Adolescent immunisation in Africa in the decade of vaccines

Leila Hussein Abdullahi (HSSLEY001)

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Supervisor:

Prof Gregory D Hussey

Co-supervisors:

Prof Charles S Wiysonge

Dr Benjamin M N Kagina

Declaration

I, Leila H Abdullahi, hereby declare that the work on which this thesis is based is my original work, except where acknowledgements indicate otherwise.

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

Rationale: There are many public health benefits of targeting adolescent for immunisation. However, and in many settings, adolescents do not get optimal benefits from immunisation. In the decade of vaccines (2011-2020), adolescent immunisation is a topical subject. An up-to-date and synthesized research on adolescent immunisation is lacking.

Overall purpose: The purpose of the PhD thesis was to characterize adolescent immunisation in the decade of vaccines.

Research methods: First, we conducted a comprehensive narrative review of the literature (chapter 2) on adolescent immunisation. Then, we conducted systematic reviews (chapters 3 and 4). One of the systematic reviews assessed the strategies to improve uptake of vaccines among adolescents. The other systematic review assessed the knowledge, attitudes and practices of adolescents and their parents and teachers towards immunisation. Finally (chapter 5), we conducted a cross-sectional study to describe the challenges experienced, and lessons learnt during the introduction of national human papillomavirus (HPV) vaccination programmes in Africa.

Findings: Adolescents are an important group to target with primary, booster or catch up immunisation. Some global initiatives have advocated for adolescent immunisation. Multiple reasons, among them, lack of knowledge and access to immunisation services are barriers to adolescent immunisation. There exist multiple strategies to improve uptake of vaccines among adolescents. For example, health education, financial incentives, mandatory vaccination, and class-based school vaccine delivery. The

evidence suggests that a combination of strategies may be more effective than one strategy alone in enhancing uptake of vaccines by adolescents.

Knowledge of vaccines, immunisation and vaccine preventable diseases was found to be suboptimal among key stakeholders of adolescent immunisation in Africa. We found a disconnect between the level of knowledge on immunisation and the uptake of vaccines, an interesting finding that warrants further research in Africa. Six African countries shared the lessons learnt and experiences during the national introduction of HPV vaccination programmes that targeted adolescent girls. There were similarities in the results among the participating countries. The challenges included: logistical co-ordination, identification of the target population, obtaining political support, integration with other school programmes and stakeholder engagement. A lesson learnt was that schools are a convenient site to access and vaccinate adolescents.

Conclusion: Adolescent immunisation is not routinely practiced in many countries. The introduction of HPV vaccines has created an ideal opportunity to build platforms for adolescent immunisation. Research on adolescent immunisation is limited, more so in low and middle-income countries. Existing research shows a combination of strategies can be used to enhance uptake of vaccines among adolescents. Strong advocacy programmes are required to drive the global agenda of adolescent immunisation, particularly in Africa.

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- **Abdullahi LH**, Kagina BMN, Wiysonge CS, Hussey GD. Improving vaccination uptake among adolescents (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD011895. DOI: 10.1002/14651858.CD011895.
- **Abdullahi LH**, Kagina BM, Cassidy T, Adebayo EF, Wiysonge CS, Hussey GD. Knowledge, attitudes and practices on adolescent vaccination among parents, teachers and adolescents in Africa: a systematic review protocol. Systematic Reviews 2014;3:100. DOI: 10.1186/2046-4053-3-100.

Abstract presented at a congress with data from this thesis

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Abbreviations

AEFI	Adverse events following immunisation
AEOI	Adverse effects of the intervention
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CBAs	Controlled before-after studies
CDC	Centre for Disease Control and Prevention
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CERQual	Confidence in the Evidence from Reviews of Qualitative research
CI	confidence intervals
CME	Continuing medical education
CORNET	National network of paediatric continuity clinics
DARE	Database of Abstracts of Reviews of Effectiveness
DoV	Decade of Vaccines Collaboration
DPT	Diphtheria pertussis tetanus
EHR	Electronic health record
EPI	Expanded Programme on Immunisation
EPOC	Cochrane Effective Practice and Organisation of Care
GAVI	Global Alliance for Vaccines and Immunisation
GIVS	Global Immunisation Vision and Strategy
GRADE	Grades of Recommendation, Assessment, Development and Evaluation

GR-PBRN	Greater Rochester practice-based research networks
GVAP	Global Vaccine Action Plan
HAV	Hepatitis A virus
HBM	Health Belief Model
HBV	Hepatitis B Virus
HepB	Hepatitis B
HIC	High-income countries
HIT	Health information technology
HIV	Human immunodeficiency virus
HPV	Human Papillomavirus
HREC	Humans Research Ethics Committee
ICC	Intra-cluster correlation coefficient
ICTRP	International Clinical Trials Registry Platform
IMD	Invasive Meningococcal Disease
ITS	Interrupted time series studies
LMICs	Low and middle-income countries
M.tb	Mycobacterium tuberculosis
MCV	Meningococcal conjugate vaccines
MD	Mean differences
MDG	Millennium Development Goal
MDG4	Fourth MDG goal
Men A	Neisseria meningitidis group A
MeSH	Medical subject headings

MMR	Measles, mumps and rubella
MOC	Maintenance of certification programmes
NIH	US National Institutes of Health
NITAG	National Immunisation Technical Advisory Groups
NRF	National Research Foundation
PCV	Pneumococcal conjugate vaccine
PPSV	Polysaccharide pneumococcal vaccine
RCT	Randomised control trials
RQ	Rhetorical questions
RR	Risk ratios
SAGE	Strategic Advisory Group of Experts
SDG	Sustainable Development Goals
SLVC	School-located vaccination clinics
TB	Tuberculosis
Td	Diphtheria
Tdap	Tetanus, diphtheria and pertussis
UCT	University of Cape Town
UN	United Nations
UNPF	United Nations Population Fund
UNICEF	United Nations Children Fund
USA	United States of America
VACFA	Vaccines for Africa Initiative
VPDs	Vaccine preventable diseases

VZV	Varicella zoster virus
WHO	World Health Organisation

Definition of terms

Adolescent	Any child from 11 to 19 years of age
Immunisation gap	Lack of immunisation with WHO recommended vaccines
Knowledge	Understanding of any related topic on adolescent vaccines
Attitude	The feelings towards adolescent vaccines, as well as any preconceived ideas that one may have towards vaccination.
Practice	The ways in which one demonstrates the knowledge and attitude (and any other influences) through actions.

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Chapter 1

General introduction

About this chapter:

The chapter describes the rationale and goal of the PhD project. We also provide a preview of different studies conducted, including the methods used to achieve the goal of the project. Highlights of the key findings and possible policy implications are also provided in this chapter.

Immunisation is a key global public health strategy used to combat vaccine preventable diseases (VPDs) in all population groups. Routine immunisation services delivered via the Expanded Programme on Immunisation (EPI) target children because they are the most vulnerable population group. (1, 2). Currently, adolescents, an increasing population group (3) does not get optimal benefits from immunisation. The main reason for this is the absence of structured programmes to vaccinate this population group. Furthermore, immunisation research on optimal strategies to reach and vaccinate adolescents is limited. Therefore, the research focus for this thesis is to generate new and relevant knowledge on adolescent immunisation. The knowledge will be used by researchers and policy makers as a starting point to develop or strengthen adolescent immunisation programmes.

Following the eradication of small pox in 1979 (4, 5), global immunisation efforts have prioritized the eradication of polio (6), elimination of measles (7) and neonatal tetanus (8) as well as the control of several VPDs (9). Crucially global eradication, elimination

and control, of VPDs must involve immunisation of all population groups, including adolescents. Therefore, targeting adolescents for immunisation should be a key global public health strategy in the control of VPDs. For example, a vaccine against human papillomavirus (HPV) is primarily targeted to preadolescent (9-12 years old) and adolescent (13-19 years old) populations. Optimal uptake of immunisation services by adolescents is critical to control VPDs. Synthesized research on effective immunisation strategies that can enhance uptake of vaccines by adolescents is limited.

Therefore, the goal of this PhD thesis was to develop a concise review highlighting the critical issues on adolescent immunisation as well as conduct an evidence synthesis on the topic. Specific evidence synthesis focused on the strategies or interventions to achieve improved uptake of adolescent vaccines. Another focus of the evidence synthesis was the knowledge, attitudes and practices (KAP) by adolescents on the immunisation. Finally, we characterized experiences, challenges and lessons learnt during the introduction of national routine adolescent immunisation with HPV vaccines by a few African countries.

To achieve the goal of this thesis, we used a mixed method approach. First, we conducted a narrative review on adolescent immunisation. We chose this method as to our knowledge, there was no review that gave a detailed insight on the topic. In this narrative review (chapter 2), we defined the adolescent immunisation gap and the rationale for providing specific vaccines to adolescents as part of a broader strategy to control VPDs. In addition, we provided insights on the need to develop adolescent immunisation platforms. As some countries have already introduced routine adolescent immunisation, we wanted to collate the existing knowledge on the topic.

Second, we conducted an evidence synthesis on strategies or interventions used to improve uptake of vaccines among adolescents. For this study (chapter 3), we conducted a systematic review through the Cochrane Effective Practice and Organisation of Care (EPOC) group. Third, we conducted a Campbell style systematic review (chapter 4) on the knowledge, attitudes and practices (KAP) of adolescents, their parents and their teachers towards immunisation. In chapter 4, we restricted the evidence synthesis to Africa, a continent where routine adolescent immunisation is at early stages of development. The introduction of HPV vaccines targeting adolescents is a key developmental milestone for adolescent immunisation in Africa.

Fourth, and finally, we conducted a cross sectional study (chapter 5) to describe the experiences, challenges and lessons learnt by key partners during HPV vaccine introduction in Africa. The HPV vaccination programme targeted preadolescent and adolescent girls. A questionnaire was administered to the key partners from eight African countries that had successfully introduced HPV vaccines at a national level by the end of 2016. This study involved in-depth face-to-face interviews and self-administered online questionnaires as qualitative methods for data collection.

We were able to achieve the goal of the PhD thesis using the mixed method approach. From the narrative review, we were able to describe in detail the rationale of implementing adolescent immunisation, including the specific vaccines required for this population group. From the Cochrane review, we successfully generated and evaluated the available evidence on the effects of different interventions to improve uptake of vaccines by adolescents. The systematic review on KAP showed the paucity of research information on the topic in Africa. Nevertheless, available evidence showed

that, although adolescents had low levels of knowledge on immunisation, this population group was receptive to vaccination, particularly HPV vaccination. The cross-sectional study showed similarity in the lessons learnt, experiences and challenges across the participating countries. Fundamentally, the challenges were mainly logistical.

Taken together, studies in this thesis have contributed to new knowledge on adolescent immunisation. Our narrative review advocates for governments to prioritize adolescent immunisation programmes. The findings from the Cochrane review are valuable to immunisation policy makers interested in improving the uptake of immunisation services by adolescents. The KAP study shows gaps in research on adolescent immunisation in Africa. A disconnect between the level of knowledge on immunisation versus uptake of vaccines was an interesting finding that warrants further research in Africa. Many African countries are in the process of introducing national routine HPV vaccination targeting preadolescent and adolescent girls. The similarity in lessons learnt, experiences and challenges during the introduction of HPV vaccine validates the critical need to disseminate adolescent immunisation research in Africa. This information is useful for other countries in Africa that are planning to introduce HPV vaccination programmes, and possibly, other adolescent vaccines.

Chapter 2

A Literature review on adolescent immunisation: past, present and future

About this chapter:

In this chapter, we review the global vaccination initiatives focussing on adolescent immunisation. We also introduce and define the concept of adolescent immunisation gap as well as provide a detailed insight on the following: importance of adolescent immunisation; need to develop primary adolescent vaccination platforms; and, the barriers preventing the optimal uptake of adolescent vaccines. We also discuss some specific vaccines recommended for adolescents.

Publication: A slightly modified version of the chapter will be submitted to the Journal of Adolescent Health.

Abstract

Globally, uptake of vaccines by adolescents is suboptimal despite evidence showing that vaccines are among the most successful and cost-effective public health interventions. In many settings, there are no platforms to conduct adolescent immunisation. Furthermore, immunisation programmes targeting adolescents are relatively new in LMICs where many health challenges are endemic. Significantly recent global vaccination initiatives advocate for adolescent immunisation. There are three main reasons why adolescents need to be vaccinated with catch-up and booster vaccines: achievement of primary immunisation of new vaccines, catch-up on missed vaccinations and boosting of waning immunity.

Prior to achieving optimal uptake of vaccines by adolescents in LMICs, policy formulators will first have to understand the multiple factors that may enhance or reduce uptake of the vaccines in this age group.

Currently and in many settings, new adolescent immunisation services and other adolescent health interventions are standalone programmes. Hence, for future adolescent health programmes to succeed it will be vital that there is integration with the Expanded Programme on Immunisation (EPI).

This is a comprehensive review on the global literature about adolescent vaccination with the aim to describe: the immunisation gap during the adolescence period; the importance of adolescent immunisation; the need to develop primary adolescent vaccination platforms; and, the barriers preventing the optimal uptake of adolescent vaccines.

Key words

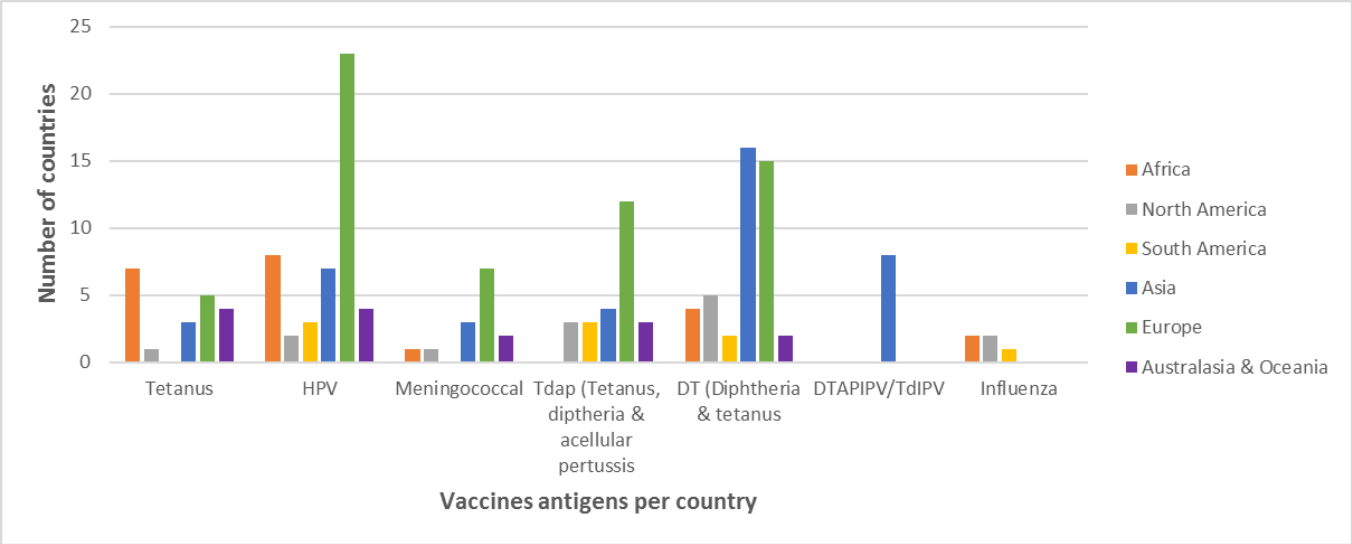
Immunisation gap, adolescent, vaccination platforms, uptake, barrier and importance

Adolescent immunisation: Introduction

Immunisation is one of the most cost effective public health strategies utilised to promote health (10). Immunisation prevents an estimated 2.5 million deaths annually and millions more lives are spared from the devastating morbidity associated with VPDs (11, 12). The Global Alliance for Vaccines and Immunisation (GAVI) projected that vaccinations administered between 2011 and 2020 will avert more than 23 million potential deaths (13).

Globally, the World Health Organisation (WHO) launched the EPI in 1974 (5). The EPI remains the main platform used to vaccinate children early in life (5, 9). In contrast, for adolescents and adults, there are no globally structured public health vaccination platforms (14). Between 2010 and 2018, some countries introduced adolescent immunisation but few of these countries are in Africa (**Figure 1**) (15). Recent global vaccination initiatives (16, 17) advocate for life course (including adolescents) immunisation. These vaccination initiatives have enabled several countries in Africa to commit to adolescent immunisation.

Figure 1: Countries that introduced vaccine antigens targeting adolescents 2015-2018



Source: http://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/ (15).

Global vaccination initiatives

To effectively control VPDs, there is global appreciation that immunisation of adolescents in all settings must be improved. Recent global vaccination initiatives have emphasized the need to expand immunisation beyond the childhood phase. Below, we describe the major global vaccination initiatives and highlight those with an emphasis on adolescent immunisation.

Expanded Programme on Immunisation

The global effort to use vaccination as a public health intervention started when EPI was launched by the WHO in 1974 (5). Subsequently, small pox was officially eradicated in 1979 (4, 5, 9). The EPI, which focusses on infants and young children has achieved notable successes. For example, global average vaccine coverage rates for vaccines

containing diphtheria, pertussis and tetanus antigens increased from less than 5% in 1974 to over 85% in 2018 (18).

To maximize the benefits of immunisation, there has been efforts to integrate EPI with other health services. For example, with screening programmes, such as eyesight, hearing, oral hygiene and deworming (19). The integration of EPI with these other health services has been used as a strategy to address some of adolescent health needs (20, 21). However, specific immunisation services focused to adolescents remain limited in the majority of LMICs.

Millennium Development Goals

In the year 2000, the global community made a historic commitment to eradicate extreme poverty and improve the health and welfare of the world's poorest by 2015 (22). The commitment was embodied in the United Nations (UN) Millennium Development Goals (MDGs) that had eight goals (23). Of these goals, specifically relevant to immunisation was the fourth MDG goal (MDG4) that committed governments to reduce mortality rates among children under five by two-thirds between 1990 and 2015 (23). Immunisation was considered an essential component of MDG4 (23). The MDG4 focussed on immunisation of infants and children, but not adolescents.

Global Alliance for Vaccines and Immunisation

The GAVI was established in 2000 (24). The aim of GAVI is to create equal access to new and underused vaccines for children, particularly in poor settings (24). By 2016, several countries (25) were beneficiaries of GAVI support in many ways among them,

the introduction of new vaccines: Pneumococcal Conjugate Vaccine (PCV) and the rotavirus vaccine being an example (25).

Working alongside WHO and United Nations Children Fund (UNICEF), the GAVI initiative has supported the improvement of services such as adequate, predictable, and affordable supply of vaccines (1, 26). In 2016, the GAVI revised the initiative's strategic plan to include building of sustainable immunisation programs and increasing equitable use of vaccines in lower-income countries (27). The GAVI is supporting several LMICs to introduce HPV vaccination in adolescent populations (28, 29).

Global Immunisation Vision and Strategy

Building on the success of EPI, WHO and UNICEF launched the Global Immunisation Vision and Strategy (GIVS) in 2005 (30, 31). The primary objective of GIVS was to achieve a two-thirds reduction of mortality and morbidity associated with VPDs by 2015 (30, 31). To achieve this objective, the GIVS advocated for the expansion of immunisation services beyond the traditional paediatric focus (31). The GIVS recognised the benefits of providing immunisation services to adolescents and adults.

The Decade of Vaccines Collaboration

In 2010 at the World Economic Forum, the Decade of Vaccines Collaboration (DOV) initiative was launched with a seed fund of USD10 billion from Bill and Melinda Gates Foundation over the next 10 years (32). The aim of the initiative was to bring the benefits of vaccines to all people no matter where they live between 2010 and 2020 (32). The DOV was central to developing the Global Vaccine Action Plan (GVAP).

The Global Vaccine Action Plan

In 2012, the World Health Assembly endorsed the Global Vaccine Action Plan (GVAP) 2011–2020 (16, 33). The GVAP is guided by six principles: country ownership; shared responsibility and partnership; equity; integration; sustainability; and, innovation (16). Improving equity, routine vaccination coverage, as well as targeting the hard-to-reach and marginalized populations are the key focus areas in the GVAP framework (16). GVAP 2011-2020 states that "the benefits of immunisation should be more equitably extended to all children, adolescents and adults" (16). The GVAP is thus another global initiative that highlights the need for adolescent immunisation.

Sustainable Development Goals

In 2015, the UN General Assembly established the Sustainable Development Goals (SDGs) which included 17 universal goals, 169 targets, and 230 indicators for a period between 2015 and 2030 (17). The SDGs builds on the success and momentum of the MDGs, but have a broader scope (17). Health is a core element of the SDGs and the aim of improving vaccination programmes is well stated (17, 34). Specifically, SDG goal three calls for governments to ensure healthy lives and promote well-being for all ages (34). The SDG goal three is in line with addressing adolescent immunisation gap: calling for an expansion of the EPI schedule.

Summary on global vaccination initiatives

Since 1974, several global initiatives that promotes immunisation have been developed, starting with EPI to the SDGs in 2015. The EPI, MDGs, GAVI initiatives, broadly focused in the main on childhood immunisation and not adolescents. Promoting equity

has become a key strategy for improving routine vaccination coverage for all, as well as for hard-to-reach and marginalized populations. Thus, the introduction of GIVS, GVAP and the SDGs, which promote expansion of immunisation services beyond the traditional paediatric scope, is welcomed. The WHO, as the global leading agency in setting immunisation and vaccines-related policies, now advocates for immunisation for all, including adolescents.

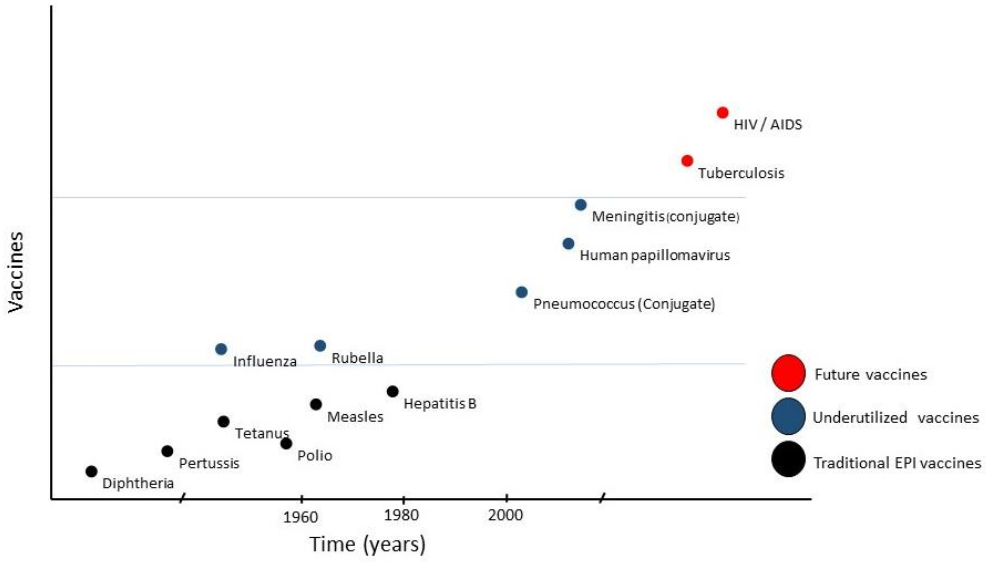
Adolescent immunisation gap

The WHO defines adolescents as young persons aged 10 to 19 years (35). The adolescence phase has three stages of development that can be categorised as early (10-13 years), mid (14-16 years) and late (>17years) (3, 35). According to the 2014 United Nations Population Fund (UNFPA) report, adolescents and youths account for 28% of the total global population (3). Therefore, providing optimal health care to this large and young population is crucial for sustainable development, necessary to fulfil the vision of the GVIS, GVAP and SDGs.

The 10-13 years old group is the primary immunisation population for new vaccines like HPV while the 10-17 years old group is targeted for booster immunisation with WHO recommended vaccines like Tdap (29, 36). Over the last decade, the number of recommended vaccines for adolescents has grown substantially (36-38). Currently, there are over 13 vaccines available globally that are recommended for use among adolescents (36). Later in this review, we discuss the recommended schedules for these vaccines. The 13 recommended adolescent vaccines include traditional, underutilised and future vaccines (**Figure 2**) (36). Absence of providing the recommended vaccines to the adolescent population create an immunisation gap.

Traditional vaccines refer to measles, pertussis, tetanus, diphtheria, polio and hepatitis B (2). Vaccination coverage of these vaccines are used as a standard measure of the programme's ability to reach the target population. The term "under-utilised vaccines" refers to vaccines that have been available for several decades in High-Income Countries (HICs) but are not universally available in LIMCs. Examples are haemophilus influenza type b (Hib), influenza and HPV vaccines (39, 40).

Figure 2: Past, current and future adolescent vaccines



Source: *http://www.who.int/immunization/policy/Immunization_routine_table1.pdf?ua=1* (36)

Why vaccinate adolescents?

There are many benefits of vaccinating adolescents. Firstly, high vaccination coverage among adolescents is likely to improve population herd immunity. Vaccination during

infancy and childhood may not induce lifelong immunity, and booster doses may, therefore, be required during adolescence (41, 42). In the absence of boosting, the vaccine-specific immunity among adolescents may decline because some vaccines administered early in life induce short-lived immunity that wanes over time, leading to a susceptible population later in life (43-45). For example, a population-based study showed a declining immunity during adolescence in individuals who received a single dose of varicella vaccine in childhood (46).

In situations of waning immunity, it is recommended that booster doses of the vaccines previously administered in childhood should be provided later in life to maintain vaccine-induced immunity (42-45). For example, with reports showing changing epidemiology of pertussis (47), the dogma of lifelong protection after pertussis childhood immunisation appears incorrect (47). Pertussis infections cause significant morbidity to adolescents and young infants (47, 48), thus the need for a booster dose during adolescence period.

The second benefit is to catch-up adolescents who may have missed vaccination during early childhood. Current WHO guidelines recommend vaccinating adolescents, who have not previously received vaccines against measles, mumps, rubella, varicella, hepatitis B, and polio (36, 43-45). Despite the recommendations, in Africa, adolescent vaccination coverage remains largely suboptimal and poorly documented, save for HPV vaccine in some countries (2).

The third benefit of vaccinating adolescents is the potential to reduce the morbidity and mortality associated with VPDs among children (43-45). The VPDs in adolescents increase the risk of infections among unvaccinated or under-vaccinated children, as the

adolescents can transmit VPDs (42, 44, 45, 48). For instance, in countries where Meningococcal B and C disease predominated, meningococcal carriage prevalence peaked at 23.7% in 19-year-olds, versus 4.5% in infants, 7.7% in 10-year-olds, and 7.8% in 50-year–olds (49). Thus, in some settings, adolescents have the highest burden of meningococcal carriage compared to infants and children. Therefore, adolescents should be prioritized for booster vaccination against *Neisseria menengitidis* (48, 49).

Invasive meningococcal disease (IMD) risk is associated with the carriage of *Neisseria meningitidis* pathogen and closeness of interpersonal contacts of asymptomatic carriers; therefore, university settings are an ideal environment for meningococcal transmission (50). Among first year university students, the IMD prevalence in an institution increased from 6.9% on day 1 to 23.1% on day 4 in the first week of term in October, and was up to 34.2% in some groups in December (51).

The fourth benefit of immunising adolescents is the reduction of the school absenteeism which can interfere with continuity in education and healthy development towards adulthood (41, 44, 45). Influenza infections are an important cause of excess school absenteeism in adolescents (52). Due to seasonal influenza, school going adolescents miss important academic time in school and their parents often miss work or other activities to care for the sick offspring (52). The classic study by Monto et al. demonstrated that vaccinating 86% of all school children and adolescents against influenza resulted in a reduction of student absenteeism during influenza outbreaks (53). Hence, reduction of morbid events during adolescence period can reduce the absenteeism associated with illness (41, 44, 45).

The fifth benefit is that adolescents are at risk of developing several VPDs, including HPV, a virus that is associated with onset of sexual activities, likely occurring during this age period. Infection with HPV during adolescence is mostly asymptomatic. The symptoms are mainly detected later in adulthood. It must be stressed that relevant evidence must guide the prioritization of specific vaccines targeting adolescents. For example, booster vaccination due to waned immunity following childhood vaccination may not be a priority in settings where subsequent exposure to infection is likely to stimulate anamnestic response and subsequent protection from the VPD. In contrast, high coverage for primary vaccination with novel vaccines (e.g HPV) should be prioritized in settings where HPV vaccination programme is not optimal or non-existent. Therefore, providing HPV immunisation during adolescence and not any other phase of life is currently the most optimal strategy to control cancers associated with the virus (29). Furthermore, vaccines currently under development, like those against human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (M.tb), are likely to target adolescents (37). Therefore, studies focussing on improved understanding of adolescent vaccination are critical and will become increasingly relevant in the future.

The last reason is an indirect benefit of adolescent immunisation that is also observed in the case of HPV vaccination. Evidence shows that optimal HPV vaccination coverage in girls alone can protect boys from HPV associated illnesses (54, 55). Other vaccines with indirect benefit are those against pneumococcus and influenza (56, 57).

Elimination and eradication of VPDs is the quintessential public health goal for an immunisation programme. For many VPDs, this public health goal will be achieved by complementing the existing immunisation services with the implementation of

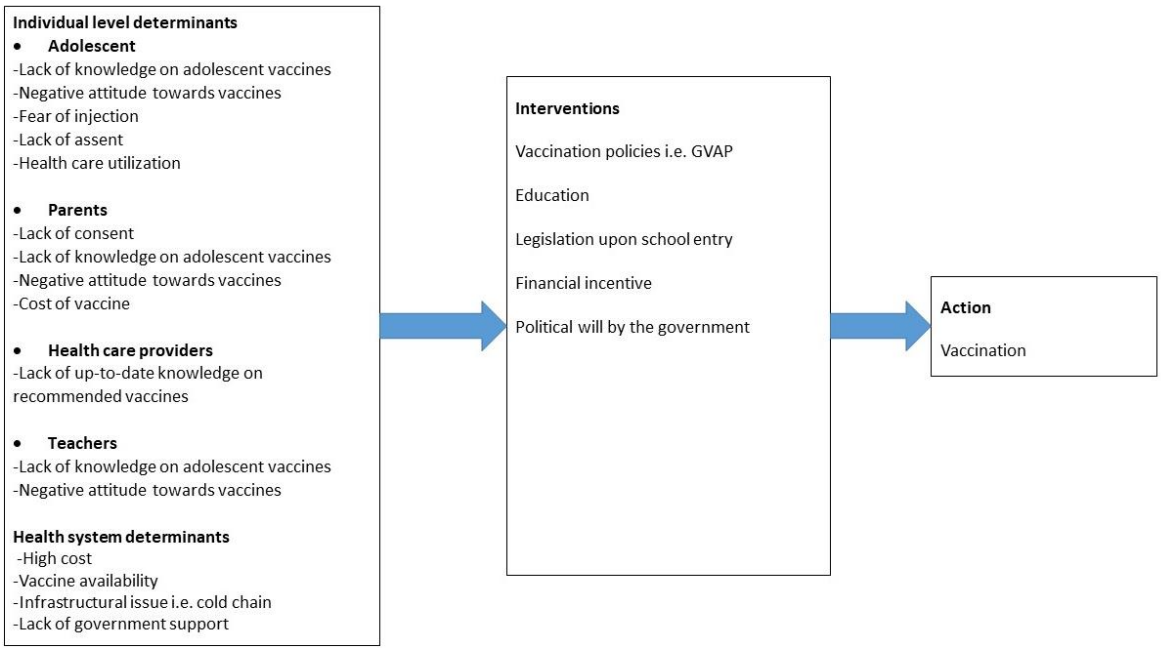
adolescent immunisation (58). Despite the global recommendations to vaccinate adolescents, several hurdles have prevented the closure of the adolescent immunisation gap in many settings. These hurdles include lack of optimal knowledge, attitude and practices towards immunisation, vaccines and VPDs. Other hurdles include health infrastructural inadequacies, and financial constraints (59-61). These hurdles need to be addressed for immunisation programmes to introduce adolescent vaccination or improve the uptake of adolescent vaccines.

Challenges preventing optimal uptake of adolescent vaccines

Adolescent immunisation against pathogens such as HPV, *Neisseria menengitidis Clostridium tetani*, *Corynebacterium diphtheriae*, *Bordetella pertussis* and poliovirus have been successfully rolled out in some HICs (2, 62). Some LMICs are also making steady progress in the introduction and implementation of adolescent immunisation (62). The delay in the introduction of adolescent immunisation in LMICs could be due to many reasons such as awareness, resource limitations and lack of political will from the governments (60, 61).

Barriers to achieving optimal vaccination uptake among adolescents are multifactorial. The barriers can be broadly categorised into individual-level determinants and health system determinants. **Figure 3** shows a conceptual framework summarizing the factors that could lead to suboptimal uptake of adolescent vaccines as well as possible interventions. Understanding these challenges will be the first step to design interventions aimed at improving the uptake of immunisation services targeted to adolescents.

Figure 3: Potential factors influencing the uptake of immunisation



Source: Adapted from conceptual model developed by Briss et al 2000 (63).

Healthcare workers play a vital role in promoting vaccination (64). However, in many settings, adolescents usually visit health care workers only when unwell, and so, there are limited opportunities to inform the adolescents about the importance of immunisation (64, 65). In addition, most LMICs lack or have poor infrastructural programmes specific for delivering immunisation services to adolescents, leading to less contacts between adolescents and the healthcare system (65-67).

Another challenge that hinders optimal adolescent vaccine uptake is lack of knowledge about immunisation, vaccines and VPDs among key role players like parents, teachers, adolescents and health care providers (60, 61). For example, due to lack of accurate immunisation knowledge among parents, they may decline to give parental consent for their adolescents to be vaccinated (59). This may in turn lead to low vaccine uptake.

Evidence from two systematic reviews discussed the importance of immunisation knowledge among key stakeholders in relation to improving adolescent vaccination uptake (61, 68). One of the systematic review showed a high acceptance and uptake of HPV vaccine by the targeted population, in settings where adolescents, parents and teachers had positive attitudes and practices towards the vaccines (61). Therefore, adequate knowledge and positive attitudes towards vaccination among parents, teachers and adolescents is crucial to improve uptake of vaccines among adolescents (61).

High cost of new vaccines and unavailability of vaccines are known barriers to achieving high vaccination coverage among adolescents in LMICs (69, 70). In a 2014 modelling study, the cost of delivering three doses of HPV vaccine in South Africa was estimated to be ZAR510 (US$50) per learner in a government school where the fees are subsidised (69). Ironically, in the private sector where the parents pay out of pocket, the cost of the same HPV vaccine was US$130 for the three doses (69). GAVI recognizes the benefits of adolescent immunisation against HPV and therefore, the initiative has included HPV vaccines in the portfolio of new vaccines that countries can seek support (28). Hence, LMICs, which are GAVI-eligible have now immensely improved their chances of introducing HPV vaccination (28, 71). By the end of 2017, six countries were approved for GAVI HPV national vaccine introduction support: Bolivia, Guyana, Honduras, Rwanda, Sri Lanka and Uganda (25).

Another factor that may influence vaccine uptake among adolescents is misinformation on vaccine safety. For example, adolescents' fear of adverse events following

vaccination may cause less interest in vaccination which in turn causes the adolescent to refuse assenting to immunisation, resulting to reduced vaccination coverage (72).

Recommendations on adolescent immunisation

The WHO recommends routinely vaccinating 11 or 12 years old with meningococcal conjugate vaccines (MCV), the combined tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, influenza and the HPV vaccines (36). Additionally, WHO recommends vaccination against measles, mumps, rubella, varicella, hepatitis B, and polio for those who were previously not fully immunised (**Table 1**) (36). Furthermore, WHO also recommends vaccines for high-risk adolescents as highlighted in **Table 1** (36). Future adolescent vaccines may include those against tuberculosis (TB) and HIV.

Table 1: WHO recommended routine immunisation schedule for children aged 10 to 18 years (June 2016)

Vaccines	Disease targeted	10yrs	11-12yrs	13-15yrs	16-18yrs
Vaccines for routine administration to all Adolescents					
Meningococcal conjugate vaccine	Meningitis		1st dose		booster
Tetanus, diphtheria, & acellular pertussis (Tdap) vaccine	Tetanus, diphtheria, & pertussis		1st dose		
Human papillomavirus (HPV) vaccine	Human papillomavirus		3 dose series		
Influenza vaccine (live attenuated influenza vaccine or inactivated influenza vaccine)	Influenza	Annual vaccination 1 dose only			
Catch-up vaccines for adolescents not fully immunized previously					
Inactivated poliovirus (IPV) vaccine	Polio	1 dose			
Measles, mumps, rubella (MMR) vaccine	Measles, mumps, rubella (MMR)	1 dose			
Varicella (VAR) vaccine	Varicella (VAR)	1 dose			
Hepatitis A (HepA) vaccine	Hepatitis A (HepA)	1 dose			
Hepatitis B (HepB) vaccine	Hepatitis B (HepB)	1 dose			
Vaccines for certain high-risk adolescents					
Pneumococcal conjugate vaccine	Pneumonia	1 dose			
Hepatitis A (HepA) vaccine	Hepatitis	1 dose			
Meningococcal conjugate vaccine	Meningitis	1 dose			

Source: World Health Organisation (36).

Globally, WHO leads the development of evidence-based immunisation policy recommendations. The independent Strategic Advisory Group of Experts (SAGE) on Immunisation is tasked with providing guidance to WHO on global policy recommendations and strategies (73). The WHO has placed a high priority on each

country to take ownership in the development of national decision-making process regarding immunisation and vaccine related issues (73). The ownership at national level is aided by presence of functional National Immunisation Technical Advisory Groups (NITAGs) (74).

To recommend the introduction of adolescent vaccines among adolescents, NITAGs need to use evidence-based approaches. Such approaches include development of a clear policy question as well as recommendation framework (74). Important elements to consider for the recommendation framework on the introduction of vaccines for adolescents are the local epidemiology of VPDs and socio-cultural and economic factors (74).

Recommended adolescent vaccines:

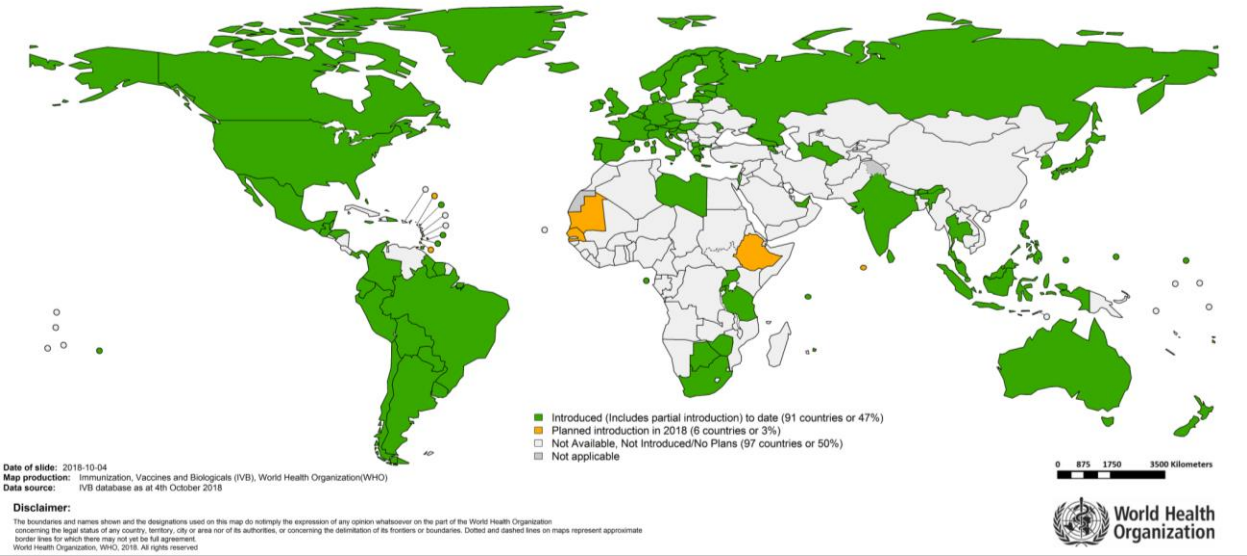
Human Papillomavirus Vaccine

The HPV vaccine is administered to prevent HPV infection and cervical cancer (75-77). The HPV causes virtually all cases of genital warts and cervical cancer (29). Cervical cancer is the second most commonly diagnosed cancer in women globally and the disease is highly prevalent in LMICs (78).

The risk for HPV infection is high soon after sexual debut and there is a peak prevalence of 24% in women younger than 25 years (29, 78, 79). Reports suggest the estimated HPV prevalence globally among women is 11.7% (79). By region, the highest reported adjusted HPV prevalence is in sub-Saharan Africa, with a prevalence of 24% (79).

Since 2006, three vaccines are available, namely Cervarix®, Gardasil® and Gardasil 9®. The vaccines are recommended for use in young women and these vaccines target at least two of the high-risk HPV types (16 and 18) (29, 77-79). Despite the HPV vaccines' proven safety, efficacy and cost-effectiveness, Africa and Asia are the two continents that as of 2018 lagged in the introduction of the HPV vaccines, (see **Figure 4**) (80).

Figure 4: Global introduction of human papillomavirus vaccination programme



Source: https://www.who.int/immunization/monitoring_surveillance/data/en/ (80).

Meningococcal Conjugate Vaccines

The MCV are administered to prevent invasive meningococcal infections caused by *Neisseria meningitides* (81). Six serogroups A, B, C, W135, X and Y of *Neisseria meningitides* can cause epidemics (81). Crowding is an important risk factor associated with an increased risk for meningococcal disease (81).

Meningococcal disease occurs primarily in children and adolescents (81). In Africa, major epidemics have been attributed to serogroup A and occur in the African "meningitis belt" (81). In the African "meningitis belt", the WHO definition of a meningococcal epidemic is >100 cases/100 000 population/year (81). An outbreak outside the meningitis belt may be defined as a substantial increase in IMD (81).

The target age for meningococcal A vaccine is 1-29 years (81). As of 2017, 21 countries in the African meningitis belt had introduced the vaccine at a national level with the hope of eliminating meningococcal A epidemics from this region (82).

Tetanus, Diphtheria, and Pertussis Vaccines

The Tdap (tetanus, diphtheria, and acellular pertussis) vaccine is administered to prevent tetanus, diphtheria and pertussis (83, 84). Interestingly, pertussis had been largely a forgotten public health disease after the introduction and attainment of high coverage for routine pertussis immunisation programmes (83, 84). However, pertussis continues to be a public health concern despite high vaccination coverage among infants.

Pertussis disease has been reported to show resurgence in some countries (83, 84). There are many reasons for this including a rapid waning of the immunity after childhood vaccination, particularly with acellular vaccines (83). The Tdap vaccine contains a reduced dose of the pertussis antigens and is approved for use in adolescents and adults (36, 84). Adolescents and adults serve as the reservoir of pertussis infection and source of transmission to infants who are too young to receive a full series of pertussis immunisations (83).

Pertussis is estimated to cause 50 million cases and 300 000 deaths every year (85). Case-fatality rates in developing countries are estimated to be as high as 4% in infants (85). The WHO recommends a booster dose of the tetanus, diphtheria and acellular Tdap vaccine at age 11-12 years old (36). Currently and globally, only a few countries have implemented the Tdap vaccine among adolescents (15, 80).

Influenza

Influenza A and B viruses are respiratory pathogens that causes seasonal influenza epidemics and sporadic outbreaks (86) . Influenza occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children (86, 87). In temperate climates, seasonal epidemics are experienced mainly during the winter while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly (86, 87).

The influenza vaccine is administered to prevent infection caused by the influenza virus (86). Influenza vaccination is recommended on an annual basis for all persons older than 6 months including adolescents (36). Influenza vaccine uptake is generally low, even among the high-risk groups such as pregnant women (87). For instance, in United States during the 2011- 2012 influenza season, the vaccination rate for individuals aged 5 to 17 years was 45.1% (87). Few, if any, African countries have a policy for adolescent influenza vaccination.

Additional adolescent vaccines:

In addition to the above vaccines, WHO guidelines recommend vaccination against measles, mumps, rubella, varicella, hepatitis B, and inactivated polio for those who have not previously received these vaccines as a catch-up dose (36).

Measles, mumps and rubella (MMR) is a live attenuated vaccine. Measles is a highly infectious respiratory disease that can result in severe to permanent complications while mumps virus causes an acute viral syndrome with parotid swelling (88, 89). The rubella virus causes German measles, which is a generally mild infection with a characteristic rash (90). Adolescents who are not previously vaccinated should get two doses of MMR while those who only received one dose previously, should get the second dose as a booster (36).

Varicella (chickenpox) is an acute, highly contagious disease caused by the varicella zoster virus (VZV) and is widely distributed (91). Burden of severe disease and mortality due to varicella and herpes zoster is substantially lower than that of other currently VPDs (91). However, the public health value of varicella vaccination in lowering morbidity and mortality due to VZV, particularly in vulnerable population groups, is well established (47, 91). Therefore, it is recommended that adolescents who were not fully vaccinated or have no history of immunity from the disease should get two doses of the vaccine against varicella (36).

Polio is a highly infectious disease caused by a virus that invades the nervous system (92). Most individuals infected with the virus will not experience any symptoms at all (92). Since widespread use of the vaccine globally in the 1950's, polio has been

eliminated in most countries (92). According to WHO, the polio virus circulates among the world's poorest and most marginalized communities particularly in Pakistan, Somalia, Afghanistan and Nigeria (93), and recently, Democratic republic of Congo (94). Therefore, it is recommended that adolescents who did not receive a complete vaccine series as a child should complete the series (36).

Hepatitis A is a contagious liver disease caused by the hepatitis A virus (HAV) (95). Risk factors for hepatitis A include travel from low to high endemic settings (95). If not naturally immunised early in life and in the absence of vaccination, HAV infection can be a large public health concern among adolescents and adults (95). Effective vaccines against the virus are available and the local epidemiology data need to be considered prior the introduction of vaccines against hep A in adolescents (36, 95).

Hepatitis B is a serious liver disease caused by the hepatitis B virus (HBV) (96). Hepatitis B virus (HBV) immunisation before HBV exposure is the most effective means to prevent HBV transmission (96). Each year about 3,000-5,000 people die from cirrhosis or liver cancer caused by HBV (96). The hepatitis B vaccine is currently administered as three doses over a six-month period (36). The hepatitis B vaccine should be given to adolescents not previously immunized (36).

Pneumococcal disease is caused by a common bacterium (*Streptococcus pneumoniae*) that invades different parts of the body including lungs, bloodstream, brain and ears (97). The PCV is recommended for adolescents with certain underlying conditions like diabetes or chronic heart, lung, liver, or kidney disorders (97). Globally about 6.8 million

children and adolescents aged 2 to 18 years have these chronic illnesses that place them at high risk for pneumococcal disease (36, 97).

Future vaccines

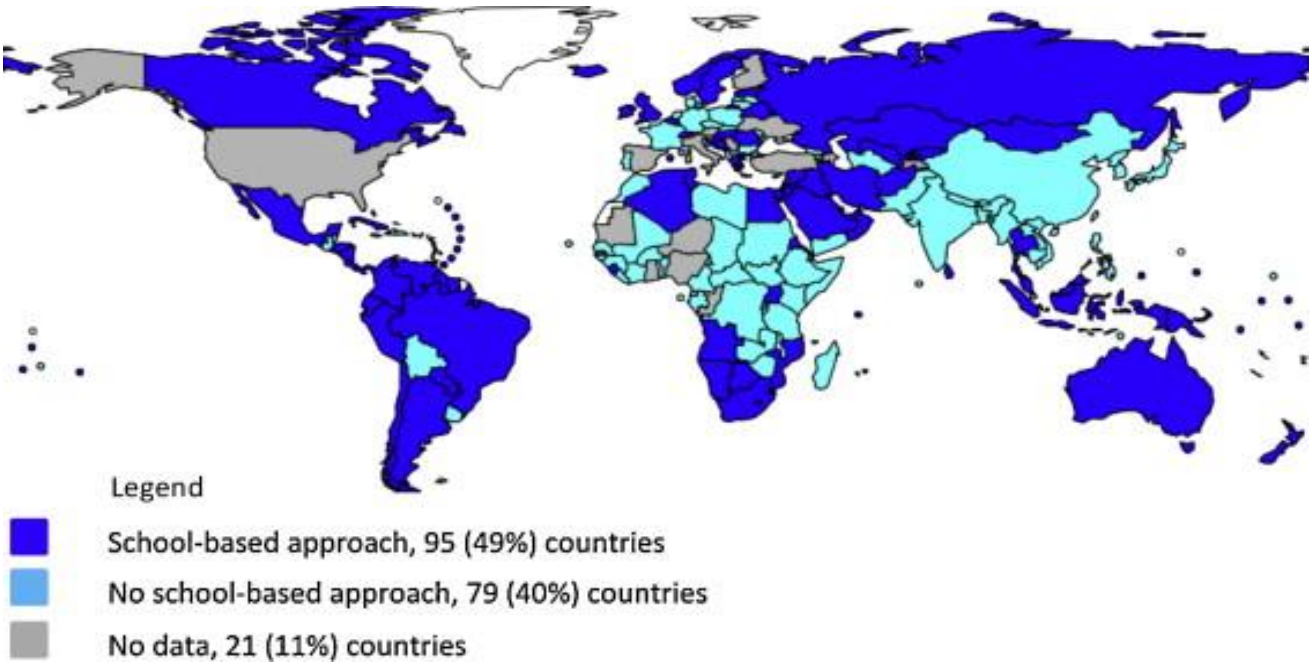
Future vaccines under development, such as those against HIV and TB will likely target adolescents, because this age group has the highest risk of contracting and transmitting these diseases (37, 42).

Vaccination strategies targeting adolescents

Maintaining high vaccine uptake rates is an essential component to the success of any vaccination programme and various strategies to reach adolescents have been used globally (98, 99). The strategies include school-based approaches, mass immunisation campaigns, child health days and immunisation weeks (98, 100).

Currently, schools have been used most often as the delivery platform for vaccinating school-aged children (101, 102). This approach has the advantage that the children can easily be reached with minimal logistic costs and time constraints (98, 101). By 2012, of the countries that have implemented or demonstrated HPV vaccination, school-based approaches to immunisation delivery was used in most of the countries (95 countries [49%]), **Figure 5** (98). School-based immunisation was used more commonly in HICs 64% compared to LMICs 28% (98).

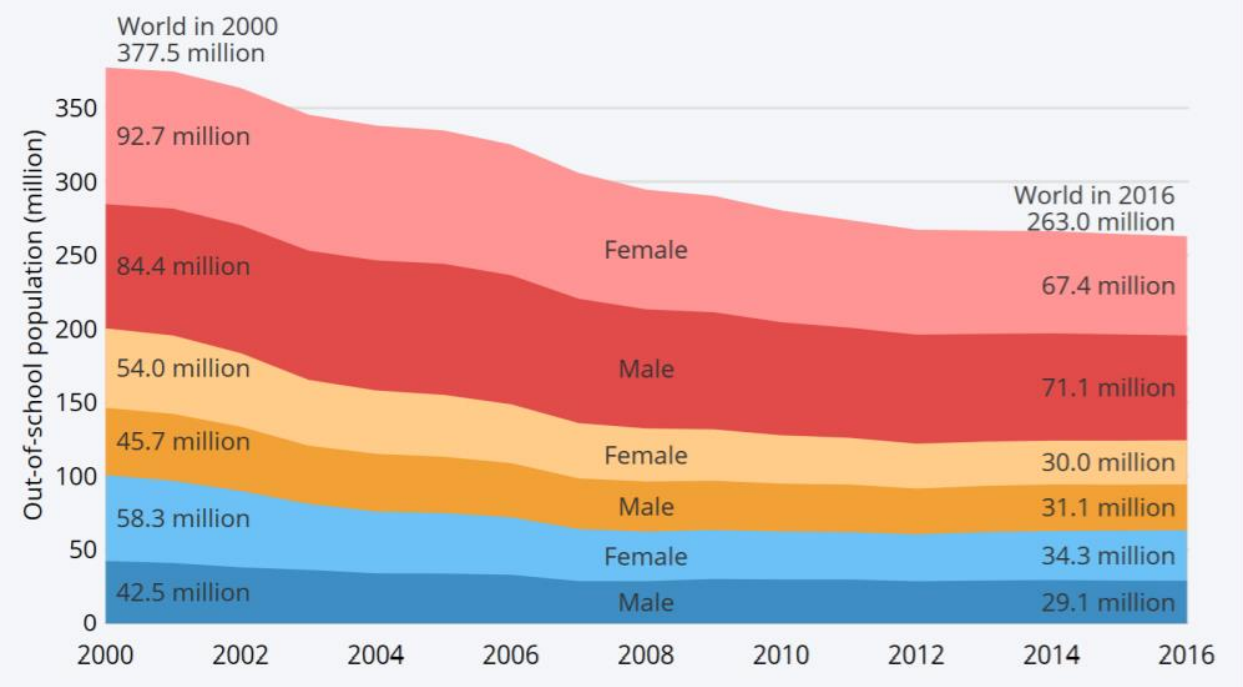
Figure 5: School-based approaches to immunisation delivery



Source: https://doi.org/10.1016/j.vaccine.2014.11.037 (98).

School-based vaccination programmes may not be entirely successful in countries with suboptimal school attendance rate, especially in LMICs (98). However, remarkable progress has been made on school enrolment, particularly in the early 2000s, in pursuit of the MDG goal of Education for all (103). As a result, the number of out-of-school children of primary school-age worldwide fell by 42% between 2000 and 2012 (103). However, millions of children remain unreached in LMICs. In 2016, about 67 million primary children were out of school (**Figure 6**) (103). Of the 67 million out of school, half the number were adolescents mainly living in sub-Saharan Africa (103).

Figure 6: Out of school primary children & adolescents by region and sex, 2000-2016



Source: http://uis.unesco.org/sites/default/files/documents/fs48-one-five-children-adolescents-youth-out-school-2018-en.pdf (103).

In addition to the challenge of poor school attendance, it is costly to use school-based delivery method to reach adolescents in countries that do not have an existing integrative health platform at schools (98, 100). The LMICs currently introducing HPV vaccination have reported intense resource requirements for the school-based delivery strategy (100). Most of the LMICs have reported optimal uptake of HPV vaccines through the demonstration projects (62, 100). Therefore, other strategies such as mass immunisation campaigns, facility-based, child health days and immunisation weeks can be used to complement school-based vaccination programmes in settings with poor school attendance rates (98).

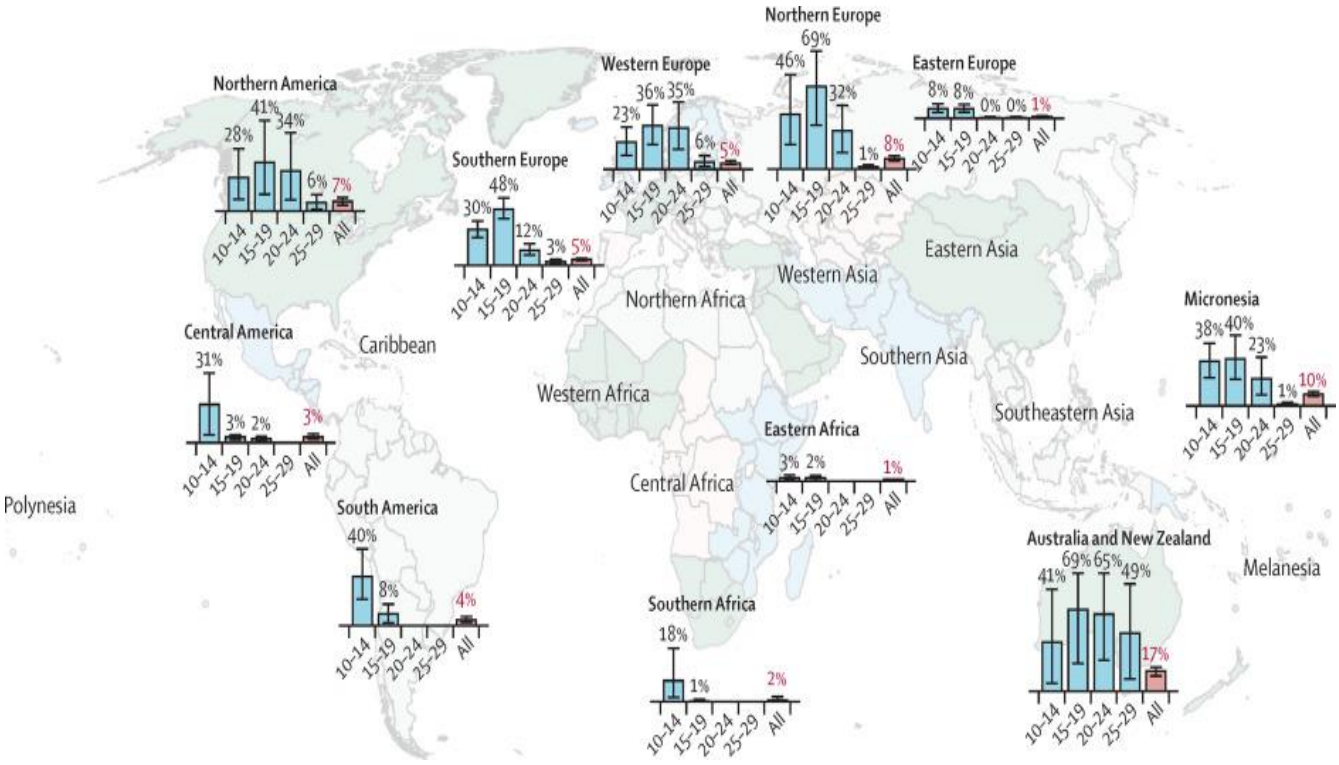
Various interventions have been found to enhance the strategies towards improving adolescent immunisation uptake (67). Some of the interventions like vaccination policy requirements for entrance to school and financial incentives for adolescents and parents have been shown to improve the uptake on adolescent vaccines (67).

Adolescent immunisation coverage - a focus on HPV vaccine

Most programmes on adolescent vaccination have targeted the ages between 11 to 12 years, although vaccines such as MCV4 target older adolescents between 16-17 years (36, 77). Since 2006, 64 countries have introduced HPV vaccines through national immunisation programmes (62). Most of the 64 are high or upper middle- income countries where a platform for the adolescent vaccination is well-established (100). By 2015, 33 million (32%) of females aged 10–20 years had received the full dose of HPV vaccine and 42 million (41%) had received at least one dose (62). Strikingly, only 1.4 million HPV vaccinated adolescent girls that received at least one dose were from LMICs (62).

Despite the lack of established adolescent vaccination platforms in LIMCs, estimated HPV vaccination coverage among targeted cohorts was higher (89%) in LMICs compared to 44% in HICs (62). This data may partly be explained by the growing concerns of HPV vaccine safety in HICs (62). Northern Europe, Australia, and New Zealand presented the highest age-specific coverage rates, all reaching 69% of females currently aged 15–19 years (62).

Figure 7: HPV vaccine coverage rates by geographical region and age



Source: https://doi.org/10.1016/S2214-109X(16)30099-7 (62).

Of the 62 HPV national programmes implemented, 42 (67%) programmes delivered the vaccine through schools (62). However, if adolescents missed these school visits, supplementary immunisation methods, such as following up at primary health-care centres, were used to complement the school-based programme (62). In Africa, all the seven African countries that nationally implemented the HPV vaccine as at 2018 used schools as a delivery strategy (104). Additional 23 African countries were reported to have conducted pilot studies to introduce the HPV vaccine in 2016 (80).

During the national HPV implementation in Africa, one of the important lessons learnt is that of political will (105, 106). For example, in South Africa, active early involvement of high-level stakeholders, including parliamentarians and representatives of the Ministry

of Health and Ministry of Education, led to rapid acceptance of the vaccine and the programme.

Optimal understanding of the lessons learnt and challenges facing HPV vaccine delivery will guide the developments of better adolescent immunisation programmes in all settings. Improved adolescent HPV immunisation programmes will result in significant improvements in other adolescent vaccinations, like MCV, Tdap, influenza and other additional catch-up vaccines. Establishing and strengthening adolescent immunisation programmes by improving equity, routine vaccination coverage, and hard-to-reach populations are essential measures required to achieve the GVAP 2011-2020 (31).

Conclusions

Introduction and implementation of adolescent immunisation is feasible in all settings, as demonstrated by HPV vaccination. Although the adolescence and young adulthood periods are generally thought to be healthy time periods, several public health and social problems either peak or start during these periods. Hence, adolescents are an important group to target with vaccination, which is a proven and one of the most cost effective public health interventions to promote health.

School-age is an entry point for targeting adolescent health. Therefore, adolescent vaccination will be cost efficient if integrated with existing adolescent school health programmes. In addition, there is an opportunity for strengthening integration, including vaccination. Over and above, strengthening the integration will improve coordination and ownership between the departments of health and education.

Engagement with key stakeholders is crucial. Adolescents, parents, teachers and health care workers are the important key stakeholders that need to be educated and engaged during implementation of adolescent vaccination. Early face-to-face engagement with communities will improve their knowledge and awareness, leading to improved vaccination uptake among adolescents. Engagement of other key stakeholders like parliamentarians and government parties is vital in building political will at all levels and ensuring provision of funding for successful vaccine introduction.

Currently new adolescent vaccines like HPV and other adolescent health programme are standalone programmes, which may create confusion as to which department should coordinate delivery. For future adolescent health programme to succeed, it will be vital to be owned and driven by EPI. Even though GIVS aimed to address adolescent immunisation gap ten years ago, there is still no success in improving the uptake and establishments of adolescent vaccination programmes. We, therefore, suggest the development and implementation of up-to-date and evidence-based adolescent immunisation policies in all settings.

Contributions

Leila Abdullahi wrote this chapter under supervision of Prof. Greg Hussey, Dr. Benjamin Kagina and Prof. Charles Wiysonge.

Chapter 3

Improving vaccination uptake among adolescents; a systematic review

About this chapter:

In this chapter, we evaluate the existing evidence on the different interventions that can be used to improve the uptake of vaccines among adolescents. To minimize repetition in the thesis, the background section has been modified. The background section is therefore not the same as that of the version submitted to Cochrane for publication.

Publication: Submitted to the Cochrane Effective Practice and Organisation of Care group (Currently under editorial review)

A protocol was published from this chapter. See the link below:

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011895/pdf

Abdullahi LH, Kagina BMN, Wiysonge CS, Hussey GD. Improving vaccination uptake among adolescents (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No: CD011895. DOI: 10.1002/14651858.CD011895.

Abstract

Background

Adolescent immunisation is a rapidly growing topic in the field of vaccinology. The topic has received more attention since the launch of the GVAP initiative, advocating for an extension of the benefits of immunisation more equitably and beyond the childhood period. In recent years, large numbers of programmes have been launched to increase the uptake of different vaccines in adolescent populations; however, vaccination coverage among adolescents remains sub-optimal. Therefore, understanding and evaluating the various interventions that can be used to improve adolescent immunisation is crucial. The review evaluates the effects of different interventions to improve vaccines uptake among adolescents.

Objectives

To evaluate the effects of interventions to improve vaccine uptake among adolescents.

Search methods

Between February and April 2017, we conducted a literature search for relevant studies conducted from the inception time of the databases to April 2017. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), which is part of The Cochrane Library, MEDLINE, Ovid; PubMed, NLM (for studies not in MEDLINE), EMBASE, Ovid, CINAHL, EBSCOhost, Africa-Wide Information, EBSCOhost, Global Health, Cab Direct, Scopus, and Science Citation Index and Social Sciences Citation Index and ISI Web of Knowledge (for papers citing any of the included studies in the review). For related systematic reviews we searched Cochrane Database

of Systematic Reviews (CDSR), part of The Cochrane Library; Database of Abstracts of Reviews of Effectiveness (DARE), part of The Cochrane Library, and PDQ-Evidence. In addition, we searched the reference lists of relevant articles, WHO International Clinical Trials Registry Platform, Clinicaltrials.gov, and various electronic databases of grey literature.

Selection criteria

Eligible studies were randomised control trials (RCTs), non- randomised control trials (non-RCTs), interrupted time series studies (ITS) and controlled before-after studies (CBAs). The eligible participants are adolescents (defined as girls and boys aged 10 to 19 years). The participants are eligible for WHO-recommended vaccines. Additional eligible participants are the parents of the adolescents as well as healthcare providers.

Data collection and analysis

Two authors independently screened the literature search outputs, reviewed full texts to identify potentially eligible studies, extracted data and assessed risk of bias for the selected studies. The two authors extracted data from the selected studies in duplicate, resolving discrepancies by consensus. Data analysis included calculation of the risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI) where appropriate. We pooled study results using random-effects meta-analyses and assessed the certainty of the evidence using Grades of Recommendation, Assessment, Development and Evaluation (GRADE).

Main results

From the literature search, we identified 16 studies that met the inclusion criteria (eight RCTs, four cluster randomised control trials (cRCTs), three nRCTs and one CBA. Twelve studies were conducted in the United States of America (USA), while there was one study from each of the following countries: Australia, Sweden, Tanzania and the United Kingdom (UK). Ten studies had unclear or high risk of bias. We broadly categorised three interventions as adolescent-oriented, provider-oriented, or health-system-oriented. Further sub-categorization of two of the three broad interventions were as follows; for the interventions targeting adolescents, the sub-categories were health education, health education plus financial incentives, financial and non-financial incentives and finally, legislative interventions such as vaccination requirements for school attendance; for the provider-oriented interventions, sub-categorization included multi-component provider intervention (i.e. repeated contacts, individualized feedback, education sessions), provider prompt intervention (education and performance feedback) and multi-faceted provider and parent intervention.

The interventions to improve adolescent vaccine uptake targeted different participants: parents (reported by four studies), providers (two studies) and adolescents boys and/or girls (seven studies). Five studies had mixed participants that included healthcare providers and parents, healthcare providers and adolescents, as well as parents and adolescents. The main outcome of interest was the vaccination coverage among adolescents. Eleven studies evaluated the uptake of human papillomavirus (HPV) and three evaluated the uptake of vaccines against hepatitis B virus. Additionally, three

studies evaluated the uptake of various vaccines including Tdap, MCV, HPV, and influenza.

Health education probably improves HPV vaccine uptake compared to usual care (four studies, 3876 participants: RR 1.56, 95%CI 1.26 to 1.93; I^2 = 17%; moderate certainty evidence). One large study showed that a complex multi-component health education intervention probably leads to a marginal decrease in hepatitis B vaccine uptake, compared to simplified information leaflets on the vaccine (17411 participants: RR 0.98, 95%CI 0.97 to 0.99; moderate certainty evidence).

Financial incentives may improve HPV vaccine uptake compared to no incentives (one study, 500 participants: RR 1.45, 95%CI 1.05 to 1.99; low certainty evidence) and health education and financial incentives may improve hepatitis B vaccine uptake compared to usual care (one study, 104 participants: RR 1.38, 95%CI 0.96 to 2.00; low certainty evidence).

Mandatory vaccination probably also improves hepatitis B vaccine uptake compared to no mandatory vaccination (one study, 6462 participants: RR 4.24, 95%CI 3.94 to 4.56; moderate certainty evidence).

With moderate certainty of evidence, provider prompts probably have little or no effect, compared to usual care, on completion of Tdap (one study, 3520 participants: RR 1.05, 95%CI 0.99 to 1.11), MCV (one study, 3520 participants: RR 1.05, 95%CI 0.99 to 1.11), HPV vaccine (one study, 1771 participants: RR 1.06, 95%CI 0.87 to 1.30), and influenza vaccine (one study, 3520 participants: RR 1.05, 95%CI 0.96 to 1.15) vaccination schedules.

A multi-facetted intervention targeting providers and parents involving social marketing and health education probably improves HPV vaccine uptake (two studies, 26206 participants: RR 1.42, 95%CI 1.26 to 1.60; I^2 = 0%; moderate certainty evidence).

A class-based school vaccination strategy probably increases HPV vaccine uptake more than an age-based school vaccination strategy (one study, 5537 participants: RR 1.09, 95%CI 1.06 to 1.13; moderate certainty evidence).

Authors' conclusions

Our review findings suggest there are various strategies that have been evaluated to improve adolescent immunisation, including health education, financial incentives, mandatory vaccination, and class-based school vaccine delivery. However, all the evidence is of low to moderate certainty. This implies a high likelihood that the true effect sizes of the interventions will be substantially different from those found in this review, with availability of higher quality evidence on the topic. Additional research on interventions to improve uptake of vaccines among adolescents is therefore needed, especially in LMICs where the information on the topic is limited.

Plain language summary

Improving vaccination uptake among adolescents

This Cochrane Review aimed to assess the effects of diverse approaches to increase the number of adolescents who get vaccinated. Cochrane researchers collected and analysed all relevant studies to answer this question and found 16 studies.

Key messages

This review shows that several different approaches may increase the number of adolescents who get vaccinated. The approaches include giving health education, offering gifts, and passing laws. However, more research is needed to understand what approaches work best, especially in LMICs.

What was studied in the review?

The WHO recommend several vaccines for 10 and 19 years old (adolescents). One of the vaccines is offered specifically to this age group, the HPV vaccine. Others are booster vaccines, also given to younger children, such as hepatitis B vaccines, and diphtheria, tetanus, and pertussis vaccines.

Many adolescents do not get the recommended vaccines. Governments and organisations have tried different approaches to vaccinate adolescents. One approach is to target adolescents, their parents and communities. This can be done, for instance, by giving information and education about vaccines; reminding when the vaccines are due; or giving adolescents a reward or gift to get vaccinated. Another approach is to target healthcare providers, for instance through information, reminders, or feedback

about their practice. A third approach is to make vaccines more accessible to adolescents. This can be done, for instance, by making vaccines free or cheap or by offering vaccines closer to home, including at schools. A fourth approach is to pass laws about vaccination for adolescents. For instance, in some countries, students must prove they have been vaccinated before being enrolled at school.

What are the main results of the review?

The review authors found 16 relevant studies. Twelve of the studies were from USA. The other studies were from Australia, Sweden, Tanzania, and UK. These studies showed the following:

- *When adolescents (girl or/and boys) and their parents are given vaccination information and education,* more adolescents probably get HPV vaccines, but slightly fewer adolescents probably get hepatitis B vaccines (moderate certainty evidence)
- *When adolescents are given gift vouchers*, more adolescents may get HPV vaccines (low certainty evidence). *When adolescents and their parents are given vaccination education, cash and gift packages*, more adolescents may get hepatitis B vaccines (low certainty evidence)
- *When laws are passed* stating that adolescents must be vaccinated to go to school, more adolescents probably get hepatitis B vaccines (moderate certainty evidence)
- *When healthcare providers are reminded* to vaccinate adolescents when they open their electronic medical charts, this probably has little or no effect on the number of

adolescents who get Tdap, meningococcal, HPV, or influenza vaccines (moderate certainty evidence)

- *When healthcare providers and parents are targeted in several ways*, including through vaccination education, phone calls and radio messages, more adolescents probably get HPV vaccines (moderate certainty evidence).

These studies compared the use of these approaches (health education, gifts and rewards, laws, or reminders) to using no approaches.

In addition, one study from Tanzania gave vaccination information to all girls that were in school class 6 but were not necessarily of the same age. They were compared to girls who were given vaccination information because they were all born in the same year but were not necessarily in the same class. This study showed that the class-based approach probably led to more girls getting HPV vaccines (moderate certainty evidence) than age-based approach.

How up-to-date is this review?

The review authors searched for studies that had been published up to April 2017.

Background

Description of the condition

Immunisation of adolescent is a key global strategy in the control, elimination and eradication of VPDs. In many settings, adolescents usually turn to physicians only when they are ill and so, there are limited opportunities to inform them that vaccines are important and should be administered (64, 102). Adolescents visiting the physicians are more interested in their current health condition than possible benefits of preventing future VPDs (64). Schools have been used extensively as a delivery platform for vaccinating large numbers of school-aged children (65, 66, 101, 102, 107). However, school-based vaccination programmes may not be entirely successful in countries with sub-optimal school attendance rates (44, 108). School attendance rates in LMICs are variable due to factors such as geographical location, socio-cultural and economic status (43, 44, 108). Strategies such as mass immunisation campaigns can be used to complement school-based vaccination programmes in settings with poor school attendance rates (109).

The most commonly reported barriers to adolescent vaccination include lack of knowledge about immunisation, vaccines and VPDs; negative attitudes towards vaccination by adolescents, parents, teachers and healthcare providers; poor access to vaccines; and financial constraints (59, 60, 110, 111).

Description of the intervention

Interventions to enhance the uptake of vaccines by adolescents may be multi-pronged, targeting adolescents and their communities as well as targeting healthcare providers, and/or the health system.

Recipient-oriented interventions

Interventions targeting adolescents and their communities (including their parents and teachers) may include education, reminders, incentives, and mandatory vaccination.

Interventions to 'inform' or 'educate' enable adolescents and their communities to understand the meaning and relevance of vaccination (112). Such interventions may be delivered face-to-face or via written mail, telephone conversation, audio visual presentation or drama, printed materials, web sites, multi-media campaigns, or community events (112). These types of interventions may be directed at individuals or groups, and may include information about VPDs; the risks and benefits of vaccines; where, how and when to access vaccine services; and/or who should be vaccinated (112-114). Adolescents and communities may receive education about vaccines through prominently displayed posters in waiting rooms, brochures, e-mails, and website resources (115).

Client reminder or recall interventions involve reminding members of a target population that vaccinations are due (reminders) or late (recall). Reminders and recalls are delivered using various methods, such as telephone calls, letters, or postcards (63, 112-116). The contents of reminder/recalls may include personalised information related to a specific upcoming or missed appointment (112, 115).

Adolescent or community incentives involve providing financial or other incentives to motivate people to accept vaccinations (63, 113, 116). Incentives can be rewards or gifts (116).

Mandatory vaccination refers to a law or policy that requires students to show proof of immunisation records prior to school admission; and failure to do this denies admission (63, 113, 116).

Provider-oriented interventions

Provider-oriented interventions may include reminders, audit and feedback, and education.

Provider reminder interventions inform vaccinators that individual clients are due for vaccinations. Reminders may be delivered through client charts, computer, electronic mail, or postal mail, among many others (63, 113, 114, 116, 117)

Audit and feedback for vaccinators involves retrospectively evaluating the performance of the vaccinators in administering vaccines and providing feedback to them (63, 113-116). This information is given to providers to motivate them to improve immunisation services.

Provider education involves giving information regarding vaccinations to providers to increase their knowledge and to encourage them to adopt positive attitudes towards vaccination. Techniques by which information is delivered can include written materials, videos, lectures, continuing medical education programmes, and computerised software (63, 114-117).

Health system interventions

Outreach programmes include school-based immunisation and mass campaigns. School-based immunisation outreach is intended to improve delivery of vaccinations to school-going children (116). School-based interventions usually include vaccination-related education of students about either provision of vaccinations or referral for vaccinations (63, 113, 116). Mass campaign programmes target adolescents both in school and out of school (109).

Expanding access in healthcare settings is used to increase the availability of vaccines in the medical or public health settings in which vaccinations are offered. This can be achieved using several methods such as: increasing or changing the hours during which vaccination services are provided; delivering vaccinations in clinical settings in which they were previously not provided (e.g. emergency departments, inpatient units or subspecialty clinics); or reducing administrative barriers to obtaining vaccination services within clinics (e.g. developing a 'drop-in' clinic or an 'express lane' vaccination service) (63, 115, 116).

Reducing out-of-pocket costs can be implemented by subsiding the costs of vaccines, paying for vaccinations, providing insurance coverage, or reducing co-payments for vaccinations at the point of service (63, 113, 116).

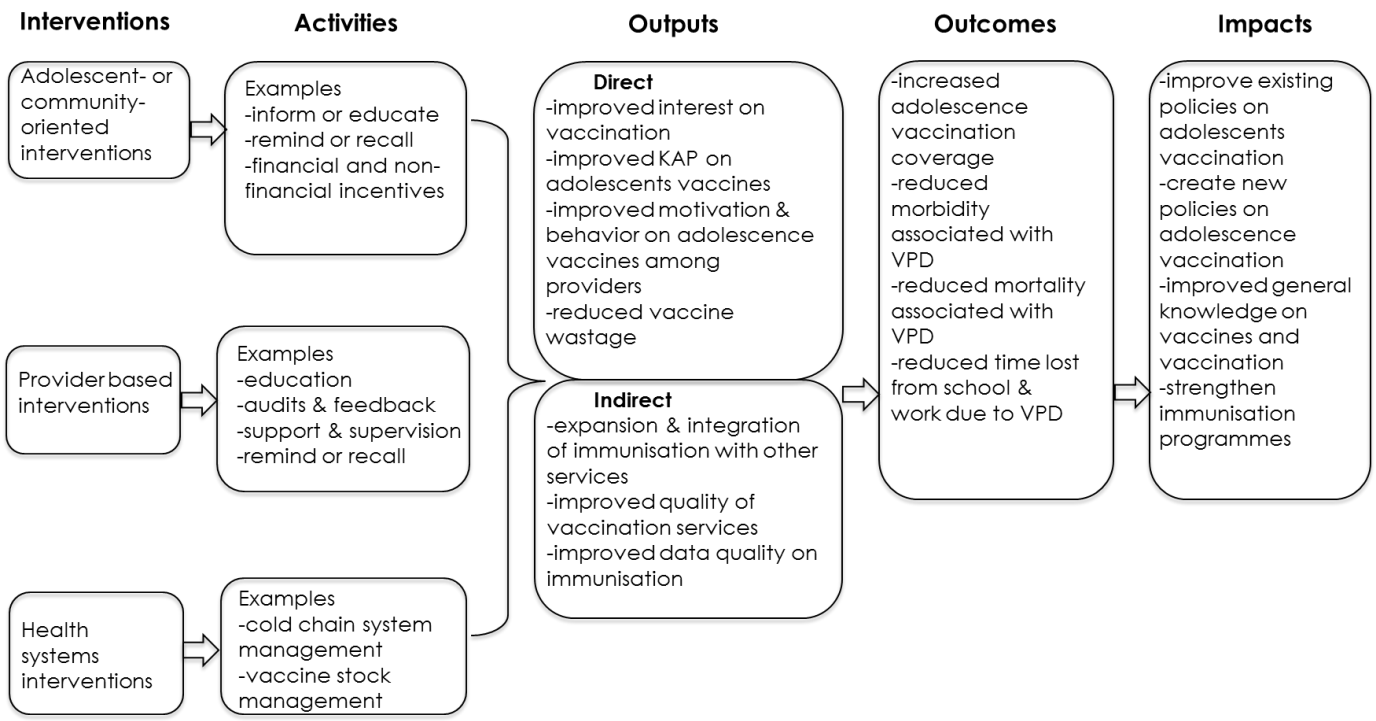
Multi-component interventions

Multi-component interventions are approaches that include more than one strategy, with the aim of addressing a variety of barriers to adolescent vaccine uptake. Such interventions could enable communities to be aware of the immunisation services available to them, demonstrate the utility and relevance of these services, provide community members with the knowledge and information base to effectively take advantage of the services, and incorporate a variety of associated provider or health system strategies to improve immunisation uptake (63, 113, 116).

How the intervention might work

We have proposed a logic model (**Figure 8**), which shows how different interventions, alone or in combination, will have an influence on adolescent vaccination.

Figure 8: Logic framework on interventions for improving uptake of adolescent vaccines



Source:

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011895/epdf/full (67)

No logic model or conceptual framework has been described that shows an integrated perspective on interventions to increase vaccination among adolescents. The evidence-based conceptual model of factors that influence HPV vaccination among adolescent girls has, however, been described (118). This model suggested a useful framework for examining the impact of personal, interpersonal, organisational and broader community as well as societal factors on vaccination (118). Our logic model proposes that such factors, alone or in combination, will have an influence on adolescent vaccination.

Why it is important to do this review

Adolescents represent 25% of the global population (3) yet, there is a knowledge gap around interventions to improve vaccine uptake among adolescents, especially in LMICs. Our review proposes to evaluate the evidence on strategies that can be adopted to improve vaccine uptake among adolescents. Such strategies will not only improve the uptake of current vaccines among adolescents but are also likely to increase the uptake of future vaccines targeted to this population group. In addition, this review could be used to advocate for strengthening of existing adolescent vaccination policies and to formulate new policies on the vaccination of adolescents where none currently exist.

We are not aware of any previous Cochrane systematic review that has evaluated interventions to improve adolescent vaccine uptake. However, some reviews have evaluated various interventions to improve adolescent HPV vaccination (119-121). The interventions evaluated in these reviews are not categorised as intended in our review. There are also reviews that have evaluated various strategies to improve immunisation coverage in children or the whole population (113, 114, 122-124). These reviews considered general barriers to immunisation and assessed the effects of a variety of interventions (113, 114, 122-124).

Objectives

To evaluate the effects of interventions/strategies to improve vaccine uptake among adolescents.

Methods

This is a Cochrane review and therefore, we used the Methodological Expectations of Cochrane Intervention Reviews (MECIR). The methods used conformed to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). The MECIR checklist is included in **Appendix 1**.

Criteria for considering studies for this review

Types of studies

We included the following study designs: RCTs, non-RCTs, ITS and CBAs. All these study designs meet the quality criteria used by the EPOC Group (125). The EPOC Group Risk of Bias criteria is an adaptation of the Cochrane Risk of Bias tool in chapter eight and published in the Cochrane Handbook (126). We included both individually randomised and cluster-randomised control trials. For cRCTs, we only included those with at least two interventions and two control clusters. Following the EPOC criteria, we included an ITS study only if outcomes were measured during at least three points before and three points after the intervention. For a CBA study to be included in the review, it must include at least two intervention groups and at least two comparable control groups, with simultaneous data collection.

We excluded simple pre-post designs, cRCTs and non-RCTs with only one intervention or control site and CBA studies without concurrent data collection in intervention and comparison groups; in accordance with the EPOC criteria for inclusion of studies in systematic reviews of effects (125).

Types of participants

Boys and girls aged 10 to 19 years eligible for WHO-recommended vaccines and their parents or healthcare providers.

In the case of studies with interventions directed at mixed populations of children and adolescents or adolescents and adults, we excluded a study if specific data for adolescents was not reported.

Types of interventions

Intervention

- Recipient oriented interventions (i.e. interventions targeting adolescents and their communities), for example:
    - interventions to communicate with adolescents and/or their caregivers/parents about adolescent immunisation;
    - financial and non-financial incentives for adolescents and/or their caregivers/parents and;
    - Mandatory vaccination: vaccination requirement for high school and university attendance.
- Provider-oriented interventions, for example:
    - any intervention to reduce missed opportunities for vaccination (e.g. audit and feedback); and
    - health education, training, and supportive supervision.
- Health system interventions, for example:
    - interventions to improve the quality of services, such as provision of reliable cold chain systems, provision of transport for vaccination, vaccine stock management;
    - outreach programmes, e.g. school-based immunisation and mass vaccination campaign for out-of-school adolescents;
    - expanded services, e.g. extended hours for immunisation services;

    - increased immunisation budget; and
    - integration of immunisation services with other services.
- Multi-component interventions.

Exclusions

We excluded interventions to remind or recall recipients or providers of immunisation services, as there is already a Cochrane review on this topic (122).

Comparisons

- Standard immunisation practices in the study setting;
- Alternative interventions; and
- Similar interventions implemented with different degrees of intensity.

Types of outcome measures

Primary outcomes

Adolescent vaccination coverage, that is, the proportion of adolescents who have received the recommended dose(s) of the vaccine studied.

Secondary outcomes

- Proportion of adolescents completing the schedule;
- Equitable uptake of immunisation (as defined by the study authors);
- Knowledge, attitudes, and beliefs;
- Adverse events following immunisation;
- Adverse effects of the intervention;
- Cost of the intervention; and
- Incidence of VPDs

Search methods for identification of studies

With the assistance of the Cochrane EPOC Information Specialist, we developed comprehensive and highly sensitive search strategies on both published and unpublished databases, with no restrictions on language or publication date. The search strategies for the electronic databases incorporated the Cochrane EPOC search strategy for RCTs, non-RCTs, CBAs and ITS studies (125), combined selected MeSH and free-text terms relating to adolescent vaccination uptake literature globally.

Electronic searches

We searched from the following databases for primary studies:

- Cochrane Central Register of Controlled Trials (CENTRAL) Issue 1 2017, part of *The Cochrane Library* (www.cochranelibrary.com) (searched 15.02.2017);
- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE 1946 to 2017, Ovid (searched 15.02.2017);
- Embase 1974 to 2017 February 14, Ovid (searched 15.02.2017);
- CINAHL 1981 to 2017, EBSCOhost (searched 17.02.2017);
- Africa-Wide Information from the 19th century until 2017, EBSCOhost (searched 15.02.2017);
- Global Health 1973 to 2017 Week 05, Ovid (searched 15.02.2017);
- Scopus, Elsevier (searched 17.02.2017); and
- Science Citation Index Expanded; Social Sciences Citation Index, 1987-present, and Emerging Sources Citation Index 2015-present, Web of Science Core

Collection, Thompson Reuters (searched 24.04.2017) (for papers citing any of the included studies in the review).

We searched from the following databases for related reviews:

- Cochrane Database of Systematic Reviews (CDSR) Issue 3 2017, part of *The Cochrane Library* (www.cochranelibrary.com) (searched 09.03.2017);
- Database of Abstracts of Reviews of Effects (DARE) Issue 2 2015, part of *The Cochrane Library* (www.cochrenelibrary.com) (searched 15.02.2017);
- Health Technology Assessment Database (HTA) Issue 4 2016 (searched 15.02.2017);
- PDQ-Evidence (searched 13.02.2017).

See **appendix 2** for the used search strategies.

Search from other resources

Grey literature:

- World Health Organization (WHO) (http://www.who.int/) (searched 15.02.2017).
- Gavi, the Vaccine Alliance (http://www.gavi.org) (searched 15.02.2017).
- United Nations Children's Funds (UNICEF) (http://www.unicef.org/) (searched 15.02.2017).
- PATH Vaccine Resources Library (http://www.path.org/) (searched 15.02.2017).
- US Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/) (searched 15.02.2017).
- The Communication Initiative Network (http://www.comminit.com/) (searched 15.02.2017).
- Grey Literature Report (http://www.greylit.org) (searched 15.02.2017).
- OpenGrey (http://www.opengrey.eu/) (searched 15.02.2017).

- Electronic Development and Environment Information System (http://www.eldis.org/) (searched 15.02.2017).
- Immunization basics (http://www.immunizationbasics.jsi.com) (searched 15.02.2017).

Trial registries:

- Word Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) (searched 15.02.2017).
- ClinicalTrials.gov, US National Institutes of Health (NIH) (http://clinicaltrials.gov/) (searched 15.02.2017).

Reference lists: We searched the reference lists of potentially eligible studies and relevant previous reviews.

Data collection and analysis

Selection of studies

Two authors (LA and BK) screened the search outputs to select potentially eligible studies. LA then obtained the full text of potentially eligible studies and two authors (LA and VN) independently conducted the final study selection for inclusion in the review. We resolved any disagreements regarding the inclusion of studies by discussion or by consulting a third author (BK and CW). We used a PRISMA flow chart to summarise the search and selection of studies for the review. We included a table of all included studies in the review and documented the reasons for exclusion of studies.

Data extraction and management

Two authors (LA and VN) independently extracted data from selected studies using an adapted version of the Cochrane data extraction form. Disagreements on study selection and data extraction were resolved by consensus between the two review authors, failing which a third author (BK) arbitrated. Prior to use, we piloted the data extraction form on four studies identified randomly from the list of included studies.

The data extraction form included the following items:

- Setting of the study (city and country)
- Type of study: individual RCT, cRCT, non-RCT, CBA, or ITS studies
- Type of participants: adolescents, parents/caregivers, health care providers
- Type of interventions: name of intervention, frequency, timing, delivery method, venue of delivery
- Type of outcomes measured: vaccine coverage, knowledge, attitudes and beliefs, cost of intervention, adverse effects of the intervention, adverse events following immunisation, equity.

Assessment of risk of bias in included studies

We applied the Cochrane EPOC 'Risk of bias' criteria (127) for RCT, non-RCT, CBA, and ITS studies, as appropriate. For each included study, we reported our assessment of risk of bias, i.e. low, high, or unclear risk for each domain, together with a descriptive summary of the information that influenced our judgement. Two review authors (LA and VN) applied the criteria independently and discussed any disagreements with a third review author (BK or CW).

Measures of intervention effect

We expressed the result of each study as a risk ratio with its corresponding 95% confidence interval (CI) for dichotomous data. We grouped studies with broadly similar types of participants, interventions, study designs, and outcomes to get feasible results for an overall estimate of effect. See **Table 2** for measures of effect specified in the protocol, but not used in the review.

Unit of analysis issues

We did not encounter 'unit of analysis' issues in this review. Four included studies were cRCTs based on matched pairs of clusters (128-131). We did not re-analyse these data as matching cannot be considered in re-analyses in such studies unless the raw data are available. The studies, however, conducted appropriate analyses of the data, and we have provided the results as reported in the studies. See **Table 2** for methods specified in the protocol, but not used in the review.

Dealing with missing data

We did not experience any missing data thus we did not contact the primary study authors for missing data. In **Table 2**, we have indicated methods specified in the protocol, but not used in the review.

Assessment of heterogeneity

We reviewed heterogeneity in the type of intervention, the type of setting, study design, and risk of bias of included studies to make an assessment of the extent to which the included studies were similar to each other. We examined the levels of heterogeneity between study results using the Chi² test of homogeneity (with significance defined at

the alpha level of 10%). We quantified any statistical heterogeneity between study results using the I^2 statistic. We regarded heterogeneity as substantial if the I^2 was greater than 50% (126).

Assessment of reporting biases

Test for asymmetry with a funnel plot was not feasible because the number of included studies for each meta-analysis was less that the recommended 10 studies. We have archived methods for assessing reporting biases in **Table 2**, for use in future updates of this review.

Data synthesis

We pooled data from studies of similar study designs, similar interventions, similar participants, and similar outcomes in a meta-analysis using the random-effects model; if there was no significant statistical heterogeneity, methodological difference, or high risk of bias. For outcomes with substantial variation between studies in the reported interventions, participants, study designs and outcome measures, we did not pool the results but summarised the findings in a narrative format. Overall, we interpreted the study findings by considering the methodological quality of the studies and the strength of the evidence. For each observed effect, we explicitly stated the strength of evidence and drew conclusions. See **Table 2** for data synthesis methods specified in the protocol, but not used in the review.

Subgroup analysis and investigation of heterogeneity

We did not have sufficient data to conduct planned subgroup analyses (**Table 2**). However, we conducted a post-hoc subgroup analysis exploring the effect of variations

in the intervention (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4) or comparison (Analysis 4.1) groups on vaccination coverage. We used the Chi² test for subgroup differences to test for subgroup interactions.

Sensitivity analysis

We planned to perform sensitivity analyses based on unit of analysis errors, risk of bias, and missing data (**Table 2**). However, available data were insufficient to perform these analyses.

Summary of findings

We created Summary of findings (SOF) tables for the main intervention and comparisons included the primary outcome: vaccination coverage. We used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence at outcome level (132). Two review authors independently assessed the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias). We used methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of interventions (126), and the EPOC worksheets (133), using the GRADEpro software. We resolved disagreements on certainty ratings by discussion, provided justification for decisions to downgrade the ratings using footnotes in the table, and made comments to aid readers' understanding of the review where necessary. We used plain language statements to report these findings in the review (134).

Table 2: Unused methods (67)

Method	Approach

Measures of treatment effects	We will express the result of each study as a mean difference with its 95% CI for continuous data. We will analyse ITS studies using a regression analysis with time trends before and after the interventions. We will present the results for the outcomes as change in level and slope.
Unit of analysis issues	If investigators report cluster-randomised trial data as if the randomisation was performed on the individuals rather than the clusters, we will request the intra-cluster correlation coefficient (ICC) from the study authors; failing this, we will obtain external estimates of the ICC from similar studies or available resources. Once established, we will use the ICC to re-analyse the trial data to obtain approximate correct analyses. We will adjust the data by inflating the standard errors, i.e. multiplying them by the square root of the design effect. We plan to report the effect estimates and the corrected standard errors from cluster-randomised trials with those from parallel-group design trials, noting that the analysis of data from that specific study suffers from unit of analysis error. If insufficient information is available to control for clustering in this way, we will enter data into RevMan using individuals as the unit of analysis. We will then perform sensitivity analyses to assess the potential bias that may have occurred as a result of the inadequately controlled clustered trials. We will also perform sensitivity analyses if we obtained the ICCs from external sources, to assess the potential biasing effects of inadequately controlled cluster-randomised trials.
Dealing with missing data	Where necessary, we will contact the corresponding authors of included studies to supply any unreported data. We will describe missing data and dropouts for each included study in a 'Risk of bias' table, and discuss the extent to which the missing data could alter our results. For CBA studies where relative measures are not available, we will estimate the difference between outcome measures at two time points for both baseline and after the intervention and then compare the difference between the groups. On the other hand, if ITS studies are incorrectly analysed by the authors and provide the data points, we will re-analyse ITS studies using a regression analysis with time trends before and after the intervention, which adjust for autocorrelation and any periodic change.
Assessment of reporting bias	We will use a funnel plot to investigate the risk of publication bias by intervention type, provided 10 or more studies are included in the analysis for each intervention type. We will critically examine the funnel plot for asymmetry both visually and with the use of formal tests. For continuous and dichotomous outcomes, we will use the test proposed by Egger and the test proposed by Harbord, respectively. In situations where asymmetry is detected by either test or by visual assessment, we will perform further exploratory analyses to investigate it. This will include reviewing the included studies for small sample size studies and their intervention effect.
Data synthesis	We will report ITS studies as changes in level and slope. If ITS studies are incorrectly analysed by the authors and provide the data points, we will re-analyse them using a regression analysis with time trends before and after the intervention, which adjust for autocorrelation and any periodic change.
Subgroup analysis and investigation of heterogeneity	Where sufficient data are available, we will conduct subgroup analyses, which will explore the effects of; vaccine given including frequency of the vaccine; availability of a policy on adolescent vaccination including vaccination schedule; equity (school-based interventions or mass campaign programmes); and country income status (World Bank classification as either HICs or LMICs).
Sensitivity analysis	Where sufficient data are available, we will conduct, if applicable, a sensitivity analysis to establish whether the meta-analysis results for the treatment effect

	are influenced by study designs and overall risk of bias. We will perform sensitivity analyses by excluding studies with a particular study design and studies with high risk of bias.

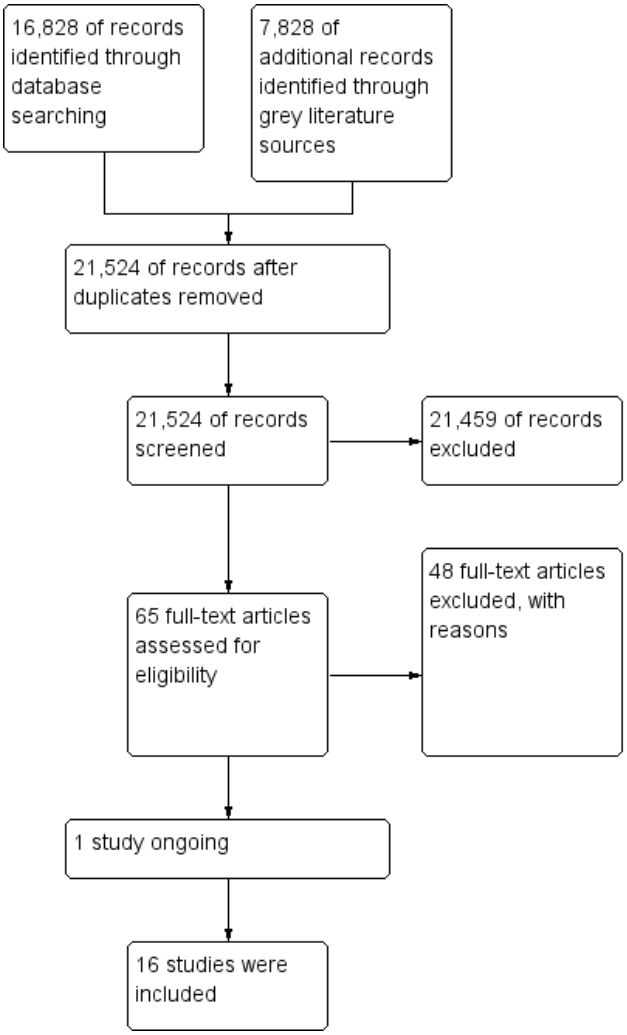
Results

Description of studies

Results of the search

We identified 24,656 records from the electronic databases and other sources. After excluding 3,132 duplicates, we screened 21,524 records, and found that 21,459 records were not relevant to our review question. We reviewed the remaining 65 potentially eligible full-text articles for inclusion and excluded 48 of them for reasons given in the table of excluded studies (**Appendix 3**). Sixteen studies met the inclusion criteria and were included in the review (**Table 3**). One study (135) is ongoing as at the time of completion of this review. The search process and selection of studies is presented in **Figure 9**.

Figure 9: Study flow diagram.



Included studies

Study design and setting

Sixteen studies met the review inclusion criteria. Eight studies were RCTs with individuals as the unit of randomisation (136-143); four studies were cRCTs that used health facilities or schools as the unit of randomisation (128-131); three studies were non-RCTs with at least two intervention and two control arms (144-146); and one study (147) was a CBA study with two intervention and two control arms.

Twelve studies were conducted in the United States of America (USA) (128, 131, 136, 137, 139-141, 143-147); one study was conducted in Australia (142); one study was conducted in Sweden (129); one study was conducted in the United Kingdom (UK) (138); and one study was conducted in Tanzania (130).

Participants

Two studies enrolled girls only (130, 136), five enrolled boys and girls (129, 138, 142, 145, 146), three enrolled parents (131, 137, 140), and two enrolled healthcare providers (143, 147).

Four studies enrolled mixed participants, comprising of adolescents and parents (141), adolescents and healthcare providers (128), and parents and healthcare providers (139, 144). The healthcare providers included physicians, nurses, and physician assistants as shown in the characteristics of included studies (**Table 3**).

Table 3: Characteristics of included studies

Study ID	Study design	Country	Participants	Intervention	Comparison	Duration of interventions	Vaccine target	Outcomes (assessed similarly)
Cates 2014 (144)	Non-randomised trial	USA	Parents & health providers	Mult-faceted providers and parents	Usual care	Three months	HPV	Vaccination coverage
Diclemente 2015 (136)	Randomized trial	USA	Adolescents	Health education	Usual care	30 minutes	HPV	Vaccination coverage
Fiks 2016 (147)	Controlled before-after study	USA	Health Provider	Provider incentives	Usual care	1 year	HPV	Vaccination coverage Cost
Gargano 2015 (137)	Randomised trial	USA	Parents	Health education	Usual care	2 years	Tdap, MCV, HPV, Influenza	Knowledge & attitude
Grandahl 2016 (129)	Cluster-randomised trial	Sweden	Adolescents	Health education	Usual care	30 minutes	HPV	Vaccination coverage
Mantzari 2015 (138)	Randomised trial	United Kingdom UK	Adolescents	Financial incentives	Usual care	6 months	HPV	Vaccination coverage
Paskett 2016 (139)	Randomized trial	USA	Parents and health providers	Multi-faced providers and parents	Usual care	-	HPV	Vaccination coverage Knowledge & attitude
Perkins 2015 (128)	Cluster-randomised trial	USA	Adolescent and health providers	Multi-component provider intervention	Usual care	2 years	HPV	Vaccination coverage
Rickert 2015 (140)	Randomised trial	USA	Parents	Health education	Usual care	I hour	HPV	Adverse effects

Schwarz 2008 (141)	Randomised trial	USA	Adolescents and caregivers	Health education plus financial incentives	Usual care	21 months	HepB	Vaccination coverage Knowledge & attitude
Skinner 2000 (142)	Randomized trial	Australia	Adolescents	Health education	Usual care	1 year	HepB	Vaccination coverage Knowledge & attitude
Staras 2015 (145)	Non-randomised trial	USA	Adolescents	Health education	Usual care	3 months	HPV	Vaccination coverage
Szilagyi 2015 (143)	Randomised trial	USA	Health providers	Provider prompts	Usual care	2 month	Tdap, MCV, HPV, Infleunza	Vaccination coverage
Wilson 2005 (146)	Non-randomised trial	USA	Adolescent	Mandatory school entry vaccination	Usual care	-	HepB, Td, and MMR	Vaccination coverage
Winer 2016 (131)	Cluster-randomised trial	USA	Parents	Health education	Usual care	30–40 min	HPV	Vaccination coverage
Watson-Jones 2012 (130)	Cluster-randomised trial	Tanzania	Adolescents	Class-based vaccination	Age-based vaccination	12 months	HPV	Vaccination coverage Cost Adverse events

Interventions and comparisons

1) *Recipient-oriented interventions*

The recipient-oriented intervention studies assessed health education (129, 131, 136, 137, 140, 142, 145), financial incentives (138), health education and financial incentives (141), and a school entry law mandating vaccination (146); compared to usual care.

In four of the five health education studies, participants in the intervention arm received structured 30-40 minutes interactive education on the target VPD, vaccine recommendations, vaccine schedule, and vaccine efficacy and safety. Participants in the comparison "usual care" group received general health education or education on the prevention of a specific non-vaccine related condition (129, 131, 136, 145). In the fifth study, participants in the education arm received a complex multi-component intervention that included a resource fact sheet and assessment; an information video and questions designed to engage the adolescent audience; small group discussions; and an activity to locate resource information on the Internet. However, both the intervention and comparison arms received information brochures consisting of one-page folded coloured leaflets; outlining in simple terms, the risks of the target disease and the benefits and side effects of vaccination (142).

2) *Provider -oriented interventions*

The provider-oriented intervention studies assessed provider prompts (143), incentives (147), and a multi-faceted intervention (128); compared to usual care.

3) *Recipient and provider (multi-faceted)-oriented interventions*

Two studies assessed multi-faceted interventions aimed at both recipients and providers of vaccination services (139, 144); compared to usual care.

4) Health system intervention

One study compared a class-based vaccination strategy to an age-based strategy (130).

Outcomes

All sixteen studies reported data on the primary outcome of interest, vaccination coverage. Eleven studies (128-131, 136, 138-140, 144, 145, 147) evaluated completion of the HPV vaccination schedule. Three studies (141, 142, 146) assessed uptake of vaccines against hepatitis B virus. Finally, three studies (137, 143) reported data on uptake of tetanus-diphtheria-acellular- pertussis (Tdap), meningococcal conjugate vaccine, HPV, and influenza vaccines.

Other pre-defined outcome measures reported by the included studies are: knowledge, attitudes, beliefs, and practice (137, 139, 141, 142); cost of the intervention (130, 147); adverse events following immunisation (130); and adverse effects of the intervention (140).

Pre-defined outcomes not reported by the included studies are incidence of vaccine-preventable diseases and equitable uptake of immunisation.

Excluded studies

We excluded 48 studies and the reasons are provided in the table of excluded studies (**Appendix 3**). The most common reasons for exclusion were ineligible study designs and interventions.

Risk of bias in included studies

We summarised the risk of bias assessment in each of the included studies (**Figures 10** and **11**).

Allocation (selection bias)

The risk of selection bias (random sequence generation) was low for nine studies (128, 129, 131, 136, 138-140, 142, 143), unclear for three studies (130, 137, 141), and high for four studies (144-147).

The risk of selection bias (allocation concealment) was low for six studies (129, 130, 136, 138, 140, 143), unclear for seven studies (131, 137, 139, 141, 142, 144, 146), and high for three studies (128, 145, 147).

Blinding (performance bias and detection bias)

Risk of performance bias (blinding of participants and personnel) was low for two studies (138, 143), unclear for nine studies (128, 131, 136, 137, 139, 141, 142, 145, 146), and high for five studies (129, 130, 140, 144, 147).

The risk of detection bias (blinding of outcome assessments) was low for two studies (129, 136), unclear for twelve studies (128, 131, 137-146), and high for two studies (130, 147).

Incomplete outcome data (attrition bias)

The risk of attrition bias (incomplete outcome data) was low for ten studies (130, 131, 136, 138-143, 147), unclear for four studies (128, 129, 144, 146), and high for two studies (137, 145).

Selective reporting (reporting bias)

Selective reporting was categorised as low risk in twelve studies (128-130, 136, 138, 139, 141, 143-147) and unclear in four studies (131, 137, 140, 142).

Other potential sources of bias

All studies reported similar baseline characteristics between the intervention and control groups. In Addition, all studies reported no differences in the outcome measures at baseline and during intervention. One study (RCT (58)) reported a possible contamination of controls with the interventions, but none of the other studies reported contamination of control the interventions assessed. We did not have reasons to indicate that other biases were introduced into the remaining studies, over and above the ones reported above.

Figure 10: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

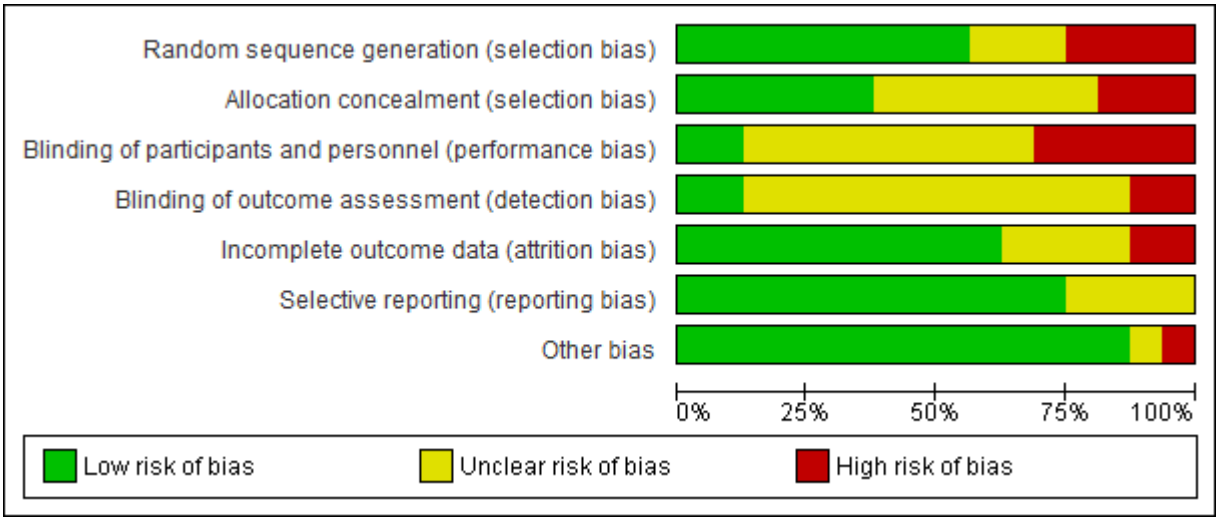
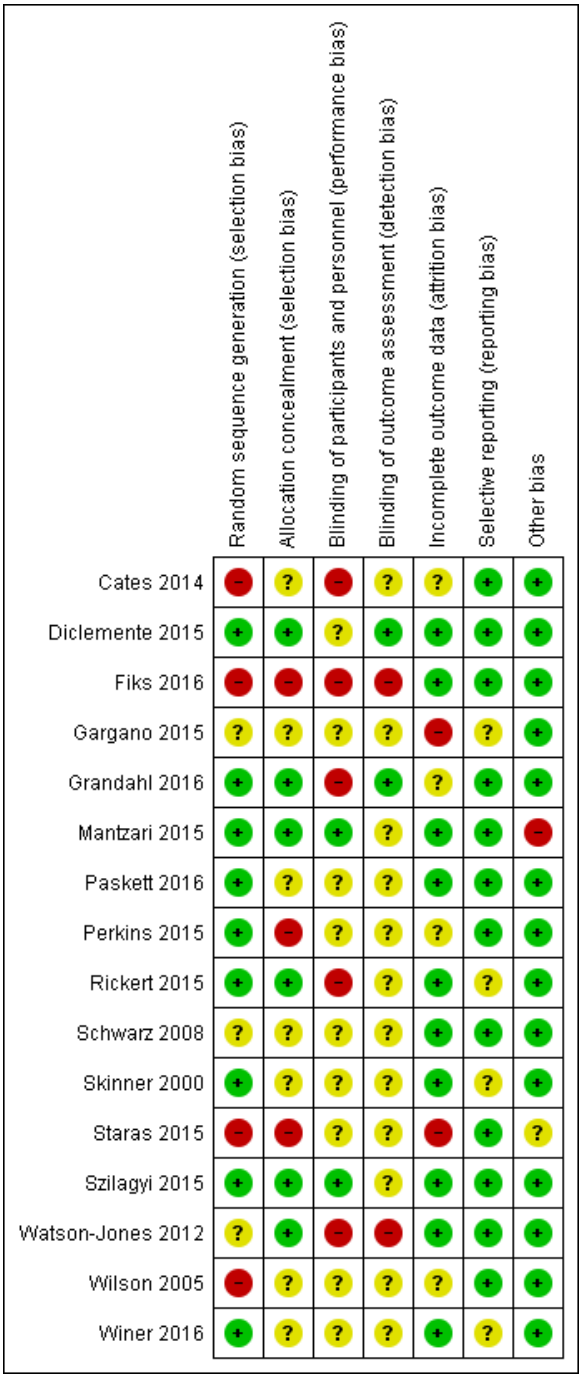


Figure 11: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

1. Recipient-oriented interventions

1.1 Health education compared to usual care on vaccination coverage

Four studies (RCT(136); cRCT(129, 131); nRCT(145)) show that health education probably improves HPV vaccination coverage (3876 participants: RR 1.56, 95%CI 1.26 to 1.93; I^2 = 17%; moderate certainty evidence; (**Figure 12** Analysis 1.1) (Summary of findings; **Table 4**). Our main concern with the evidence was the high risk of bias in the included studies. However, one large study (RCT(142)) suggests that a multi-component health education intervention probably leads to a marginal decrease in the uptake of three doses of the hepatitis B vaccine, compared to simplified information leaflets on the vaccine (17411 participants: RR 0.98, 95%CI 0.97 to 0.99; moderate certainty evidence; (**Figure 13** Analysis 1.2) (Summary of findings; **Table 4**).

Figure 12: Analysis 1.1: Human papillomavirus (HPV) vaccine series

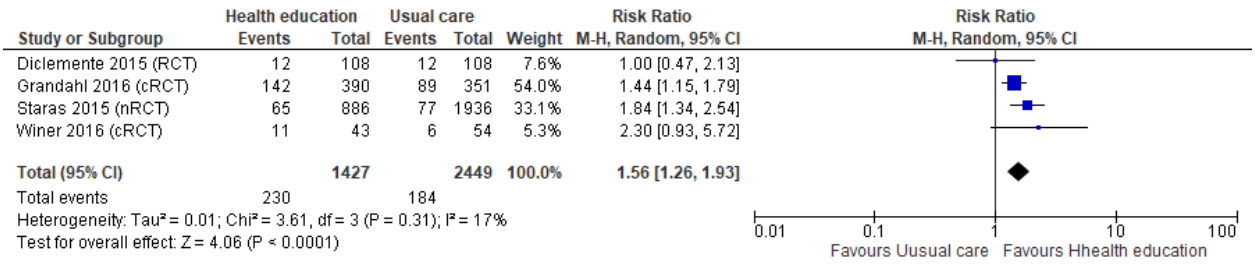


Figure 13: Analysis 1.2: Immunisation rate of Hepatitis B vaccine (HPV 3 dose)

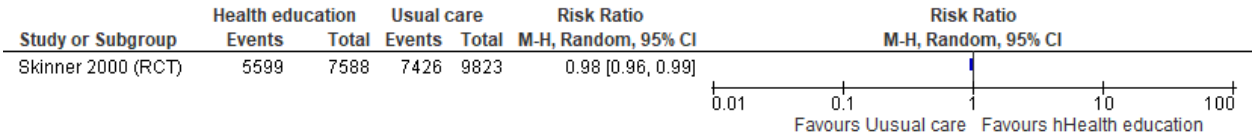


Table 4: Summary of findings :Vaccination education compared to usual care
Population: Adolescents and parents
Setting: Australia, Sweden, and United States of America
Intervention: Vaccination education

Comparison: Usual care

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Comments
	With usual care	With health education				
Uptake of human papillomavirus vaccine	75 per 1,000	117 per 1,000 (95 to 145)	RR 1.56 (1.26 to 1.93)	3876 (4 studies)	⨁⨁⨁⊖ Moderate [1]	Health education probably improves vaccine uptake.
Uptake of three doses of hepatitis B vaccine	756 per 1,000	741 per 1,000 (726 to 748)	RR 0.98 (0.96 to 0.99)	17411 (1 study)	⨁⨁⨁⊖ Moderate [1]	Health education probably leads to a marginal decrease in vaccine uptake.

***The anticipated absolute effect in the intervention group** (and its 95% confidence interval) is based on the assumed likelihood of being vaccinated in the usual care group and the **relative effect** of the intervention (and its 95% CI).

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

** **GRADE Working Group grades of evidence**

High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†Substantially different = a large enough difference that it might affect a decision

Footnotes

[1] Downgraded by 1 level due to high risk of bias in included study.

1.2 Health education compared to usual care on KAP

One study (RCT(137)) determined the relationship between attitudes of parents of middle- and high-school students and acceptance of school-located vaccination clinics for all four recommended adolescent vaccines (HPV, meningococcal conjugate, Tdap, and Influenza). The study suggests that perceived severity of illness and intention to vaccinate may lead to parental acceptance of school-located vaccination clinics.

Another study (RCT(142)) reveals that a specifically designed hepatitis B vaccine education curriculum package may improve knowledge of the targeted disease and vaccination among students.

1.3 Health education compared to usual care on adverse events

One study (RCT(140)) reported that health education did not have any adverse events in relation to adolescent vaccination. Health education plus financial incentives

1.4 Financial incentives compared to usual care on vaccination coverage

One study (RCT(138)) found that financial incentives may improve coverage with the first dose of the HPV vaccine (500 participants; RR 1.45, 95%CI 1.05 to 1.99; **Figure 14** Analysis 2.1). We judged the certainty of the evidence as low (Summary of findings **Table 5**), because of concerns regarding study limitations and imprecision of the effect.

Figure 14: Analysis 2.1, HPV vaccine initial uptake

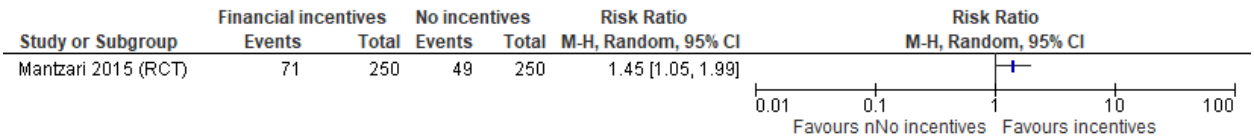


Table 5: Summary of findings: Financial incentives compared to no incentives

Patient or population: Adolescents
Setting: United Kingdom
Intervention: Financial incentives
Comparison: No incentives

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Comments
	With no incentive	With financial incentives				
Uptake of human papillomavirus vaccine	196 per 1,000	284 per 1,000 (206 to 390)	RR 1.45 (1.05 to 1.99)	500 (1 study)	⨁⨁⊖⊖ Low[1,2]	Financial incentives may improve vaccination coverage.

***The anticipated absolute effect in the intervention group** (and its 95% confidence interval) is based on the likelihood of being vaccinated in the "no incentive" group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio
**** GRADE Working Group grades of evidence**
High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
†Substantially different = a large enough difference that it might affect a decision

Footnotes
[1] Downgraded by 1 level for high risk of bias in included study.
[2] Downgraded by 1 level for imprecision of findings.

1.5 Health education and financial incentives compared to usual care on vaccination coverage

A small study (RCT(141)) compared health education and financial incentives to usual care, and reveals that the intervention may improve completion of the full series of three doses of the hepatitis B vaccine (104 participants: RR 1.38, 95%CI 0.96 to 2.00; **Figure 15** Analysis 3.1). We judged the certainty of the evidence on the effects of the intervention as low (Summary of findings **Table 6**, because of concerns regarding the high risk of bias in the included study and imprecision of the findings.

Figure 15: Analysis 3.1, Immunisation rate of Hepatitis B vaccine (3 dose)

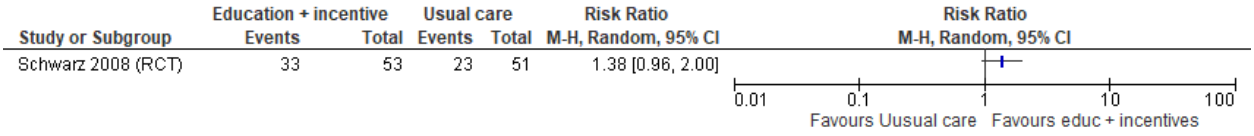


Table 6*:* Summary of findings: Vaccination education plus financial incentives compared to usual care

Population: Adolescents and parents
Setting: United States of America
Intervention: Vaccination education plus financial incentives
Comparison: Usual care i.e. education on a non-vaccine topic

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Comments
	With usual care	With health education and incentives				
Uptake of three doses of hepatitis B vaccine	451 per 1,000	622 per 1,000 (433 to 902)	RR 1.38 (0.96 to 2.00)	104 (1 study)	⨁⨁⊖⊖ Low [1,2]	Health education plus financial incentives may improve vaccination coverage.

***The anticipated absolute effects in the intervention group** (and its 95% confidence interval) is based on the likelihood of being vaccinated in the usual care group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio
**** GRADE Working Group grades of evidence**
High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
†Substantially different = a large enough difference that it might affect a decision

Footnotes
[1] Downgraded by 1 level for high risk of bias in included study.
[2] Downgraded by 1 level for imprecision of findings.

1.6 Health education and financial incentives compared to usual care on KAP

The study by Schwarz and colleagues (RCT(141)) suggests that a culturally appropriate educational video on hepatitis B vaccine may improve vaccine knowledge and may improve return rates for the vaccine.

1.7 Mandatory vaccination versus usual care on vaccination coverage

Wilson et al (nRCT(146)) assessed the effect of mandatory hepatitis B vaccination for elementary school entry in the state of Missouri in the USA. The study compared students in the ninth grade (affected by the hepatitis B vaccination law) and 12th grade (not affected by the law) in the state. The study showed that making vaccinations mandatory probably improves vaccination coverage (6462 participants: RR 4.24, 95%CI 3.94 to 4.56; **Figure 16** Analysis 4.1).

In addition, the study compared the 9th grade in Missouri (affected by the mandatory vaccination law) to 9th grade in the state of Kansas (not affected by the law); and confirmed that mandating vaccination probably improves uptake of the vaccine (6462 participants: RR 3.92, 95%CI 3.65 to 4.20; **Figure 16** Analysis 4.1).

We judged the certainty of the evidence as moderate (Summary of findings **Table 7**, because of the high risk of bias in the included study.

Figure 16: Analysis 4.1, Immunisation rate of Hepatitis B vaccine (HPV 3 dose).

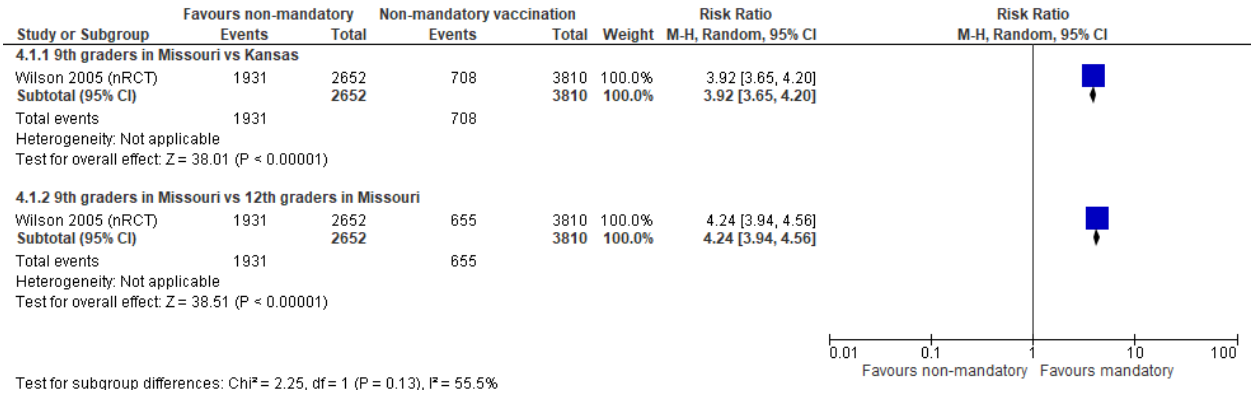


Table 7: Summary of findings: Mandatory vaccination versus usual care

Population: Adolescents
Setting: United States of America
Intervention: School entry law mandating vaccination
Comparison: Usual care

Outcomes	Absolute effects* (95% CI)	Relative effect	№ of participants	Certainty of the evidence	Comments

	With usual care	With mandatory vaccination	(95% CI)	(studies)	(GRADE)**	
Uptake of three doses of hepatitis B vaccine	172 per 1,000	729 per 1,000 (677 to 784)	RR 4.24 (3.94 to 4.56)	6462 (1 study)	⊕⊕⊕⊖ Moderate[1]	Mandating vaccination probably improves vaccination coverage.

***The anticipated absolute effects in the intervention group** (and its 95% confidence interval) is based on the likelihood of being vaccinated in the no-intervention group and the **relative effect** of the intervention (and its 95% CI).
Missouri mandated hepatitis B vaccination for elementary school entry in 1997 and for middle school in 1999. Kansas mandated hepatitis B for elementary school entry in 2004, after this study.
CI: Confidence interval; **RR:** Risk ratio
****GRADE Working Group grades of evidence**
High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
†Substantially different = a large enough difference that it might affect a decision

Footnotes
[1] Downgraded by 1 level for high risk of bias in the included study.

2. Provider-oriented interventions

2.1 Provider prompts compared to usual care on vaccination coverage

Szilagyi et al (RCT (143)) assessed the impact of provider prompts compared to usual care on the uptake of various recommended adolescent vaccines (**Figure 17-20** Analysis 5.1-5.4). The study shows that provider prompts probably make little or no difference to the uptake of Tdap (3520 participants: RR 1.05, 95%CI 0.99 to 1.11; **Figure 18** Analysis 5.2); meningococcal (3520 participants: RR 1.05, 95%CI 0.99 to 1.11; **Figure 19** Analysis 5.3); HPV (1771 participants: RR 1.06, 95%CI 0.87 to 1.30; **Figure 17** Analysis 5.1), and influenza (3520 participants :RR 1.05, 95%CI 0.96 to 1.15; **Figure 20** Analysis 5.4) vaccines. We judged the certainty of the evidence as moderate (Summary of findings **Table 8**), because of concerns regarding imprecision of findings.

Figure 17: Analysis 5.1, HPV vaccination uptake

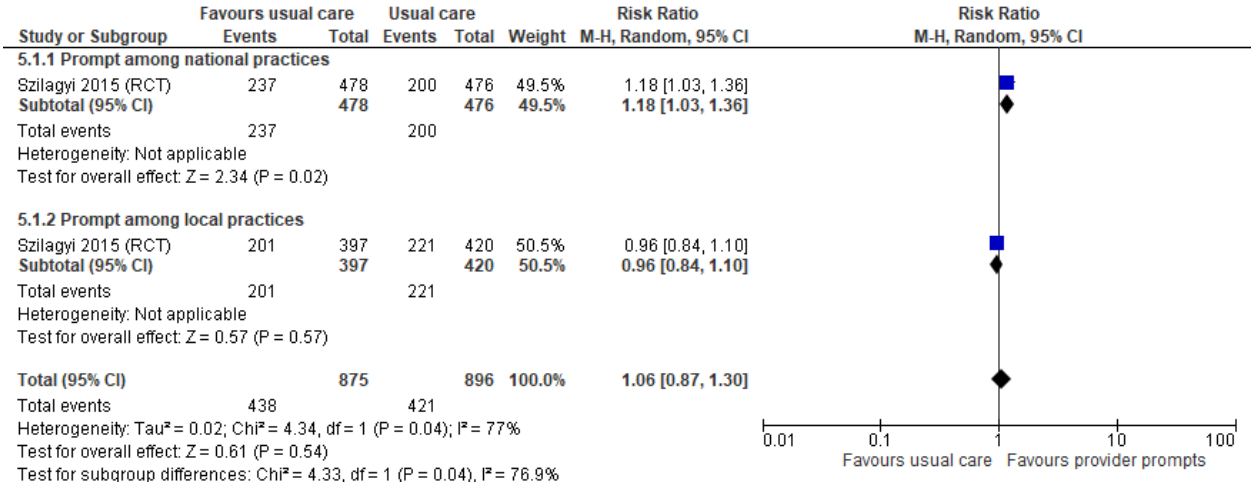


Figure 18: Analysis 5.2, Tdap vaccination uptake

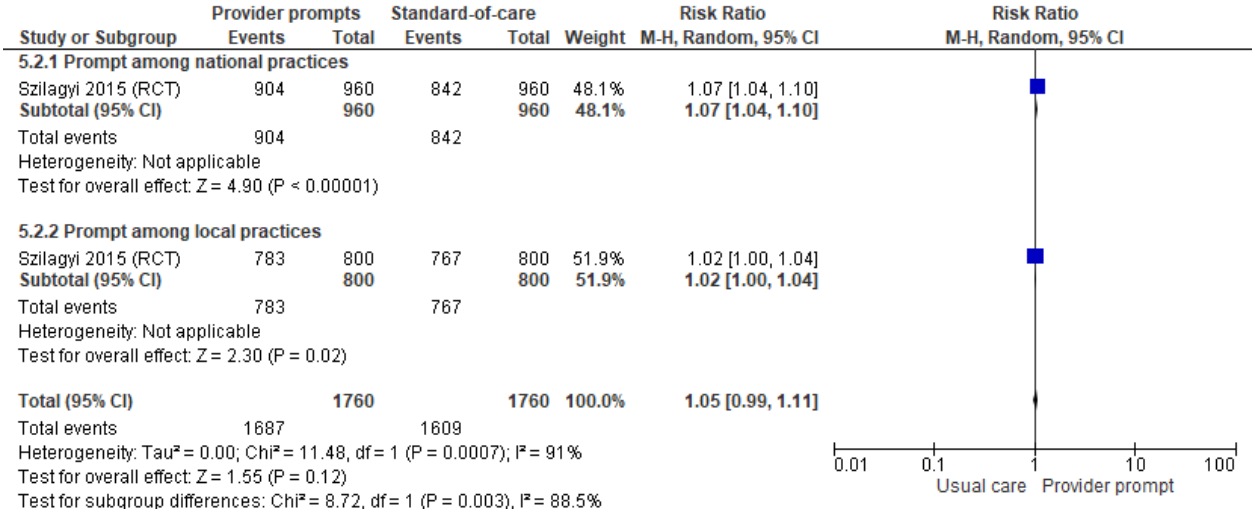


Figure 19: Analysis 5.3, MCV4 vaccination uptake

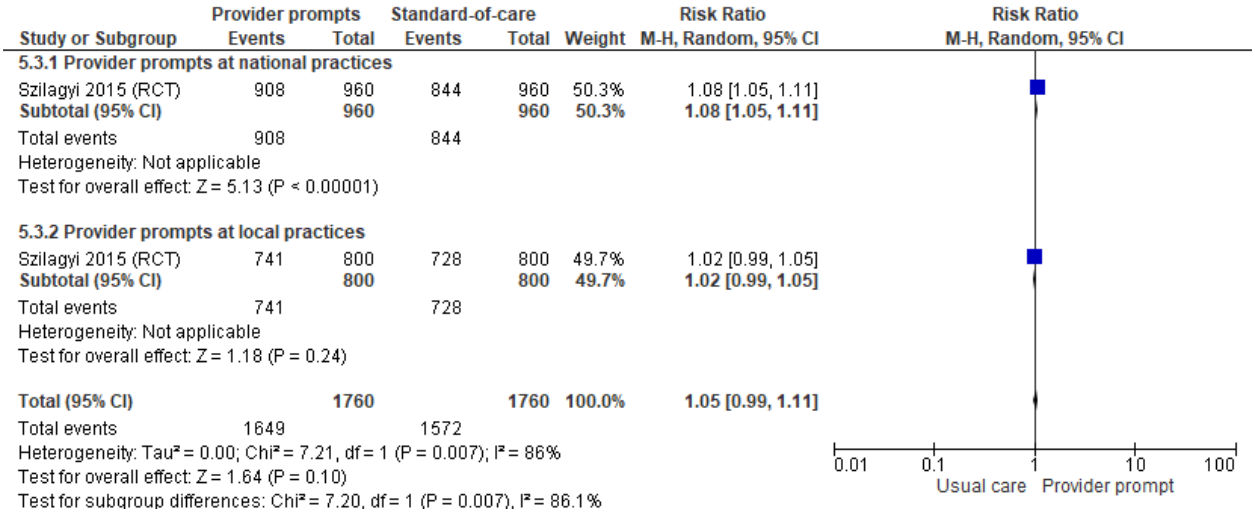


Figure 20: Analysis 5.4, Seasonal influenza vaccination uptake

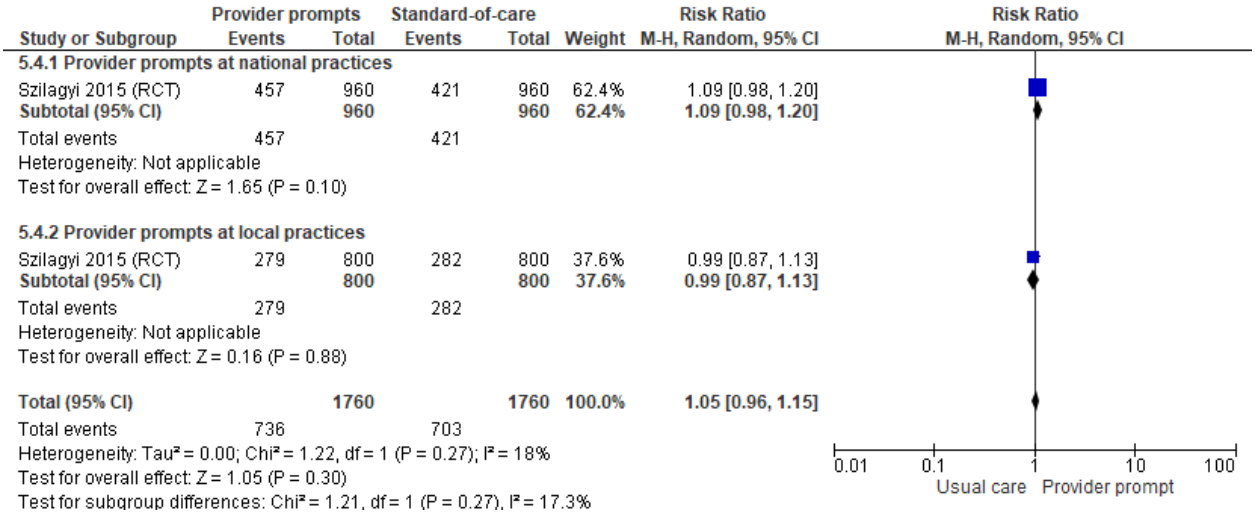


Table 8: Summary of findings: Provider prompts compared to usual care

Population: Healthcare workers
Setting: United States of America
Intervention: Provider prompts
Comparison: Usual care

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certaintyof the evidence (GRADE)**	Comments
	With usual care	With provider prompts				
Uptake of Tdap vaccine	914 per 1,000	960 per 1,000 (905 to	RR 1.05 (0.99 to 1.11)	3520 (1 study)	⨁⨁⨁⨀ Moderate[1]	Provider prompts probably make little or no difference to uptake of Tdap vaccine

		1000)				
Uptake of Men vaccine	893 per 1,000	938 per 1,000 (884 to 991)	RR 1.05 (0.99 to 1.11)	3520 (1 study)	⊕⊕⊕⊖ Moderate[1]	Provider prompts probably make little or no difference to uptake of the meningococcal conjugate vaccine
Uptake of HPV3	470 per 1,000	498 per 1,000 (409 to 611)	RR 1.06 (0.87 to 1.30)	1771 (1 study)	⊕⊕⊕⊖ Moderate[1]	Provider prompts probably make little or no difference to completion of HPV vaccine schedule
Uptake of seasonal influenza vaccine	399 per 1,000	419 per 1,000 (383 to 459)	RR 1.05 (0.96 to 1.15)	3520 (1 study)	⊕⊕⊕⊖ Moderate[1]	Provider prompts probably make little or no difference to uptake of the seasonal influenza vaccine

*__The anticipated absolute effects in the intervention group__ (and its 95% confidence interval) is based on the likelihood of being vaccinated in the usual care group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **Tdap**: tetanus-diphtheria-acellular pertussis; Men: meningococcal conjugate vaccine; HPV3: three doses of human papillomavirus vaccine.
**** GRADE Working Group grades of evidence**
High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
†Substantially different = a large enough difference that it might affect a decision
Footnotes
[1] Downgraded by 1 level for imprecision of findings.

2.2 Provider incentives compared to usual care on vaccination coverage

One study (CBA (147)) looked at the effect of maintenance of certification (MOC) programme contingent on captured opportunities for HPV vaccination i.e. visits at which an eligible adolescent patient saw a paediatrician or nurse practitioner and received a dose of the HPV vaccine. MOC clinicians increased their captured opportunities for HPV vaccination, relative to nonparticipating clinicians, by 5.7 percentage points for the first dose of HPV given during preventive visits and by 0.7 and 5.6 percentage points for the first and second doses of HPV given during acute care visits. Therefore, compared to

usual care, MOC programmes may lead to an increase in captured opportunities for HPV vaccination.

Fiks et al (CBA (147)) evaluated the costs required to implement the MOC programme. The authors calculated the total cost of each of the following components: creation of the performance feedback reports, time spent on creating and delivering the educational content, and time spent by participating providers on (1) group calls, (2) reviewing data, and (3) planning/ implementing practice change. The estimated total cost of the MOC programmes was $17,887 ($662 per participant), of which $17,064 was for participant time spent on the programmes.

2.3 Multi-component provider interventions compared to usual care on vaccination coverage

Perkins 2015 (cRCT (128)) assessed the effects of a four-component provider intervention package (education session, repeated contacts, individualized feedback, and incentives) and found that the intervention may improve the uptake of the next needed HPV vaccine dose.

3. Provider and recipient-oriented interventions

3.1 Provider and parent multifaceted intervention compared to usual care on vaccination coverage

Cates et al (nRCT (144)) assessed the effects of a social marketing intervention among parents and providers and Paskett et al (RCT (139)) assessed the effects of multi-component education of both providers and parents. Combining the data shows that using a multi-faceted provider and parent intervention probably improves HPV

vaccination coverage (two studies, 26206 participants: RR 1.42, 95%CI 1.26 to 1.60; I^2 = 0%: **Figures 21** Analysis 6.1). We judged the certainty of the evidence as moderate (Summary of findings **Table 9**), because of concerns regarding high risk of bias in the included studies.

Figure 21: Analysis 6.1, HPV vaccination uptake

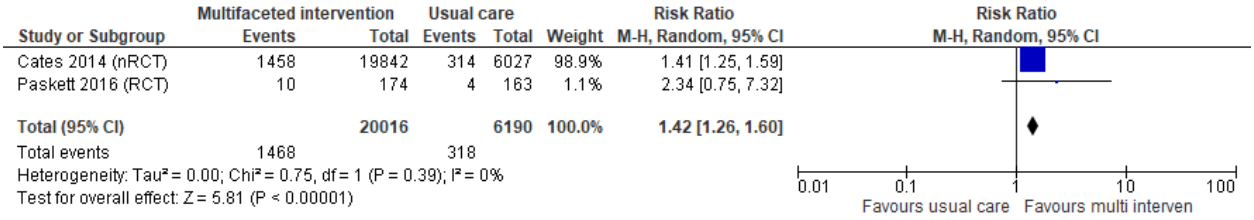


Table 9: Summary of findings: Provider & parent multi-faceted intervention compared to usual care

Population: Healthcare workers and parents
Setting: United States America
Intervention: Multi-faceted intervention
Comparison: Usual care

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Comments
	With usual care	With multi-faced intervention				
HPV vaccine uptake	51 per 1,000	73 per 1,000 (65 to 82)	RR 1.42 (1.26 to 1.60)	26206 (2 studies)	⨁⨁⨁⨀ Moderate [1]	Multi-faceted intervention probably improves HPV vaccination coverage

*__The anticipated absolute effects in the intervention group__ (and its 95% confidence interval) is based on the likelihood of being vaccinated in the usual care group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio
**** GRADE Working Group grades of evidence**
High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
†Substantially different = a large enough difference that it might affect a decision

Footnotes
[1] Downgraded by 1 level for high risk of bias in the included studies.

3.2 Provider and parent multifaceted intervention compared to usual care on KAP

Paskett 2016 (RCT (139)) suggests that multi-component education of both providers and parents may increase knowledge about HPV infection and HPV vaccine among providers and parents.

4. Health systems interventions

4.1 Class-based compared to age-based school vaccination on vaccination coverage

Watson-Jones et al (cRCT (130)) assessed the effect of two HPV vaccine delivery strategies and showed that class-based delivery probably leads to higher HPV vaccine uptake than an age-based delivery strategy (one study, 5537 participants: RR 1.09, 95%CI 1.06 to 1.13; **Figure 22** Analysis 7.1). We judged the certainty of the evidence as moderate (Summary of findings **Table 10**), because of concerns regarding high risk of bias in the included study.

Figure 22: Analysis 7.1, HPV vaccination uptake

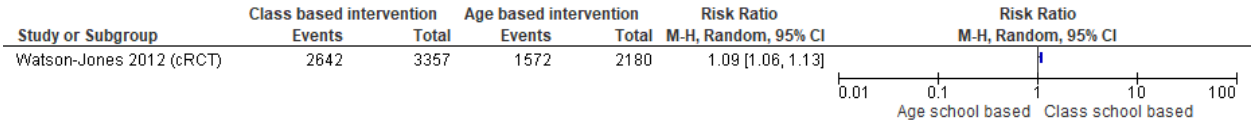


Table 10: Summary of findings: Class-based compared to age-based HPV vaccine delivery

Population: Adolescents
Setting: Tanzania
Intervention: Class-based vaccination
Comparison: Age-based vaccination

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Comments
	With age-based delivery	With class-based delivery				

HPV vaccination uptake	721 per 1,000	786 per 1,000 (764 to 815)	RR 1.09 (1.06 to 1.13)	5537 (1 study)	⨁⨁⨁⊖ Moderate[1]	Class-based vaccination probably leads to higher HPV vaccine uptake than age-based vaccination.

*__The anticipated absolute effects in the intervention group__ (and its 95% confidence interval) is based on the likelihood of being vaccinated in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

****GRADE Working Group grades of evidence**

High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†Substantially different = a large enough difference that it might affect a decision

Footnotes

[1] Downgraded by 1 level for high risk of bias in the included study.

The study by Watson-jones and colleagues (cRCT (130)) collected data on the costs of class-based versus age-based delivery of the HPV vaccine in Tanzania found the class-based vaccination strategy to be less expensive. It costed 52 and 67 US Dollars per girl vaccinated in a class-based strategy in urban and rural schools, respectively; compared to 87 and 98 US Dollars respectively, for the age-based delivery system.

Watson-jones and colleagues study (cRCT(130)) reported 11 AEFI. One AEFI was considered to be related to HPV vaccination. The AEFI consisted of a generalized rash after the first dose of an HPV vaccine in a 12-year-old student. This resolved within a week without treatment. The student was not given further doses of the vaccine. The study did not report if the 11 AEFIs were in the age-based or class-based group for delivering HPV vaccines.

Discussion

Summary of main results

We found that educating adolescents and their parents about the importance of vaccinations, passing laws stating that adolescents must be vaccinated prior enrolment at school, or using class-based rather than age-based approaches for delivering vaccines probably improves adolescent vaccination coverage. Adolescent vaccination coverage is also probably improved through targeting parents and healthcare providers with a combination of vaccination education, phone calls, and radio messages. In addition, providing adolescents and their parents with financial incentives alone or in combination with vaccination education may improve adolescent vaccination coverage. Finally, reminding healthcare providers to vaccinate adolescents when they open their

electronic medical charts probably makes little or no difference to adolescent vaccination coverage. From the data included in this review, we are uncertain about the costs of the interventions tested and their effects on knowledge and attitudes to adolescent vaccination.

Overall completeness and applicability of evidence

Our systematic review is comprehensive: we included all known types of interventions for improving vaccination coverage (except recipient-oriented reminders (122)), all vaccines recommended by WHO for boys and girls aged 10 to 19 years (36), and all settings. We identified only 16 eligible studies which showed possible benefits for the following interventions: recipient-oriented education, legislation, and financial incentives; provider education; and, tailored school outreach programmes.

One study showed a complex hepatitis B vaccine education curriculum package has no benefit (142). The participants were 17,411 boys and girls in 235 schools in Melbourne, Australia. The adolescents in the intervention group received four structured lessons on hepatitis B vaccine, including: (1) a resource fact sheet and assessment, (2) an information video and questions designed to engage the adolescent audience, (3) a small group discussion, and (4) an activity to locate resource information on the Internet. In addition, adolescents in both the intervention and comparison arms received the usual government information brochures. The latter were one-page folded coloured leaflets, outlining in simple terms, the risks of hepatitis B and benefits and side effects of vaccination. The authors found a 2% relative decrease in the uptake of three doses of the hepatitis B vaccine in the intervention compared to the usual care group (142). This might be an indication that interventions for improving immunisation coverage

(irrespective of the audience) need to be comprehensive, and yet be as simple as possible. Rosenbaum and colleagues have shown that non-research individuals struggle to understand the text and numbers (148). They recommend that to render summaries of health information easier to assimilate and more useful to end users, the summaries needs to clear, and easy to read or scan quickly.

This review has several limitations. Firstly, 15 of the 16 included studies were conducted in HICs, mainly the USA, in which vaccination services are readily available to adolescent girls and boys. Such a scenario is not necessarily possible in all other settings; therefore, the findings from these studies need to be interpreted with caution when applied to different settings. Secondly, there is limited information from the studies on the cost-effectiveness of the interventions tested. The costs of interventions were reported in only two studies, including a provider incentive intervention (147) and a health system intervention (130). Although both studies focused on HPV vaccination, the costs varied, due to diversity in interventions, study settings, and methods of calculating costs and items included in the calculations. Therefore, when applying the findings of this review to any setting, local costings should be undertaken; particularly in settings differing from those of the original investigations. Thirdly, the studies included in this review did not report information on equity. It is possible that the implementation of interventions may increase inequity if they are not adapted to populations in remote and under-served areas in countries or if there is substantial variability in socio-economical characteristics among populations receiving the interventions. Given these contextual issues, any adolescent vaccination programme implemented based on our review

findings should include a monitoring component to assess the performance of the intervention within the given context.

One study in our review was conducted in a country defined by the World Bank as LMIC (130). The study compared class-based and age-based strategies for delivering HPV vaccines among 5,537 girls in 134 primary schools in northwest Tanzania. There was a 9% relative increase in vaccination coverage among eligible girls in schools assigned to a class-based approach, compared to girls in schools using an age-based strategy. This is an important finding and is readily applicable to other LMICs that do not have established immunisation programmes for adolescents, but have introduced or are contemplating to introduce HPV vaccination (149) and other vaccines for adolescents. School health programmes can have an advantage of integrating various existing health services at minimal increase in cost (101). In line with our findings, a previous review of school-based programmes in 17 countries found that school-based programmes lead to substantial increases in HPV vaccination coverage (150).

Although the effect sizes reported in this review are small to moderate, even relatively small effect sizes for interventions aimed at increasing uptake of adolescent vaccines are clinically important in large populations. We therefore believe that this review is an important resource for countries and international organisations, in the context of the GVAP; a "framework to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities" (151).

Certainty of evidence

Using the GRADE approach, we judged the certainty of the evidence on the effects of included interventions on our primary outcome (adolescent vaccination coverage) as either moderate or low. Among the interventions targeting adolescents and their communities, we judged the certainty of the evidence as moderate for education (**Table 4** Summary of findings) and legislation mandating vaccination (**Table 7** Summary of findings); and low for financial incentives (**Table 5** Summary of findings) and a combination of education and financial incentives (**Table 6** Summary of findings). Regarding provider-oriented interventions, we assessed the certainty as moderate for provider prompts (**Table 8** Summary of findings). For the combination of recipient and provider interventions, we assessed the certainty of evidence as moderate (**Table 9** Summary of findings). Lastly, on health system interventions, we judged the certainty of the evidence as moderate for class-based compared to age-based delivery of vaccines to adolescents (**Table 10** Summary of findings). Our main concerns with the evidence related to study limitations. Most of the included studies have an unclear or high risk of bias. The main limitations were non-randomisation, non-concealment of allocation, and no blinding among outcome assessors (**Figure 10** and **11**).

Potential biases in the review process

We minimised potential biases in the review process by adhering to Cochrane guidelines (126). We conducted comprehensive searches without limiting the searches to a specific language. Two authors independently assessed study eligibility, extracted data, and assessed the risk of bias in each included study. The eligible cRCTs reported that they adjusted for cluster effects. However, there is some level of subjectivity in the determination of concerns that are serious enough to require rating down (or up) the

evidence; and it is possible that others would have arrived at slightly different levels of certainty of evidence.

Agreements and disagreements with other studies or reviews

Few recent systematic reviews have assessed the effectiveness of interventions for improving adolescent immunisation coverage (119-122, 152). Das and colleagues searched three databases for studies published up to December 2014 and included 23 studies on the effectiveness of interventions to improve vaccination coverage among adolescents. The authors reported evidence of moderate certainty from 13 studies, suggesting that vaccination requirement for schooling, immunisation reminders, and national permissive recommendation increase vaccination coverage in adolescents (120). Smulian and colleagues, in the second review, searched five databases and included 34 intervention studies published to May 2015. The authors report that many types of intervention strategies (targeting recipients, providers, and the health system) lead to increases in HPV vaccination coverage in different settings (152). In the third review, Jacobson Vann and colleagues searched four databases to January 2017; for trials, CBA studies and ITS evaluating vaccination-focused recipient reminders in children, adolescents, and adults in any setting. The review included 10 relevant studies showing high certainty evidence that reminders improve adolescent vaccination coverage (122).

In the fourth review, Walling and colleagues searched three databases for studies published to April 2014 and included 51 studies on the interventions that have increased HPV vaccination uptake coverage among adolescents and young adult. The authors reported that school health programmes increase vaccination coverage in adolescents

(119). Crocker-Buque and colleagues is the fifth review that searched close to nine databases until June 2016 but only looked at Organisation for Economic Co-operation and Development countries only. The review looked at interventions to reduce inequalities in vaccine uptake in children and adolescents. The study concluded that multicomponent interventions can be used to increase vaccination uptake, however the author did not specify which intervention work best from adolescent in relation to children (121).

The reviews by Das et al (120) and Smulian et al (152) have some overlap with our review in terms of included studies, but many studies included in the two reviews do not meet the EPOC criteria for inclusion of studies in systematic reviews of effects (125). Had we included recipient-oriented reminders in our review, there would have been enhanced overlap between our review findings and those from the Jacobson et al (122) review, specifically, in terms of studies that assessed this intervention for improving adolescent vaccination coverage. Our systematic review therefore complements earlier relevant reviews on the topic.

In addition to the summary of evidence, we further assessed the quality of the five related reviews using A MeaSurement Tool to Assess Systematic Reviews scale (AMSTAR2) tool (153). Summary on the quality of the systematic review with justification together with description on the evidence is elaborated in **Table 11** below.

Table 11: Descriptive summary on the evidence of the existing systematic review

Study 1D	No of studies included	Duration of study	Population	Target vaccines	Quality assessment of systematic reviews by AMSTAR	Quality assessment justification
Walling 2016 (119)	51 studies	2006-2015	Men and/or women 11–26 y old	HPV	Moderate	A comprehensive literature search strategy was not used and the author did not provide a list of excluded studies. It was not clear if the author performed investigation of publication bias.
Das 2016 (120)	23 studies	Inception of database to 2014	Adolescents and youth	Measles, MMR, TDap, Varicella, Rubella & HPV	Moderate	The author did not provide a list of excluded studies and it was not clear if the author performed investigation of publication bias.
Crocker-Buque 2017 (121)	41 studies	2008 and 2015	Children and young people (CYP) from birth to 19 years	Measles, MMR, TDap, Varicella, Rubella, HPV & Influenza	Low	The author did not provide a list of excluded studies and It was not clear what technique the author used for assessing the risk of bias. Additionally, it was not clear if the author performed investigation of publication bias.
Jacobson Vann 2018 (122)	75 studies	update to Jan 2017	Children (birth to 18 years) or adults (18 years and up	All vaccines	High	All the domains of AMSTAR was clearly addressed in this review
Smulian et al 2016 (152)	34 studies	2006 to 2015	Adolescents	HPV	Low	The author did not provide a list of excluded studies and the author did not elaborate what technique they used for assessing the risk of bias and if they conducted investigation of publication bias. Additionally, the study did not report on the source of funding.

Furthermore, findings from our review as well as other related reviews on the topic supports our proposed logic model. Specifically, and as proposed in the logic model, various interventions show benefits in improving uptake of vaccines by adolescents. Nevertheless, neither data from our review nor from other related reviews is sufficient to support some of the outcomes (e.g. reduction of VPDs) or support some of the impacts (e.g. immunisation policies) of the various interventions as depicted in the proposed logic model. Regardless of this limitation, findings from our review can be used as a starting point to develop policies aimed at improving uptake of vaccines among adolescents.

Authors' conclusions

Implications for practice

We found that educating adolescents and their parents about the importance of vaccinations, passing laws requiring adolescents to be vaccinated as a condition for school enrolment, or using a class-based approach for delivering vaccines probably increases the uptake of vaccines among adolescent girls and boys. The certainty of the evidence for these interventions was moderate, implying that monitoring of the impact is likely to be needed and an impact evaluation may be warranted if these interventions are implemented to improve uptake of vaccines by adolescents.

In addition, we found low certainty evidence that adolescent vaccination coverage may be improved through providing adolescents and their parents with financial incentives, alone or in combination with education; giving incentives to providers of vaccination

services; and use of a multi-faceted package of interventions for providers of vaccination services, including education, repeated contacts, individualised feedback and incentives. The low certainty of the evidence for these interventions implies that an impact evaluation is warranted if any of the interventions is implemented for improving adolescent vaccination coverage.

Implications for research

Although the effect of interventions for improving adolescent vaccination coverage is context-specific, most of the currently available evidence on interventions is from HICs. Therefore, to have a global picture, there is a need for rigorous evaluations on interventions to improve adolescent vaccination in LMICs. Given that there is little or no evidence from existing studies on the costs of implementing the identified interventions, future studies should include this important aspect in the design. Other aspects to include in the future studies are socio-cultural and economic status as well as equity.

In addition, to strengthen the current evidence base, there is a need for appropriate design, implementation and reporting of rigorous evaluations on interventions for which this review has found low certainty evidence of benefits (e.g. recipient incentives, provider incentives, optimal combination of effective interventions, etc.), moderate certainty evidence of little or no benefits (provider prompts), possibility of harm (multi-component hepatitis B education), and interventions for which we found no eligible studies (e.g. expansion of access to adolescent vaccination services, integration of adolescent vaccination with other services).

Contributions

Leila Abdullahi developed the protocol with support from Prof. Greg Hussey, Dr. Benjamin Kagina and Prof. Charles Wiysonge. Leila Abdullahi and Valentine Ndze screened titles, abstracts, and extracted data in duplicate. Benjamin Kagina and Charles Wiysonge arbitrated where discrepancies occurred. Leila Abdullahi wrote the final draft with support from Prof. Greg Hussey, Dr. Benjamin Kagina, Prof. Charles Wiysonge and Dr. Valantine Ndze.

Differences between protocol and review

A new author was added during the review process i.e. Valantine N Ndze. In the review we did not conduct subgroup and sensitivity analyses, as specified in the protocol, due to lack of data. See **Table 2** for methods specified in the protocol, but not used in the review.

Chapter 4

Knowledge, attitudes and practices on adolescent vaccination among adolescents, parents and teachers in Africa: a systematic review

About this chapter:

In this chapter, we conducted a comprehensive, up-to-date qualitative and quantitative systematic review on knowledge, attitudes and practices on adolescent vaccination among parents, teachers and adolescents in Africa.

Publication: The systematic review and its protocol are both published, and the citations are shown below:

Systematic review: Abdullahi LH, Kagina BM, Cassidy T, Adebayo EF, Wiysonge CS, Hussey GD. Knowledge, attitudes and practices on adolescent vaccination among adolescents, parents and teachers in Africa: A systematic review. Vaccine 2016; 34(34):3950-60.

https://doi.org/10.1016/j.vaccine.2016.06.023

Systematic review protocol: Abdullahi LH, Kagina BM, Cassidy T, Adebayo EF, Wiysonge CS, Hussey GD. Knowledge, attitudes and practices on adolescent vaccination among parents, teachers and adolescents in Africa: a systematic review protocol. Systematic Reviews 2014 3:100

https://doi.org/10.1186/2046-4053-3-100

Abstract

Introduction: Vaccines are the most successful and cost-effective public health interventions available to avert morbidity and mortality associated with VPDs. Despite global progress in adolescent health, many adolescents in Africa still get sick and die from VPDs due to lack of vaccination. Adolescents, parents and teachers are key players in the development and implementation of adolescent vaccination policies. Optimal knowledge, attitudes and practices towards adolescent vaccination among these key players may improve vaccine uptake among adolescents. We conducted a qualitative and quantitative systematic review on knowledge, attitudes and practices of adolescent vaccination among adolescents, parents and teachers in Africa.

Methods: We searched PubMed, Cochrane Central Register of Controlled Trials, Scopus, Web of Science, WHOLIS, Africa Wide and CINAHL for eligible quantitative studies (RCTs, CBAs, ITS, cohort, case-control and cross-sectional). In additional, from the same databases, we searched qualitative primary studies (focus group discussions, interviews, direct observation, case studies, ethnography and action research). There was no time restriction applied to the search. We also checked reference lists of included studies for eligible studies and searched grey literature. Two authors independently screened the search outputs, selected studies and extracted data; resolving discrepancies by consensus and discussion. Qualitative data were analysed using thematic analyses where applicable, while analyses from quantitative studies used different methods based on the type of outcomes.

Results: We included 18 cross-sectional studies in this review. The included studies were conducted in 10 out of the 54 countries in Africa. The 18 studies focused on a wide range of adolescent vaccines. Thirteen studies evaluated vaccines against HPV, while each of the remaining five studies, evaluated vaccines against rabies, HIV, tetanus toxoid, tuberculosis and adolescent vaccines in general. Among the key players, we found low to moderate levels of knowledge about adolescent vaccination. Positive attitudes and practices towards adolescent vaccination, especially against HPV were reported. Despite the low knowledge, our results showed high levels of acceptability to adolescent vaccination among adolescents, parents and teachers.

Conclusions: It was evident in our review that all key demographics (parents, adolescents and teachers) were receptive towards adolescent vaccines. We propose relevant policy makers in Africa to consider continuous education programmes such as those aimed to inform the parents, adolescents and teachers on adolescent vaccination.

Key words: Adolescents, parents, teachers, knowledge, attitudes and practice, vaccination barriers, Africa

Background

There is evidence that vaccination during childhood, may in some instances, induce a short-lived immunity (16, 43-45). To ensure vaccine-induced immunity persists beyond childhood through to late adulthood, booster doses (for example during adolescence) of some vaccines (such as tetanus and pertussis) are recommended (16, 43-45). However, such booster vaccine doses needed during adolescence are not widely given, particularly in Africa (43). Both programmatic and individual challenges may partly explain the lack of booster vaccination during adolescence in Africa (14).

The WHO defines adolescents as young persons aged 10 to 19 years (2, 154). Taking this definition, and looking at age-specific global data reported in 2018, adolescents, accounted for nearly 25% of the world's population (155). Furthermore, adolescent population growth in Africa is reported to be the fastest in the world (155). From a vaccination standpoint, the public health authorities in Africa need to respond appropriately to the rapid growth of the adolescent population.

If booster adolescent vaccines are successfully introduced in Africa, enormous public health benefits such as reduced transmission and treatment costs of VPDs will be achieved (43, 44). Additional public health benefits of adolescent vaccination programmes are: primary immunisation (new vaccines such as those against HPV) and catch-up immunisation (such as hepatitis B vaccines) (42, 44).

Data from settings where adolescent immunisation programmes have existed show that unique challenges are faced when vaccinating adolescents (60, 63). Therefore, public

health authorities in Africa need to consider developing adolescent immunisation programmes that consider the challenges of targeting adolescents for immunisation.

Challenges of adolescent immunisation include: a) lack of relevant vaccination knowledge among key players (adolescents, parents and teachers) (42, 59, 60, 66, 156-161); b) negative attitude towards vaccination among adolescents, parents and teachers (156-158, 160, 161); and, c) anti-vaccination practices among adolescents, parents and teachers (156). Teachers are crucial players, especially for adolescent vaccines delivered through school programmes (65, 162). We summarize these challenges using knowledge, attitude and practices (KAP).

A decision-making axis is known to exist among adolescents, parents or guardians and the teachers (60, 161). For example, for an adolescent to decide on being vaccinated or not, support from the parent, the teacher or even both is crucial. The decision by the adolescent accepting or rejecting vaccination, as well as the parent or teacher supporting the decision, is influenced by the KAP among the three key players. We propose that if two or all three key players (adolescents, parents and teachers) have optimal KAP towards vaccination, uptake of vaccines by adolescents would significantly increase in most settings.

The assessments of knowledge and attitude among adolescents, parents, and healthcare workers, towards HPV vaccines are well documented (60, 157-161). In contrast, and to the best of our knowledge, assessments of KAP among adolescents, parents and teachers on the other adolescent vaccines are lacking. We therefore

conducted a systematic review on KAP towards adolescent vaccination among adolescents, parents and teachers in Africa.

Objectives

Primary objective

a) Assess the KAP among adolescents, parents and teachers on the adolescent vaccination in Africa

Secondary objective

b) Assess the association between KAP on adolescent vaccination among the key players with vaccination coverage among adolescents in Africa

Methodology

This review protocol was published in the PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42014010395. We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist (**Appendix 4**).

Types of studies selected

For quantitative studies, we included RCTs, CBAs, ITS, cohort studies, case-control studies, and cross-sectional studies. Focus group discussions, interviews, direct observation, case studies, ethnography and action research were considered for selection as qualitative studies.

Study participants

Adolescents, parents and teachers were considered as the study participants. We used the WHO definition of adolescents (young persons aged 10 to 19 years) (154). The person who nurtures or looks after a child or plays the role of a guardian to the child was considered as the parent. We defined a teacher as a professional who teaches or instructs an adolescent at a formal school (162).

Primary outcomes

- KAP among the study participants which meet at least one of the following definitions:
- Knowledge: Information possessed on adolescent vaccination.
- Attitudes: Opinion on adolescent vaccination/vaccines that involves a vaccine-related act or its omission.
- Practices: Observable actions towards adolescent vaccination.

Secondary outcome

- Vaccination coverage with a clear definition of numerator and within a specified period.

Study settings

Any country in Africa

Search strategy

All the electronic searches were conducted on 29 August 2014. The detailed search strategy is included in the protocol previously published (**Appendix 5)** (163). We developed a sensitive search strategy for both qualitative and quantitative studies that combined relevant medical subject headings (MeSH) and free-text terms (163). The terms used were related to KAP towards adolescent vaccination among parents, teachers and adolescents. In addition, individual names for all African countries were used in the search process. We did not use date restrictions during the search.

The peer reviewed articles in the following electronic databases were screened:

- PubMed
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Scopus
- Web of Science
- World Health Organization Library Information System WHOLIS
- Africa Wide
- CINAHL

In addition, we searched web sites and databases for grey materials; WHO (http://www.who.int/); GAVI (http://www.gavialliance.org/); UNICEF (http://www.unicef.org/); PATH Vaccine Resources Library (http://www.path.org/); US Centres for Disease Control and Prevention (CDC) (http://www.cdc.gov/); The Communication Initiative Network (http://www.comminit.com/); and, Immunization

Basics (http://www.immunizationbasics.jsi.com/Index.html). Reference lists of relevant reviews and all eligible search records were also assessed for relevant studies.

Study selection

Two authors screened the titles and abstracts of the search records using a pre-designed screening guide. The two authors identified potentially eligible studies and retrieved full texts of all records deemed potentially eligible by the two authors. Then, the two authors independently examined all the studies for eligibility and compiled a list of studies that met the inclusion criteria. Finally, the two authors compared the lists and resolved discrepancies by discussion and consensus.

A PRISMA flow chart showing a summary of the records searched and selected was generated (**Figure 23**).

Data extraction

Two authors independently extracted data from the selected studies using standardised data-extraction forms (163). Disagreements between the two authors were resolved by consensus, failing which a third author arbitrated.

Assessment of the risk of bias and synthesis of evidence

The risk of bias for the included studies was assessed using the Critical Appraisal Skills Programme (CASP) for assessing the methodological quality of the qualitative studies (164). The quality assessment tool by Hoy et al., 2012 was used for observational studies (165). For each study, two authors independently provided an assessment of the level of the risk of bias (i.e. low, high, or unclear). The two authors compared the

results of the risk of bias assessments and resolved any discrepancies by discussion and consensus; and if this failed to resolve the disagreement, a third author arbitrated.

The quality of evidence for our findings was evaluated using Confidence in the Evidence from Reviews of Qualitative research (CERQual). The CERQual approach was used to describe how much confidence to place in individual review findings from the synthesis of qualitative evidence (166). The Hoy et al., 2012 tool, modified by Werfalli and colleagues, allows a scoring system that categorizes high risk studies if the overall score is 0-5 points, moderate risk if overall score is 6-8 and, low risk if overall score is >8 points (Table 11) (167).

Table 12: Risk of bias and quality assessment tool for observational studies (cross-sectional studies)

Items	**Quality Score**
External Validity	(4 points)
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of nonresponse bias minimal?	(1 point)
Internal Validity	(6 points)
1. Were data collected directly from the subjects (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all subjects?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)

Overall score	**Quality**
0-5 points	**Low Risk:** Further research is very unlikely to change our confidence in the estimate
6-8 points	**Moderate Risk:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate
>8 points	**High Risk:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

Source: http://dx.doi.org/10.1136/bmjopen-2013-004747 (167)

Qualitative and quantitative data analyses

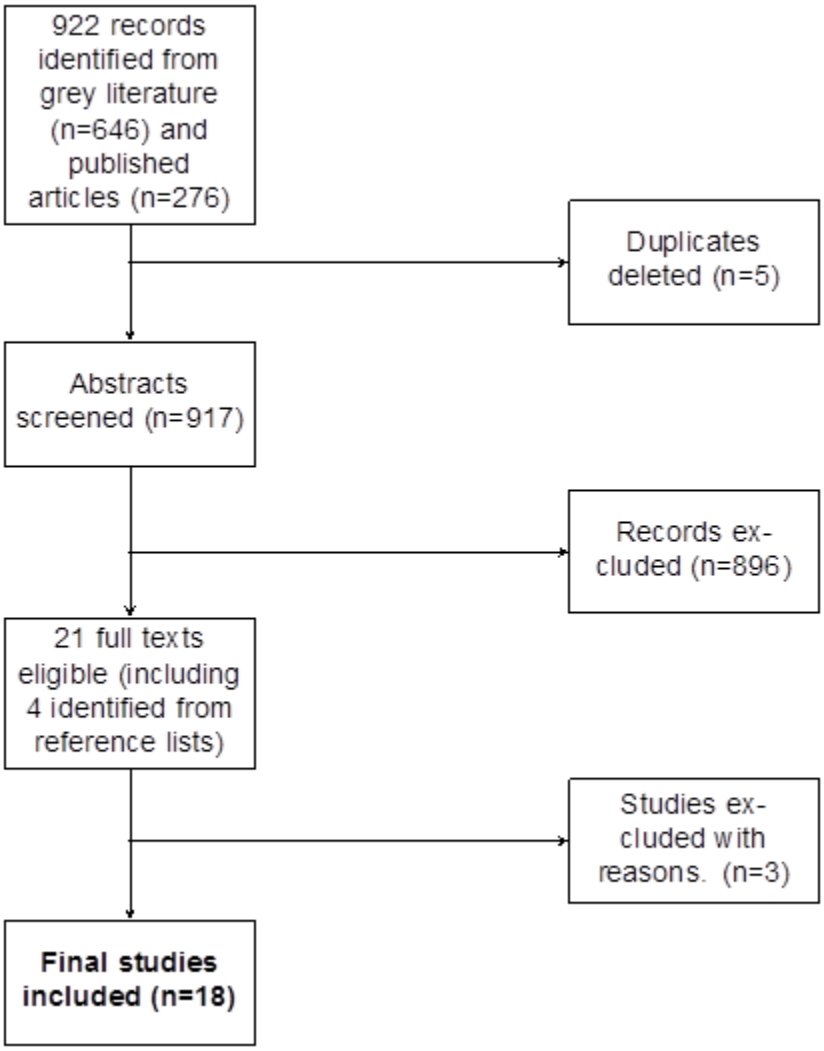
Qualitative analysis was based on thematic synthesis of qualitative data which was independently coded by two authors. The resulting themes are discussed. Quantitative analysis was based on the types of outcome variables as well as the study designs. A pooled statistical analysis was not possible due to high level of heterogeneity. None of the studies were similar enough to combine in a meta-analysis. We used the Fisher's exact test to compare the level of knowledge among the key demographics stratified by the study settings. There were not sufficient data to conduct any subgroup analyses. We therefore provided a narrative summary of the results.

Results

Search of relevant records

Our search yielded 922 records from all databases and grey literature. After removing five duplicates, we screened 917 records; 896 of the records were excluded based on eligibility criteria that were evaluated from titles and abstracts. We retrieved the full text of 21 potential eligible records; four articles of which were from the search of reference lists. Of the 21 records, 18 studies met our inclusion criteria and three studies were excluded because: a) the population studied was not well defined (168); b) it was a sub study of an included study (160); or, c) the outcome was not KAP (169).

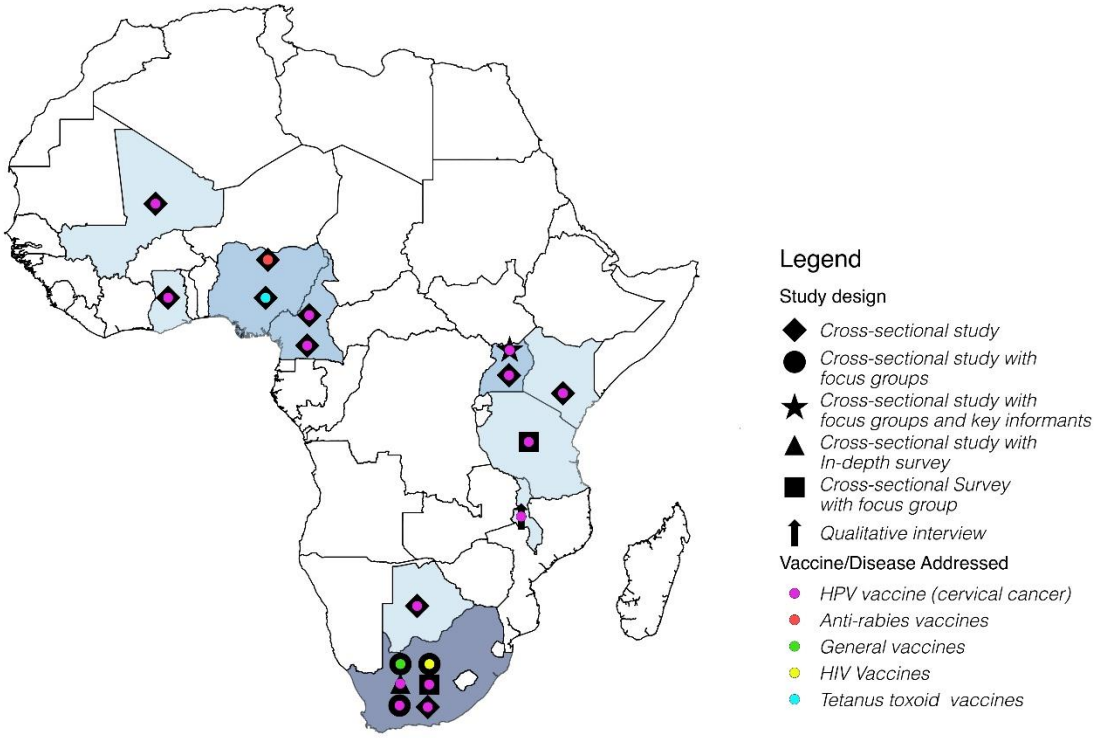
Figure 23: The PRISMA diagram shows a summary the search and screening of the relevant records.



Study settings

The majority (6/18 i.e. 33%) of the studies were conducted in South Africa (43, 157, 158, 170-172). Cameroon (173, 174), Uganda (175, 176) and Nigeria (177, 178) each contributed two studies while the rest of the countries (Kenya, Ghana, Tanzania, Botswana, Mali and Malawi) had only one study (179-184). Included studies were therefore from 10 out of 54 countries in Africa (**Figure 24**).

Figure 24: Geographical distribution of the selected studies, types of study designs and vaccines investigated



Additionally, we assessed the study settings information. Five studies (28%) were conducted in rural settings (157, 173, 174, 178, 183), three (16%) in urban (158, 170, 181), five (28%) in both urban and rural (171, 172, 175, 176, 184) and five (28%) in peri-urban settings (43, 177, 179, 180, 182) (**Table 12**).

Table 13: Summary of included studies- demographic characteristics

Study ID	Study country and settings	Study design	Target age group	Sample size
Anti-rabies vaccines				
Dzikwi A et al 2012 (177)	Nigeria, peri-urban	Cross-sectional study	Adolescents	447
General vaccines				

Zipursky S et al 2010 (43)	South Africa, urban	Qualitative cross-sectional study with focus groups	Adolescents	63
HIV Vaccines				
Sayles J at al 2009 (171)	South Africa, urban and rural	Qualitative cross-sectional study with focus groups	Parents	42
HPV vaccine (cervical cancer)				
Ayissi C et al 2012 (173)	Cameroon, rural	Cross-sectional study	Adolescents	553
Becker-Dreps S et al 2010 (179)	Kenya, peri-urban	Cross-sectional study	Parents	147
Coleman M et al 2011 (180)	Ghana, peri-urban	Cross-sectional study	Parents	264
DiAngi Y et al 2011 (181)	Botswana, urban	Cross-sectional study	Parents	376
Francis S et al 2010 (172)	South Africa, urban	Cross-sectional study	Parents	86
Francis S et al 2013 (170)	South Africa, urban	Qualitative cross-sectional study with focus groups	Parents.	24
Galagan S et al 2012 (175)	Uganda, urban and rural	Cross-sectional study	Parents	1489
Katahoire R et al 2008 (176)	Uganda, urban and rural	Qualitative cross-sectional study with focus groups and key informants	Adolescents, parents & teachers	178
Katz I et al 2013 (158)	South Africa, urban	Qualitative cross-sectional study with In-depth survey	Adolescents& parents	77
Poole D et al 2013 (182)	Mali,	Cross-sectional study	Adolescents&	51

	peri-urban		parents	
Ports K et al 2013 (183)	Malawi, rural	Qualitative interview	Parents	30
Remes P et al 2012 (184)	Tanzania, urban and rural	Qualitative cross-sectional Survey with focus group	Parents, adolescents & teachers	169
Wamai R et al 2012 (174)	Cameroon, rural	Cross-sectional study	Parents	317
Tetanus toxoid vaccines				
Orimadegun A et al 2014 (178)	Nigeria, rural	Cross-sectional study	Adolescents	851
Tuberculosis vaccines				
Mahomed H et al 2008 (157)	South Africa, rural	Qualitative cross-sectional study with focus group	Adolescents & parents.	270

Study characteristics of the included records

All the 18 studies were cross-sectional design with 8 studies being qualitative cross-sectional studies. Ten of the 18 studies utilized self-administered questionnaires and analysed the results quantitatively (172-175, 177-182). Six studies used in-depth interviews and were analysed qualitatively (43, 158, 170, 171, 183, 184). Two studies combined data collection methods of self-administered questionnaire and focus group discussion (157, 176). Combined, a total of 5434 participants (median 173.5, range 24 to 1489 per study) were studied from the included records.

Adolescent vaccines studied from the included records

The HPV vaccine was investigated in 13 (72%) of the studies (158, 170, 172-176, 179-184). Each of the five remaining studies investigated vaccines against TB (157), tetanus (178), rabies (177) and HIV (171), and adolescent vaccines in general (43). In all studies, participants did not reveal any preference on certain vaccines over others, including booster vaccines.

Aims of the included studies

The outcomes of all the included studies were based on the aim of the studies (43, 157, 158, 170-184). Broadly, the aims of the included studies were to assess the knowledge, attitude and awareness/acceptability of a specific vaccine preventable disease i.e. HPV, TB, tetanus, HIV, rabies and the associated vaccines. Three studies aimed to evaluate the association of the previous interventions and level of knowledge as well as awareness (173-175).

Reported outcomes from the included studies

Three studies (173-175) were interventional: evaluating sensitization campaigns (157, 158, 170, 171, 173-175, 177-183) and communication strategies (175) to enhance knowledge, attitudes and practices to promote uptake of adolescent vaccines. These three studies (173-175) already had an existing vaccination programme in place when the studies were conducted (**Table 13**). All other included studies did not report any existing vaccination programme during the study periods (**Table 13**).

Sixteen studies assessed knowledge (43, 157, 170-174, 176-184) and a similar number of studies evaluated attitudes and practices (43, 157, 158, 170-175, 177-183) as

outcomes. Two studies evaluated knowledge only among teachers (176, 184) while nine studies investigated KAP among adolescents (43, 157, 158, 173, 176-178, 182, 184). Fourteen studies reported KAP on adolescent vaccination among parents (157, 158, 170-172, 174-176, 179-184) (**Table 12**).

The 13 studies on HPV-vaccine focused on three main sub-themes: Knowledge of HPV vaccination or cervical cancer, attitude towards HPV vaccines and practice of HPV vaccination. The remaining five studies focused on KAP of other adolescent vaccines (TB, tetanus, HIV, rabies and adolescent vaccines in general). None of the included studies evaluated vaccination coverage among adolescents.

Table 14: Summary of included studies- interventions and knowledge, attitude and practice outcomes

Study ID (Country)	Aim of the study	Interventions	Existing vaccination programme	Outcomes evaluated	
				Knowledge	Attitude and practice
Ayissi C et al 2012 (Cameroon) (173)	To measure the effectiveness of the CBCHS sensitization campaign intervention and to gauge the level of awareness about HPV and HPV vaccine	CBCHS sensitization campaign	Community based programme	High knowledge on cervical cancer and HPV vaccine. Awareness of HPV (86.8%), cervical cancer (82.3%), and prevention of HPV infections through vaccination (75.9%)	A positive attitude towards HPV vaccine. Most adolescents (80%) recommend girls of ages 9–13 years be vaccinated against HPV infections
Becker-Dreps S et al 2010 (Kenya) (179)	Assess vaccine acceptability in community	None	None	Low knowledge of HPV vaccine and knowledge of cervical cancer. 15% had heard of cervical cancer and none on HPV vaccine.	95% of women had a positive attitude and were willing to have their daughters vaccinated with HPV vaccine, with preference for an inexpensive vaccine requiring fewer doses.
Coleman M et al 2011 (Ghana) (180)	To assess knowledge, attitudes and acceptability of human papillomavirus (HPV) vaccination	None	None	89% of the women had a high knowledge on cervical cancer in Ghana; however, 45% of the women had moderate knowledge on HPV vaccine.	76% of the women had a positive attitude and believed that all women regardless of their sexual practices should receive it. However, they were very concerned" about unknown side effects associated with the vaccine.
DiAngi Y et al 2011 (Botswana) (181)	To examine HPV vaccine acceptability for adolescent girls and its predictors among healthcare-seeking adults	None	None	Low knowledge on HPV and HPV vaccine. 35% had knowledge on HPV while 9% were aware on HPV vaccine; however, 75% wanted more information about it.	88% of the parents had a positive attitude; they would get HPV vaccine for their adolescent daughters mostly if it were available with other childhood vaccines. However, there was a negative attitude among a few (22%) stating their daughter would be more likely to have sex if they got the vaccine

Dzikwi A et al 2012 (Nigeria) (177)	To obtain baseline information about the knowledge and practice about rabies	None	None	There was a moderate (50%) among formal schools' goers to low (32%) among informal education settings knowledge on rabies.	Positive attitude with 63% and 87% of the children bitten by dogs in the formal and informal schools respectively received hospital treatment or African treatment.
Francis S et al 2013 (South Africa) (170)	To compare findings about cervical cancer prevention, HPV, and the acceptance of the HPV vaccine among residents	None	None	There was lack of awareness and understanding about HPV and its association with cervical cancer.	There were positive thoughts about a vaccine to prevent cancer and concern that the receipt of the HPV vaccine may influence adolescent sexual behaviour.
Galagan S et al 2012 (Uganda) (175)	To evaluate the association between Information, education and communication materials and activities and community influencers with initial uptake of HPV vaccine.	Promoting HPV vaccines through a variety of communication strategies.	Pilot vaccination programme	N/A	There were positive attitude In Uganda with high uptake 85% (year 1) and 82% (year 2) if the parent had had contact with a person promoting the vaccine.
Katz I et al 2013 (South Africa) (158)	To elucidate factors influencing HPV vaccine uptake among a sample of low-income adolescents receiving the vaccine for the first time	None	None	N/A	There is a negative attitude among boys assuming that that HPV only affects girls only.
Mahomed H et al 2008 (South Africa) (157)	To determine knowledge levels about TB and vaccines amongst adolescents, their attitudes and that of their parents towards research and invasive procedures	None	None	Knowledge of tuberculosis was moderate (63%) but knowledge of vaccines was poor 41%	There was a positive attitude among the participants as they were willing to participate in research or get vaccinated if they were well informed about

					benefits and safety.
Orimadegun A et al 2014 (Nigeria) (178)	To evaluate the understanding of adolescent girls in high school about tetanus and identify factors associated with knowledge of the disease	None	Health facility programme for child bearing women but not for adolescent girls	64% of the respondents had poor knowledge while 40.4% claimed they knew about tetanus as an 'acute serious disease'; however only 46% of them correctly defined it.	Over half (56.2%) of respondents had negative attitudes towards introduction of "tetanus immunisation to students in the school.
Poole D et al 2013 (Mali) (182)	To assess HPV knowledge and HPV vaccine acceptability	None	None	Low knowledge on HPV & HPV vaccine; 49% knew HPV causes cervical cancer, 14% did not know who was susceptible to HPV infection and only 9.8% of participants heard of cervical cancer.	Positive attitude among all (100%) participant; they reported being willing to receive HPV vaccination. However, 68% would only receive immunisation against HPV if the vaccine were available at no cost to participant.
Ports K et al 2013 (Malawi) (183)	To elucidate potential barriers and facilitators to human papillomavirus (HPV) vaccination	None	None	All the women heard about cervical cancer; however, women's knowledge about HPV and cervical cancer was limited.	Women were extremely accepting of vaccines and efforts to prevent cervical cancer since it was perceived to be a serious health concern.
Sayles J at al 2009 (South Africa) (171)	To identify key barriers and motivators to future HIV vaccine uptake among a population that interfaces with the health system	None	None	Low level of knowledge on HIV vaccines. HIV vaccine had not really been heard about before	75% of participants were willing with their friends/family to take an approved HIV vaccine if available.
Wamai R et al 2012 (Cameroon) (174)	To measure the effectiveness of the CBCHS sensitization programme intervention in educating the parents on HPV, cervical cancer and HPV vaccines	CBCHS sensitization campaign programme	Community based programme	High knowledge 75% & 90% among parents/guardians about HPV & cervical cancer, and the use of the HPV vaccine against HPV infections.	Positive attitude among parents to vaccinate their daughters; however cost of the vaccine may be the most influential factor in parents' decisions to vaccinate their daughters.

Zipursky S et al 2010 (South Africa) (43)	To find out about knowledge and attitudes of adolescents towards vaccines	None	None	Knowledge of vaccines and immunisation issues was low amongst the adolescents	There is a high level of acceptability of vaccines, which increased once their purpose and preventative nature was explained.
Francis S et al 2010 (South Africa) (172)	To examine knowledge, attitudes and beliefs around HPV and cervical cancer	None	None	Moderate knowledge;61% of participants heard of cervical cancer while low knowledge; 29% heard of HPV infection	46% willing to vaccinate their child. expressed interest in vaccinating their child if they had access to the HPV vaccine
Katahoire R et al 2008 (Uganda) (176)	To gauge the policy environment—structures and processes required for policy formulation for HPV vaccine introduction	None	None	Majority of respondents were unaware that cervical cancer is caused by HPV.	None
Remes P et al 2012 (Tanzania) (184)	To learn what people knew about cervical cancer and HPV vaccination	None	None	Generally, most welcomed a vaccine to prevent cervical cancer and most parents said they would agree to have their daughter vaccinated although some adopted a “wait and see” approach. Most had a strong belief that vaccines prevent diseases	None

KAP towards adolescent vaccination

From the 18 records included for our review, 12 (78%) evaluated knowledge of adolescent vaccines among parents (157, 170-172, 174, 176, 179-184), and 8 (44%) among adolescents (43, 157, 173, 176-178, 182, 184) and 2 (11%) among teachers (176, 184).

Our limited sample size could not allow us to reliably compare the KAP between the represented countries. However, in all study settings and countries, sub-optimal knowledge about the VPDs and the associated vaccines was prevalent (157, 170, 172, 176, 178-183). We used a Fisher's exact test to compare the level of knowledge stratified by the study settings. There was no difference in the level of knowledge by participants living in rural, urban and peri-urban **(Appendix 6, supplementary table 1b)**.

Elements of knowledge frequently assessed were by asking parents, adolescents and/or teachers if they were aware of HPV. In addition, study populations were asked if they could correctly identify HPV as the causative agent of cervical cancer. Optimal knowledge on vaccination can be considered as basic and correct understanding of the disease, aetiology of the disease and the existing preventative vaccination measures available against the disease. In all studies on HPV, even though the study participants reported to be aware of cervical cancer, the participants were unaware of the HPV and vaccine to prevent the virus, as well as how the two are linked to cervical cancer (158, 170, 172-176, 179-184). Some study participants were reported to think that HPV vaccination could negatively influence the sexual behaviour and in general, cancer only affects women (170, 181). A similar observation was noted among study participants with moderate knowledge on TB

disease but low knowledge about the vaccines against TB (157). Two studies (11%) did not assess knowledge but assessed attitudes and practices towards adolescent vaccines (158, 175).

Levels of knowledge among parents (157, 170-172, 174, 176, 179-184), adolescents (43, 157, 173, 176-178, 182, 184) and teachers (176, 184) were mixed ranging from low, moderate and high. There were no standardized criteria for categorizing knowledge as low, moderate or high across studies. However, we observed that the term low knowledge was generally used when less than 50% of participants had adequate knowledge on the specific information of the vaccine under evaluation. Similarly, the terms moderate and high knowledge were used when the participants with adequate specific information of the vaccine under evaluation was between 51-70% and from 71% upwards respectively.

Three studies (17%) demonstrated high levels of knowledge (two on HPV vaccines (173, 174) and three on cervical cancer (173, 174, 180) among parents and adolescents. Five studies (28%) reported moderate levels of knowledge, of which three were among parents, one study among teachers and three studies among adolescents on vaccines against HPV (172, 180, 184), rabies among adolescents (177) and TB disease among parents and adolescents (157). Levels of knowledge among parents, teachers and adolescents on vaccines against HPV and/or cervical cancer, TB, HIV and tetanus were found to be low in eleven (61%) studies (43, 157, 170-172, 176, 178, 179, 181-183). We used a Fisher's exact test to assess if the level of knowledge was different among the three key participants. The level of knowledge did not differ among parents, teachers and adolescents (**Appendix 6, supplementary table 1a**).

Sixteen (89%) studies focused on attitudes and practices toward adolescent vaccines like tetanus, TB and cervical cancer among parents, adolescent and teachers (43, 157, 158, 170-175, 177-183)] while two (11%) studies did not assess attitudes or practices (176, 184). Most studies 14 (88%) showed that participants had positive attitudes towards vaccination against HPV, tetanus, TB and HIV (43, 157, 158, 171-175, 177-180, 182, 183).

Adolescents largely (58%) reported a positive attitude on vaccination against HPV (43, 157, 158, 173, 177, 178, 182). The two studies conducted among teachers did not report any outcomes on attitudes and practices on adolescent vaccination (**Table 13**). Two (11%) studies reported negative attitudes towards HPV vaccines. Negative attitudes were beliefs that the vaccine might negatively influence adolescent sexual behaviour and that cancer only affects girls (170, 181).

Main themes

A) Acceptability and willingness to vaccinate adolescents**:** high acceptance levels of the HPV vaccine was reported among adolescents, reflecting a positive attitude (157, 170-172, 174, 179-183). In general, the data showed willingness by parents to get the adolescents vaccinated against HPV. Additionally, both parents and adolescents indicated willingness to accept HPV vaccination if the doctors recommended it (173, 180) and, if part of other childhood vaccines (181). In general, included studies did not report accessibility to vaccination services as well as the cost of the vaccines. However, three (17%) studies indicated that participants would agree to be vaccinated against HPV if access to the vaccine was easy and came at no extra cost (174, 179, 182). Regardless of vaccine acceptability, vaccine safety and sides effects were a major concern in one of the studies (180).

B) Need for education and awareness of adolescent vaccination**:** two studies suggested an increased need of education and awareness about cervical cancer, HPV and HPV vaccination (173, 174). Furthermore, participants in the studies with existing vaccination programmes reported a high level of knowledge (173-175). Existing programmes can therefore be used as a platform to educate and raise awareness on adolescent vaccines. Parents, teachers and adolescents understood the importance of being knowledgeable on adolescent vaccines, particularly HPV, its characteristics and associated risks, and the benefits of the HPV vaccine (158, 170, 172-174, 176, 179-184).

Quality assessment of the included studies

All eight qualitative studies reported the aims of the studies and described the study methods. Ethics approvals, informed consents and confidentiality were reported in six studies while two studies did not report any information regarding ethics. All the eight studies described the recruitment process of the study participants. Largely, non-compliance with quality criteria for most records was due to unclear reporting of the methodology.

Most of the qualitative studies (7/8 i.e. 88%) explained a minor concern on the assessment of methodological limitations, relevance, coherence, and adequacy of data. Six and one study had a minor and moderate methodological limitation respectively. All the studies were relevant to the African settings and data were reasonably consistent within and across all studies. Overall, all the studies had a rich data that addressed the research question and aim. **Figure 25** and **26** show the details of the quality assessment of both the qualitative and quantitative studies respectively.

Figure 25: Risk of bias graph for qualitative studies

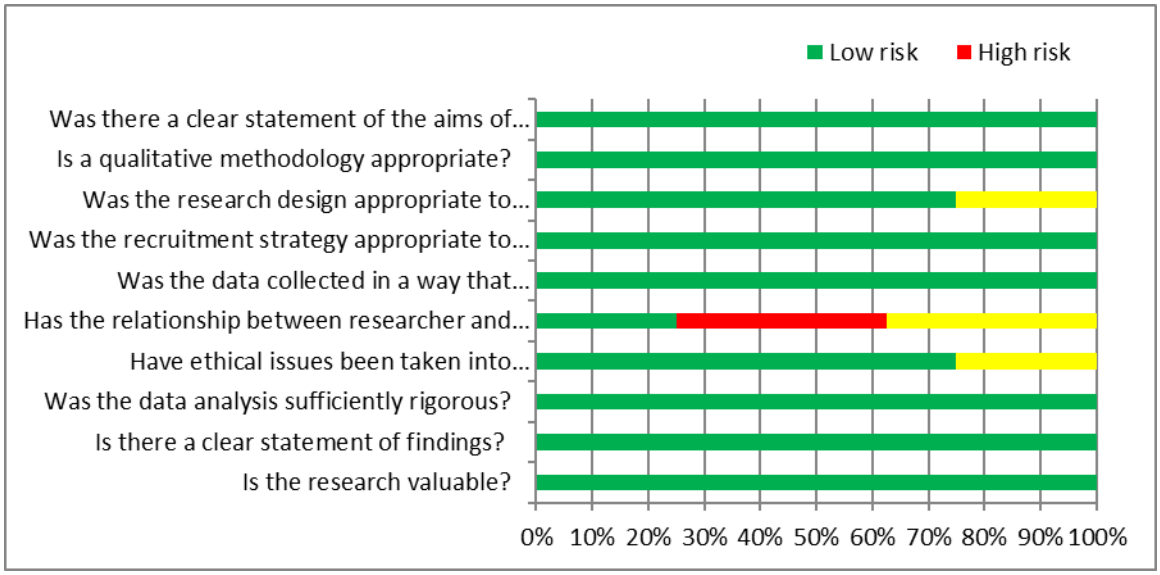
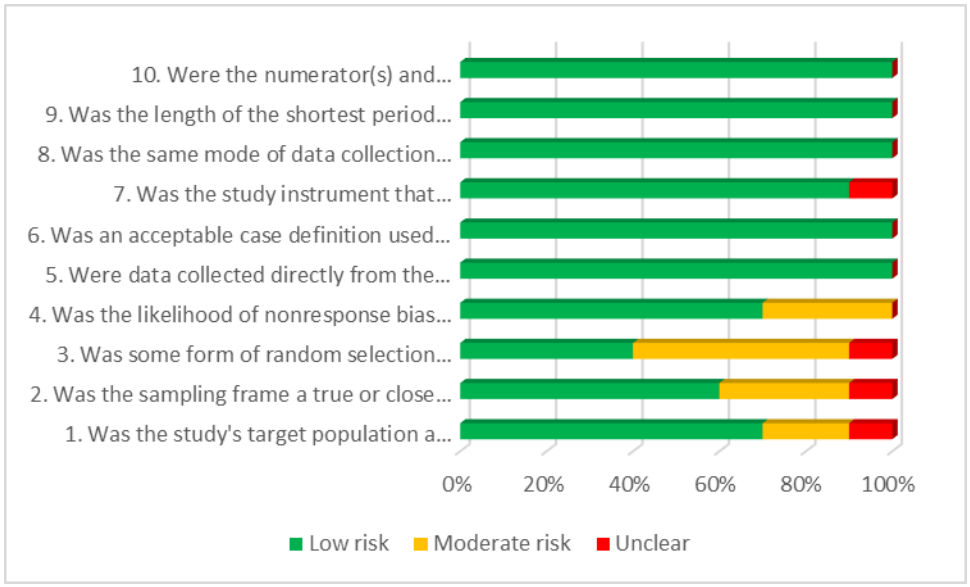


Figure 26: Risk of bias graph for quantitative studies



Synthesis of evidence

We scored the strength of the evidence for qualitative studies using CERQual (166) whereas for quantitative studies, we used the Hoy et al., scoring principles (165). We then classified the overall strength of evidence as high, moderate, low, or not clearly stated (165). The quality of evidence for quantitative studies was low, which implies 'further research is very unlikely to change our confidence in the estimate' (**Table**

14). The confidence of evidence for qualitative studies was moderate, suggesting that 'the review finding is a reasonable representation of the phenomenon of interest' (**Table 15**).

Table 15: Quality of evidence for quantitative studies

Total no. of studies	**10 studies**
Overall score	**5 (Low risk)**
Overall score	**Quality**
0-5 points	**Low Risk:** Further research is very unlikely to change our confidence in the estimate
6-8 points	**Moderate Risk:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate
>8 points	**High Risk:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

Source: https://www.ncbi.nlm.nih.gov/pubmed/22742910 (165)

Table 16: Summary of finding table on the quality of evidence

Summary of finding on the quality evidence of qualitative studies

Population: Adolescents, teachers and parents
Settings: South Africa [five studies], Uganda [one studies], Tanzania and Malawi [one study each]
Intervention: No intervention
Comparison: No comparison

Outcomes	**Impacts**	**No of Participants (studies)**	**Quality of the evidence (CERQUAL)**
Knowledge, attitude and practice	All studies showed an increase KAP toward adolescent vaccine but the impact is not evident in these studies	669 participants (8 studies)	⊕⊕⊕⊖ Moderate*

* We rated down the quality of the evidence by one points, because of minor concern on the assessment of methodological limitations in included studies.

The CERQual approach—Definitions of levels of confidence in a review finding.
High confidence: It is highly likely that the review finding is a reasonable representation of the phenomenon of interest.
Moderate confidence: It is likely that the review finding is a reasonable representation of the phenomenon of interest
Low confidence: It is possible that the review finding is a reasonable representation of the phenomenon of interest.
Very low confidence: It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

Source: https://doi.org/10.1186/s13012-017-0690-9 (166)

Discussion

After a comprehensive assessment of 922 relevant records from several databases and grey literature, only 18 studies were included in our review. The included studies were conducted in 10 out of 54 African countries. The lack of many included studies and representation of only 10 countries highlight the enormous gap in adolescent vaccination research in the continent. Participants reported willingness to be vaccinated against HPV if access to the vaccine was easy and at no cost while vaccine safety and side effects were reported as major concerns in one study. Doctors' recommendations on the need to be vaccinated as well as including adolescent vaccines in routine programmes were noted factors that could improve uptake of vaccines by adolescents.

Our review showed low to moderate level of knowledge and positive attitudes among parents and adolescents on vaccination. However, we could not evaluate if the KAP could influence vaccine uptake as no study had assessed the association of these outcomes. Recommendations to be vaccinated, including having adolescent vaccines in the routine schedule, ease of access to vaccines as well as provision of free adolescent vaccination were reported as factors that may improve uptake of vaccines by adolescents.

Irrespective of the study setting or country, there was a general lack of understanding of the vaccines and VPDs among the study participants. It appeared that participants from the rural settings were more likely to have a positive attitude towards vaccination, as well as to vaccinate their adolescents compared to participants in the urban settings. Two of the three studies that reported to have an

existing vaccination programme reported a high level of knowledge on the HPV disease and HPV vaccine, suggesting the importance of the existing programmes on improving KAP.

Like a previous systematic review (68), our review identified low to moderate levels of knowledge, positive attitudes and practices on adolescent vaccines, especially against cervical cancer. Despite the low knowledge, there were high levels of acceptability of adolescent vaccination among teachers, parents and adolescents. We found that parents, teachers and adolescents understood the importance of being knowledgeable on adolescent vaccines, particularly against HPV. Sensitization programmes and communication strategies were reported as viable interventions to enhance knowledge and attitudes and promote improved coverage of adolescent vaccination.

Africa has many public health challenges, among them, high burden of VPDs. Our findings show that research on adolescent vaccination is lacking in Africa. It was encouraging to find that both parents and adolescents have positive attitude towards HPV vaccination. These findings agree with high HPV vaccination coverage reported by the five countries that had introduced the HPV vaccine in Africa (130, 173, 185-189). We propose that the lessons learnt from the HPV vaccination programme in Africa be used to develop and implement adolescent vaccination programmes in the continent.

Other adolescent vaccinations against TB, tetanus, rabies and HIV were reported by the included studies. HIV and TB are endemic in Africa and the vaccines against these diseases are in advanced development stages; therefore, more research on adolescent vaccination in Africa is critical (16, 45). In Africa, tetanus vaccines are

currently given at health facilities and to antenatal mothers (178). There is need for local evidence on whether booster tetanus vaccines should be introduced to adolescents and possibly via school-based programmes as is the case in some settings (178). African countries with existing maternal tetanus vaccination programmes, and those that have introduced school-based adolescent HPV vaccination programmes will experience benefits of increased knowledge and awareness towards adolescent immunisation, and this will make it easier for the adolescents to accept other vaccines, such as tetanus, when required.

The findings of our review are subject to several limitations. We searched only for papers and reports written in English. However, we crosschecked reference lists of the relevant records to identify any additional studies. Some studies did not clearly distinguish between attitudes and practices as outcomes. Therefore, in this review, we could not report these outcomes entirely separate. The quality of evidence from the included studies was not strong to give us confidence in making recommendations on this topic. However, continuous educational programmes to improve KAP on adolescent vaccination among the key stakeholders may prove to be a valuable health investment by the African governments.

Conclusion

There are two main themes that emerged in this review. Firstly, there are high levels of acceptability and willingness to vaccinate adolescents against HPV by all the three key groups: adolescents, teachers and parents. This holds true even when knowledge levels are low. Secondly, it is evident in the review that all the three key groups need to be educated more on adolescent vaccination as well as increased

awareness on the topic. Although attitudes were generally positive, lack of optimal knowledge may lead to misconceptions, which in turn hinders vaccine uptake.

Contributions

Leila Abdullahi wrote the protocol with supervision from Greg Hussey and Benjamin Kagina. Leila Abdullahi conducted the data extraction and risk of bias assessment alongside Tali Cassidy and Esther Adebayo in duplicate. Leila Abdullahi wrote the drafts of the review with support from Tali Cassidy, Esther Adebayo, Greg Hussey, Charles Wiysonge and Benjamin Kagina.

Chapter 5

Challenges and lessons learnt during the introduction of human papillomavirus (HPV) vaccination programmes in Africa; A cross-sectional study

About this chapter:

We conducted a cross-sectional study to investigate the experiences, challenges and lessons learnt by key stakeholders (government representatives, funding agencies, National Immunisation Technical Groups (NITAGs) and implementing agencies) of the African countries that had introduced HPV vaccine to the adolescent population. The results generated from this study are useful to other countries that are planning to implement HPV vaccination into their national programme, especially in Africa. In addition, the study findings can help countries to better plan current and future HPV as well as other adolescent vaccine introduction.

Publication: The study will be submitted to the *Human Vaccines and Immunotherapeutics* Journal.

Abstract

Introduction: Infection with HPV significantly increases the risk of developing cervical cancer later in life. Therefore, globally, the introduction of HPV vaccine targeted to pre-adolescent and adolescent girls has been on the rise since the licensure of the vaccines from 2006 to 2009. However, the introduction of HPV vaccines has been relatively slow in Africa. As of the end of 2016, only eight of the 54 African countries were reported to have introduced HPV vaccination at a national level. Our study aimed to investigate the experiences, challenges and lessons learnt by the key participants during national HPV vaccine introduction in Africa.

Methods: A questionnaire was administered to selected key participants from eight African countries. The eight countries had successfully introduced HPV vaccine at a national level by the end of 2016. We used in-depth interviews and self-administered online questionnaires for data collection and analysis. Data reporting was blinded with no naming of the country or the key participants. Narrative and thematic reporting were used to describe the results. Permission to conduct the study was obtained from the Humans Research Ethics Committee (HREC) of the University of Cape Town.

Results: We obtained results from six of the eight targeted countries. The challenges reported during HPV vaccination programmes were: identifying the target population, using school-based vaccine delivery strategy, obtaining political support, the need to integrate HPV vaccination with existing school health programmes and engaging diverse stakeholders. These challenges were similar in all the six countries. Lesson learnt was school-based delivery strategy is a successful approach for national HPV vaccination. Another lesson was that, identifying the girls

for vaccination at schools was less challenging if implemented through a class-based and not an age-based approach.

Conclusions: Most African countries do not have established platforms to deliver vaccines to pre-adolescent and adolescent populations. The successful introduction of HPV vaccine through school-based vaccination strategies among African countries may have created a platform to deliver other adolescent vaccines. The similarity of the study findings across the six participating countries further strengthens the need to document and disseminate the challenges and lessons learnt during HPV vaccine introduction in Africa. Documentation and dissemination of the challenges as well as lessons learnt is useful to other countries in Africa that plan to introduce the HPV vaccination programme, and possibly, other adolescent vaccines.

Key words: HPV vaccine, Implementation, Immunisation programmes, School-based vaccination, adolescents

Background

Implementation of global, regional and national immunisation policies plays an important role in combating the burden of VPDs (190). An important policy strategy to combat VPDs in many countries is the strengthening of the EPI which in turn support the introduction of new vaccines. African countries have traditionally lagged behind the HICs in the introduction of new vaccines (191). It is therefore not surprising that even after several years post HPV vaccine licensure, only a handful of African countries had introduced the vaccine as at 2016 (62). In Africa, introduction of new vaccines such as that against HPV may be accelerated in countries with functional NITAGs.

The NITAGs are established and mandated to give advice to the national health departments on immunisation, with the aim of strengthening the EPI and as a result, advocate for the introduction of new vaccines (74). Functional NITAGs collaborate with the departments of health and other key stakeholders to strengthen the EPI. This collaboration is essential for the introduction of new vaccines, as well as expansion of immunisation services to all populations. South Africa, one of the very first countries to introduce national HPV vaccination programme to school-aged girls in Africa has one of the oldest NITAG in the region (192).

In Africa, similar to many other regions, the primary focus of EPI is the delivery of immunisation services to children, and not to adolescents, adults and the elderly (5). As a result of the EPI focus to children, structured delivery of immunisation services to the adolescents is suboptimal in many African countries (193). As new vaccines targeting adolescents such as against HPV become available (37), there is need to expand the delivery of immunisation services to the adolescent population.

African countries continue to record a more rapid increase of adolescent population than countries in other continents (3). There is evidence on the benefits of vaccinating adolescents, which include boosting of the waning immunity induced during childhood (36, 42). Furthermore, initiatives on immunisation, such as GIVS, GVAP and SDGs have supported the call to extend immunisation services to adolescents (16, 17, 30). Therefore, African countries will need to invest more resources and develop national immunisation policies that specifically target adolescents.

In this study, we evaluated the lessons and challenges learnt by a few African countries that had nationally implemented vaccination against HPV as at 2016. Infection with HPV significantly increases the risk of developing cervical cancer later in life (29). Additionally, HIV infected men as well as men who have sex with other men have an increased risk of anal, penile and throat cancers associated with HPV infection (194).

Globally, cancer of the cervix is the fourth most common cancer among women (195). In 2012, cervical cancer accounted for 15% of all cancers among women (195). In Africa, programmes to combat cancer are compounded by multiple health priorities (196). Vaccinating adolescents against HPV offers an effective intervention of preventing cervical cancer in all settings (99, 197).

The primary target group for HPV vaccination is girls aged 9–13 years (198), prior to the onset of sexual activity (75, 76). Despite the HPV vaccines' proven safety, efficacy and cost-effectiveness, only eight African countries had reported HPV vaccine introduction at a national level by the end of 2016 (99). The countries were: Libya, Lesotho, Rwanda, Uganda, South Africa, Botswana, Mauritius and Seychelles

(99). The delay in HPV vaccine introduction among African countries could be due to many reasons such as awareness, resource limitations and absence of adolescent vaccination programmes (43).

The national departments of health, funding and implementing partners as well as NITAGs are key stakeholders in the introduction of HPV vaccines in Africa. To our knowledge, the experiences, challenges and lessons learnt by the key stakeholders involved in HPV vaccine introduction in Africa are not aggregated. Findings from our study are useful to other countries that will introduce HPV vaccines in Africa.

Objective

To investigate the reported experiences, challenges and lessons learnt during HPV vaccine introduction by eight African countries.

Methods

In this study, we adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Appendix 7).

Ethics

Prior to the start of the study, ethical approval was obtained from the HREC of the Faculty of Health Sciences, University of Cape Town (**HREC Ref: 703/2015) (Appendix 10)**. Written participation consent forms were obtained from the study participants. Example of participant information and consent form are available on **Appendix 8**. Confidentiality was observed during the interview process with the use of blinded transcripts.

Inclusion criteria

All countries in Africa that had implemented national HPV vaccination programme in 2016.

Sample size

This was not a hypothesis testing study. Hence, we did not calculate the required sample size. Our target sample size was all countries in Africa with national HPV vaccination programme as at 2016. From the eight countries that had implemented national HPV vaccination programme in Africa, one key representative (convenient sampling) was invited to participate.

Study design and period

A cross-sectional study conducted between 2015 and 2016.

Recruitment of the study participants

In November 2015, we identified and sent invitations to key representative from five African countries. In addition, in November 2016, we invited key representatives from additional three African countries. All invited representatives were from countries that had introduced national HPV vaccination in 2016. The selection of the representatives was done through referral sampling (contacts from academics, implementing agencies and governments). The key representatives were defined as members of NITAGs, officials from the departments of health at national level as well as from international organisations such as the WHO and UNICEF. To participate in the study, the key representatives must have been actively involved in the introduction of the HPV vaccination programme in the selected countries.

Questionnaire administration

Prior to interviewing the participants, a questionnaire was developed and pretested. The pretesting was aimed at enhancing clarity and accuracy of the data collection process. The pretesting was done by administering the questionnaire to four different persons involved in the implementation of HPV vaccination programme in South Africa. During the pretesting process, we developed an interviewer guide with a set of questions aimed at helping the interviewer to direct the conversation towards the topics of interest. The interview guides are shown in **Appendix 9**.

One of the study team members (LHA) administered the questionnaires to all the key representatives. Five representatives from five countries were interviewed via face-to-face while attending a vaccinology course held in South Africa. One representative from the sixth country completed the questionnaire remotely after we sent the questionnaire via email.

Missing data

Two representatives from the seventh and eighth countries never responded to the questionnaires we sent to them via email. Follow up telephone calls to these two representatives to get them complete the questionnaires were unsuccessful.

Data management and analysis

Five of the face-to-face interviews were digitally recorded. The digitally recorded data were coded with ATLAS (version 6) for analysis. From the questionnaire completed and sent via email, data was abstracted for analysis and reporting. Data reporting was blinded: no naming of the country or the participant. Narrative reporting and grouped themes were used to describe the results based on the most common words and terms that were similar and repetitively used by the key representatives.

Results

In total, six key representatives out of the eight targeted provided data for this study. The six representatives were from six different countries. The descriptive characteristics of the six representatives interviewed are shown in **Table 16.**

Table 17: Characteristics of the key stakeholders interviewed

Country code	Type of organisation	Position held by the representative	Role in HPV vaccination programme
A	Government	Programme manager	Adviser on implementation of programme
B	Government	EPI director	In-charge of implementation of programme
C	International organisation	New vaccine focal person	Adviser on implementation of programme
D	Government	Programme manager	In-charge of implementation of programme
E	Government	Programme manager	In-charge of implementation of programme
F	Government	Programme manager	In-charge of implementation of programme

From the six participants interviewed, information about the targeted population for vaccination as well as the HPV vaccination delivery strategy used is provided in **Table 17**.

Table 18: Characteristics of the population targeted for vaccination and delivery strategies used to deliver HPV vaccine

Countries	Sex targeted	Vaccine delivery approach	Target age group
A	Female	School-based	9-13
B	Female	School-based	9
C	Female	School-based	10

D	Female	School-based	12
E	Female	School-based	9-13
F	Female	School-based	9-12

Challenges during the implementation of the national HPV vaccination programme

Using data collected from the six countries, we grouped the challenges and lessons learnt during the implementation of the national HPV vaccination programme into themes. Thematic challenges and lessons reported by the participants were very similar in all the six countries (**Table 18**).

The participants from all the countries reported the following as challenges: identifying the target population group for HPV vaccination, obtaining political support, using school-based vaccine delivery strategy, integrating HPV vaccination programme with existing school health programmes, and engaging multiple stakeholders.

Identifying the target age group

All the countries represented in this study opted to deliver HPV vaccination through the school-based strategy and targeted girls only. At schools, there was need to correctly identify girls aged between 10 to 13 years who are the target group for HPV vaccination. To identify the girls, a challenge was encountered. The challenge was on whether to use grade-based or age-based approach to identify the girls for HPV vaccination.

For example, during the piloting of the HPV vaccination, country A (**Table 17**) started with age group 9 to18 years but due to logistic constraints, this target age group could not be optimally reached. Hence, some girls missed the intended HPV vaccine

at school and were referred to the nearest health facilities. Subsequently, during the national roll out, all the six countries reported that HPV vaccination programme was implemented using class-based approach. This approach presumed that the targeted (10-13 years old) age group, which is recommended for HPV vaccination by WHO (198), will be found in a given class.

The HPV vaccination schedules were synchronized with the academic calendar to avoid loss to follow-up. In addition, school teachers played a crucial role to assist in the follow-up and regularly communicated information on the vaccination dates to the targeted girls. Primary schooling in all the six participating countries is compulsory, hence school-based strategy was chosen as the most efficient strategy to reach the highest number of targeted girls with HPV vaccination. The school-based delivery strategy was complemented by an outreach strategy, like health facility strategies to vaccinate non-school going girls.

Using school-based vaccine delivery strategy

In Africa, as is the rest of the world, the EPI routinely focusses on delivering vaccination services to children. In the absence of an existing vaccination platform to reach pre-adolescent and adolescent girls with HPV vaccines, new vaccine delivery strategy was needed. During the period of HPV vaccine introduction by the African countries, there was evidence from high income countries such as Canada showing school-based programme is feasible (199).

Participants in our study reported the introduction of HPV vaccines through the school-based strategy required the departments of health and education to develop a new collaborative partnership. The collaborative partnership involved the department of health's EPI programme take lead with HPV vaccine demonstration initiatives while the department of education led the school-based initiatives such as

engagements with the learners and their parents. The co-ordination of these inter-departmental initiatives for optimal delivery of HPV vaccination was reported as a challenge. Prior engagement meetings between officials from both departments were necessary to ensure complete and on time dosing of the HPV vaccines to the targeted girls. Such engagement meetings were reported to be operationally demanding and time consuming.

Obtaining political support

During the pilot phase, all the six countries reported the demonstration results of HPV vaccination programme were shared with parliamentarians to solicit for political support. The parliamentarians showed interest in the vaccination programme from the start and this political support facilitated the necessary commitment from the government to scale up to the national level. Political leadership may change after a limited period whereas the vaccination programme is a long-term intervention. The participants indicated that a possible lack of political support in the future could compromise the national HPV vaccination programme.

Integrating HPV vaccination with existing school health programmes

Some countries have existing school health programmes (such as vision screening, deworming and nutritional supplementations) for school-aged children who may also be the target group for HPV vaccination. Country B, as an example reported to have a vision screening programme among grade 5 learners at primary schools. Grade 5 learners were also targeted by the HPV vaccination programme in the country. Most of the existing school health programmes are characterized by a single visit to the institutions by the health care providers as opposed to HPV vaccination which, depending on whether two or three doses, requires more than a single visit.

Furthermore, health service teams from the department of health and not the HPV vaccination teams are involved with the existing school health programmes. The use of two different teams from one department of health visiting the same school with different aims was reported as a challenge. In country B for example, there was an observed need to harmonize the implementation of these two health programmes (vision screening and HPV vaccination). Although this was reported as a challenge in terms of logistics, it can also be an opportunity to integrate the provision of school health services. Therefore, future plans by many countries are to have new school-based health interventions piggy back on the HPV vaccination programme, provided the additional logistical challenges are addressed.

Engaging multiple stakeholders

Multiple stakeholder engagement was mentioned as a challenge by all participants. Unlike an established EPI where delivery of vaccination services is routinely common and generally accepted, HPV vaccination was different in many ways, among them being the targeted population (adolescents) and delivery through the schools. The multiple stakeholders engaged included parliamentarians, key officials from the department of education including the school heads and teachers, learners as well as the parents. Engaging the diverse stakeholders was reported as time consuming and laborious. Additionally, obtaining consents to get vaccinated (which is not the case with EPI) was also needed from learners and their parents. This was reported as a challenge.

The participants voiced funding challenges that required collaboration of local and international organisations to secure complementary financial, technical and operational support.

Table 19: Documented experiences during the implementation of the national HPV vaccination programme

Identifying the target age group	Using school-based vaccine delivery strategy	Obtaining the political will	Integrating HPV vaccination with existing school health programmes	Engaging multiple stakeholders
Challenges experienced				
Target age of 9-13 years- routinely, this age group is not targeted for vaccination among African countries. A new strategy was therefore needed to correctly identify the age group, and this proved to be a challenge.	School-based vaccine delivery strategies - unlike EPI which is well established among many African countries, routine school vaccination programme is not well established. Participants interviewed reported the extensive consultative planning that preceded the vaccination as a challenge.	Parliamentarians involved during HPV implementation plan- the benefits of political support are well recognized in promoting vaccination programmes. The participating stakeholders raised concerns of the hard work needed to gain the support of prominent politicians during the implementation of the HPV vaccination	Integration of the HPV vaccination with existing school health programme- School-based vaccinations as well as provision of other health services inadvertently results to disruption of learning. To minimize the learning disruptions while maximizing the benefits, HPV vaccination can be delivered together with other existing school-based health programmes. Planning how best to achieve the integration of all health programmes at school was identified as a future challenge as well as an	Several key stakeholders that were engaged included, officials from the departments of education as well as the school heads and teachers, parents as well as partners of the departments of health- sustained and diverse stakeholder engagements was noted as a challenge and crucial element to the success of HPV vaccination. Maintaining multiple stakeholder engagement was listed as a challenge.

			opportunity.	
Lessons learnt				
Feasible to select eligible girls based on grade/class as opposed to the specific age by use of the birth records.	Schools can successfully be used as a venue for HPV vaccinations. This is applicable in countries where primary school enrolment is high.	Political endorsement is critical to community acceptance. The political endorsements received during the HPV vaccination programmes can be expanded to include other vaccines to strengthen immunisation through political support.	Integration can reduce the costs of the programme. There exists an opportunity to provide additive health services together with the HPV vaccination programme. The integration is seen as an opportunity to improve health service delivery to the school going children with minimal disruption to the educators and learners.	Coordination of various stake holders is crucial for successful implementation of national HPV vaccination programme

Lessons learnt during the implementation of national HPV vaccination programmes in the six countries

Lesson 1: In school, identifying eligible girls for HPV vaccination based on the grade/class is more feasible than by age. However, some eligible girls born after mid-year are likely to be missed during HPV vaccination if already in the higher grade. The proportion of this missed population need to be quantified.

Lesson 2: School-based delivery strategies can be successfully used to deliver HPV vaccines to learners among African countries with high primary school enrolment. In case of missed vaccination opportunities, healthcare facilities can be used as venues for catch up vaccinations. Delivery of HPV vaccines through school-based programmes may also achieve high coverage levels, if there is high school enrolment in the targeted age group.

Lesson 3: Obtaining political support during the implementation of the HPV vaccination programme is crucial. In addition, political endorsement by national and district government leaders is critical for community acceptance.

Lesson 4: Integrating HPV vaccine programme to existing school-based health programmes is a logistical challenge but also, an opportunity as the integration can reduce the costs of the health programmes delivered to school-aged learners.

Lesson 5: Adequate preparation, engaging diverse and relevant stakeholders including teachers and parents is crucial to ensure the successful implementation of an HPV vaccination programme.

Lesson 6: Additional support from local and international partners is needed to ensure sustainability of the HPV vaccination programmes. Support by local partners is crucial to ensure HPV vaccines get to the hard to reach populations in a timely manner.

Discussion

In this study, we identified the challenges and lessons learnt during the implementation of HPV vaccination programmes. Inter-departmental co-ordination, identifying the target age group for HPV vaccination, obtaining political support and engaging diverse stakeholders were reported as the main challenges. The challenges were similar among the African countries that have implemented HPV vaccination programme. The similarities of the challenges across the study countries were surprising as the continent's immunisation challenges are not homogenous (200). However, in general, countries in Africa have many similar competing public health priorities and the continent has lagged with DTP3 coverage (200-202).

The delivery of HPV vaccines to the school girls required prior engagements and the co-ordination of the departments of health and education. Both departments had to plan around the timing of vaccinating the girls during the school period. Additionally, the departments of health had to plan on logistical delivery of the vaccines and the health workers to the schools. Despite these challenges, our results suggest good leadership and careful co-ordination could overcome these challenges. Furthermore, lessons learnt from this co-ordination can be used to integrate existing and future school-based health interventions with HPV vaccination to expand the delivery of vaccines to the adolescents (203, 204).

The WHO guidelines recommend the ideal target population for HPV vaccination be 10-13 years old, before onset of sexual activity (198). However, among the participating countries, it was difficult to accurately establish the right age of the girls before sexual activity. This is likely to be the case among many African countries not participating in this study. Research on sexual debut years for adolescents in Africa can guide optimal choice of age to initiate HPV vaccination.

A few African countries that started to pilot HPV vaccination with age-based approach used the birth date records to identify the age of the girls eligible for vaccination. This age-based approach presented a challenge as the birth date records were often not available. On the other hand, the challenge with the class-based approach was that children who are born mid-year may miss vaccination as they will have moved to the next class not targeted for HPV vaccination. Hence, if the missed targeted population is large, the effectiveness of HPV vaccination programmes in such countries will be sub-optimal, not forgetting that boys are not targeted by the programme. The approach to select girls for HPV vaccination based on grade as opposed to age through school-based vaccination strategy appeared universally ideal in our study.

The study participants alluded to the huge effort needed to obtain political support as well as reach a consensus among diverse and key stakeholders. In all the participating countries, endorsement of the HPV vaccination programme by the politicians was a pre-requisite. Political leadership that understands and embraces the value and public health benefits of immunisation is therefore crucial for national HPV vaccination programme in Africa.

Resource mobilisation for HPV vaccination programmes required engagements of diverse stakeholders. Broadly, advocacy and communication were needed to address this challenge. Many African countries, with support from international partners have made considerable progress to strengthen advocacy and communication on immunisation services (200). However, in Africa, as is the case globally much more effort is still needed to improve advocacy and communication on vaccination (205, 206). The lesson learnt from this challenge was the support by local and international partners, including politicians is crucial to initiate and sustain the HPV vaccination programmes in Africa. The sustainability will need strengthened advocacy and communication, not just for HPV vaccination, but for other routine immunisation services.

In this study, primary schooling in all the six countries was compulsory. This made the school-based vaccination strategy the preferred method to reach the highest number of targeted girls with HPV vaccination. However, school-based vaccination strategies may not be entirely successful in countries with suboptimal school attendance rate. There is a study that has shown supplementary immunisation activities (SIAs) including the use of outreach health facilities could be an option to target non-school going adolescents (207).

We propose collaboration among African countries to document and share the lessons learnt during HPV vaccine introduction. There is a recent study showing high inter country collaboration on immunisation research in Africa (208). We identify collaborations that document and share immunisation research information as platforms to foster further discussions on the introduction of other adolescent vaccines. The

lessons learnt by the countries included in this study can be of great use to other African countries planning to introduce national HPV vaccination programmes.

Conclusion

All the six countries used schools as the main sites for vaccination. Most targeted girls attended school due to the universal and free primary education programme in these countries. Schools therefore provided an easy and convenient site to access the eligible population. The school team that included the head teachers, teachers and school management embraced the HPV vaccination programme. The school team worked closely with the department of health to ensure there was minimal disruption of classes and the vaccination day does not coincide with important school programme like exam sessions. For situation where targeted learners are inevitably absent on vaccination days, health facility approach can be used to catch up and mop up.

Limitations and validity of the study

Out of 54 African countries, findings for this study are from six countries only, for reasons already provided in the methods section. This limitation is further compounded by the fact that we only interviewed one representative per country. Therefore, extrapolation of the findings to the entire continent must be done with caution. Another limitation is the use of questionnaires alone to collect data, without conducting focus group discussions. This was because of resource limitations.

Authors' contributions

GDH and BMK conceived the study and provided overall leadership. LHA conducted the study and wrote the drafts of the manuscript with support from BMK, CSW and GDH. All authors reviewed and approved the final manuscript.

Competing interest

None

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Chapter 6

Discussion and conclusion

About this chapter:

The chapter summarizes all the key findings from the PhD project and implications for policy and practice. We also discuss the projects' strengths and limitations.

The purpose of the PhD thesis was to characterize adolescent immunisation in the Decade of Vaccines. We used multiple approaches to successfully achieve this. Results and discussions of each of the approach are provided in detail in each of the chapters. Therefore, in this final chapter, we provide a succinct summary of the key findings as well as recommendations for considerations on adolescent immunisation by the policy makers.

Key findings:

There are several public health reasons suggesting that immense benefits could be achieved if adolescent immunisation is implemented in all settings. Recently the global community through a number of initiatives have advocated for adolescent immunisation to reduce the burden of VPDs among adolescents. The rapid introduction of HPV vaccination programme in many countries attests to this commitment. However, many other vaccines that are beneficial to adolescents are not routinely provided to this population in many countries. As a result, there exist an adolescent immunisation gap. We recommend more effort from individual countries and more support by the global community to address the immunisation gap.

In many settings, there is paucity of data on the vaccination coverage among adolescents, especially in LMICs. This is partly because routine adolescent immunisation is not well established in LMICs. Nevertheless, we can assume that apart from HPV vaccine, uptake of other adolescent vaccines is low in many countries. We showed that diverse barriers can contribute to suboptimal uptake of adolescent vaccines. These barriers are likely to be context specific. Understanding and removing these barriers are key steps to address the immunisation gap. We therefore recommend improved research, advocacy, communication and engagement by all immunisation stakeholders to address the adolescent immunisation gap.

Existing research from HICs shows different types of strategies or interventions can be effective in improving the uptake of vaccines among adolescents. However, research on strategies to improve vaccine uptake among adolescents in LMICs is limited. In LMICs, we recommend context specific research to translate evidence into action, concomitantly addressing the adolescent immunisation gap.

Optimal stakeholder knowledge on vaccines and VPDs is crucial for adolescent immunisation programmes. Educating the key stakeholders, in particular parents, teachers and adolescents, can positively influence the attitudes and practice towards vaccination and may have several long-term benefits. For example, well informed adolescents as future parents, are more likely to encourage their children to be vaccinated. We recommend countries to develop and implement educational programmes, aimed at enhancing relevant knowledge on vaccines, immunisation as well VPDs among the key stakeholders.

In Africa, as is the case in many other LMICs, introduction of HPV vaccines is seen as an ideal platform to build adolescent immunisation as well as provide other health interventions targeted towards adolescents. There were significant challenges experienced during the introduction of national HPV vaccination programme in these African countries. From the challenges experienced, key lessons were learnt, among them being that schools are convenient sites to access and vaccinate adolescents. School-based vaccination platform can be supplemented by health facilities and outreach programmes to reach all the adolescents.

We recommend African countries planning to implement national HPV vaccination to document and publicly disseminate the experiences and lessons learnt in the implementation process. Collation and dissemination of such information, together with our findings will be very useful to many other African countries planning to do likewise. Importantly, the information can be used by all countries in Africa to develop evidence-based adolescent immunisation programmes.

Between 2015 and 2016, we conducted a study on challenges faced by eight African countries that had introduced national HPV vaccination programme. Worrying, no additional countries in Africa are reported to have introduced HPV vaccine two years later (2018). This is a big concern considering the documented benefits of HPV vaccination programmes in Africa. We recommend strong advocacy programmes in Africa to address the adolescent immunisation gap.

Strengths of the projects

1. We used evidence-based approach to answer most of our research questions. Evidence-based research is a robust method used to generate information that in turn, can be used to strengthen an immunisation programme.
2. There is paucity of knowledge on adolescent immunization, mostly in Africa. Hence this study contributes to the knowledge base in the field.
3. In chapter 5 the focus was on countries in Africa implementing HPV vaccination. The experiences and challenges are useful for other countries planning to do so as well.

Limitations of the projects

1. Majority of available evidence on adolescent immunisation was for HPV vaccine. There was limited information on a catch up, booster or future adolescent vaccines
2. HPV implementation in Africa is a new concept and its implementation is happening slowly hence paucity of data.
3. In Chapter 5 as an example, we found that the respondents gave similar experiences and challenges of a school based programme as a successful platform therefore, the study might not have information for the countries that need to try other methods of implementing HPV vaccination like health facility based programme.

Contributions

Leila Abdullahi wrote this chapter under the supervision of Prof. Greg Hussey, Dr. Benjamin Kagina and Prof. Charles Wiysonge.

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Appendices

Appendix 1: Methodological Expectations of Cochrane Intervention Reviews (MECIR) Checklist. (Chapter 3)

Methodological Expectations of Cochrane Intervention Reviews

Intervention Cochrane Review - checklist for authors

This checklist is designed to help you (the authors) complete your Cochrane Review. Please complete each item in the checklist by entering Y (or N/A if item is not applicable to your Cochrane Review) into the blue shaded cells before checking your Cochrane Review into Archie, and email the completed checklist to: cohg@manchester.ac.uk. The editorial team will return your Cochrane Review to you if the form is incomplete or not received. There is a 'Notes' section at the end of the form to alert the editorial team to the reason for any incomplete checks.

The checklist should be used in conjunction with the *Cochrane Handbook for Systematic Reviews of Interventions* (www.cochrane-handbook.org) and the Methodological Expectations of Cochrane Intervention Reviews (MECIR; ww.editorial-unit.cochrane.org/mecir). MECIR includes methodological standards for the *conduct* of reviews (items C1-C80) and for the *reporting* of reviews (items R1-R108).

Cochrane Review title:	**Improving vaccination uptake among adolescents**
Cochrane Review number:	**N/A**
Contact person:	**Leila H Abdullahi**
Date:	27/12/2018

1. General

1.1	Y	All the authors listed on the Cochrane Review have seen and approved this version of the Cochrane Review, and take full responsibility for the accuracy of its contents.
1.2	Y	Incorporated any standard text provided by the Cochrane Review Group (CRG).

1.3	Y	Activated the relevant headings in RevMan and completed each section.
1.4	Y	Completed a validation check in RevMan (File menu > Reports > Validation report), and made corrections where possible.
1.5	Y	Completed a spell check in RevMan (Tools menu > Check spelling).
1.6	Y	The text is clearly written and all technical and medical terms are explained for non-expert readers.

2. Title and review information

(see Cochrane Handbook Section 4.2; MECIR standards R1, R2, R35)

2.1	Y	Title is the same as the published Cochrane Protocol, unless a change has been agreed with the CRG.
2.2	Y	Authors are listed in the correct order and have agreed to the order in which they are listed.
2.3	Y	Names and details of all authors and the contact person appear correctly, or the CRG has been notified of any necessary corrections.
2.4	Y	Entered the last date on which every component of your search was up-to-date in the 'Date of search' field. If your sources were searched on several different dates, entered the earliest date.
2.5	Y	Completed the 'Next stage expected' field, estimating when you will update the Cochrane Review (usually after two years).

3. Abstract

(see Cochrane Handbook Section 11.8; MECIR standards R3 to R13)

3.1	Y	Included 1000 words or fewer (though with a preference for them to be up to 700 words only).

Background

3.2	Y	Explained the context or elaborated on the context, purpose and rationale of the review.

Objectives

3.3	NA	Expressed in the form 'To assess the effects of [intervention or comparison] for [health problem] for/in [types of people, disease or problem and setting if specified]'.

Search methods

3.4	Y	Provide the date of the last search from which records were incorporated into the review, and an indication of the databases and other sources searched.

Selection criteria

3.5	Y	Summarize eligibility criteria of the review including information on study design, population and comparison.

Data collection and analysis

3.6	Y	Summarize any noteworthy methods for selecting studies, collecting data, evaluating risk of bias and synthesising findings. For many reviews it may be sufficient to state "We used standard methodological procedures expected by The Cochrane Collaboration".

Main results

3.7	Y	Included the total number of studies and participants.
3.8	Y	Provide a brief description of key characteristics that will determine the applicability of a body of evidence (e.g. age, severity of condition, setting, study duration).
3.9	Y	Provide a comment on the risk of bias.
3.10	Y	Report findings for all primary outcomes irrespective of strength and direction of the result, and availability of data.
3.11	Y	Ensure that any findings related to adverse effects are reported. If adverse effects data were sought, but availability of data was limited, this should be reported.
3.12	Y	Included the same summary statistics as those in the review, and presented statistics in a standard way (e.g. 'OR 2.31; 95% CI 1.13 to 3.45'). Ensure that readers will understand the direction of benefit and the measurement scale used and that confidence intervals are included where appropriate.
3.13	Y	Included risks of events (percentage) or averages (for continuous data) for both comparison groups.
3.14	Y	Ensure that key findings are interpretable or are re-expressed in an interpretable way. For instance, they might be re-expressed in absolute terms (e.g. assumed and corresponding risks, NNTs, group means), and outcomes combined with a standard scale (e.g. SMD might be re-expressed in units that are more naturally understood.
3.15	Y	If overall results are not calculated, included a qualitative assessment or a description of the range and pattern of the results.
3.16	Y	Added no information that is not in the Cochrane Review.

Authors' conclusions

3.17	Y	Included a succinct conclusion drawn directly from the findings of the review.
3.18	Y	Avoided giving advice or recommendations.
3.19	Y	Included any important limitations of data and analyses.

3.20	Y	Ensure that reporting of objective important outcomes, results caveats, and conclusion is consistent across the text, abstract, PLS and SOF.

4. Plain Language Summary

(see Cochrane Handbook Section 11.9)

4.1	Y	The Plain Language Summary title is the same as the Cochrane Review title, or restates the title using plain language terms.
4.2	Y	Included 400 words or fewer, and considered using section headers to aid readability.
4.3	Y	Included a statement about why the review is important (e.g. a plain language definition of and background to the healthcare problem, signs and symptoms, prevalence, description of the intervention and comparison and the way they are used, and the questions to be answered by the review).
4.4	Y	Included the date up to which studies have been searched and incorporated.
4.5	Y	Included the main findings of the review (e.g. numerical summaries in a general and easily understood format), including the primary outcome and adverse effects, even if the results were not statistically significant or no results were found. The word 'risk' has been avoided when reporting harms.
4.6	Y	Included the total number of studies and participants.
4.7	Y	Included a brief comment on any limitations of the review (e.g. studies with a high risk of bias, inconsistent results between trials, deviations from the intended population or intervention, imprecise results).
4.8	Y	The results and conclusions are consistent with those in Cochrane Review text and abstract.
4.9	Y	Added no information that is not in the Cochrane Review or abstract.

5. Background, Objectives and Methods

(see Cochrane Handbook Section 4.5; MECIR standards R19 to R54)

5.1	Y	All sections are the same as those in the published Cochrane Protocol, or any changes have been noted in the 'Differences between protocol and review' section, including new methods added and planned methods that could not be implemented (e.g. due to lack of data).
5.2	Y	Changed the text referring to the methods of the Cochrane Review from the future tense to the past tense.
5.3	Y	Consulted the CRG Trials Search Co-ordinator regarding implementation of the search strategy.

5.4	Y	In the 'Search methods for identification of studies' section, reported the date range for which each source was searched, and the dates on which each search was conducted.
5.5	Y	In the 'Search methods for identification of studies' section, included a link to the Appendix containing the complete set of search terms used in each electronic database.

6. Results

(see Cochrane Handbook Section 4.5)

6.1 Description of studies

(see MECIR standards R55, R56, R57, R58, R59, R61)

6.1.1	Y	Reported the outcomes of the search, including the total number of hits found from electronic databases, the number of potentially relevant studies found from other sources, the number of records remaining after duplicates were removed, the number of papers retrieved in full text, the number of papers excluded at each stage with the reasons for exclusion, and the final number of included studies.
6.1.2	Y	Included links to the 'Characteristics of included studies', 'Characteristics of excluded studies' and, if appropriate, 'Characteristics of studies awaiting classification' and 'Characteristics of ongoing studies' tables.
6.1.3	Y	If contact with the authors of any included studies was attempted, reported how many were contacted and what responses were received.
6.1.4	Y	Given a brief overview of the studies included in the Cochrane Review, including the number of participants, and the comparability of their populations, settings and interventions.
6.1.5	Y	No results from studies have been reported in this section.

6.2 Risk of bias of included studies

(see MECIR standards R73 to R74)

6.2.1	Y	Given a concise summary of general risk of bias in the results of included studies, including variability across studies and any important flaws in individual studies.
6.2.2	Y	The summary of the risk of bias is consistent with the information presented in the 'Risk of bias' tables.
6.2.3	Y	Included a link to the 'Characteristics of included studies' table.
6.2.4	Y	If any 'Risk of bias' figures have been created, included a link to these.

6.3 Effects of interventions

(see MECIR standards R75 to R77, R79 to R91, R95 to R98)

6.3.1	Y	Summarised the results in a structured way (e.g. organised by comparison and then outcome).
6.3.2	Y	Reported the outcomes in the same order as listed in the 'Types of outcome measures' section, and primary and secondary outcomes are identified.
6.3.3	Y	Reported the available results for each comparison, outcome and subgroup described in the Cochrane Protocol, including those for which no results were found and those that were not statistically significant.
6.3.4	Y	Reported the results using the statistics and methods described in the 'Methods' section.
6.3.5	Y	Ensure that all statistical results presented in the main review text are consistent between the text and the 'Data and analysis' tables.
6.3.6	Y	Explain how studies measuring an outcome of interest using different scales (such as alternative rating scales that measure symptoms or behaviour) were combined, stating whether positive or negative values reflect benefit or harm.
6.3.7	Y	Ensure that key findings are interpretable, or are re-expressed in an interpretable way (MECIR standard R88).
6.3.8	Y	Comment on the potential impact of studies that apparently measured outcomes but did not contribute data that allowed the study to be included in synthesis.
6.3.6	Y	Included links to all analyses, figures, tables, appendices.
6.3.7	Y	Restrict the number of Tables and Figures to a small number to convey key findings without affecting the readability of the results.
6.3.8	Y	Presented the number of studies and participants included, as well as a measure of uncertainty (e.g. 95% confidence interval), for each result.
6.3.9	Y	Conducted sensitivity analyses as described in the Cochrane Protocol, if appropriate, and reported the results.
6.3.10	Y	Investigated heterogeneity as described in the Cochrane Protocol, if appropriate, and reported the results.
6.3.11	Y	Investigated the possible impact of bias on results as indicated in the Cochrane Protocol, including possible biases relating to study design and reporting bias.
6.3.12	Y	Not confused 'no evidence of effect' with 'evidence of no effect'.
6.3.13	Y	Clearly identified any post-hoc analyses that were not planned at the Cochrane Protocol stage.
6.3.14	Y	Not included any interpretation of results.

6.3.15	Y	Referred to the Summary of findings table(s) and included links.

7. Discussion

(see Cochrane Handbook Section 4.5; MECIR standards R99, R100)

7.1	Y	Included the standard headings when writing the Discussion
7.2	Y	Briefly summarised the included studies and their results in plain language, including the risk of bias, areas of uncertainty and completeness of the available evidence.
7.3	Y	Checked that this section does not include any new results not reported in the previous section.
7.4	Y	Considered both the statistical significance and clinical or policy implications of the results.
7.5	Y	Considered the context and applicability and context of the results to different groups (e.g. consumers, carers, policy makers, health professionals, vulnerable/disadvantaged groups).
7.6	Y	Discussed the strengths and limitations of the Cochrane Review.
7.7	Y	Discussed the findings in the context of current knowledge, including other reviews in the field.

8. Authors' conclusions

(see Cochrane Handbook Section 4.5; MECIR standards R101, R102)

8.1	Y	Implications for practice: Avoided making recommendations and limited conclusions to those that can be supported by the findings of the Cochrane Review.
8.2	Y	Implications for research: If recommending additional research, specific suggestions about how the research should be conducted (e.g. study designs, outcome measurements) as well as what research should be conducted (e.g. different populations, interventions) have been made.

9. Acknowledgements

(see Cochrane Handbook Section 4.5; MECIR standard R103)

9.1	Y	Acknowledged those people who contributed to the Cochrane Review but are not named as authors, and included the reasons for acknowledging each person.
9.2	Y	Permission has been granted from all the people named to include them in this section.

10. Contributions of authors

(see Cochrane Handbook Section 4.5; MECIR standard R104)

10.1	Y	Described each author's contribution to the design and development of the Cochrane Protocol and the Cochrane Review.

11. Declarations of interest

(see Cochrane Handbook Section 4.5; MECIR standard R105)

11.1	Y	Completed for each author, noting present or past affiliations that that may lead to a real or perceived conflict of interest, including whether authors are investigators on studies likely to be included in the review. If no potential conflicts are identified for a particular author, "None known" has been stated.

12. Differences between protocol and review

(see Cochrane Handbook Section 4.5; MECIR standards R79; R106; R107)

12.1	Y	Reported any changes in the Cochrane Review authorship since the Cochrane Protocol was published.
12.2	Y	Reported any differences in the methods used between the Cochrane Protocol and the Cochrane Review, including anything that was changed, added or removed from the proposed methods.
12.3	Y	Given a rationale for any differences between the Cochrane Protocol and the Cochrane Review, and the rationale is not driven by the findings of the Cochrane Review.

13. Tables

13.1 Characteristics of included studies

(see Cochrane Handbook Section 11.2; MECIR standards R60, R62 to R70)

13.1.1	Y	The table does not include study results or information that should be included in the 'Risk of bias' assessment.
13.1.2	Y	If appropriate, any available information on study funding has been included in an extra row in the table.
13.1.3	Y	Avoided using abbreviations or acronyms and, where used, the full term has been provided in the footnotes.

Methods

13.1.4	Y	Listed the study design (e.g. “randomised controlled trial”), including whether the study differs from a standard parallel group design (e.g. cross-over or cluster-randomised), and the duration of the study including start and end dates if available.

Participants

13.1.5	Y	Stated the number of participants and described their location, context, health status, age, and sex. Enough information has been provided for users of the Cochrane Review to determine the applicability of the study to their population, and to allow exploration of differences across studies.

Interventions

13.1.6	Y	Described each intervention group in the study in enough detail for each intervention to be replicated in practice (if possible), including dose/frequency, components, mode of administration, and duration of each intervention.

Outcomes

13.1.7	Y	Listed either the outcomes from the study that are considered in the Cochrane Review, or all outcomes measured or reported in the study. For each outcome, the time points measured have been described, as well as the tools, units and definitions used to measure the outcome.

13.2 Risk of bias

(see Cochrane Handbook Chapter 8; MECIR standard R72)

13.2.1	Y	Activated rows in the table to assess sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues.
13.2.2	Y	Judged each parameter of the Risk of Bias table appropriately to indicate whether the study is at high, low or unclear risk of bias.
13.2.3	Y	In each judgement, the evidence of bias, the likely direction of bias, and the likely magnitude of bias have been taken into consideration, and judgements are consistent with Table 8.5.c of the Handbook.
13.2.4	Y	Provided detailed, clearly identified quotes from the study text and additional comments where necessary to support each judgement.
13.2.5	Y	Avoided using abbreviations or acronyms and, where used, provided the full term in the footnotes.

Random sequence generation (selection bias)

13.2.6	Y	Described the method for generating the allocation of participants to the intervention groups, and whether it was random, quasi-random or non-random.

Allocation concealment (selection bias)

13.2.7	Y	Described whether the assignment of participants to intervention groups was concealed throughout the recruitment and allocation process (before the interventions began).

Blinding of participants and personnel (performance bias)

13.2.8	Y	Described who was blinded or masked during the conduct of the trial, including an assessment of the success of blinding.
13.2.9	Y	Considered the possible impact of blinding for each outcome reported in the Cochrane Review and, if appropriate, created additional rows in the table for outcomes at different levels of risk.

Blinding of outcome assessment (detection bias)

13.2.10	Y	Described who was blinded or masked during the outcome assessment and analysis of the trial, including an assessment of the success of blinding.
13.2.11	Y	Considered the possible impact of blinding for each outcome reported in the Cochrane Review and, if appropriate, created additional rows in the table for outcomes at different levels of risk.

Incomplete outcome data (attrition bias)

13.2.12	Y	Described the completeness of the available data, including information about withdrawals, exclusions, imputation of missing data and 'as treated' analysis.
13.2.13	Y	Included an assessment of the possible impact of the incomplete data based on the proportion of missing values (dichotomous), the plausible effect size (continuous), the balance of missing data between intervention groups, and the reasons for incompleteness.
13.2.14	Y	Considered the possible impact of incomplete outcome data for each outcome and time point reported and, if appropriate, created additional rows in the table for outcomes or time points at different levels of risk.

Selective reporting (reporting bias)

13.2.15	Y	Considered availability of the study protocol, and whether there is any evidence of outcomes added, not reported, reported incompletely, or reported using measures, methods or subsets of data that were not pre-specified.

Other bias

13.2.16	Y	Described any other concerns about the study (e.g. baseline imbalance, early stopping) have been described.

13.2.17	Y	Issues that do not have direct implications for bias (e.g. sample size, ethical approval) have not been included.

13.3 Characteristics of excluded studies

(see Cochrane Handbook Section 4.6.3; MECIR standard R57)

13.3.1	Y	Listed studies that may appear to meet the eligibility criteria, but which were excluded.
13.3.2	Y	Given a brief reason why each study was excluded from the Cochrane Review (e.g. inappropriate comparator intervention). If a reason applies to more than one study, it is expressed in the same way each time.
13.3.3		Further information about the studies (e.g. location or results) has not been included.

13.4 Characteristics of studies awaiting classification

(see Cochrane Handbook Section 4.6.4; MECIR standard R58)

13.4.1	Y	Provided detailed information, if possible, similar to the Characteristics of included studies table.
13.4.2	Y	In any blank cells, “Not yet assessed” or “Not known” has been stated as appropriate.

13.5 Characteristics of ongoing studies

(see Cochrane Handbook Section 4.6.5; MECIR standard R59)

13.5.1	Y	Provided detailed information, if possible, similar to the Characteristics of included studies table.
13.5.2	Y	In any blank cells, “Not yet assessed” or “Not known” has been stated as appropriate.

13.6 Summary of findings

(see Cochrane Handbook Section 11.5 and Section 12.2; MECIR standards R97, R98)

13.6.1	Y	Included a ‘Summary of findings’ table in the Cochrane Review. Additional ‘Summary of findings’ tables have been included if the Cochrane Review includes more than one major comparison or substantially different populations.
13.6.2	Y	Briefly described the population, setting and intervention in the studies relevant to each table.
13.6.3	Y	Selected a maximum of seven important outcomes to be reported in each table, and included these outcomes whether or not data were found in the included studies.
13.6.4	Y	Included one or more adverse effect outcome in each table.

13.6.5	Y	Named each outcome in plain language, and clearly described any tools, units and definitions used to measure the outcome, including the direction of benefit and upper and lower limits of any numerical scales.
13.6.6	Y	Selected an assumed risk for each outcome based on either the control group risk(s) in the included studies, or an external source (e.g. well-conducted epidemiological study), and have included a footnote explaining the choice.
13.6.7	Y	Checked that all results appear correctly and are consistent with the results presented in the 'Data and analyses' and 'Results' sections of the Cochrane Review.
13.6.8	Y	Entered a GRADE assessment for each outcome, including footnotes to explain judgements.
13.6.9	Y	Included comments explaining any additional information required by the reader, including explanations for any outcomes for which results cannot be displayed in the standard format.
13.6.10	Y	Included explanations of any abbreviations in footnotes.
13.6.11	Y	Footnotes are referenced in the text using superscript letters (e.g. [a])

13.7 Additional tables

(see Cochrane Handbook Section 4.6.7)

13.7.1	Y	Each table has a brief and informative heading.
13.7.2	Y	Cells in the table containing row or column headings are formatted in heading style, by selecting Toggle heading/cell from the Table menu in RevMan.
13.7.3	Y	Included explanations of any abbreviations in footnotes.
13.7.4	Y	If footnotes have been used, these are referenced in the text using superscript letters (e.g. a).
13.7.5	Y	Where possible, 'non-essential' tables moved to the 'Appendices'.

14. References

All sources of information in the Cochrane Protocol must be appropriately referenced to prevent plagiarism. All reference citation IDs and references in the reference list must be consistent with the Cochrane Style Guide (http://www.cochrane.org/sites/default/files/uploads/Cochrane-Style-Guide_4-1-edition.pdf). In particular, please check the following items:

14.1 In the text

14.1.1	Y	Checked that a link has been created wherever a reference citation ID appears in the text of the Cochrane Review using the Find and Mark Links tool.

14.1.2	Y	Grouped reference citation IDs and links in the text in alphabetical or chronological order, surrounded by round brackets and separated by semi-colons.

14.2 In the reference lists

(see Cochrane Handbook Section 4.7; MECIR standard R71; Style guide)

14.2.1	Y	Reference citation IDs are in the correct format (first author or group abbreviation and year of publication, e.g. Smith 1983 or UKPDS 1990)
14.2.2	Y	Included each journal title in full, with no abbreviations.
14.2.3	Y	Checked how each reference is displayed to remove unnecessary punctuation.
14.2.4	Y	Where applicable, listed the first six authors before using 'et al.'
14.2.5	Y	Written the page numbers correctly (e.g. 354-7).
14.2.6	Y	Included the date accessed in any references to web pages.

References to studies

14.2.7	Y	Grouped all the references relevant to each study under a single study ID.
14.2.8	Y	If two or more references are listed under a study ID, one has been nominated as the primary reference.
14.2.9	Y	Specified whether data for each study includes published, unpublished or both sources, and whether unpublished data were sought.

Additional references

14.2.10	Y	Included other references cited in the text of the review, aside from studies assessed for inclusion (e.g. cited in the 'Background' or 'Methods' sections).

Other published versions of this review

14.2.11	Y	Included references to any previous or derivative published versions of this Cochrane Review.

15. Data and analyses

(see Cochrane Handbook Section 4.8; MECIR standards C51, R92, R93, R94)

15.1	Y	Comparison names are consistent with the 'Objectives', 'Types of Interventions' and 'Effects of interventions' sections.
15.2	Y	Presented the outcomes in the same order as the 'Types of outcome measures' and 'Effects of interventions' sections.

15.3	Y	Outcome names are consistent with the 'Types of outcome measures' and 'Effects of interventions' sections.
15.4	Y	Outcome names include brief information on the tools, units, definitions, and time points, if appropriate.
15.5	Y	Changed the 'Group' labels on the forest plots from 'Experimental' and 'Control' to the actual intervention groups used in the comparison.
15.6	Y	Changed the 'Graph' labels on the forest plots from 'Favours experimental' and 'Favours control' to reflect the actual intervention group names.
15.7	Y	Checked that the 'Graph' labels indicate the correct direction of effect (for negative outcomes, the left side favours the experimental group; for positive outcomes, the left side favours the control group).
15.8	Y	Set the scale of each forest plot so the point estimates and confidence intervals can be seen clearly, and if possible so that the plots are consistent between outcomes on similar scales.
15.9	Y	Meta-analysis totals for outcomes or subgroups with only one included study are not displayed.
15.10	Y	Meta-analysis totals combining more than one measurement from the same individuals in the same study are not displayed.
15.11	Y	The statistical options used in the forest plots are correct and consistent with the 'Methods' section, including the statistical method (e.g. Peto or inverse variance), analysis model (e.g. fixed effect or random effects), and effect measure (e.g. risk ratio or odds ratio).
15.12	Y	Checked any outlying or unexpected results for data entry and transcription errors.

16. Figures

(see Cochrane Handbook Section 4.9 and the RevMan User Guide for specifications on size and resolution; MECIR standard R85)

16.1	Y	Permission received to reproduce any figures from external sources included in the Cochrane Review.
16.2	Y	Each figure has a brief caption describing the purpose of the figure, and acknowledging its source.
16.3	Y	All figures used are scaled so that a reader can see the complete picture within the RevMan window.
16.4	Y	All figures are of a sufficient resolution and quality for publication.

16.5	Y	Restrict the number of figures and tables to a small number to convey key findings without affecting the readability of the text.

17. Sources of support

(see Cochrane Handbook Section 4.10; MECIR standard R108)

17.1	Y	Listed all sources of funding and in-kind support, including internal sources (e.g. the home institution of any author) and external sources (e.g. grant funding).

18. Appendices

(see Cochrane Handbook Section 4.12)

18.1	Y	The title of each appendix is clear and informative.
18.2	Y	Copied the complete set of search terms used for each electronic database into an Appendix.

19. Style

(see Cochrane Style Guide at http://www.cochrane.org/training/authors-mes/cochrane-style-resource)

19.1	Y	Removed all highlighting, notes and tracked changes from the Cochrane Review.
19.2	Y	All text uses the active voice (i.e. “two review authors extracted data”, not “data were extracted by two review authors”)
19.3	Y	Proofread the Cochrane Protocol carefully in accordance with the Cochrane Style Guide Basics.
19.4	Y	Explained all acronyms and abbreviations (e.g. World Health Organization (WHO)).
19.5	Y	If additional subheadings have been added, the appropriate Heading Style has been selected using the drop-down box on the RevMan toolbar.
19.6	Y	Written numbers up to and including ‘nine’ as words, and numbers 10 or higher as numerals (excluding those at the start of a sentence and numbers appearing in tables or figures).
19.7	Y	Included a space before and after all units of measurement and mathematical symbols (e.g. 5 mL, P = 0.03).
19.8	Y	If reporting P values, P is written in upper case and without a hyphen.

Appendix 2: Search term (Chapter 3)

Medline, Ovid

#	**Searches**
1	(vaccin* and (uptake or coverage)).ti.
2	(vaccin* adj (uptake or coverage)).ab.
3	or/1-2
4	Immunization/
5	Immunization Schedule/
6	Immunization, Secondary/
7	Immunization Programs/
8	Immunotherapy, Active/
9	Vaccination/
10	Mass Vaccination/
11	or/4-10
12	Diphtheria/
13	Tetanus/
14	Bordetella Infections/
15	Bordetella Pertussis/
16	Whooping Cough/
17	Measles/
18	Mumps/
19	Rubella/
20	Poliomyelitis/
21	Poliomyelitis, Bulbar/
22	Tuberculosis/
23	Tuberculosis, Pulmonary/

24	Mycobacterium Tuberculosis/
25	Hepatitis A/
26	Hepatitis A virus/
27	Hepatitis A Virus, Human/
28	Hepatitis B/
29	Hepatitis B, Chronic/
30	Hepatitis B virus/
31	Chickenpox/
32	Papillomavirus Infections/
33	Herpesviridae Infections/
34	Herpes Simplex/
35	Herpes Genitalis/
36	Herpes Labialis/
37	Herpes Zoster/
38	Meningococcal Infections/
39	Meningitis, Meningococcal/
40	Neisseria meningitidis/
41	exp HIV Infections/
42	HIV/
43	HIV-1/
44	HIV-2/
45	Neoplasms/
46	or/12-45
47	11 and 46
48	Diphtheria-Tetanus-Acellular Pertussis Vaccines/
49	Diphtheria-Tetanus-Pertussis Vaccine/

50	Diphtheria-Tetanus Vaccine/
51	Pertussis Vaccine/
52	Vaccines, Combined/
53	Diphtheria Toxoid/
54	Tetanus Toxoid/
55	Measles-Mumps-Rubella Vaccine/
56	Measles Vaccine/
57	Mumps Vaccine/
58	Rubella Vaccine/
59	Poliovirus Vaccines/
60	Poliovirus Vaccine, Oral/
61	Poliovirus Vaccine, Inactivated/
62	Tuberculosis Vaccines/
63	BCG Vaccine/
64	Viral Hepatitis Vaccines/
65	Hepatitis A Vaccines/
66	Hepatitis B Vaccines/
67	Chickenpox Vaccine/
68	Papillomavirus Vaccines/
69	Meningococcal Vaccines/
70	AIDS Vaccines/
71	or/48-70
72	((diphtheria? or tetanus or bordetella or pertussis or whooping cough or measles or mumps or rubella? or rubeola or mmr or polio* or infantile paralysis or tuberculosis or tuberculoses or bcg or calmette* or hepatitis or chickenpox or varicella or papilloma* or herpes or meningococcal or meningitidis or meningitis or acquired immunodeficiency syndrome or aids or human immunodeficiency virus or hiv? or cancer? or neoplasm?) adj3 (vaccin* or revaccinat* or immunization or immunisation or immunotherapy)).ti,ab.
73	((tripe or combin*) adj vaccin*).ti,ab.

74	or/72-73
75	3 or 47 or 71 or 74
76	Adolescent/
77	Adolescent Health Services/
78	(adolescent? or youth? or young adult? or teenager? or teen? or juvenile?).ti,ab.
79	or/76-78
80	75 and 79
81	randomized controlled trial.pt.
82	controlled clinical trial.pt.
83	multicenter study.pt.
84	pragmatic clinical trial.pt.
85	non-randomized controlled trials as topic/
86	interrupted time series analysis/
87	controlled before-after studies/
88	(randomis* or randomiz* or randomly).ti,ab.
89	groups.ab.
90	(trial or intervention? or effect? or impact? or multicenter or multi center or multicentre or multi centre).ti.
91	(controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or evaluat* or time series or time point? or repeated measur*).ti,ab.
92	or/81-91
93	exp Animals/
94	Humans/
95	93 not (93 and 94)
96	review.pt.
97	meta analysis.pt.
98	news.pt.

99	comment.pt.
100	editorial.pt.
101	cochrane database of systematic reviews.jn.
102	comment on.cm.
103	(systematic review or literature review).ti.
104	or/95-103
105	92 not 104
106	80 and 105

Appendix 3: Table of excluded studies (chapter 3)

Study ID	Reason for exclusion
Anjum 2012 (209)	This is a simple pre and post cross-sectional survey with no controls
Bar-Shain 2015 (210)	The intervention is a reminder
Bennett 2015 (211)	The age of participants is 18-26 years, not separated to cater for 18-19 yrs
Broutet 2013 (204)	This is a review
Catledge 2014 (212)	This is a pre and post survey
Chan 2015 (213)	This is a pre and post study
Chapman 2010 (214)	This is a pre- and post cross-sectional survey
Chaves 2000 (215)	This is written in Spanish
Chou 2014 (216)	This is a pre- and post-consultation surveys
Chung 2015 (217)	The intervention is a reminder
Dawson 2015 (218)	This is a pre and post intervention study
Dempsey 2015 A (219)	This is a pre and post intervention study
Dempsey 2015 B (220)	This is a pre and post study
Donahue 2016 (221)	The intervention is a reminder
Dorji 2015 (222)	This is a descriptive study, with no intervention and control arms
Farmar 2016 (223)	This is a pre and post intervention study
Fujiwara 2013 (224)	This is a questionnaire survey, with no intervention and control
Furlan 2010 (225)	This is published in Portuguese
Gargano 2014 (226)	This is a descriptive study with no intervention
Gillespie 2011 (227)	This is a questionnaire survey in an ineligible age group
Gordon 2013 (228)	This is a descriptive study, with no intervention
Gottvall 2010 (229)	This is a quasi-experimental intervention study
Hadley 2014 (230)	This is a descriptive study
Hofman 2013 (231)	This is a pre and post-test evaluation

Hull 2016 (232)	This is a pilot cross over study
Iqbal 2016 (233)	The age group is 11-25 years and data not stratified by age group
Kim 2015 (234)	This is a pre and post-test study
Kwan 2011 (235)	This is a pre and post evaluation study
Kwang 2016 (236)	This is a pre and post study in an ineligible age group
Lai 2013 (237)	This is a quasi-experimental time series study
LaMontagne 2011 (187)	This was a cross-sectional study
Marek 2012 (238)	This is a simple pre-post survey
Meneses 2015 (239)	This is a re and post intervention with no control
Moss 2012 (240)	This is a pre and post intervention survey
Ortiz 2016 (241)	This is a pilot cross sectional study
Perkins 2016 (242)	This is a cross sectional survey
Pierre-Victor 2017 (243)	This a pre and post study
Reiter 2011 (244)	This is a pre and post evaluation study
Ruffin 2015 (245)	The intervention is a reminder
Sales 2011 (246)	This is a pre and post study
Soldan 2006 (247)	This is a review
Spleen 2012 (248)	This is a pre-test/post-test assessment
Stokley 2015 (249)	This is a review
Szilagyi 2011 (250)	The intervention is a reminder
Tiro 2016 (251)	This is a pre and post survey
Unti 1997 (252)	This is a pre and post survey
Won 2015 (253)	The outcomes in this study are trust and participation in school-located immunisation programmes, and none of our outcomes of interest is reported
Zhou 2003 (254)	This is a pre and post intervention survey

Appendix 4: PRISMA checklist (Chapter 4)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	98
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.	99-100
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	101-102
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	103
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.	103
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.	103-104
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.	105
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	213
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).	106
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.	106

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	106
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.	106
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	107
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.	107

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).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
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.	108
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.	109-114
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).	123
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.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	123-124
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
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).	125

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).	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	127
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.	127

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(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 5: Search strategy for PubMed database (chapter 4).

Recent queries in PubMed (as of 20th April 2014)	
Search	Query
#7	(((((((ALGERIA) OR (ANGOLA) OR (BENIN) OR (BOTSWANA) OR (BURKINA FASO) OR (BURUNDI) OR (CAMEROON) OR (CANARY ISLANDS OR "CANARY ISLANDS") OR ((CAPE VERDE) OR "CAPE VERDE") OR (CENTRAL AFRICAN REPUBLIC) OR (CHAD) OR (COMOROS) OR (CONGO) OR (DEMOCRATIC REPUBLIC CONGO) OR (DJIBOUTI) OR (EGYPT) OR ((EQUATORIAL GUINEA) OR "EQUATORIAL GUINEA") OR (ERITREA) OR (ETHIOPIA) OR (GABON) OR (GAMBIA) OR (GHANA) OR (GUINEA) OR ((GUINEA BISSAU) OR "GUINEA BISSAU") OR (IVORY COAST) OR ((COTE D'IVOIRE) OR "COTE D'IVOIRE") OR (KENYA) OR (LESOTHO) OR (LIBERIA) OR ((LIBYA) OR (LIBIA) OR (JAMAHIRIYA) OR (JAMAHIRYIA)) OR (MADAGASCAR) OR (MALAWI) OR (MALI) OR (MAURITANIA) OR (MAURITIUS) OR (MOROCCO) OR ((MOZAMBIQUE) OR (MOCAMBIQUE)) OR (NAMIBIA) OR (NIGER) OR (NIGERIA) OR (REUNION) OR (RWANDA) OR ((SAO TOME) OR "SAO TOME") OR (SENEGAL) OR (SEYCHELLES) OR ((SIERRA LEONE) OR "SIERRA LEONE") OR (SOMALIA) OR ((SOUTH AFRICA) OR "SOUTH AFRICA") OR ((ST HELENA) OR "ST HELENA") OR (SUDAN) OR (SWAZILAND) OR (TANZANIA) OR (TANGANYIKA) OR (TOGO) OR (TUNISIA) OR (UGANDA) OR ((WESTERN SAHARA) OR "WESTERN SAHARA") OR (ZAIRE) OR (ZAMBIA) OR (ZIMBABWE) OR (AFRICA[MH]) OR (SOUTH* AND AFRICA*) OR (WEST* AND AFRICA*) OR (EAST* AND AFRICA*) OR (NORTH* AND AFRICA*) OR (CENTRAL* AND AFRICA*) OR (SUB SAHARAN AFRICA*) OR (SUBSAHARAN AFRICA*) OR (AFRICA*) NOT (((GUINEA PIG*) OR "GUINEA PIG*") OR ((ASPERGILLUS NIGER) OR "ASPERGILLUS NIGERâ€□))))) AND (((((("Vaccination"[Mesh]) OR vaccination) OR "Immunization"[Mesh]) OR immunization) OR immunisation)) AND ((("Adolescent"[Mesh]) OR adolescent) OR teenager)) AND ((accept) OR ((((((((((((((Attitude to Health[MeSH Terms]) OR "Health Knowledge, Attitudes, Practice"[Mesh]) OR Health Knowledge, Attitudes, Practice) OR Patient Acceptance of Health Care[MeSH Terms]) OR acceptance) OR acceptability) OR knowledge) OR awareness) OR belief*) OR attitude) OR perception) OR adherence) OR compliance) OR willingness) OR uptake) OR understanding))) AND ((((((((((("MC-4 vaccine" [Supplementary Concept]) OR meningococcal-conjugate (MCV4)) OR meningococcal-conjugate) OR "Papillomavirus Vaccines"[Mesh]) OR "Influenza Vaccines"[Mesh]) OR "Tetanus"[Mesh]) OR tetanus) OR Influenza) OR

	("Diphtheria"[Mesh] AND "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh])) OR "Pertussis Vaccine"[Mesh]) OR Diphtheria-Tetanus-acellular Pertussis Vaccines) OR "Influenza, Human"[Mesh]) Sort by: [relevance]
#6	(((ALGERIA) OR (ANGOLA) OR (BENIN) OR (BOTSWANA) OR (BURKINA FASO) OR (BURUNDI) OR (CAMEROON) OR (CANARY ISLANDS OR "CANARY ISLANDS") OR ((CAPE VERDE) OR "CAPE VERDE") OR (CENTRAL AFRICAN REPUBLIC) OR (CHAD) OR (COMOROS) OR (CONGO) OR (DEMOCRATIC REPUBLIC CONGO) OR (DJIBOUTI) OR (EGYPT) OR ((EQUATORIAL GUINEA) OR "EQUATORIAL GUINEA") OR (ERITREA) OR (ETHIOPIA) OR (GABON) OR (GAMBIA) OR (GHANA) OR (GUINEA) OR ((GUINEA BISSAU) OR "GUINEA BISSAU") OR (IVORY COAST) OR ((COTE D'IVOIRE) OR "COTE D'IVOIRE") OR (KENYA) OR (LESOTHO) OR (LIBERIA) OR ((LIBYA) OR (LIBIA) OR (JAMAHIRIYA) OR (JAMAHIRYIA)) OR (MADAGASCAR) OR (MALAWI) OR (MALI) OR (MAURITANIA) OR (MAURITIUS) OR (MOROCCO) OR ((MOZAMBIQUE) OR (MOCAMBIQUE)) OR (NAMIBIA) OR (NIGER) OR (NIGERIA) OR (REUNION) OR (RWANDA) OR ((SAO TOME) OR "SAO TOME") OR (SENEGAL) OR (SEYCHELLES) OR ((SIERRA LEONE) OR "SIERRA LEONE") OR (SOMALIA) OR ((SOUTH AFRICA) OR "SOUTH AFRICA") OR ((ST HELENA) OR "ST HELENA") OR (SUDAN) OR (SWAZILAND) OR (TANZANIA) OR (TANGANYIKA) OR (TOGO) OR (TUNISIA) OR (UGANDA) OR ((WESTERN SAHARA) OR "WESTERN SAHARA") OR (ZAIRE) OR (ZAMBIA) OR (ZIMBABWE) OR (AFRICA[MH]) OR (SOUTH* AND AFRICA*) OR (WEST* AND AFRICA*) OR (EAST* AND AFRICA*) OR (NORTH* AND AFRICA*) OR (CENTRAL* AND AFRICA*) OR (SUB SAHARAN AFRICA*) OR (SUBSAHARAN AFRICA*) OR (AFRICA*) NOT (((GUINEA PIG*) OR "GUINEA PIG*") OR ((ASPERGILLUS NIGER) OR "ASPERGILLUS NIGERâ€))))
#5	((((((((((("MC-4 vaccine" [Supplementary Concept]) OR meningococcal-conjugate (MCV4)) OR meningococcal-conjugate) OR "Papillomavirus Vaccines"[Mesh]) OR "Influenza Vaccines"[Mesh]) OR "Tetanus"[Mesh]) OR tetanus) OR Influenza) OR ("Diphtheria"[Mesh] AND "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh])) OR "Pertussis Vaccine"[Mesh]) OR Diphtheria-Tetanus-acellular Pertussis Vaccines) OR "Influenza, Human"[Mesh]
#4	(accept) OR ((((((((((((((Attitude to Health[MeSH Terms]) OR "Health Knowledge, Attitudes, Practice"[Mesh]) OR Health Knowledge, Attitudes, Practice) OR Patient Acceptance of Health Care[MeSH Terms]) OR acceptance) OR acceptability) OR knowledge) OR awareness) OR belief*) OR attitude) OR perception) OR adherence) OR compliance) OR willingness) OR uptake) OR understanding)

#3	((((((((((((((Attitude to Health[MeSH Terms]) OR "Health Knowledge, Attitudes, Practice"[Mesh]) OR Health Knowledge, Attitudes, Practice) OR Patient Acceptance of Health Care[MeSH Terms]) OR acceptance) OR acceptability) OR knowledge) OR awareness) OR belief*) OR attitude) OR perception) OR adherence) OR compliance) OR willingness) OR uptake) OR understanding
#2	(("Adolescent"[Mesh]) OR adolescent) OR teenager
#1	((((("Vaccination"[Mesh]) OR vaccination) OR "Immunization"[Mesh]) OR immunization) OR immunisation

Web sites and databases for grey materials:

World Health Organisation (WHO) (http://www.who.int/), Global Alliance for Vaccine and Immunization (GAVI) (http://www.gavialliance.org/), United Nation Children's Funds (UNICEF) (http://www.unicef.org/), PATH Vaccine Resources Library (http://www.path.org/), US Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/), The communication initiative network (http://www.comminit.com/), and Immunization basics (http://www.immunizationbasics.jsi.com/Index.html)

Appendix 6: Supplementary table 1a & b (Chapter 4)

Supplementary Table 1a & b: Summary on the statistical fishers exact test on level of knowledge on the three key demographics i.e. (teacher or parents or adolescents) and settings.

Variable Key

Participants:
- 1=parents
- 2=teachers
- 3=adolescents

Knowledge:
- 1=low
- 2=moderate
- 3=high

Setting: 1=urban
- 2=rural
- 3=peri-urban
- 4=urban & rural

1 a) Use Fisher's exact test to test association between knowledge and participants as some cells are <5

knowledge	participants 1	2	3	Total
1	9	1	4	14
2	3	1	3	7
3	2	0	1	3
Total	14	2	8	24

Fisher's exact = 0.831

1 b) Use Fisher's exact test to test association between knowledge and setting as some cells are <5

| knowledge

setting	1	2	3	Total
1	4	1	0	5
2	3	1	2	6
3	3	2	1	6
4	4	3	0	7
Total	14	7	3	24

Fisher's exact = 0.709

Appendix 7: STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

(Chapter 5)

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	129
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	130-131
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	132-134
Objectives	3	State specific objectives, including any prespecified hypotheses	134
Methods			
Study design	4	Present key elements of study design early in the paper	135
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	135
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	135
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	135

		group	
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	135
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	135
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	NA
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	136
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	137
		(b) Give reasons for non-participation at each stage	137
		(c) Consider use of a flow diagram	137

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	137-138
		(b) Indicate number of participants with missing data for each variable of interest	136
Outcome data	15*	Report numbers of outcome events or summary measures	137-138
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	138-145
Discussion			
Key results	18	Summarise key results with reference to study objectives	145-147
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	148
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	148
Generalisability	21	Discuss the generalisability (external validity) of the study results	148
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	149

Appendix 8: Participant information and consent form (Chapter 5)

TITLE OF THE RESEARCH PROJECT: Challenges and lessons learnt during the introduction of vaccines to adolescents in Africa: a focus on Human Papillomavirus (HPV) vaccines

Investigator: Leila H Abdullahi

Supervisors: Prof. Gregory D Hussey, Prof. Charles S Wiysonge and Dr. Benjamin M Kagina

Address: Vaccines for Africa Initiative (VACFA), Faculty of Health Sciences,

University of Cape Town, Anzio Road, Observatory 7925

Contact number: 021 650 6066

Introduction and aim of the study

We are investigating the experiences, challenges and lessons learnt by the key stakeholders during the introduction of HPV vaccines. We have selected you to take part in this research study because you are a key stakeholder.

Please carefully read the form prior to consenting to participate.

This study has been ***submitted to*** the Health Research Ethics Committee at University of Cape Town for ***review and approval*** **(*HREC REF 703/2015*).** The study will be conducted according to the standard ethical guidelines and principles. In addition you

have been granted permission from your national authorizing official. However, you may withdraw consent to participate at any time if you feel uncomfortable to participate.

- The aim of this study is to investigate the challenges and lessons learnt by African countries during the introduction of HPV vaccine.

- The study will take place in Cape Town, South Africa, where all the selected members will be invited to participate in the interview panel. Alternatively for those participants that cannot make it to Cape Town we will send self-administered questionnaire via email.

- Key stakeholders (government representatives, funding agencies, NITAGs and implementing agencies) from Lesotho, Libya, Rwanda, Uganda and South Africa have been selected to participate in this study. The interview will take approximately thirty minutes.

Benefits: There are no direct benefits to you as a participant. Your participation will help us to better understand the factors that hinder the introduction of HPV vaccines in Africa. This information will be published and made accessible to other African countries that are planning to implement HPV vaccination into their national programme. The information can help the countries to plan better on the HPV vaccines introduction.

Risk: There are no risks.

Voluntary participation and right to withdraw from the study: Your participation is completely voluntary. You have the right to withdraw your involvement at any time ***before or*** during the interview, if you do not wish to continue.

Confidentiality: The information provided will be blinded. We will not record your name or any other information that can identify you. Only the researchers will have access to the information from the questionnaires, which will be stored in a safe place. During the publication of the findings, we will not mention the names of the participants.

Compensation: We will not provide money compensation for your participation in this study. For those participants who will come to Cape Town, the cost of flight and accommodation from and to your country will be covered **as part of your sponsorship to attend the 11th annual African vaccinology course, hosted by VACFA and** to be held in November 2015.

Other additional information:

- For other questions about the study, you may contact the investigators Leila H Abdullahi (email: leylaz@live.co.za.; phone: +27 21 406 6066) or Benjamin Kagina (email: benjamin.kagina@uct.ac.za; phone: + 27 21 4066066) in the Western Cape, South Africa.

- You can contact the Health Research Ethics Committee through Ms. Lamees Emjedi phone: +27 21 406 6338 if you have any concerns or complaints that have not been adequately addressed by the investigators.

- You will receive a copy of this information and consent form for your own records.

Consent form for individual participant

By signing below, I ……..……. agree to take part in a research study entitled: *challenges and lessons learnt during the introduction of vaccines to adolescents in Africa: a focus on Human Papillomavirus (HPV) vaccines)*.

I declare that:

- I have read and understood the information provided to me about the study as well as the consent form.
- I understand the study team is interested in hearing my personal views, and my name will not be mentioned in any reports arising from this study.
- I understand that my discussions with the study team will be recorded using a voice recorder and noted on paper or written version to complete when sent to you via email.
- I had a chance and still have a chance to ask questions. All my questions have been/will be adequately answered.
- I understand that taking part in this study is ***voluntary, I can withdraw my participation anytime*** and I have not been coerced to participate. The study might take 30 minutes and I have the right to withdraw from the study at any time.
- I will not be penalised or prejudiced in any way after withdrawing from the study.

Signed at (*place*) .....…..... On (*date*) ……...……...

....

Signature of participant **Signature of witness**

Appendix 9: Questionnaire (Chapter 5)

Study semi-structured in-depth interview guide on challenges experienced and lessons learnt during the introduction of vaccines to adolescents in Africa: a focus on Human Papillomavirus (HPV) vaccines

For the following questions with response boxes☐, mark the appropriate box with an x to indicate your response.

General information

1. Category of the stakeholder

   Government representatives ☐

   Funding agencies ☐

   Implementing agencies ☐

   NITAGs member ☐

   Other ☐

2. What was your role during the HPV vaccine introduction……

3. Vaccination target age group in your country……..

4. Vaccination target gender? Female ☐ Female and male ☐

5. How many doses? One ☐ Two ☐ Three ☐

6. Was there an evaluation study after successful introduction of HPV vaccine

   Yes ☐ No ☐

7. If yes, what method of the evaluation was used?

A. Finance

1. How were the costs of HPV vaccines financed in your country? E.g. Delivery costs and /or HPV vaccine costs

2. Did your country develop a financial sustainability plan for the HPV vaccine programme

B. Political

1. Describe any political influence (negative or positive) that played a role during the introduction of HPV vaccine in your country?

C. Health system delivery

1. What were the various strategies used during HPV vaccination implementation

   E.g. Health facility based, school-based, outreach programmes like community visits, integrated services:

2. Kindly explain the lessons and challenges you experienced on the strategies used to increase vaccination coverage among adolescents in your country/setting.

D. Factors that affect the introduction of HPV

1. What are the factors that hindered the introduction of HPV vaccine in your country?

   E.g. Religious, cultural, knowledge, finances, infrastructure, training of health staff etc.

E. Challenges faced during HPV introduction

1. Minor (defined as unforeseen or foreseen that could not stop introduction if not addressed).

2. Major (defined as unforeseen or foreseen that needed to be overcome prior to the introduction).

F. Lessons learned during HPV introduction

1. What could you do differently if the process was to be repeated again

2. Advice or suggestions to other countries wanting to introduce HPV?

G. Coverage (vaccination).

1. What was the HPV vaccination coverage (dose 1) and (dose 2)?
2. How was the vaccination coverage calculated?
3. Other adolescents' vaccines in consideration?

Appendix 10: Ethics approval (Chapter 5)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

03 November 2015

HREC REF: 703/2015

Prof G Hussey
Medical Microbiology VACFA
IIDMM
W & B North Room N2.09A
FHS

Dear Prof Hussey

PROJECT TITLE: CHALLENGES AND LESSONS LEARNT DURING THE INTRODUCTION OR ADOLESCENT VACCINES IN AFRICA: A FOCUS ON HUMAN PAPILLOMAVIRUS (HPV) VACCINES (PhD-candidate-L Abdullahi)

Thank you for your response letter dated 20 October 2015, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th November 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student:-Leila Abdullahi is also involved in this project.

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:703/2015