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Prevention of cervical cancer in rural China: Evaluation of HPV vaccination and primary HPV screening strategies

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ABSTRACT

Comprehensive evaluation of the cost-effectiveness of HPV vaccination in China has not previously been performed. The objective of this study was to evaluate vaccination as an alternative or addition to primary HPV screening with *care*HPV (Qiagen, Gaithersburg, USA), and to assess the threshold total cost per vaccinated girl (CVG) at which strategies involving vaccination would become viable compared to screening-only strategies in rural China. We used data from field studies in Shanxi Province to support modelling of HPV vaccination and screening, including local information on sexual behaviour, HPV prevalence, test accuracy, treatment protocols and costs. We evaluated several strategies involving screening once or twice per lifetime or at regular 5-yearly intervals, with or without vaccination of young females at age 15 years, assuming 70% coverage for both screening and vaccination. We also predicted cross-sectional cancer incidence each year to the year 2050 for a range of strategies. We found that strategies involving vaccination would be cost-effective at CVGs of US$50–54 or less, but at CVGs >$54, screening-only strategies would be more cost-effective. If vaccination of young cohorts is combined with two rounds of *care*HPV screening for women aged 30–59 years in 2012 and 2027, a predicted indicative 33% reduction in cervical cancer incidence by 2030 would be sustained until 2050, with incidence rates decreasing thereafter. In conclusion, taking into account estimated vaccine delivery costs (for 3 doses), a per-dose HPV vaccine cost of approximately <$9–14 would be required for strategies involving vaccination to be cost-effective. Overall, combined screening and vaccination approaches are required to maximise outcomes in rural China.

1. Introduction

Cervical cancer remains an important health problem among women in China, and a significant proportion of the burden is observed in rural settings [1]. New technologies for primary and secondary prevention of disease related to human papillomavirus (HPV) infection, which is causally implicated in virtually all cervical cancers, underpin promising investment opportunities to improve public health. To date, no national cervical screening program has been established in mainland China. Demonstration sites for visual-inspection (VIA) based screening initiatives have been established [2], and a government-sponsored VIA and cytology screening program has been introduced in some regions [3]. However, these technologies rely on extensive quality assurance for continued success, which will be difficult to employ on a large scale throughout China, particularly in rural areas. In addition, VIA screening was not associated with mortality benefit in a large randomised trial in India [4]. In contrast, a single round of HPV screening was associated with a 50% reduction in cervical cancer mortality over relatively short-term (8 year) follow-up [4]. The *care*HPV technology for HPV

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screening, developed by Qiagen (Gaithersburg, MD, USA) with support from PATH (Seattle, WA, USA), has been designed for lower resource settings with a pricing target of <US$5 to accredited programs. A recent study in rural China found *care*HPV to have high sensitivity for cervical intraepithelial neoplasia grade 2 or above (CIN2+) [5] and prior analyses have demonstrated that *care*HPV screening is likely to be cost-effective in this setting [6,7].

Prophylactic HPV vaccines are not yet licensed in China, but at least two in-country Phase III trials are ongoing [8]. These involve the Gardasil (Merck) quadrivalent HPV 16/18/6/11 vaccine and the Cervarix (GSK) bivalent HPV 16/18 vaccine, and are designed to investigate the safety and efficacy of prophylactic HPV vaccination in Chinese females [8]. A second generation vaccine protecting against 7 oncogenic types (and HPV types 6 and 11, implicated in the development of anogenital warts) is on the horizon [9]. There are also efforts within China to develop HPV vaccines, although these are currently at the pre-clinical stage [10–13]. At this stage, it is not known whether a full-scale initiative to vaccinate girls in China will be viable in the foreseeable future, nor is it clear which vaccine would be used.

Because HPV vaccination does not increase the clearance of established infections, it is ideally targeted at young females before sexual debut. Therefore, in principle, the ideal intervention strategy would involve initiation of HPV vaccination of younger cohorts combined with the introduction of a screening intervention targeting older women. Although the cost-effectiveness of a vaccination-only strategy in China has undergone initial assessment as part of broad analyses of several countries [14,15], a comprehensive evaluation specific to China, and taking into account screening options has not previously been performed. Therefore, the aims of this study were to evaluate HPV vaccination as an alternative or addition to primary *care*HPV screening in rural China, and to assess the threshold cost per vaccinated girl (CVG) at which strategies involving vaccination would become viable compared to feasible strategies involving screening in this setting.

2. Methods

2.1. Modelling approach

We used a dynamic model of sexual behaviour and HPV transmission, interfaced with a cohort model of the natural history of CIN, invasive cancer staging and survival, and cervical screening, diagnosis and treatment of precancerous lesions. The structure and parameters were based on previous models [16–18] but adapted to incorporate locally acceptable management pathways for rural China, and all-cause mortality and cervical cancer survival in this setting [7]. Because we have previously found that screening more frequently than every 5 years is not cost-effective in rural China [7], for the current evaluation we considered strategies involving once-lifetime screening at 35 years and twice-lifetime screening at 30 and 45 years, and 5-yearly screening between the ages of 30 and 59 years. We considered each screening strategy alone or in combination with vaccinating 15 year old girls, and also considered a vaccination-only strategy. Based on coverage rates achieved in a demonstration project we assumed screening coverage rates of 70% [7], and for simplicity we assumed the same coverage rate for vaccination; the impact of these assumptions were explored in sensitivity analyses.

2.2. Local data sources

We focused our analysis on rural Shanxi Province in central north China. Shanxi has been thought of as a high risk area for cervical cancer, based in part on the findings of an 1970s mortality survey [19], although more recent survey data indicate much lower rates [20]. Because of its reputation as a high risk area, a number of important cervical cancer studies have been conducted in Shanxi, and our models incorporated self-reported female sexual behaviour information derived from an IARC study [21], test accuracy information on *care*HPV from the PATH-sponsored START project [5], and colposcopy accuracy data from the SPOCCS-1 study [22] (more detail is provided in the Appendix).

2.3. Vaccine assumptions

After consultation with local opinion leaders, we chose 15 years as the most appropriate age for ongoing vaccination of young females (we did not consider catch-up vaccination in this setting). The majority of females in mainland China experience sexual debut at ages >16 years [23]; and in rural Shanxi the majority debut at >18 years [23]. For protection against cervical cancer, a best case approach to vaccine efficacy was taken, and we assumed that the vaccine directly or cross-protected against infection with all oncogenic types; but we did not model the protective effect of HPV vaccination against other cancers or anogenital warts. This approach allowed us to determine the maximum feasible vaccine costs and effects in relation to prevention of cervical cancer. In sensitivity analysis we considered the effects of imperfect vaccine degree of protection, shorter duration of protection and waning of protection (Appendix).

2.4. Costs

The costs of screening, diagnosis and treatment for precancer were collated using a micro-costing approach, and included the costs of consumables, equipment, staff time and transportation. Cervical cancer treatment costs were estimated from a hospital charge audit. More detail and final aggregated costs for screening, diagnosis and treatment are presented in the Appendix. Data on HPV vaccine delivery costs in this setting are not yet available, and therefore we calculated the threshold CVG at which vaccination would be cost-effective. The CVG includes the unit costs for vaccine and delivery costs including wastage, freight and supplies. We used costing studies of Hepatitis B virus (HBV) vaccination in China to derive a feasible range for the proportion of the CVG comprising direct vaccine costs, and thus obtained an indication of the maximum per-dose vaccine cost, assuming administration of 3 doses would be required to confer full protection.

2.5. Pre-intervention predictions and calibration

We calibrated the dynamic model, populated with information on sexual behaviour from females in rural Shanxi, to rates of age-specific oncogenic HPV prevalence in this population [7,21]. To characterise uncertainty in the fitted HPV prevalence, and to inform probabilistic sensitivity analysis (PSA) of the outcomes of the evaluation, we ran the model using a range of assumed values for natural history parameters such as the duration of infection, the waning of naturally conferred immunity and the per-partnership transmission probabilities in different sexual activity groups for males and females (Appendix). The model was run with a total of 10,000 HPV natural history parameter sets, and the output was compared to observed data on HPV prevalence in females aged 15–59 years [21]; models with outputs within range of the observed data were retained.

2.6. Effectiveness and cost-effectiveness evaluations

For each strategy, we calculated the predicted average reduction in age-standardized cervical cancer incidence and mortality (standardized to the WHO world standard population) and the