Scoping views to a single dose human papillomavirus (HPV) vaccine schedule amongst vaccine policy makers in low and middle-income countries

Kate Gallagher, Helen Kelly, Naomi Cocks, Sandra Mounier-Jack, Sandra Dixon, Natasha Howard, Deborah Watson-Jones

London School of Hygiene & Tropical Medicine

20th April 2018

Contents

List of Tables

1 Background

Invasive cervical cancer (ICC), caused by persistent infection with human papillomavirus (HPV), is a major public health problem, especially in developing countries[1]. Globally, in 2012 there were approximately 528,000 new cases and 266,000 cervical cancer related deaths with over 80% of cases occurring in low and middle-income countries (LMIC)[2, 3]. In settings where effective cervical screening programs are available, the incidence of cervical cancer has markedly decreased[3, 4]. However, in many developing countries, screening programs are not in place or are only available on a limited scale, and women frequently present late with the disease leading to high associated morbidity and mortality rates.

Primary prevention for cervical cancer is now possible through vaccination with one of three licensed vaccines; the bivalent HPV vaccine (2vHPV) that prevents HPV16 and 18 infection, the quadrivalent HPV vaccine (4vHPV) that prevents HPV6/11/16/18 infections and the nonavalent vaccine (9vHPV) that prevents HPV6/11/16/18/31/33/45/52/58 infections. These vaccines also have high efficacy against persistent infection with HPV vaccine genotypes, a necessary pre-requisite for the development of cervical cancer and related cervical lesions[5].

In 2014, the Strategic Advisory Group of Experts on Immunisation (SAGE) revised recommendations for the bivalent and quadrivalent HPV vaccines from a schedule of three doses to two doses at an interval of at least 6 months for girls aged 9-14 years old[6] based on evidence of non-inferior immunogenicity[7-10]. Recommendations state that girls aged 15 years or older and HIV seropositive girls should receive three doses as per original dosage recommendations[6].

A recent study collating evidence and lessons learnt from HPV vaccine delivery in LMIC found that countries achieved high coverage, especially if they used predominantly school-based delivery strategies[11]. By the end of 2016, Gavi, The Vaccine Alliance, had become the primary conduit through which LMICs could gain financial support for HPV vaccine introduction and Gavi had supported 23 countries to conduct HPV vaccine demonstration programmes. Although an increasing number of LMIC have applied for Gavi support and been approved for national scale-up in recent years, the sustained financial commitment required for vaccine procurement and delivery is a key factor in some governments' hesitancy to initiate national HPV vaccine programmes[11]. This is especially true for countries that are in the process of transitioning out of full financial support from Gavi. These countries must increase their co-financing commitments over time until they are responsible for purchasing the vaccine at the full Gavi price (currently US$4.50 per dose)[12].

There is some evidence that a single dose of HPV vaccine may provide protective immune responses to prevent incident and persistent HPV infection with vaccine genotypes. A combined, post-hoc analysis of 7,466 women aged 18-25 years enrolled in two trials in Costa Rica and the USA who received fewer than the recommended number of doses suggested equivalent efficacy of one, two and three doses of the bivalent HPV vaccine (2vHPV) against vaccine-type persistent infection over a median follow-up of 4 years [13, 14]. Although antibody levels (measured in geometric mean titres) four years post-vaccination were lower among girls receiving one dose compared to girls receiving either two or three doses, antibody levels were nine-times higher than those elicited by natural infection and remained constant up to seven years post-vaccination[15]. In India, 17,729 girls aged 10-18 years participating in a clinical trial that was suspended because of events unrelated to the study

received one, two or three doses of the quadrivalent HPV vaccine (4vHPV). Single-dose recipients elicited lower detectable concentrations of neutralising antibodies to HPV 16 and 18 than two or three dose recipients[16]. However, anti-HPV16 and 18 antibody avidity in the one-dose group at 18 months was non-inferior to the results after the three-dose regimen at 18 months. The frequency of incident HPV 16, 18, 6, and 11 infection was similar irrespective of the number of vaccine doses received, and no persistent HPV 16 or 18 infections were detected in any dose group at a median follow-up of 4.7 years (IQR 4.2–5.1).

Two observational (non-trial related) studies have evaluated antibody response after one, two and three doses of HPV vaccine, one in Uganda after 2vHPV[17] and one in Fiji after 4vHPV[18]. In both studies, girls who were previously vaccinated were recruited and enrolled to determine seropositivity and antibody titers to HPV vaccine types. Antibody was determined at three years post-vaccination in the Uganda study and at six years post-vaccination in the Fiji study. In both studies, GMTs after one dose of HPV vaccine were lower than after two or three doses. In the Uganda study, GMTs after one/two doses of bivalent vaccine did not meet the threshold to be declared non-inferior to three doses. However, GMTs of antibody in adolescents who received only one dose in Uganda were still higher than women who received one dose of 2vHPV vaccine in the CVT, among whom there were no breakthrough cases of disease up to four years after vaccination[15, 19]. In the Fiji study, no significant differences in the GMTs across all four HPV types were found between girls who previously received two or three doses of 4vHPV. Antibody was detected among one dose recipients six years after vaccination, but GMTs were significantly lower than among two- or three-dose recipients. Immune memory, as measured by the anamnestic response after a challenge dose of 2vHPV, was evident in all one-, two- and three-dose vaccine recipients.

A recent systematic review of evidence from post-licensure studies of the effectiveness of HPV vaccination by the number of doses reported highest effectiveness with three doses but almost half of the studies found some evidence of effectiveness with one dose[20]. Of two studies that reported vaccine effectiveness for reduction of prevalent vaccine type infection (HPV 16 or 18), one found statistically significant effectiveness for three doses but not for two doses or one dose [21]. In the second study[22], statistically significant effectiveness was found for three doses, two doses and one dose. Neither study performed a formal comparison of effectiveness of three doses vs fewer doses; confidence intervals for the effectiveness estimates of three, two and one dose(s) overlapped. Among six studies reporting anogenital warts as an outcome, four included a comparison of three, two and one doses with no dose; all found highest effectiveness with three doses, and lower but significant effectiveness with two doses. Three of the four studies found significant effectiveness with one dose [23-27]. Six studies evaluated vaccine effectiveness for prevention of cervical cytological or histological abnormalities[28-33]. Outcomes assessed were based on histology only (two), cytology only (two), and both cytology and histology (two). Histological abnormalities evaluated included cervical intraepithelial neoplasia (CIN) grade 1, 2 and 3 or CIN2+ (CIN grade 2 or worse or adenocarcinoma in situ [AIS]) and CIN3/AIS. Among the six studies, all found effectiveness after three doses. Four studies found some effectiveness for prevention of high grade histological abnormalities with two doses, and two studies found effectiveness with one dose, in some age groups, in analyses with longer buffer periods [29, 30]. Most two-dose vaccine recipients received two doses at a one- or two-month interval; a longer interval between two doses had no impact on the effectiveness estimate in the one study that examined this [30]. No data are currently available on the immunogenicity or efficacy of one dose compared to two or three doses of the nonavalent vaccine (9vHPV).

Currently there are several studies underway to investigate efficacy and/or immune responses of a single dose HPV vaccine compared to recommended dose regimens. These include the ESCUDDO trial in Costa Rica [clinicaltrials.gov registration: NCT03180034][34], the DoRIS trial in Tanzania

[clinicaltrials.gov registration: NCT02834637][35] and the HANDS trial in The Gambia [Research Councils UK registration: MC_EX_MR/N006070/1][36].

As scientific evidence is being gathered from these trials, it is important to understand the policy implications and challenges of changing schedules. In the context of the ongoing single dose vaccine trials and opportunistic analyses of the effectiveness of one dose in HPV vaccine programmes or cohorts with low vaccine schedule completion [17, 18, 20], we approached policy advisors in LMIC for their views on the existing evidence for a one dose schedule, analysed the motivators and barriers to change existing schedules and what further information would be needed to inform a policy change to a one dose schedule in their countries in future.

2 Aims and objectives

We aimed to interview vaccination policy advisors (members of the National Immunization Technical Advisory Group [NITAG]) or Expanded Program Immunization [EPI] managers in LMIC to understand motivators and barriers to a one dose human papillomavirus (HPV) vaccine schedule.

The specific objectives were:

1. To identify key motivators, barriers and information needs for a future, hypothetical, further reduction in the HPV vaccine schedule from two doses to one dose, informed by the lessons and experience during the transition from three to two doses in LMIC;
2. To summarize the perceived implications of a further schedule change on the choice of delivery strategy and the perceived cost and sustainability of the programme;
3. To collate and synthesize attitudes towards any past/current experience of off-label vaccine use and the processes needed to implement policy that includes off-label vaccine use.

3 Methods

3.1 Country selection

Low or middle-income countries (as classified by the World Bank) with some experience of HPV vaccine delivery through a demonstration programme, pilot or national programme were mapped and approached for interview. Due to study timelines, countries were prioritized for interview through purposive selection process and were approached in the first instance if they (i) supported a National Immunization Technical Advisory Group (NITAG) or equivalent group which critically assesses evidence to inform government policy on vaccinations or (ii) had existing links with the study team. The final selection of countries included in the study was based on whether the Key Informants (KI) consented to be interviewed.

3.2 Interview participants

Between one and three key stakeholders per country were approached for interview as potential KIs. KIs and their contact details were identified through Ministry of Health (MoH) websites and through the study investigators' existing contacts and informal collaborators. KIs considered for inclusion comprised (i) members of the NITAG, (ii) Expanded Programme on Immunzation (EPI) managers and/or HPV focal points within the EPI programme, or (iii) EPI country partners and/or international bodies (e.g. WHO country office, UNICEF). Once the KIs were identified, they were contacted by telephone and/or email to enquire about their interest in participating in the study.

3.3 Interview procedures

A semi structured interview topic guide (**Annex 1**) was developed to outline the main areas of inquiry for the qualitative interviews with policy makers and technical advisors. Key motivators and barriers for a one dose HPV vaccine schedule and what information would be needed in any hypothetical future discussions around a further schedule change were explored. Interviewees were asked to describe the potential implications of a change in schedule on the delivery strategy, perceived cost and sustainability of the programme and the possibilities for integration of HPV vaccine into the

routine immunisation schedule. Their experience in implementing 'off-label' vaccine policy and the decision making processes that led to any prior or current 'off-label' vaccine use, were explored.

The first approach to a KI was made via email (**Annex 2**) and included a one page project summary (**Annex 3**). If no response was received within 7 days, a reminder email was sent or, if contact numbers were available, a call was made. Contacts were logged on a contact spreadsheet. If a KI agreed to take part in the study, an Informed Consent Form (ICF) (**Annex 4**) was emailed to the KI for signature, signed and returned prior to interview. Interviews were conducted over the telephone or by skype and recorded (with written informed consent). If interviewees did not consent to be recorded then the notes taken were written up directly after the interview. The interview was conducted with the aid of the interview topic guide (**Annex 1**) and probes used when necessary during the interview. An informal interview style was used, including both closed and open-ended questions, in order to gain as much information as possible. Interview recordings were either transcribed professionally (n=10), or by staff conducting the interview (n=10), or by translators (n=8). Due to difficulties in arranging time for phone interview, two interviewees responded to interview questions by email.

3.4 Data management and synthesis

A standardized data extraction tool was established using Excel 2013 to synthesize the information from interview transcripts. Transcribed interviews were entered by the interviewer (NC) and independently verified by a second team member (HK). The interview transcripts and recordings were on secure servers only accessible by the study team. Qualitative information was synthesized according to three themes linked to each of the three objectives (**Table 1)**. Although the anonymity of interviewees was maintained for data storage purposes, as per the informed consent procedure, participants indicated their consent for their job title and country of interview to be used in reporting and other dissemination materials (**Annex 4)**.

Table 1. Summary of key informant interview questions, by objective

	Question
Objective 1: Motivators, barriers and information needs to support a future, hypothetical schedule change	What are the perceived advantages of one-dose schedule?
	What are the potential barriers to a one-dose schedule?
	How would a decision on any future schedule change be made and who would be involved?
	What information/evidence would be needed for a future schedule change?
	What other factors influence the decision to change schedule?
	Would a one-dose schedule influence the country's decision to continue/re-start/pause the HPV vaccine programme?
Objective 2: Perceived implications of a further schedule change on the choice of delivery strategy and the perceived cost and sustainability of the programme	How might a change to a one-dose schedule influence the recommended delivery strategy for HPV vaccine?
	How might a change to a 1-dose schedule influence the integration of HPV vaccine into the routine immunisation schedule? or integration with other interventions?
	What might be the implications of a change to a one-dose schedule on the affordability and sustainability of the HPV vaccine programme?
Objective 3: Experience with off-label vaccine use	What experience do you know of, in your country, of off-label vaccine use (using a vaccine outside of manufacturer recommendations)?
	If there has been experience of off-label use: how was the initial decision made to deliver the vaccine outside of manufacturer recommendations?

	If there has been no experience of off-label use: how might a decision be made to use a vaccine off label (i.e. who would be the key actors involved, stakeholders, advisory groups and data needs to inform decision)?

3.5 Ethics

Ethical approval for this study was granted by the Ethics Committee of the London School of Hygiene and Tropical Medicine (no. 9010-1, 2 August 2017).

4 Results

4.1 Description of participating countries and interviewees

Representatives from 27 LMIC were approached and at least one KI from 18 countries provided written consent to be interviewed. Country representation included 9 (50%) countries from the Africa region, 5 (28%) from Latin America, 3 (17%) from South East Asia and 1 (6%) European country (**Table 2**). At the time of interview, 12 countries were Gavi-eligible (3-year average gross national income per capita <1580 USD[12]). One of these (Uganda) had already introduced HPV vaccine nationally and the remaining 11 had plans to introduce the vaccine soon (**Table 2**). Two countries were transitioning away from Gavi support (Bolivia and Moldova) and four countries were not eligible for Gavi support (Argentina, Brazil, Colombia and Peru).

Thirty interviews were conducted from August to December 2017. More than one representative was interviewed for 11 countries (two interviews were conducted for Kenya, Nigeria, Uganda, Zimbabwe, Lao PDR, Nepal, Bolivia, Colombia, Peru and Moldova, and three interviews were conducted for Ethiopia; **Table 2**). A single interview was conducted for the remaining seven countries. Interviews were conducted with nine EPI managers, 10 NITAG members, five WHO/national immunization managers and six other individuals (an economist/policy advisor in the Department of Policy, Planning, and Health Care Financing [Kenya], an immunization programme coordinator [Ethiopia], a coordinator of oncological gynecology, National Institute of Cancer in Colombia [Colombia], two WHO country Vaccine Officers [Nepal], a former Minister of Health [Peru]). The KI (a NITAG member) from one country in sub-Saharan Africa requested that the country remain anonymous (Country Z).

Table 2. Summary of the participating countries, HPV vaccine experience and key informants

Region	Country	Gavi eligibility status	National Programme Status[1]	HPV vaccine experience	Stakeholders interviewed
Africa	Ethiopia	Eligible	Soon to introduce (Gavi application successful, projected introduction 2018)	Gavi demo 2015-17	1. WHO Routine Immunization Officer 2. National Immunisation Programme Officer 3. National Immunisation programme Coordinator
	Kenya	Eligible	Soon to introduce (Gavi application sucessful, projected introduction 2019)	GAP demo 2011; Gavi demo 2013-17	1. Economist/ Policy Advisor for the Department of Policy, Planning, and Health Care Financing 2. National Immunization Programme Officer
	Lesotho	Eligible	Introduced 2012-16 (paused)	GAP demo(s) 2009-2011; National 2012-2016	1. WHO Immunization Officer for Lesotho
	Country 'Z'	Eligible	Unknown	Gavi demo 2014-15	1. NITAG Member
	Nigeria	Eligible	Unknown	None	1. NITAG member 2. NITAG member
	Senegal	Eligible	Soon to introduce (Gavi application successful, projected introduction 2018)	Gavi demo 2015-17	1. EPI manager, coordinator of national immunization programme
	Uganda	Eligible	Introduced 2015	Demo(s) 2008-14 Natl. 2015-	1. EPI Team Leader 2. EPI HPV Focal Person

Region	Country	Gavi eligibility status	National Programme Status[1]	HPV vaccine experience	Stakeholders interviewed
	Zambia	Eligible	Soon to introduce (Gavi application sucessful; projected introduction 2019)	GAP demo 2013-14	1. National EPI Manager
	Zimbabwe	Eligible	Soon to introduce (Gavi application successful, projected introduction 2018)	Gavi demo 2015-17	1. Director of Epidemiology and Disease Control and Zimbabwe NITAG Chairperson 2. EPI Manager
South East Asia	Lao PDR	Eligible	Soon to introduce (Gavi application sucessful; projected introduction 2019)	Gavi demo 2013-15	1. National immunisation Programme Manager 2. NITAG member
	Nepal	Eligible	Unknown	Demo 2008-2015	1. Technical advisor to NITAG 2. Vaccine Officer for WHO Nepal Office
	Solomon Islands	Eligible	Soon to introduce (Gavi application successful; projected introduction 2019)	Gavi demos 2015-17	1. EPI Programme Officer
Latin America	Argentina	Ineligible	Introduced 2011	Natl[2]: 2011-	1. Director of Preventable Diseases (MoH)
	Bolivia	Accelerated transition phase[3]	Introduced 2017	Demos 2009-2011 Natl.: 2017-	1. PAHO/WHO Bolivia EPI Consultant 2. President of NITAG
	Brazil	Ineligible	Introduced 2014	Demos 2010-12 Natl. 2014-	1. Coordinator of National Immunization Program at MoH, NITAG member
	Colombia	Ineligible	Introduced 2012	Natl. 2012-	1. NITAG and EPI National Coordinator 2. Other
	Peru	Ineligible	Introduced 2011	Demos 2007-2010 Natl. 2011-	1. Former Minister of Health; Dean of the Public Health Faculty at the Cayetano Heredia in Peru 2. NITAG President
Eastern Europe	Moldova	Fully self-financing	Unknown	Gap Demo 2010-11	1. Head of Epidemiology Department of preventable diseases through vaccination within the National Centre for Public Health and NITAG member 2. NITAG Secretary

[1]The status of the country's plans for national Introduction of HPV vaccine was informed by investigator's previous contact with the country representatives and Gavi's forcasting of successful applications. 'Soon to introduce' meant an application for HPV vaccine support had been prepared by country representatives (and may have been submitted for Gavi's consideration or a date for submission was planned).

[2]National programme was modified in 2017 to include delivery to boys and catch up vaccination to 26 years of age for people living with HIV.

[3]Gavi support was provided for the first year of the national programme only.

4.2 Perceived advantages of a 1 dose HPV vaccine schedule

Of the 30 KIs interviewed, 27 KIs (90%) representing all 18 countries thought that a future, hypothetical schedule change to a single dose HPV vaccine schedule would be supported by key stakeholders within their country. Three KIs did not respond to the question directly. KIs cited the following potential advantages of a single dose HPV vaccine schedule: a reduction in programme costs, operational or logistical advantages (such as easier implementation of one dose in schools including less interruption of school activities, fewer visits and ease of integration into routine immunisation

services/ other outreach activities), high vaccine coverage (uptake of the first dose was reported to be high in previous HPV vaccine programmes but some countries had experienced lower second dose coverage, which had reduced the overall reportable coverage), easier integration with other services (e.g. annual child health days), reduced cold chain storage requirements, potentially increased community acceptability (due to fewer visits and injections) and a potential to expand vaccination to other groups (such as boys or older women [Brazil]), given the reduced cost of a one dose schedule (**Table 3**).

Table 3. Perceived advantages of a single dose HPV vaccine schedule

Perceived advantages of a 1-dose schedule	KIs N=30[1]	Countries N=18
Reduction in costs	15	11
Operational/logistical advantages[1]	15	12
High coverage	7	7
Easy integration into routine immunisation	4	3
Lower cold chain requirement	3	2
Increased community acceptability	3	3
Potential to extend vaccination to other groups	1	1
Did not respond	3	3

[1]KIs cited more than one advantage; [1]Operational or logistical advantages refers to easier implementation of one dose in schools including less interruption of school activities, fewer visits and ease of integration into routine immunisation services.

The KI from the Solomon Islands reported that a schedule reduction could be well received by communities because parents would no longer have to keep track of how many doses their daughters had been given and that health care workers (HCW) would also find vaccine delivery logistically simpler:

> *"[A one dose schedule] will be less work for nurses. The current schedule takes time, takes a lot of their energy. If they have one dose schedule then they go to schools and it's less time vaccinating just one cohort of girls…. so they have more time doing other activities in the clinics….We have a high problem with logistics and transportation in the country. A one dose schedule would have a good advantage for the nurses in the clinics." KI, Solomon Islands*

4.3 Perceived barriers to a 1 dose HPV vaccine schedule

KIs from the same country were not always in agreement in their perception of potential barriers to the introduction of a single dose schedule. Fourteen KIs from 13 countries (Argentina, Bolivia, Brazil, Lao PDR, Lesotho, Moldova, Country Z, Nepal, Nigeria, Solomon Islands, Uganda, Zimbabwe and Peru) did not anticipate any barriers to the hypothetical introduction of a one dose HPV vaccine schedule in their country.

Eight other KIs from 6 countries (Ethiopia, Kenya, Lao PDR, Senegal, Zambia and Zimbabwe) cited concerns around gaining community or individual acceptance of a single dose schedule in place of two/three doses as a potential barrier to a one dose HPV programme. KIs referred to the potential for individuals or communities to question whether one dose is sufficient to provide adequate protection, given the mobilisation and communication to date on the importance of receiving two or three doses (**Table 4**). In Kenya, there was concern that a further schedule change to one dose rapidly after the

schedule was reduced from three to two doses, could be perceived by communities as a lack of sufficient evidence on which schedule is effective:

> *"It does raise concerns of very fast changes. i.e. it implies that comprehensive research was not really done at the outset and we are more on a trial and error phase which many are not comfortable with." KI, Kenya.*

Seven KIs from six countries (Colombia, Ethiopia, Kenya, Uganda, Zambia and Zimbabwe) cited potential acceptability issues among HCWs as a potential barrier to a one dose HPV vaccine programme, given that their training to date has specified two/three doses. In Uganda, there were challenges with HCW when the HPV vaccine schedule was reduced fromthree to two doses. Although training was conducted, information was received at different times and the change in practice among HCWs after training was not immediate, so whilst some health workers in the country were administering two doses, others were still giving three doses. The KI recommended that a clear communication strategy would be needed to ensure that both HCWs and communities understood the recommendations around a further schedule reduction to assure them that one dose would provide effective protection.

In Peru, the KI explained that a formal recommendation from the WHO would be advantageous to support the dose change and would be useful to dispel any resistance propagated by anti-vaccine groups. KIs from three countries mentioned the potential for information around a further schedule change to be used negatively by girls who have been affected by adverse events following immunisation, anti-vaccine groups or the media (Colombia, Peru, Kenya):

> *“I think [a one dose schedule] could be very good for the ones who are not vaccinated yet, but could be a ‘battle horse’ for the ones who are saying that they suffered adverse effects from the vaccine, because they could use a further schedule reduction to say “you gave us more doses than we needed and that is why we got ill”.” KI, Colombia*

> *“I always fear the anti-vaccine groups. For example, if in some years ahead someone who received only one dose developed cancer” KI, Peru*

Other health systems disadvantages were also cited. One Ethiopian KI mentioned that a single visit would impact the frequency of contact between the HCW and the adolescent, thereby decreasing the opportunity for the provision of sexual and reproductive health (SRH) services for adolescents. Five KIs stated that sourcing the resources needed for the retraining of HCWs and remobilisation of the community would be a challenge if no extra support was provided (Kenya, Ethiopia, Bolivia, Uganda, Country Z). Other perceived financial implications of a reduction to a one dose schedule are collated in Section 4.6.

Table 4. Perceived barriers to 1 dose HPV vaccine schedule

Perceived barriers to 1 dose HPV vaccine schedule	KIs N=30[1]	Countries N=18
No barriers perceived	14	13
Community or individual acceptance[1]	8	6
Acceptability among healthcare workers	6	6
Negative media or anti-vaccine groups	3	3
Cost of re-mobilisation/ retraining necessary	5	5

Did not respond	2	2

[1]KIs cited more than one barrier. [1] Community or individual acceptance refers to communities questioning whether one-dose is sufficient/ mis-trust.

4.4 Decision making body and evidence needed for change to vaccine programme

The decision-making body, processes and evidence needed for a future HPV vaccine schedule change described by KIs are summarised in **Tables 5, 6, 7, 8.**

KIs from all but three countries (Lesotho, Nepal and the Solomon Islands) reported that their countries had a NITAG in place, although some NITAGs had been recently established and so had still limited functionality. Countries used a variety of different governmental departments to research and review available vaccine-related information and to make decisions on vaccine introduction or changes to current vaccination programmes within their country **Tables 5, 6, 7, 8.**

All KIs from all 18 countries stated that at least one source of information would be required as part of the decision-making process around a future, hypothetical HPV vaccine schedule change (some KIs cited multiple sources). KIs from nine countries (Ethiopia, Senegal, Uganda, Laos, Nepal, Solomon Islands, Bolivia, Peru and Kenya) thought that a WHO position paper or a WHO recommendation would be required before policy makers would consider a change to a one dose HPV schedule. KIs from eight countries (Lesotho, Country Z, Senegal, Uganda, Argentina, Brazil, Peru and Zambia) stated that evidence on the efficacy of one dose of HPV vaccine against HPV infection and/or clinical endpoints to compared to two or three doses, would be important in the decision-making process around a change in schedule. KIs from 10 countries (Lesotho, Country Z, Nigeria, Senegal, Nepal, Argentina, Bolivia, Brazil, Colombia and Moldova) said that evidence on the immunogenicity of one dose of HPV vaccine compared to two or three doses would be important for the decision-making process. Countries are classified into groups based on the highest level of evidence perceived to be required for a change of HPV vaccine schedule in **Table 9**. Only KIs from Argentina stated explicitly that policy makers would not necessarily need to wait for formal WHO recommendations to enact a change in vaccination policy (e.g. schedule or dosage), unless it was an issue with significant controversy.

Other data considered important for policy makers to consider if deliberating over a change to a one dose HPV vaccine schedule were evidence on durability of protection (KIs from Country Z, Zimbabwe, Laos, Nepal, Bolivia and Colombia); cost-effectiveness data on a single dose HPV vaccine programme (2 KIs: Country Z and Peru) and ‘untold experiences’ (i.e. experiences from other researchers or implementers of one dose programmes) by one KI from Nigeria.

The Nepal WHO officer stated that there might be interest in Nepal to help generate data on the immunogenicity and effectiveness of a single dose of HPV vaccine.

Table 5. Summary of decision making body, decision-making process and reported evidence needs in countries from the African region, as reported by KIs

Country	Decision making body	NITAG (Yes/No)	Decision-making process for vaccine policy	Reported evidence needed for any consultation on a further change to the HPV vaccine schedule
Ethiopia	The Inter-Agency Coordinating Committee (ICC) makes the final decision on all national vaccination programmes, (vaccine introductions and delivery strategies)	Yes	The NITAG deliberates over new vaccine introductions and drives discussion around changing vaccine schedules. The ICC receives advice from the NITAG to inform a decision. ICC Meetings are held every 2 weeks involving working groups, technical advisors and national immunisation coordinators. When new evidence is available it is reviewed at these fortnightly meetings and formal requests to the NITAG are issued for their recommendation. The ICC also discuss the evidence available with partners globally, regionally and nationally, including groups from the professional healthcare society.	- WHO recommendations - Data from demonstration projects/ national programmes from other countries implementing one dose - Data on non-inferior immune response of one dose compared to two or three doses
Kenya	MoH working group including other stakeholders e.g. Ministry of Education (MoE), WHO and UNICEF, other MoH departments (reproductive health, health promotion and cancer programme).	Yes	A proposed change to a programme is presented to the NITAG and a recommendation from the NITAG is requested. The NITAG will form a working group, who will develop a policy recommendation. The working group present this recommendation to the NITAG and they will come up with the final recommendation. Finally the recommendation is presented back to the cabinet secretary and the MoH.	- WHO recommendations - Due to lack of in-country data, data from other countries on efficacy of one dose would be useful especially in the context of HIV given the high prevalence.
Lesotho		No but the country is in the process of forming one (early stage development)	Currently, decisions are made by the EPI and the MoH with involvement from the Reproductive Health Programme and Department of Disease Control. When the country made the decision to change from 3 to 2 doses, the recommendations from WHO were submitted to the MoH and the dose schedule was changed.	- Data demonstrating non-inferiority of immune responses (evidence from other countries would be considered when no national level data is available)
Nigeria	MoH working group including professors in community health/ public health, infectious diseases, pathology, and gynaecologists.	Yes (formed in 2015)	The NITAG meets quarterly. The NITAG is composed of individuals from a broad range of backgrounds. Recommendations pass to the MoH. The National Primary Healthcare Development Agency within the MOH is in charge of implementation of vaccines and all of the operational aspects.	- Information on costs - 'Untold experiences' from researchers who have implemented one dose vaccine - Immunogenicity data from other countries, especially similar African countries - Evidence from peer reviewed journals on one dose safety/ duration of protection

Country	Decision making body	NITAG (Yes/No)	Decision-making process for vaccine policy	Reported evidence needed for any consultation on a further change to the HPV vaccine schedule
Senegal	The Comités de Coordination Inter-Agences (CCIA) or Interagency Coordination Committees (ICC)	Yes	The CCIA would follow the WHO guidelines and consider all available evidence as provided in the WHO guidelines with advice from the NITAG. The CCIA would also consider the potential benefits of dose reduction, e.g. reduction in resources needed for 1 dose administration, finance and avoiding drop-out/loss-to-follow-up for further doses. Senegal has a broad involvement from the MoH, MoE, Ministry of Finance and civil society representatives and international partners.	- WHO position paper - Evidence of one dose non-inferiority vs. two/three doses (immunogenicity and efficacy against infection)
Uganda	MoH and the Supporting Immunization and Vaccination Advisory Committee (SIVAC)	Yes	NITAG consults and evidence is presented and discussed. This is then presented to the MoH and the Supporting Immunization and Vaccination Advisory Committee (SIVAC) who make the final decision.	- WHO recommendations - Evidence of non-inferiority of immune responses and efficacy against infection and clinical endpoints.
Zimbabwe	MoH, MoE, the communicable and non-communicable disease units, the Child Health team.	Yes	During the process of dose reduction from 3 to 2 dose HPV vaccine, the NITAG, MoH, MoE, the communicable and non-communicable disease units reviewed the evidence and recommendations. For the HPV vaccine, they needed to go beyond the traditional EPI approach, because the age group was well outside the under 5 year old target age group. Different stakeholder groups were needed to review evidence and give advice on implementation/ vaccine delivery. A strategic advisory group was formed specifically for decisions concerning the HPV vaccine. The Permanent Secretary of the MoH is the chair of this new group.	- Non-inferiority of 1 dose in terms of duration of protection (i.e. would girls need a booster at some point if they were only getting one dose?) with in-country/ regional data on effectiveness.
Country 'Z'	The Research Institute of National Health.	Yes	NITAG review evidence with Research Institute of National Health. Then recommendations are made to MoH who have final decision.	- Immunogenicity of one dose, and evidence of duration of protection; - Research on financial impact, including cost-effectiveness analysis

Table 6. Summary of decision making body, decision making process and evidence used in countries from South East Asian region

Country	Decision making body	NITAG (Yes/No)	Decision making process	Evidence needed for consultation
Laos PDR	National Immunisation Committee (NIC) including members from the MoH, Ministry of Science, Ministry of Planning and Investment and MoE	Yes	The NITAG reviews all the evidence available and invite scientists to present and reviews the evidence with them. The NITAG make recommendations after this review and present it to the NIC. The NIC is led by the MoH. The decision makers (the NIC) aim to balance the investment and benefit to the country and so once they review the recommendations of NITAG the NIC make a decision.	- WHO position paper (Concrete evidence from the WHO that one dose achieves the same level of immunogenicity as 2 doses) - Research from other countries including African countries, European regions, America, Australia including data on the incidence and prevalence of cancer in the country. - Evidence on duration of protection would also be important.
Nepal	National Committee for Immunization Practice (NCIP) represented by various government and independent experts	No	Various factors govern the decision-making including cost, sustainability, overall safety, and effectiveness of vaccine. Whenever an application to Gavi for any new vaccine introduction is made, the application needs to be endorsed by the Inter Agency Coordination Committee (ICC), Ministry of Finance, and the Ministry of Health.	- WHO position paper - Established evidence showing the non-inferiority of 1 dose in terms of immune response and effectiveness including the long-term protection (regional and country level data is required).
Solomon Islands	EPI technical working group, Director of Reproductive Health, ICC, MoH	No	The decision-making process starts with the EPI technical working group which forms a committee chaired by the Director of Reproductive Health. This committee reviews evidence, presenting any advantages and disadvantages of a new policy/ a policy change and then makes a recommendation to the ICC and MoH who make the final decision. The final decision is therefore based on the information provided by the EPI technical working group.	- WHO recommendations, - Evidence of non-inferiority of one dose (in terms of immune responses or against infection endpoints) from other countries.

Table 7. Summary of decision making body, decision making process and evidence used in countries from South American region

Country	Decision making body	NITAG	Decision making process	Evidence needed for consultation
Argentina	The MoH department of Disease Control and Prevention	Yes	- Internal plan at MoH level showing the need of the new vaccine strategy (e.g. reduction to one dose) - An internal evaluation of the programmatic (logistic) aspects including an evaluation of human resource requirements - Once the decision is taken around logistic/ programmatic feasibility, the NITAG evaluates the evidence - The NITAG makes the scientific recommendation - The scientific recommendation is evaluated at the MoH level, and the decision is taken.	- Non-inferiority of 1 vs. 2 doses in terms of immunogenicity and efficacy against cervical disease from international research as well as from national and local data (surveillance data available from a national register of cervical lesions and cervical cancer)
Bolivia	The MoH, the Pan-American Health Organization (PAHO), WHO and The Immunization National Program.	Yes	The NITAG will analyse all the information and will present a report and a suggestion to the MoH.	- WHO/ PAHO position paper - Recommendations from the vaccine manufacturer - Evidence showing that 1 dose HPV vaccine has a non-inferior immune response compared to 2/3 doses (i.e. that antibody titres are equivalent and durable) - A formal recommendation from the TAG (Consultant Technical Group)
Brazil	Technical Committee of Immunisation: paediatricians, immunologists, gynaecologists, and immunization coordinators (state and municipal level).	Yes	The Committee meets twice a year to evaluate evidence and define the immunisation policy around the country. This group is advisory, providing recommendations to MoH. The MoH works together with other directors from the Ministry of Health to decide on recommendations using the scientific evidence and economical sustainability.	- Data on immunogenicity, safety, international evidence on infection and clinical outcomes (there are not enough national studies in relation to the vaccines)
Colombia	the Ministry of Health and Social Welfare make final decision.	Yes	The NITAG includes representatives from National Academic of Medicine, Paediatricians organization and Immunology organizations. They make recommendations and the MoH, who also consults the Colombian Federation of Obstetrics and Gynaecology, the Colombian Society of Paediatrics, the Colombian Federation of Perinatology, the National Institute of Health and the National Institute of Oncology, and PAHO. The MOH then needs to comply with the recommendations.	- Non-inferior immunogenicity (or immunobridging studies) and efficacy of 1 dose compared to 2 doses and duration of protection - Lessons from other countries that introduce a single dose
Peru	MoH	Yes	The Minister of Health invites experts in the NITAG to review evidence on issues (NITAG or PAHO can also intiate an evidence review at NITAG). The expert committee discuss it. If necessary they would bring more experts and finally vote on the decision. Usually the decision is unanimous. The Minister of Health ratifies policy for the change.	- WHO position paper - Cost-effectiveness data; - International or national data showing that the efficacy with one dose at least the same level demonstrated by two doses

Table 8. Summary of decision-making body, decision making process and evidence used in countries from East European region

Country	Decision making body	NITAG (Yes/No)	Decision making process	Evidence needed for consultation
Moldova	MoH	Yes	The NITAG and WHO give recommendations to the MoH who makes the final decision.	- The immunogenicity of one dose would be sufficient evidence

Table 9. Countries classified by the highest level of evidence that KIs perceived may be needed for any future discussions on a further reduction of the HPV vaccine schedule

	Reported evidence needed for consideration of a dose reduction		
Countries	**Immunogenicity data**	**Efficacy data against a clinical endpoint (+/- immunogencity data)**	**WHO position paper (+/- immunogencity and efficacy data)**
	Nigeria Colombia Moldova	Lesotho Country Z Argentina Brazil Zambia Zimbabwe	Ethiopia Senegal Uganda Laos Nepal Solomon Islands Bolivia Peru Kenya
Total	3	6	9

4.5 Perceived implications of schedule change on HPV vaccine delivery strategy

KIs from all 18 countries discussed the perceived implications of a schedule change on vaccine delivery strategy. As background, the main strategies used for HPV vaccine delivery, in pilots or national programmes, as reported by KIs were school-based, school-based with community outreach for out of school girls and health facility-based strategies with/without community outreach (**Table 10**). Health facility-based delivery with/without community outreach represented the delivery strategy most integrated with existing routine health facility activities whereas school-based strategies generally represented a campaign style delivery approach.

Table 10. HPV vaccine delivery experience and perceived implications of a further schedule change to the vaccine delivery strategy

Country	HPV vaccine experience	National Programme Status	Delivery strategy experience	KI perspective on delivery strategy for 1 dose schedule
Ethiopia	Gavi demo 2015-17	Soon to introduce (Gavi application successful, projected introduction 2018)	Demo exp: School based + community outreach Natl. plans: School based	No change
Kenya	GAP demo 2011; Gavi demo 2013-17	Soon to introduce (Gavi application sucessful, projected introduction 2019)	Natl. plans: School based	No change but would propose to integrate with another service delivered in schools such as deworming or health education on hygiene i.e the school health days or malezi bora campaigns
Lesotho	GAP demo(s) 2009-2011; National 2012-	Introduced	Natl. exp: School-based	Integrate into routine immunisations services at the health facility with outreach
Country 'Z'	Gavi demo 2014-15	Unknown	Demo exp: School + health centre based + outreach	Uncertain; potentially integrated with annual vitamin A campaigns
Nigeria	None	Unknown	N/A	Uncertain
Senegal	Gavi demo 2015-17	Soon to introduce (Gavi application successful, projected introduction 2018)	Demo exp/ Natl. plans: School + health centre based + outreach	No change
Uganda	Demo(s) 2008-14 Natl. 2015-	Introduced	Natl. exp: health facility based + outreach	No change
Zambia	GAP demo 2013-14	Soon to introduce (Gavi application sucessful; projected introduction 2019)	Demo exp: Schools + health facilities	Potentially integrate into Child Health Week campaign, which includes deworming and immunisation
Zimbabwe	Gavi demo 2015-17	Soon to introduce (Gavi application successful, projected introduction 2018)	Demo exp: School + health centre based + outreach. Natl. plans: School + health facility	No change
Lao PDR	Gavi demo 2013-15	Soon to introduce (Gavi application sucessful; projected introduction 2019)	Demo exp: School + health centre based + outreach.	Unknown
Nepal	Demo 2008-2015	Unknown	Demo exp: School + health centre based	No change
Solomon Islands	Gavi demos 2015-17	Soon to introduce (Gavi application successful; projected introduction 2019)	Demo exp: School + health centre based + outreach.	No change; easier to integrate with TT and Oral Polio vaccine outreach delivered by the chool health programme
Argentina	Natl: 2011-	Introduced	Natl. exp: school + Health facility + outreach (dependent on province)	No change; currently integration of Hepatitis B, rubella, meningitis and first dose of HPV
Bolivia	Demos 2009-2011 Natl.: 2017-	Introduced	School based	No change; possibly integrate with tetanus

Brazil	Demos 2010-12 Natl. 2014-	Introduced	Natl. exp: school + Health facility	No change. Integrated with Meningitis C and diphtheria vaccine
Colombia	Natl. 2012-	Introduced	Health centres	No change
Peru	Demos 2007-2010 Natl. 2011-	Introduced	Natl. Exp: School based	No change
Moldova	Gap Demo 2010-11	Unknown	Demo. Exp: School-based	Uncertain

Information collated from KIs and Gavi application documents at gavi.org

The majority of KIs stated that a change in schedule would not alter the recommended delivery strategy for HPV vaccine in their country (**Table 10)**. KIs from just two countries (Country Z and Zambia) mentioned that a single dose strategy may be easier to integrate with existing annual health day campaigns rather than delivery through their routine existing health system activities and therefore a change of delivery strategy may be considered.

KIs from 6 countries (Nigeria, Kenya, Ethiopia, Lesotho, Country Z, Zambia) felt that integration of HPV vaccine delivery with other services could be easier with a single dose schedule e.g. if combining vaccination with annual health days or other annual vaccine campaigns. Delivery of HPV vaccine together with other services was perceived to be more cost-effective than delivering HPV vaccine alone.

KIs from Bolivia mentioned that a further dose reduction could present the opportunity for vaccinating a wider cohort such as a wider age group or another target group, or that the money saved could potentially also go to another vaccine programme.

4.6 Implications of a 1 dose HPV vaccine schedule on affordability of vaccine supply and delivery

In total, 22 KIs from 15 countries offered their perspectives on the implications of a change in schedule on the cost and sustainability of the HPV vaccine programme. The KIs from the same country were all in agreement on this point. Four KIs from 3 countries (Senegal, Solomon Islands, Uganda) were unsure as to what extent the reduction of schedule would affect the cost of the HPV vaccination programme, stating that the cost would depend on the cost of the single dose formulations and the delivery strategy used. The remaining 18 KIs from 12 countries (Argentina, Bolivia, Brazil, Ethiopia, Kenya, Lao, Lesotho, Moldova, Country Z, Nepal, Zambia, Zimbabwe) perceived that a reduction in schedule would reduce the overall cost of vaccine procurement and delivery. KIs from 2 countries (Bolivia, Brazil) mentioned that the cost-savings of a reduction in HPV vaccine schedule could be used to invest in other interventions . Lesotho mentioned that a reduction in schedule and concomitant reduction in programme cost could help re-start the national HPV vaccination programme.

> *"The country is preparing to start the vaccine again after it stopped. There is a strong need to reintroduce the vaccine now, so a one dose schedule would be more than appreciated." KI Lesotho*

The KI from Moldova stressed that despite a potential reduction in cost, political will would need to increase for the HPV vaccine to be successfully introduced nationally:

> *"There is not sufficient political support at this moment… it took us a lot of effort to convince them [the government] to do the pilot. The key to the decision to introduce will be deeply rooted in the financial aspects. Currently the National Immunization Program is entirely*

covered from the State budget and HPV vaccine is the most expensive one out of the whole spectrum of vaccines proposed for funding by the Immunization Program" KI Moldova

As stated in the barriers section, KIs from five countries (Kenya, Ethiopia, Bolivia, Uganda, Country Z) said that it may be a challenge to source the additional resources needed for social mobilisation and HCW retraining on a change in schedule.

Despite recognising that a reduced schedule could potentially substantially reduce the cost of the HPV vaccine programme, KIs from 7 countries (Ethiopia, Lao, Country Z, Nepal, Solomon Islands, Uganda, Zimbabwe) mentioned residual concerns over the sustainability of their HPV vaccine programme.

"It is already hard to sustain the vaccines that we have in our programme, introducing a new one is increasing the burden that we already have. But of course, if you're going for the one dose approach it would be much, much easier to manage." KI Country Z

Two KIs (Ethiopia, Zimbabwe) specifically stated that for the programmes to be sustainable, the cost of the vaccine still needs to reduce, despite a one dose schedule and Gavi support.

"[One dose] will help in the shorter-term… HPV will only be sustained longer-term if the price of that 1 dose is negotiated again" KI Ethiopia

"The price of the vaccine still needs to be reduced even with a reduction to one dose." KI Zimbabwe

Among the 12 countries eligible for Gavi support, the restricted time period in which the country will benefit from Gavi support for HPV vaccine was mentioned by 8 KIs in 6 countries (Ethiopia, Lao PDR, Country Z, Nepal, Solomon Islands, Zimbabwe) as a contributing factor to their assessment of the implications of a one dose schedule on cost and sustainability of the HPV programme.

"Current national rollout support from Gavi ends in 2021. The country is going to take on board [the cost of] not just HPV vaccine, but other vaccines as well. It is now in the level of the executives. They are aware of our transition, that we are graduating soon from Gavi, so they are working out whether other support will come once we have graduated from Gavi." KI Solomon Islands

KIs from Kenya and Uganda specifically stated that a single dose programme could alleviate costs and resources associated with tracing and catch-up of girls who miss their second/third dose.

In two countries (Bolivia and Brazil) the provision of specific vaccines is enshrined by law, once a vaccine is included in the national immunisation programme, the government guarantees its availability. KIs reported they would therefore be able to spend the savings from a reduced HPV vaccine schedule on vaccinating a wider cohort of girls or older women or reallocate fnds to introduce a different vaccine.

4.7 Experience with off-label vaccine use

KIs from nine of the 18 countries interviewed knew of no prior experience of off-label vaccinations in their country (Ethiopia, Kenya, Country Z, Nigeria, Senegal, Uganda, Zimbabwe, Lao PDR and Moldova), and felt that the country would need to have WHO recommendations in place to proceed with any future off-label use. KIs from four (24%) countries reported that policy makers were currently considering off-label vaccination: the delivery of fractional doses of inactivated polio vaccine (IPV;

Lesotho, Zambia, Nepal and the Solomon Islands), and an out of cold chain (OCC) project for Hepatitis B vaccine was also reported by the Solomon Islands (**Table 11)**. KIs from all five of the Latin American countries interviewed reported that the country had previous experience of using vaccines off-label or outside current recommendations (Argentina, Bolivia, Brazil, Colombia, Peru, **Table 11**). This included off-label experiences with Hepatitis A, polio and pertussis vaccines.

Table 11. Summary of experience of past or current 'off-label' vaccine use in the national immunisation programmes of nine countries

Country	Past/current	Reported experience
Africa region		
Lesotho	'under consideration'	Fractional dosage of IPV
Zambia	'under consideration'	Fractional dosage of IPV
South East Asia/Oceania		
Nepal	'under consideration'	Fractional dosage of IPV
Solomon Islands	Current	An out of cold chain project for Hepatitis B vaccine Fractional dose IPV also 'under consideration'
Latin American region		
Argentina	Past	- Reduction in Hepatitis A vaccine schedule from two to one dose - Reduction in pneumococcal conjugate vaccine schedule from four to three doses - Reduction in varicella vaccine schedule from two to one dose - Administration of pertussis vaccine to pregnant women
Bolivia	Past	Prolonged storage and use of multi-dose vials of IPV beyond manufacturers recommendations
Brazil	Past	Reduction in Hepatitis A vaccine schedule from two to one dose
Colombia	Past	Pertussis vaccine in pregnant women and fractional dose IPV
Peru	Past	Early adoption of pneumococcal conjugate vaccine reduced schedule of three doses (the '2+1' schedule)

<u>Case studies of off-label vaccine use</u>

The KI from **Argentina** reported several experiences of off-label use, outside of manufacturer recommendations. These included (i) administration of a pertussis vaccine in pregnant women, off-label but within WHO recommendations; (ii) Reduction in Hepatitis A vaccine (HAV) schedule from two doses to one dose, off-label and outside of recommendations; (iii) early adoption of a reduced schedule of pneumococcal conjugate vaccine in children in a schedule of three doses (two primary doses and a booster dose) rather than four doses, off label but within WHO recommendations; (iv) one dose varicella vaccine rather than two doses, off-label and outside of WHO recommendations. The decision to change the Hepatitis A vaccine schedule from two doses at 12 and 18 months of age, to one dose was made in the context of budget constraints due to flooding around the country, an outbreak of Hepatitis A and limited supply of HAV in 2005. Policy makers decided to prioritise high coverage with a single dose, nationwide in unvaccinated children, rather than implement a low coverage programme of two doses, to prevent another outbreak. At this time, there was a committee in place which was smaller than the NITAG and an expert group who made the recommendation to reduce the schedule with participation from representatives from the provinces. The epidemiological surveillance group synthesised and evaluated the evidence on one dose HAV schedule and, once a one

dose programme was initiated, conducted surveillance every five years to evaluate the need for a second dose.

In **Bolivia**, the reported experience of off-label use of the inactivated polio vaccine (IPV) in 2014-15 was in the context of a global shortage of available vaccine. The KI reported that the country considered two options: (i) extending the use of multi-dose vials beyond manufacturer recommendations to reduce wastage, and (ii) using a fractional dose (1/5th of the full IPV dose) administered intradermally. Manufacturer recommendations stated that the multi-dose vial should be discarded within 8 hours of first puncture but, by the time the vaccine was introduced in Bolivia in 2015, the WHO had devised recommendations to allow the vial to be used for up to 28 days after first puncture under certain storage conditions. These recommendations were informed by well-designed studies that indicated the vaccine was stable for 28 days following first puncture. Regional meetings of NITAG and MOH representatives, coordinated by Pan-American Health Organization (PAHO), were organised across the Latin American continent. The Bolivian NITAG generated a formal recommendation to the MoH that supported the extended use of the multi-dose vaccine vials to reduce wastage and extend the supply of the vaccine. The MoH subsequently organised training and information to prepare for the change and this to be implemented. The MOH reportedly encountered no challenges when making the decision, given the evidence from well-designed studies that indicated that the vaccine was stable for 28 days. However, there was some resistance from health professionals who queried why national recommendations and those on the label differed.

In Brazil, a single dose schedule of hepatitis A vaccine is used rather than the recommended 2 dose schedule. The NITAG initiated the recommendation during a period of low vaccine stock following evidence from published studies that a single dose is approximately 80% effective. The immunisation program at the MoH took the recommendation to the Minister of Health for the final decision. The MoH then informed the media. There were no barriers to the off-label use of HAV as the community and civil society recognised the importance of the vaccine and the constraints on supply.

In **Colombia**, the KI reported that the HPV vaccine programme initially started with a schedule of 3 doses (0, 2 and 6 months) but this changed quickly to a 0/6/60 months schedule as there was some evidence showing that the 3rd dose was not necessary. Two KIs reported that the government in Colombia had been considering the dose reduction before the dose change was approved by the WHO or at the national level by the NITAG. Colombia also has used the pertussis vaccine (Tdap) among pregnant women without a strong recommendation from PAHO. In 2012 and 2013, there were some outbreaks of pertussis and pregnant women were vaccinated following evidence from different studies and a recommendation from the NITAG. There were few barriers when implementing these changes. Efforts were made to communicate with the scientific community, and specifically with doctors, paediatricians and gynaecologists. Training was organised and guidelines published, and the changes were well accepted by the medical community and the community in general. Due to low stocks of the polio vaccine, Colombia is currently preparing for fractionated IPV use. Approximately 11,000 health workers have been trained in the intradermal delivery, using 1/5 of the recommended dose.

<u>Countries with no experience of off-label use</u>

The **Zimbabwe** KI explained that introduction of new vaccines or changes to vaccines have to go through the Zimbabwe Medicines Control Authority. The MoH works closely with the regulators who must be notified if there is a change to a formulation or dose and to conduct quality assurance. This can be a lengthy process so, if there was to be a dose reduction, the MoH and the regulators would need advanced warning so that the introduction of a one dose vaccine would not be delayed. The only

way to waiver the full registration process with the Medicines Control Authority would be in an emergency such as an outbreak. The vaccine would still have to be re-registered but the MoH could begin implementation whilst the registration process was on-going.

Lao PDR has no experience in using vaccines off-label. The KI suggested that healthcare workers like nurses would be very reluctant not to follow manufacturer or WHO recommendations. The IPV vaccine shortage is used as an example. Despite the fact that the WHO suggested fractional dosing, this was not implemented in Lao PDR to avoid confusion among healthcare workers.

A summary of study findings is presented in **Table 11** with more detailed summary of information from KI interviews in **Supplementary Table 1**.

Table 12. Summary of some key findings

Country	Date of national HPV vaccine intro'	Readiness and perceived advantages			Barriers			Information needs	
		Would support 1-dose	NITAG in place	Experience of off-label vaccine use	Community mobilisation needed[1]	HCW mobilisation needed[2]	Concerns over negative media	WHO recommendation required	Other country lessons on 1-dose
Ethiopia	2018*	Yes	Yes	No	Yes	Yes		Yes	Yes
Kenya	2019*	Yes	Yes	No	Yes	Yes	Yes	Yes	
Lesotho	2012-16	Yes	None (in development)	Under consideration					
Country Z	NA	Yes	Yes						
Nigeria	NA	Yes	Yes	No					
Senegal	2018*	Yes	Yes	No	Yes			Yes	
Uganda	2015-	Yes	Yes	No		Yes		Yes	
Zambia	2019*	Yes	Yes	Under consideration	Yes	Yes			
Zimbabwe	2018*	Yes	Yes	No[3]	Yes	Yes			
Lao PDR	2019*	Yes	Yes	No[3]	Yes			Yes	Yes
Nepal	NA	Yes	Yes	Under consideration				Yes	
Solomon Islands	2019*	Yes	None	Yes (current)				Yes	
Argentina	2011-	Yes	Yes	Yes (past)				No[4]	
Bolivia	2017-	Yes	Yes	Yes (past)				Yes[5]	
Brazil	2014-	Yes	Yes	Yes (past)					
Colombia	2012-	Yes	Yes	Yes (past)		Yes	Yes		Yes
Peru	2011-	Yes	Yes	Yes (past)			Yes	Yes	
Moldova	NA	Yes	Yes	No					

[1]Concerns were raised over community acceptance of (another) schedule change/ mistrust/ the additional resources needed to re-mobilise the community

[2]Concerns over health care worker acceptance of a new schedule and the additional resources needed for re-training.

[3]KIs indicated any approval for off-label use would take a long time to be processed and/or would not be considered

[4]KIs in Argentina were the only KIs to indicate that WHO recommendation would not necessarily be needed prior to introduction of a change in HPV schedule (other KIs either explicitly stated they would be needed or did not mention them)

[5]Bolivian KIs also mentioned manufacturer recommendations for the schedule change may be needed.

*Projected introduction date based on Gavi application; NA: unknown/ not available

5 Discussion

Key immunisation stakeholders from 27 countries were approached for interview on the potential implications of a future, hypothetical further reduction of the HPV vaccine schedule from two to one doses. Thirty KIs from 18 countries (67%) provided written consent to be interviewed.

Overall, the KIs interviewed in this study suggested there would be support for a hypothetical future simplification of the HPV vaccine schedule to a single dose. It was generally acknowledged that this would reduce the resources required for delivery, the discomfort and inconvenience to the vaccinees and the financial commitment required for vaccine procurement. A number of KIs stressed that, although a single dose schedule might alleviate some of the logistical and financial challenges of HPV vaccine delivery, there remained a need for strong political will, social mobilisation and healthcare worker training to ensure programme success and longevity. Some KIs also called for continued efforts to reduce the vaccine per-dose cost, citing residual concerns over HPV vaccine programme sustainability.

The decision-making processes and information needs for a future hypothetical one dose schedule change were fairly similar across countries. NITAGs were perceived to play an important role in independently assessing evidence and providing a recommendation to the decision-makers. WHO recommendations on vaccine introduction and delivery also play a key role, especially in Africa, in decisions to introduce or change vaccine programmes. WHO recommendations were reported as being used to reassure communities about a change in vaccine policy should negative media or rumours arise. KIs from half of the countries interviewed stated that they felt a WHO recommendation for a single dose schedule would be needed prior to a schedule change in their country. KIs from three of the 18 countries specifically stated that they would want to hear lessons from other countries that had introduced a single dose schedule, i.e. that they would not want to be the first to implement. There were concerns that the change in policy could fuel negative media coverage of the national immunisation programme. Only KIs from Argentina stated explicitly that policy makers would not necessarily need to wait for formal WHO recommendations to enact a change in HPV vaccination policy, but that they may wait if the change was likely to be a controversial issue.

Known prior experience of off-label vaccine use was concentrated in the South American countries that were interviewed. Here, schedule reductions for Hepatitis A, varicella and pneumococcal conjugate vaccines were introduced nationally without/prior to WHO recommendations. There may be other examples of off-label vaccine use that were not reported by the KIs.

There were a number of study limitations. We were not able to collect information from nine of the 27 countries approached for interview and the interviews conducted represented the individual opinion of the KIs rather than a consensus reached by those making vaccination policy. There may be different conclusions drawn if the outlined decision-making processes in the country were followed e.g. on the information needed prior to a schedule reduction or the implications of a schedule change on the recommended delivery strategy.

Randomised controlled trials are underway to analyse whether 1-dose delivers non-inferior immunogenicity and efficacy to 2 and 3 dose regimens. In conclusion, we found wide ranging support among 27 vaccine policy makers and advisors from 18 LMICs for a future further reduction in the HPV vaccine schedule to a single dose if there were immunological data and/or clinical evidence of efficacy to support this change.

Supplementary Table 1. Summary of key factors involved in decision on HPV dose reduction (from 2/3 to 1 dose)

Country	Key decision makers + summary of decision making	Potential support for 1 dose by policy makers?	Evidence necessary to make change	Factors that may influence decision	Perceived advantages for one dose	Barriers to dose reduction	Experience of off-label use?
Benin	NITAG will review evidence (immunogenicity and efficacy against HPV/clinical endpoints) from peer reviewed publications and WHO papers and consult with MoH and MoF.	Not a NITAG member or WHO EPI representative so did not want to respond	Data on immunogenicity among young girls demonstrating that 1 dose is not inferior to 2-doses	Availability of trial data showing non-inferiority of immune response	Easily integrated into routine immunisation services	None cited, but notes that acceptability among HCW and community would need to be addressed	Did not want to respond to this question
Ethiopia	Evidence and information is reviewed by the NITAG who make a recommendations to the ICC (Inter-Agency Coordinating Committee). The ICC make the final decision.	Yes – provided there is adequate evidence that one dose is effective against cervical cancer and cost effective	WHO position paper; Discussion with partners globally, regionally, nationally, including groups from the professional healthcare society; evidence gathered from different countries as well as other journals or articles	WHO position paper; Regulator has put WHO pre-qualification as one of the requirements to register the vaccine to enter into the country, as well as WHO endorsement	There will be logistical/programmatic advantages as it will be easier to deliver (in one visit) and would improve coverage; integration with other programmes (adolescent sexual health programme)	Acceptance by HCW or the community that 1 dose is as effective as 2/3 doses. One dose schedule reduces time HCW spends with child (less opportunity to advocate on sexual health). Public might query the frequency of dose change (3 ->2 ->1)	No off label example given but decisions around this topic would be made by the ICC. The NITAG recommendation would have an influence on any decision made. They would want to align in country recommendations with WHO recommendations with the manufacturer recommendations.
Kenya	TAG follow recommendations by WHO. DATA & literature is reviewed and MoH make final decision.	Yes- if community accepts it. More affordable	The review from 3 to 2 then 1 dose in such a short time span makes KI sceptical as believes it shows lack of thorough evidence collection on which schedule is actually effective before recommending to countries.		More affordable	Community acceptance –when changing from 3 to 2 doses communities felt their girls were getting less protection and there was negative media coverage for HPV.	No experience given
Lesotho	No NITAG (in development). EPI and MoH; involvement from members of Reproductive Health Programme and Department of Disease Control. No requirement for WHO recommendation.	Yes	Data from other countries demonstrating non-inferiority	Social mobilisation activity	1 dose vaccine will be more easily integrated into routine immunisation services at health facilities. It will be more cost-effective	No barriers (provided there is a good communication strategy in place)	No experience but currently considering using fractional doses of IPV due to stock shortages

Country	Key decision makers + summary of decision making	Potential support for 1 dose by policy makers?	Evidence necessary to make change	Factors that may influence decision	Perceived advantages for one dose	Barriers to dose reduction	Experience of off-label use?
Liberia	MoH, MoE and Ministry of Gender and Development; IIC (Independent Information Commission) and Technical Advisory Group (TAG). The EPI, ICC and TAG review the evidence together at meetings and form a decision on the best course of action to take.	Yes	WHO position paper, Evidence that one dose is non-inferior to 2/3 doses; evidence on durability of infection (will 1 dose be sufficient protection for life?)	No response	It would likely increase coverage compared to multi-dose vaccine	Acceptability by the community. Good communication strategy required, targeting community leaders, parents and girls (there is a low level of understanding around the HPV vaccine and distrust within the communities around healthcare programmes)	No experience
Country Z	NITAG review evidence with Research Institute of National Health. Then recommendations are made to MoH who have final decision.	Yes- it would have a big economic impact on acquisition and implementation of the vaccine.	Immunogenicity of 1 dose, Will these girls be protected in 30 years (duration of protection). Research on financial impact, is the cost reduction worth reducing the dose?		Economic impact on acquisition and implementation of the vaccine.	Does not think there would be any barriers. Some community acceptance issues perhaps.	No, Discussions on the Polio vaccine but no recommendations made for off label use.
Nigeria	NITAG advises the MoH on what that new new should be introduced	Yes- more feasible and acceptable	'untold experiences' from other researchers with respect to one dose compared to 2/3 dose. For immunogenicity data, they would consider data from other countries, especially African countries Duration of protection			None perceived	No experience
Senegal	NITAG, Comités de Coordination Inter-Agences (CCIA) ; MoH, MoE, Ministry of Finance and civil society representatives and international partners. Recommendations are made by the NITAG. The CCIA take on board these recommendations and review	Yes	WHO position paper ; Evidence that one dose is non-inferior to 2/3 doses	Resources to mobilise and to inform the people about the change in policy	Reduction in resources and finance needed; avoidance of drop-out or loss to follow up of girls.	No barriers perceived, provided there is a good communication strategy in place to address potential issues of acceptability by HCW and community	No experience

Country	Key decision makers + summary of decision making	Potential support for 1 dose by policy makers?	Evidence necessary to make change	Factors that may influence decision	Perceived advantages for one dose	Barriers to dose reduction	Experience of off-label use?
	all the evidence before making the final decision.						
The Gambia	NITAG still in its early stages. Decision for HPV involves the cervical cancer technical working group (consisting of Immunisation programme, Hospitals, gynaecologists, The Medical Council, Civil Society, Department of Reproductive Health and Child Development). This working group examine evidence and make recommendations to the ICC and the MoH who make the final decision.	Yes- The most at risk group are out of school girls, a 1 dose would make it easier to make sure out of school girls were covered. And it would reduce cost slightly.	Non-inferiority of immune responses of 1 dose vs. 2/3 dose		Reaching out of school girls.	KI was confident that there would not be any barriers. Health care workers would welcome a 1 dose and community would accept 1 dose.	No experience of off label use. They have completed a study on how they would introduce a fractional dose of IPV as campaign set up due to stock shortages but this has not been introduced. Decision process for off label use would involve the NITAG who would make recommendations to the ICC and MoH. If it was regarding a 1 dose schedule for HPV the cervical cancer technical working group would also be involved in reviewing evidence with the NITAG.
Uganda	NITAG; The MOH contacts the NITAG for advice and the NITAG will come up with a recommendation after reviewing evidence.	Yes	WHO position paper; evidence on effectiveness of one dose compared with 2 doses of the HPV vaccine.	Resources to mobilise and to inform the people about the change in policy	Only one visit required – perhaps higher coverage will be achieved	Acceptability by HCW or the community	No experience
Zambia	NITAG review with technical working groups and MoH then final decision made by the ICC	Yes	Would like in country data as well as data from other countries of clinical efficacy and immunogenicity		Could potentially combine it with bi-annual health week.	Minimal barriers if there is adequate social mobilisation to ensure community acceptance.	They gave 2 doses of HPV before the manufactures had changed the label.Currently considering fractional dose of IPV.
Zimbabwe	NITAG, MoH, MoE, Department of Communicable and Non-communicable disease units; Child Health team. Evidence is reviewed by the above and the MoH make the final decision.	Yes – provided there is adequate evidence that one dose is as effective as 2/3 doses	Evidence that one dose would still protect girls at given (recommended) age and duration of protection	Interviewee suggested that evidence on efficacy of 1 dose in older women (in their early 20s) would be considered important (linked to	There will be logistical/programmatic advantages as it will be easier to deliver (in one visit)	Acceptance by HCW or the community that 1 dose is as effective as 2/3 doses	Any new vaccines or changes to vaccine administration must be reviewed by the Zimbabwe Medicines Control Authority. The MoH works closely with the regulators who must be notified if

Country	Key decision makers + summary of decision making	Potential support for 1 dose by policy makers?	Evidence necessary to make change	Factors that may influence decision	Perceived advantages for one dose	Barriers to dose reduction	Experience of off-label use?
				age of first marriage) – would they need a booster later?			there is a change to formulation or dose and conduct quality assurance. The only way to waiver the full registration process with the Medicines Control Authority would be in an emergency such as an outbreak
Lao PDR	NITAG, National Immunisation Committee (NIC) made up of: MoH, Ministry of Science, Ministry of Planning and Investment, Ministry of Education; UNICEF. Evidence is reviewed by the NITAG with scientists. They then report to the National Immunisation Committee (NIC) who analyse everything. Once they review the recommendations of NITAG the NIC make a decision about the vaccine.	Yes - provided there is sufficient evidence demonstrating non-inferiority of 1 dose, it would be accepted by policy makers as it would be easier for implementation.	WHO position papers; research from other countries; Evidence on duration of protection	No response	There will be logistical/programmatic advantages as it will be easier to deliver	Acceptance by HCW or the community. Public might query the frequency of dose change (3 ->2 ->1), especially if a neighbouring country may still be using 2-doses. Good communication strategy required	No experience
Nepal	The NITAG called the National Committee for Immunization Practice (NCIP); represented by various government and independent experts	Yes	WHO position paper; long term protection would need to show non inferiority to the 2 -dose or 3- dose schedule. Regional and country level data if available		Easier to implement, cheaper and would require less cold chain storage	None perceived from district or field level but there may be questions on the change at the policy level, county level, committee level and Ministry level – WHO position paper would be needed	Fractional dose of IPV
Solomon Islands	No NITAG. EPI technical working group where the director of reproductive health chairs the committee; recommendation to the MoH executive, permanent secretary for the MoH is the	Yes- It would be very convenient. Teams will go to the schools once a year, if the evidence shows it has an impact and it works	WHO recommendations, the impact of the one dose, what works well in schedules in other countries, what would be the advantage of one dose in our setting (data from	No response other than information they would require.	Logistically easier, time saving for healthcare professionals delivering the vaccine, more sustainable in the long term.	No barriers if sensitization programme is well implemented to make sure it is accepted by the communities.	started an out of cold chain (OCC) project for hep B vaccine but currently still using the monovalent that is currently used in the country we haven't gone as far as to use Controlled

Country	Key decision makers + summary of decision making	Potential support for 1 dose by policy makers?	Evidence necessary to make change	Factors that may influence decision	Perceived advantages for one dose	Barriers to dose reduction	Experience of off-label use?
	chairperson- they make final decision.	and approved through the right channel.	other countries that have trialled one dose).				Temperature Chain (CTC) where we can use the off label vaccine
Argentina	NITAG, or **CONAIN** [Comisión Nacional de Inmunizaciones] is an independent commission; including representatives of scientific societies, a Provincial Representative who represent the 4 regions of the country, and a representative from PAHO. CONAIN makes the recommendations but final decisions are taken by the MoH.	Yes	the non-inferiority of 1 dose vs. 2 dose in terms of immunogenicity and efficacy against cervical disease from international research as well as from national and local data		Fewer doses would guarantee a higher coverage, decrease in financial cost and feasibility/programmatic efforts.	None perceived	Various experiences: including reduced dose of Hepatitis A vaccine – decision made through NITAG (CONAIN)
Bolivia	NITAG, PAHO, WHO, the Immunization National Program. The NITAG check the evidence presented from studies, trials, WHO recommendations and formal recommendations from The Immunization National Program, Pan America Health Organization (PAHO), SAGE (Strategic Advisory Group of Experts) and WHO. The NITAG and OPS then generate formal recommendations to the Health Ministry.	Yes - provided that studies generate evidence demonstrating one dose would provide the same immunity over time as two doses of the vaccine. - It would likely be supported from an economic perspective, and because of the operational and logistical advantages to delivery	WHO position paper, manufacture recommendations; (prospective) evidence showing that 1 dose HPV vaccine has a non-inferior immune response compared to 2/3 doses; formal recommendation from the TAG (Consultant Technical Group) is required from PAHO and the SAGE (Strategic Advisory Group of Experts) from WHO, together with the trial evidence demonstrating non-inferiority of clinical endpoints	Time to the availability of the trial data on the duration of immunity.	Economic and operational advantages, easier to implement and reduces cost.	Acceptability by HCW or the community who are familiar with 2-dose (addressing concerns that 1 dose is as effective as 2/3 doses)	Experience with using the polio vaccine off-label in 2014 due to shortage of available vaccine – the solution was to extend the use of opened vials beyond manufacturer recommendations. Regional Latin American meetings were organised by PAHO, and involved the NITAG and MoH. Evidence was presented from studies demonstrating stability of the vaccine up to 28 days (beyond manufacturer recommendations). There was no resistance from the authorities in the countries. However, there were some challenges encountered with HCW.When considering the use of HPV vaccine off-label, there

Country	Key decision makers + summary of decision making	Potential support for 1 dose by policy makers?	Evidence necessary to make change	Factors that may influence decision	Perceived advantages for one dose	Barriers to dose reduction	Experience of off-label use?
							would need to be evidence demonstrating that 1- dose would have the same immunity over time as the two dose schedule. This evidence on 1 dose should be made available (in addition to WHO endorsement) for presentation at the annual regional meeting
Brazil	The Technical Committee of Immunisation includes paediatricians, immunologists, gynaecologists, and coordinators of immunization at the state and municipal level. The Committee meets twice a year to evaluate evidence and define the immunisation policy around the country.	Yes	immunogenicity, safety, international evidence on infection and clinical outcomes (there are not enough; The Committee also verifies whether changes that are have been already recommended by others regulatory agencies and other countries have been made and any recommendations from PAHO are considered		Higher coverage would be obtained; allow opportunity to extend the vaccination program (older women >15 yrs).	None perceived but training of HCW will be required and social campaigns needed to inform public	Various experiences: including reduced dose of Hepatitis A vaccine (due to low quantities available); decision through NITAG
Colombia	NITAG review and make recommendations with Colombian Federation of Obstetrics and Gynaecology, the Colombian Society of Paediatrics, the Colombian Federation of Perinatology, the National Institute of Health and the National Institute of Oncology, and PAHO then the Ministry of Health and Social Welfare make final decision.	Yes- it is more affordable	Scientific data on immunogenicity. Strong evidence one dose will be as effective as 2-doses in protecting girls in 30 years (duration of protection).		Easier to implement, could incorporate into a routine immunisation programme. For e.g., they have an annual health week where they give children immunisations and vitamins. It could be incorporated into this perhaps.	Community acceptance- there is a lot of mistrust in the vaccine due to claims of side effects. Participation in schools dropped considerably so delivery strategy was switched to health centre. Would need a lot of help to get the public back on board with HPV.	Yes- whooping cough vaccine in pregnant women, and fractionated polio intradermic vaccine (due to low stock)

Country	Key decision makers + summary of decision making	Potential support for 1 dose by policy makers?	Evidence necessary to make change	Factors that may influence decision	Perceived advantages for one dose	Barriers to dose reduction	Experience of off-label use?
Peru	NITAG includes an expert committee from MoH, from different societies (like the paediatrician's society), academic sector and PAHO – the change is discussed and if necessary they would bring more experts and vote on the decision. Once approved, the policy change is implemented.	Yes provided there is evidence demonstrating non-inferiority	WHO position paper; efficacy of two doses), plus the analysis done by the Office of Health Technology Assessment, which includes the cost/benefits evidence. We would need the [international or national] data showing that the effectivity with one dose would be at least the same level showed by two doses.		Increased uptake/coverage	Community acceptance and anti-vaccine groups	MMR vaccine [measles, rubella and mumps]: 2 doses at 12/18 months. The recommendation is 2 doses at 12/48 months; **anti-pneumococci vaccine in children:** 3 doses 2+1: means 1st dose at 2 months, 2nd dose at 4 months and 3rd dose at 12 months
Moldova	NITAG make recommendations to MoH. MoH take on board recommendations from NITAG and WHO and make final decision	Yes- reduces cost and easier to administer.	Immunogenicity		Reduces cost and easier to administer.	Minimal – might need supplementary information campaigns	No experience given

6 References

1. Bosch, F.X., et al., *Comprehensive control of human papillomavirus infections and related diseases.* Vaccine, 2013. **31 Suppl 7**: p. H1-31.
2. IARC, *GLOBOCAN 2012. Cervical Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Available at:* http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
3. Parkin, D.M. and F. Bray, *Chapter 2: The burden of HPV-related cancers.* Vaccine, 2006. **24 Suppl 3**: p. S3/11-25.
4. Denny, L., et al., *Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries.* Lancet, 2016.
5. Schiller, J.T., X. Castellsague, and S.M. Garland, *A review of clinical trials of human papillomavirus prophylactic vaccines.* Vaccine, 2012. **30 Suppl 5**: p. F123-38.
6. WHO *Human papillomavirus vaccines: WHO position paper, October 2014*. Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2014. 465-492.
7. Lazcano-Ponce, E., et al., *Overcoming barriers to HPV vaccination: non-inferiority of antibody response to human papillomavirus 16/18 vaccine in adolescents vaccinated with a two-dose vs. a three-dose schedule at 21 months.* Vaccine, 2014. **32**(6): p. 725-32.
8. Dobson, S.R., et al., *Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial.* JAMA, 2013. **309**(17): p. 1793-802.
9. Toh, Z.Q., et al., *Reduced dose human papillomavirus vaccination: an update of the current state-of-the-art.* Vaccine, 2015. **33**(39): p. 5042-50.
10. Dobson SR, et al., *Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial.* . JAMA : the journal of the American Medical Association, 2013. **17**(309): p. 1793-802.
11. Gallagher, K.E., et al., *Lessons learnt from human papillomavirus (HPV) vaccination in 45 low- and middle-income countries.* PLoS One, 2017. **12**(6): p. e0177773.
12. GAVI Alliance. *HPV vaccine support* http://www.gavi.org/support/nvs/human-papillomavirus/. [cited 2018 18 March].
13. Kreimer, A.R., et al., *Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials.* The Lancet Oncology, 2015. **16**(7): p. 775-786.
14. Kreimer, A.R., et al., *Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine.* J Natl Cancer Inst, 2011. **103**(19): p. 1444-51.
15. Safaeian, M., et al., *Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial.* Cancer Prev Res (Phila), 2013. **6**(11): p. 1242-50.
16. Sankaranarayanan, R., et al., *Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study.* Lancet Oncol, 2016. **17**(1): p. 67-77.
17. LaMontagne, D.S., et al., *Immunogenicity of bivalent HPV vaccine among partially vaccinated young adolescent girls in Uganda.* Vaccine, 2014. **32**(47): p. 6303-11.
18. Toh, Z.Q., et al., *Sustained Antibody Responses 6 Years Following 1, 2, or 3 Doses of Quadrivalent Human Papillomavirus (HPV) Vaccine in Adolescent Fijian Girls, and Subsequent Responses to a Single Dose of Bivalent HPV Vaccine: A Prospective Cohort Study.* Clin Infect Dis, 2017. **64**(7): p. 852-859.
19. Kreimer, A.R., et al., *Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine.* J Natl Cancer Inst, 2011. **103**(19): p. 1444-51.
20. Markowitz, L.E., et al., *Human Papillomavirus Vaccine Effectiveness by Number of Doses: Systematic Review of Data from National Immunization Programs.* Vaccine, In Press.
21. Kavanagh, K., et al., *Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types.* Br J Cancer, 2014. **110**(11): p. 2804-11.
22. Cuschieri, K., et al., *Impact of partial bivalent HPV vaccination on vaccine-type infection: a population-based analysis.* Br J Cancer, 2016. **114**(11): p. 1261-4.
23. Herweijer, E., et al., *Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma.* Jama, 2014. **311**(6): p. 597-603.

24. Blomberg, M., et al., *Dose-Related Differences in Effectiveness of Human Papillomavirus Vaccination Against Genital Warts: A Nationwide Study of 550,000 Young Girls.* Clin Infect Dis, 2015. **61**(5): p. 676-82.
25. Navarro-Illana, E., et al., *Effectiveness of HPV vaccines against genital warts in women from Valencia, Spain.* Vaccine, 2017. **35**(25): p. 3342-3346.
26. Perkins, R.B., et al., *Impact of Number of Human Papillomavirus Vaccine Doses on Genital Warts Diagnoses Among a National Cohort of U.S. Adolescents.* Sex Transm Dis, 2017. **44**(6): p. 365-370.
27. Lamb, F., et al., *Timing of two versus three doses of quadrivalent HPV vaccine and associated effectiveness against condyloma in Sweden: a nationwide cohort study.* BMJ Open, 2017. **7**(6): p. e015021.
28. Gertig, D.M., et al., *Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study.* BMC Med, 2013. **11**: p. 227.
29. Crowe, E., et al., *Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia.* Bmj, 2014. **348**: p. g1458.
30. Brotherton, J.M.L., et al., *Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: Observational cohort of young women in Australia.* Papillomavirus Research, 2015. **1**: p. 59-73.
31. Hofstetter, A.M., et al., *Human Papillomavirus Vaccination and Cervical Cytology Outcomes Among Urban Low-Income Minority Females.* JAMA Pediatr, 2016. **170**(5): p. 445-52.
32. Kim, J., et al., *Effect of human papillomavirus vaccination on cervical cancer screening in Alberta.* Cmaj, 2016. **188**(12): p. E281-8.
33. Pollock, K.G., et al., *Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland.* Br J Cancer, 2014. **111**(9): p. 1824-30.
34. ClinicalTrials.gov. *A Feasibility study for the One-dose Clinical Trial (1DT), Costa Rica.* https://clinicaltrials.gov/ct2/show/NCT02799732?term=1DT&rank=1. 2017 [cited 2017 18 May].
35. ClinicalTrials.gov. *A Dose Reduction Immunobridging and Safety Study of Two HPV vaccines in Tanzanian Girls (DoRIS).* https://clinicaltrials.gov/ct2/show/NCT02834637?term=NCT02834637&rank=1. 2017 [cited 2017 18 May].
36. Research Councils UK. *A randomised observer-blind, non-inferiority trial to evaluate alternative human papillomavirus schedules in young females in West Africa.* http://gtr.rcuk.ac.uk/projects?ref=MC_EX_MR%2FN006070%2F1. 2017 [cited 18 May 2017].