Plos Medical journal submission. It summarises the background, outlines the methods used, presents and discusses the results.

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Contents

ABBREVIATIONS

AEFI	Adverse event following immunisation
ATT	Anti-tetanus toxoid
CENTRAL	Cochrane Central Register of Controlled trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DTP	Diphteria, Tetanus, Pertussis
EPI	Expanded Programme on Immunisation
GAVI	The Global Vaccine Alliance
GIVS	Global Immunisation Vision and Strategy
GVAP	Global Vaccine Action Plan
HBV	Hepatitis B virus
HIC	High Income Countries
HPV	Human Papillomavirus
LMIC	Low and Middle Income Countries
MeSH	Medical subject heading
MMR	Measles, Mumps, Rubella
NIP	National Immunisation Programme
PDQ-Evidence	Pretty Darn Quick-Evidence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA-TT	Serogroup A meningococcal polysaccharide-tetatus toxoid
SBV	School Based Vaccination
SIA	Supplemental immunisation activities
SIGN	Scottish Intercollegiate Guidelines Network

Tdap	Tetanus, Diphtheria, acellular Pertussis
UNICEF	United Nations Children's Fund
WHO	World Health Organisation
WHOLIS	World Health Organization Library Information System
wP	Whole cell pertussis
VPD	Vaccine preventable diseases

PART A: PROTOCOL

INTRODUCTION

Background

Immunisation is a key public health strategy that has been practiced since the discovery of smallpox vaccine in 1796 [1]. In 1974, the Expanded Programme on Immunisation (EPI), a global initiative aimed at a more optimal use of available vaccines was started [2]. Through EPI, millions of lives, especially those of young infants are saved every year [2]. However, vaccine preventable diseases (VPDs) still contribute a significant portion to the public health burden in many countries, especially those in Africa [3]. Globally, it is now appreciated that EPI alone, is not enough to optimize the benefits of available vaccines.

There are multiple reasons which explain the relatively high burden of VPDs in some African countries. Among these reasons is the high prevalence of low vaccination coverage rates in some countries [4, 5]. High vaccination coverage rates are necessary to provide herd immunity against the targeted VPDs [6]. It is therefore important to assess other vaccination strategies that can be used to complement the EPI to maximize the benefits of available vaccines in the control of VPDs.

In one of the many strategies to address the low vaccination coverage rates in some settings, the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) launched the Global Immunisation Vision and Strategy (GIVS) in 2006 [7]. The GIVS was a ten year framework aimed at helping countries immunise people of all age groups, by optimally using a wide range of available vaccines to reduce the morbidity and mortality of VPDs [7]. The GIVS recognized the need to extend the benefits of immunisation beyond childhood period [7]. The EPI is structured to deliver immunisation services during the childhood period and not to adolescents or adults. For GIVS to be successful there was a need to develop novel vaccination strategies to reach adolescents and adults with vaccines.

Five years post the GIVS initiation, an improvement in routine vaccination coverage as well as the use of new vaccines and reduction of mortality of certain VPDs was noted [8]. However, the need for more efforts in order to achieve the set goals for the global immunisation and child survival was also noted [8]. In 2011, the WHO in collaboration with member states launched the Global Vaccine Action Plan 2011-2020 (GVAP) in order to cater for the next decade of vaccination. The GVAP reinforced the goals of GIVS while adding new ones and providing guidelines to evaluate the impact of the plan [9]. Though the aims of GIVS and GVAP are to vaccinate people of all age groups, Africa has lagged behind in expanding the immunisation services to adolescents and adults [10]. In Africa, there is limited or absence of structured programmes to vaccinate school age children and adolescents.

Immunisation in Africa is mostly carried out through the EPI. The aim of the EPI is to make immunisation services available to all children aged 0-5 years. With the development and licensing of new vaccines, the number of vaccines recommended for inclusion into EPI is rapidly growing [11] and also, the need to expand immunisation services to adolescents and adults [7, 9].

The inclusion of vaccines targeting school age children and adolescents has been a challenge for several African countries because this age group does not correspond to that targeted by the EPI. The WHO classifies children aged 10 to 19 years as adolescents [12]. Some African countries have used school based vaccination (SBV) strategies and supplemental immunisation activities (SIAs) to deliver vaccines such as human papillomavirus (HPV), tetanus, rubella, measles and hepatitis B to school age children and adolescents [13, 14].

One of the key vaccines recommended by WHO for inclusion into routine programs which targets school age children and adolescents is the HPV vaccine. As of 2016, five African countries have introduced the HPV vaccine into their national programs while a further 22 have

conducted demonstration projects to assess feasibility of HPV vaccine introduction [15]. Almost all African countries have adopted a school based approach. This approach is used as the model of choice because it facilitates accessibility to the target population of girls aged 9 to 13 years.

Through the SBV strategy, two main options are used to select children to be vaccinated; the age of the child or the grade [14]. As recommended by WHO, the selected school age children receive two doses of the HPV vaccine with a six months interval [16, 17]. Several countries using this strategy have reported high vaccination coverage rates [18-20]. The success of this school based approach has been attributed to proper community sensitisation, and the use of existing health resources [20]. Nonetheless, several key challenges have been reported such as complex logistics to bring the immunisation services to the schools, low school attendance rates, inadequate finances, poor cervical cancer knowledge, school absenteeism and fear of side effects [21-24]. Supplemental immunisation activities could be used as an alternative to reach adolescents and adults in settings such as Africa, where the school enrolment rate is not 100%.

Supplemental immunisation activities, also known as mass vaccination campaign refers to an immunisation strategy where a large number of people are vaccinated within a defined geographical area and period [25]. This is usually done in order to rapidly increase the immunity level of the target population in the face of an outbreak or potential outbreak. The SIAs are carried out to complement routine immunisation as well as during the introduction of a new vaccine into the routine immunisation programme [25]. The benefits of using SIAs to complement the routine immunisation programmes have been recognized for decades. The SIAs are reported to have an optimal vaccination coverage rate and are considered cost effective. Most importantly SIAs help in the control of VPDs [26-28]. Since 1988 they have helped reduce the global incidence of polio by 99% [29]. Similarly the use of SIAs targeting smallpox over several years permitted the disease eradication by 1980 [25].

In comparison to the SBV, SIAs may be a better option for the delivery of vaccines to school age children as well as adolescents. SIAs could be used to deliver HPV vaccines as well as other adolescent vaccines against diseases such as tetanus, acellular pertussis, diphtheria and meningococcal disease [10, 30]. SIAs would permit harmonisation of the immunity levels of the population before the vaccine is delivered by the routine immunisation services, as is the case with HPV vaccine [25]. Recently, there are studies showing that HPV vaccine could potentially be delivered as a single dose schedule instead of the two dose schedule that is currently being used in most countries [31, 32]. The mobile and fixed strategies used during SIAs allow vaccinators to reach and vaccinate the target population irrespective of attendance or non-attendance of school. Using SIAs therefore, could have an advantage over the school based immunisation strategy in that mass vaccination ensures that everyone in the susceptible targeted population group has been immunised, hence closing the immunisation gap as recommended by the GIVS and GVAP initiatives [7, 9].

Our systematic review study therefore proposes to evaluate the feasibility of using SIAs as an alternative to school based HPV vaccine delivery strategy, as well as the delivery of other adolescent vaccines in African countries.

Objectives

The objective of this systematic review is to compare the effectiveness of supplemental immunisation activities and school based vaccination strategies in the administration of vaccines to school age children and adolescents in Africa.

METHODS

Study registration

This protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol 2015 (PRISMA-P) and is registered with PROSPERO CRD42017057475.

Criteria for considering studies for this review

Types of studies

Included studies will consist of randomised controlled trials (RCTs), non-RCTs, cluster-RCTs, interrupted time series, controlled before-and-after, cohort, cross-sectional and case-control studies. All included studies will be primary studies. Reviews will be excluded.

Types of participants

Participants will include school age children and adolescents (5-19 years) living in Africa.

Types of interventions

Studies evaluating SIAs also called mass immunisation campaigns will be included. SIAs are mass vaccination campaigns within a defined geographical area and period regardless of the previous vaccination status of the target population [33] . Studies reporting on mass campaigns delivering services other than vaccination e.g. sensitisation as well as SIAs targeting age groups outside 5-19 years old will be excluded.

Types of comparators

Studies looking at school based vaccination strategies will be included. This strategy entails vaccinating children in schools either based on their grades or their ages. Depending on the vaccine, multiple doses may be administered at specified intervals.

Types of outcome measures

Primary outcome

- Vaccination coverage
- Costs of vaccine delivery

Secondary outcome

- Effects on routine vaccination/child health services

Search method for identification of studies

An extensive search will be carried out to identify all relevant studies. Both published and unpublished literature will be searched. No restriction will be placed on language or period.

The following electronic databases will be searched for peer reviewed primary studies using both medical subject headings (MeSH) and free text terms relating to vaccination, children, adolescents and Africa; PubMed, Africa Wide, Cochrane Central Register of Controlled trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), World Health Organization Library Information System (WHOLIS), Web of Science, PDQ (Pretty Darn Quick)-Evidence and Scopus. The detailed search strategy is provided in the appendix (**S1 Table)**. The following databases will also be searched for grey literature (reports, non-reviewed and non-published papers); WHO, The Global Vaccine Alliance (GAVI) and UNICEF. We will browse reference lists of relevant publications to identify other potential studies.

Data collection and analysis

Selection of studies

The titles and abstracts of eligible studies obtained through the search will be screened independently by two study team members. The two study team members will then independently read the full text of the retained studies and mark the studies for either inclusion or exclusion. Where differences arise the two team members will reach a consensus by discussion and if need be a third study team member will be consulted. The study selection process will be illustrated using the PRISMA flow chart.

Data extraction

A data collection form will be designed and used independently by the two study team members to extract data from the included studies (**S1 Form**). The data extraction form will first be piloted by the two team members using the same studies to assess comprehension. In case of discrepancies with data extraction, the two study team members will discuss and if no agreement, a third study team member will be consulted and the differences will be resolved by consensus. Data will be extracted on four main aspects; participants, intervention, comparison and outcomes.

- Intervention/comparison: type of vaccination strategy (SBV or SIA), the aim of the vaccination activity, its duration, the type and number of personnel carrying out the vaccinations.
- Participants: age, gender, socio-economic status
- Outcomes: coverage, costs, effects on routine vaccination/child health programs

Assessment of risk of bias in included studies

Experimental studies will be assessed using the Cochrane Collaboration's tool for assessing risk of bias [34]. The other study designs will be assessed using the Scottish Intercollegiate Guidelines Network (SIGN) checklist [35] and the Hoy modified tool [36] where applicable. The following biases will be assessed:

- Selection bias: random sequence generation, concealment allocation, comparability of groups at baseline
- Performance bias: blinding of participants and interviewers/care providers, comparability of care between both groups

- Attrition bias: percentage lost to follow-up, measures put in place to limit loss to follow-up, non-response rate, missing outcome data
- Detection bias: blinding of assessors, methods used to measure outcomes
- Other biases

Studies assessed using the SIGN checklist will be scored as 'High quality', 'Acceptable' or 'Unacceptable', those assessed using the Cochrane tool will be scored as 'High risk', 'Low risk', 'Unclear' and those assessed using the Hoy modified tool will be scored as 'Low risk', 'Moderate risk' or High risk' of bias. Where discrepancies arise, a consensus will be arrived at through discussion by the two reviewers and a third will be consulted if need be.

Assessment of reporting biases

A funnel plot will be constructed to assess the risk of publication bias per type of intervention if each intervention type included in the meta-analysis has over 10 studies of varying sizes. It will be examined for asymmetry visually and statistically using the Egger test and Harbord test [37, 38].

Data synthesis and analysis

Data will be presented in text, tables and figures. An overview of the risk of bias of included studies will also be presented. Statistical analysis will be carried out using Stata v. 14.0.

Results from studies reporting vaccination coverage will be expressed as percentages. Reported cost of vaccines shall be standardised to United States dollars (USD). The effects of the vaccination strategy (school based or SIA) on routine vaccination and health programmes will be expressed as the proportion of people in the catchment area seeking health services before and after the intervention.

Where data from the included studies is homogeneous, results will be pooled for meta-analysis using a random effects model due to probable clinical and methodological heterogeneity. Pooled statistics for vaccination coverage and effect on routine health programmes shall be expressed as risk ratios with their 95% confidence interval (95% CI) while those for cost of vaccines shall be expressed as the standardised mean difference (SMD) with its 95% CI. Where a meta-analysis cannot be carried out due to substantial heterogeneity, the results will be reported in a narrative form.

Data will be pooled to assess heterogeneity. This will be assessed firstly by visually inspecting the forest plots. Secondly, the Chi-squared test for homogeneity with a significance level set at 10% will be used. Finally, the I^2 statistic will be used to quantify any statistically significant heterogeneity between study results and rated as 'low' for $\leq$ 49% and 'moderate' for 50-74% and 'high' for $\geq$ 75%.

Efforts will be made to retrieve missing data by contacting the corresponding authors' for the included studies. Where this is not possible, values will be imputed for primary outcomes in order to enable an intention-to-treat analysis. The other outcomes will be analysed with only available data.

Subgroup analysis will be carried out based on the study design, type of vaccines, study setting and the age of the participants if possible. Sensitivity analysis will be carried out where imputations were done for the primary outcomes and also to determine if the study designs, study period or publication type have an impact on the results of the meta-analysis.

ETHICS

Systematic reviews use publicly available data, and therefore do not require formal ethical review. Notwithstanding, this protocol shall be submitted to the University of Cape Town Departmental Research Committee for approval. The findings of this review shall be available online through the university library and shall also be submitted for publication in a peer-reviewed journal.

DISCUSSION

Most vaccines in Africa are administered through the EPI hence leaving the 5-19 year olds vulnerable to some VPDs such as cervical cancer and group A meningococcal meningitis. According to WHO, in Africa, cervical cancer is responsible for 22% of all female cancers and 23 per100,000 female deaths [39]. On the other hand Meningococcus A is responsible for large epidemics resulting in many deaths with nasal carriage highest among 5 – 14 year olds [40].

The importance of immunising this age group (5-19) is rapidly being appreciated by public health systems. Our review will generate useful data on the strategy that can best deliver vaccines to this population.

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PART B: LITERATURE REVIEW

INTRODUCTION

Vaccination has played a big role in the control, elimination and even eradication of some infectious diseases such as measles, polio and smallpox respectively [1, 2]. Nonetheless, some vaccine preventable diseases (VPDs) such as pneumococcal disease, cervical cancer and rotavirus still contribute significantly to the overall infectious diseases burden in Africa [3-5]. Several reasons, among them suboptimal vaccination coverage, lack of access as well as hesitancy to vaccination may explain the high burden of VPDs in Africa [6]. In order to mitigate the burden of VPDs, vaccination would have to be accessible to all age groups. The Expanded Programme on Immunisation (EPI) is the main platform used globally to provide childhood vaccination services. Extension of the immunisation services to school age children and adolescents has been recommended by the World Health Organisation (WHO) [7].

School age children and adolescents are susceptible to VPDs due to reasons such as waning of the immunity achieved after childhood vaccination and lack of immunity against some VPDs targeting only this age group. To improve vaccination coverage in Africa, strategies such as Supplemental Immunisation Activities (SIAs) and School Based Vaccinations (SBV) are used in many settings to complement the EPI [8-10]. The SIAs and SBV strategies can target broader age group populations not normally included in the EPI. In addition, these two EPI complementary outreach strategies promote higher vaccination coverage which is a key element in the fight against VPDs. This review therefore focuses on the use of SIAs and SBVs as complementary strategies to the EPI in order to reduce the burden of VPDs in school age children and adolescents.

SECTIONS OF THE REVIEW

The first section explores the burden of specific VPDs among school age children as well as adolescents in Africa. The second section gives an overview of the challenges faced by the EPI

in providing vaccines to school age children and adolescents. The last section evaluates the utilisation of SIAs and SBV as complementary strategies to reach school age children and adolescents with vaccination services.

SEARCH STRATEGY

Key terms such as vaccines, mass campaigns, immunisation, immunization, school based immunisation, adolescent and school age children were used to identify the relevant literature. The following electronic databases and websites were searched for peer-reviewed journals or reports: PubMed, Africa Wide, UpToDate, CINAHL, WHOLIS, CENTRAL the World Health Organisation (WHO) website and Google Scholar.

No restriction was placed on the type of study design, study period or language. Articles or reports that reported about vaccination in children or adolescents were included as well as studies that focused on SIAs or SBVs.

IMPORTANCE OF VACCINATING SCHOOL AGE CHILDREN AND ADOLESCENTS

Overview

Vaccine preventable diseases (VPDs) have one distinct characteristic: there exists a vaccine capable of preventing the infection. The WHO list 25 VPDs whose vaccines already exist [11]. Future vaccines against infectious diseases such as *Mycobacterium tuberculosis* (M.tb), HIV, ebola, zika, malaria among others are under development [11]. In comparison to adults, infants are at the highest risk of contracting VPDs because they have a "naïve" immune system against the disease causing pathogens [12]. From birth until a few months later, babies are immune to very few pathogens like the measles virus due to antibodies acquired from their mothers [12]. Immunity to other pathogens can only be acquired either through vaccination or natural

infection [12]. Therefore; the EPI in most countries mainly focuses on immunising during the childhood phase of life to protect the young infants from infectious pathogens. The need to vaccinate school age children and adolescents has recently become a very topical issue in vaccinology [13].

There are several reasons that make vaccination of school age children and adolescents important. First is catch up as some infants miss routine vaccinations delivered via EPI leaving these children susceptible to VPDs [7, 14]. Second, for some VPDs such as tetanus, diphtheria and pertussis, immunity acquired after infant immunisation wanes over time thus requiring booster doses later in life to sustain the immunity [15]. Third, some VPDs such as rubella have shown a shift in age distribution from infancy to adolescence in some settings [7, 16]. Finally, new vaccines such as HPV are developed to target pre-adolescent and adolescent age groups [10] and it is also likely that future vaccines against HIV will target adolescents.

The WHO recommends addition of vaccines targeting older children into national EPIs or the extension of existing ones to the older age groups [17]. The vaccines recommended for school age children and adolescents include HPV, diphtheria, tetanus, pertussis, measles, rubella, hepatitis B and meningococcal disease [7, 17]. In agreement with the WHO recommendations, a majority of High Income Countries (HICs) now routinely vaccinate older children and adolescents [18, 19]. However, implementation of the WHO recommendations to vaccinate older children and adolescents has been slow in most of the Low and Middle Income Countries (LMICs) [13].

In Africa, weak surveillance systems are prevalent partly due to underfunding and competing interests [20]. As a result, data on the regional burden of many VPDs among older children and adolescents is limited in Africa. Lack of epidemiological data may be another barrier to the inclusion of the vaccines recommended by the WHO for older children and adolescents into

national EPIs in Africa [21]. Below, we discuss some reported information on the burden of VPDs for which the WHO has recommended vaccinations for, among school age children and adolescents.

Disease burden

- *Cervical cancer, preventable by HPV vaccine*

The human papillomavirus (HPV) is a necessary cause for the development of cervical cancer [22]. Depending on the serotype of the virus, infection can lead to low risk genital infection or high risk invasive cancers [23]. Cervical cancer is the third most common cancer in women worldwide and one of the leading causes of cancer related deaths among women in developing countries [24]. In Africa, according to the 2015 WHO report, cervical cancer was responsible for 22% of all female cancers, and 23 per 100,000 female deaths per year [24]. A study carried out in Burkina Faso among adolescents showed that 41.5% of the study population tested positive for at least one high risk HPV genotype [25]. Similarly, 64.7% South African women were reported to be positive for at least one high risk HPV genotype [26]. The HPV infection and consequently cervical cancer can be prevented by the vaccination of 9-14 year old girls with the HPV vaccine [17].

- *Diphtheria, Tetanus and Pertussis preventable by Tdap (Tetanus, Diphteria, Acellular Pertussis) vaccine*

Diphteria is a bacterial infection caused by the toxin producing *Corynebacterium diphtheriae*. C. diphtheriae is transmitted through contact with respiratory droplets or skin lesions [27]. Due to vaccination, diphtheria is becoming a rare disease globally. In 2015 there were 4530 reported cases globally [28]. However, the disease is still sporadic in many parts of the world [29] and remains a public health problem in countries with low vaccination coverage [28]. School age

children and adolescents can be protected from diphtheria by receiving a booster dose of the Tdap vaccine [17].

Pertussis also known as whooping cough is caused by the bacteria *Bordetella pertussis*. Infection occurs through direct contact with secretions from the nose or mouth of an infected person [30]. Adolescent infection has been largely attributed to waning immunity obtained after immunisation early in life [15, 31]. Studies suggest that adolescent and adult infection serve as the source of infection to younger children [30, 32]. A study carried out among adolescents in South Africa showed that 15% of the study group did not show any detectable antibody titres against pertussis [33]. Furthermore, in the same study, among the adolescents with detectable antibody levels, it was not known if these titres were protective [33]. School age children 5-6 years can be protected from pertussis by receiving a booster dose of a whole cell pertussis (wP) containing vaccine while older children can receive a booster dose of the Tdap vaccine [17].

Tetanus is caused by spores from the bacteria *Clostridium tetani*. These spores are found in the soil and cause infection when they enter a flesh wound. Tetanus still remains a threat to many lives in Africa. Maternal and neonatal tetanus were targeted for global elimination by 2015 but only 27 countries in Africa have achieved this goal as of 2017 [34, 35]. A study conducted by Scobie *et al*., in three African countries showed that children aged 5-14 had a lower immunity to tetanus than those <5 years, and men ≥ 15 years had a lower immunity compared to women [36]. Another study carried out in Ivory Coast evaluated the mortality and morbidity of tetanus among children 0 – 15 years and showed that 59.5% of the cases admitted in hospital were > 5 years and 22% of them died [37]. Children aged 5-14 and men ≥15 are the most vulnerable group in Africa due to the waning immunity. Anti-tetanus toxoid (ATT) or booster doses of the

Tdap vaccine should also be administered to school age children and adolescents to prevent tetanus [17].

- *Hepatitis B, preventable by Hepatitis B vaccine*

Hepatitis B is a viral liver disease caused by the Hepatitis B virus (HBV). The HBV is transmitted through contact with infected bodily fluids (blood, semen, saliva). The WHO estimates that 5-10% of the general population in Africa live with the virus [38]. Most children and adolescents infected with HBV are also co-infected with HIV. A study carried out in Tanzania among children and adolescents showed that 9.6% of the study population was HIV/HBV co-infected [39] while another study carried out in Zambia reported a similar infection burden of 10.4% [40]. According to the WHO recommendations, school age children and adolescents at high risk for Hepatitis B who were not immunised in infancy should receive 3 doses Hepatitis B vaccine in order to prevent disease [17].

- *Measles and Rubella preventable by MMR (Measles, Mumps, Rubella) vaccine*

Measles is caused by the measles virus. Infection occurs through inhalation of droplets from respiratory or throat secretions from an infected person. The introduction of the measles vaccine has led to a significant drop in the number of measles cases globally [41]. However, measles still remains endemic in some parts of Africa and Asia [41]. Large epidemics can still be seen in parts of Southern Africa and this is threatening the achievement of the WHO goal of eliminating measles by 2020 [42]. As of February 2017, Africa registered 36260 cases compared to 55263 in 2016 [43]. Due to under reporting, the true burden of the measles disease is believed to be much greater in Africa and globally. Measles mostly affects children but cases have also been reported among adolescents and adults. Adult infection occurs usually in the case where the person missed their routine infant vaccination or received only one dose of the measles vaccine [7]. A study carried out by Goodson et al., showed that the mean age of

measles cases in Africa was 79 months [44]. Measles infection in school aged children and adolescents can be prevented by the administration of 2 doses of measles vaccine alone or in combination [17].

Congenital rubella syndrome which results from a pregnant women infected with rubella passing the virus to her foetus is the most devastating form of rubella [45]. A review conducted by Goodson et al., on the epidemiology of rubella in Africa showed that the infection occurred across all age groups with 68% of cases occurring in people ≥ 4 years and 5% among women of child-bearing age [46]. Rubella is detected through the surveillance system designed for measles hence many cases may be misclassified as measles. Children 5-19 years are at risk of acquiring the disease due to the shift in the age group infected by rubella. Nonetheless, vulnerable populations to rubella can be protected by administration of at least one dose of the MMR vaccine [17].

- *Meningococcal meningitis, preventable by PsA-TT vaccine*

Neisseria meningitidis is responsible for a majority of meningitis cases in Africa. Most cases occur within the Sub-Saharan meningitis belt which is made up of 26 countries [47]. N. meningitis group A is responsible for most of the disease in this region but other serotypes B, C, W and X have recently caused epidemics too [48, 49]. Nasal carriage of the bacteria has been shown to be highest among 5-14 year olds [50]. The introduction of a vaccine against meningoccocus A (PsA-TT) in 2010 has led to a significant drop in the incidence of disease caused by the serotype A [51]. Lingani et al., reported an incidence rate of 0.27 cases per 100,000 inhabitants in 10 countries in the belt before the introduction of the vaccine in 2010 compared to 0.02 cases per 100,000 inhabitants in 2011-2013 after the vaccine introduction [52]. School aged children and adolescents who are at risk for meningitis A can prevent the

spread of the bacteria or getting the disease by being vaccinated with one dose of PsA-TT vaccine [51].

THE CHALLENGES OF THE EPI IN DELIVERING VACCINES TO SCHOOL AGE CHILDREN AND ADOLESCENTS

The EPI has been successful in Africa with vaccination coverage of the third dose of the diphtheria, tetanus, pertussis vaccine (DTP3) increasing from 8% in 1980 to 76% in 2015 [53]. Periodically, new vaccines are being recommended by WHO for addition into national EPI programmes. Some of these new vaccines now target school age children and adolescents [17]. However, introduction of the new vaccines by African national immunisation programmes (NIPs) has been slow. The EPI in Africa is faced with several challenges ranging from suboptimal policies to poor service delivery which prevents the programme from meeting the target coverage among the primary target population (0-5 years). In our view, in order to extend routine immunisation services to older age groups, the African EPI would have to overcome the following challenges;

- *Policies, programme management*

Most African countries do not have adequate policies and guidelines for immunisation which define the roles of each stakeholder and describe the standard operating procedures for vaccination, monitoring, disease surveillance, data management or communication [54]. This leads to confusion of leadership roles and poor ownership of the programme especially at the periphery [55]. There is little or no evidence to inform on which sectors need reinforcement or which new vaccines need to be introduced [6]. Strengthening of the programme management is therefore critical to address the EPI challenges in Africa.

- *Sustainable financing*

National EPIs are subject to budget cuts due to competing national programmes. These budget cuts are motivated by high vaccination coverage or absence of outbreaks. On the other hand there is low sourcing for funds from donors [55]. The low funding leads to a drop in the quality of services and the inability to meet the agreements signed with international partners such as The Global Vaccine Alliance (GAVI),

The GAVI finances the introduction of new vaccines into NIPs for most African countries [56]. The initiative also finances demonstration projects such as for HPV vaccine introduction, mass campaigns (measles-rubella, meningitis A) or provides introduction grants in GAVI eligible countries. The GAVI beneficiary countries are supposed to self-finance routine delivery of the vaccines within several years of the campaigns [56]. However, many countries still lag behind.

- *Service delivery*

The EPI uses health facilities as its main delivery centre in addition to the outreach strategy which entails providing services to children several kilometres away from the nearest health facilities. Unfortunately, some older children including adolescents, hardly use health services for different reasons; perceived sub-optimal care provided by the health facilities, lack of finances to pay for services, preoccupation with other activities during the day such as school, self-perceived state of good health [57, 58]. A more structured platform is therefore needed to make vaccines accessible to this older age group.

Understaffing is a challenging issue that is routinely reported by many of the EPI centres. Coupled to the understaffing is the high staff turnover and reliance on in service training. The end result is vaccinators and managers are not adequately skilled to carry out their functions which require a degree of specialty [6]. The staff shortage has led to the use of community health workers as vaccinators who are less skilled and knowledgeable and prone to cause more

immunisation errors [54]. Increasing the number of staff required to cater for the older children places a considerable strain on an already stretched programme [59].

- *Cold chain and logistics management*

Extending services to older children means an increase in the quantity of vaccines that need storage, transporting and tracking. This implies increasing the capacity of the cold chain and logistics management at the national and district levels. Vaccine storage is already a concern in most settings especially those that lack electricity [6]. Inadequate storage and transport can destroy vaccines leading to huge financial ramifications as the new vaccines are more expensive than the regular vaccines [54]. Poor stock management due to inadequate supply and distribution of vaccines and consumables leads to vaccine stock outs in some areas and overstocking in others.

- *Communication, community involvement and advocacy*

Low community awareness of vaccination services, inadequate follow-up of parents by health staff, stock out of vaccines at vaccination centres and poor handling of rumours generated after an adverse event following immunisation (AEFI) are reported as major obstacles preventing the EPI from attaining its goal [54, 59].

COMPLEMENTARY IMMUNISATION STRATEGIES TO REACH SCHOOL AGE CHILDREN AND ADOLESCENTS

Overview

The foundation of routine immunisation in most countries is the EPI. Through EPI, several vaccines delivery strategies to the target populations are used. As the delivery of vaccination services through the EPI are mainly done at a health facility, additional vaccination delivery

methods are necessary to reach populations such as school age children and adolescents whose contacts with health facilities are infrequent. The additional vaccine delivery strategies used usually depend on the objectives of the vaccination programmes. These vaccination delivery strategies include fixed, outreach, mobile or door-to-door [60].

- Fixed: This strategy involves the delivery of vaccines by health workers at an existing health facility. Vaccination is usually rendered every day or on specific days throughout the week.
- Outreach: Involves the delivery of vaccines by health workers or volunteers at a location in the community other than the regular vaccination site on specific dates. The location and vaccination dates are usually publicised well in advance.
- Mobile: Involves a team of health workers and volunteers who travel to hard to reach areas such as islands and mountainous villages to administer vaccines to the target population. This team usually spends several days vaccinating the community.
- Door-to-door: A team of volunteers and health workers move from house to house vaccinating the target population.

To extend the benefits of immunisation to school age children and adolescents, routine immunisation can broadly utilize SIAs and SBVs.

Supplemental Immunisation Activities (SIAs) strategy

The SIAs, also known as mass vaccination campaigns involve fixed, outreach, door-to-door and mobile strategies aimed at vaccinating a large number of people within a short period regardless of their previous vaccination status [1]. The fixed strategy involves using existing vaccination sites like health facilities while the other strategies entail vaccinating the target population in their homes or at local gatherings such as markets, churches, schools.

Due to its door-to-door component, SIAs have the capacity to reach a majority of the target population resulting in a better vaccination coverage which provides the herd immunity needed to prevent disease transmission. This property of SIAs makes it useful for several immunisation objectives:

- Eradication: SIAs were used for the eradication of smallpox in 1980 [1] and are currently being used for the eradication of polio by 2018 [61]. Smallpox is the only disease to achieve an eradication status after global vaccination efforts from 1966-1980. Polio is the next disease targeted for eradication. Synchronised SIAs are being carried out in endemic and susceptible countries to break transmission of wild and vaccine derived poliovirus [62].
- Control of outbreaks: SIAs are used during outbreaks to quickly interrupt disease transmission. These outbreaks usually occur due to poor vaccination coverage achieved during routine immunisation or infection in populations not covered by the EPI. This has been the case with measles, yellow fever and cholera. SIAs used during such outbreaks target infant to adult populations [63-65].
- Introduction of new vaccines into the EPI: New vaccines are often being recommended by WHO for addition into national EPIs. The high vaccination coverage achieved during SIAs allows for the harmonisation of the immunity levels of the target population before its delivery through EPI. This was the case with the introduction of the meningococcal meningitis vaccine MenAfricVac in the Sub-Saharan African meningitis belt in 2010. Mass vaccination campaigns targeting people aged 1-29 were carried out in 15 countries [66, 67]. These countries were encouraged to include the vaccine into the national EPIs within 1-5 years after the mass campaign.

Despite these benefits, SIAs have been thought to negatively impact routine immunisation and health systems. Some reports argued that during SIAs, routine immunisation activities and

regular activities in the health facilities are interrupted [66]. Moreover, frequent SIAs targeting different diseases may make care-givers reluctant to take their children to clinics for routine vaccines thinking it will be delivered at home [68, 69]. On the other hand, resources, both human and financial that would have been spent on strengthening the EPI are thought to be spent on planning for the SIA, vaccinators, transport for mobile teams and much more [70, 71].

School Based Vaccination (SBV) strategy

The SBV is an outreach strategy which involves vaccination of children enrolled in school and within the school grounds during or after school hours. This strategy takes into account the previous vaccination status of the child and should not be confused with vaccination of children in schools during SIAs. The target group of the children is determined by their age or grade. This strategy has been widely used for the delivery of HPV vaccine to young girls in Africa [72].

Several benefits have been associated with this mode of service delivery for vaccines targeting school age children especially HPV. First, one of the aims of routine immunisation is to vaccinate all persons eligible and SBV has been shown to achieve a high coverage [73]. In most settings, a majority of children aged 5 to 19 years are enrolled in schools though this may vary depending on urban or rural areas. Hence vaccinating children in schools ensures a high vaccination coverage [73]. Second, SBV facilitates the administration of vaccines requiring several doses. Older children who hardly use health services may fail to return for subsequent doses of a vaccine delivered at a health centre thus a school setting facilitates the follow up and vaccination of students who missed a dose [74, 75]. Third, SBV enables adequate planning and resource management. The exact number of children targeted is known beforehand by using school registers hence, sufficient vaccines and related materials can be ordered and stored adequately [74]. Fourth, SBV helps increase awareness of diseases in the community. Before any vaccination session, caretakers are invited for an education meeting or the children are

given information packs and consent forms which they hand to their caretakers. In several settings, female caretakers of targeted girls for vaccination have been offered HPV screening [75, 76]. Lastly, other health services such as deworming can be delivered alongside SBV [77] as well as increased benefits of bringing partnership between health and education departments.

The delivery of HPV through school based vaccination has faced several challenges. First is the identification of the target vaccination group using the learners' grade as a criteria. The WHO recommends vaccination of children 9-14 years old. Using the grade criteria, grade 4 to 6 is usually targeted for vaccination because most of the learners fall within the specified age group. However, this brings confusion because children who do not meet the age criteria are found in grades 4 to 6 [74, 78]. Second, girls who do not attend school do not have the opportunity to get the HPV vaccine [78]. This can be problematic in areas with low school attendance rates. In some settings the vaccine is made available at the health centre for a limited period for girls who do not attend school or missed school during the vaccination session [76]. Related to this second point, a substantial number of girls in private schools, for example in South Africa, do not get free HPV vaccination from the government. Third is the sensitisation of the learners and guardians. Consent from guardians is a requirement before children can be vaccinated in schools or during SIAs. These guardians include both the teachers and the legal guardians. Vaccination is hampered when head teachers refuse vaccination of children in their schools and in the case where school vaccination has been permitted, legal guardians do not consent [74, 76].

CONCLUSION

Vaccine preventable diseases remain a public health burden for Africa but the availability of vaccines combined with the best vaccine delivery strategy can alleviate this burden. The EPI

has been largely successful in delivering vaccines to children < 5 years although a lot can be done to improve. However, due to the epidemiological changes of some VPDs and the development of new vaccines, vaccines targeting older children are now recommended for inclusion into the EPI. Strategies such as SIAs and SBV can be used by the EPI to reach school age children and adolescents. In the presence of resource constraints as is in the case in Africa, NIPs may be required to use SIAs or SBV. Systematised evidence is not available on which strategy would be more effective. We therefore planned a systematic review to evaluate which strategy (SIA or SBV) is more effective for the delivery of vaccines to 5-19 year olds in Africa.

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PART C: MANUSCRIPT

MANUSCRIPT FORMATTED FOR PLoS MEDICINE JOURNAL

School based versus supplemental vaccination strategies in the delivery of vaccines to 5-19 year olds in Africa – a systematic review[1]

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ABSTRACT

Background

Some vaccine preventable diseases still remain a public health burden in many African countries. The occurrence of vaccine preventable diseases in all age groups has led to the realization of the need to extend routine immunisation services to school age children and adolescents. Supplemental immunisation activities (SIAs) and school based vaccination (SBV) are two common strategies used to complement the EPI in vaccine delivery. Therefore, this review aimed to assess the effectiveness of SIAs compared to SBV in the administration of vaccines to 5-19 year olds in Africa.

Methods and findings

Systematic review methods (protocol number CRD42017057475) were used to address our study aim. Electronic databases were searched up to March 30, 2017 for primary studies investigating the delivery of vaccines via SIAs or SBV to 5-19 year olds. To be included in the review, studies must have reported any of the following outcomes: vaccination coverage, cost of the vaccination strategy or effect of the strategy on routine immunisation. During the search, no restriction was placed on language or the study period. The search was complemented by browsing reference lists of potential studies. Out of the 4938 studies identified, 31 studies met our inclusion criteria. Both SIAs and SBV showed high vaccination coverage. This result should be interpreted with caution due to the high heterogeneity observed across the included studies. The SIAs reported a higher coverage of 91% (95% CI: 84%, 98%) than SBV which had a coverage of 75% (95% CI: 67%, 83%). In most settings, SBV was reported to be more expensive than SIAs. The SIAs were found to negatively affect routine immunisation services.

Conclusions

Both SIAs and SBV are routinely used to complement the EPI in the delivery of vaccines in Africa. In settings where school enrolment is suboptimal as is the case in many African countries, our results show SIAs may be more effective in reaching school age children and adolescents than SBV. The SBV has only been tested in the delivery of two or three dose HPV vaccine to adolescent girls, whereas SIAs have been tested in the delivery of different types of vaccines. Our results re-iterate the importance of systematic evidence to best inform African authorities on the optimal delivery strategies of vaccines targeting school age children and adolescents into their immunisation programme.

AUTHOR SUMMARY

Why was this study done?

- Vaccine preventable diseases (VPDs) are a public health burden in Africa due to low vaccination coverage. All age groups are at risk of VPDs in the absence of optimal vaccination coverage.
- Extension of routine vaccination services to school age children and adolescents has been recommended by global immunisation organisations in order to fight VPDs. However, uptake of vaccines in older children and adolescents in Africa is slow, partly due to the absence of a structured delivery platform.
- To evaluate the use of supplemental immunisation activities (SIAs) and school based vaccination (SBV) as potential vaccine delivery platforms to school aged children and adolescents.

What did the researchers do and find?

- A systematic review was conducted. Several (31) studies were identified that reported any of the following outcomes: vaccination coverage, cost of vaccine delivery strategy or effect of either strategy (SIA or SBV) on routine immunisation services.
- The SIAs achieved a higher vaccination coverage than SBV.
- The SBV is a more expensive strategy than SIAs.
- The SIAs negatively affected routine immunisation.

What do these findings mean?

- In settings where school enrolment is low, SIAs would be a better vaccine delivery option than SBV.
- Policies on vaccination need to be revised based on the existing local evidence to ensure the most optimal vaccine delivery strategies are used, particularly to school age children and adolescents.

INTRODUCTION

The Expanded Programme on Immunisation (EPI) was founded in 1974 to provide immunisation services to children both nationally and globally [1]. The EPI has proven to be a cost effective public health strategy with reports suggesting that due to the programme, millions of infants' lives have been saved against vaccine preventable diseases (VPDs) [1]. Despite the widespread implementation of EPI, some VPDs still remain a public health burden in a majority of the African countries[2]. Low vaccination coverage rates in children and the inability to reach populations not targeted by the EPI are likely contributors to the high prevalence of VPDs in Africa [3, 4].

Routinely, school aged children and adolescents are not the primary target of EPI and as a result, an immunisation gap among this population is observed in many settings [5]. In this light, the WHO recommends several vaccines for school aged children and adolescents to be included in national immunisation programmes (NIP). The WHO recommended vaccines to older children include HPV, diphtheria, tetanus, pertussis, measles, rubella, hepatitis B and meningococcal vaccine [5, 6]. Most High Income Countries (HICs) have implemented these WHO recommendations but most Low and Middle Income Countries (LMICs) have not [7-9].

Several reasons justify the inclusion of school aged children and adolescents into NIPs. First, infants who miss routine vaccinations remain susceptible to VPDs as they grow older [5, 10]. Second, immunity acquired through infant immunisation for some VPDs like tetanus, diphtheria and pertussis wanes over time thus requiring booster doses later in life [11]. Third, epidemiological changes have led to a shift in the age group infected by certain VPDs like rubella from infancy to adolescence, thus requiring a shift in the age group targeted for immunisation [12]. Lastly, new vaccines under development such as against HIV and

tuberculosis (TB) are likely to target older children and adolescents. In the absence of structured vaccine delivery programs for school age children and adolescents, many settings use school based vaccination (SBV) and supplementary immunisation activities (SIAs) to reach these groups.

Supplementary immunisation activities, also known as mass vaccination campaigns refer to an immunisation strategy where a large number of people are vaccinated within a defined geographical area and period regardless of their previous vaccination status [13]. The success of SIAs in outbreak control as well as in the eradication of smallpox is well documented [13-16]. However, there are reports suggesting negative effects of SIAs on the routine health services, including EPI [17, 18].

School based vaccination is the vaccination of school children on school premises within school hours. This delivery platform is fairly new to the EPI compared to SIAs [19], particularly in Africa. Currently in Africa, the main vaccine administered through SBV strategy is the HPV vaccine. Among the advantages of SBV are high vaccination coverage and the possibility to extend other health services to school age children [20-22]. However, in Africa, there are millions of children not attending school [23] and are missed by SBV strategy.

Therefore our study aimed to compare the effectiveness of using SIA or SBV to deliver vaccines to 5-19 year olds in Africa.

METHODS

A protocol for this review was developed and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol 2015 (PRISMA-P) (**S1 Checklist**). The protocol was registered with PROSPERO (CRD42017057475) [24].

Search strategy

A search was carried out to identify all relevant studies. Both published and unpublished literature was searched up to March 30, 2017. No restriction was placed on the publication language or period. The following electronic databases were searched using both medical subject headings (MeSH) and free text terms relating to vaccination, children, adolescents and Africa (**S1 Table**); PubMed, Africa Wide, Cochrane Central Register of Controlled trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), World Health Organization Library Information System (WHOLIS), Web of Science, PDQ (Pretty Darn Quick)-Evidence and Scopus. The following grey literature databases were searched for reports, non-reviewed and non-published papers; WHO, Gavi, The Vaccine Alliance (GAVI) and UNICEF. The reference lists of the included publications were evaluated to identify other potential studies.

Study selection

The following criteria was used to select primary studies for inclusion: (1) the study was either a randomised controlled trial (RCTs), non-RCT, cluster-RCT, interrupted time series, controlled before-and-after, cohort, cross-sectional or case-control studies; (2) participants were school aged children to adolescents (5-19 years) living in Africa; (3) supplementary immunisation activities (SIAs) or school based vaccination (SBV) were the vaccination strategies under investigation; (4) vaccination coverage, cost of vaccine delivery or effect of either strategy (SIA or SBV) on routine health services including EPI were reported as any of the outcomes. Retrieved articles were independently screened by two reviewers (HEC and LA). Where eligibility was unclear, a review was carried out by a third independent reviewer (BK). The same process was carried out for review of the full text of eligible studies.

Data extraction

HEC and LA independently reviewed each included study and extracted data using a piloted data extraction form (**S1 Form**). Where discrepancies arose HEC, LA and BK reached a consensus by discussion. Corresponding authors were contacted for missing data and some of them provided the missing information.

Quality assessment of included studies

Experimental studies were assessed using the Cochrane Collaboration's tool for assessing risk of bias [25], while the Hoy *et al.*, modified tool was used for cross-sectional studies [26]. Studies using the Cochrane checklist were scored as 'High risk' or 'Low risk'. Those using the Hoy *et al.*, checklist were scored as High risk' or 'Moderate risk' or 'Low risk' of bias. Studies with high risk of bias were rated as poor quality studies while those with moderate and low risk of bias were rated as moderate and high quality studies respectively. Where discrepancies arose, a consensus was arrived at through discussion by HEC and LA. The nine studies reporting data on the costs had variable study designs, some of them with no known tool for quality assessments. As our only interest from these studies was the cost of the strategy irrespective of the study design, there were no quality assessments done for the nine studies.

Data synthesis and analysis

Data was analysed using Stata v. 14.0. Results from the studies reporting vaccination coverage were expressed as percentages. Reported costs of the delivery strategies were standardised to United States Dollars (USD) if reported in a different currency. The costs of the strategies (SBV or SIA) and their effects on routine vaccination were presented in a narrative form.

A meta-analysis for vaccination coverage using a random effects model with inverse variance proportion was carried out. Pooled statistics for vaccination coverage were expressed as proportions with 95% confidence interval (95% CI) as opposed to risk ratios proposed in the

protocol because of the study designs of the included studies. Coverage was expressed as a prevalence in all studies reporting this outcome and not as a risk hence our decision to report proportions. Subgroup analyses were carried to evaluate vaccination coverage per strategy stratified by vaccines or study setting. Missing values were imputed in order to enable an intention-to-treat analysis. A sensitivity analysis was then carried out where imputations were done to see if the result differed from that without imputations.

Visual inspection of forest plots, the Chi-squared test for homogeneity with a significance level set at 10% and the I^2 statistic were used to assess and quantify any heterogeneity between study results. Heterogeneity was rated as 'low' for ≤ 49% and 'moderate' for 50-74% and 'high' for ≥ 75% using the I^2 statistic.

RESULTS

Literature search

Three thousand seven hundred and nineteen (3719) studies were identified through searching electronic peer reviewed databases. A further 1461 were identified from grey literature. An additional five studies were identified from the reference lists of potential articles only. After duplicates were removed 4938 studies were left. The titles and abstracts of the 4938 studies were screened and 4872 were excluded. The full text of the remaining 65 were retrieved and assessed for eligibility. Out of the 65, 31 met our inclusion criteria (**Fig 1**).

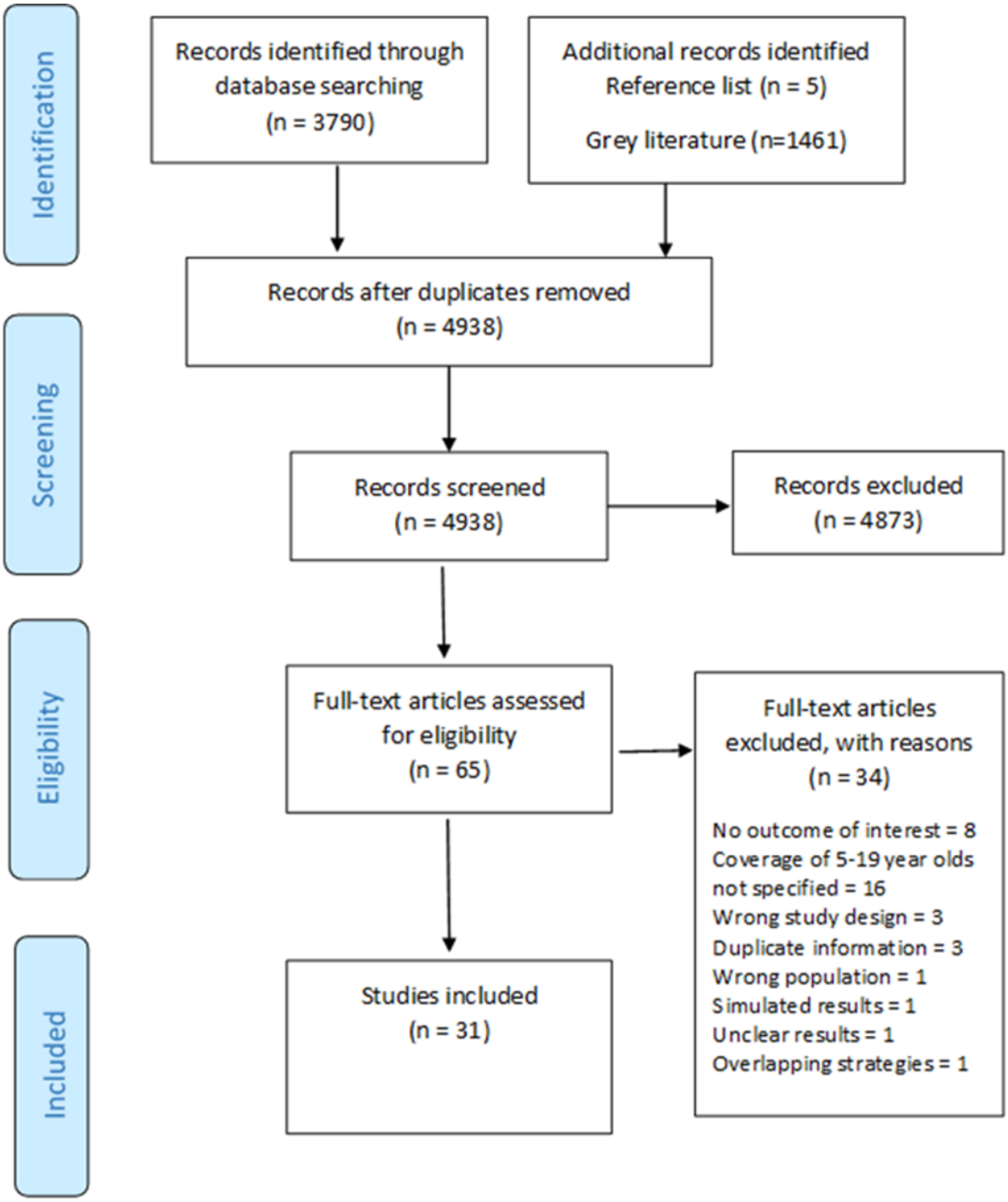

Fig. 1. PRISMA flowchart for selection of included studies

Characteristics of included studies

A total of 31 studies were included in our review. There were 20 cross-sectional studies [22, 27-45], eight economic evaluation studies [46-53], one cluster-randomised trial [54], one epidemiological report [55] and one interrupted time series [56]. The included studies were published between 1993 and 2016 with only three studies published before 2000 [44, 45, 55]. A total of 17 African countries (**Fig.2**) and five different vaccines were represented from all the included studies are shown. Zanzibar, one of the 17 countries is too small to be shown on the map. Except four of the included studies that were written in French [43, 45, 49, 52], the rest were in English. One of the study team members (HEC) is French literate and translated the four articles. In terms of vaccine delivery strategy, 20 and 11 studies assessed SIAs [28-31, 33, 35-37, 42-45, 48-53, 55, 56] and SBV [22, 27, 32, 34, 38-41, 46, 47, 54] respectively.

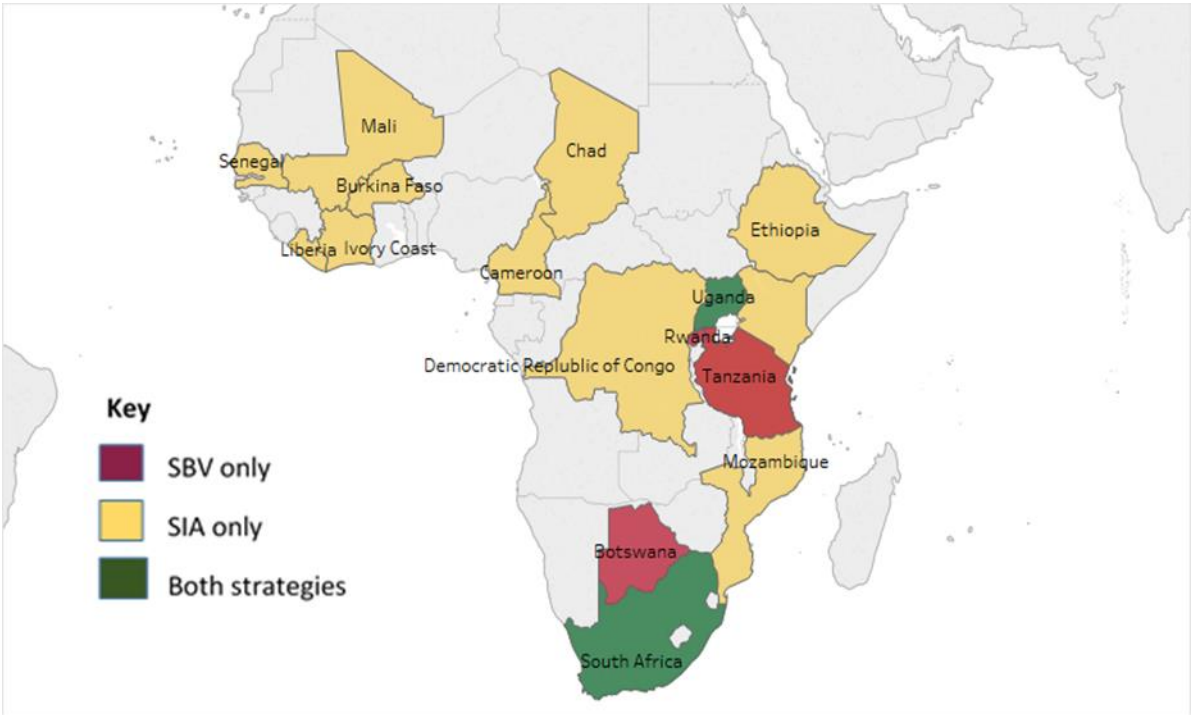

Fig 2. Countries and vaccine delivery strategies represented by the 31 included studies

Risk of bias and quality assessment

Using the Hoy modified tool, a 10 item scale was used to assess the internal and external validity of the 20 cross-sectional studies. Ninety-five percent (19) of the studies were of high quality (low risk of bias) meaning further research is very unlikely to change our confidence in the estimate of the study outcomes. Five percent (1) of the studies were of moderate quality (moderate risk of bias) meaning further research is likely to have an important impact on our confidence in the estimate of the outcomes (**Fig 3b**). For the internal validity, all the studies defined which participants were considered to have been vaccinated (by self-report or vaccination card) and used the same data collection tool for all the participants. However, five studies did not mention if the tool used was standardised [28, 33, 41, 44, 45]. Ten studies collected information from proxies (parents or guardians of vaccinated children) [28-31, 33, 35, 42-45]. All the studies calculated vaccination coverage as the 'number vaccinated divided by the number of the targeted population'. For the external validity, all the studies had representative samples in terms of age and sex. Random sampling was used in all except four studies [32, 34, 36, 38]. Similarly, a majority of the studies had a low non-response rate except three studies [32, 39, 45].

The Cochrane checklist was used to assess the clustered-randomised trial [54] and interrupted time series [56] study (**Fig 3a**).

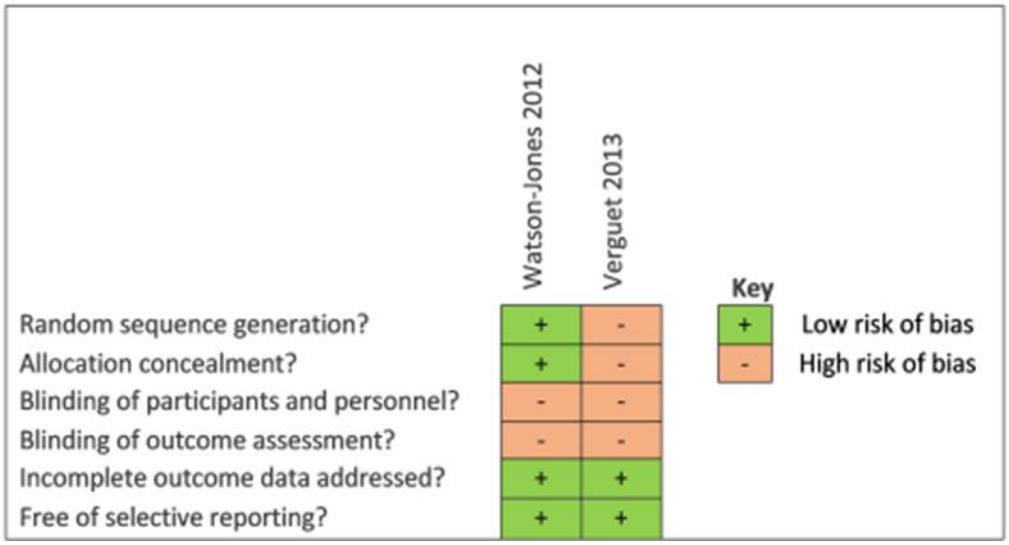

Fig 3a. Risk of bias for experimental studies

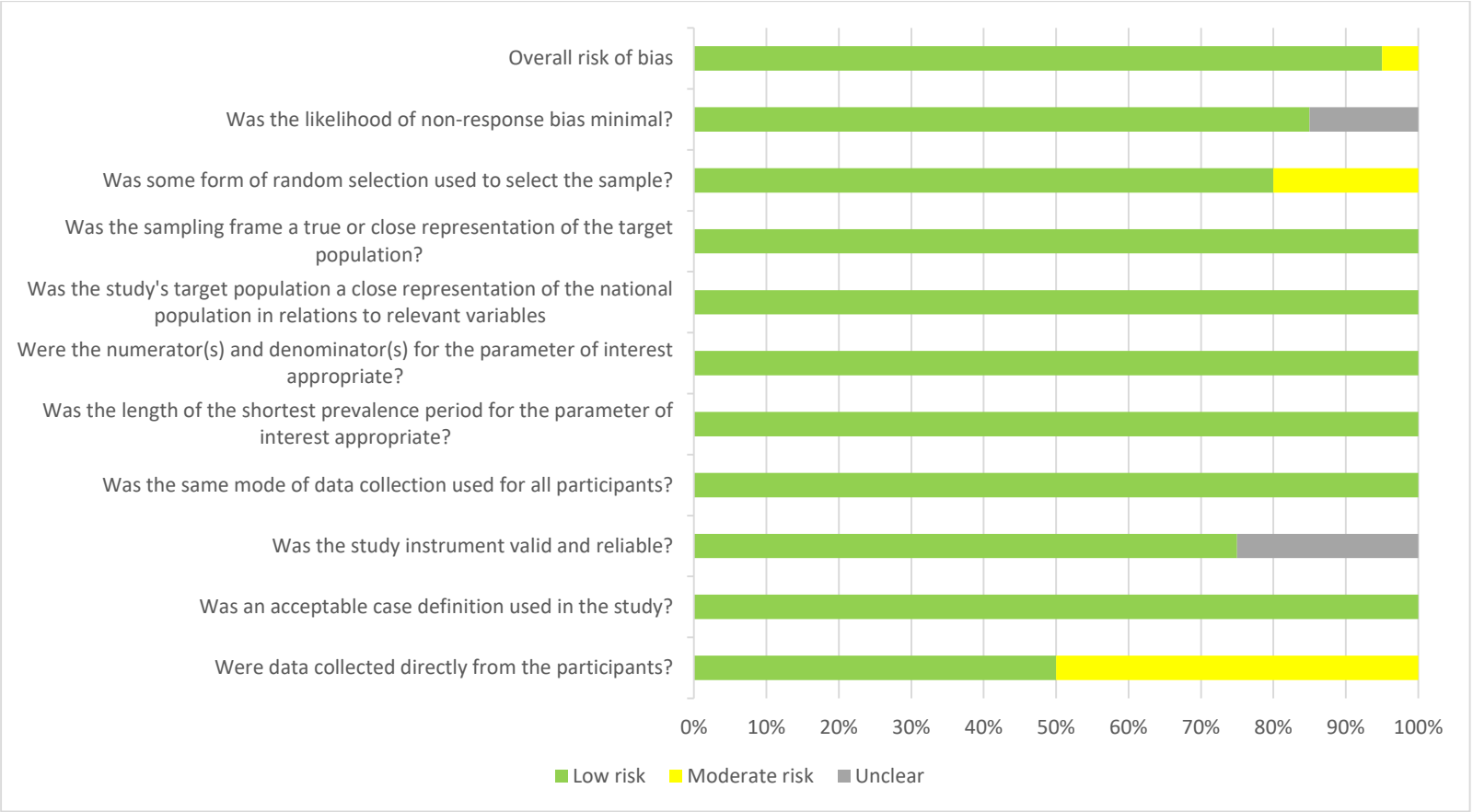

Fig 3b. Risk of bias for cross-sectional studies

Vaccination coverage

SIAs: Twelve studies reported vaccination coverage for SIAs. Ten studies were surveys while two [55, 56] were census. Three studies reported coverage data on meningitis PsA-TT vaccine [28, 29, 43], five on measles vaccine [30, 31, 33, 55, 56], two on yellow fever vaccine [35, 42], one on cholera vaccine [37] and one on meningitis A/C vaccine [45]. Vaccination coverage for SIAs ranged from 48.5% to 98% (**Table 1**).

Table 1. Characteristics of the included studies reporting vaccination coverage for SIAs

First author and year of publication	Setting	Vaccine	Targeted population | Vaccinated population	Age group of interest	Coverage
Ouatara *et al.*, 2013	Urban/rural	Meningitis (PsA-TT)	817 | 782	6-15	95.6%
Meyer *et al.*, 2015	Urban/rural	Meningitis (PsA-TT)	10001 | 9741	6-15	97.4%
Tall *et al.*, 2015	Urban	Meningitis (PsA-TT)	232 | 210	5-19	90.5%
Luquero *et al.*, 2011	Urban	Measles	-	5-15	95%
Spiegel *et al.*, 1993	Urban	Meningitis (bivalent A C)	850 | 833	5-19	98%
Gil Cuesta *et al.*, 2015	Urban	Measles	-	5-15	87.4%
Ohuma *et al.*, 2009	Rural	Measles	378 | 334	5-15	88.3%
Huhn *et al.*, 2005	Displaced	Yellow Fever (17D)	25230 | 12238	5-14	48.5%
Cavailler *et al.*, 2006	Urban	Cholera (rBS-WC)	-	5-14	62.1%
Bagonza *et al.*, 2013	Rural	Yellow Fever	201 | 197	5-15	98%
CDC, 1999	Urban/rural	Measles	4045498 | 3495415	5 -14	86%
Verguet *et al.*, 2013	Urban/rural	Measles	10383500 | 7579955	5-14	73%

A meta-analysis of a pooled estimate of coverage was conducted (**Fig 4**). A pooled estimate of 86% (95% CI: 80%, 93%) was observed. Three studies were excluded from the pooled meta-analysis due to missing sample sizes [30, 31, 37]. However, after imputation of the sample sizes no major difference was seen in the pooled coverage (**Fig 5**).

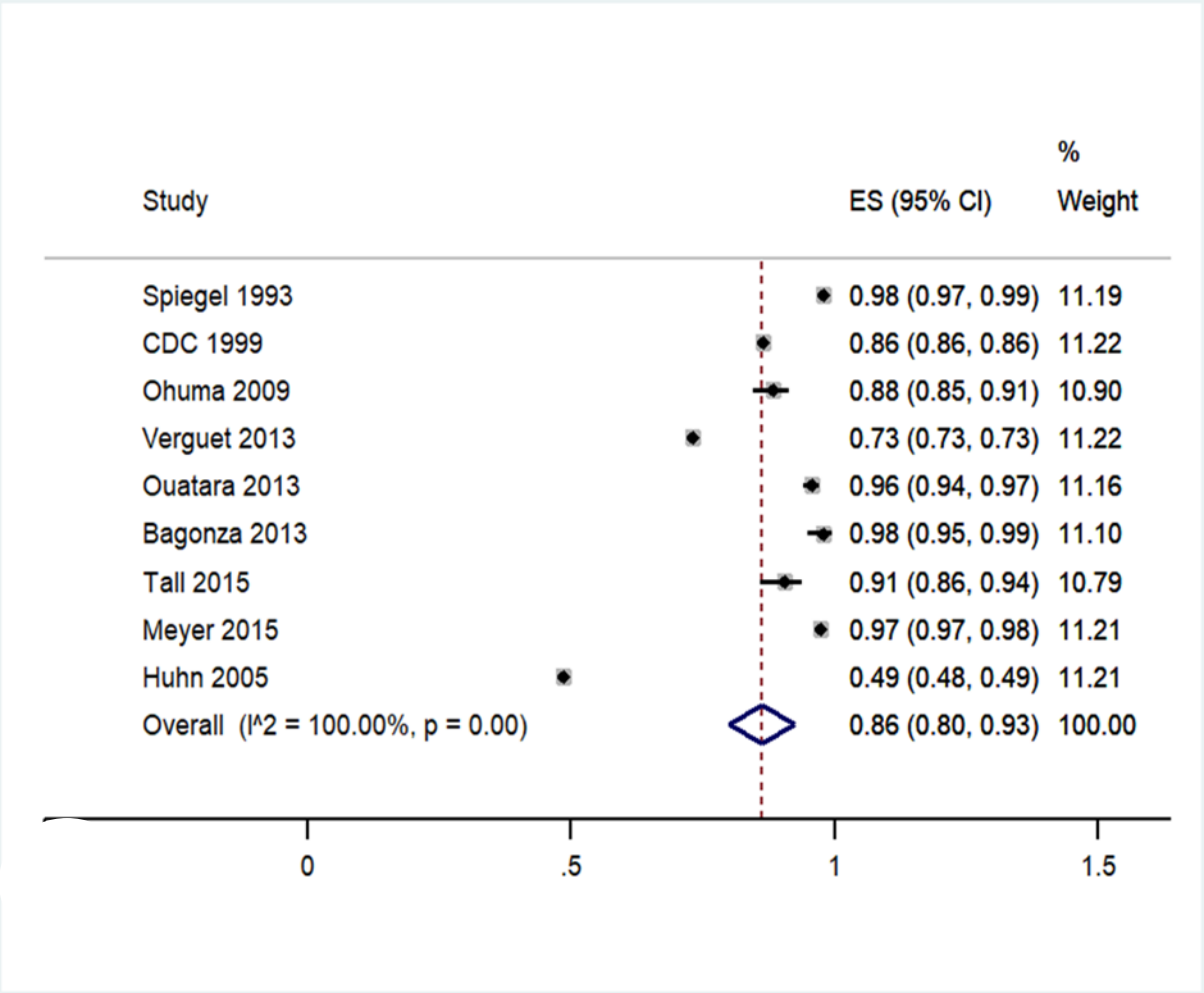

Fig. 4. Forest plot showing vaccination coverage for SIAs

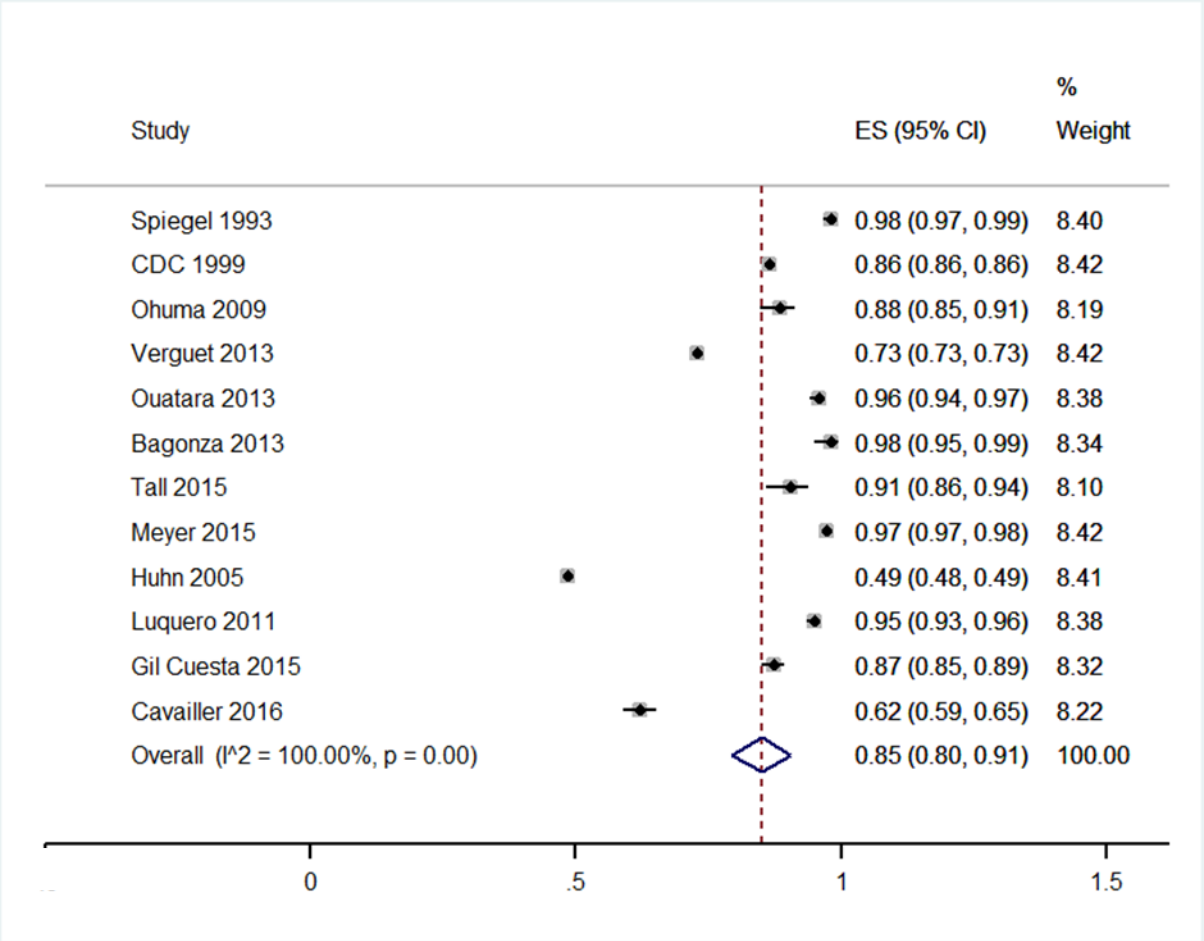

Fig 5. Forest plot showing vaccination coverage for SIAs with imputed data

SBV: Eight studies reported vaccination coverage for school based vaccination (**Table 2**). All the studies reported coverage of the HPV vaccine among girls aged 9-19 years. Four studies reported a combination of a grade and age based approach for identifying the target girls for the vaccination [27, 32, 34, 54] while three reported a grade based only approach [22, 39, 40]. Vaccination coverage of completed doses among the targeted population ranged from 42.4 – 97.4%. A meta-analysis of the studies gave a pooled coverage of 75% (95% CI: 67, 83) (**Fig 6**).

Table 2. Characteristics of included studies reporting vaccination coverage for SBV

First author and year of publication	Setting	Vaccine	Selection criteria	Targeted population | Vaccinated population	Age range	Coverage
Raesima *et al.*, 2015	Urban	HPV	Grade/Age	2488 | 1967	9-14+	79%
Binagwaho *et al.*, 2012	Urban/rural	HPV	Grade	94141 | 88927	12	94.4%
Moodley *et al.*, 2013	Rural	HPV	Grade/Age	963 | 938	9-14	97.4%
Snyman *et al.*, 2015	Rural	HPV	Grade/Age	965 | 495	9-14	51.2%
Botha *et al.*, 2015	Urban/rural	HPV	Grade	3465 | 1859	9-12	53.7%
Watson-Jones *et al.*, 2012	Urban/rural	HPV	Grade/Age	5532 | 4211	12-13	76.1%
La Montagne *et al.*, 2011	Rural	HPV	Grade	2008: 3459 | 3131 2009: 2835 | 2512	-	90.5% 88.6%
Katagwa *et al.*, 2014	Rural	HPV	Age	415 | 176	9-19	42.4%

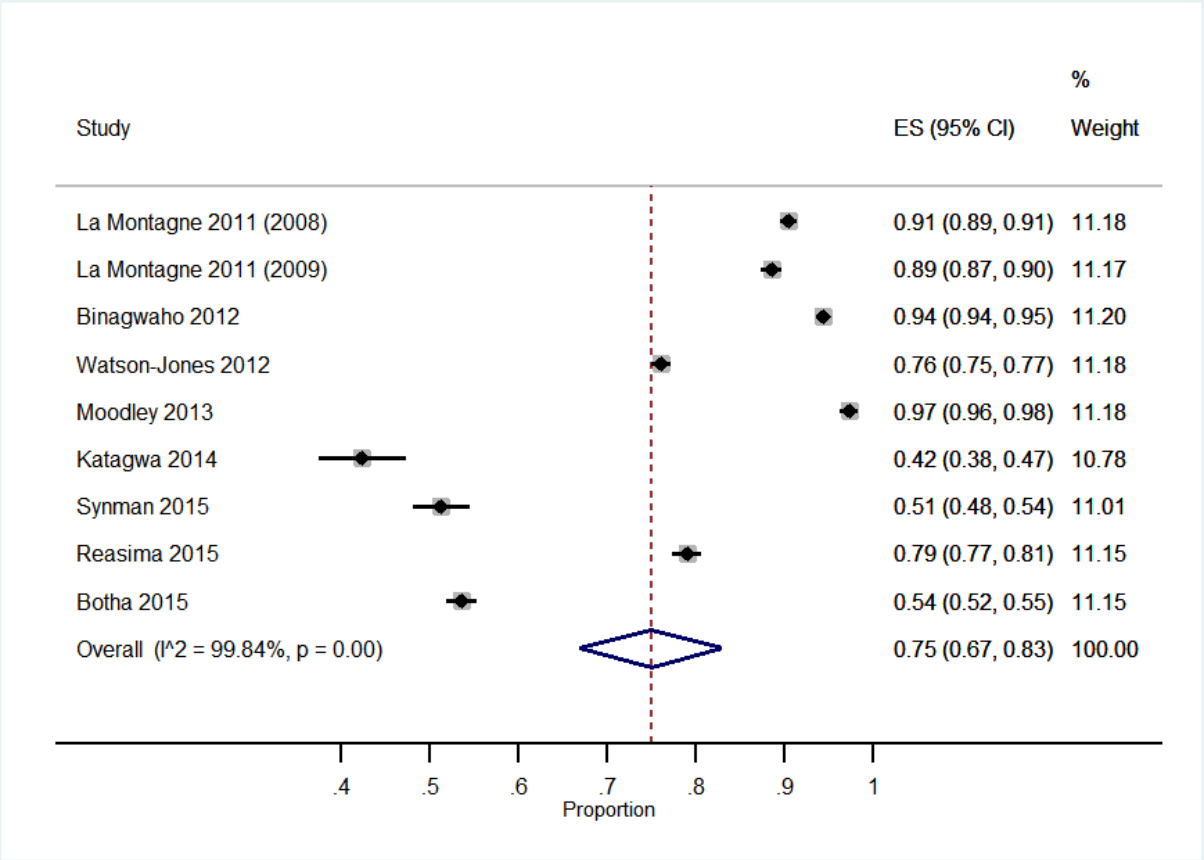

Fig. 6. Forest plot showing vaccination coverage for SBV

Comparison of vaccination coverage: To compare the two vaccine delivery strategies, pooled estimates for SIAs (mass campaigns) and SBV were evaluated. The SIAs and SBV had a pooled coverage of 91% and 75%; respectively. (**Fig 7**). For this comparison and subsequent analyses, Huhn *et al.*'s, study [35] was not included in the meta-analysis as the targeted population (displaced) in the study is not the routine group for SIAs.

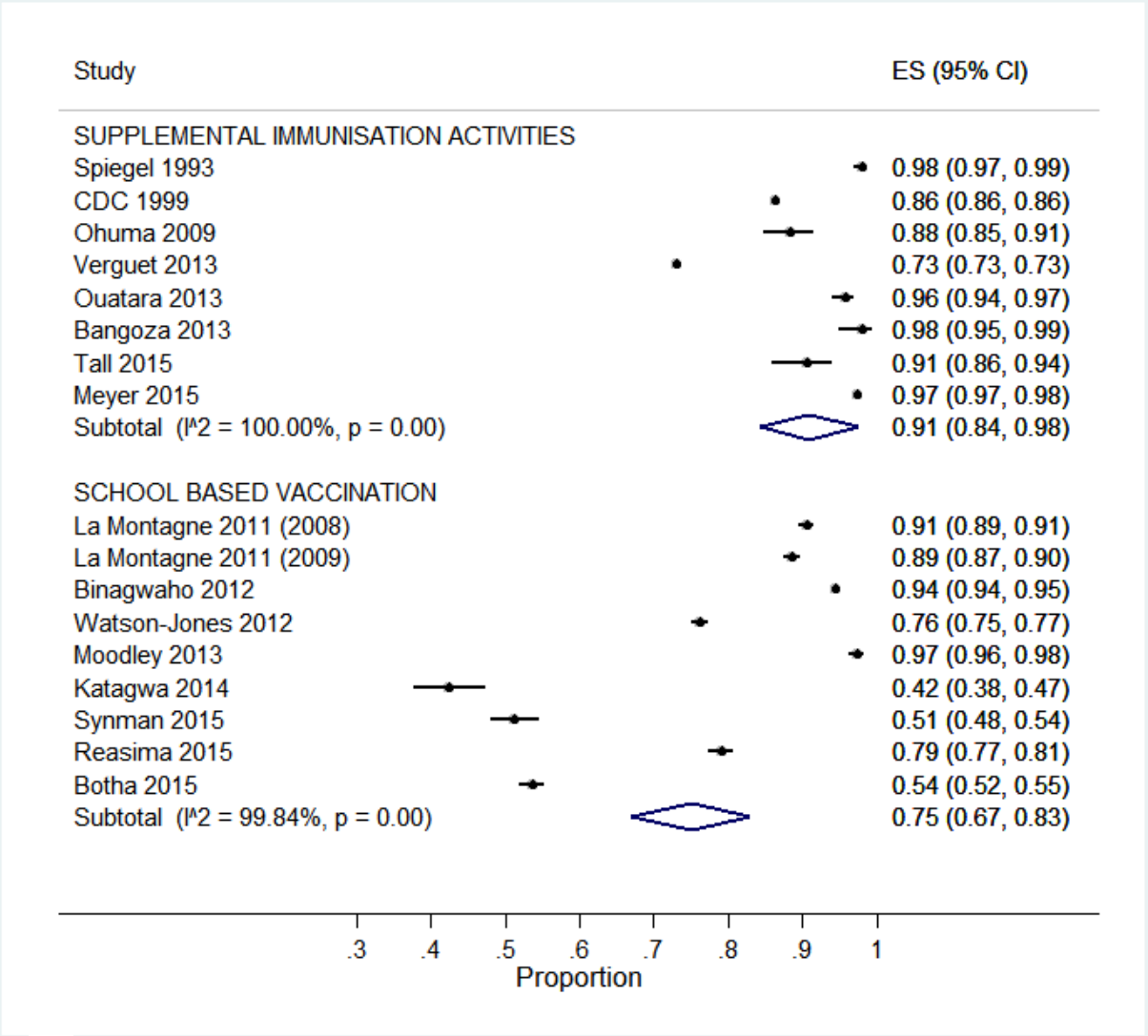

Fig. 7. Comparison of vaccination coverage per strategy

Subgroup analyses for vaccination coverage

Subgroup analyses were carried out to evaluate if vaccination coverage varied by setting in the case of both strategies or by vaccine for SIAs.

Setting: For SIAs, vaccination coverage did not vary much per setting (**Fig 8**). Coverage was highest in urban areas (97%, 95% CI: 96, 98) and lowest in a mixed setting (88%, 95% CI: 79, 98).

Similarly for SBV, there was little variation of coverage across setting. Coverage in urban areas represented by one study was 79% (95% CI: 77, 81), rural areas 74% (95% CI: 63, 85) and mixed settings 75% (53, 97).

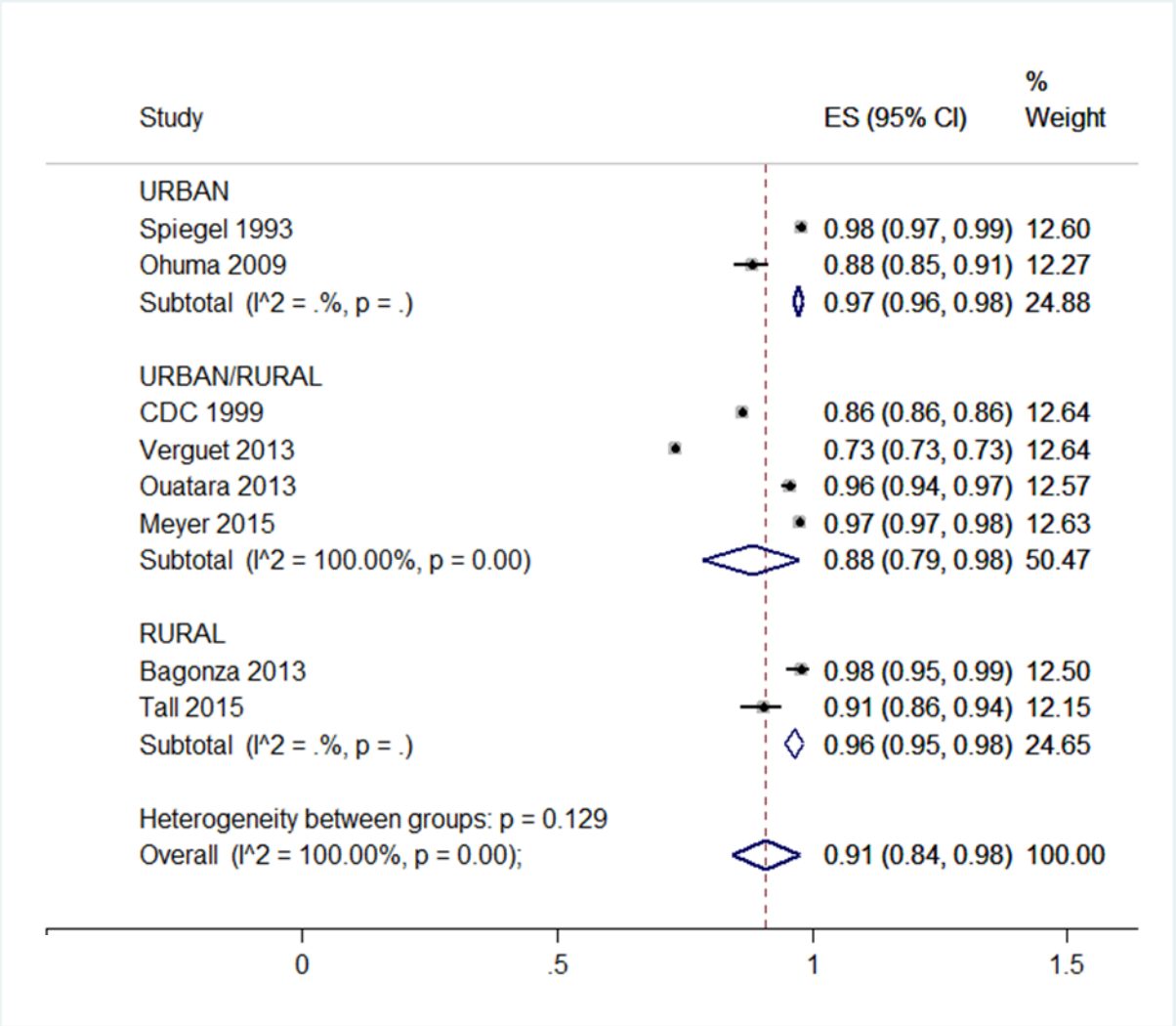

Fig 8. Subgroup analysis of SIA coverage per setting

Vaccine: There was some variation in coverage with regards to the vaccine (**Fig 9**). Measles campaigns reported the lowest coverage 83% (95% CI: 72, 93). Meningitis campaigns had a coverage of 96%, (95% CI: 94, 98) while the only study on yellow fever reported a coverage of 98% (95% CI: 95, 99).

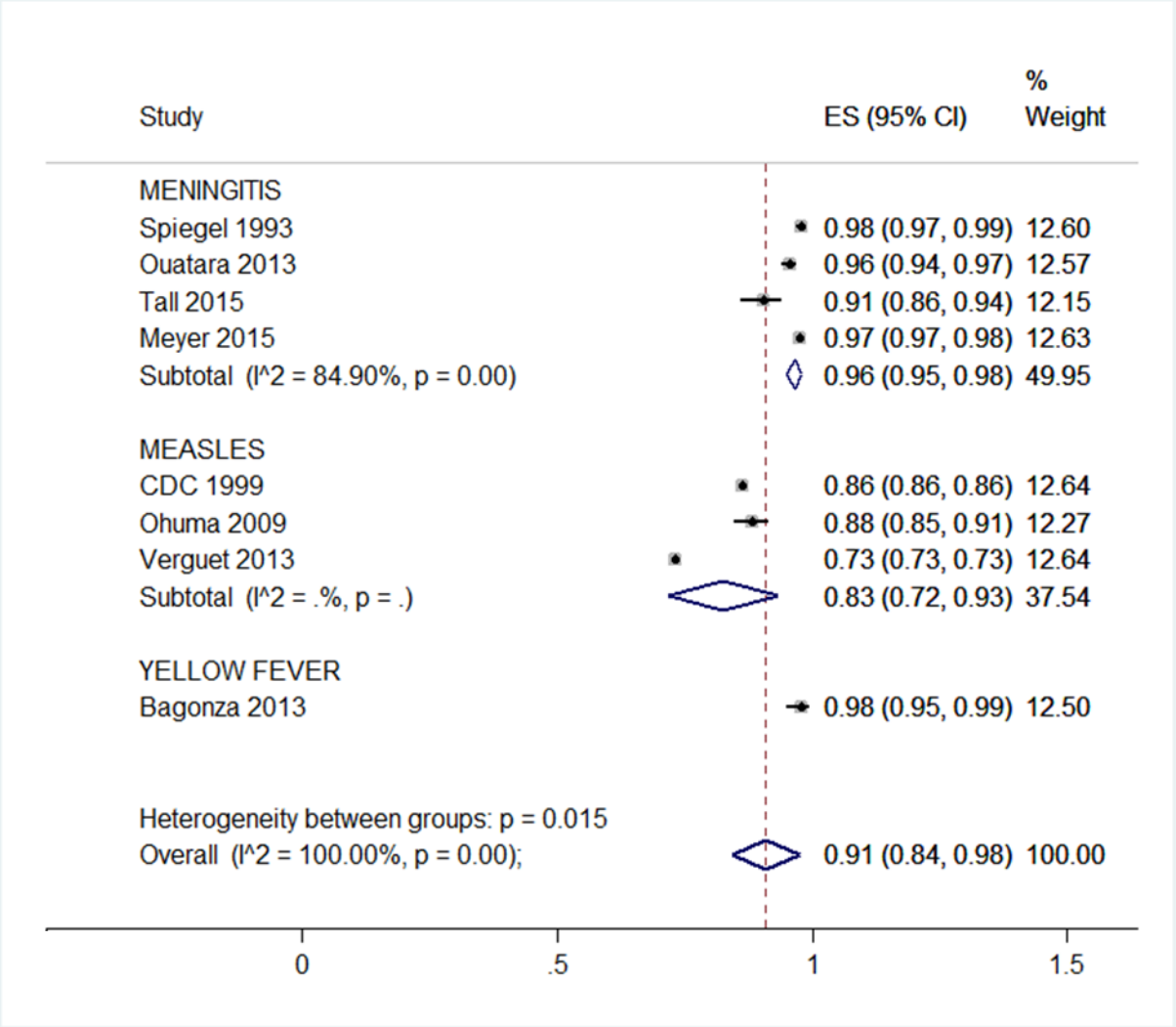

Fig 9. Subgroup analysis of SIA coverage per vaccine

Cost of vaccine delivery strategy

SIAs: Seven studies reported the cost of organising SIAs (**Table 3**). These results represent the costs spent on the total target population for the campaign. It was not feasible to separate the amount spent for 5-19 year olds only. The campaigns targeted people aged 6 months and older with the number of vaccinated people across all studies ranging from 23921 to 12,649,448. The vaccines administered were against measles, cholera, meningitis A/C and yellow fever and all were administered as a single dose. Two studies reported on campaigns where two vaccines were administered simultaneously [48, 52].

A majority of the total cost across the studies was used to procure vaccines and consumables. The highest proportion (86%) was reported by da Silva *et al*., for the combined yellow fever and meningitis A/C campaign in Senegal [52]. Salaries of health staff and international supervisors were another source of high expenditure. Other reported minor expenses included training of personnel, social mobilisation, transport, maintenance of equipment, cold chain and management of AEFI.

SBV: Two studies reported the cost of HPV vaccination in Tanzania and Uganda [46, 47] (**Table 3**). In Tanzania, 4211 girls were vaccinated with three doses of HPV vaccine either based on age or class. Schools were chosen from both urban and rural settings. The total economic cost for the project was 349,400 USD. The vaccine cost 5 USD/dose. The total cost per fully immunised girl in urban areas were 66 USD and 100 USD for class-based and age-based approach respectively; and in rural areas, 78 USD and 107 USD for class-based and age-based approach respectively. Administration and supervision (salaries) of the project and procurement of vaccines accounted for the major expenses. The reported minor expenses in the study included training, cold chain, waste management and social mobilisation. In Uganda, 3038 girls in a rural setting were vaccinated with three doses of HPV vaccine using a class based approach. The total economic cost (cost of all resources used regardless of who paid) was 30,646 USD. The vaccine cost 0.2 USD/dose. The total economic cost per fully immunised girl was 9.5 USD. Salaries of staff accounted for the greatest part of the cost followed by micro-planning, staff training, community mobilisation (start-up costs). Other expenses included supplies, cold chain, vehicles and transportation.

Table 3. Characteristics of included studies reporting the cost of the vaccination strategy

First author and year of publication	Setting	Targeted age group (Years)	Vaccine	Vaccinated population	Cost of strategy USD	Cost per fully immunised person	Major sources of expenditure (%)
School based vaccination							
Quentin *et al*., 2012	Urban/Rural	12-13	HPV	4,211	349,367	66-107	Salaries (42) Procurement (34)
Levin *et al.*, 2013	Rural	Grade 5	HPV	3,038	306,463	9.5	Salaries (40) Start-up costs (27)
Supplemental immunisation activities							
Verguet *et al*., 2013	Urban/Rural	5 - 14	Measles/ Polio	12,649,448	36,859,000	2.9	Personnel (58.3) Vaccines (30.6)
Zengbé-Acray *et al*., 2009	Urban	> 6 months	Yellow fever	2,610,994	2,382,582	0.9	Vaccines and consumables (80.6)
Legros *et al.*, 1999	Displaced	≥ 1	Cholera	27,607	14,655	0.53	Transport of vaccines (61.8) Consumables (21.8)
Wallace *et al*., 2014	Rural	6 months-15	Measles	457,035	380,052	72.29	Vaccines and consumables (67) Salaries (23)

da Silva *et al*., 2003	Urban/rural	1-25	Yellow fever/ Meningitis A/C	85,925	62,055.44	72.2	Vaccines and consumables (86)
Uzicanin *et al*., 2004	Urban/rural	9 months - 14	Measles	-	Western Cape: 927,287	0.96	Vaccine administration (73%)
				-	Mpumalanga: 781,858	0.87	
Schaetti *et al*., 2012	Urban/rural	≥ 2	Cholera	23,921	760,000	30	Vaccines (67.1) Salaries of international staff (14.4)

Effect on routine immunisation

SIA: Two studies reported the effect of SIAs on routine immunisation and health services. Mounier-Jack *et al.,* reported on a 10 day meningitis A campaign in Mali, in 2010 [36] while Verguet *et al*., reported on a 3 weeks measles campaign in South Africa in the same year [56]. Both SIAs reported a negative effect on routine immunisation (**Table 4**).

Low attendance: Both studies reported a decrease in the number of children attending the child clinics during the vaccination period. Mounier-Jack *et al.,* reported a 71-74% decrease in the number of children vaccinated during the campaign [36] while Verguet *et al.*. reported an 8% decrease in the number of children who were weighed [56].

Redeployment of health staff: During the SIAs, staff in charge of routine immunisations were either deployed as supervisors for the campaign. This led to the closure of routine immunisation services in some districts during the campaign period.

Cold chain management: In Mali, routine vaccines were relocated and stored at the regional and district level so fridges could be made available to store the campaign vaccine [36].

SBV: One study in Rwanda reported on the effect of HPV vaccination on routine immunisation [38] (**Table 4**). According to Torres-Rueda *et al.,* the vaccination activity which lasted 2 days had no effect on routine immunisation services [38]. There was no change in the demand for routine immunisation and health services.

Table 4. Characteristics of included studies reporting effect on routine immunisation

First author and year of publication	Country	Setting	Vaccine	Duration of strategy	Effect
Supplemental immunisation activities					
Mounier-Jack *et al*., 2014	Mali	Urban/rural	Meningitis (PsA-TT)	10 days	Negative effect. Fewer children vaccinated through routine immunisation during vaccination campaign than expected.
Verguet *et al*., 2013	South Africa	Urban/rural	Measles	3 weeks	Negative effect. The use of child health services decreased during the vaccination campaign
School based vaccination					
Torres-Rueda *et al*., 2016	Rwanda	Urban/rural	HPV	2 days	No or minimal effect. Routine immunisation continued during the vaccination campaign with the same demand for services.

DISCUSSION

Both SIAs and SBVs are supplementary EPI programs in many settings, including Africa. Our results show both strategies attain high coverage with SIAs showing greater coverage than SBVs. However, we showed SIAs negatively affect the provision of routine health services, particularly the EPI. In settings like Africa where many resource challenges prevail, the use of both SIAs and SBVs to reach school age and adolescents is questionable.

The high coverage achieved by SIAs reported in this review corroborates with the past successes of smallpox eradication, achieved by complementing EPI with SIAs [57]. Interestingly, coverage of the SIAs was high irrespective of the vaccine and setting, and this attests to the robustness of the strategy. Despite being a new strategy in Africa and being used

for the introduction of HPV vaccines, SBV was able to achieve a high coverage. Our findings are similar to those obtained in HICs where the SBV strategy is more established and used for routine immunisation to this age group [58].

In terms of vaccine coverage, our review supports what is already known: both SIAs and SBV are good options to complement the EPI. However, other factors such as the costs of the strategy, school attendance and existing immunisation policies have to be taken into consideration when deciding which of the two strategies to use in any given setting. Local evidence should be used to evaluate which vaccine delivery strategy is more optimal to reach school age children and adolescents in Africa.

SBV is likely to be more cost-effective than SIAs in countries with high school enrolment. In this review, countries reporting SBV coverage had national primary school attendance rates ranging from 84.2-98.5% during the period the SBV projects were carried out [59]. Similarly, SBV is likely to be optimal in countries with strong inter-ministerial collaboration. Collaboration between health and education sectors is crucial to ensure smooth implementation of SBV strategies [60]. Conversely, SBV strategy is unlikely to be optimal in countries without sufficient financial commitment. School based vaccination has been reported to be an expensive strategy which may be feasible on a small scale but not sustainable at a national level [61]. Our findings support reports that SBV is an expensive strategy.

Supplemental immunisation activities, could be the preferred strategy in countries where campaigns are regularly used to complement infant immunisation. The experience in organising SIAs and community awareness of this strategy can be used to extend the vaccination services to school age children and adolescents. Additionally, the SIAs are able to reach non-school going children. Majority of African countries have millions of non-school going children who will miss vaccines delivered by SBV programs. The negative impact of

SIAs on routine immunisation and health services due to the overlapping of resources (financial and human) and duration of the campaigns is a key concern that should be minimized wherever SIAs are used.

Strengths and limitations

We comprehensively and systematically searched as well as used data from peer-reviewed and non-reviewed sources. This study adhered to the PRISMA guidelines of conducting systematic reviews. Nonetheless, our review had several limitations. Firstly, we missed a lot of information on vaccination coverage because age specific coverage was not reported in some of the retrieved studies. Secondly, we observed a high heterogeneity during the meta-analysis. The heterogeneity was likely due to differences across studies of factors such as the age groups included, study designs, settings and period. This high heterogeneity calls for caution when interpreting the coverage achieved by both strategies. Thirdly, the only vaccine administered via SBV was the HPV vaccine which is a new and more expensive vaccine administered in several doses. These characteristics probably render HPV less acceptable than older vaccines used during SIAs thus accounting for some of the differences observed in terms of SBV coverage. Fourthly, the absence of a harmonised method of analysing the costs of SIAs and SBVs may have accounted for some of the differences in cost observed across countries. Lastly, few studies were found reporting the effect of SIAs or SBV on routine immunisation and health services so our findings may not reflect the true effect.

Implication for policy and research

Local evidence is crucial in the review and development of immunisation policies. Both SIAs and SBVs are routinely used in Africa to vaccinate older children. In settings where school enrolment is low as is the case in many African countries, our results show SIAs may be more effective in reaching school age children and adolescents than SBV. In Africa, the SBV has mainly been tested in the delivery of two or three dose HPV vaccine to adolescent girls while

SIAs have been used for diverse vaccines and on a larger scale. Further research is therefore needed to assess the sustainability of SBV for nationwide delivery of vaccines to school age children and adolescent in resource constraint settings that are prevalent in Africa. As discussed, one vaccine delivery strategy will not be optimal in all African countries. Our results re-iterate the importance of systematic evidence to best inform African authorities on the optimal delivery strategies of vaccines targeting school age children and adolescents into the immunisation programme.

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APPENDIX

SI Checklist. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-26
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19-21
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	na

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

S1 Table. SEARCH STRATEGY

	Search terms
#4	#1 AND #2 AND #3
#3	Angola OR Republic of Angola OR Algeria OR The People's Democratic Republic of Algeria OR Botswana OR Benin OR Dahomey OR Republic of Benin OR Burkina Faso OR Burkina OR Republic of Upper Volta OR Burundi OR Republic of Burundi OR Central African Republic OR Chad OR Republic of Chad OR Cameroon OR Republic of Cameroon OR Republic of Cameroun OR Cote D'ivoire OR Ivory Coast OR Republic of Cote D'ivoire OR Jamahiriya OR Djibouti OR Republic of Djibouti OR Arab Republic of Egypt OR Egypt OR Democratic Republic of the Congo OR DR Congo OR Congo-Kinshasa OR DRC OR Zaire OR Eritrea OR State of Eritrea OR Ethiopia OR Federal Democratic Republic of Ethiopia OR The Gambia OR Republic of the Gambia OR Ghana OR Republic of Ghana OR Gabon OR Gabonese Republic OR Guinea OR Republic of Guinea OR Guinea-Conakry OR Guinea-Bissau OR Republic of Guinea-Bissau OR Kenya OR Republic of Kenya OR Liberia OR Republic of Liberia OR Madagascar OR Republic of Madagascar OR Malawi OR Republic of Malawi OR The Warm Heart of Africa OR Mali OR Republic of Mali OR Mozambique OR Republic of Mozambique OR Libya OR State of Libya OR South Africa OR Tunisia OR Namibia OR Lesotho OR Kingdom of Lesotho OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Kingdom of Morocco OR Nigeria OR Federal Republic of Nigeria OR Sao Tome and Principe OR Democratic Republic of Sao Tome and Principe OR Senegal OR Republic of Senegal OR Seychelles OR Sudan OR Republic of the Sudan OR North Sudan OR Swaziland OR Kingdom of Swaziland OR Ngwane OR Niger OR Republic of Niger OR Rwanda OR Republic of Rwanda OR Sierra Leone OR Republic of Sierra Leone OR Somalia OR Federal Republic of Somalia OR South Sudan OR Republic of South Sudan OR St Helena OR Tanzania OR United Republic of Tanzania OR Republic of Tanganyika and Zanzibar OR Togo OR Togolese Republic OR Uganda OR Republic of Uganda OR Western Sahara OR Zambia OR Republic of Zambia OR Zimbabwe OR Republic of Zimbabwe OR Rhodesia
# 2	Child [MeSH] OR Adolescent [MeSH] OR children OR teenagers
#1	Mass vaccination [MeSH] OR Mass immunization OR Mass vaccination OR vaccination campaigns OR immunization campaigns OR Supplemental immunisation activities OR school immunisation programs OR school vaccination strategies

S1 Form: DATA EXTRACTION FORM

Please fill in the relevant spaces and tick the right box. Indicate the page reference for each data collected in the provided space.

Section A: Details of data extractor

1. Name:_____
2. Extraction date:…… ……. D D M M Y Y Y Y

Section B: Study eligibility

1. Study ID (First author and year):_____
2. Title of study and publication reference:_____

_____

_____

3. Corresponding author's name and contact details:_____

_____

4. Type of study design (eg. RCT):_____
5. Is the study carried out in Africa?.....Yes ☐ No ☐
6. Does the study focus on supplemental immunisation activities or school based vaccination programmes?.....Yes ☐ No ☐
7. Does the study target children aged 5 – 19 years?.....Yes ☐ No ☐
8. Does the study report the following outcomes:

- Vaccination coverage of the strategy used…….....Yes ☐ No ☐
- Cost of vaccines used…….....Yes ☐ No ☐
- Use of routine immunisation and health services before the vaccination activity…… ……..Yes ☐ No ☐
- Use of routine immunisation and health services after the vaccination activity……... ……..Yes ☐ No ☐

Decision:…….Accepted ☐ Rejected ☐

Reason for rejection (if applicable):_____

Section C: Participants

1. Targeted age group:_____

   Gender:……Male ☐ Female ☐ Both ☐

   Setting:…….Rural ☐ Urban ☐ Displaced ☐ Other ☐

Notes:_____

_____

Section D: Intervention/Comparator

1. Type of strategy:……SIA ☐ School based ☐
2. Objective of the strategy:_____

_____

3. Name of vaccine used:_____
4. Duration of the strategy: Start date _____(dd/mm/yyyy)

   End date _____ (dd/mm/yyyy)
5. Number of vaccinators used: _____
6. Profession of vaccinators:……Doctors ☐ Nurses ☐

   Community health workers ☐ Others (specify)_____
7. Method of sensitisation for the vaccination activity: Media ☐ Letters to parents ☐ Town criers ☐ Flyers/Posters ☐ Door to door ☐

   Others (specify) _____

Notes:_____

_____

Section E: Outcomes

1. Number of children/adolescents:

	Male	Female	Total
targeted:	_____	_____	_____
vaccinated:	_____	_____	_____

2. Reported vaccination coverage: _____
3. Number of reported adverse events following immunisation: _____
4. Cost of the vaccine used (in reported currency): _____
5. Cost of the vaccination strategy (if reported): _____

(NB. Duplicate 1-5 if vaccination activity carried out in several sessions)

6. Number of children/adolescents targeted for routine immunisation and health services in the catchment area: _____
7. Number of children/adolescents using routine immunisation and health services before the campaign: _____

8. Number of children/adolescents using routine immunisation and health services after the campaign: _____

Conclusion from authors: _____

_____

_____

Notes: _____

_____

S1 Text. PLOS MEDICINE SUBMISSION GUIDELINES

Style and format

Length	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for Symbol font.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout and spacing	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. List all non-standard abbreviations (with definitions) in alphabetical order in a separate section at the beginning of the manuscript. Keep abbreviations to a minimum.
Reference style	PLOS uses "Vancouver" style, as outlined in the ICMJE sample references. See reference formatting examples and additional instructions below.

Manuscript organisation

Abstract

The Abstract comes after the title page in the manuscript file. The abstract text is also entered in a separate field in the submission system.

The research article Abstract is divided into the following three sections: Background, Methods and Findings, and Conclusions. It should contain all the following elements (items in square brackets are needed only for some study types).

Please use the same format for abstracts submitted as presubmission inquiries. *PLOS Medicine* does not have a specific length requirement for abstracts submitted as part of the manuscript, but no more than 300 words can be submitted in the online interface of the manuscript submission system. If abstracts are longer than 300 words, please submit the first 300 words to the system.

Background

This section should clearly describe the rationale for the study. It should end with a statement of the specific study hypothesis and/or study objectives.

Methods and Findings

- Describe the study participants or what was studied (e.g., patient population, cell lines; be as specific as possible, including numbers of individuals studied). Describe the study design, intervention if applicable, main methods used, primary outcome measure(s), and length of follow up if applicable.
- [If appropriate, include how many participants were assessed out of those enrolled. For survey research, include the response rate.]
- [If critical to the understanding of the paper, describe how results were analyzed, i.e., which specific statistical tests were used.]
- Describe the main outcomes and quantify the results using a measure of precision (e.g., 95% confidence interval). Describe any adverse events.
- Describe the main limitations of the study.

Conclusions

- Provide a general interpretation of the results with any important recommendations for future research.
- [For a clinical trial, provide any trial identification number(s) and name(s) (e.g., trial registration number, protocol number or acronym).]

Introduction

The Introduction should put the focus of the manuscript into a broader context. As you compose the Introduction, think of readers who are not experts in this field. Include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned so that a non-expert reader can delve into these issues further. The Introduction should conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved.

Methods

The Methods should provide enough detail for reproduction of the findings. Protocols for new methods should be included, but well-established methodological procedures may simply be referenced. A full description of the methods should be included in the manuscript itself rather than in a supplemental file.

Methods should also include a section with descriptions of any statistical methods used. The description should conform to the criteria outlined by the Uniform Requirements, as follows:

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

Submit detailed protocols for newer or less established methods. Well-established protocols may simply be referenced. Protocol documents for clinical trials, observational studies, and other **non-laboratory** investigations may be uploaded as supporting information.

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The Results section should include all primary and secondary outcome measures analyzed. The section may be divided into subsections, each with a concise subheading. Tables and figures central to the study should be included in the main paper. The Results section should be written in past tense.

PLOS journals require authors to make all data underlying the findings described in their manuscript fully available without restriction, with rare exception.

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Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Discussion

The Discussion should be concise and tightly argued. It should start with a brief summary of the main findings. It should include paragraphs on the generalizability, clinical relevance, strengths, and limitations of your study.

You may wish to discuss the following points also:

- How do the conclusions affect the existing knowledge in the field?
- How can future research build on these observations and what are the key experiments that must be done?

Acknowledgments

Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution.

Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named.

Do not include funding sources in the Acknowledgments or anywhere else in the manuscript file. Funding information should only be entered in the financial disclosure section of the submission system.

References

Any and all available works can be cited in the reference list. Acceptable sources include:

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References are listed at the end of the manuscript and numbered in the order that they appear in the text. In the text, cite the reference number in square brackets (e.g., "We used the techniques developed by our colleagues [19] to analyze the data"). PLOS uses the numbered citation (citation-sequence) method and first six authors, et al.

Do not include citations in abstracts or author summaries.

Make sure the parts of the manuscript are in the correct order *before* ordering the citations.

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Because all references will be linked electronically as much as possible to the papers they cite, proper formatting of the references is crucial.

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A reference management tool, EndNote, offers a current style file that can assist you with the formatting of your references. If you have problems with any reference management program, please contact the source company's technical support.

Journal name abbreviations should be those found in the National Center for Biotechnology Information (NCBI) databases.

Source	**Format**
Published articles	Hou WR, Hou YL, Wu GF, Song Y, Su XL, Sun B, et al. cDNA, genomic sequence cloning and overexpression of ribosomal protein gene L9 (rpL9) of the giant panda (*Ailuropoda melanoleuca*). Genet Mol Res. 2011;10: 1576-1588. Devaraju P, Gulati R, Antony PT, Mithun CB, Negi VS. Susceptibility to SLE in South Indian Tamils may be influenced by genetic selection pressure on TLR2 and TLR9 genes. Mol Immunol. 2014 Nov 22. pii: S0161-5890(14)00313-7. doi: 10.1016/j.molimm.2014.11.005 *Note: A DOI number for the full-text article is acceptable as an alternative to or in addition to traditional volume and page numbers.*
Accepted, unpublished articles	Same as published articles, but substitute "Forthcoming" for page numbers or DOI.

Source	Format
Web sites or online articles	Huynen MMTE, Martens P, Hilderlink HBM. The health impacts of globalisation: a conceptual framework. Global Health. 2005;1: 14. Available from: http://www.globalizationandhealth.com/content/1/1/14.
Books	Bates B. Bargaining for life: A social history of tuberculosis. 1st ed. Philadelphia: University of Pennsylvania Press; 1992.
Book chapters	Hansen B. New York City epidemics and history for the public. In: Harden VA, Risse GB, editors. AIDS and the historian. Bethesda: National Institutes of Health; 1991. pp. 21-28.
Deposited articles (preprints, e-prints, or arXiv)	Krick T, Shub DA, Verstraete N, Ferreiro DU, Alonso LG, Shub M, et al. Amino acid metabolism conflicts with protein diversity; 1991. Preprint. Available from: arXiv:1403.3301v1. Cited 17 March 2014.
Published media (print or online newspapers and magazine articles)	Fountain H. For Already Vulnerable Penguins, Study Finds Climate Change Is Another Danger. The New York Times. 29 Jan 2014. Available from: http://www.nytimes.com/2014/01/30/science/earth/climate-change-taking-toll-on-penguins-study-finds.html. Cited 17 March 2014.
New media (blogs, web sites, or other written works)	Allen L. Announcing PLOS Blogs. 2010 Sep 1 [cited 17 March 2014]. In: PLOS Blogs [Internet]. San Francisco: PLOS 2006 - . [about 2 screens]. Available from: http://blogs.plos.org/plos/2010/09/announcing-plos-blogs/.
Masters' theses or doctoral dissertations	Wells A. Exploring the development of the independent, electronic, scholarly journal. M.Sc. Thesis, The University of Sheffield. 1999. Available from: http://cumincad.scix.net/cgi-bin/works/Show?2e09
Databases and repositories (Figshare, arXiv)	Roberts SB. QPX Genome Browser Feature Tracks; 2013 [cited 2013 Oct 5]. Database: figshare [Internet]. Available from: http://figshare.com/articles/QPX_Genome_Browser_Feature_Tracks/701214.
Multimedia (videos, movies, or TV shows)	Hitchcock A, producer and director. Rear Window [Film]; 1954. Los Angeles: MGM.

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