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Improving vaccination uptake among adolescents (Protocol)

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[Intervention Protocol]

Improving vaccination uptake among adolescents

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effects of interventions to improve vaccine uptake among adolescents in low, middle and high-income countries.

BACKGROUND

Vaccines are among the most successful and cost-effective public health interventions available for preventing the morbidity and mortality caused by vaccine-preventable diseases (Centers for Disease Control and Prevention 2006). However, vaccine-preventable diseases remain a major cause of morbidity and mortality among adolescents and young adults (Decade of Vaccines Collaboration 2013). Vaccinating adolescent girls before the onset of sexual activity with vaccines against human papillomavirus (HPV) can substantially reduce the risk of cervical cancer later in life. Therefore, with most vaccines, the public health benefits of vaccinating adolescents is mainly observed in early to late adulthood. Globally, cervical cancer is the fourth most frequent cancer among women with an estimate of 530,000 new cases reported in 2012 (World Health Organization 2015). Cervical cancer accounted for 7.5% of all female cancer deaths globally in 2012 (World Health Organization 2015). Many vaccine-preventable diseases and deaths among young adults are due to low vaccination coverage among the adolescent group. In addition, there are no adolescent vaccination policies in the majority of low- and middle-income countries (LMICs) (Principi 2013; World Health Organization 2015). There is therefore a need to conduct studies that can inform public health policy-makers on better strategies to increase vaccine uptake among adolescents.

Immunisation with an effective vaccine results in individuals acquiring protective immunity against the targeted pathogen. When sufficiently large number of individuals are vaccinated within a population, herd immunity develops and this prevents the spread of the targeted infectious disease within both vaccinated and unvaccinated individuals (Lee 2005; Mackroth 2010; Zipursky 2010). Due to their immature immune systems, infants and younger children are more vulnerable to infectious pathogens than adults. Therefore, most vaccines are administered early in life (Principi 2013; Rodewald 1998). However, immunity induced by some vaccines, such as diphtheria, tetanus and pertussis, wanes over time, leading to suboptimal immunity and less herd immunity around the onset of adolescence (Decade of Vaccines Collaboration 2013; Lee 2005; Mackroth 2010; Zipursky 2010). It is therefore necessary to give booster vaccines during adolescence to maintain protective immunity. In some settings, these booster

vaccines are never administered to adolescents and young adults (Principi 2013; World Health Organization 2015).

Vaccines given during adolescence include, among others, those against HPV, tetanus, diphtheria and acellular pertussis (Tdap), as well as meningococcal disease (Gilkey 2014; Harris 2009). Future vaccines, such as those against human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (M.tb), are likely to target adolescents as the primary population (Gowda 2012; Zipursky 2010). Extending vaccination throughout the life course, including adolescence, is a strategy advocated by the Global Vaccine Action Plan (GVAP) 2011-2020 (Decade of Vaccines Collaboration 2013). The rationale for the strategy of reaching individuals throughout life is to achieve the highest reduction in the incidence of vaccine-preventable diseases. Therefore, it is crucial to achieve optimal adolescent vaccination uptake (Clements 2004; Mackroth 2010; Zipursky 2010). We propose that studies that can inform health policy-makers on potential approaches to improving the uptake of vaccines among adolescents are urgently needed. This is particularly so in sub-Saharan Africa where there are few established national programmes for vaccinating adolescents.

The World Health Organization (WHO) defines adolescents as persons aged between 10 and 19 years (WHO; WHO 2009). Targeting adolescents with relevant vaccines offers three benefits: catch-up on missed vaccinations, boosting of waning immunity and primary immunisation with new vaccines (Brabin 2008; Mackroth 2010). The WHO recommends vaccinating 11- or 12-year olds against *Neisseria meningitidis*, *Bordetella pertussis* and HPV (World Health Organization 2014). Additionally, WHO guidelines recommend vaccinating adolescents against measles, mumps, rubella, varicella, hepatitis B and polio if they have not previously been vaccinated as a catch-up strategy (Lee 2005; Society for Adolescent Health & Medicine 2013; World Health Organization 2014). Despite these recommendations, most LMICs are yet to implement adolescent-focused vaccination policies (Shapiro 2007).

Optimal vaccination coverage rates among adolescents would result in reduced morbidity and mortality associated with vaccine-preventable diseases, as well as reduced disease spread to children and the elderly (Lee 2005; Principi 2013; Zipursky 2010). The 2014 global statistics show that 25% of the world population (1.8 billion) consists of young people aged 10 to 24 years (Population Reference Bureau 2013), suggesting that optimal vaccination coverage among the large number of young persons would achieve enormous public health benefits, which include reduced disease transmission through herd immunity and a healthier population (Mackroth 2010; Zipursky 2010). A logical strategy for improving vaccine uptake is the introduction of national routine adolescent immunisation programmes in LMICs. This strategy has been proposed by the GVAP 2011-2020 (Decade of Vaccines Collaboration 2013). The Decade of Vaccines Collaboration states that "the benefits of immunisation should be more equitably extended to all children, adolescents and adults" (Decade of Vaccines Collaboration 2013). Some high-income countries have reported high vaccine uptake among adolescents (Principi 2013). In most LMICs, especially in sub-Saharan Africa, routine adolescent vaccination programmes do not exist (Shapiro 2007). In all settings, effective interventions are needed to increase and sustain high and equitable uptake of vaccines among adolescents. Our review will establish the strategies associated with high vaccine uptake in all settings and assess the applicability of these strategies in LMICs.

Description of the condition

Adolescent vaccination delivery strategy

Most countries lack specific healthcare programmes for adolescents, leading to less contact between adolescents and the healthcare system (Mackroth 2010; Principi 2013; Wiysonge 2012a; Wiysonge 2012b). 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 (Cawley 2010; Principi 2013). Healthcare provider advice that a vaccine is best administered as soon as possible in a vaccination centre only works for infants and children but not for adolescents (Principi 2013). Adolescents are more interested in their current health condition than possible future vaccine-preventable diseases (Principi 2013). Schools have been used extensively as a delivery platform for vaccinating large numbers of school-aged children (Barry 2013; Cawley 2010; Harris 2009; Principi 2013; Robbins 2011; Tsu 2009). However, school-based vaccination programmes may not be entirely successful in countries with suboptimal school attendance rates (Mackroth 2010; Warren 2004; Watson-Jones 2012; Zipursky 2010). School attendance rates in some LMICs are variable and often poor due to factors such as geographical location, socio-economic status and gender (Mackroth 2010; Warren 2004; Watson-Jones 2012; Zipursky 2010). Strategies such as mass immunisation campaigns can be used to complement school-based vaccination programmes in settings with poor school attendance rates (Clements 2004).

Common barriers to adolescent vaccination

The most common barriers to vaccination include lack of knowledge about vaccines and vaccine-preventable diseases, negative attitudes towards vaccination from adolescents, parents, teachers and healthcare providers, poor vaccine infrastructure programmes and financial constraints (Gowda 2012; Machingaidze 2013; Society for Adolescent Health & Medicine 2013).

Lack of knowledge about vaccines and vaccine-preventable diseases in key role-players, such as parents, teachers, adolescents and healthcare providers, is a major challenge that hinders optimal vaccine uptake by adolescents (Brabin 2008; Cawley 2010; Gowda

2012; Harris 2009; Mahomed 2008; Society for Adolescent Health & Medicine 2013; Wiysonge 2012a). Parents (defined as one who nurtures and raises a child or a relative who plays the role of guardian) (Oxford Dictionaries a) are routinely involved in the decision-making process about vaccine administration to their children. Teachers (defined as a professional person who teaches or instructs) (Oxford Dictionaries b) can play a crucial role in adolescent vaccination uptake since school-based vaccination programmes, where they exist, are a popular platform for vaccination of adolescents (Barry 2013; Tsu 2009).

Healthcare providers give advice to parents and adolescents on vaccination. The ability of healthcare providers to keep up-to-date with knowledge on vaccines is essential, particularly when new vaccines are recommended (Gowda 2012; Principi 2013). Healthcare providers should continuously read the latest editions of the WHO adolescent vaccine guidelines to improve their knowledge of vaccines (World Health Organization 2014). Careful and factual advice on vaccination to adolescents and their guardians by healthcare providers will result in more willingness to get vaccinated.

In some situations, the final decision on whether an adolescent will be vaccinated or not may be entirely dependent on the parents. For example, adolescents, and in particular those at an earlier age (10 to 13 years old) (WHO; WHO 2009), may not have an independent final decision on whether to get vaccinated (Barry 2013; Principi 2013). Therefore, educating adolescents about vaccination may have long-term positive benefits on vaccine uptake among this age group (Barry 2013; Principi 2013). It is likely that more vaccine-informed adolescents may be more able than less informed peers to positively guide and influence their parents and peers on vaccinations. In addition, adolescents are future parents and investing resources in educating adolescents about vaccination will likely lead to improved uptake of vaccines by their children (Barry 2013). Hence, adequate knowledge and positive attitudes towards vaccination among parents, teachers and adolescents may improve the uptake of vaccines among adolescents (Gowda 2012; Mahomed 2008).

Another factor that may influence vaccine uptake among adolescents is vaccine safety. Adolescents' fear of adverse events following vaccination may lead to less interest in getting vaccinated, resulting in reduced vaccination coverage (Principi 2013).

The high cost of new vaccines and the unavailability of vaccines are known barriers to achieving high vaccination coverage among adolescents in LMICs (Perlman 2014; Principi 2013). For example, although the high cost of HPV vaccines (two doses are required) precludes access, continued price reduction for HPV will allow governments in LMICs to provide the vaccine to the target population (Kaddar 2013; Perlman 2014). In Africa, several countries, namely Rwanda, Uganda, Cameroon, Tanzania, Lesotho and South Africa, have introduced HPV vaccination to prevent cervical cancer through school-based programmes (Perlman 2014).

Description of the intervention

Interventions to enhance the uptake of vaccines by adolescents may be multi-pronged:

Adolescents and their communities-oriented interventions

- Interventions to 'inform' or 'educate' enable adolescents and their communities to understand the meaning and relevance of vaccination (Willis 2013). Such interventions may be delivered face-to-face or via written mail, telephone conversation, audio visual presentation or drama, printed materials, websites, multi-media campaigns or community events (Willis 2013). These types of interventions may be directed at individuals, groups and providers and may include information about vaccine-preventable diseases; the risks and benefits of vaccines; where, how and when to access vaccine services; and who should be vaccinated (Oyo-Ita 2014; Williams 2011; Willis 2013). Adolescents and communities may receive education about vaccines through prominently displayed posters in waiting rooms, brochures, e-mails and website resources (Stinchfield 2008).
- Client reminder/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 (Briss 2000; Oyo-Ita 2014; Stinchfield 2008; Task Force on Community Preventive Services 2000; Williams 2011; Willis 2013). The contents of reminder/recalls may include personalised information related to a specific upcoming or missed appointment, or may be more focused on promoting general awareness of available vaccines (Stinchfield 2008; Willis 2013). We will not include adolescent reminder/recall of immunisation services in this review, as there is already a Cochrane review on this intervention (Jacobson 2005).
- Adolescent or community incentives involve providing financial or other incentives to motivate people to accept vaccinations (Briss 2000; Oyo-Ita 2014; Task Force on Community Preventive Services 2000). Incentives can be rewards or gifts (Task Force on Community Preventive Services 2000).

Legislative interventions

- This involves a proof of vaccination record during school or college entrance. These are laws or policies that require students to show proof of immunisation records prior to school admission; failure to do this denies admission (Briss 2000; Oyo-Ita 2014; Task Force on Community Preventive Services 2000).

Provider-oriented interventions

- Provider reminder/recall interventions inform vaccinators that individual clients are due (reminder) or overdue (recall) vaccinations. Reminders may be delivered through client charts, computer or postal/electronic mail among many others (Briss 2000; Oyo-Ita 2014; Task Force on Community Preventive Services 2000; Ward 2012; Williams 2011). We will not include provider reminder/recall of immunisation services, as there is already a Cochrane review on this intervention (Jacobson 2005).
- Audit and feedback for vaccinators involves retrospectively evaluating the performance of the vaccinators in administering vaccines and providing feedback to them (Briss 2000; Oyo-Ita 2014; Stinchfield 2008; Task Force on Community Preventive Services 2000; Williams 2011). 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 (Briss 2000; Stinchfield 2008; Task Force on Community Preventive Services 2000; Ward 2012; Williams 2011).

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 aged between five and 18 years (Task Force on Community Preventive Services 2000). School-based interventions usually include vaccination-related education of students about either provision of vaccinations or referral for vaccinations (Briss 2000; Oyo-Ita 2014; Task Force on Community Preventive Services 2000). Mass campaign outreach programmes target adolescents both in school and out of school. For the age group that is out of school, mass campaign outreach programmes can be used to complement school-based vaccination programmes in settings with poor school attendance rates (Clements 2004).
- Expanding access in healthcare settings to increase the availability of vaccines in the medical or public health clinical settings in which vaccinations are offered. This can be achieved using several methods such as: reducing the distance from the setting to the population; 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) (Briss 2000;Stinchfield 2008; Task Force on Community Preventive Services 2000).
- Reducing out-of-pocket costs. This 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 (Briss 2000; Oyo-Ita 2014; Task Force on Community Preventive Services 2000).

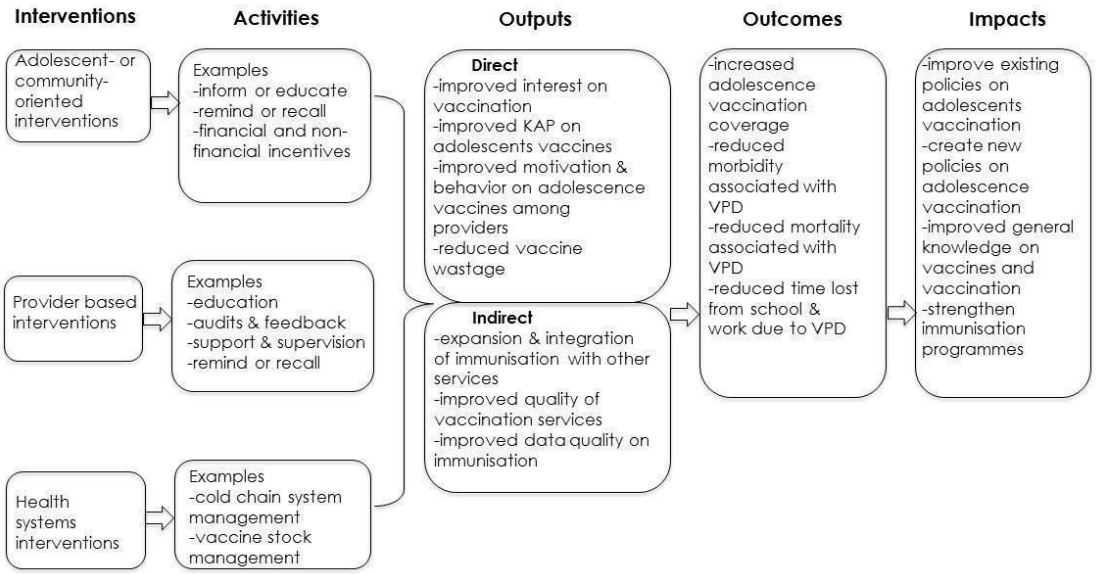
Multicomponent interventions

Multicomponent interventions are approaches that include more than one intervention, with the aim of addressing a variety of barriers and health concerns in relation to adolescents vaccine uptake. Such interventions would 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 to also incorporate a variety of associated provider or health system strategies to improve immunisation rates (Briss 2000; Oyo-Ita 2014; Task Force on Community Preventive Services 2000).

How the intervention might work

A logic model of interventions used to increase adolescent vaccination and the associated health outcomes is shown in Figure 1.

Figure 1. Logic framework on interventions for improving uptake of adolescent vaccines



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 (Fernández 2010). This model suggested a useful framework for examining the impact of personal, interpersonal, organisational and broader community as well as societal factors on vaccination (Fernández 2010). Our logic model proposes that such factors, alone or in combination, will have an influence on adolescent vaccination.

Interventions improve vaccine uptake among adolescents through the following:

- Increasing demand for immunisation services by adolescents, for example:
  - interventions to inform or educate adolescents and/or their parents;
  - interventions to remind or recall adolescents and/or their parents;
  - financial and non-financial incentives for adolescents and/or their parents; and
  - vaccination requirement for high school or university attendance.
- Enhancing access to immunisation services through provider-oriented interventions, such as:
  - education, audit and feedback to healthcare workers;
  - reminders and recall for healthcare workers; and
  - supportive supervision of healthcare workers.
- Enhancing access to immunisation services through health system-oriented interventions, such as:
  - reliable cold chain systems;
  - improved vaccine stock management;
  - regular outreach sessions, i.e. school based programmes and mass campaign programmes;
  - expansion of vaccine services; and
  - integration of immunisation with other health services.
- Increasing both demand for and access to immunisation services, for example multicomponent interventions.

Why it is important to do this review

There is a knowledge gap around interventions to improve vaccine uptake among adolescents, especially in LMICs. Adolescents represent 25% of the global population. High-income countries (HICs) have reported high adolescent vaccine uptake, yet in LMICs there are no existing programmes for routine vaccination of adolescents. Our review proposes to evaluate the evidence on the strategies that can be adopted to improve vaccine uptake among adolescents and to assess the applicability of these strategies in LMICs. Such strategies will not only improve the uptake of current vaccines among adolescents, but are also likely to increase

the uptake of future vaccines against tuberculosis (TB) and HIV. In addition, this review will be used to formulate new policies on the vaccination of adolescents where none exist and to advocate for strengthening existing adolescence vaccination policies. We are not aware of any previous systematic review that has assessed interventions to improve adolescent immunisation. However, a number of reviews have assessed various strategies to improve immunisation coverage in children or the whole population (Jacobson 2005; Kaufman 2013; Oyo-Ita 2014; Saeterdal 2012; Williams 2011; Willis 2013). One review assessed the reminder/recall intervention in a whole population. This review only found one study on a reminder and recall intervention in adolescents (Jacobson 2005). The authors found that an autodialer intervention was not successful in significantly increasing immunisations (Jacobson 2005). In the other reviews, concepts such as vaccination strategy interventions and barriers to immunisation have been well described (Jacobson 2005; Kaufman 2013; Oyo-Ita 2014; Saeterdal 2012; Williams 2011; Willis 2013). In our review, we will use a similar approach among the adolescent population.

OBJECTIVES

To evaluate the effects of interventions to improve vaccine uptake among adolescents in low, middle and high-income countries.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider the following study designs: randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs), interrupted time series designs (ITS) and controlled before-after studies (CBAs), which meet the quality criteria used by the Cochrane Effective Practice and Organisation of Care (EPOC) Group (EPOC 2015a). We will include both individually randomised and cluster-randomised controlled trials. For cluster-RCTs, we will only include those with at least two intervention and two control clusters. Following the EPOC Group criteria, we will include an ITS study only if outcomes are measured during at least three points before and three points after the intervention, and we will exclude simple pre-post designs. 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 will exclude CBA studies and non-RCTs that have only two study locations, in accordance with the EPOC Group criteria for inclusion of studies in systematic reviews of effects (EPOC 2015a).

Types of participants

Adolescents (defined as individuals 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 will exclude a study if specific data for adolescents are not reported.

Types of interventions

Intervention

- Adolescents and their communities-oriented interventions, for example:
  - interventions to communicate with adolescents and/or their caregivers about adolescent immunisation;
  - financial and non-financial incentives for adolescents and/or their caregivers.
- Legislative interventions:
  - vaccination requirement for high school and university attendance.
- Provider-oriented interventions, for example:
  - any intervention to reduce missed opportunity (e.g. audit and feedback, provider reminders); 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 outreach and mass campaign outreach for age groups that will be out of school;
  - expanded services, e.g. extended hours for immunisation services;
  - increased immunisation budget;
  - integration of immunisation services with other services.
- Other interventions intended to improve adolescent immunisation coverage, including multi-component interventions.

Exclusions

We do not plan to include interventions to remind or recall recipients or providers of immunisation services, as there is already a Cochrane review on this topic (Jacobson 2005).

Equity considerations

The listed interventions are likely to have less or no impact on adolescents who are not attending formal schooling (Mackroth 2010;

Warren 2004; Watson-Jones 2012; Zipursky 2010). Therefore, we propose to assess other interventions aimed at non-school attending adolescents, such as mass campaign programmes (Clements 2004). For studies addressing school-based interventions or mass campaign interventions, we will conduct a subgroup analysis if sufficient data are available.

Comparisons

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

Types of outcome measures

Primary outcomes

- Vaccination coverage (the proportion of adolescents who have received the recommended dose of the vaccine in a study).

Secondary outcomes

- Cost of the intervention.
- Knowledge, attitudes and beliefs.
- Adverse events following immunisation.
- Adverse effects of the intervention.
- Incidence of vaccine-preventable diseases.
- Proportion of adolescents completing the schedule.

We will include studies that meet the inclusion criteria but do not report the outcomes needed for this review and describe them in the table of 'Characteristics of included studies'.

Search methods for identification of studies

We will develop comprehensive and highly sensitive search strategies, with the assistance of the Cochrane EPOC Group Trials Search Co-ordinator, for both published and unpublished articles, with no restrictions on language or publication date. The search strategies for the electronic databases will incorporate the Cochrane EPOC Group search strategy for RCTs, non-RCTs, CBAs and ITS studies (EPOC 2015a), combined with selected MeSH and free-text terms relating to adolescent vaccination uptake literature globally.

Electronic searches

We will search the following databases for primary studies up to 21. Sept. 2015:

- Cochrane Central Register of Controlled Trials (CENTRAL) 2015, part of *The Cochrane Library* (www.thecochranelibrary.com);
- MEDLINE, Ovid;
- PubMed, NLM (for studies not in MEDLINE);
- EMBASE, Ovid;
- CINAHL, EBSCOhost;
- Africa-Wide Information, EBSCOhost;
- Global Health, Cab Direct;
- Scopus;
- Science Citation Index and Social Sciences Citation Index, ISI Web of Knowledge (for papers citing any of the included studies in the review).

We will search the following databases for related reviews:

- Cochrane Database of Systematic Reviews (CDSR) 2015, part of *The Cochrane Library* (www.thecochranelibrary.com);
- Database of Abstracts of Reviews of Effectiveness (DARE) 2015, part of *The Cochrane Library* (www.thecochranelibrary.com);
- PDQ-Evidence.

See Appendix 1 for the MEDLINE search strategy.

Searching other resources

Grey literature

- World Health Organization (WHO) (http://www.who.int/).
- Global Alliance for Vaccine and Immunisation (GAVI) (http://www.gavialliance.org/).
- United Nations 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/), http://www.nyam.org/library, http://www.opengrey.eu/, http://www.eldis.org/.
- Immunization basics (http://www.immunizationbasics.jsi.com/Index.html).

Trial registries

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

We will also search the reference lists of all eligible papers for relevant studies.

Data collection and analysis

Selection of studies

Two authors (LH and BK) will screen the titles and abstracts to select potentially eligible studies. We will then obtain the full text of potentially eligible studies and two independent authors will conduct the final selection for inclusion in the review. We will resolve any disagreements regarding the inclusion of studies by discussion or by consulting a third author. We will use a PRISMA flow chart to summarise the search and selection of studies for the review. We will include a table of all included studies in the final review and document the reasons for exclusion of studies.

Data extraction and management

Two authors will independently extract data from selected studies using an adapted version of the Cochrane data extraction form. Disagreements on study selection and data extraction will be resolved by consensus between the two review authors, failing which a third author will arbitrate. Prior to use, we will pilot the data extraction form on at least four studies identified randomly from the list of included studies.

The data extraction form will include the following eligibility criteria:

- Setting of the study (city and country).
- Type of study: individual RCT, cluster-RCT, non-RCT, CBA and ITS studies.
- Type of participants: adolescents, caregivers, health providers.
- Type of interventions: frequency, timing, delivery method, venue of delivery, deliverer of adolescent and community health, health system and multi-component interventions.
- Types of outcomes measured: vaccine coverage (i.e. proportion of adolescents immunised in a population based on the different interventions), knowledge, attitudes and beliefs, cost of intervention, adverse effects of the intervention, adverse events following immunisation, proportion of adolescents completing schedule and incidence of vaccine-preventable diseases. We will include studies that meet the inclusion criteria but do not report the outcomes needed for this review and describe them in the table of 'Characteristics of included studies'.

Assessment of risk of bias in included studies

We will apply the Cochrane EPOC Group 'Risk of bias' criteria (EPOC 2015b) for randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs), controlled before-after studies (CBA) and interrupted time series (ITS) studies to determine the risk of bias of all eligible studies. For each included study, we will report 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 will apply the criteria and we will discuss any disagreements with a third review author.

Measures of treatment effect

We will express the result of each study as a risk ratio with its corresponding 95% confidence interval (CI) for dichotomous data, or a mean difference with its 95% CI for continuous data. We will group studies with broadly similar types of participants, interventions, study designs and outcomes to get feasible results for an overall estimate of effect. 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 (Ramsay 2003).

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 (Campbell 2000). Once established, we will use the ICC to reanalyse 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 (Higgins 2011). 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 (Higgins 2011). 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 (Donner 2001).

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 (Ramsay 2003).

Assessment of heterogeneity

We anticipate substantial variation in study results due to differences in the type of intervention, the type of setting, study design and risk of bias. We will describe in detail the anticipated variation to be assessed based on clinical/contextual heterogeneity, i.e. the facility at which vaccination was provided (school or healthcare centre), high- versus low-income countries, gender differences, whether the recipients were healthy or not. School attendance rates in some LMICs are variable and often poor therefore we anticipate variation in equity with the type of intervention that targets this group. On the other hand, knowledge of and attitudes to adolescent vaccination are different between HIC and LMIC vaccine recipients. We will examine statistical heterogeneity between study results using the Chi² test of homogeneity (with significance defined at the alpha level of 10%). We will quantify any statistical heterogeneity between study results using the I² statistic. We will regard heterogeneity as substantial if the I² is greater than 30% (Higgins 2011).

Assessment of reporting biases

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 (Egger 1997) and the test proposed by Harbord (Harbord 2006), 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 pool data from studies of similar interventions, similar participants, similar outcomes and similar study designs in a meta-analysis using the random-effects model if there is no significant statistical heterogeneity, methodological difference or high risk of bias. If we encounter variation between studies in the reported interventions, participants, study designs and outcome measures, we will not pool the results but summarise the findings in a narrative format. 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. Overall, we will interpret the study findings by taking into account the methodological quality of the studies and the strength of evidence. For each observed effect, we will explicitly state the strength of evidence and draw conclusions.

'Summary of Findings' table and assessing the of certainty of evidence

We will use the GRADE approach to assess the certainty of evidence at outcome level (Guyatt 2008). We will set out the main findings of the assessment across studies in 'Summary of findings' tables prepared using GRADE profiler software (GRADEpro GDT). We will include the following outcomes in the Summary of Findings table: vaccination coverage, cost of intervention, knowledge, attitudes and beliefs, adverse events following immunisation, adverse effects of the intervention, incidence of vaccine-preventable diseases and proportion of adolescents completing the schedule.

The GRADE approach results in an assessment of the certainty of a body of evidence as high, moderate, low or very low (Guyatt 2008). High certainty evidence implies that "further research is very unlikely to change our confidence in the estimate of effect". Moderate certainty evidence means that "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate". Evidence is considered of low certainty if "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate", and very low certainty if "we have very little confidence in the effect estimate" (Balshem 2011).

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). We will use the Chi² test for subgroup differences to test for subgroup interactions.

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.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Medline, Ovid

#	Searches	Results
1	(vaccin* and (uptake or coverage)).ti.	2155
2	(vaccin* adj (uptake or coverage)).ab.	5760
3	or/1-2	6632

(*Continued*)

4	Immunization/	43773
5	Immunization Schedule/	9277
6	Immunization, Secondary/	7181
7	Immunization Programs/	8257
8	Immunotherapy, Active/	2298
9	Vaccination/	59448
10	Mass Vaccination/	2324
11	or/4-10	120620
12	Diphtheria/	5821
13	Tetanus/	8732
14	Bordetella Infections/	889
15	Bordetella Pertussis/	4661
16	Whooping Cough/	7213
17	Measles/	12252
18	Mumps/	3918
19	Rubella/	7497
20	Poliomyelitis/	16087
21	Poliomyelitis, Bulbar/	616
22	Tuberculosis/	58190
23	Tuberculosis, Pulmonary/	68710
24	Mycobacterium Tuberculosis/	40363
25	Hepatitis A/	18147
26	Hepatitis A virus/	903
27	Hepatitis A Virus, Human/	511

(*Continued*)

28	Hepatitis B/	38784
29	Hepatitis B, Chronic/	11087
30	Hepatitis B virus/	21651
31	Chickenpox/	6891
32	Papillomavirus Infections/	18094
33	Herpesviridae Infections/	13314
34	Herpes Simplex/	13129
35	Herpes Genitalis/	4344
36	Herpes Labialis/	1140
37	Herpes Zoster/	8959
38	Meningococcal Infections/	5498
39	Meningitis, Meningococcal/	4839
40	Neisseria meningitidis/	7423
41	exp HIV Infections/	247938
42	HIV/	17360
43	HIV-1/	70967
44	HIV-2/	3965
45	Neoplasms/	324983
46	or/12-45	930573
47	11 and 46	28632
48	Diphtheria-Tetanus-Acellular Pertussis Vaccines/	802
49	Diphtheria-Tetanus-Pertussis Vaccine/	2524
50	Diphtheria-Tetanus Vaccine/	327
51	Pertussis Vaccine/	4706

(*Continued*)

52	Vaccines, Combined/	2049
53	Diphtheria Toxoid/	2870
54	Tetanus Toxoid/	6660
55	Measles-Mumps-Rubella Vaccine/	2321
56	Measles Vaccine/	6228
57	Mumps Vaccine/	1632
58	Rubella Vaccine/	2972
59	Poliovirus Vaccines/	1172
60	Poliovirus Vaccine, Oral/	3691
61	Poliovirus Vaccine, Inactivated/	2562
62	Tuberculosis Vaccines/	1306
63	BCG Vaccine/	17353
64	Viral Hepatitis Vaccines/	3419
65	Hepatitis A Vaccines/	1484
66	Hepatitis B Vaccines/	8128
67	Chickenpox Vaccine/	1717
68	Papillomavirus Vaccines/	4923
69	Meningococcal Vaccines/	2612
70	AIDS Vaccines/	7238
71	or/48-70	73086
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	73091

(*Continued*)

	immunotherapy)).ti,ab	
73	((tripe or combin*) adj vaccin*).ti,ab.	1743
74	or/72-73	74012
75	3 or 47 or 71 or 74	117319
76	Adolescent/	1708075
77	Adolescent Health Services/	4723
78	(adolescent? or youth? or young adult? or teenager? or teen? or juvenile?).ti,ab	324075
79	or/76-78	1836581
80	75 and 79	19423
81	randomized controlled trial.pt.	411691
82	controlled clinical trial.pt.	91681
83	multicenter study.pt.	196215
84	pragmatic clinical trial.pt.	210
85	non-randomized controlled trials as topic/	28
86	interrupted time series analysis/	78
87	controlled before-after studies/	59
88	(randomis* or randomiz* or randomly).ti,ab.	634375
89	groups.ab.	1505036
90	(trial or intervention? or effect? or impact? or multicenter or multi center or multicentre or multi centre).ti	1833915
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	3393251
92	or/81-91	5837461
93	exp Animals/	18518807

(*Continued*)

94	Humans/	14399247
95	93 not (93 and 94)	4119560
96	review.pt.	2052355
97	meta analysis.pt.	60297
98	news.pt.	177550
99	comment.pt.	669752
100	editorial.pt.	396325
101	cochrane database of systematic reviews.jn.	11883
102	comment on.cm.	669752
103	(systematic review or literature review).ti.	66358
104	or/95-103	7117780
105	92 not 104	4220689
106	80 and 105	6674

CONTRIBUTIONS OF AUTHORS

LA, BK, CW and GH conceived the study, participated in the development of the protocol and approved the final version for publication.

DECLARATIONS OF INTEREST

Leila H Abdullahi: None known.

Benjamin MN Kagina: None known.

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