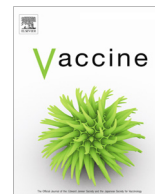


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Review

Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials

Hilary S. Whitworth^{a,d,*}, Katherine E. Gallagher^b, Natasha Howard^c, Sandra Mounier-Jack^c, Gladys Mbwanji^d, Aimée R. Kreimer^e, Partha Basu^f, Helen Kelly^a, Mélanie Drolet^g, Marc Brisson^{g,h}, Deborah Watson-Jones^{a,d}

^a Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

^b Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

^c Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom

^d Mwanza Intervention Trials Unit, National Institute of Medical Research, Mwanza, Tanzania

^e National Cancer Institute, National Institute of Health, Bethesda, MD, United States

^f International Agency for Research on Cancer, World Health Organization, Lyon, France

^g Centre de recherche du CHU de Québec, Université Laval, Québec, Canada

^h Department of Social and Preventive Medicine, Laval University, Québec, Canada

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ABSTRACT

Objectives: This study aimed to systematically review the literature on the efficacy and immunogenicity of single-dose HPV vaccination compared to no vaccination or multi-dose schedules among vaccine trial participants.

Methods: Medline, EMBASE, Global Health Database and Cochrane Central Register of Controlled Trials were searched for publications and conference abstracts (dated January 1999–August 2018) using MeSH and non-MeSH terms for human papillomavirus AND vaccines AND (immunogenicity OR efficacy/effectiveness) AND dosage. Search results were screened against pre-specified eligibility criteria. Data were extracted from included articles, and a narrative synthesis conducted on efficacy against HPV16/18 infection and humoral immunogenicity.

Results: Seven of 6,523 unique records identified were included in the review. Six were nested observational studies of participants randomised to receive two or three doses in three large HPV vaccine trials, in which some participants did not complete their allocated schedules. One small pilot study prospectively allocated participants to receive one or no vaccine dose. Frequency of HPV16/18 infection was low (e.g. <1% for 12-month-persistent infection) in all vaccinated participants up to seven years post vaccination and did not significantly differ by number of doses ($p > 0.05$ in all cases). Frequency of infection was significantly lower in one-dose recipients compared to unvaccinated controls ($p < 0.01$ for all infection endpoints in each study). HPV16/18 seropositivity rates were high in all HPV vaccine recipients (100% in three of four studies reporting this endpoint), though antibody levels were lower with one compared to two or three doses.

Conclusions: This review supports the premise that one HPV vaccine dose may be as effective in preventing HPV infection as multi-dose schedules in healthy young women. However, it also highlights the paucity of available evidence from purpose-designed, prospectively-randomised trials. Results from ongoing clinical trials assessing the efficacy and immunogenicity of single-dose HPV vaccination compared to currently-recommended schedules are awaited.

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* Corresponding author at: LSHTM, Keppel Street, London WC1E 7HT, UK.

E-mail address: hilary.whitworth@lshtm.ac.uk (H.S. Whitworth).

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1. Introduction

In May 2018, the Director General of the World Health Organization (WHO) issued a global call for action to eliminate cervical cancer within the 21st century [1]. Cervical cancer is the second most common cancer among women under 65 years worldwide (after breast cancer), and the leading cause of cancer-related mortality in women under 70 years in many low and middle-income countries (LMICs), particularly in sub-Saharan Africa [2]. Nearly all cases of cervical cancer are caused by infection of the cervix with human papillomavirus (HPV), a sexually transmitted infection that can also result in other anogenital cancers, oral cancers, and clinical sequelae such as anogenital warts (AGW) in men and women [3]. Achieving the WHO's goal of cervical cancer elimination will rely on a number of strategies, including widespread vaccination against HPV infection [4].

There are three commercially-available HPV vaccines, Cervarix® (GlaxoSmithKline (GSK) Biologicals, Belgium), Gardasil® and Gardasil-9® (both Merck & Co., United States of America (USA)), all of which are highly efficacious and immunogenic [5–7]. Whilst the vaccines were initially licensed in a three-dose schedule, in 2014 the WHO changed its recommendation to a two-dose schedule with an interval of at least six months in immunocompetent adolescents aged 9–14 years based on evidence of non-inferiority of post-vaccination antibody levels for two versus three doses (as well as recognition of cost savings and programmatic advantages of a two-dose schedule) [8]. A three-dose schedule over six months is still recommended in persons aged 15 years or older and HIV-positive individuals. Modelling studies using data from high-income countries (HICs) suggest that a number of different vaccination strategies (including or excluding cervical screening of older women) could enable elimination of specific HPV types [9] and cervical cancer [10,11]. However, the current multi-dose schedules are expensive and complex to deliver, particularly for LMICs [12]. As of November 2019, only 23.5% of low-income and 23.4% of

lower-middle income countries had included HPV vaccination in their national immunisation schedule, compared with 79.1% of HICs [13].

Several observational studies have suggested that even a single dose of HPV vaccine may be effective against vaccine-type HPV infection [14,15]. A single-dose schedule could significantly reduce costs of vaccine supply and simplify delivery, thus increasing accessibility and sustainability of HPV vaccination programmes in many LMICs [16]. A recent systematic review, aiming to evaluate vaccine effectiveness against HPV infection and associated clinical disease by number of doses received through national immunisation programmes, found some effectiveness afforded by one dose [17]. Two or three-dose schedules appeared more effective than a single dose. However, a number of limitations in the studies included in the review are likely to have impacted on estimates of effectiveness, most biasing the reduced-dose schedules away from showing effectiveness. For example, women who did not complete the recommended dosing schedules were, on average, of lower socioeconomic status and had earlier reported age of sexual debut, both risk factors for HPV infection at the time of vaccination, potentially resulting in differential rates of undetected prevalent HPV infection across the dose groups at vaccination. Additionally, risk of misclassification of both exposure and outcome were high, the former due to recall bias and the latter due to diagnostic and/or interviewer bias.

Randomised controlled trials (RCTs) designed to compare the efficacy and/or immunogenicity of one dose of HPV vaccine versus two- or three-dose schedules are underway in Costa Rica (ESCUDDO; NCT03180034), Kenya (KEN-SHE; NCT03675256), the Gambia (HANDS; NCT03832049) and Tanzania (DoRIS; NCT02834637) [15,18]. However, efficacy and immunogenicity data already exist from participants who received a single dose of HPV vaccine through earlier clinical trials, typically due to non-completion of a two- or three-dose schedule [14,15]. Whilst still considered as observational evidence, these studies benefit

from inclusion of data on age and HPV infection (viral DNA and antibody) status at enrolment, as well as reliable reporting of vaccination history (i.e. number and timing of doses received), unlike the studies of national immunisation programmes. We are not aware of any previous RCTs that specifically randomised participants to receive a single dose of HPV vaccine. The current study aimed to systematically review the available literature on the efficacy and immunogenicity of single-dose HPV vaccination compared to either no vaccination or to two- or three-dose schedules among participants who received HPV vaccine through clinical trials.

2. Methods

2.1. Study design and research questions

We conducted a systematic review of the literature to address two key research questions. First, 'Does one dose of HPV vaccine provide non-inferior efficacy against HPV infection and associated clinical outcomes, and produce non-inferior immune responses, compared to a two-dose or three-dose HPV vaccination schedule?'. Second, 'Does one dose of HPV vaccine provide efficacy against HPV infection and associated clinical outcomes compared to no HPV vaccination?'. We considered the second research question (to evaluate whether one dose is better than no dose) important from a public health perspective. Even if the protection afforded by a single dose is lower than multi-dose schedules, the impact on population-level infection prevalence could be high if the reduced costs and simplified delivery logistics mean that implementation and coverage increase globally.

Specific objectives were to evaluate whether: (i) rates of vaccine-type HPV infection and associated clinical disease outcomes were comparable following one versus two or three doses of the same HPV vaccine; (ii) rates of vaccine-type HPV infection and associated clinical disease outcomes were significantly lower following one dose of HPV vaccine compared to no vaccination; and (iii) humoral immune responses (antibody seropositivity and titres) induced by one dose of HPV vaccine were comparable to those induced by two or three doses of the same vaccine. Our systematic review was designed to identify and evaluate any previous clinical trials that specifically randomised participants to receive a single dose of HPV vaccine (versus other comparator arms), as well as studies of HPV vaccine clinical trial participants who received only one dose due to non-completion of an alternative dosing schedule that they were originally randomised to receive.

2.2. Search strategy

We searched Medline, EMBASE, Global Health Database and Cochrane Central Register of Controlled Trials systematically for publications and conference abstracts using Medical subject heading (MeSH) and non-MeSH terms under the following themes: human papillomavirus AND vaccines AND (immunogenicity OR efficacy/effectiveness) AND dosage. MeSH terms and operators were adapted as required for each database searched. The specific search terms and limits used for each database are provided in Supplementary Table 1. Searches were limited to articles published between 01 January 1999 (a highly conservative estimate of the earliest date at which data on HPV vaccines might be available) and 14 August 2018, and (where allowed by the database) studies conducted in humans. No language restrictions were applied. All database searches were performed by one author (HSW), and results were exported to a single Endnote library, allowing exclusion of duplicates. HSW additionally hand-searched reference lists

of relevant review articles and all full-text articles identified for inclusion through the database searches.

2.3. Eligibility screening

Search results were screened using pre-defined eligibility criteria, conforming to the Population/Participants, Intervention, Comparator, Outcome, Setting/Study design (PICOS) format (Supplementary Table 2) [19]. Titles and abstracts of all search results were first double-screened for eligibility by two of five reviewers (HSW, KEG, SMJ, NH, GM), based on a limited number of eligibility criteria. Articles were excluded if they did not describe a research study of human participants who had received Cervarix[®], Gardasil[®] or Gardasil-9[®], and/or did not generate data on immunogenicity, infection and/or disease outcomes. Full texts of all remaining and potentially-relevant publications were subsequently double-screened by two of the five reviewers against full eligibility criteria (Supplementary Table 2). For both abstract and full-text screening, eligibility results were confirmed by consensus across duplicate reviews. A third reviewer acted as a tie-breaker where duplicate screening results were discrepant.

2.4. Data extraction

Data were extracted by one author (HSW) using a standardised extraction form. Extracted data included: publication details, target population and setting, study design, study population, intended and actual intervention and comparators, evaluated outcomes, results and findings, and authors' conclusions (Supplementary Table 3). Tabulated results data were independently extracted by a second author (HK).

2.5. Quality assessment

Included studies were assessed for selection bias (i.e. the selection of participants in each dose group), confounding, retention and survival bias, misclassification of exposure and outcome, and statistical analysis approach. Study populations were evaluated for generalisability. Where articles described a sub- or post-hoc analysis of a clinical trial cohort, the 'parent' clinical trial population was additionally assessed for generalisability. Biases were specifically assessed for the probability that they would artificially increase the vaccine efficacy in the one-dose group, or artificially decrease the vaccine efficacy in the three-dose group. Quality assessment findings were compiled in a descriptive synthesis by one author (KEG), and agreed on by all other authors.

2.6. Data synthesis and analysis

A narrative synthesis was conducted by HSW using three elements: (i) development of a preliminary synthesis of findings of included studies; (ii) exploration of relationships within and between studies; and (iii) assessment of the robustness of the synthesis.

Infection endpoints evaluated in this review were as reported in included studies. To standardise statistical reporting of incidence risk, persistence and prevalence, we used raw event and denominator data extracted from each article to calculate proportions (expressed as percentages (%)) and 95% confidence intervals (95% CI). We used the exact (Clopper-Pearson) method for calculating CIs for proportions, assuming a binomial distribution. We further calculated unadjusted infection risk ratios (RRs) and prevalence ratios (PRs) for one- versus two- or three-dose HPV vaccine arms, and for one-dose HPV vaccine versus control (no HPV vaccine) arms. The Haldane-Anscombe correction was used for calculation

of RRs and PRs where no events were detected in one or both comparison arms [20]. Fisher's exact test (2-sided) was used to assess for statistical significance between the groups and to compute p-values. RRs and PRs calculated for one versus two or three doses must be interpreted with caution because of potential for selection bias due to differences in follow up between the groups.

In the absence of a known correlate of protection for HPV vaccination, we did not limit data capture for this systematic review to a specified humoral immunogenicity endpoint and instead included any data on binding and/or neutralising antibody seropositivity, titres and/or avidity. To standardise statistical reporting of seropositivity results, we used extracted data on numbers of participants seropositive for HPV16/18 antibodies and denominator data to calculate seropositivity proportions (%) and 95% CIs, as above. Geometric mean (GM) antibody titres or MFI and 95% CIs are presented as shown in the articles.

Pooling and meta-analysis of data from multiple studies was not considered appropriate due to heterogeneity in study designs and methods. All analyses were performed using Stata, version 15.0 (Stata, College Station, Texas).

2.7. Registration

This review was registered in PROSPERO, and the protocol is available online (registration ID: 110162). Reporting adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19].

3. Results

3.1. Search results

Of 6,523 unique records identified from the four databases (Fig. 1), 6,026 were excluded during title and abstract screening.

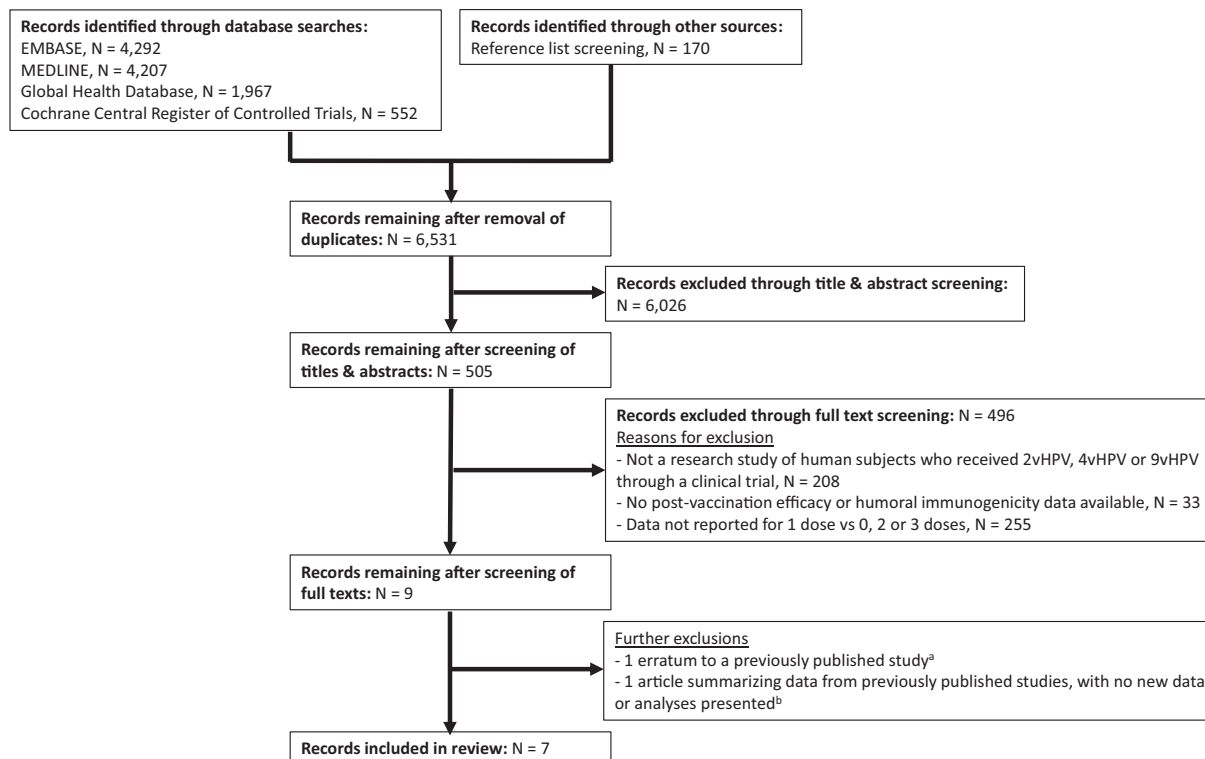


Fig. 1. Systematic review flow diagram. ^aCorrected results presented in the erratum [21] were incorporated into data extraction for the corresponding article [22]. ^bArticle [23] presents previously published data from CVT [22,24–26].

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A further 498 articles were excluded during full-text screening. Nine articles met all eligibility criteria [21–29]. Of these, one [21] was an erratum to a previously published study [22] (that also met inclusion criteria) and one [23] summarised data from multiple previously published studies [22,24–26] (all of which also met inclusion criteria) but did not present any new data or analyses. Therefore, seven articles were included in this review (Fig. 1; Table 1) [22,24–29]. No additional eligible records were identified through screening of reference lists of included articles [22,24–29] and relevant reviews [5,14,17,21,23,30]. Of the seven included studies, six were considered as observational studies because allocation to the dosing schedule arms (i.e. one dose versus alternative schedules or no vaccination) was according to what participants actually received rather than participants being prospectively allocated to a specific dosing schedule [22,24–28]. One small randomised study prospectively allocated participants to one HPV vaccine dose versus no vaccination [29].

3.2. Nested observational studies of one-dose HPV vaccination

All six observational studies were based on data from three clinical trials [27,31,32]. Two studies were based on the International Agency for Research on Cancer (IARC) Trial of Two Versus Three Doses of HPV Vaccine in India [27,28]. Three studies [22,24,26] were based on the Costa Rica Vaccine Trial (CVT) [31], and one [25] was based on combined data from CVT [31] and the Papilloma Trial Against Cancer in Young Adults (PATRICIA) Trial [32].

3.2.1. IARC India HPV vaccine trial

The IARC India HPV Vaccine Trial was designed as an open-label cluster-randomised trial aiming to compare two versus three doses of Gardasil[®] among healthy unmarried females aged 10–18 years in India [27]. Participants were recruited from 188 geographical clusters across nine locations from September 2009 and

Table 1
Summary of studies selected for inclusion in systematic review, in order of date published.

Reference, location	Study design	HPV-vaccinated population (healthy females in all studies)								Control group
		No. in efficacy cohort	No. in immuno. Cohort	Age at vaccination (years)	Baseline HPV16/18 DNA status ^a	Baseline HPV16/18 Serology ^a	Vaccine administered	Vaccination schedule(s)	Follow-up duration	
Kreimer 2011, Costa Rica [24] ^b	Post-hoc analysis of RCT (CVT)	3,575	NA	18–25	HPV16 and 18 positive excluded; Unstated proportion HPV16 or 18 positive	Unstated proportion positive (<i>method not stated</i>)	Cervarix [®]	3d (M0,1,6), 2d (M0,1/0,6) 1d (M0)	Efficacy: 4 years	3,578 healthy females receiving HAV in CVT
Safaeian 2013, Costa Rica [22] ^c	Post-hoc analysis of RCT (CVT)	NA	390	18–25	5% HPV16 or 18 positive	15% HPV16 positive (<i>by IgG ELISA</i>)	Cervarix [®]	3d (M0,1,6), 2d (M0,1/0,6) 1d (M0)	Immuno: 4 years	115 healthy HPV16/18 seropositive females in CVT, pre-vaccination
Kreimer 2015, multiple LMIC & HIC worldwide [25] ^d	Combined retrospective analysis of CVT and PATRICIA data	12,159	NA	15–25	HPV16 and 18 positive excluded; Unstated proportion HPV16 or 18 positive	Unstated proportion positive (<i>method not stated</i>)	Cervarix [®]	3d (M0,1,6), 2d (M0,1/0,6) 1d (M0)	Efficacy: 4 years	12,194 healthy females receiving HAV in CVT or PATRICIA
Sankaranarayanan 2016, India [27] ^e	Prospective observational cohort study	2,649	1,552 – 1,937	10–18	Not measured; unmarried	5% of immuno. cohort HPV16 positive, 5% HPV18 positive; Not reported for efficacy cohort (<i>by Luminex</i>)	Gardasil [®]	3d (M0,2,6), 2d (M0,2/0,6) 1d (M0)	Efficacy: 4 years Immuno: 3 years	None
Scherer 2016, USA [29] ^f	Randomised unblinded pilot intervention study.	NA	5	27–45	Not measured	HPV16 positive (<i>by IgG binding assay</i>)	Gardasil [®]	1d (M0)	Immuno: 6 months	5 healthy HPV16-seropositive unvaccinated females
Sankaranarayanan 2018, India [28] ^e	Prospective observational cohort study	5,655	879 – 1937	10–18	Not measured; unmarried	Not reported	Gardasil [®]	3d (M0,2,6), 2d (M0,2/0,6) 1d (M0)	Efficacy: 7 years Immuno: 4 years	1,481 age-matched healthy unvaccinated females
Safaeian 2018, Costa Rica [26] ^g	Prospective observational cohort study of prior CVT participants	2,449	486	18–25	8% HPV16/18 positive	38% HPV16/18 positive (<i>by IgG ELISA</i>)	Cervarix [®]	3d (M0,1,6), 2d (M0,1/0,6) 1d (M0)	Efficacy & immuno: 7 years	2,386 age-matched healthy unvaccinated females

CVT: Costa Rica Vaccine Trial; D: Dose; HAV: Hepatitis A vaccine; HIC: High income country; HPV: Human papillomavirus; Immuno.: Immunogenicity; LMIC: Low or middle-income country; M: Month; No.: Number; PATRICIA: Papilloma Trial Against Cancer in Young Adults Trial; USA: United States of America.

^a HPV16/18 DNA status refers to PCR/genotyping results in cervical samples; HPV16/18 serology refers to antibody seropositivity results in serum or plasma. Baseline refers to pre-vaccination.

^b Analytic cohort included all 7,153 CVT participants who were seen each year during four years of follow-up, and who were not HPV16 and 18 DNA positive at baseline. At enrolment, participants were randomised to receive HPV vaccine (n = 3,575) or HAV (3,578). HAV control arms received vaccine and were followed up according to the same schedule as HPV vaccine arms.

^c Included all 270 CVT participants who received one or two HPV vaccine doses, and a random selection of 120 participants who received three HPV vaccine doses, all with sera available for each study visit. Pre-vaccination samples from 115 HPV16/18-seropositive CVT participants (DNA status not reported) were used as single timepoint controls.

^d Analytic cohort included all 25,055 CVT and PATRICIA participants who had adequate follow up and available HPV DNA results at baseline, and who were not HPV16 and 18 DNA positive at baseline. Inadequate follow up was defined as no M12 or later visit, or <300 days between the M12 (or later) visit and the last study visit. At enrolment, participants were randomised to receive HPV vaccine (n = 21,013) or HAV (12,042). HAV control arms received vaccine and were followed up according to the same schedule as HPV vaccine arms. Results were additionally reported in the study for a 'naïve' cohort excluding women who were HPV DNA positive for any of 14 high-risk HPV types, HPV16/18 seropositive, and cytology positive at enrolment. Results from the 'naïve' cohort are not included in the current systematic review.

^e Efficacy cohort included all IARC India HPV Vaccine Trial participants (all unmarried at enrolment) who received one or more doses of HPV vaccine and had at least one cervical sample collected during follow up (2,649 up to Y4; 5,655 up to Y7). Collection of cervical samples commenced six months after delivery of a baby or 12 months after marriage, whichever was earlier. Participants for the immunogenicity cohort were selected by convenience sampling; numbers of samples vary at each time point. 1,481 age-matched healthy married and HPV-unvaccinated control participants were enrolled two years after the start of enrolment into the IARC India HPV Vaccine Trial and followed up for four years.

^f Included 10 HPV16-positive females with ≤ 5 heterosexual lifetime partners. Five were randomised to receive one dose of Gardasil[®] and five to receive no vaccine. Both arms were enrolled together and followed up at the same timepoints.

^g Efficacy cohort included all 2,449 HPV-vaccinated CVT participants who agreed to enter the long-term follow up study at the end of the four-year trial. The immunogenicity cohort included a subset of 321 one- or two-dose participants who were tested previously [22] and had sufficient available sera, and a random subset of 165 three-dose participants. 2,836 age-matched healthy and HPV-unvaccinated women were enrolled at the start of the long-term follow up study and followed up for three years.

randomised to either two or three dose arms by computer-generated random allocation. However, in April 2010, the Indian government suspended all HPV vaccine trials for reasons not related to the IARC India HPV Vaccine Trial, and enrolment into the trial therefore stopped early. At the point of suspension, 17,729 participants had been recruited (88.6% of the targeted recruitment of 20,000 girls), but many had not yet completed their full dose schedules. Thus, the clinical trial of two versus three HPV vaccine doses became a prospective observational cohort study of one versus two versus three vaccine doses.

Of the two publications arising from the IARC India HPV Vaccine Trial, the first presents HPV infection and immunogenicity data up to 48 months following the first vaccine dose for participants who received one dose (at day (d) 0), two doses (at d0 and either month (m) 2 or m6) and three doses (at d0, m2 and m6) [27]. The second presents immunogenicity data up to 48 months, and HPV infection data up to seven years, following the first vaccine dose for the same dosing schedules [28]. A supplementary cohort of married, unvaccinated females aged 18–23 years (corresponding to the age of the married vaccinated females at the time of follow up) was recruited from different study sites in India during 2012 to 2015, allowing comparison of HPV infection data between participants vaccinated with one, two or three doses and those who had not received any vaccine doses.

3.2.2. CVT

The CVT was a community-based double-blind RCT aimed at evaluating the efficacy of a three-dose regimen of Cervarix® against persistent vaccine type-specific HPV infection and subsequent development of HPV-associated pre-cancerous lesions among healthy women aged 18–25 years in two regions of Costa Rica [31]. Potential participants were identified from a census of young females conducted in the target regions four years earlier. A total of 7,466 women were recruited from seven study clinics between June 2004 and December 2005, all of whom were randomized to receive three doses of either HPV vaccine or Hepatitis A vaccine (HAV; control). Some women did not complete their full vaccination schedule for reasons including pregnancy, colposcopy referral, other medical conditions, vaccine refusal or missed study visits.

The first identified one-dose study arising from CVT describes a post-hoc analysis of HPV infection data up to 48 months following first vaccine dose in participants who received one dose (at d0), two doses (at d0 and either m1 or m6) and three doses (at d0, m1 and m6) [24]. The second study describes a post-hoc analysis of HPV vaccine-induced immunogenicity up to m48 for the same dosing schedules [22]. A subsequent manuscript extends these HPV infection and immunogenicity data from this study to seven years following first vaccine dose [26]. At the completion of the randomized, blinded phase of CVT, control participants were offered the HPV vaccine. Thus, for the most recent (2018) study, a new cohort of 2,836 unvaccinated women, age-matched to the trial participants, were recruited to replace the original control group [26].

3.2.3. PATRICIA trial

The PATRICIA trial was a large-scale phase III double-blind RCT among healthy women aged 15–25 years from 14 countries in Asia Pacific, Europe, Latin America and North America, also aiming to evaluate the efficacy of a three-dose regimen of Cervarix® [32]. The PATRICIA trial enrolled 18,729 women between May 2004 and June 2005, all of whom were randomised to receive three doses of HPV or HAV (control). 18,644 women received at least one vaccine dose; some participants did not receive all scheduled doses for similar reasons as in CVT.

One study identified for inclusion in our systematic review reports a post-hoc analysis of combined CVT and PATRICIA trial

data [25]. This publication describes HPV infection data up to 48 months following first vaccine dose in participants who received one dose (at d0), two doses (at d0 and either m1 or m6) and three doses (at d0, m1 and m6).

3.3. Intervention study of one-dose HPV vaccination

The only intervention study is a small pilot study conducted in the USA aimed at evaluating memory B cell responses following one dose of HPV vaccine compared to no vaccine in participants with prior HPV16 infection [29]. The study randomised ten healthy HPV16-seropositive women aged 27–45 years at d0 to receive one dose of Gardasil® or no intervention. Humoral immunogenicity results for the two arms are presented up to m6. Additional memory B cell evaluations described in the paper were outside the remit of this review.

3.4. HPV16 and 18 infection

HPV16 and 18 infection results for participants who received one HPV vaccine dose compared to any comparator group are reported in five of the included studies [24–28]. HPV infection-related outcome measures most commonly reported include one-time or cumulative incident infection, and 6 or 12-month persistent infection. Three studies report results up to four years post-vaccination [2], and two up to seven years. Methods used for detection of infection and definitions of endpoints reported by each of the five studies are summarised in Supplementary Table 4.

Table 2 summarises efficacy results for each of the five studies. Incident, persistent and prevalent infection with HPV16 and 18 were extremely low in all participants who received any HPV vaccine, and significantly lower than participants who were either unvaccinated or received HAV. All studies reported comparable efficacy against HPV16 and 18 infection in one-dose and two- or three-dose arms. In CVT, vaccine efficacy against incident 12-month persistent HPV16 or 18 infection at four years post vaccination with 2vHPV (when participants were aged 22–29 years) was 80.9% (95%CI 71.1–87.7%) in the three-dose arm, 84.1% (95% CI 50.2–96.3%) in the two-dose arm, and 100% (95%CI 66.5–100%) in the one-dose arm. In the PATRICIA trial, equivalent vaccine efficacies (when participants were aged 19–29 years) were 88.2% (95% CI 84.6 to 91.0%), 100% (95% CI 60.7–100%) and 76.8% (95% CI –118 to 99.1%), respectively. In the IARC India HPV vaccine trial, no persistent HPV 16 or 18 infections were detected in any of the dosage groups (one, two or three doses) at four years post vaccination with 4vHPV (when participants were 14–22 years).

At seven years post vaccination in CVT (when participants were aged 25–32 years), cumulative incident HPV16/18 infection among 2vHPV recipients ranged from 1.5% (95%CI 0.2–5.3%) in the one-dose arm to 4.3% (95%CI 3.5–5.3%) in the three-dose arm. In the IARC India HPV vaccine trial, cumulative incident HPV16 and 18 infections at the same time point (when participants were aged 17–25 years) was 0.9% (95%CI 0.5–1.7%) in the three-dose arm, 0.9% (95%CI 0.5–1.7%) in the two dose arm, and 1.6% (95%CI 1.1–2.3%) in the one-dose arm. The rates of persistent HPV16 or HPV18 infection in the IARC trial at 7 years were 0.2% (95%CI 0.0–0.9%) in the three-dose arm, 0% each in two-dose and single-dose arms and 1.2% (95% CI 0.7–2.1%) in the unvaccinated women.

None of the included studies reported efficacy against other HPV-associated endpoints, such as pre-cancerous lesions or anogenital warts.

3.5. Immunogenicity results

HPV16 and 18 humoral immunogenicity results for participants who received one HPV vaccine dose compared to any comparator

Table 2
Summarised HPV16/18 infection results up to four and seven years following vaccination from studies reporting efficacy data for participants who received one versus two or three vaccine doses, and versus unvaccinated participants.

Reference	Follow up duration	Infection endpoint ^a	3 dose HPV arm		2 dose HPV arm ^b		1 dose HPV arm		Control arm ^c		RR or PR (95%CI), p value ^d		
			# events / participants	% (95%CI) ^d	# events / participants	% (95%CI) ^d	# events / participants	% (95%CI) ^e	# events / participants	% (95%CI) ^d	1 dose/ 3 doses ^e	1 dose/ 2 doses ^e	1 dose/ control
CERVARIX[®]													
One-time incident and cumulative incident infections													
Kreimer 2015[25]	Mean: 4.0y SD: 0.7y	One-time incident	529/11,110	4.8 (4.4–5.2)	22/611	3.6 (2.3–5.4)	8/292	2.7 (1.2–5.3)	45/251	17.9 (13.4–23.2)	0.6 (0.3–1.1)	0.8 (0.3–1.7)	0.2 (0.1–0.3)
Safaeian 2018[26]	Median: 6.9y IQR: 6.5–7.3y	One-time incident	9/2,042	0.4 (0.2–0.8)	0/78	0.0 (0.0–4.6)	0/134	0.0 (0.0–2.7)	–	–	0.8 (0.0–13.6)	0.6 (0.0–29.2)	–
		Cumulative incident	88/2,036	4.3 (3.5–5.3)	3/78	3.8 (0.8–10.8)	2/133	1.5 (0.2–5.3)	–	–	1.0 (0.3–1.4)	UTC (0.4–1.2)	–
											0.17 (0.1–1.4)	0.36 (0.1–2.3)	–
One-time prevalent infections													
Safaeian 2018[26]	Median: 6.9y IQR: 6.5–7.3y	One-time prevalent	20/2,043	1.0 (0.6–1.5)	1/79	1.3 (0.0–6.9)	0/134	0.0 (0.0–2.7)	158/2,382	6.6 (5.7–7.7)	0.4 (0.0–6.1)	0.2 (0.0–4.8)	0.1 (0.0–0.9)
											0.63 (0.0–6.1)	0.37 (0.0–4.8)	<0.01 (0.0–0.9)
Persistent infections^h													
Kreimer 2011[24]	Median: 4.2y ^g	6 m persistent	37/2957	1.3 (0.9–1.7)	5/422	1.2 (0.4–2.7)	0/196	0.0 (0.0–1.9)	15/188	8.0 (4.5–12.8)	0.2 (0.0–3.2)	0.2 (0.0–3.5)	0.0 (0.0–0.5)
		12 m persistent	25/2957	0.9 (0.6–1.2)	3/422	0.7 (0.1–2.1)	0/196	0.0 (0.0–1.9)	10/188	5.3 (2.6–9.6)	0.3 (0.0–4.8)	0.3 (0.0–5.9)	0.0 (0.0–0.8)
Kreimer 2015[25]	Mean: 4.0y SD: 0.7y	6 m persistent	114/11,104	1.0 (0.8–1.2)	4/611	0.7 (0.2–1.7)	1/292	0.3 (0.0–1.9)	24/250	9.6 (6.2–13.9)	0.3 (0.0–2.4)	0.5 (0.1–4.7)	0.0 (0.0–0.3)
		12 persistent	84/11,104	0.8 (0.6–0.9)	3/611	0.5 (0.1–1.4)	1/292	0.3 (0.0–1.9)	17/249	6.8 (4.0–10.7)	0.5 (0.1–3.2)	0.7 (0.1–6.7)	0.1 (0.0–0.4)
											0.72 (0.1–3.2)	1.00 (0.1–6.7)	<0.01 (0.0–0.4)
GARDASIL[®]													
One-time incident and cumulative incident infections													
Sankaranarayanan 2016 [27]	Median: 4.7y IQR: 4.2–5.1y	Cumulative first incident	2/536	0.4 (0.0–1.3)	4/526	0.8 (0.2–1.9)	10/870	1.1 (0.6–2.1)	–	–	3.1 (0.7–14.0)	1.5 (0.5–4.8)	–
											0.17 (0.7–14.0)	0.059 (0.5–4.8)	–
Sankaranarayanan 2018 [28]	Up to 7y ^f	Cumulative incident	11/1,180	0.9 (0.5–1.7)	11/1,179	0.9 (0.5–1.7)	30/1,823	1.6 (1.1–2.3)	92/1,481	6.2 (5.0–7.6)	1.8 (0.9–3.5)	1.8 (0.9–3.5)	0.3 (0.2–0.4)
											0.1 (0.9–3.5)	0.1 (0.9–3.5)	<0.01 (0.2–0.4)
Persistent infections^h													
Sankaranarayanan 2018 [28]	Up to 7y ^f	12 m persistent	1/604	0.2 (0.0–0.9)	0/608	0.0 (0.0–0.6)	0/959	0.0 (0.0–0.4)	14/1,141	1.2 (0.7–2.1)	0.2 (0.0–5.1)	0.6 (0.0–31.9)	0.0 (0.0–0.7)
											0.39 (0.0–5.1)	UTC (0.0–31.9)	<0.01 (0.0–0.7)

CI: confidence interval; HPV: Human papillomavirus; IQR: Inter-quartile range; M; Month; PR: Prevalence ratio; RR: Risk ratio; SD: Standard deviation; UTC: Unable to compute; Y: Year.

^a Definitions of infection endpoints used in each study are provided in Supplementary Table 4.

^b Results are shown only for two-dose arms where participants received dose one at day 0 and dose two at day 180.

^c Results are shown for one-dose control vaccine (HAV) arms for Kreimer et al. [24] and Kreimer et al. [25], and unvaccinated control arms for Sankaranarayanan et al. [28] and Safaeian et al. (2018; persistent infection only) [26]. Comparison of the single-dose HPV vaccine arm with the single-dose HAV (rather than multi-dose HAV) arm in the Costa Rica trial minimises the potential for selection bias due to differences in follow up. No control arm was reported in Sankaranarayanan et al. [27].

^d Proportions (%), unadjusted RRs and PRs, 95%CI and 2-sided Fisher's exact p values were calculated by the authors of this review using data provided in the included articles. Haldane-Anscombe correction was used for calculation of RRs and PRs where no events were detected in one or both comparison arms [20]. In most cases, the 95%CI for proportions calculated by the authors of this review matched those reported in the included studies. Where they do differ, the 95%CI calculated in this review are wider than those reported in the articles.

^e Risk and prevalence ratios calculated for one versus two or three doses must be interpreted with caution because of potential for selection bias due to differences in follow up between the groups.

^f Mean, median, IQR or SD were not reported for this study.

^g IQR or SD were not reported for this study.

^h Sankaranarayanan et al. detected no persistent infections in any arm up to the median follow up of 4.7y among 838 women with two or more samples available for analysis [27].

ⁱ STATA does not compute a p value using Fisher's exact test where both numerators are 0.

group are reported in five of the included studies [22,26–29]. HPV16 and 18 immunogenicity-related outcome measures most commonly reported include: seropositivity, geometric mean (GM) antibody levels (titres or MFI) and antibody stability. Some studies additionally reported on antibody avidity (the strength at which an antibody binds to an antigen) or seropositivity and/or titres of neutralising antibodies (antibodies that specifically prevent viral infection of a cell though neutralisation of its biological effect). Methods used for measurement of immune responses and, where applicable, definitions of endpoints reported by each of the five studies are summarised in Supplementary Table 5.

Table 3 summarises seropositivity, antibody level and stability results for the four studies comparing one dose versus other vaccine dosage schedules. The proportions of participants reportedly seroconverting to HPV16 and/or 18 antibody-positive were generally high in all HPV vaccine arms, reaching 100% in some studies. However, the definition of seroconversion differs between studies (Supplementary Table 5). Antibody levels were significantly lower with one dose than for two or three doses. However, whilst levels for two and three-dose arms declined following an initial increase, plateauing thereafter, this trend was typically less pronounced in the one-dose arms, in which levels remained more stable throughout follow-up (Fig. 2). Furthermore, antibody levels were significantly higher in participants vaccinated with one dose of HPV vaccine compared to pre-vaccination levels in participants with natural infection (where included).

In CVT, post-vaccination HPV16/18 antibody avidity was lower in the reduced dosage groups; however, avidity remained stable between the 4 and 7-year time points within each of the dosage groups. Proportions of CVT participants who were seropositive for HPV16/18 neutralising antibodies at month 48 were similar across the HPV vaccine dosage arms. In the IARC India HPV vaccine trial, HPV16/18 antibody avidity was comparable across the dosage groups at 18 months post vaccination, but neutralising antibody levels were lower in reduced dose schedules.

In the small randomised study by Scherer *et al.*, four of the five HPV16-seropositive women receiving one dose of HPV vaccine exhibited increases in HPV16 and 18 binding antibody levels and neutralisation against HPV16 by one month following vaccination, and responses remained increased compared to baseline at month 6. Two women had increases in HPV16 and 18 binding antibody levels at one week post vaccination. Conversely, non-neutralising antibodies were observed in women with natural HPV infection, and no changes in antibody responses were seen among the five infected women who did not receive any HPV vaccine dose.

3.6. Quality assessment

The quality of evidence from all seven studies was assessed, and a descriptive synthesis is presented in Supplementary Table 6 for the CVT, PATRICIA and IARC India HPV Vaccine trials. The presence of enrolled comparator groups of young women who did not receive HPV vaccine in these trials allowed authors to assess the risk of bias and the presence of a number of confounders that could have artificially inflated the vaccine efficacy in the one-dose group or deflated the vaccine efficacy in the three-dose group. Sociodemographic characteristics (e.g. age, household income, education level), HPV seropositivity at baseline, and the incidence of non-vaccine type HPV infections during follow up (proxy measures for participants' risk of HPV16/18 exposure during follow-up) were very similar across comparator groups (dose groups and control groups). Participants' reasons for non-completion of the vaccination schedule and rates of loss-to-follow up (indicators of survival bias) were also very similar across all comparator groups and were controlled for in some analyses conducted by the authors of the included studies (but not analyses conducted in this systematic

review). The risk of exposure or outcome misclassification was low and the included analyses were appropriate.

The intervention study by Scherer *et al.* was a very small ($n = 5$ per arm) pilot study among HPV16 seropositive women, limiting the precision of estimates and generalizability of results. Allocation to one-dose HPV vaccine versus no intervention was randomized but not blinded; however, the latter point likely has little implication as the study endpoints were immunological.

4. Discussion

Our systematic review presents strong epidemiological evidence that a single dose of HPV vaccine may be protective against HPV16 and HPV18 infection. The five included studies that evaluated efficacy endpoints found that HPV16/18 infection was rare (0% to <5% for one-time incident infection, and 0% to <1% for 12-month persistent infection) among participants who received any HPV vaccination up to four or seven years after dose one, regardless of the number of doses received [24–28]. Infection rates were significantly lower in all HPV vaccine arms than in study participants who were either unvaccinated or received control vaccine. Furthermore, no study found any difference in HPV16/18 infection incidence, persistence or prevalence between participants who received one versus two versus three HPV vaccine doses by year four or year seven.

Our findings contrast with the conclusions of a previous systematic review of data from national HPV vaccination programmes, which included two studies evaluating efficacy of Cervarix[®] against HPV16/18 prevalence at 4–5 years post vaccination [17]. One study reported statistically significant effectiveness for one, two and three doses of HPV vaccine compared to no vaccination, but effectiveness was lower for one-dose than for multi-dose schedules [33]. The other study found statistically significant effectiveness for three, but not one or two, vaccine doses compared to no vaccination [34]. Other studies included in the same review reported either no efficacy of single-dose HPV vaccination, or reduced efficacy compared to two- or three-dose schedules, for other clinical endpoints including anogenital warts and cervical abnormalities [17]. However, as reported by the review authors, several features of the included studies could have led to an underestimation of the effectiveness of one or two-dose schedules. In particular, recipients of one- or two-doses in national programmes where three-dose schedules were recommended proved to be, on average, older at vaccination, of lower socioeconomic status, and younger at first sexual exposure. These factors may be associated with higher risk of HPV infection at vaccination and exposure post-vaccination, both of which would adversely impact vaccine effectiveness estimates of one or two doses.

CVT and PATRICIA trial participants were tested for HPV infection prior to vaccination, enabling the subsequent analyses included in those studies and our review to evaluate effectiveness of HPV vaccine by number of doses received specifically among participants who were HPV16/18 DNA negative at baseline. Although the IARC India HPV Vaccine Trial did not test for HPV infection at baseline, participants were young unmarried females who were likely to have a very low risk of HPV infection at baseline. Additionally, regular sampling throughout the follow-up period in CVT, PATRICIA and the IARC India HPV Vaccine Trial allowed detection of new infections occurring post-vaccination. In the individual study analyses, vaccine efficacies for each HPV vaccine dose group were calculated against control groups who did not receive HPV. Control groups and their respective HPV vaccine dose groups were balanced with respect to potential confounders, such as proxies of sexual activity and economic status.

Table 3
Summarised HPV16/18 seroprevalence, GM antibody level and antibody avidity results up to 84 months following vaccination from studies reporting immunogenicity data for participants who received one versus two or three doses.

Reference	Time point	# seropositive ^b /participants (% Seropositive, 95%CI ^c)			GM titers/MFI (95%CI)			
		3 doses	2 doses ^a	1 dose	3 doses	2 doses ^a	1 dose	Naturally-infected
CERVARIX[®]								
HPV16								
Safaeian 2013 [22] ^d	D0	18/120 (15.0, 9.1–22.7)	–	6/78 (7.7)	<LOD	<LOD	<LOD	–
	M6	–	–	–	724 EU/ml	102 EU/ml	145 EU/ml	–
	M12	–	–	–	2,034 EU/ml	1,484 EU/ml	115 EU/ml	–
	M24	–	–	–	1,115 EU/ml	837 EU/ml	124 EU/ml	–
	M36	–	–	–	899 EU/ml	642 EU/ml	136 EU/ml	–
	M48	78/79 (98.7, 93.1–100.0)	52/52 (100.0, 93.2–100.0)	120/120 (100, 97.0–100.0)	748 EU/ml (648–865)	520 EU/ml (422–641)	137 EU/ml (106–178)	15 EU/ml (11–19)
Safaeian 2018 [26]	M48	2,043/2,043 (100.0, 99.8–100.0)	79/79 (100.0, 95.4–100.0)	134/134 (100.0, 97.3–100.0)	803 EU/ml (708–909)	555 EU/ml (447–690)	205 EU/ml (165–255)	–
	M84	2,043/2,043 (100.0, 99.8–100.0)	79/79 (100.0, 95.4–100.0)	134/134 (100.0, 97.3–100.0)	716 EU/ml (630–814)	460 EU/ml (367–576)	194 EU/ml (158–237)	–
HPV18								
Safaeian 2013 [22] ^d	D0	–	–	–	<LOD	<LOD	<LOD	–
	M6	–	–	–	408 EU/ml	53 EU/ml	76 EU/ml	–
	M12	–	–	–	827 EU/ml	763 EU/ml	71 EU/ml	–
	M24	–	–	–	471 EU/ml	446 EU/ml	69 EU/ml	–
	M36	–	–	–	369 EU/ml	358 EU/ml	74 EU/ml	–
	M48	–	–	–	335 EU/ml (285–392)	305 EU/ml (238–391)	70 EU/ml (54–91)	15 EU/ml (12–19)
Safaeian 2018 [26]	M48	2,043/2,043 (100.0, 99.8–100.0)	79/79 (100.0, 95.4–100.0)	134/134 (100.0, 97.3–100.0)	360 EU/ml (313–414)	296 EU/ml (240–366)	112 EU/ml (93–134)	–
	M84	2,043/2,043 (100.0, 99.8–100.0)	79/79 (100.0, 95.4–100.0)	134/134 (100.0, 97.3–100.0)	322 EU/ml (281–369)	270 EU/ml (221–330)	125 EU/ml (105–150)	–
GARDASIL[®]								
HPV16								
Sankaranarayanan 2016 [27] ^e	D0	46/1,000 (4.6, 3.4–6.1)	52/937 (5.5, 4.2–7.2)	–	MFI 11 (10–12)	MFI 9 (8–10)	–	–
	M7	308/308 (100.0, 98.8–100.0)	316/317 (99.7, 98.3–100.0)	–	MFI 5,460 (5,195–5,738)	MFI 6,125 (5,785–6,485)	–	–
	M12	–	–	260/528 (49.2, 44.9–53.6)	–	–	MFI 106 (96–116)	–
	M18	311/313 (99.4, 97.7–99.9)	312/314 (99.4, 97.7–99.9)	255/476 (53.6, 49.0 – 58.1)	MFI 1,209 (1,105–1,323)	MFI 1,222 (1,116–1,338)	MFI 113 (102–126)	–
	M36	225/271 (83.0, 78.0–87.3)	197/278 (70.9, 65.1–76.1)	166/510 (32.5, 28.5–36.8)	MFI 221 (197–247)	MFI 163 (147–181)	MFI 72 (66–78)	–
Sankaranarayanan 2018 [28]	M36	271/271 (100.0, 98.6–100.0)	278/278 (100.0, 98.7–100.0)	510/510 (100.0, 99.3–100.0)	MFI 221 (197–247)	MFI 163 (147–181)	MFI 72 (66–78)	–
	M48	239/239 (100.0, 98.5–100.0)	243/243 (100.0, 98.5–100.0)	397/397 (100.0, 99.1–100.0)	MFI 196 (170–226)	MFI 197 (172–225)	MFI 86 (75–99)	–
HPV18								
Sankaranarayanan 2016 [27] ^e	D0	41/1,000 (4.1, 3.0–5.5)	63/937 (6.7, 5.2–8.5)	–	MFI 6 (5–7)	MFI 5 (4–5)	–	–
	M7	308/308 (100.0, 98.8–100.0)	317/317 (100.0, 98.8–100.0)	–	MFI 2,942 (2,733–3,167)	MFI 3,068 (2,812–3,347)	–	–
	M12	–	–	304/528 (57.6, 53.2–61.8)	–	–	MFI 50 (45–55)	–
	M18	307/313 (98.1, 85.9–99.3)	305/314 (97.1, 94.6–98.7)	259/476 (54.4, 49.8–59.0)	MFI 377 (337–422)	MFI 269 (241–299)	MFI 46 (40–51)	–

(continued on next page)

Table 3 (continued)

Reference	Time point # seropositive ^b /participants (% Seropositive, 95%CI ^f)			GM titers/MFI (95%CI)			Naturally-infected
	3 doses	2 doses ^a	1 dose	3 doses	2 doses ^a	1 dose	
M36	249/271 (91.9, 88.0–94.8)	238/278 (85.6, 80.9–89.5)	271/510 (53.1, 48.7–57.5)	MFI 184 (162–208)	MFI 117 (104–132)	MFI 45 (41–49)	–
Sankaranarayanan 2018 [28]	271/271 (100.0, 98.6–100.0)	278/278 (100.0, 98.7–100.0)	510/510 (100.0, 99.3–100.0)	MFI 184 (162–208)	MFI 117 (104–132)	MFI 45 (41–49)	–
M48	239/239 (100.0, 98.5–100.0)	243/243 (100.0, 98.5–100.0)	397/397 (100.0, 99.1–100.0)	MFI 133 (115–154)	MFI 120 (105–136)	MFI 47 (41–53)	–

CI: confidence interval; HPV: Human papillomavirus; M Month; RR: Risk ratio.

^a Results are shown only for two-dose arms where participants received dose one at day 0 and dose day at day 180.

^b Definitions of seropositivity used in each study are provided in Supplementary Table 5.

^c Seropositivity proportions (%) and 95%CI were calculated by the authors of this review using data provided in the included articles.

^d HPV GMTs (95%CI) among 113 unvaccinated but naturally infected controls were 15 (11–19) for HPV16 and 15 (12–19) for HPV18 [22]. This article did not report rates of seropositivity for M6, 12, 24 or 36 for HPV16, or at any time point for HPV18. It also did not report 95%CI for HPV16/18 antibody titres prior to M48; 10th, 25th, 75% and 90th percentiles were reported in the article but not presented in this review.

^e Month 48 results not shown as reported only for two- and three-dose arms, not for the one-dose arm.

^f Month 48 results not shown as reported only for two- and three-dose arms, not for the one-dose arm.

Direct comparisons of vaccine efficacy across different HPV vaccine dose groups (for example, one versus two doses, and one versus three doses, as presented in this review) could be affected by selection bias by comparing potentially different populations. The risk is that the one-dose groups are, on average, less healthy and more at risk of HPV infection than the three-dose groups. Despite this potential bias, vaccine efficacy is high in the one-dose group, and point estimates are comparable across the dose groups (albeit with wide confidence intervals). Furthermore, in the CVT, PATRICIA and IARC India HPV Vaccine trials the incidence of infection with HPV genotypes not targeted by the allocated HPV vaccines was similar across vaccinated participants, regardless of the number of doses received, providing further reassurance against potential bias and confounding relating to underlying characteristics of participants not completing their allocated vaccine schedule.

From the five included studies reporting immunogenicity endpoints, most (and, in some studies, all) participants who were HPV16/18 seronegative at baseline and vaccinated against HPV seroconverted to HPV16 and/or 18, regardless of the number of doses received [22,26–28]. HPV16/18-specific antibody levels were significantly higher post-vaccination in participants who received multiple vaccine doses compared to those who received only one dose. However, levels were significantly higher in one-dose participants than in unvaccinated controls with natural infection. A recent systematic review found that HPV antibodies acquired through natural HPV infection were protective against later HPV infection in females [35]. Thus, the observed antibody levels induced by single-dose HPV vaccination are likely to be clinically beneficial. Also, whilst levels among two- or three-dose participants typically increased up to approximately 12 months after vaccination and then declined significantly before plateauing, levels in one-dose participants remained relatively stable after the initial increase (up to the end of follow up in each study). In the few studies evaluating neutralising antibodies, seroconversion rates were very high across all HPV vaccine arms but, again, absolute levels were significantly higher in those receiving multiples doses.

Two key studies have compared immune responses following one- versus multi-dose HPV vaccination provided through national immunisation programmes [36,37]. Similarly to the study results included in our review, LaMontagne *et al.* found higher HPV16/18 GM titres approximately 40 months following vaccination in two- and three-dose compared to one-dose Cervarix[®] recipients (aged 10–11 years at the time of vaccination; all female) in Uganda [36]. Toh *et al.* detected lower HPV16/18-specific neutralising antibody titres among Fijian girls aged 15–19 years who received one compared to two or three doses of Gardasil[®] six years previously, though titres were five to 30 times higher in one-dose participants than in unvaccinated controls [37]. However, in both studies, the percentage of girls who were seropositive for vaccine-type HPV antibodies was high across all vaccinated arms, regardless of the number of doses received. In a subsequent Canadian study of girls aged 13–18 years, all were HPV16/18 seropositive following a single dose of Gardasil[®] provided through the national vaccination program three to eight years previously [38]. These immunogenicity studies are informative but affected by many of the same limitations as the national programme-based efficacy studies included in the previous systematic review by Markowitz *et al.* [17].

Although the evidence suggests that magnitudes of antibody responses are lower following single-dose HPV vaccination compared to multi-dose schedules, this may have limited clinical significance. All three studies in our systematic review evaluating infection and immunogenicity endpoints within the same populations reported comparable efficacy of one-, two- and three doses of HPV vaccination against HPV16/18 infection despite differences in antibody levels between the groups [26–28]. The lower limit of

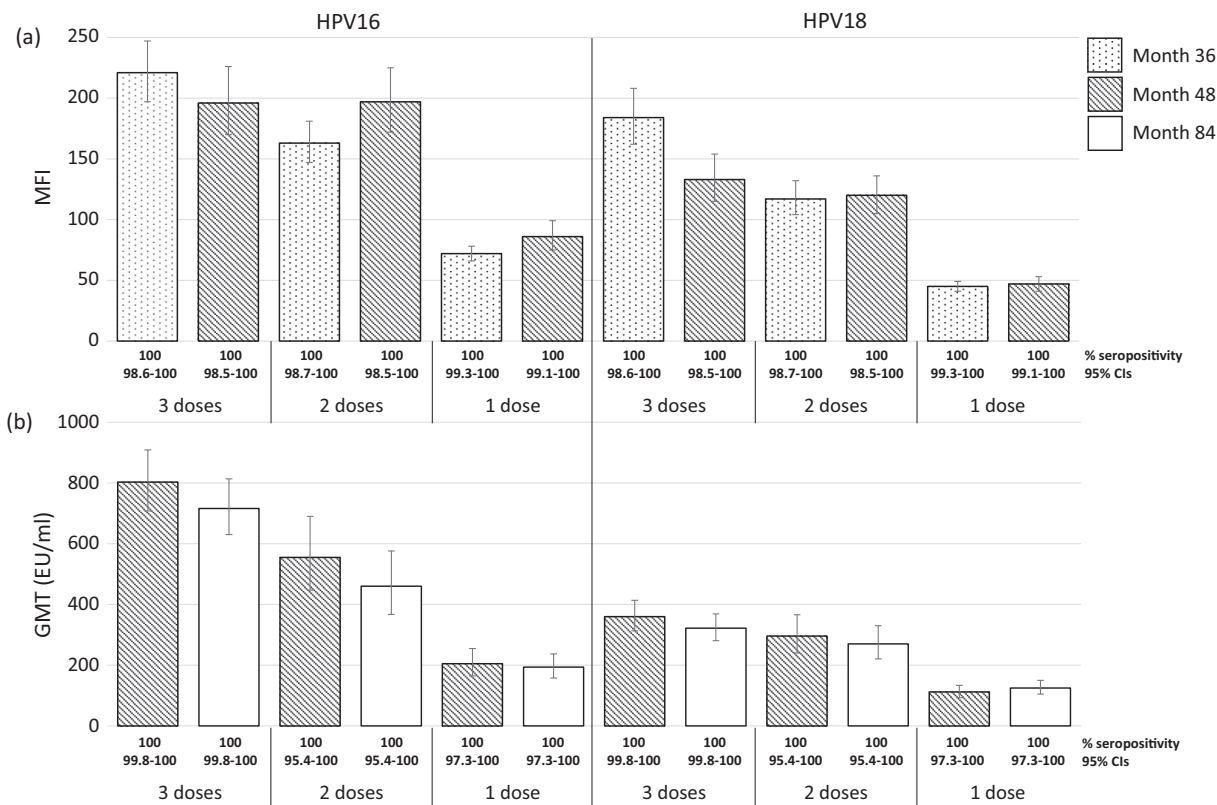


Fig. 2. Magnitude of anti-HPV16 and 18 antibody responses (a) at 36 and 48 months post vaccination with 3, 2 or 1 dose of Gardasil in the IARC India HPV vaccine trial, and (b) at 48 and 84 months post vaccination with 3, 2 or 1 dose of Cervarix in the CVT. Data shown are MFI with 95% CIs for Gardasil and GMT (EU/ml) with 95% CIs for Cervarix. Corresponding seropositivity rates (and 95% CI) for each dosage group at the same time point are shown below the bars. Definitions of seropositivity in the two trials are shown in Supplementary Table 5.

antibody levels required to provide protection against HPV infection is unknown [39].

This systematic review is limited by the small number of studies reporting clinical trial-based evaluations of single-dose HPV vaccination, and in some studies, limited sample size of the one-dose group. We identified only seven publications describing studies of single-dose HPV vaccination compared to either no vaccination or two- or three-dose schedules. Six were observational studies arising from three randomised clinical trials (that were investigating efficacy and immune responses in three doses versus control, or two versus three doses), with participant allocation to one-dose or comparator arms occurring retrospectively (due to non-completion of originally-allocated schedules). Only one very small pilot study allocated participants to one-dose versus no-dose arms prospectively.

Furthermore, our review was not able to evaluate the effects of gender, age or HIV status, as proposed in our study protocol, as all studies conducted to date have been in young, healthy females. This highlights a paucity of evidence in alternative target populations. Additionally, all trial-based data of single-dose HPV vaccination published to date come from Cervarix® and Gardasil® recipients; no studies have evaluated Gardasil-9®. Whilst 12 national programme-based studies included in the published review by Markowitz *et al.* report on vaccine efficacy against AGW and cervical abnormalities [17], the trial-based efficacy studies in our trials-based review reported only on HPV infection endpoints.

Studying CVT, PATRICIA and IARC India HPV Vaccine Trial-derived cohorts for evaluation of single- versus multi-dose vaccination schedules minimises many of the biases that confound the national programme-based studies, despite the retrospective allo-

cation to exposure versus comparator arms. However, retrospective allocation is still sub-optimal, so this approach does not preclude the requirement for gold-standard purpose-designed, prospectively-randomised, controlled trials. Also, although the point estimates of vaccine effectiveness in the trial-based observational studies are high, the confidence intervals around the estimates are very wide, which limits any strong conclusions from these data on whether one dose is sufficient for protection.

It was not possible to combine results of the included studies and perform a meta-analysis in this review due to considerable heterogeneity between the studies (with respect to the vaccine used, reasons for participants receiving a single dose, time points evaluated, efficacy outcomes measured and laboratory assays used). Thus, the data presented in our systematic review do not benefit from the increased power and improved estimates of the size of effect that are usually achieved through performing a meta-analysis. Investigators conducting new and ongoing clinical trials and observational studies aiming to evaluate single-dose HPV vaccination are now working together to standardise methods, time points, endpoints and definitions [15,39]. This will allow immunobridging between immunogenicity and efficacy trials, as well as meta-analysis of data, which will be important for further development of mathematical models for projecting long-term sustainability of protection and immune responses.

5. Conclusions

Our systematic review of the literature on single-dose HPV vaccination from clinical trials supports the premise that one dose may be as effective in preventing HPV infection as two or three doses in healthy young females up to seven years post-

vaccination. Seropositivity rates were high among all HPV vaccine recipients, also up to seven years post-vaccination. However, sustained durability of the immune response will be fundamental to longer-term protection, so further follow up of participants who received different dosing schedules is important.

Whilst producing promising results, our systematic review also highlights the existing paucity of available evidence appropriate for informing policies and guidelines on HPV vaccination strategies. Ongoing clinical trials [14,18] assessing the efficacy and immunogenicity of single-dose HPV vaccination compared to currently-recommended schedules will go a long way towards addressing this knowledge gap for the target populations in those trials. However, research on the efficacy of, and immune responses to, single-dose HPV vaccination may need to be expanded to other target groups such as boys, alternative age groups and HIV-positive individuals, and should evaluate all licensed HPV vaccines, as well as promising new vaccines currently in development.

6. Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Author contributions

HK, HSW and KEG developed the review protocol with input from all authors. HSW developed the search strategy with input from HK, KEG and DWJ. Database searches were performed by HSW, and screening of search results according to eligibility criteria was performed by HSW, KEG, NH, SMJ and GM. HSW extracted data from included articles, produced data tables, performed data analyses and conducted a narrative synthesis. KEG contributed to planning of data presentation and analyses. Final data tables and analyses were verified by HK, and all authors reviewed and agreed upon the narrative synthesis. Quality assessment of included studies was conducted by KEG, and reviewed and agreed upon by all authors. Writing of the manuscript was led by HSW and all authors contributed.

Conflict of interest

DWJ and ARK are investigators in ongoing clinical trials specifically designed to evaluate the efficacy and/or immunogenicity of one dose compared to two and/or three doses of HPV vaccine; the DoRIS study (DWJ) and the ESCUDDO study (ARK). All other authors have no conflicts of interest to declare.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.12.017>.

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