



Review

Female human papillomavirus (HPV) vaccination: Global uptake and the impact of attitudes

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ABSTRACT

Human papillomavirus (HPV) is the causative agent in cervical cancer and has been implicated in a range of other malignancies. Preventative vaccines are now internationally available and provide high levels of protection from common viral strains. The introduction of a comprehensive vaccination programme (except 'program' in computers) could prevent over 60% of current cervical cancer cases, but this is dependent on such programmes achieving a high level of coverage. In this review, we summarise the current trends in female HPV vaccination coverage throughout the world, and place it in the context of available research on attitudes towards vaccination amongst the public and health professionals.

Where countries have the resources for mass vaccination programmes, uptake has varied. School-based opt-out programmes consistently achieve highest coverage, whilst countries and regions without systematic vaccination schemes have low coverage. In all countries, the success of vaccination programmes is dependent on the support of the public and healthcare professionals. Whilst public acceptance is dependent on multiple factors, it has repeatedly been shown that recommendation by a health professional, particularly clinicians, is key to vaccine uptake. Worryingly, it appears that a proportion of clinicians still have significant reservations about promoting vaccination, particularly for younger age groups. A commitment now, to fully educating both the public and clinicians, has the potential to make a dramatic future impact.

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1. Cervical cancer: a global inequality

Cervical cancer is responsible for over 275,000 female deaths each year, with more than 500,000 new diagnoses annually [1]. Over 85% of deaths occur in low- and middle-income countries

(LMICs), with India alone accounting for over a quarter of cases. Other areas with the highest incidence rates include parts of Africa and South America, whilst lowest rates are seen in Europe, Western Asia and North America [1]. In East Africa, age standardised rates of cervical cancer mortality are 25.3 per 100,000, compared to just 1.7 in North America. Even within countries with low cervical cancer mortality, cancer risk is significantly affected by deprivation and ethnicity. In the USA, African-American women are twice as likely to die from cervical cancer when compared to non-Hispanic white women, whilst States in the Deep South experience higher

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mortality rates than Northern States [2]. In the UK also, the most vulnerable sectors of society consistently show an increased burden of disease [3].

The huge disparity in cancer deaths between high and LMICs, while multifactorial, is largely due to the lack of access to cervical cancer screening programmes. In the UK for example, it is estimated that the introduction of a structured screening programme, in the face of a rising incidence, has prevented over 80% of potential cancer deaths, or up to 5000 women each year [4]. Within countries with screening programmes, the increased mortality seen for certain ethnic minorities and lower socioeconomic groups also appears largely explained by differences in the uptake and follow-up of screening [5,6]. In LMICs, comprehensive screening is extremely difficult to institute. Such countries lack the infrastructure to support comprehensive national programmes, and implementing and maintaining a screening service would be prohibitively expensive [7].

2. Human papillomavirus and vaccination

Human papillomavirus (HPV) is now widely acknowledged as the causative agent in cervical cancer. Multiple HPV strains are capable of infecting the anogenital tract, although only a high-risk subset of these are oncogenic. The two most common are HPV-16 and -18, which between them are found in 60–78% of cervical squamous cell carcinomas and 72–94% of adenocarcinomas [8]. High-risk HPV infections are also implicated in anogenital (anal, penile, vulval, vaginal) and oropharyngeal cancers [9].

Two HPV vaccines are currently commercially available. Gardasil, a quadrivalent vaccine developed by Merck, protects against two oncogenic strains (16, 18) and two responsible for anogenital warts (6, 11). GlaxoSmithKline's Cervarix covers only HPV-16 and -18. Evidence suggests these vaccines provide nearly 100% protection for these strains [10]. Moreover, Cervarix appears to provide cross protection against other oncogenic strains (HPV-31/33/45) [11]. For both vaccines, it is currently recommended that girls have 3 doses over a period of 6 months, with vaccination commencing before sexual debut [12], conventionally beginning between ages 10 and 13.

Based on an assumed efficacy and coverage of nearly 100%, it is estimated that a comprehensive vaccination programme could result in up to a 76% reduction in cervical cancer-related deaths [13]. If coverage falls to 80%, only 60% of deaths would be prevented, though this does not take into account the potential benefit of herd immunity. Modelling outcomes in the poorest countries, it was predicted that 70% coverage would be sufficient to achieve reductions in lifetime risk of cervical cancer of between 31.1–60.1%. In a 10-year scenario, a comprehensive international vaccination programme with 70% coverage was predicted to prevent the future deaths of a staggering 3 million women vaccinated as adolescents [14].

In contrast to cervical cancer screening, vaccination programmes have the potential to be very cost-effective in both the poorest [13], as well as high income [14], countries, although this will be dependent on equitable vaccine pricing. The advent of cervical cancer vaccines provides an opportunity to tackle the health burden experienced by both marginalised sectors within developed countries, and low-income nations. Whilst the cost and practicalities of the transport and administration of an injectable, temperature-sensitive vaccine are all critical factors that require careful consideration, realising the maximum benefits of vaccination will require the mass participation of the public and health professionals.

Despite proven clinical efficacy, the coverage of vaccination programmes has varied considerably, both within and between

countries. With current and future generations of vaccines, the only barrier to significant clinical benefit is now a case of increasing coverage [10]. Whilst considerations for LMICs are initially economic, even in countries with universal provision uptake has varied. The purpose of this review was to explore current global trends in HPV vaccine coverage, and to explore how public and health professional knowledge may be key determinants in programme success.

3. HPV vaccination of girls: uptake successes and failures

Adequate coverage is key to the success of HPV vaccination programmes, but successes in countries with the financial resources to support mass vaccination have been mixed. In a review of 2010 data from the USA, only 14% of girls under the age of 12 had received a first vaccination dose [15]. Including girls of all ages, 14% had received the required 3 doses. Hispanic, Asian and African-Caribbean girls were even less likely to have received the full course [15]. Information collected by the Centre for Disease Control and Prevention concluded there was a year-on-year increase in vaccine uptake, with 32% of girls receiving ≥ 3 doses in 2010 [16]. Worryingly, in a 2010 survey of over 2000 parents in the USA, of the responders whose daughters were not already vaccinated, 60% were not interested in vaccinating their daughters or were unsure [15].

By 2010, 18 European countries had instituted HPV vaccination programmes [17], though these tended to be in the countries that already had the lowest cervical cancer mortalities. Vaccine coverage in Europe overall appears significantly better than the USA. Highest rates are seen when vaccination is delivered in school-based programmes, as in regions of Spain [18], and in Scotland, where September 2011 figures reported 92% of girls progressing through the system had received a first dose, with 81% completing the course [19]. Three-dose coverage in England, which also has a school-based programme, was 76% in 2010 [20].

In the Netherlands, where healthcare providers delivered vaccination and recruitment was by letters of invitation, first-dose uptake within the early years of the programme was 50% [21]. France, which offered vaccination on request and reimbursed only a proportion of the costs, achieved only 28.5% coverage with 3 doses [22]. Studies in the States have confirmed that school-based systems are usually more successful at achieving high coverage, with minimum levels of 65% in schools-based programmes, as compared to 19% with alternative strategies [23], supporting the findings from Europe. Australia, which also implemented a school-based programme in 2007, had achieved an average three-dose coverage for girls aged 15 of 72% by 2009 [24]. One notable exception to this trend is Portugal, where three-dose coverage of 81% was achieved in 2010 through a health centre-based programme [17]. It is important to note, however, that Portugal has a long-running, well-organised and fully subsidised registry-based vaccination infrastructure, which was already providing high levels of coverage with its existing vaccine programmes.

Although 33 countries worldwide had vaccination programmes in place by 2010, few of these were in developing countries [25]. Pilot schemes, designed to test vaccination feasibility in LMICs, have been conducted in India, Peru, Uganda and Viet Nam. The majority of these achieved coverage of over 70%, with up to 99% coverage in one centre [26], and lessons learned will be used to guide future large-scale projects. One notable success is in Rwanda, where a partnership with Merck led to the donation of 2 million doses of Gardasil over 3 years. Here, thanks to a well-planned and highly structured school-based campaign, 3-dose coverage across the country of over 93% was achieved [27].

Table 1
Common concerns raised by the public about HPV vaccination [23,31,36,63], together with relevant data.

Concern	Evidence to date
Side-effects and safety	No significant difference in serious adverse events between vaccine and placebo cohorts [64,65].
Efficacy	Nearly 100% protection from HPV-16 and -18 up to 7 years (limit of data collected so far) [10]. Up to 76% reduction in cervical cancer deaths is predicted [13]. It is important to stress that cervical cancer screening will still be absolutely necessary.
Interactions	None known
Dosing	3 recommended, but 2 may be sufficient [66]. Booster doses may be required at a later date.
Cost	Will vary on a country-by-country basis, though most aim to support the most vulnerable sectors of society.
Perceived risk of infection/disease	Mean global prevalence of HPV infection is 11.7%, though it is over 30% in some countries [67]. In 2008, it is estimated infection was responsible for 610,000 cancer deaths (4.8% of all cancers) [68].
Potential of vaccination to promote sexual activity	A study of over 1300 girls found no evidence of increased sexual activity [69].

4. Public attitudes to HPV vaccination

All new and existing vaccination programmes face challenges in communicating a coherent health message and encouraging public participation. Common concerns raised by the public, and potentially applicable to all vaccines, centre on potential side-effects, interactions and a scepticism about a convincing a health need or benefit [28]. These negative fears are often the very ones highlighted by doctors as reasons they predict why people may refuse vaccination. In fact, self-reported knowledge of HPV vaccination and healthcare provider recommendation often appear as equal, if not more significant determinants of public uptake [29].

Unlike the majority of previous vaccine programmes, HPV vaccination presents unique potential barriers to acceptance: HPV is a sexually transmitted infection and vaccination, to be most effective, has to be administered to girls before sexual debut. In a USA-based study of teenage girls, there was a 10% likelihood of sexual debut by the age of 14, with figures as high as 17% in particular ethnic groups [30]. As such, to be most effective, vaccination must begin at an early age.

Perhaps due to concerns of the public reaction to these issues, multiple studies have surveyed public attitudes to the HPV vaccine. Levels of public acceptance are generally high [31–33], with some studies showing over 80% of parents broadly in favour of vaccination [34], though figures have been as low as 42% in studies of young women's attitudes [35]. Multiple studies have assessed whether caregivers' concerns about a vaccination's ability to influence sexual behaviour would affect their decision to vaccinate, but the significant majority have concluded that it is not a decisive factor [23,36,37]. In contrast, vaccine safety and efficacy are key parental concerns [23,36] (see Table 1 for a summary of concerns).

There is conflicting evidence as to whether cost plays a role in affecting public attitudes to vaccination in high income countries. It is likely that, in countries or regions without universal health coverage, limited medical resources, or lower incomes, it will be a much more significant factor. In a systematic review of largely USA-based research, having insurance was positively associated with completing a full vaccination course in 3 studies, whilst in one, vaccination rates were highest in those with private as opposed to state insurance [23]. A Swedish study found that parents were slightly less willing to participate in a paid as opposed to free HPV vaccination programme [38], whereas researchers in Italy found cost to have no effect [39].

Knowledge of HPV, cervical cancer and vaccine in both caregivers and teenage girls is positively associated with uptake [23,36]. Caregivers satisfaction with the information they receive is also important [23]. As a source of information, clinician and/or healthcare provider recommendation is consistently given as one of the top, if not most important, factors in the likelihood of girls or parents accepting vaccination [36,40–46]. One study found women who had not received a strong recommendation for vaccination from their doctor were 4 times less likely to accept vaccination [44]. In one of the largest surveys to date, including over 2000 parents in the USA, insufficient knowledge and a lack of recommendation by their family doctor were key determinants of uncertainty or distrust of vaccination [15]. In two studies looking retrospectively at parents of girls who had been vaccinated, and evaluating which factors influenced their decision, clinician recommendation was reported as a principle factor [45,46]. In support of the importance of knowledge in influencing parental attitudes, studies in which educational interventions have been explored demonstrate that simple strategies have the potential to greatly improve uptake. In an Australian study, a single page of information was sufficient to favourably change the decisions of 65% of parents who were previously undecided, and 20% of those previously opposed [47]. Consistent with the findings above, a systematic review of the literature conducted in 2011 concluded that the most consistent trends across multiple studies of factors affecting parental attitudes was a requirement for more information, and reassurance from healthcare professionals [36].

Some studies have shown that, within countries, certain racial or ethnic groups may have lower levels of acceptance than the national average [15,40,48,49]. Targeting information and education to these groups may help to maximise the efficiency of any interventions.

Fewer studies have investigated attitudes to HPV vaccination in LMICs, and those that have, tend to focus on urban rather than rural populations. Whilst it is difficult to generalise across countries and populations, knowledge of both cervical cancer and HPV vaccination seems often to be low, though this does not necessarily have a negative impact on acceptance. An Indonesian study, for example, found 96% of responders would support HPV vaccination despite only 66% having heard of cervical cancer and 17% having heard of the virus [50]. A study spanning urban areas in four Asian countries found poor knowledge (only 6% of responders knew HPV caused cervical cancer). Better knowledge was associated with an increased likelihood of accepting vaccination [51], consistent with findings in high income countries. Research targeting rural women in Malaysia also found very poor knowledge, though nearly two-thirds of women still indicated an intention to be vaccinated. Increased knowledge and physician recommendation were both associated with increased vaccine acceptability [52]. As in Asian studies, studies in both Kenya and Tanzania have found very low knowledge, though acceptance of HPV vaccination was high [53–56]. In Kenya, over 90% of women surveyed in two studies supported HPV vaccination against genital warts and/or cervical cancer, though low cost was critical to acceptance in both [53,54]. Of interest, a minority of respondents in both Tanzanian studies cited concerns about fertility as a reason for refusing vaccination [55,56], with responders from one study stating concerns that previous vaccination programmes had harmed reproductive ability [55]. In a survey of rural and urban mothers from Southern India, only Hindu mothers had heard of cervical cancer or HPV infection. Although initially sceptical of a link between a virus and cancer, they were very positive about vaccination in general and, after information was provided, were willing to consider vaccination. Cost and side effects were key concerns [57]. In an affluent, highly educated study population from Eastern India, 33% had not heard of cervical cancer. After receiving a short information sheet, 74%

Table 2
Barriers to female HPV vaccine recommendation as reported by clinicians.

Barriers to female HPV vaccine recommendation as reported by clinicians
Concerns about how parents/women will react to discussions [72,73].
Reluctance to raise issues related to sexuality [73,74].
Concerns about the young age of vaccination [73,75].
Fears that the vaccine will promote early or high-risk sexual behaviour [76].
A perception that their patient cohort are at a low risk of infection [77].
Concerns about financial coverage/reimbursement [72,78].
Incomplete understanding of the potential benefits of vaccination [79].
Feeling under informed [32,80].
Negative media reporting [82].

supported vaccination [58]. Evidence suggests that knowledge in South America may also be poor [59–61], though in countries such as Argentina there have been concerted efforts to raise awareness [62].

The importance of health professional recommendation to attitudes to HPV vaccination has been demonstrated in LMICs as well as high income countries [50–52,58]. A study of professionals in Kolkata found 60% of women considered their physician's recommendation as the most important factor in deciding about vaccinations [58]. Of 132 women, across four Asian countries, who had accepted vaccination for themselves or their children, 91% reported their doctor as the most influential factor in their decision. The next most important were information leaflets received from health professionals [51]. In an Indonesian study in which 84% of responders were female, the spouse/partner was the person most likely to influence attitudes to vaccination for 70%, with the next most influential group being health professionals (22%) [50]. In Argentinean research, conducted prior to HPV vaccine inclusion in the national vaccine schedule, the most common reason given by women for not receiving vaccination was failure of their doctors to mention or recommend it [62], despite a preceding media campaign to raise awareness.

5. Health professionals' attitudes to HPV vaccination

Having demonstrated that an informed public is more likely to accept vaccination, and that clinicians and other healthcare providers are the most trusted people to disseminate this evidence, it is therefore critical to examine attitudes amongst these groups. As early as 12 years ago, information was available demonstrating clinician recommendation would be key to public attitudes to HPV vaccination [40]. Despite this, relatively few studies have looked at healthcare providers attitudes, with little research in the UK to date.

Unfortunately, such studies have found that clinicians are not always the strongest advocates of HPV vaccination, particularly in the USA. One study of a mixed cohort of medical specialties conducted as recently as 2009 reported only 35% of responders would always recommend vaccination to young adolescents [63]. A separate study targeting American paediatricians found only 46% were willing to recommend vaccination for girls under 12, rising to 77% for 13–15 year olds [64]. Table 2 details reasons given for a reluctance to recommend vaccination common to multiple studies.

Whilst other studies have found higher levels of acceptance, this reluctance to vaccinate younger age ranges is a recurrent theme, both in the UK [65] and USA [66,67], with the proportion of doctors willing to vaccinate increasing as the proposed age of vaccination increases. This is a worrying finding, as it suggests doctors do not fully appreciate that early vaccination, before any prospect of HPV exposure, is crucial to the success of any national campaign.

Overall, in the initial period of vaccine introduction, a significant proportion of clinicians and healthcare professionals surveyed felt under-informed and ill-prepared to advocate for vaccination [32,68,69]. This lack of information had a negative impact on

their willingness to recommend vaccination [65,70], reducing the likelihood of recommendation by as much as 60% [69]. The same was also true of nurses surveyed [71]. In countries that utilise a school-based approach to vaccination, school nurses play a significant role in promoting uptake. One small study in the UK found only 16% of responders rated their knowledge as adequate [72] and subsequent studies have suggested that this cohort need further training [73]. A more recent study of American clinicians suggested they might be underestimating the potential benefit of HPV vaccination, which extends protection not just to cervical cancer, but also to other anogenital malignancies and some oropharyngeal cancers [74]. Doctors have also been reported to rate their knowledge higher than it was scored objectively [75], suggesting they may not always appreciate the need to seek out further information.

Many doctors have reported concerns about how parents would react to the potentially controversial issues unique to HPV vaccination [51,67,68,76] and this may affect their likelihood of recommending vaccination [65]. This does not seem unique to physicians in high income countries [51,68]. In fact, these fears appear largely unfounded in the majority of populations surveyed to date [23,32,36,37,58] and this misconception could be easily rectified.

More research is needed to investigate how healthcare professionals in LMICs could be best supported in improving knowledge and acceptance of HPV vaccination. In countries with less developed health infrastructures, nurses, health workers and community leaders are likely to face an increased burden in disseminating information. Research, where available, has tended to focus on physicians and medical students. A 2006 study of medical students and physicians in Brazil found 80% were in favour of vaccination, though 31% felt the indicated age should be 15 and over. 15% of responders who felt fully informed did not support vaccination at any age, though the study did not investigate possible reasons for this [77]. A study of medical students in India found 76% were aware of HPV vaccination, with the figure substantially higher for women than men. 79% of women and 53% of men supported vaccination, but the study did not explore how these attitudes would affect recommendations to their future patients [78]. In a large pan-Asian study of physicians, whilst nearly all responders were aware of HPV vaccines, 39% did not feel vaccination should take place before sexual debut, and approximately a fifth of responders felt vaccination should be reserved only for 'promiscuous' individuals [51]. A fifth of all doctors surveyed felt talking about HPV vaccination was a potentially sensitive subject, though in the same study, only one parent reported feeling embarrassed by such a discussion. When they investigated factors affecting the likelihood of initiating conversations about vaccination, the authors found sufficient knowledge to be one of the most significant. The most popular source for receiving information was other doctors. Advice from the Government/Ministry of Health was the single factor most likely to change attitudes towards recommending vaccination. Of note, doctors were relatively pessimistic about their own abilities to alter parental decisions about vaccination [51].

Whilst physicians' attitudes to vaccination seem largely positive, some countries may require additional input to overcome potential barriers to acceptance. In Saudi Arabia, for example, where cervical cancer is the 11th most common cause of female cancer deaths [79], one study found that, even after the provision of information about HPV vaccination, only 50% of doctors were willing to recommend vaccination to their patients [80].

In a study of nurses' knowledge in Northern Thailand, which did not look directly at attitudes towards vaccination, 80% of responders were aware that HPV caused cervical cancer, though two-thirds did not know if vaccination had major side effects [81]. A small study of Turkish nurses and midwives in 2010 found 92% were aware of HPV vaccination, while 78% desired vaccination

themselves. Again, willingness to recommend vaccination was not investigated [82]. A survey of nurses in Pakistan in 2009 found only 9% had heard of the vaccine. When asked for their preferred source of further information, equally cited were other health professionals and mass media [83].

The potentially detrimental impact of an under-informed public and clinical body on vaccine coverage is illustrated by the Netherlands. Despite a programme of active recruitment for vaccination, first dose uptake was as low as 31% in some regions [21], a third of that achieved in Scotland and one of the worst in Europe. A reportedly active anti-vaccination lobby [21,84] was assisted in sowing doubts by conflicting expert advice [85,86], with some calling for delays in implementation while safety data and long-term outcomes were reviewed. Alarmist reporting is not restricted only to the Netherlands [87], but divided clinical opinion can clearly have a particularly damaging effect. Significantly, in regions of the Netherlands that involved doctors in vaccine promotion programmes, vaccine uptake was higher [21], again illustrating the potential influence of clinicians.

In contrast to the Netherlands, Rwanda represents a model to inform future programme development. Here, a thoroughly planned school-based vaccination scheme was preceded by a comprehensive national education campaign. By recruiting health professionals, religious leaders, prominent politicians and teachers as advocates from the very beginning, Rwanda has achieved coverage of more than 90% [27], despite the publication of potentially damaging criticisms about HPV vaccination in the country [88].

6. Conclusions

Of nearly 1000 deaths from cervical cancer in the UK each year, a comprehensive vaccination programme with the current generation of vaccines could, in the future, potentially prevent over 700 of them [13]. The UK looks set to achieve its targets for vaccine coverage and realise this dramatic health benefit, but of the high income countries, it is in a relative minority. In the provision of vaccination to low-income countries, which bear the overwhelming burden of cervical cancer deaths, work has barely begun.

Countries that possess the financial resources to support mass vaccination, and have yet to achieve the required minimum levels of coverage, must now review the available evidence. Those states and regions that have instituted school-based, opt-out systems have consistently achieved the best coverage. In low income countries, a mixed approach may be most beneficial [89]. There is an absolute need to educate parents, guardians and young people about the basic facts of cervical cancer and the HPV vaccine. Doctors and healthcare workers will be the most influential and best-placed groups to effect changes in attitudes, but they themselves require clear and concise information. The type and emphasis of information required may vary between and even within countries, depending on the differing concerns and attitudes of various groups and nationalities. Research suggests that educational needs in LMICs may be higher, but experience from Rwanda demonstrates that with sufficient planning and a wide, active engagement policy prior to implementation, high coverage can be achieved.

We now possess the means to prevent over two-thirds of cervical cancer deaths and, with the next generation of vaccines, could potentially be capable of eradicating almost all cervical cancer. With such powerful weapons at our disposal, we have an obligation to ensure we realise their full potential.

Conflict of interest

The authors confirm there are no conflicts of interest pertaining to the article.

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