

# Human papillomavirus–16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong

CME

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**Objective** To assess the immunogenicity and safety of human papillomavirus–16/18 AS04-adjuvanted cervical cancer vaccine in Chinese women aged 18 to 35 years enrolled from Hong Kong.

**Design** Double-blind, randomised controlled trial with vaccine and placebo groups.

**Setting** Single-centre study in Hong Kong.

**Participants** Three hundred women enrolled (150 per group) between March 2006 and June 2007.

**Interventions** Subjects received three doses of human papillomavirus–16/18 vaccine or placebo (aluminium hydroxide), administered intramuscularly at 0, 1, and 6 months.

**Main outcome measures** Human papillomavirus–16/18 seroconversion rates and geometric mean titres at month 7 (in human papillomavirus–16/18 recipients); reactogenicity and safety (in all subjects).

**Results** A total of 294 women completed the study (148 in the vaccine group, 146 in placebo group). All initially seronegative subjects in the vaccine group had seroconverted for human papillomavirus–16/18 antibodies by month 7. Anti-human papillomavirus–16 and anti-human papillomavirus–18 antibody geometric mean titres were 10 422 (95% confidence interval, 8730–12 442) EL.U/mL and 4649 (3975–5437) EL.U/mL, respectively. High compliance (99% in both groups) was observed for the three-vaccination course. The frequencies of local injection site reactions were higher in the vaccine than placebo group; pain being the most common symptom in both groups. Regarding solicited symptoms, fatigue and myalgia were the most frequent in both groups. Five serious adverse events (four in vaccine group, one in placebo group) were reported, but all were considered unrelated to the vaccinations.

**Conclusion** The human papillomavirus–16/18 AS04-adjuvanted vaccine was highly immunogenic, safe, and generally well tolerated in Chinese women from Hong Kong.

## Key words

Adjuvants, immunologic; Cervical intraepithelial neoplasia; Human papillomavirus 16; Human papillomavirus 18; Uterine cervical neoplasms

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## Introduction

Cervical cancer is the second most common cancer in women worldwide; the global disease burden in 2007 amounting to nearly 555 100 new cases and 309 800 deaths.<sup>1</sup> In Hong Kong, which has emerged as a new affluent economic area in Asia, cervical cancer was reported as the eighth most common cause of cancer-related deaths in women in 2007.<sup>2</sup> According to the Hong Kong Cancer Registry, there were 129 registered cervical cancer deaths (accounting for 2.7% of all cancer registered deaths in women) in that year.<sup>2</sup> The corresponding crude death rate was 3.5/100 000 women and the age-standardised mortality rate was reported as 2.3/100 000.<sup>2</sup> An opportunistic ‘record and recall’ Cervical Screening Programme has been launched in March 2004 by the Hong Kong Department of Health in collaboration with health care providers in the public and private sectors. Despite this programme, the chance of developing cervical cancer in the lifetime of a Hong Kong woman is estimated to be as high as 1 in 104,<sup>3</sup> which therefore remains a matter of concern.<sup>4</sup>

The causal association between oncogenic human papillomavirus (HPV) infection and cervical cancer is well established.<sup>5</sup> There are about 200 different HPV types that have been identified; 15 of which are considered high-risk types that are associated with cervical

## 以AS04佐劑的人類乳頭瘤病毒-16/18子宮頸癌疫苗對香港華籍婦女的抗體水平和安全性

<b>目的</b>	評估以AS04佐劑的人類乳頭瘤病毒-16/18子宮頸癌疫苗對18至35歲香港華籍婦女的抗體水平和安全性。
<b>設計</b>	以疫苗組和安慰劑組進行雙盲隨機控制測試。
<b>安排</b>	單一機構研究，香港。
<b>參與者</b>	2006年3月至2007年6月期間參與的300名婦女（每組150人）。
<b>干預</b>	他們於測試開始、1個月和6個月分別接受三針人類乳頭瘤病毒-16/18疫苗或安慰劑（氫氧化鋁）肌肉注射。
<b>主要結果測量</b>	疫苗組於注射人類乳頭瘤病毒-16/18後7個月的血清轉化率和幾何平均滴度，以及所有參與者的致反應作用和安全性。
<b>結果</b>	共294名婦女（疫苗組148名、安慰劑組146名）完成研究。疫苗組內所有最初帶血清陰性的婦女於注射人類乳頭瘤病毒-16/18抗體7個月後均有血清轉換情況。抗人類乳頭瘤病毒-16和抗人類乳頭瘤病毒-18抗體的幾何平均滴度分別為10 422（95%置信區間，8730-12 442）EL.U/mL和4649（3975-5437）EL.U/mL。研究也顯示參與者於三針療程的高順從性（兩組均達99%）。較多疫苗組婦女於注射部位出現局部反應；而疼痛是兩組最常見的症狀。疲勞和肌痛為兩組最普遍的預見症狀。5名參與者（疫苗組4名、安慰劑組1名）出現嚴重不良反應，但全部均與疫苗接種無關。
<b>結論</b>	以AS04佐劑的人類乳頭瘤病毒-16/18疫苗具高度抗體水平和安全，且對香港華籍婦女的耐受性也較高。

cancer. Of the different types identified, HPV-16 and -18 are the most common oncogenic types globally,<sup>6</sup> and contribute to over 70% of all invasive cervical cancer cases worldwide.<sup>7,8</sup> Most of the other high-risk types have a phylogenetic relation with either HPV-16 (-31, -33, -35, -52, and -58) or HPV-18 (-39, -45, -59, and -68). The distribution of these oncogenic HPV serotypes may vary in different parts of the world.<sup>9</sup> In Asia, HPV-16 and -18 are the most commonly reported in women with invasive cervical cancer, followed by HPV-58, -33, and -52.<sup>10</sup> Previously published studies have also confirmed a higher prevalence of HPV-16 and -18 in Hong Kong Chinese women.<sup>11,12</sup>

The cervical cancer burden can be reduced by vaccination against certain HPV types. This strategy is being rapidly established as the new paradigm for cervical cancer prevention. The World Health Organization (WHO) recognises cervical cancer and other HPV-related diseases as a global health problem and recommends the inclusion of routine HPV vaccination in national immunisation programmes.<sup>13</sup> The HPV-16/18 AS04-adjuvanted

vaccine (Cervarix; GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium) is now licensed in at least 100 countries worldwide. Large randomised trials have demonstrated that the vaccine has a good safety profile and high efficacy for reducing high-grade cervical intraepithelial neoplasia (CIN) caused by HPV-16 and -18.<sup>8,14,15</sup> In Hong Kong, the HPV-16/18 AS04-adjuvanted vaccine was licensed in 2008 for women aged 10 to 25 years. While a large amount of data is available regarding the immunogenicity, safety, and efficacy of this vaccine worldwide, there are limited corresponding data available about this vaccine's impact in women from China (including Hong Kong).

This study therefore aimed to evaluate the immunogenicity, safety, and reactogenicity of the HPV-16/18 AS04-adjuvanted cervical cancer vaccine when administered to women of Chinese ethnicity residing in Hong Kong.

## Methods

### Study design

Healthy women aged 18 to 35 years were enrolled in this double-blind, single-centre study conducted in Hong Kong after providing written informed consent. Subjects were randomised (1:1) to receive either the HPV-16/18 AS04-adjuvanted vaccine or placebo. Women who were receiving any investigational or non-registered drug or vaccine were excluded, as were those who had received AS04-adjuvant or HPV vaccine. Those having a chronic disease (eg cancer or autoimmune disorder), or were pregnant, breastfeeding or planning to conceive were also excluded.

The study was conducted in accordance with Good Clinical Practice guidelines. The study protocol was approved by the Independent Ethics Committee for an investigational centre (study number: 106001; www.clinicaltrials.gov: NCT00306241).

### Study vaccine composition

Each dose (0.5 mL) of the HPV-16/18 vaccine contained 20 µg each of HPV-16 and -18 L1 (structural protein of HPV) virus-like particle (VLP) and adjuvanted with a proprietary AS04 (3-O-desacyl-4'-monophosphoryl lipid [50 µg] adsorbed on aluminium hydroxide [Al(OH)<sub>3</sub>, 500 µg]).

The placebo (manufactured by GSK) consisted of 500 µg of aluminium as Al(OH)<sub>3</sub> without any viral antigen.

Three doses of either the HPV-16/18 L1 VLPAS04-adjuvanted vaccine or placebo were administered intramuscularly at months 0, 1, and 6. All subjects were followed up until month 7.

## Randomisation sequence and allocation

The randomisation of study vaccine or placebo was performed at GSK Biologicals, Rixensart, using a standard Statistical Analysis System (SAS Institute, North Carolina, US) program. The investigator was responsible for implementing randomisation sequence at the study site. Randomisation was performed at two levels:

### (1) Randomisation of supplies

A randomisation list was generated using a standard SAS program and was used to number the vaccines. Randomisation was in blocks (to attain a 1:1 ratio) to achieve a balanced treatment allocation throughout the study. A single treatment number was used for each patient to uniquely identify the doses administered to the subject.

### (2) Randomisation of subjects

Age stratification (18-25 years and 26-35 years) was used for all the enrolled subjects to ensure that an approximately equal number of subjects were enrolled in each stratum. Treatment allocation was performed at the investigator site using a central randomisation system on the internet (SBIR). The randomisation algorithm used a minimisation procedure upon being provided with a subject number and the subject's age in order to determine the subject's treatment number.

Thus, randomisation was not performed separately for the stratified and balanced blocks.

## Assessment of immunogenicity

Serum samples were collected from subjects pre-vaccination and at month 7 (ie 1 month post-dose 3) to evaluate the antibody response against HPV types -16 and -18 using enzyme-linked immunosorbent assay (ELISA) [Methodology of MedImmune, UK, adapted by GSK Biologicals]. The assay cut-offs for anti-HPV-16 and anti-HPV-18 antibodies were 8 ELISA units/millilitre (EL.U/mL) and 7 EL.U/mL, respectively.

Seroconversion/seropositivity rates for anti-HPV-16 and anti-HPV-18 antibodies were calculated with their 95% confidence intervals (CIs). Geometric mean antibody titres (GMTs) with 95% CIs and the antibody titre ranges were also tabulated. For antibody titres below the assay cut-off, an arbitrary value of half of the cut-off was used for GMT calculations.

## Assessment of safety and reactogenicity

Each subject used diary cards to record solicited local symptoms (pain, redness, and swelling at the injection site) and solicited general symptoms for 7 days (days

0-6) following each vaccine dose. Solicited general symptoms were fever, headache, fatigue, gastrointestinal disturbance (nausea, vomiting, diarrhoea, and/or abdominal pain), arthralgia, myalgia, rash, and urticaria. The intensity of each adverse event was graded on a 3-point scale (from 1 to 3) based on the extent of discomfort experienced. Grade 3 (the most severe) symptoms were defined as pain preventing normal day-to-day activity, redness and swelling over part of the body exceeding a diameter of 50 mm, fever with an axillary temperature of higher than 39.0°C, urticaria over four parts of the body, or any other general symptoms that interfered with normal activities.

The percentage of doses followed by solicited (local and general) and unsolicited symptoms during the 7-day and 30-day follow-up period, respectively were calculated with their exact 95% CIs. During the entire study period, serious adverse events (SAEs), medically significant conditions, pregnancies, and new-onset chronic diseases such as asthma, type 1 diabetes, allergies, and autoimmune disorders were recorded. Medically significant conditions were defined as events that prompted emergency room or physician visits unrelated to common diseases or routine visits for physical examination or vaccination. New-onset chronic diseases were those based on a review of the subject's pre-vaccination medical history.

## Statistical analysis

The primary immunogenicity analysis was performed on the according-to-protocol cohort, which included subjects who met eligibility criteria, complied with protocol-defined procedures, and for whom post-vaccination assay results were available for antibodies against at least one study vaccine antigen. Primary analysis of safety was on the total vaccinated cohort (ie all subjects who received at least one dose of the vaccine).

A sample size of 120 evaluable subjects was required in the vaccine group to demonstrate, with at least 92% power, that seroconversion rates obtained for HPV-16 and HPV-18 antigens 1 month after the complete vaccination course were no less than 90%. Statistical analysis was performed using Proc StatXact 5.0 software (Cytel Software Corporation, Massachusetts, US) through SAS.

## Results

### Demography and attrition

Between March 2006 and June 2007, a total of 300 women were enrolled, randomised into two groups (150 each) and vaccinated with at least one dose of vaccine or placebo (total vaccinated cohort). All

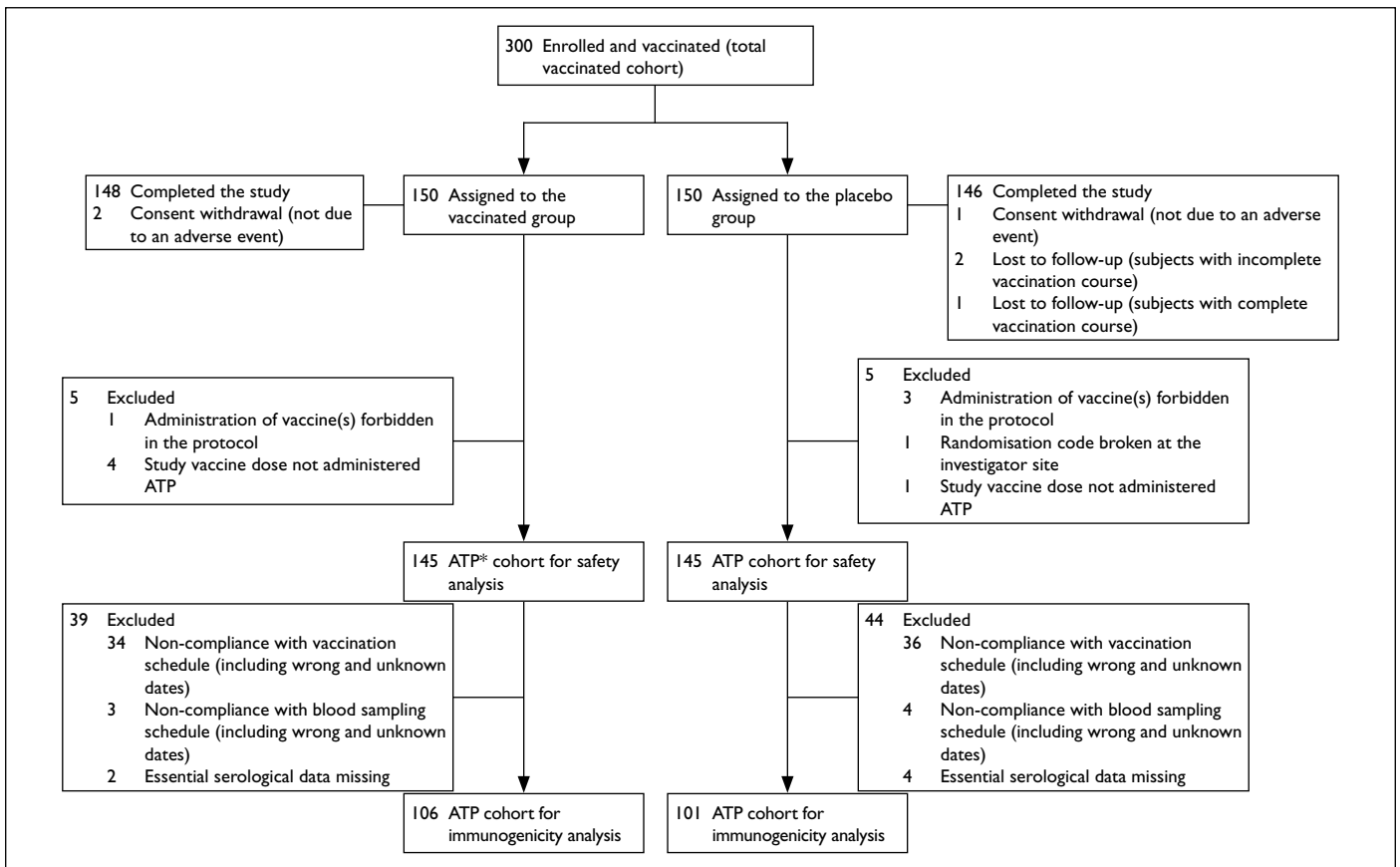


FIG 1. Study participants flowchart  
\* ATP denotes according-to-protocol

TABLE I. Baseline serological status (total vaccinated cohort)

Serological status for HPV-16 and -18 antibodies*		No. (%) of subjects†	
HPV-16 IgG	HPV-18 IgG	Vaccine group (n=150)	Placebo group (n=150)
Seropositive	Seropositive	9 (6)	3 (2)
Seropositive	Seronegative	12 (8)	8 (5)
Seronegative	Seropositive	12 (8)	9 (6)
Seronegative	Seronegative	114 (76)	126 (84)
Serology not available for at least one vaccine antigen		3 (-)	4 (-)

\* HPV denotes human papillomavirus, and IgG immunoglobulin G  
† Vaccine group = subjects who received the HPV-16/18 L1 virus-like particle AS04-adjuvanted vaccine; placebo group = subjects who received aluminium hydroxide

subjects were of Chinese ethnicity and had a mean age of 26 (standard deviation, 4) years. Of these, 294 women completed the study (148 in the vaccine group, and 146 in the placebo group) [Fig 1].

**Immunogenicity**

Baseline serological status (total vaccinated cohort) prior to vaccination showed that the majority of

subjects in the vaccine (76%) and placebo (84%) groups were seronegative for both HPV-16 and HPV-18 antibodies (Table 1).

In the according-to-protocol cohort for immunogenicity, all initially seronegative subjects in the vaccine group had seroconverted for both anti-HPV-16 and anti-HPV-18 antibodies by month 7 (Tables 2 and 3). In the placebo group, 2% had seroconverted for anti-HPV-16 antibodies by month 7 (Tables 2 and 3). Additionally at month 7, respective GMTs of 10 422 (95% CI, 8730-12 442) EL.U/mL and 4649 (95% CI, 3975-5437) EL.U/mL were observed for anti-HPV-16 and anti-HPV-18 antibodies in initially seronegative subjects in the vaccine group.

All initially seropositive subjects in the vaccine group remained seropositive at month 7 (Tables 2 and 3). At month 7, seropositive vaccine recipients demonstrated anti-HPV-16 and anti-HPV-18 GMTs of 6511 (95% CI, 4491-9440) EL.U/mL and 4055 (95% CI, 2981-5514) EL.U/mL, respectively.

**Safety and reactogenicity**

Compliance in returning the filled-in diary card (all doses) was high (>99% in both groups). The

TABLE 2. Immune response to human papillomavirus (HPV)-16 (according-to-protocol cohort)

Pre-vaccination status/timing	No.†	Antibody titre $\geq 8$ EL.U/mL (95% confidence interval)‡	GMT (95% confidence interval) [EL.U/mL]¶
<b>Vaccine group*</b>			
Seronegative†			
Pre-vaccination	87	0 (0-4)	4 (4-4)
1 month post-dose 3	87	100 (96-100)	10 422 (8730-12 442)
Seropositive†			
Pre-vaccination	18	100 (82-100)	37 (22-61)
1 month post-dose 3	18	100 (82-100)	6511 (4491-9440)
Total			
Pre-vaccination	105	17 (11-26)	6 (5-7)
1 month post-dose 3	105	100 (97-100)	9614 (8182-11 297)
<b>Placebo group*</b>			
Seronegative†			
Pre-vaccination	90	0 (0-4)	4 (4-4)
1 month post-dose 3	90	2 (0.3-8)	4 (4-5)
Seropositive†			
Pre-vaccination	10	100 (69-100)	30 (15-58)
1 month post-dose 3	10	90 (56-100)	21 (9-46)
Total			
Pre-vaccination	100	10 (5-18)	5 (4-6)
1 month post-dose 3	100	11 (6-19)	5 (4-6)

\* Vaccine group = subjects who received the HPV-16/18 L1 virus-like particle AS04-adjuvanted vaccine; placebo group = subjects who received aluminium hydroxide

† Seronegative: subjects with antibody titre <8 EL.U/mL prior to vaccination; seropositive: subjects with antibody titre  $\geq 8$  EL.U/mL prior to vaccination

‡ No. of subjects with pre-vaccination results available in each group

§ Percentage of subjects with concentration within specified range

¶ Geometric mean antibody titres (GMT) calculated on all subjects

proportion of patients with solicited and unsolicited symptoms was generally higher in the vaccine group (90% [95% CI, 86-92%] of all administered doses) than the placebo group (77% [95% CI, 72-81%] of all administered doses) during the 30-day (days 0-29) post-vaccination follow-up period.

The frequencies of solicited local injection site symptoms (pain, redness, and swelling) were higher in the vaccine than the placebo groups, pain being reported most often in both groups; 85% (95% CI, 81-88%) versus 62% (95% CI, 58-67%), respectively (Fig 2). Grade 3 pain was reported after 8% of doses in the vaccine group and 1% of doses in the placebo group. The mean duration of solicited local symptoms for both the vaccine and placebo groups was: pain for 4.0 days and 2.5 days, redness for 3.3 days and 3.0 days, and swelling for 3.6 days and 2.6 days, respectively. In the vaccine group, grade 3 redness and swelling were reported after 0.5% and 1.8% of doses, respectively, with a mean duration of 2.0 days for both symptoms. No grade 3 symptoms were reported by patients in the placebo group. The range for the mean duration of grade 3 symptoms was 2.5 to 4.0 days in both the vaccine and placebo groups.

In all, 97% of the subjects in both groups

received complete vaccination courses. Fatigue was reported after 44% (95% CI, 40-49%) of doses in the vaccine group and after 31% (95% CI, 27-36%) in the placebo group; corresponding figures for myalgia were 40% (95% CI, 35-44%) and 25% (95% CI, 21-30%) [Fig 3]. The durations of solicited general symptoms during the 7-day (days 0-6) follow-up period were similar in both groups. In both groups, grade 3 solicited general adverse events were infrequent (<2%).

At least one unsolicited symptom was reported after 29% (95% CI, 25-35%) of doses in the vaccine group and after 22% (95% CI, 18-26%) in the placebo group. The most frequently reported unsolicited symptom labelled in the Medical Dictionary for Regulatory Activities Primary System Organ Class was 'infections and infestations', after 11% of doses in the vaccine group and 9% in the placebo group. The symptoms included features of influenza, nasopharyngitis, and gastroenteritis. The second most common unsolicited group of symptoms was related to the nervous system (headache and dizziness), reported after 5% of doses in the vaccine group and 3% in the placebo group.

During the entire study period, three patients

TABLE 3. Immune response to human papillomavirus (HPV)-18 (according-to-protocol cohort)

Pre-vaccination status/timing	No.‡	Antibody titre ≥7 EL.U/mL (95% confidence interval)§	GMT (95% confidence interval) [EL.U/mL]¶
<b>Vaccine group*</b>			
Seronegative†			
Pre-vaccination	88	0 (0-4)	4 (4-4)
1 month post-dose 3	88	100 (96-100)	4649 (3975-5437)
Seropositive†			
Pre-vaccination	16	100 (79-100)	15 (11-22)
1 month post-dose 3	16	100 (79-100)	4055 (2981-5514)
Total			
Pre-vaccination	104	15 (9-24)	4 (4-5)
1 month post-dose 3	104	100 (97-100)	4552 (3960-5232)
<b>Placebo group*</b>			
Seronegative†			
Pre-vaccination	90	0 (0-4)	4 (4-4)
1 month post-dose 3	89	3 (1-10)	4 (4-4)
Seropositive†			
Pre-vaccination	8	100 (63-100)	24 (12-48)
1 month post-dose 3	8	75 (35-97)	23 (7-79)
Total			
Pre-vaccination	98	8 (4-16)	4 (4-5)
1 month post-dose 3	97	9 (4-17)	4 (4-5)

\* Vaccine group = subjects who received the HPV-16/18 L1 virus-like particle AS04-adjuvanted vaccine; placebo group = subjects who received aluminium hydroxide  
 † Seronegative: subjects with antibody titre <7 EL.U/mL prior to vaccination; seropositive: subjects with antibody titre ≥7 EL.U/mL prior to vaccination  
 ‡ No. of subjects with pre-vaccination results available in each group  
 § Percentage of subjects with concentration within specified range  
 ¶ Geometric mean antibody titres (GMT) calculated on all subjects

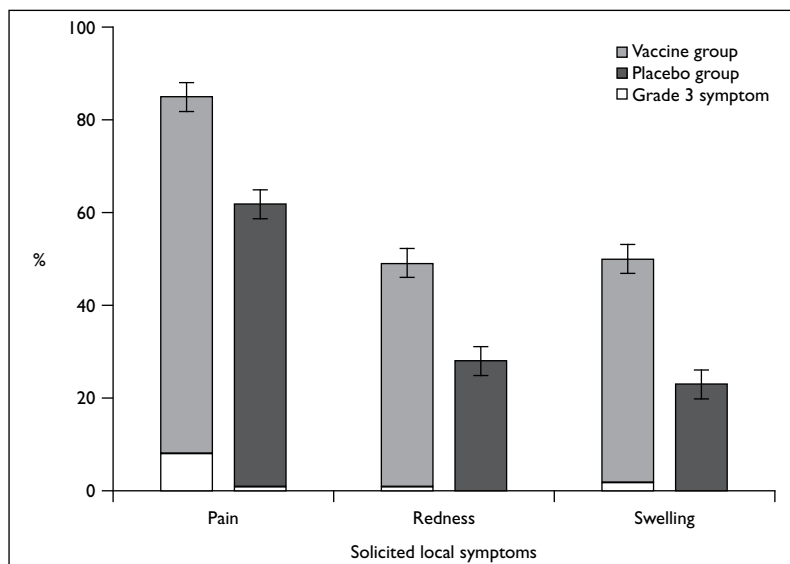


FIG 2. Overall frequency of solicited local symptoms during days 0-6 post-vaccination (total vaccinated cohort)  
 Error bars represent 95% confidence intervals

and one patient in the placebo group had an SAE (pelvic inflammatory disease). All five SAEs were considered to be unrelated to the injections, and there was no fatality.

Medically significant conditions were reported by 28% (95% CI, 21-36%) and 16% (95% CI, 11-23%) of the subjects in the vaccine and placebo groups, respectively. In all, 12 subjects reported at least one new-onset chronic disease based on GSK assessment; 5% (95% CI, 2-10%) in the vaccine group and 3% (95% CI, 0.7-7%) in the placebo group. Four pregnancies were reported during the entire study period (two in each group). One pregnancy in the vaccine group resulted in a normal birth and a healthy child, while the other three pregnancies were interrupted (elective abortions) due to personal/socio-economic reasons.

### Discussion

The burden of cervical cancer remains moderately high in Hong Kong, in contrast to other economically comparable western countries.<sup>4</sup> Presently available cervical cancer prevalence data for women and young adolescent girls in Hong Kong may be

in the vaccine group had four SAEs (abdominal pain, irritable bowel syndrome, dizziness, and headache),

insufficient to advocate widespread introduction of HPV vaccination.<sup>16</sup> Data with this vaccine are available from numerous countries, but are limited for women of Chinese ethnicity. This study, which was conducted to evaluate immunogenicity, safety, and reactogenicity of the HPV-16/18 AS04-adjuvanted cervical cancer vaccine in Hong Kong Chinese women, helps address this issue to some extent.

Before vaccination, the majority of women in our study were seronegative for both HPV-16 and -18 antibodies. All initially seronegative women in the vaccine group seroconverted to both antigens with high GMT levels. Similar high immune responses were also observed in all initially seropositive subjects in the vaccine group. This indicates that prior exposure to natural infection with HPV does not affect the immune response generated by the HPV-16/18 cervical cancer vaccine. Also the high GMT levels in initially seropositive women are important as natural infection may not guarantee protection against re-infection or confer sufficient long-term protection.<sup>17,18</sup> Prophylactic vaccination with the HPV-16/18 AS04-adjuvanted cervical cancer vaccine may help protect women from developing cervical cancer, by inducing sustained antibody responses. In the global clinical programme, this vaccine has demonstrated immune responses to both vaccine antigens that persist up to 7.3 years,<sup>19</sup> at levels substantially higher than those induced by natural infection. The unique AS04-adjuvant system used in this formulation might play an important role in inducing high and persistent antibody titres and may even induce a degree of cell-mediated immunity.<sup>20</sup> In a previous study, this AS04-adjuvant formulation was observed to be immunologically superior to the same antigens adjuvanted with aluminium alone.<sup>20</sup>

Women in our study (aged 18-35 years) exhibited a vaccine response comparable to that reported in other large global efficacy studies (of women aged 15-25 years) in which efficacy against HPV-16/18 infection and CIN 2+ has been confirmed.<sup>21,22</sup> Also, the results in our cohort were in line with those in another phase III trial where the vaccine was immunogenic in women aged 15 to 55 years.<sup>23</sup> As in other countries where efficacy trials have shown favourable results, our study suggests that the vaccine may also confer similar clinical efficacy in reducing HPV infections and CIN lesions in Hong Kong.

This study also showed that the vaccine was generally well tolerated in our local population, though some injection site symptoms and solicited general symptoms (fatigue and myalgia) were more common in the vaccine group than in the controls, which was also consistent with previously reported findings.<sup>21,24</sup> Women remained very compliant, indicating that side-effects did not prevent successful completion of vaccination courses.

Our results suggest that HPV vaccination may

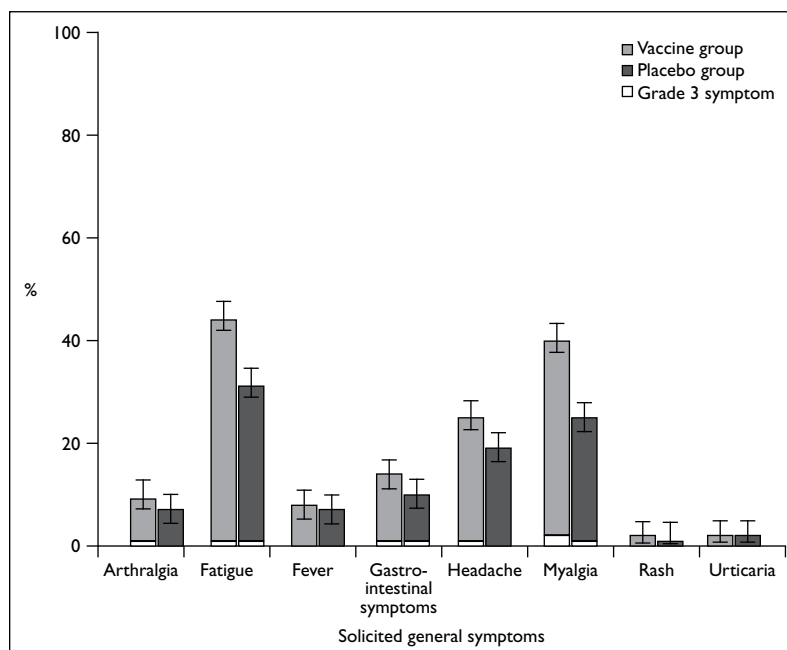


FIG 3. Overall frequency of solicited general symptoms during days 0-6 post-vaccination (total vaccinated cohort)\*

Error bars represent 95% confidence intervals

\* Grade 3 solicited general symptoms (being <2.0%) were rarely reported in either group

be as effective in cervical cancer prevention in Hong Kong as in other countries worldwide. According to the WHO, the largest impact of HPV vaccination is expected to result from targeting young adolescent girls before they become sexually active.<sup>13</sup> Unlike countries such as UK and Australia where a national immunisation programme against HPV is in place for adolescent girls, in Hong Kong vaccination is mainly opportunistic, and women have to pay for the vaccine. Experience from cervical cytology screening programmes suggest that an opportunistic system is likely to benefit only a limited, low-risk group within the population. Thus, whilst over 60% of Hong Kong women have had cervical smears,<sup>3</sup> only 20% of women aged more than 60 years have been tested.<sup>25</sup> Likewise, without a population vaccination programme, a low uptake is to be expected from 'opportunistic vaccination'. While the vaccine would confer most protection when administered to women who have never been exposed to the virus (ie before they become sexually active), the majority of local women believe that only those who are sexually active should be vaccinated.<sup>26</sup> Thus, despite the high efficacy and availability of the study vaccine in Hong Kong, without effective measures to correct misconceptions about HPV vaccination and target women before sexual exposure, availability of vaccination is unlikely to yield a significant reduction in cervical cancer.

Previous studies in our population suggested

that despite largely inadequate knowledge on cervical cancer and HPV infection, the acceptability of the cervical cancer vaccine was high.<sup>26</sup> Findings from this study demonstrated that the vaccine was generally well tolerated and effective in generating an immune response, which provides reassuring information for women considering such prophylaxis. Details about side-effects and their likely time frame could help women develop realistic expectations. Data from this study may also provide a scientific basis for consideration of a population-wide cervical cancer vaccination programme for Hong Kong in the future.

In conclusion, the present study confirms that the HPV-16/18 AS04-adjuvanted vaccine is highly immunogenic and generally well tolerated in 18-to-35-year-old Hong Kong Chinese women. Together with an improved cervical cancer screening programme, HPV vaccination promises to significantly reduce this cancer disease burden in Hong Kong.

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### Declaration

The authors declare the following conflicts of interest: HYS Ngan, ANY Cheung, KF Tam, and KKL Chan have received honoraria and travel grants from GlaxoSmithKline Biologicals for scientific meetings. HW Tang, D Bi, D Descamps, and HL Bock are/were employees of GlaxoSmithKline Biologicals, which is the commercial entity that sponsored the study. In addition, HL Bock is also a shareholder of GlaxoSmithKline Biologicals.

GlaxoSmithKline Biologicals was the funding source and was involved in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals paid all costs associated with the development and publishing of the present manuscript (ClinicalTrials.gov Identifier: NCT00306241).

The corresponding author had full access to the data and had final responsibility for submission of the publication.

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