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

Karen Canfell[a,c,*,1], Ju-Fang Shi[a,b,c,1], Jie-Bin Lew[a], Robert Walker[a], Fang-Hui Zhao[b], Leonardo Simonella[a,c], Jun-Feng Chen[d], Rosa Legood[e], Megan A. Smith[a], Carolyn Nickson[a,f], You-Lin Qiao[b,**]

[a] Cancer Epidemiology Research Unit, Cancer Council NSW, Woolloomooloo, New South Wales, Australia
[b] Department of Cancer Epidemiology, Cancer Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, PR China
[c] School of Public Health, University of Sydney, Australia
[d] Dalian Medical University, Dalian, China
[e] The London School of Hygiene and Tropical Medicine, London, United Kingdom
[f] Centre for Women's Health, Gender and Society, Melbourne School of Population Health, University of Melbourne, Victoria, Australia

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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

* Corresponding author at: Cancer Epidemiology Research Unit, Cancer Council NSW, Woolloomooloo, New South Wales, Australia. Tel.: +61 2 93341852; fax: +61 2 83023550.
** Corresponding author at: Department of Cancer Epidemiology, Cancer Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, PR China. Tel.: +86 10 8778 8489; fax: +86 10 6771 3648.
E-mail addresses: karenc@nswcc.org.au (K. Canfell), qiaoy@cicams.ac.cn (Y.-L. Qiao).
[1] Joint first authors.

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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

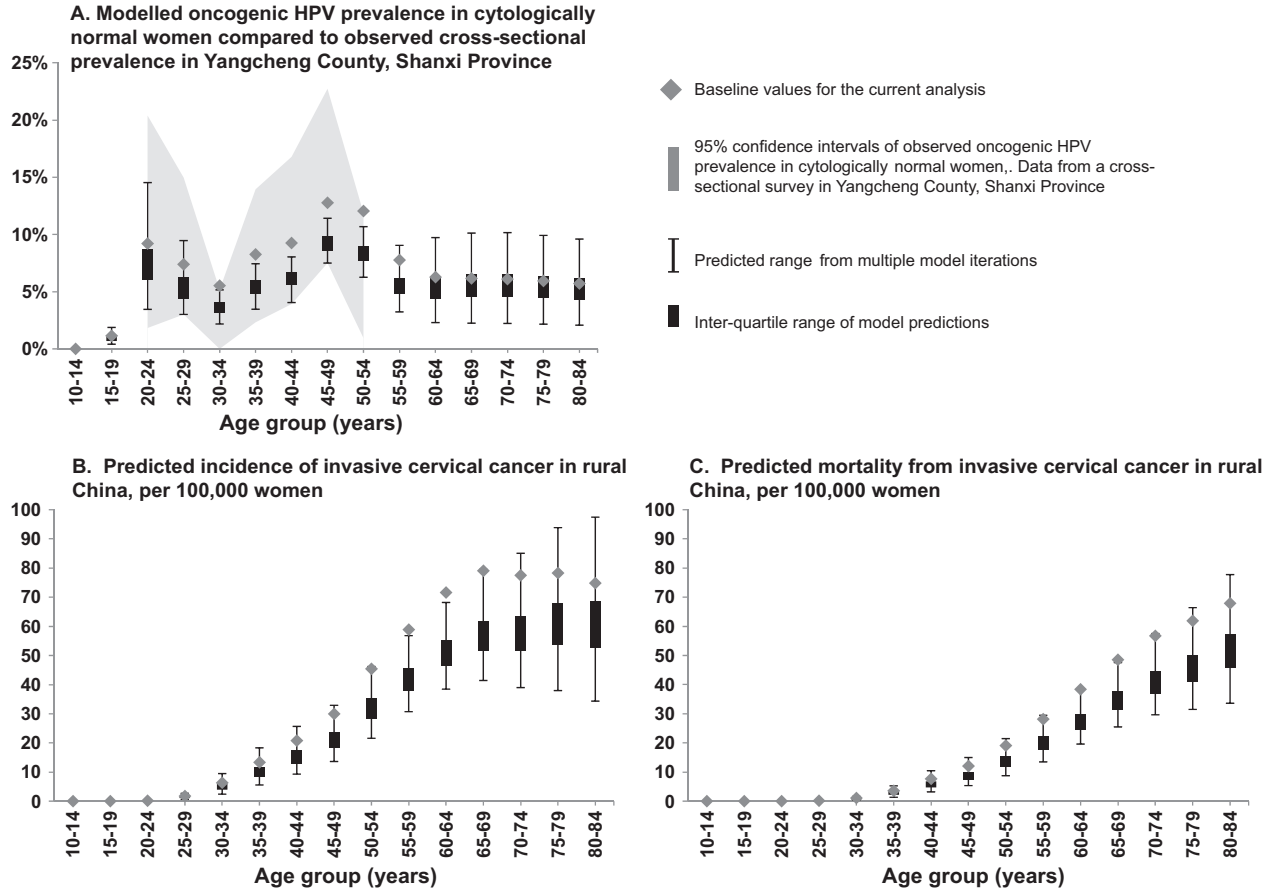

Fig. 1. Fitted age-specific oncogenic HPV prevalence, and predicted cervical cancer incidence and mortality, prior to any intervention.

number of premature deaths averted over the lifetime of 100,000 women. We performed standard cost-effectiveness analyses by identifying the cost-effectiveness frontier and calculating the incremental costs-effectiveness ratio (ICER) of strategies on the frontier compared to the next most cost-effective strategy. We performed threshold analysis to identify the CVG at which the vaccination-only strategy and combined vaccination and screening strategies were cost-effective. We also performed a second form of threshold analysis in which we considered the cost-effectiveness ratio (CER) of each potential strategy in relation to no intervention, and calculated the CVG at which vaccination of young cohorts would be a better alternative to screening these same women when they are older. This form of analysis is in accordance with recommendations to compare each potential intervention to no intervention [24], and gives additional information to policy makers about the trade-off between vaccination-only and screening-only options.

We calculated all cost-effectiveness ratios as cost per life year saved (LYS). A societal perspective was used. A 3% discount rate was used (starting at age 10 years), based on WHO guidelines [25]. Costs were calculated in Chinese Yuan, but presented in US dollars (1 USD = 6.6505 Chinese Yuan; 1 October 2010). The local gross domestic product (GDP) per capita for Shanxi Province (US$3077 in 2008 [26]) was used as the cost-effectiveness threshold for the evaluation; formally, interventions with ICERs less than this value are considered "very cost-effective" [25].

Standard cost-effectiveness analysis based on lifetime effects and costs for a single cohort cannot fully characterise the combined effect of screening and vaccination when these are implemented across women of different ages in the population. To quantify the cross-sectional effect of each intervention strategy, we used a multiple cohort approach to characterise different levels of risk in vaccinated cohorts (taking into account herd immunity for the effect of vaccination on reducing infections) and to model either rounds of once- or twice-off screening at specific times, or regular screening. For this analysis, we assumed vaccination will commence in 2012 and/or that *care*HPV screening of women aged 30–59 years will be conducted in one or two rounds in 2012 and/or 2027, or that regular 5-yearly screening will be initiated in 2012. We then determined the reduction in cancer incidence in the population by the year 2050 and estimated average discounted annual costs for Shanxi Province (starting discounting in 2010) and the associated cost per female aged 15–84 years over the short term (2012–2020) and the longer term (2012–2050), using recent population data from Shanxi (see the Appendix).

2.7. Sensitivity analysis

We performed extensive sensitivity analysis of the findings, using one-way and PSA approaches to assess the uncertainty of the trade-off for screening vs. vaccination strategies. The PSA allowed exploration of the joint uncertainty in costs and effects across natural history parameters, screening and vaccination parameters and costs. The baseline parameters and parameters for sensitivity analysis are summarized in the Appendix.

3. Results

Fig. 1 shows the predictions for age-specific HPV prevalence, and cervical cancer incidence and mortality prior to any intervention. The observed HPV prevalence among cytologically normal women shows a "flat" or "double-peak" pattern by age in this population [21]. The model-fitted HPV prevalence for women

Table 1
Predicted average reduction in age-standardized cervical cancer incidence and mortality, and number of deaths averted over the lifetime of 100,000 women, to age 85 years, compared to no intervention (at coverage rates of 70% for both screening and vaccination).

Intervention strategy	Incidence	Mortality	Number of deaths averted over the lifetime of 100,000 women
Once-lifetime screening (at 35 years)	9.3%	11.2%	93
Twice-lifetime screening (at 30 + 45 years)	19.1%	22.1%	189
5-Yearly screening (between 30 and 59 years)	37.1%	42.6%	374
Vaccination only (at 15 years)	70.4%	70.0%	612
Once-lifetime screening (at 35 years) + Vaccination (at 15 years)	73.2%	73.5%	640
Twice-lifetime screening (at 30 + 45 years) + Vaccination (at 15 years)	76.2%	76.8%	670
5-Yearly screening (between 30 and 59 years) + Vaccination (at 15 years)	81.7%	83.0%	726

Table 2
Implied maximum per dose vaccine cost under various threshold CVGs.

	Threshold CVG	Approximate threshold per dose cost[a]
A. For strategies involving vaccination to be cost-effective, compared to the next most cost-effective strategy		
Twice-lifetime screening and vaccination (on the cost-effectiveness frontier and the ICER equal to the local GDP per capita)	$54	$10–14
Once-lifetime screening and vaccination	$52	$10–13
Vaccination only	$50	$9–13
B. For vaccination-only to be a better alternative to screening-only strategies, compared to no intervention		
Vaccination vs. 5-yearly screening	$39	$7–10
Vaccination vs. twice-lifetime screening	$30	$6–8
Vaccination vs. once-lifetime screening	$29	$5–7

[a] Based on a feasible range of delivery costs from 25% to 44% per vaccinated girl, and assuming 3 doses are delivered.

without CIN reflected this pattern, and the age-standardised prevalence was 8.0% (range: 3.5–8.4%); consistent with the observed prevalence of 8.1% (95% CI: 2.1–13.6%). Corresponding baseline estimates and ranges for the age-standardized cervical cancer incidence and mortality were 18.5 (range: 9.1–20.1) and 9.6 (range: 4.7–10.4) per 100,000 women, respectively. Although local data from IARC-certified registries are not available in Shanxi Province, the predicted baseline incidence is within the range of the calculated average rate observed in less-developed countries in IARC registries; which is between 16 [27] and 22 [28] per 100,000 women. The predicted mortality to incidence ratio for this rural setting is 0.52, which is, as expected, somewhat higher than a recent estimate of the national value for China (0.44) [29].

Table 1 shows the predicted effectiveness of each strategy. The reduction in age-standardized cancer incidence over the lifetime of the cohort ranges from ~9% (for once-lifetime screening) to 82% (for vaccination with 5-yearly screening), with corresponding reductions in cancer mortality (11–83%), and in the number of premature deaths averted over the lifetime of 100,000 women (93–726 deaths). Slightly higher reductions in mortality compared to incidence are predicted for the strategies involving screening, due to the detection and treatment of early stage cancer cases in this previously unscreened population. Fig. 2 shows the results of the incremental cost-effectiveness analysis, depicting the cost-effectiveness frontier curves at CVGs of $50 and $87. At a CVG of $50 or less, all strategies are on the frontier. At a CVG of $52, vaccination-only is not cost-effective but vaccination combined with once or twice-lifetime screening is cost-effective; and at CVG of $54, a combined strategy with twice-lifetime screening (but not once-lifetime screening) would be cost-effective. For CVG values of >$54, all strategies involving vaccination are either dominated by screening-only strategies, or too expensive to be cost-effective. We

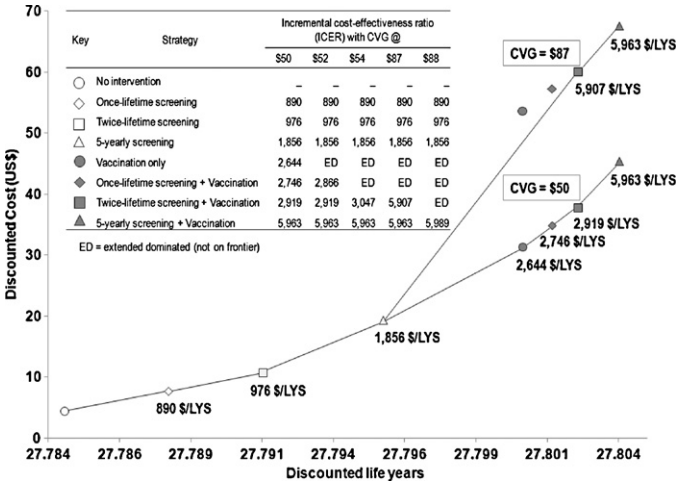

Fig. 2. Incremental cost-effectiveness frontier as a function of cost per vaccinated girl (CVG). The figures depicted on the frontier curves indicate the ICER for non-dominated strategies. If an intervention's ICER is less than the local GDP per capita ($3077 in Shanxi Province), it is considered very cost-effective.

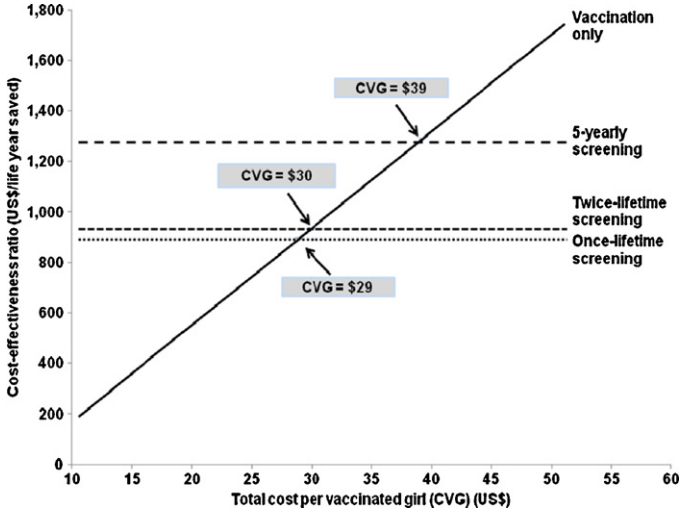

Fig. 3. Cost-effectiveness ratio (CER) for various vaccination-only and screening-only strategies compared to no intervention, as a function of cost per vaccinated girl (CVG). The marked points indicate the CVG at which the cost-effectiveness of a vaccination-only strategy is equivalent to the screening-only strategy, compared to no intervention.

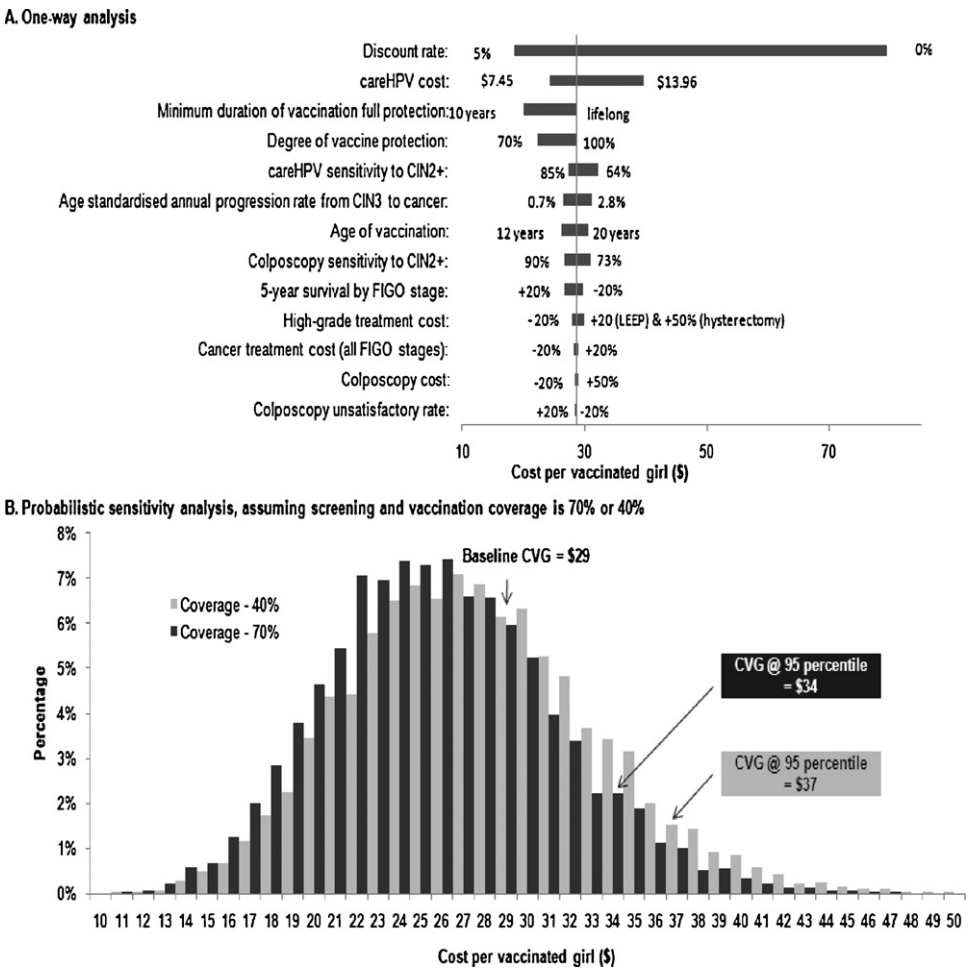

Fig. 4. A. One-way sensitivity analysis for threshold CVG at $29, for vaccination-only to be as cost-effective as once-lifetime screening, compared to no intervention. The costs of *care*HPV and other screening and diagnostic tests used in the sensitivity analysis are aggregated and include consumables, labour and equipment, as well as the unit test cost. B. The result of the PSA at coverage rates of 70% and 40% for both screening and vaccination, demonstrating that the baseline estimate of $29 for the threshold CVG at is at the higher end of the range of feasible values; 95% of model iterations in the PSA found a threshold CVG of ~$34 or less when screening and vaccination coverage rates were 70%. A similar pattern was obtained for the much lower coverage rate of 40% but with 95% of values indicating a CVG of ~$37 or less (<10% difference), showing that the results are relatively robust to the coverage assumptions made in the analysis. The modest difference observed with lower coverage is due in part to the allocation of overhead costs of screening increasing the per-woman cost, which in turn slightly raises the maximum CVG for vaccination. (However, since the per-girl allocation of overhead costs for vaccination is also expected to increase at lower coverage rates, this finding does not necessarily imply an increase in the per-dose maximum vaccine cost.). Parameters varied and distributions used in sensitivity analyses are described in the Appendix.

found that vaccination combined with regular 5-yearly screening was not cost-effective even at low CVGs because the incremental costs were too expensive compared to vaccination combined with twice-lifetime screening. For HBV vaccination in China, the proportion of total vaccination costs related to direct vaccine costs for 3 doses has been reported as 56–75% [30–32]; this range is consistent with prior HPV vaccination evaluations in developing countries [14,33,34]. Thus, the maximum vaccine unit cost per dose in order for strategies involving vaccination to be cost-effective, implied by our maximum CVG of $50–54, is $9–14 (Table 2).

Fig. 3 shows the results for the cost-effectiveness ratio (CER) of screening-only and vaccination-only strategies, compared to no intervention, as a function of the CVG. For the CER of vaccination to be equivalent to the CERs of once-lifetime, twice-lifetime, and 5-yearly screening, the CVG would need to be less than $29, $30 and $39, respectively. Fig. 4a shows the one-way sensitivity analysis for the trade-off between vaccination and once-lifetime screening. Other than the discount rate, the results are most sensitive to the cost and sensitivity of *care*HPV testing, and the duration and degree of vaccination protection, with lower vaccine efficacy assumptions and more favourable assumptions about screening both associated with a decreased threshold CVG. Fig. 4b shows the PSA findings, demonstrating that the baseline CVG estimate is at the upper end of the feasible range and that it is robust to screening and vaccination coverage assumptions, varying by <10% when coverage was varied from 40 to 70%.

An indicative predicted age-standardized rate of cervical cancer by calendar year in rural China is depicted in Fig. 5. Screening rounds in women aged 30–59 years will lead to a transient increase in cancer incidence due to detection of prevalent cancer, but cancer incidence rates would thereafter decrease due to detection and treatment of CIN. Cancer rates across the population are predicted to decrease by 33% for vaccination and two rounds of screening, or by >50% for vaccination combined with regular screening, by the year 2050. The discounted annual costs for Shanxi Province are also depicted in Fig. 5 (for a CVG of $50), and the equivalent average annual cost per woman for each strategy is given in Fig. 6. As expected, once-off screening strategies were associated with the lowest cost (averaged over the longer term), whereas combined vaccination and regular 5-yearly screening was associated

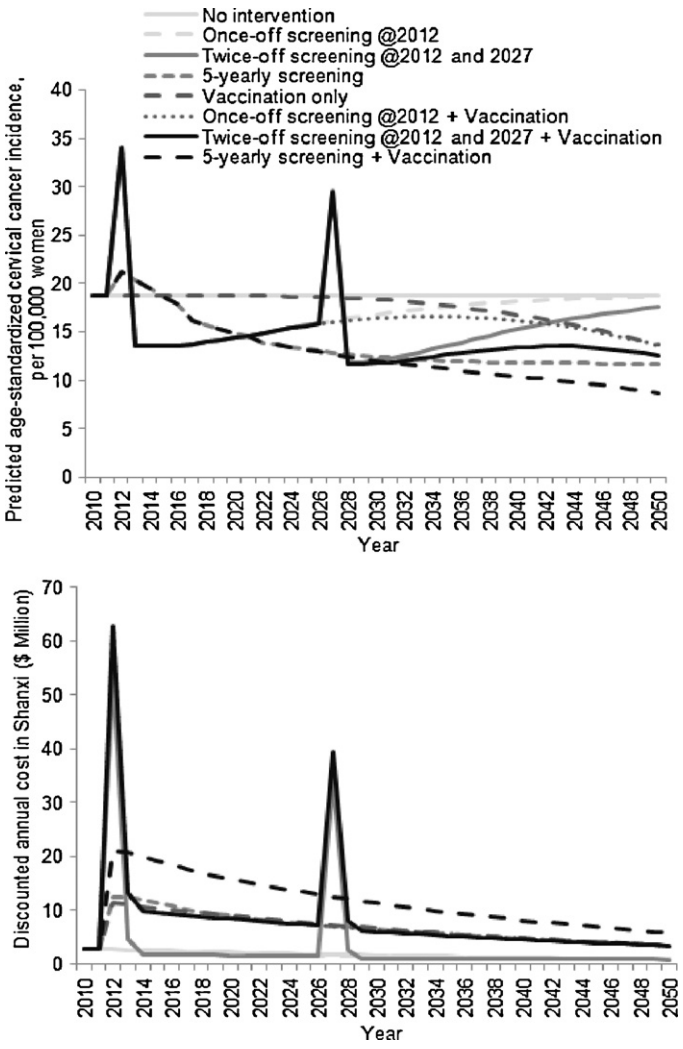

Fig. 5. Indicative predicted age-standardized cervical cancer incidence and the total annual costs in rural Shanxi Province (for CVG at $50), by calendar year, assuming 70% coverage rates for screening and vaccination. Screening rounds involving women aged 30–59 years occurring in 2012 and 2027 would lead to a transient increase in incidence due to detection of prevalent invasive cancer, but rates would thereafter decrease due to detection and treatment of CIN lesions. Ongoing vaccination of 15 year old girls starting in 2012 would begin to decrease cancer incidence after about 2025. Performing two rounds of screening combined with vaccination would lead to lower rates of invasive cancer in the years before the effect of vaccination is observed.

with the highest cost. The average annual discounted cost per woman aged 15–84 years varied from $0.68 to 1.58 over the short term (2012–2020) and from $0.24 to 1.01 over the longer term (2012–2050). The predicted average annual cost per woman for implementing vaccination and two rounds of screening between 2012 and 2050 was $0.74.

4. Discussion

To our knowledge, this is the first comprehensive analysis of the predicted effects and costs of HPV vaccination in rural China. We modelled the local context in detail, focusing on setting-specific data sources; and included an evaluation of combined screening and vaccination strategies. We found that for strategies involving vaccination to be cost-effective, the maximum cost per vaccinated girl would need to be US$50–54; and for vaccination-only to be as cost-effective as screening-only (compared to no intervention), the maximum CVG would need to be $29–39. This implies a maximum per-dose vaccine cost of between $9 and 14 for cost-effectiveness and between $5 and 10 for vaccination-only vs. screening-only equivalence. However, these per-dose cost estimates must be considered provisional and are dependent on a number of further assumptions including vaccine delivery costs, for which direct data are not available in this setting, and the requirement for three doses to achieve full efficacy (clinical studies to assess the efficacy of 2 vs. 3-dose vaccination are ongoing). In the baseline analysis we made generous vaccination efficacy assumptions in order to quantify the maximum acceptable vaccine costs in relation to cervical cancer prevention; but we demonstrated in sensitivity analysis that if lower vaccine efficacy is assumed the maximum acceptable vaccine cost decreases. Thus, our analysis provides policy-makers with an "upper end" estimate of the vaccination cost in relation to its potential impact on cervical cancer.

Prior work has included China as part of broad analysis of HPV vaccination-only strategies across several countries [14,15]; although not directly comparable, this estimate of the cost-effectiveness of HPV vaccination in China may be less favorable than our findings for rural China. The difference is likely to result, in part, from the higher assumed rates of endemic cervical cancer in our study, which specifically considered a rural population in China, leading to an increased estimate of vaccine effectiveness in saving years of life. Our more favourable estimates for the impact of vaccination again imply that our estimate of the maximum acceptable CVG is likely to be at the "upper end" in relation to cervical cancer prevention.

Although we found that vaccination-only and some combined strategies would be cost-effective at CVGs of ~$50, there remains the further question of affordability. The discounted annualised per-woman cost of vaccination with two rounds of screening appears quite modest ($0.74 to the year 2050), but the total costs in Shanxi Province would be considerable, approximately $8M per annum at a CVG of $50. China is no longer considered a GAVI-eligible country and thus may not receive extensive financial assistance for HPV vaccine supply. Health care delivery in this setting is organised at a local level with national funding for specific initiatives such as vaccination programs. However, in many situations, direct patient costs such as consumables and vaccines may have to be partially covered privately. It is likely that women's willingness-to-pay for the vaccine in this setting will be very limited; only 7.6% of 3011 urban women and 0.4% of 3013 rural women in China self-reported being willing to pay US$15 or more; and more than 60% of surveyed women reported that the acceptable price for 3-dose HPV vaccination is <US$7 [35], which is much lower than the range identified in this analysis. Therefore, it is possible that for the vaccine to be adopted in this setting, the price would need to be considerably lower than the range implied by cost-effectiveness analysis, or alternative financing mechanisms would be required.

We quantified the population-level impact of various prevention strategies, finding that ongoing vaccination combined with two rounds of screening would provide a balance between a requirement to implement cost-effective strategies, whilst yielding short and long term cervical cancer reductions in the population. In this situation, cancer incidence rates would be reduced by 33% in 2030, due mainly to screening, and stay close to this level until 2050, due to the combined effect of screening and vaccination. Although the projected decline in cervical cancer incidence is substantial, it remains limited by several factors including imperfect coverage for screening and vaccination, imperfect screening and diagnostic sensitivity and treatment efficacy, and insufficient time (even by 2050) for the full protective effect of the vaccination of younger cohorts to become apparent. We found that the most effective strategy was vaccination combined with regular 5-yearly screening; for this strategy cancer rates in 2050 would be reduced by more than half. However, this strategy was not found to be cost-effective

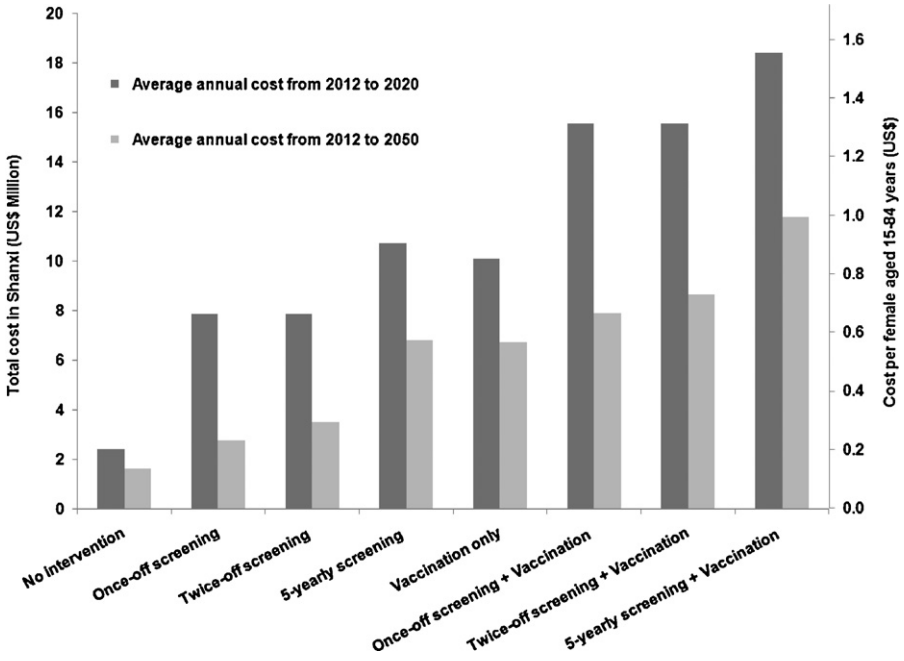

Fig. 6. Predicted average annual total costs and average annual costs per female in Shanxi Province (for CVG at $50).

when compared to vaccination combined with two rounds of screening.

In conclusion, this study provides a unique analysis, based on substantive epidemiological and costing data, of the potential long term effects and costs of adopting primary, secondary or combined strategies for cervical cancer prevention in rural China. Our findings indicate that at current international market prices for the HPV vaccine, this intervention may not be as cost-effective as cervical cancer prevention approaches which involve screening alone. However, the findings of this analysis also imply that the greatest health gains in rural China will be achieved if the implementation of HPV vaccination in adolescent girls is combined with at least two rounds of HPV screening in older women.

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Contributors: KC, JFS, JBL and YLQ had full access to all interim outputs and data from the model, and had responsibility for the integrity of the study and accuracy of the analysis. KC and YLQ were responsible for the study concept and design. JFS, FHZ, LS, JFC and YLQ acquired the data used for the model via field studies and literature review. KC, JFS, JBL and YLQ conceived the management pathways used, and analysed and interpreted the data. JFS was responsible for cost data collation with assistance from RL and JFC. JBL was primarily responsible for model implementation with assistance from RW, MAS and CN. KC and JFS drafted the manuscript. All co-authors revised the manuscript. *Conflict of interest statement:* JFS, FHZ and YLQ have been involved in epidemiologic and clinical studies in China supported by MSD and GSK. YLQ has served as a consultant to MSD. The other co-authors declare no potential conflicts of interest.

Appendix A. Detailed modelling methods

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2010.12.085.

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