Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The estimated impact of natural immunity on the effectiveness of human papillomavirus vaccination

Q1 Suzette M. Matthijsse[a,*], Jan A.C. Hontelez[a], Steffie K. Naber[a], Joost van Rosmalen[b], Kirsten Rozemeijer[a], Corine Penning[a], Roel Bakker[a], Marjolein van Ballegooijen[a], Inge M.C.M. de Kok[a], Sake J. de Vlas[a]

[a] Department of Public Health, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands
[b] Department of Biostatistics, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 27 April 2015
Received in revised form 21 August 2015
Accepted 28 August 2015
Available online xxx

Keywords:
Human papillomavirus
Cervical cancer
Modelling
Vaccination
Naturally acquired immunity
Microsimulation

ABSTRACT

Background: Mathematical modelling is used to estimate the effectiveness of HPV vaccination. These estimates depend strongly on herd immunity and thus on naturally acquired immunity, a mechanism of which little is known. We estimated the impact of different vaccination strategies on HPV-16 and HPV-18 transmission and cervical cancer incidence in the Netherlands, considering different acquired immunity mechanisms.
Methods: We used the STDSIM microsimulation model, and considered two mechanisms for acquired immunity after infection: (I) full immunity with variable duration; (II) cumulatively decreasing susceptibility to reinfection. Girls aged 13–16 years received vaccination (94.7% efficacy for HPV-16 and 92.3% for HPV-18) during a once-off catch-up campaign with 50% coverage, followed by annual vaccination of 12-year-old girls (60% coverage). Alternative vaccination scenarios included increased coverage, including boys, and lower vaccine efficacy.
Results: HPV-16 incidence reduced by 64% under mechanism I and 75% under mechanism II; HPV-18 incidence reduced by 58% and 73%, respectively, and these reductions lead to 48–56% fewer cervical cancer cases. Increasing coverage can lead to over 96% reduction in HPV incidence. Vaccinating boys reduced incidence by 79–89% for HPV-16 and 83–98% for HPV-18 in women.
Conclusions: Effectiveness estimates of HPV vaccination differ slightly between different acquired immunity mechanisms, yet these differences are unlikely to affect policy decisions. Offering vaccination to boys as well may be considered to further reduce cancer incidence.

1. Introduction

Q2 Human papillomavirus (HPV) vaccination has been implemented in many countries over the past years, focusing mainly on girls. Coverage among girls differs substantially between countries, ranging from 32% in the United States to >70% in Australia, and even exceeding 90% in Scotland [1,2]. The bivalent vaccine protects against high-risk HPV-16 and HPV-18 infections that account for approximately 80% of the cervical cancers [3,4], while the quadrivalent vaccine protects against HPV-16, HPV-18, HPV-6, and HPV-11 [5]. The bivalent vaccine was offered to girls aged 13–16 years in a mass catch-up campaign in 2009 in the Netherlands [6], and subsequently introduced in the Dutch national immunization program with 12-year-old girls being eligible for vaccination. Coverage of 58% was reached in 2013, which is much lower than the >90% coverage for other vaccinations included in this programme [7]. However, by reducing HPV prevalence in the population, vaccination not only protects those vaccinated, but (indirectly) unvaccinated individuals as well [8]. This is often called herd immunity, also in HPV modelling studies [8–11].

Mathematical modelling has been used to estimate cost-effectiveness of HPV vaccination [9–14]. These mathematical models require realistic assumptions for the transmission and infection clearance of HPV, as well as the extent and duration of acquired immunity after infection clearance. However, there is still much uncertainty regarding acquired immunity after infection clearance, and a better understanding of this process is crucial to model the effectiveness of different vaccination strategies accurately [15]. Explorative modelling studies have shown that the proportion of people developing lifelong immunity affects the

* Corresponding author. Tel.: +31 10 704 31 12; fax: +31 10 703 84 75.
E-mail address: s.matthijsse@erasmusmc.nl (S.M. Matthijsse).

http://dx.doi.org/10.1016/j.vaccine.2015.08.079
0264-410X/

predicted effectiveness of HPV vaccination [9,12]. However, these studies only varied the proportion of individuals developing lifelong immunity, and hence did not compare different biological mechanisms.

Another important aspect is the extent to which heterogeneity in sexual networks and behaviour is included in the modelling. Deterministic models may not properly account for the complexity of transmission through sexual networks [10,13,14]. The established individual-based simulation model STDSIM is well-designed to capture sexual networks and their dynamics and has recently been used to model the spread of HPV in the Netherlands [16].

In this study, we determined the impact of the current HPV vaccination programme on HPV transmission dynamics and cervical cancer incidence in the Netherlands with the STDSIM microsimulation model [16] and accounting for two different biological mechanisms of acquired immunity. In addition, we estimated the potential impact of alternative vaccination scenarios and strategies, including different coverage levels and the inclusion of boys.

2. Methods

2.1. STDSIM to model HPV transmission and control

We used STDSIM, an established stochastic microsimulation model to study the spread and control of sexually transmitted infections (STIs) [16–19]. The model simulates the life course of individuals in a dynamic heterosexual network, in which STIs, such as HPV, can spread. Each individual has its own characteristics that are either constant (e.g. sex) or subject to change (e.g. infection status). Events are determined by probability distributions, and can lead to new events (e.g. birth leads to a future event of becoming sexually active) or cancellations of future events (e.g. death cancels all scheduled events for this person). More detailed information on the model can be found elsewhere [16–19].

We have previously quantified STDSIM to the Netherlands to model the spread of HPV-16 and HPV-18, which has been extensively described elsewhere [16]. Briefly, we reproduced the Dutch population and its sexual network, based on demographic data [20,21] and national sexual health surveys [22–24]. We then introduced HPV-16 and HPV-18 in the population to estimate the transmission probabilities and acquired immunity dynamics necessary to reproduce the observed age-specific patterns in HPV-16 and HPV-18 prevalence [25–27]. The two mechanisms of acquired immunity after infection clearance used here originate from the previous study by Matthijsse et al. [16]. In the first mechanism, we assumed that everyone acquires full immunity with a variable duration (Weibull distributed; mechanism I). In the second mechanism, we assumed that susceptibility to reinfection decreases cumulatively after each subsequent infection (mechanism II).

2.2. Vaccination scenarios

The base case scenario in our analysis was similar to the vaccination strategy and observed uptake in the Netherlands: a mass vaccination campaign for 13–16-year-old girls in 2009 (50% coverage), and subsequent annual vaccination of 12-year-old girls (60% coverage) [6,7]. Vaccine efficacy was set at 94.7% for HPV-16 and 92.3% for HPV-18 [4], modelled as reduced susceptibility to infection [28]. We modelled this protection to be lifelong, since no evidence of waning has emerged from clinical trials [29]. Furthermore, vaccine efficacy is also still substantial in women previously exposed to HPV-16 and/or HPV-18 [30], hence we assumed that vaccine efficacy is independent of infection status of the girls at the moment of vaccination. Infection clearance is not accelerated by the vaccine in our model [30].

We developed several alternative scenarios to further investigate the potential impact of HPV vaccination. First, we ran the model under different assumptions regarding vaccination coverage from 2016 onwards, ranging from 30% (as was the coverage in the United States) to 100%. Second, we examined the impact of including boys in the vaccination programme from 2016 onwards, using base case target ages and coverage levels for both girls and boys. As bivalent vaccine efficacy estimates for boys are unavailable, efficacy for boys was assumed to be equal to the quadrivalent vaccine efficacy for boys (78.7% for HPV-16; 96.0% for HPV-18) [31]. Third, a preliminary report on a recent longitudinal observational study in the Netherlands showed that vaccine effectiveness against incident HPV-16/18 infections among 14–16-year-old girls was only 73%, considerably lower than the efficacy reported in trials [32]. We therefore developed two conservative scenarios for vaccine efficacy (70% and 80% for both HPV-16 and HPV-18) within the base case scenario. For these lower vaccine efficacies, we also determined the minimum coverage level for girls necessary to reach similar incidence reduction as obtained by the base case scenario.

All scenarios had the vaccine assigned independently of sexual risk behaviour [33], and accounted for the two acquired immunity mechanisms described above.

2.3. Vaccination impact

We calculated the impact of the base case and alternative vaccination scenarios as the relative decrease in HPV-16 and HPV-18 incidence in all women when a steady state is reached compared to the pre-vaccination incidence in 2008. This was also done separately for vaccinated and unvaccinated women, to determine herd immunity effects of HPV vaccination. Furthermore, we looked at HPV-16 and HPV-18 prevalence after vaccination when a steady state is reached.

Based on estimated age-specific HPV-16 and HPV-18 incidence reductions, we also estimated potential effects of the vaccination scenarios on cervical cancer incidence by applying the proportional decrease in age-specific HPV incidence to reported pre-vaccination cervical cancer incidence rates in the Netherlands, assuming that the preventable proportion is the proportion of cancers that are HPV-16 or HPV-18 positive [34]. We used the average number of incident cases in women per age group from 2004 to 2008 (i.e. before the introduction of HPV vaccination) [35]. We then calculated the proportion of these cancers caused by HPV-16 and HPV-18 by applying estimates from Guan et al. [3], who determined the positivity for HPV types in HPV-positive invasive cervical cancer in Western Europe. In cancers with multiple HPV-types present, we assumed that multiplicity of HPV infections occurs at random and that all high risk HPV types prevalent in a cancer are equally likely to have caused the cancer. We also calculated 95% binomial proportion confidence intervals (CIs) of the corrected HPV prevalences using the Clopper–Pearson method. The proportion of cervical cancers caused by HPV-16 and HPV-18 are 62.5% (95% CI: 60.4–64.5%) and 17.2% (95% CI: 15.7–18.8%), respectively. We assumed an average lag time of 20 years between acquiring an HPV infection and cervical cancer, based on the estimated duration to clinical cervical cancer in the MISCAN model [36].

2.4. Simulations

Model runs started in 1911 with almost 10,000 men and over 10,000 women, and ended in 2100 with approximately 60,000 men and 60,000 women. Incidence estimates were averaged over 1000

Please cite this article in press as: Matthijsse SM, et al. The estimated impact of natural immunity on the effectiveness of human papillomavirus vaccination. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.08.079