Public health paradoxes and the epidemiological impact of an HPV vaccine

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Abstract

Background: our understanding of human papilloma virus (HPV) and cervical cancer has improved dramatically, with a vaccine against the viral infection being a real possibility in the near future. Aims: the goal of an HPV vaccine would be to reduce the prevalence of infection and hence the risk of cervical abnormalities. However, questions arise as to how this would interact with an existing intervention, screening, which reduces the progress of cervical abnormalities to serious disease. Furthermore, will a vaccine against one genotype influence the other types within a population and will the patterns of infection and disease remain the same if the vaccine alters the timing and type of HPVs experienced within a population? What would a vaccine that only worked in one sex achieve and how widespread would the use of such a vaccine have to be? Conclusion: the above-given questions can be addressed within a theoretical framework that describes the transmission dynamics of human papilloma virus. © 2000 Elsevier Science B.V. All rights reserved.

1. Introduction

A successful prophylactic vaccine is the ultimate public health tool in the prevention of infectious disease: removing any risk of disease in those effectively immunised and, through herd immunity, reducing exposure to infection amongst the rest of the population. The success of vaccination programmes against acute, childhood viral diseases (Fenner et al., 1988; Aylward et al., 2000) has lead to a general assumption that once an effective vaccine has been developed and evaluated its use will be straightforward. As the biomedical challenge of developing a vaccine is met, consideration of its epidemiological impact can usefully address potential problems in the implementation of vaccination programmes. Such consideration is particularly complex in the case of human papilloma virus (HPV) vaccines. The major goal of using such a vaccine has to be the prevention of the major morbidity, mortality and costs associated with cervical cancer, but this has to occur within the context of the current cancer prevention strategies and in light of attitudes to sexually transmitted diseases. In this paper, we review the prevailing theory about the epidemio-
logical impact of vaccines and the questions raised by the specific problems associated with HPV.

2. An epidemiological theory for vaccination

To control an infectious disease there are only a limited number of direct parameters that can be altered by interventions. These can be neatly summarised within the framework of the reproductive number of infection, \( R_0 \). This describes the potential for the spread of an infection, and is defined for microparasites as the average number of infections caused directly by one infectious individual in an entirely susceptible population. The three central components of the basic reproductive number are the duration of infectiousness, the contact pattern of potential hosts and the likelihood of transmission on contact between an infectious and a susceptible host (Anderson and May, 1991). These are the parameters we attempt to reduce in interventions aimed at (1) increasing treatment and cure rates, (2) education or quarantine to reduce contacts or (3) barriers reducing infectiousness. In the case of vaccination, it is not the basic reproductive number that we reduce, since by definition the basic reproductive number applies to the situation when the entire population is susceptible. Rather we reduce the effective reproductive number, \( R_t \), at a given moment in time \( t \), which is the average number of infections caused by one infection in the population. This is altered by the vaccination which reduces the fraction of the population susceptible. The difference is more than just semantic, as it controls the relationship between our intervention effort and the impact we have. Fig. 1a illustrates the endemic experience of infection in a population, comparing percentage levels of reductions in parameters within the basic reproductive number with percentage increases in the fraction of the population effectively protected through vaccination. As the vaccine coverage increases, then the decreases in infection show a linear improvement, whereas other interventions become more successful as the basic reproductive number of one is reached. The two eliminate infection at the same stage when the reproductive number equals one. This is described as the critical vaccination threshold for elimination which has been the focus of much thinking with highly efficacious and effective vaccines against relatively simple childhood infections (Fig. 1b) (Garnett and Ferguson, 1996).

How would a vaccine against HPV fit into this simple theory? HPV is a sexually transmitted infection. The relationship between vaccination and infection described in Fig. 1 assumes homogeneity in the risk of acquiring and transmitting infection, which is far from true for sexually transmitted infections. Here, a majority of the population, and a majority of those acquiring infection, have a low risk of transmitting the infection further, whereas a small fraction have a high risk of acquiring and transmitting infection. This leads to a relationship between efficacious coverage and the prevalence of infection illustrated schematically in Fig. 2, where low coverage reduces prevalence dramatically in the large low risk fraction of the population, but coverage has to reach very high levels in the high risk population for elimination (Garnett, 1998). This is a two edged sword as it means an STD vaccine can be 'successful' with relatively low coverage, but that elimination will be hard to achieve.

While low coverage can be useful, in the case of sexually transmitted disease vaccines is there an opportunity for targeting? A high risk group may be the natural focus for a vaccine since these are least likely to be screened for cervical abnormalities and because they contribute most to the spread of infection. Furthermore, women suffer the majority of diseases associated with HPV, so what would the impact of a vaccine targeted at women alone be? Results from a model of bacterial STD and vaccination (Fig. 3) suggest that while targeting can be cost effective it does need to effectively capture the bulk of those at high risk to be useful. A task that is likely to be difficult. Hence, it seems likely that HPV vaccination would have to focus on the majority of the population. A single sex vaccine is more of a possibility, since the sex vaccinated is well protected by the vaccine.

Recent debate, stimulated by work in developing HIV vaccines, has focussed on a lack of sterilising immunity and whether a vaccine that
reduces transmissibility can be useful (Koopman and Little, 1995). In such a case the relationship between prevalence and coverage is like that seen when reducing the basic rather than the effective reproductive number, since the vaccine reduces the number of cases generated by an infected individual rather than the fraction of the population susceptible. A vaccine which allows infection with HPV may still alter the natural history of infection and disease and hence have an impact due to the distant relationship between infection and serious disease.

3. Human papilloma virus and disease

On the basis of DNA homology HPV has been classified into more than 80 distinct genotypes, of

Fig. 1. The relationship between reductions in the basic reproductive number and the steady state proportion of the population with infection or immune through the acquisition of natural infection ($y$), where $y = 1 - (1/R_0) - p_v$. In the case of reducing the duration of infectiousness, transmission probability or contact rate the value of $R_0$ is reduced, whereas vaccination reduces the proportion susceptible. (a) The impact of coverage on the endemic steady state. (b) The relationship between the basic reproductive rate and the critical vaccination threshold.
which more than 35 are classified as ‘genital types’. These can be further classified according to their association with cervical cancer (zurHausen, 1999; Koutsky and Kiviat, 1999). A strong epidemiological association between cervical cancer and HPV led to the conclusion that HPV is the primary risk factor and causative agent for the development of cervical cancer and its precursor lesions (Morrison et al., 1991; Munoz et al., 1992; vanBallegooijen et al., 1997). The oncogenic or high risk types of HPV contain the E6 and E7 genes which code for the tumour suppressor protein binding oncoproteins and are found in virtually all cases of invasive cervical cancer (Bosch et al., 1995; Kirnbauer, 1996). It has been estimated that type 16 causes 50% of all cervical cancer and that 80% of cervical cancer is accounted for by the four types 16, 18, 31 and 45 (Bosch et al., 1995). Despite almost all cervical cancer being caused by high risk HPV infections not all high risk HPV cause cancer. Many high risk type infections are short lived and do not lead to cancer. The prevalence of high risk types is higher than the lifetime risk of developing invasive cervical cancer, for example in The Netherlands 4 versus 1%, which, assuming that the lifetime incidence of high risk types will be much higher than their prevalence, illustrates the small fraction of infections that lead to cancer. Additionally, there are many low risk types. The low risk, nononcogenic types, of which HPV 6, 11, 42, 43 and 44 are the most common, are found in external genital warts and benign genital lesions (vanBallegooijen et al., 1997).

4. HPV vaccine

While most anti-viral vaccines are based upon the use of virions to induce anti-virion antibodies, it is difficult to produce sufficient quantities of HPV virions in cultured cells to induce a host response. Since HPV virions contain oncogenic DNA genomes, attenuated HPV virions are considered risky candidates for vaccine development. In the early 1990s it was discovered that by
inducing expression of the major HPV capsid protein (L1) in cultured eukaryotic cells, with or without the presence of the minor capsid protein (L2), it is possible to produce what are known as HPV virus-like particles, or VLPs. These VLPs are morphologically identical to the native HPV virions, though they lack the viral DNA core. Thus, they can be injected into a host, to induce an antibody response, without any oncogenic risks (Kirnbauer, 1996; Schiller, 1999).

VLP-based vaccines have been tested in multiple animal models with good results. Rabbits, dogs, and cattle vaccinated with species-specific papillomavirus VLPs and subsequently challenged with the virus have shown sterilising immunity against viral infection. To test this response, serological assays have been developed to measure the HPV VLP immune response in humans.

Production of vaccines in cultured eukaryotic cells is time consuming and very costly. For these reasons, alternative strategies for the development of an HPV vaccine are being explored in order to make the vaccine more accessible for the developing world. ‘Naked DNA’ vaccines involve injecting bacterial plasmids containing L1 proteins and a promoter directly into the vaccine recipient in an effort to induce the recipient’s own cells to produce VLPs. Since they do not require in vitro production of VLP from cultured cells, the naked DNA vaccines are likely to be less costly and less difficult to produce, making them much more attractive candidates for developing countries. The possibilities of producing VLPs in *Escherichia coli*, in live recombinant bacteria, and in edible transgenic plants are also being explored (Schiller 1999). The development of such vaccines occurs against the background of screening programmes which have a good efficacy if not always effectiveness.

5. Current control of cervical cancer

The traditional model of cervical cancer development involves a slow and uncertain progression from normal cervical cells, through pre-cancerous cervical lesions, to increasingly severe stages of invasive cancer. The pre-cancerous cervical lesions are known as cervical intraepithelial neoplasias, or CIN. CIN 2 and 3, known as high-grade SIL (HSIL) or carcinoma in situ (CIS), are more serious conditions than the early CIN 1 abnormalities. These may develop from CIN 1 lesions, but at least one study has shown that not all women with CIN 2 or 3 had any evidence of CIN 1 first (Kiviat and Koutsky, 1996). Spontaneous regression of moderate dysplasia, or CIN 2, is less common than regression from CIN 1 but probably still occurs in a majority of cases (Holowaty et al., 1999). Left untreated, however, some CIN 2 and probably most CIN 3 (severe dysplasia) will progress to cervical cancer within months or years. Overall, between 10 and 30% of the untreated CIN lesions may progress to invasive cervical cancer (Kirnbauer, 1996). Treatment of CIN and invasive cervical cancer becomes progressively more complex and costly as severity of the lesion increases. CIN can generally be treated by various methods of excision, but invasive cancer usually requires radiation, chemotherapy, or surgery (including cryosurgery, laser surgery, or hysterectomy). These higher levels of treatment are frequently uncomfortable for the patient and may involve many side effects.

All women diagnosed and treated for CIN (1, 2, or 3) can expect to survive for at least 5 years. 80–90% of those diagnosed with stage I invasive cancer will survive for at least 5 years. Far fewer will survive after treatment for higher stages of invasive cancer; 50–65% for stage II, 25–35% for stage III, and 0–15% for stage IV (Wolstenholme and Whynes, 1998; Anonymous, 1999).

Traditional cervical cancer screening is based upon microscopic examination of cervical cells for abnormalities. Introduced in the 1950s, the Papanicolaou smear test, which involves scraping cells from the cervix, staining and examining them under a microscope, is one of the most successful cancer screening tools ever developed. With varying estimates of sensitivity and specificity, the test is not perfect. Yet between 1955 and 1992, deaths from cervical cancer in the US dropped 74% as a direct result of the use of the Pap test in routine gynaecological screening (American Cancer Society, 2000). Recent improvements in the Pap technology (including liquid cell suspensions and
automated, rapid reading of results) have improved the accuracy and cost-effectiveness of Pap screening.

Most screening policies follow a triage system for detection, treatment, and follow-up of cervical abnormalities. Conservative triage schemes are based upon the assumption that most mild cervical abnormalities spontaneously regress to normal. Such schemes are, therefore, typically cautious about rushing into expensive treatments. In the UK, for example, recommended policy states that women with a smear report indicating a ‘mild’ abnormality (ASCUS or LSIL/CIN1) should return for a second smear test in 6 months. If an abnormality appears again, immediate colposcopy is indicated. If the smear is negative and is following by a second negative smear in another 6 months, she may return to a schedule of routine screening (Jenkins et al., 1996).

More aggressive triage schemes are based upon the principal that ‘it’s better to be safe than sorry’. The National Cancer Institute of the United States recommends that a woman with a mildly abnormal smear test should be re-screened in 3 months, rather than 6. A second abnormal reading indicates that immediate colposcopy is warranted. If the follow up test is normal, she should be re-screened every 6 months. After at least three consecutively negative smears, she may then return to a routine schedule of annual tests (Kaufman et al., 1997). It is the costs of treatment that may be avoided by introducing vaccination programmes in industrialised populations even if the need for screening is not removed.

The importance of regular cervical smears, where available, is often misunderstood, and as a result many women fail to be screened on a regular basis. The World Health Organisation (WHO) reports that only 50–80% of women ages 15–49 in Latin America and the Caribbean have had a Pap smear in their lifetimes (World Health Organization, 1996). In the US, a survey in 1994 revealed that a fifth of all the women aged 18–64 had not had a Pap test in the past 3 years. Only 57% of women over the age of 65 had had a smear test in the past 3 years as compared with 81% of the younger women (National Cancer Institute and National Institutes of Health, 2000).

6. Screening in developing regions

Disparities exist between the screening policies and programmes in the developing versus industrialised regions of the world. In industrialised regions, early detection means that 80% of detected cervical cancer cases are cured. In less developed regions the picture is much worse. Thus, 80% of the detected cervical cancer cases are incurable at the time of detection, and cervical cancer mortality often equals incidence. Cytology screening programmes exist, but they often lack sufficient coverage to make any significant impact, are poorly managed, and screen mainly younger women (World Health Organization, 1996).

The WHO recognises that the cytology screening programs that are used well in industrialised regions are simply not feasible as widespread policy in the developing world. They are far too expensive, do not attain adequate coverage, and often lack the manpower, technical support and expertise to guarantee quality and accuracy of results. WHO has therefore advocated alternative control approaches for developing countries. ‘Downstaging’ (visual inspection of the cervix) is advocated as the screening method of choice. Education and empowerment of women to recognise warning signals and seek treatment are deemed highly important. Countries are encouraged to build referral systems and increase the availability of basic therapies. Finally, WHO recommends combining cervical cancer screening programmes with other health services (e.g. STD services) to maximise cost-effectiveness and create strong, integrated health infrastructures (World Health Organization, 1996). However, the sensitivity and specificity of downstaging, especially in detecting early-stage lesions, and its effectiveness in providing protection from serious disease is unknown.

Despite the overall success of cervical screening programmes, several problems remain. These include high cytology failure rates, difficulties building and maintaining good cytology-based screening programmes in developing countries, and a lack of reliability and cost-effectiveness in HPV screening.
7. Patterns of disease

It is estimated that worldwide 400,000 new cases of cancer are diagnosed each year and that the actual number of cases is much higher than this. The rate of incidence varies widely from over 50 cases per 100,000 women in Swaziland, Nicaragua and Haiti, down to less than five per 100,000 women in Finland, Pakistan and China (Parkin et al., 1999). The death rate is also diverse with 21.34 per 100,000 in southern Africa, 17.45 per 100,000 in Central America, 3.44 per 100,000 in North America, 3.39 in eastern Asia and 4.88 in northern Europe. Much of the difference in patterns of disease and mortality is due to current patterns of prevention with lower incidence of disease and also fatality rates where screening is well established.

This pattern of disease has important implications for a vaccine to control infection. Where the vaccine is most needed is where the awareness of cervical cancer as a health priority is low and where the resources available for health programmes are scarce. Developing countries have the greatest need for an HPV vaccine but the cost of such a vaccine is likely to be prohibitive. Ideally, a vaccine would also reduce the incidence of disease where effective screening programmes are in place, by detecting those infections that are missed or by vaccinating those in the community that are less likely to be screened. However, these will again be those most likely to be difficult to vaccinate.

A key issue in HPV vaccine development is the number of genotypes types to include since an increasing number of types is likely to increase the cost of vaccination. However, a focus on only a limited fraction of types could increase the importance of other types in causing disease through a number of mechanisms.

1. Reduced cross protection from infection allowing the incidence of other genotypes to increase if they are released from competition

The impact of vaccinating against one strain of an infectious agent on other strains has been explored theoretically for the bacterial infections Haemophilus influenzae and Streptococcus pneumoniae as examples (Lipsitch, 1997, 1999). Serotypes present in the same system, either coexist with each other in a delicate balance of individual ‘ecological niches,’ or alternatively, one (or more) serotypes is able to completely competitively exclude other types. If this is, in fact, how different serotypes interact, then some natural questions result. What happens when you vaccinate against one or more serotypes, removing the serotype that is able to balance or outcompete the others? Does this open an ‘ecological niche’ for the nontargeted types?

Using a mathematical model, Lipsitch found that in a system with two or more serotypes (like HPV), elimination of one of those serotypes by a monovalent (fully protective against one serotype) vaccine may cause an increase in the other serotypes that is actually greater than the reduction in carriage of the targeted serotype. For a bivalent vaccine (full protection against type 1, partial protection against type 2), in a system with strong competition between types (type 1 outcompetes type 2), a higher proportion of the population (critical fraction) must be vaccinated in order to eliminate both types from the system without the appearance of type 2. At lower vaccination coverage, prevalence of type 2 will increase and not decline until type 1 has been completely eliminated (Lipsitch, 1997, 1999).

Though empirical evidence of serotype replacement in bacterial systems has been sparse and weak to date, it is a problem that needs careful attention. While Lipsitch’s studies are based upon bacterial systems, serotype replacement is a potential problem for viral systems as well. With more than 30 types of related genital HPVs now recognised, the problem of serotype replacement may be particularly applicable.

Little is known about the immune response to the genital HPV infection. The primary uncertainty is whether the immune response is type-specific or if antibodies to different types of HPV are cross-neutralising. Some reports have suggested that different HPV types, even those that are most closely related (HPV16 and 31, 18 and 45) are serologically distinct.
and do not produce cross-neutralising antibodies (Kirnbauer, 1996). This would seem to suggest that there is no interaction between different HPV types or the immune responses to them. In this case removing one type through vaccination will have little effect on the other types.

2. Reduced cross protection from disease through a decrease in cross protective types.

An important related issue is the effects of adding low-risk wart types to the vaccine. If carriage of low-risk wart types does, as recent studies suggest (Luostarinen et al., 1999; Silins et al., 1999) protect against cervical cancer related to high-risk types, will elimination of wart-types in the general population actually increase the risk of cancer from high-risk types? A longitudinal nested case-control study and case-control study published in 1999 suggest that there may be an antagonistic interaction between different types of HPV. Luostarinen et al. (1999) found that seropositivity for HPV16 was associated with an increased risk of cervical cancer among women negative for HPV 6 or 11 (OR = 5.5), but in women seropositive for HPV6 or 11, seropositivity for HPV16 was not associated with an increased risk of cancer. Silins et al. (1999) found similar results: among women seronegative for HPV6, seropositivity for HPV16 was associated with an increased risk of cervical cancer (OR = 2.39), which was expected. However, among women who were positive for HPV6, seropositivity for HPV 16 was not associated with an increased risk of cervical cancer (OR = 1). The finding that certain HPV types may be protective against the development of cervical cancer related to other types could have significant implications for the understanding of HPV carcinogenesis and the development of vaccines.

3. An increase in the association of cancers associated with currently less prevalent causal types.

It is possible that predisposing factors influence who is at risk of cancers. In these individuals type 16 HPV may be the most virulent and common cause. However, the removal of type 16 through vaccination may lead to less virulent types to cause a significant number of replacement cancers after a longer period of infection. Even if this is not the case, screening will need to be maintained to detect the residual abnormalities caused by the remaining high risk HPV types.

8. Social and behavioural side effects

The fact that HPV is a sexually transmitted disease could have adverse consequences for vaccine testing and subsequent acceptance of the vaccine. Despite public health efforts to remove the social stigma attached to sexually transmitted infections and to encourage people to actively use preventative measures and available treatments, there remains a stigma in dealing with STDs. In the short term, such stigma may prevent women from entering HPV vaccine trials, not wanting to be perceived as belonging to a high-risk group (Heyward et al., 1998). In the long term, once a vaccine is available, health officials may encounter problems ‘selling’ the vaccine to susceptible populations. Telling populations that they need a vaccine against a STD will not be straightforward. This will be exacerbated by the fact that the target population will mostly consist of adolescent girls and young women.

We might expect two primary behaviour changes if HPV vaccine recipients perceive that they are fully protected from HPV infection and cervical cancer. First, there may be an increase in risky sexual activities (either type of activity or frequency) that results in increased risk of infection by other agents. However, HPV is considered a minor infection on the STD hierarchy and is, therefore, not likely a driving force in decision making about sexual risk-taking behaviour. Perhaps of greater concern is the risk that women who have been vaccinated against HPV will believe that they are fully protected from ever getting cervical cancer and will no longer seek routine gynaecological care. This is dangerous for several reasons. First, the HPV vaccine will not protect against all of the high-risk HPV types. So, women who have been vaccinated will still be at
risk for development of cervical cancer caused by nontargeted HPV. Second, the duration of protection from the vaccine may not be life-long. Waning immunity would mean that women become increasingly vulnerable to infection, and therefore, cervical lesions, over time. Finally, while the recommended intervals between cervical screenings may be reduced in response to decreased overall risk, screening cannot be eliminated altogether. Routine gynaecological exams provide an opportunity not only to screen for cervical cancer, but also to perform inspection for other problems and to educate women on such issues as pregnancy and STDs.

9. Major obstacles in developing countries

An HPV vaccine could have the greatest utility in developing countries but there are major problems in bringing such a vaccine into widespread use. Not the least of these is the cost. Without proper surveillance systems, adequate data on the economic and health burdens of cervical cancer, and education about the link between HPV and cervical cancer, gaining political support for the allocation of resources to an HPV vaccine could prove difficult. Even with the awareness that a vaccine programme would be beneficial, funding priorities often lean towards therapeutic care rather than preventive services. A heavy, visible burden of disease from diverse causes often leads policymakers to devote more money to treatment services with immediate results rather than vaccine services whose results will not be seen for many years (Moore and Tsuda, 1999).

How might the poorest countries pay for the HPV vaccine? Most vaccines currently available are produced in industrialised countries and made available throughout the world on a ‘tiered’ pricing system. Countries are ranked by GNP into one of the four income bands, and those in the lowest bands can purchase vaccines from distributors for reduced costs. By bearing the bulk of research, development, and manufacturing costs, richer countries essentially ‘donate’ a portion of the vaccine costs to the poorest countries. The achievement of high levels of population coverage will be necessary to make a new HPV vaccine effective. Traditional childhood vaccination programmes have had remarkable success at achieving the high coverage needed to reduce persistent infections, even in less developed regions. This might be because childhood vaccinations can be easily built into existing post-natal care systems and school programmes. For example, the WHO Expanded Programme on Immunization, an initiative designed to immunise children against six infectious agents, has been able to achieve upwards of 80% coverage worldwide (Widdus, 1999).

Vaccination programmes for adults in the third world have been more problematic. For example, yellow fever vaccination coverage for adults in countries where the disease hits the hardest is traditionally less than 20%, coverage of women for tetanus toxoid is less than 50% in developing regions, and the rubella vaccine is virtually unused in the poorest developing countries (Widdus, 1999). This problem may be attributable to lower political perception of the seriousness of the conditions, poor adult health services, and fewer financial resources available for preventative care in adults. These vaccine programmes may inappropriately target specific groups (e.g. young women in urban areas) who are perceived as ‘high-risk’ and are the most easily reached, while virtually ignoring other groups (Sherlaw-Johnson et al., 1997). For an HPV vaccine programme to be truly effective, it will need to have high coverage, especially in high-risk groups. Linkages with other health care systems, improved adult health services, and education about the benefits and availability of the HPV vaccine will be vital to the achievement of high levels of coverage with an HPV vaccine.

10. Conclusions

The technological advances that allow optimism in HPV vaccine development mean that the epidemiological paradoxes relating to such a vaccine require attention. The foremost of these paradoxes is that such a vaccine would be most useful
in resource poor settings, whereas the price of new technology will limit its affordability to more wealthy populations. In the latter generating widespread vaccine uptake against resistance to STD controls while avoiding undermining current screening will be a difficult task. The major biological question surrounds the interaction of types of infection. Current biological evidence suggesting a problem associated with vaccinating against a limited number of genotypes is not strong. However, it is important that our knowledge is strengthened to be sure that there will be no perverse outcomes when introducing an HPV vaccine.

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