Introduction of MSD's Human Papillomavirus (HPV) 9 Valent Recombinant Vaccine (GARDASIL®9) Post-Marketing Commitments Reports in China

MSD's Human Papillomavirus (HPV) 4 Valent Recombinant Vaccine (hereinafter referred to as GARDASIL®) was approved for marketing in China on May 27th, 2017, and 9 Valent Recombinant Vaccine (hereinafter referred to as GARDASIL®9) was approved for marketing in China on April 28th, 2018.

MSD conducted post-marketing surveillance studies for both GARDASIL® and GARDASIL®9. One single study protocol was developed for both vaccines, entitled "Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9 (V503-056)".

However, two separate study reports were developed. MSD completed the GARDASIL®9 report in May 2022, and published it on the EU PAS registry on May 17th, 2022. The GARDASIL® report was completed in Dec 2022. As these two reports share the same study protocol, the two reports were combined into one single report to replace the GARDASIL®9 report in the EU PAS registry.

Best Regards,

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Dec 2022

Title	Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL®
Version identifier of the final study report	GARDASIL® Final Study Report V503-056, VERSION 1.0
Date of last version of the final study report	N/A
EU PAS register number	EUPAS36135
Active substance	Each dose of Quadrivalent Human Papillomavirus Recombinant Vaccine (GARDASIL®, G4) contains 20 µg HPV 6 L1 VLP, 40 µg HPV 11 L1 VLP, 40µg HPV 16 L1 VLP, and 20 µg HPV 18 L1 VLP, along with 225 µg of alum.
Medicinal product	G4: Quadrivalent Human Papillomavirus Recombinant Vaccine
Joint PASS	Not applicable
Research question and objectives	The primary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women who were vaccinated with G4 in Ningbo (vaccinated cohort). The secondary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women without HPV vaccination, who are matched to the vaccinated women on factors such as age, area of residence (rural/urban), receipt of cervical HPV/cytology testing services prior to enrollment, and other factors if appropriate in this study. Disease occurrence in Chinese women in the general population is also provided in this study.

Country(-ies) of study	China
Author	PPD Peking University Health Science Center, China
Merck Final Repository (REDS) Date	TBD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. 1 Merck Drive, P.O. Box 100, Whitehouse Station, NJ08899, US
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TABLE OF CONTENTS

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXES

1 ABSTRACT

Title

Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL®

Keywords

GARDASIL®; Post-Marketing surveillance; HPV; High Grade Cervical Intraepithelial Neoplasia

Rationale and background

Upon licensure of GARDASIL® (G4) in 2017 and GARDASIL®9 (G9) in 2018 in China, one of the requirements from the approval letter was[redacted]

This final study report presents the study results for women who were vaccinated with G4 exclusively. The results for women vaccinated with G9 (including for those who received mixed G4/G9 regimens) were presented in a separate study report, [redacted]

Research question and objectives

The primary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women who were vaccinated with G4 in Ningbo (vaccinated cohort).

The secondary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women without HPV vaccination, who were matched to the vaccinated women on factors such as age, area of residence (rural/urban), receipt of cervical HPV/cytology testing services prior to enrollment, and other factors if appropriate in this study.

Cervical Intraepithelial Neoplasia grade 2 or higher (CIN2+) that occurred from 2016 to 2021 in the general population aged 20 or above was also collected in this study.

Study design

Surveillance within a database system; observational design.

Setting

Vaccination and healthcare data from a platform used for storage of healthcare data from Ningbo (i.e., Ningbo Regional Health Information Platform, "NRHIP") was used in this database surveillance.

Subjects and study size, including dropouts

A vaccinated cohort was identified from the NRHIP and included all women who received exclusively G4 according to the "per protocol" defined schedule and who had no cervical diseases, or CIN2+ treatment or hysterectomy prior to the first dose of G4. All women from the vaccinated cohort who had cervical HPV negative and Thinprep Cytology Test (TCT) negative results within one year prior to the cohort enrollment date in the Electronic Medical Records (EMRs) were included in a vaccinated test-negative sub-cohort. Unvaccinated women were matched on age at enrollment and area of residence with vaccinated test-negative sub-cohort to constitute the matched unvaccinated cohort. In addition, women from the general population (including vaccinated and unvaccinated women) were monitored for CIN2+ occurrence.

This is a database study and all eligible women were included in the analysis. The NRHIP has a population of approximately 2.8 million female residents between the ages of 16 and 45 years. This is an observational surveillance activity. Hypothesis testing is not applicable to this study.

Variables and data sources

Exposure was defined as the receipt of at least one dose of G4 during the study period. The surveillance outcome for the vaccinated cohort and matched unvaccinated cohort was defined as histologically confirmed high-grade cervical intraepithelial neoplasia available in the NRHIP. In addition, for completeness, adenocarcinoma in situ (AIS) and invasive cervical

cancers (ICC) diagnosed during the study period and available in the NRHIP were also reported.

Results

A total of 195,457 doses of G4 were administered and 76,118 women received at least one dose of G4 and no other HPV vaccine from 9 January 2018 to 31 March 2021. The number of women who received a first dose of G4 showed an increasing trend from 2018 to 2020. 67.5% (51,360) of vaccinated women received G4 according to the per protocol definition.

Twenty-three CIN2/3 cases were observed in the G4 vaccinated cohort (N=50,051) for whom the HPV and cytological testing status at enrollment and CIN2/3 diagnosis were not known and therefore the possibility that the woman was infected with HPV before G4 vaccination cannot be excluded.

No new onset CIN2/3 case was observed during the study period in the vaccinated HPV test-negative sub-cohort (N=1,129) as well as in the matched unvaccinated cohort (N=3,311).

One AIS case and no ICC case were observed in G4 vaccinated cohort. No AIS or ICC cases were observed in the vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort.

The proportion of new CIN2/3 cases that were identified from NRHIP in the general female population (including vaccinated and unvaccinated women) was relatively stable over the observation years of 2016 to 2020, from the lowest in 2017 (113.96 per million) to the highest in 2018 (179.41 per million).

The proportion of AIS ranged from 2.30 per million in 2016 to 7.93 per million in 2020. The proportion of ICC was highest in 2017 (42.74 per million) and lowest in 2020 (33.98 per million).

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Discussion

No new onset CIN2/3 cases were observed during the study period in the vaccinated HPV test negative sub-cohort and the matched unvaccinated cohort.

Our study demonstrated that NRHIP can be used to monitor the occurrence of CIN2+ in vaccinated and unvaccinated women living in Ningbo over time.

Since G4 was introduced in China in 2017, and available in Ningbo in 2018, it is still too early to observe the impact of the vaccination on CIN2+, due to the short time since G4 introduction and low vaccination coverage.

Marketing Authorisation Holder(s)

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PPD, Peking University Health Science Center, China

2 LIST OF ABBREVIATIONS

AE	Adverse Event
AEFI	Adverse Events Following Immunization
AIS	Adenocarcinoma In Situ
CDC	Center for Disease Control and Prevention
CDE	Center for Drug Evaluation
CIN	Cervical Intraepithelial Neoplasia
CIN2	Cervical Intraepithelial Neoplasia grade 2
CIN3	Cervical Intraepithelial Neoplasia grade 3
CIN2/3	Cervical Intraepithelial Neoplasia grade 2/3
CIN2+	Cervical Intraepithelial Neoplasia grade 2 or higher
EMR	Electronic Medical Record
G4	GARDASIL®
G9	GARDASIL®9
GPP	Good Pharmacoepidemiology Practice
HGRAC	Human Genetic Resource Administration of China
HOI	Health Outcomes of Interest
HPV	Human Papillomavirus
ICC	Invasive Cervical Cancer
ICD	International Classification of Disease
IQR	Interquartile Range
IRB	Institutional Review Board
NRHIP	Ningbo Regional Health Information Platform
NSAR	Non-Serious Adverse Reaction
PMC	Post-Marketing Commitment
PQC	Product Quality Complaints
SAR	Serious Adverse Reaction

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

SOP	Standard Operating Procedure
SRC	Safety Review Committee
TCT	Thinprep Cytology Test

3 INVESTIGATORS

Principal investigator	PPD , Peking University Health Science Center, China
Coordinating investigator for each country in which the study is to be performed	NA
Sponsor contacts	PPD MSD R&D (China) Co., Ltd.
Other contacts	PPD MSD R&D (China) Co., Ltd.
Vendor/Collaborator	Peking University Health Science Center, China
Investigators	PPD , Peking University Health Science Center PPD Center for Data Science in Health and Medicine, Peking University

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
1. Safety Review Committee (SRC) chairman	PPD
2. SRC member	
3. SRC member	
4. SRC member	
5. SRC member	
6. SRC member	

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS register	Within 1 month after final protocol submission	10-Jul-2020	
Peking University Institutional Review Board approval	NA	09-Nov-2020	
Ningbo CDC Institutional Review Board approval	NA	08-Jan-2021	
Start of data collection	After HGRAC approval (targeted for 3Q, 2020)	15-Mar-2021	Delay was due to HGRAC new requirement of database preservation licensing and onsite visit delay for COVID-19
Database lock	Approximately 4 months prior to compilation of study report.	14-Jun-2022	
Final report of study results	Prior to license renewal	28-Nov-2022	Delay was due to travel restriction to Ningbo because of the COVID-19 outbreak in 2022

6 RATIONALE AND BACKGROUND

Background

In 2020, approximately 109,741 new cervical cancer cases were diagnosed and 59,060 cervical cancer deaths occurred in China. Cervical cancer is the 6th leading cause of female cancer and the 7th leading cause of cancer death in Chinese women. In Chinese women 15 to 44 years of age, cervical cancer is the 3rd leading cause of female cancer and the 3rd leading cause of cancer death {085DS5}. Nearly all cases of cervical cancer are caused by HPV, and consistent with observations worldwide, HPV 16 and HPV 18 are the genotypes most commonly associated with cervical cancer in China, followed by HPV 31, 33, 45, 52, 58 and 59{085DS5}. Over the past decade, the Chinese government has initiated activities to reduce the burden of cervical cancer in Chinese women. China initiated a free cervical cancer screening program in 2009 which targeted women in rural area. The program provided free cervical screening services to 10 million women in the first 3 years. It kept on scaling up and reached 10 million women per year during 2012-2015. The screening methods varied across the country {085DX7, 085DX2}.

As a measure of primary prevention of cervical cancer, the Chinese government has approved bivalent, quadrivalent, and nonavalent vaccines that prevent persistent HPV infection and cervical cancers and precancers caused by the HPV types targeted by the vaccines. While there is no national HPV immunization program currently implemented in China, women can receive these vaccinations at their own expense. MSD manufactures 2 of these vaccines: the quadrivalent vaccine (GARDASIL®) and nonavalent vaccine (GARDASIL®9). GARDASIL® (G4) targets HPV types 6, 11, 16, and 18 and was approved in China for use in women 20 to 45 years old in May 2017. Shortly thereafter (April 2018), GARDASIL®9 (G9), which targets HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, was approved for use in women 16 to 26 years old in China. Subsequently, G4 was approved in China for use in girls 9 to 19 years old in November 2020, and age for G9 was expanded as 9 to 45 years old in August 2022.

High efficacy of G4 and G9 against multiple endpoints was consistently observed in clinical trials in women worldwide, including Chinese women. In addition, the effectiveness of

vaccination against high-grade cervical intraepithelial neoplasia has been observed in women from various areas of the world subsequent to initiation of HPV vaccination programs, with the first effectiveness reported approximately 5 years after licensure {04HBHR, 04MWZ0, 03RMDJ}.

Rationale

Real world evidence of the impact of G4 for the prevention of high-grade cervical lesions in Chinese women is not yet available. Therefore, CCI [redacted] MSD has conducted this post-licensure surveillance of the occurrence of high-grade cervical lesions in Chinese women. This database surveillance used Ningbo Regional Health Information Platform (NRHIP). The NRHIP integrates several electronic healthcare databases, including vaccination data and EMRs from women who receive their healthcare in Ningbo and whose medical information is available in the NRHIP.

This final study report presents the study results for women who were vaccinated with G4 exclusively. The results for women vaccinated with G9 (including for those who received mixed G4/G9 regimens) a were presented in a separate study report, CCI [redacted]
CCI [redacted]

7 RESEARCH QUESTION AND OBJECTIVES

The primary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women who were vaccinated with G4 in Ningbo (vaccinated cohort). High-grade cervical intraepithelial neoplasia (CIN) is a composite outcome that includes CIN2 and CIN3.

The secondary objective was to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women without HPV vaccination (matched unvaccinated cohort), who were matched to the vaccinated women on factors such as age, area of residence (rural/urban), receipt of cervical HPV/cytology testing services prior to enrollment date and other factors if appropriate. A vaccinated HPV test-negative sub-cohort was identified from the vaccinated cohort and matched to unvaccinated women.

Rates of high-grade cervical intraepithelial neoplasia occurrence in the vaccinated and matched unvaccinated cohorts will be reported and compared, if methodologically feasible.

High-grade cervical intraepithelial neoplasia occurrence in the general population residing in Ningbo is also provided in this study as a background measure of high-grade cervical intraepithelial neoplasia occurrence in the general population.

Counts of adenocarcinoma in situ (AIS) and invasive cervical cancer in the vaccinated cohort, the matched unvaccinated cohort and the general population of women were monitored as well, to provide background information on the disease burden of cervical cancer in Ningbo.

This is an observational surveillance activity. Hypothesis testing is not applicable to this study design.

8 AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
None				

9 RESEARCH METHODS

9.1 Study design

This is a database, observational surveillance activity that used data from the NRHIP to identify women vaccinated with G4 and to monitor the occurrence of high-grade cervical intraepithelial neoplasia after vaccination during the study period. All women who were age-eligible for vaccination during the study period and who had received at least one dose of G4 but no other HPV vaccines were extracted from the NRHIP as "vaccinated women". The G4 vaccinated cohort was derived from the vaccinated women and included all women who had received exclusively G4 according to the "per protocol" defined vaccination schedule (i.e. received all 3 doses of G4 within 12 months, with at least 8 weeks between doses 1 and 2), and who had no history of cervical diseases (including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy) prior to their first dose of G4. An HPV test-negative sub-cohort was set up. Among the vaccinated cohort, all women who had cervical HPV negative and TCT (Thinprep Cytology Test) negative test results within one year prior to the cohort enrollment date were included in the "vaccinated HPV test-negative sub-cohort", and matched to unvaccinated women (Figure 1).

The unvaccinated cohort included women who had not received any HPV vaccination and who had cervical HPV negative and TCT negative results within one year prior to the cohort enrollment date and no history of cervical diseases (including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy) prior to their enrollment date. Each vaccinated woman from the vaccinated HPV test-negative sub-cohort was matched on age at enrollment and residence (urban/rural) to a maximum of three unvaccinated women. If more than three unvaccinated women were eligible to be matched to one vaccinated woman, those whose birthdates were closest to that of the vaccinated woman were selected.

For each woman from the vaccinated cohort and vaccinated HPV test-negative sub-cohort, the date of her first vaccination with G4 as recorded in the NRHIP was considered as her enrollment date. The enrollment date for the matched unvaccinated women was the same as the cohort enrollment date of her vaccinated counterpart.

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Occurrence of histologically confirmed CIN2+ was assessed in the vaccinated cohort, the vaccinated test-negative sub-cohort and in the matched unvaccinated cohort. Counts and rates of CIN2/3, AIS and ICC were reported for the cohorts. The formal comparison of the rates of high-grade cervical intraepithelial neoplasia between the vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort was not feasible due to the short follow-up period since the introduction of vaccination with G4 and low coverage of cervical screening services in Ningbo.

In addition, women from the general population were monitored for diagnosis of high-grade cervical intraepithelial neoplasia. This data was tabulated to provide context for the study findings and also to help identify secular trends that may have impacted high-grade cervical intraepithelial neoplasia diagnoses, such as changes in cervical screening methods.

Occurrence of AIS and invasive cervical cancer in the vaccinated cohort, the vaccinated HPV test-negative sub-cohort, the matched unvaccinated cohort, and the general population were also monitored to provide additional information on the burden of cervical disease in Ningbo.

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[redacted]

9.2 Setting

Vaccination and healthcare data from a platform used for storage of healthcare data from Ningbo (i.e., “NRHIP”) was used in this database surveillance. Ningbo city is located in the eastern portion of the Zhejiang province, in the southeastern part of China. Within the NRHIP catchment area, there are 4 counties (Yuyao, Cixi, Ninghai, and Xiangshan) and 6 districts (Yinzhou, Haishu, Jiangbei, Zhenhai, Beilun and Fenghua). Ningbo has a population of approximately 2.8 million local female residents between 16 and 45 years old, and its location includes large districts as well as less populated areas.

The NRHIP is one of the best regional health information platforms in China {085DLV}. The vaccine register system in the NRHIP collects information regarding vaccination records

(including vaccination with G4 or G9) in Ningbo. The NRHIP collects residents' health care information and some demographic information, including age, gender, outpatient visits, emergency room visits, hospitalizations, disease diagnoses, treatments, drug prescriptions and dispensing, laboratory testing results, etc. All local hospitals that can provide CIN2+ (CIN2, CIN3, AIS and ICC) diagnosis and treatment have been included in the NRHIP and CIN2+ records can be retrieved from the NRHIP.

The NRHIP has achieved the highest level in the National Information Interconnection Standardization Evaluation. In 2011, Ningbo started developing a platform to incorporate the different electronic healthcare and public health information databases. In 2015, the NRHIP was officially launched and it began to integrate various health data sources.

In this study, G4 vaccination data were extracted from the NRHIP from 9 January 2018 to 31 March 2021. Outcome of interest and covariates were extracted starting from 2015 (the first year of diagnosis available in the NRHIP) until 31 March 2021.

9.3 Subjects

The following study population and cohorts were formed:

9.3.1 Vaccinated population and cohorts

G4 Vaccinated women

Vaccinated women were all female residents of Ningbo who were age-eligible for G4 vaccination during the study period, who received at least one dose of G4 during the study period, and whose medical care information was available in the NRHIP. The following criteria were used to identify vaccinated women.

- ✓ Female residents registered in the NRHIP;
- ✓ Health data (EMRs data) available in the NRHIP;
- ✓ Received at least 1 dose of G4 during the study period but no other HPV vaccines;
- ✓ 20 to 45 years old at initiation of G4 vaccination.

G4 vaccinated cohort

The G4 vaccinated cohort was derived from the vaccinated women and included all women who received exclusively G4, according to the "per protocol" defined schedule and who had no cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy prior to the first dose of G4. The definition of the "per protocol" schedule is that women received all 3 doses of G4 within 12 months (≤ 12months), with at least 8 weeks (≥8weeks) between doses 1 and 2.

Inclusion criteria:

- ✓ Vaccinated women;
- ✓ Received exclusively G4 "per protocol" schedule.

Exclusion criteria:

- ✓ Had a history of cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy prior to the first dose of G4.

G4 Vaccinated HPV test-negative sub-cohort

All women from the G4 vaccinated cohort who had cervical HPV (any HPV test method) negative and TCT (Thinprep Cytology Test) negative results within one year prior to the cohort enrollment date in the EMRs were extracted as vaccinated sub-cohort, and were matched to unvaccinated women.

Inclusion criteria:

- ✓ Women from vaccinated cohort;
  - ■ who had HPV negative results within one year prior to cohort enrollment date; and
  - ■ who had TCT negative results within one year prior to the cohort enrollment date.

9.3.2 Matched unvaccinated cohort

Unvaccinated women

The unvaccinated women were comprised of eligible women who received no HPV vaccine before and during the study period.

Inclusion criteria:

- ✓ Female residents registered in the NRHIP;
- ✓ Health data available in the NRHIP;

Exclusion criteria:

- ✓ Women who received HPV vaccination.

Matched unvaccinated cohort

The matched unvaccinated cohort included unvaccinated women who had cervical HPV test negative and TCT negative results within one year prior to cohort enrollment date and no cervical disease history, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy at any time prior to date of enrollment.

Inclusion criteria:

- ✓ Unvaccinated women;
  - ■ who had HPV negative result within one year prior to cohort enrollment date; and
  - ■ who had TCT negative result within one year prior to cohort enrollment date.

Exclusion criteria:

- ✓ Women who had a history of cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy at any time prior to cohort enrollment date.

Matching process: Each eligible vaccinated woman from the G4 vaccinated HPV test-negative sub-cohort was matched to multiple potentially eligible unvaccinated women on age at enrollment (up to +/- 1 year, depending on the number of potentially eligible unvaccinated women in the NRHIP) and area of residence (urban/rural). If there were more than one

unvaccinated woman that were eligible to be matched to a vaccinated woman, they were ordered by the closeness of their birthday to that of the vaccinated woman.

For each vaccinated woman, a maximum of three unvaccinated women with the closest birth dates were kept. The cohort enrollment date for the potentially matched unvaccinated woman was the same as the cohort enrollment date of her vaccinated counterpart. After determination of the enrollment date of each potentially matched unvaccinated woman, those with cervical HPV positive or TCT positive result within one year prior to the enrollment date, or those with pre-existing cervical diseases or CIN2+ treatment or hysterectomy any time before the enrollment date were excluded.

In summary, unvaccinated women who had cervical HPV negative and TCT negative results within one year prior to cohort enrollment and had no cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy prior to date of enrollment constituted the matched unvaccinated cohort.

9.3.3 General female population

Surveillance for cervical disease in the general female population was also undertaken in order to better understand the occurrence of cervical disease reported to the NRHIP. The occurrence of cervical disease in the general female population during the study period was tabulated across the entire age range available in the NRHIP. Thus, surveillance in the general female population also included women older than age 45 years during the study period.

Inclusion criteria for the general population are:

- ✓ Female residents registered in the NRHIP;
- ✓ Health data available in the NRHIP.

In the vaccinated cohort, matched unvaccinated cohort and the general population, women with notation (EMR records) available within the NRHIP that indicates a history of cervical diseases including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia

or who have undergone hysterectomy or CIN2+ treatment before cohort enrollment were reported, but were excluded from the analysis.

9.4 Variables

9.4.1 Exposure

For the vaccinated cohort, exposure was defined as receipt of G4 as part of routine health care within Ningbo, among women who were age-eligible for vaccination at any point during the study period and whose medical data were available within the NRHIP.

9.4.2 Outcome

The surveillance outcome was defined as histologically confirmed high-grade cervical intraepithelial neoplasia (i.e., CIN2 or CIN3) available in the NRHIP. In addition, adenocarcinoma in situ (AIS) and invasive cervical cancer cases diagnosed during the study period and available in the NRHIP were reported.

The diagnosis and treatment of CIN2+ occurred within the hospital system and local laboratory and therefore CIN2+ cases are captured in the NRHIP. Women with high-grade pap abnormalities identified by the free cervical cancer screening program or from annual body check-ups are referred to local hospitals for diagnosis and treatment. All local hospitals that can provide services relevant to CIN2+ diagnosis and treatment are covered by the NRHIP, and these CIN2+ records could be retrieved and analyzed in our study.

Histological testing results in the EMRs of outpatient visits, emergency room visits and hospitalizations were used to identify CIN2 or CIN3 cases among the G4 vaccinated cohort, the G4 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort from the NRHIP. If the case was reported with a range, i.e., CIN2/3 and the exact degree of the histology result or diagnosis was not described, the highest reported grade, CIN3 in the example, was retained for the case.

Key words of histological results were used to identify AIS cases in the EMR to ensure the accuracy of the case identification. Only cases that were confirmed by histological tests were included.

Occurrence of ICC in the G4 vaccinated cohort, the G4 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort were identified from the local cancer register in the NRHIP. ICD-10 codes and key words of diagnosis were used to identify ICC cases in the cancer register in NRHIP.

The history of CIN2+ diseases was identified in the G4 vaccinated cohort, the G4 vaccinated HPV test-negative sub-cohort, the matched unvaccinated cohort and the general female population from the NRHIP. ICD-10 codes for cervical diseases including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, key words of CIN2+ diagnosis, CIN2+ treatment and hysterectomy were used to identify women with documented history of cervical diseases within the NRHIP (both EMR and cancer registry).

A CIN2+ case identification method was developed to identify CIN2+ cases in the NRHIP referring to relevant guidelines {085DWT, 085DLP, 085CDW, 085DJ8}. Gynecologists and other experts were consulted during the development of the CIN2+ case identification methods.

9.4.3 Covariates

Variables including age at first vaccine dose, residence region, cervical cytology testing status, ethnicity, marital status, parity and health insurance status were reported in this study.

9.5 Data sources and measurement

The NRHIP contains three main data sources, linkable by the use of personal identification variables: the maternal and child health care information system, the Center for Disease Control and Prevention (CDC) information system, and the hospital information system. The maternal and child health care information system collects information on antenatal health care, childbirth, child health care. The CDC information system and the hospital systems are further described below.

Ningbo CDC information system

The Ningbo CDC information system mainly collects, reports and manages information pertaining to vaccination, communicable diseases, chronic diseases, death certification, foodborne diseases, vector-borne diseases.

The CDC information system includes the vaccine register system, which has information on vaccine cold chain management, migrating children management, and digital vaccination clinics. The information system includes services such as ability to make online inquiries on vaccination information and immunization records, ability to make vaccination appointments, provide informed consent, payment, receive some consultation, and monitoring of Adverse Events Following Immunization (AEFI). The system covers 167 vaccination clinics located in 10 hospitals and 157 community health service centers in Ningbo city. The system collects general information, such as individual identifiers, name, sex, date of birth, date of vaccination, dosage, manufacturer, etc. Collection of vaccination information for children under 12 years of age has been mandatory since 2005. Since May 2017, collection of information on adult vaccination (including G4 and G9) has also been mandatory.

The CDC information system also includes the cancer register system. The cancer register is population. The main reporting channels of the cancer register are through medical institutions. Hospitals and clinics are required to routinely submit newly diagnosed clinical records of cancer to their local cancer register. Death surveillance data, insurance records, and the funeral records of patients with cancer are additional reporting sources.

Vaccination data were collected from the CDC information system using the records of vaccination of G4, G9 or other HPV vaccines extracted from the vaccination register. HPV vaccination codes were used to identify the vaccinated women to generate the vaccinated cohort.

Electronic medical records (EMRs)

The NRHIP includes EMRs that cover all 221 public hospitals and 28 large private hospitals in Ningbo city except some specialized hospitals or private clinics, such as eye hospitals and dental hospitals. Services relevant to cervical screening, diagnosis of CIN2+, or treatment of cervical lesions are not provided by these specialized hospitals or private clinics. The NRHIP collects information on outpatient and inpatient visits, disease diagnosis (ICD 10 codes, local codes, and free text of disease diagnosis), laboratory test results, drug prescription and dispensing, surgical operations, and body check-ups since 2015. Cancer treatment and deaths

outside Ningbo can be tracked and captured if they occur in Zhejiang Province. Other health information outside Ningbo is not available in the NRHIP.

9.5.1 Study Procedures

The study protocol was approved by the Institutional Review Board (IRB) of Peking University Health Science Center. The study involves secondary data analysis of data from the NRHIP which was routinely collected in Ningbo. Therefore, there was no recruitment procedure and no informed consent was required in this study. Permission of waiver of informed consent for this study was granted. The electronic claim records were de-identified. The study was also approved by the Human Genetic Resources Administration of China (HGRAC) for International Cooperation Study. Subject rights were not compromised in this study. Data from the NRHIP contained only encrypted identifiers. This encryption eliminated the risk associated with an unlikely breach of confidentiality. Only the NRHIP experts from Ningbo CDC and the Peking University study personnel had access to the data. All analyses were based on anonymized, untraceable coded identifiers. The study sponsor did not have access to the datasets.

9.6 Bias

Observational studies are vulnerable to a variety of biases, including selection bias and information bias. This study is a database study and the outcomes were measured relying on the diagnosis recorded in the NRHIP. A CIN2+ case identification method was developed for the identification of CIN2+ cases from the NRHIP, in order to minimize the potential detection bias related to the diagnosis. Key words were applied in histological testing results in the EMRs of outpatient visits, emergency room visits, and hospitalizations to identify confirmed CIN2/3 and AIS cases in the NRHIP, while ICD-10 codes and key words of diagnosis were used to identify ICC cases in the cancer register in NRHIP.

This study aims to monitor the occurrence of high-grade cervical intraepithelial neoplasia, AIS and invasive cervical cancer in vaccinated and unvaccinated women in the NRHIP. In order to reduce the selection bias between the vaccinated and the unvaccinated cohort, matching methods were used in this study.

In addition, in order to reduce confounding, several variables that might have a potential association with or an impact on vaccination exposure or cervical health outcomes were extracted from the NRHIP and analyzed in this study. These variables include ethnicity, attained age, age at the initiation of G4 vaccination, marital status, parity and health insurance status.

9.7 Study size

In this database study, all women vaccinated with G4 during the surveillance period in Ningbo and who met the inclusion criteria were included. In addition, all women from the general population (including vaccinated and unvaccinated women) whose health data were in the NRHIP and who were residents of Ningbo were followed for the identification of high-grade cervical intraepithelial neoplasia, as well as AIS and invasive cervical cancer.

9.8 Data transformation

9.8.1 Data management

All data management activities were undertaken under the supervision of Peking University and Ningbo CDC, following the procedures detailed in a separate “Data Management Plan”. The main components of the data management plan included data preparation, data linkage, data cleaning, quality description and control, database lock, analytical dataset determination, archiving and backup, training and support and data security. These procedures were intended to ensure the authenticity, integrity, and confidentiality of electronic records.

9.9 Statistical methods

9.9.1 Main summary measures

A separate detailed statistical analysis plan was developed and finalized prior to conduct of any analyses in this study, and the plan was developed using Good Pharmacoepidemiology Practice (GPP) principles for conducting observational studies.

Demographics and disease characteristics are analyzed in this study. For continuous variables, mean, standard deviation (SD), median (IQR) and range are presented. For categorical variables, the number of patients in each category and percentage were presented.

Rates of CIN2/3, AIS and invasive cervical cancer in the cohorts were estimated with 95% confidential interval (95% CI).

9.9.2 Main statistical methods

Rates of CIN2/3, AIS and invasive cervical cancer in the vaccinated and matched unvaccinated cohorts were reported but not compared as it was not methodologically feasible according to the study protocol and the statistical analysis plan. As vaccine uptake is limited and the follow-up time is still short to detect an impact on CIN2+ occurrence, no power calculation to detect statistically significant differences has been conducted.

9.9.3 Missing values

For the primary and secondary objectives, analyses are carried out using the available data. A subject with missing for a given variable will be excluded from the analyses for that variable.

9.9.4 Sensitivity analyses

Not applicable in this study.

9.9.5 Amendments to the statistical analysis plan

Not applicable in this study.

9.10 Quality control

By signing the study protocol, all parties agreed to follow all applicable standard operating procedures (SOPs). All parties also agreed to ensure that the study personnel was appropriately trained to ensure that the study was conducted and data was generated, documented, and reported in compliance with the protocol and GPP. All parties maintained transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor met with Peking University on a weekly basis, reviewed the data management plan and statistical analysis plan, conducted audit visits and set up the SRC to ensure that the oversight and conduct of the study were completed in accordance with the protocol, quality standards (e.g., GPP), and applicable laws and regulations. There was no significant quality

issue (SQI) identified during the conduct of the study. An SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data.

A data management plan was developed for this surveillance prior to data analysis, and it specified procedures to be followed to maintain high quality. This included programming practices and standardized, study-specific quality checking procedures. In addition, MSD conducted oversight visit and routine management meeting to ensure that study procedures were adequately followed and documented.

Quality of the data linkage

The data from the CDC (including vaccine register system and cancer register system) and from the hospitals (electronic medical records) information systems were integrated, verified, stored, exchanged, and shared in the NRHIP. Different datasets were linked using a personal identification (ID) number and other information, including name and birth date.

In case of missing values for the ID variables in the different data sources, to minimize the loss of data for these women during the linkage process and to ensure accurate linkage of subjects across various data sources in the platform, multiple linkage steps were utilized. A Substitute ID (hereafter SID) was generated by combining ID and name for data linkage. The SID was used as the primary index, while name and birth date were used as the secondary index when SID could not achieve data linkage.

Standardization of CIN2+ diagnoses

A CIN2+ case identification method was developed in consultation with clinical experts to identify high-grade cervical intraepithelial neoplasia cases, AIS, and cervical cancer from the NRHIP for disease history descriptions and outcomes. Diagnosis codes, key words of diagnosis from the EMRs of outpatient visits, emergency room visits and hospitalizations that were pertinent to outcomes of interest were included in these methods.

Information integrity

Vaccination register and EMR data in the NRHIP are set up and managed strictly following the local health authority's requirements and regulations. Data integrity was assessed in a

preliminary study feasibility assessment using data from 2017 in the NRHIP. All vaccination clinics in Ningbo city have been included in the system. The key variables associated with vaccination are collected in the system. All vaccination records of adults in Ningbo city have been collected in the system since 2017 with no missing IDs.

All data analyses were conducted according to the study protocol and the statistical analysis plan. Programming for this project was conducted by a primary analyst and validated by a second analyst (validation analyst) independently. For all data processing steps, an independent analyst reviewed the programs as well as the input and output datasets.

10 RESULTS

10.1 Participants

A flowchart was developed based on the data management process as following.

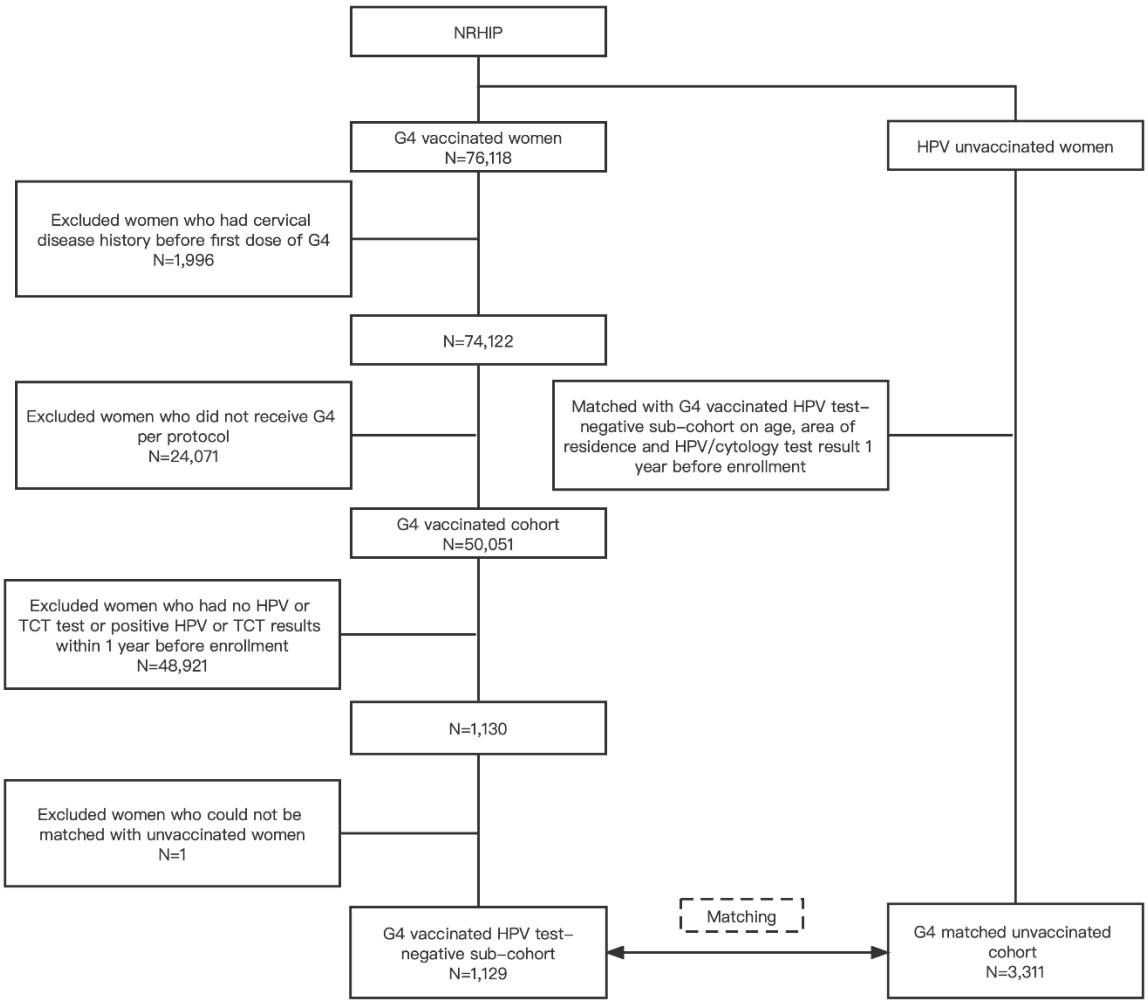

Figure 1: Flowchart of study population and cohorts

10.1.1 Protection of Human Subjects

This is a database surveillance activity that captures women who chose to receive the vaccine as part of their routine health care. No intervention was applied in this study. All participants' privacy was well-protected and database management followed local health information management requirements and local law.

The study was approved by the IRB of Peking University and Ningbo CDC with a waiver of informed consent and by the HGRAC for International Cooperation Study.

10.2 Descriptive data

Since 9 January 2018 when G4 vaccination records have become available in the NRHIP and up to the data extraction cut-off on 31 March 2021, a total of 195,457 doses of G4 were administered in Ningbo. Overall, 76,118 women were vaccinated with at least one dose of G4 and no other HPV vaccine. The number of women who received their first dose of G4 was similar in 2018 and 2019 with 11,937 and 14,180 vaccinated women, respectively, but increased sharply in 2020, with to 40,263 women receiving their first dose. During the first quarter of 2021, 9,738 women in Ningbo received a first dose of G4. Among those who received at least one dose of G4 and no other HPV vaccines, the mean age at first dose was 33.9 (SD=5.3) years. The majority of women were vaccinated at age 26 to 40 years with 26.1%, 32.3%, 24.5% at 26-30, 31-35 and 36-40 years old, respectively. Only 5.9% of the women were vaccinated between 20 and 25 years and 11.2 % between 41 and 45 years. As of 31 March 2021, 11.2%, 20.9% and 68.0% of women had received 1, 2 and 3 doses of G4, respectively. The mean time interval between dose 1 and 2, dose 2 and 3, and dose 1 and 3 was 2.3, 4.3 and 6.6 months, respectively, with low standard deviation, indicating good compliance with the recommended schedule of 0, 2 and 6 months. The vast majority of women (88.6%) received dose 1 and dose 2 with an interval of at least 8-weeks between the doses and 67.5% received the 3 doses within 12 months. Both criteria of the “per protocol” definition were met by 67.5% of the women (Table 1).

A total of 50,051 women (65.8% of the women who had received at least one dose of G4) were included in the G4 vaccinated cohort. Among these women, 10,665 (21.3%) were enrolled in 2018, 12,744 (25.5%) in 2019 and 26,642 (53.2%) in 2020, reflecting an increasing trend of women vaccinated with G4 since the introduction of the vaccine in China. As the time in 2021 (data cut-off on 31 March 2021) was too short for the women to get the complete 3-dose schedule according to the “per protocol” definition, no women could be enrolled in 2021. The mean age at cohort enrollment was 33.9 years (SD=5.28). The proportion of women from urban areas (58.6%) was higher than the proportion of women from rural areas (40.2%) (Table 2).

The number of women enrolled in the G4 vaccinated HPV test-negative sub-cohort was 1,129 (corresponding to 1.5% of women who had received at least one dose of G4 and 2.2% of those who were vaccinated according to the "per protocol" schedule). The matched unvaccinated cohort was 3,311 women, reflecting a matching ratio of maximum three unvaccinated women for every vaccinated woman.

In the G4 vaccinated HPV test-negative sub-cohort, 194 (17.2%) women were enrolled in 2018, 287 (25.4%) in 2019 and 648 (57.4%) in 2020. Also, no woman was enrolled in 2021 because the time captured was too short for the women to get the 3-dose schedule (per protocol) before the data cut-off on 31 March 2021. The mean age at cohort enrollment was 34.7 years (SD=4.96). The majority of women were from urban areas (78.7%). The percentage of women who had cervical cytology testing after cohort enrollment was 15.9%. The majority of women for whom the ethnicity was reported (89.5%) were Han Chinese. More than two-thirds of the women were married (67.1%), 18.0% were registered as single and for 14.3% the marital status was unknown. The parity status was not captured for the great majority of the women (88.4%). Most of the women (87.8%) had a health insurance (including public health insurance programs as Urban Employee Basic Medical Insurance, Urban Resident Basic Medical Insurance and Newly Cooperative Medical Scheme, but also private health insurance programs).

The proportions of women enrolled in the matched unvaccinated cohort in 2018, 2019 and 2020 were very similar to that in the G4 vaccinated HPV test-negative sub-cohort. As for the G4 vaccinated cohort, no woman was enrolled in 2021. The mean age at cohort enrollment was 34.7 years (SD=4.98), equal to the mean age of the women in the G4 vaccinated HPV test-negative sub-cohort. The majority of women were from urban areas (78.5%). The proportion of women with cervical cytology test after cohort enrollment was 14.6%, similar to the 15.9% of women from the G4 vaccinated HPV test-negative sub-cohort. Almost all women for whom the ethnicity was reported (81.7%) were Han Chinese. The proportion of women who were reported to be married (62.5%) was lower than in the G4 vaccinated sub-cohort as well as the proportion of women who reported to be single (15.0%). The marital status was missing for 21.9% of women and for the great majority (89.7%) the parity status

was not reported, similar to the G4 vaccinated HPV test-negative sub-cohort. Also in this cohort, the majority of women (78.0%), had health insurance (Table 3).

Table 1. Characteristics of women vaccinated with at least one dose of G4

Variables	G4 vaccinated women
Total number of women vaccinated with G4	76,118
Calendar year at the first dose of G4, n (%)	
2018	11,937 (15.7)
2019	14,180 (18.6)
2020	40,263 (52.9)
2021 *	9,738 (12.8)
Age at the first dose of G4 (years), mean±SD	33.9 (5.3)
<20 years, n (%) †	NA
20-25 years, n (%)	4,483 (5.89)
26-30 years, n (%)	19,864 (26.1)
31-35 years, n (%)	24,567 (32.3)
36-40 years, n (%)	18,668 (24.5)
41-45 years, n (%)	8,536 (11.2)
>45 years, n (%) †	NA
Doses received	
1 dose, n (%) ††	8,510 (11.2)
2 doses, n (%) ††	15,880 (20.9)
3 doses, n (%) ††	51,726 (68.0)
>3 doses, n (%) ††	2 (0.0)
Time interval between each dose (months), mean±SD; median (IQR), range	
Dose 1 and dose 2 (n=)	2.3 (0.7), 2.1(0.3), 0.1-36.0
Dose 2 and dose 3 (n=)	4.3 (0.8), 4.1 (0.3), 1.1-26.8
Dose 1 and dose 3 (n=)	6.6 (1.1), 6.3 (0.2), 4.0-34.0
At least 8 weeks between doses 1 and 2, n (%)	
Yes	67,460 (88.6)

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

No	8,658 (11.4)
Received 3 doses of G4 within 12 months, n (%)	
Yes	51,399 (67.5)
No	24,719 (32.5)
"Per protocol" vaccination ¶, n (%)	
Yes	51,360 (67.5)
No	24,758 (32.5)

* 2021 data collection cut-off: Mar 31st

† Women vaccinated with a first dose of G4 <20 and >45 are not included in the study

†† Women's vaccination status at the data cut-off point (women who received 1 dose or 2 doses might receive dose 2 and/or dose 3 at a later timepoint per vaccination schedule). For women whose first dose recorded in the NRHIP was coded as dose 2 or 3, we assumed that they had received previous doses out of Ningbo

¶ "Per protocol" vaccination regimen is defined as women who received all 3 doses of G4 within 12 months, with at least 8 weeks between doses 1 and 2.

Table 2. Characteristics of G4 vaccinated cohort (per protocol†)

Variables	G4 vaccinated cohort
No. of participants	50,051
Cohort enrollment year, n (%)	
2018	10,665 (21.3)
2019	12,744 (25.5)
2020	26,642 (53.2)
2021 *	0 (0.0)
Age at cohort enrollment (years), mean±SD	33.9 (5.28)
20-25 years, n (%)	2,504 (5.0)
26-30 years, n (%)	11,057 (22.1)
31-35 years, n (%)	16,256 (32.5)
36-40 years, n (%)	12,649 (25.3)
41-45 years, n (%)	7,585 (15.2)
Residence region, n (%)††	
Urban area	29,329 (58.6)
Rural area	20,119 (40.2)
Unknown	603 (1.2)

* 2021 data collection cut-off: Mar 31st

† The definition of the "per protocol" vaccination schedule is that women received all 3 doses of G4 within 12 months (≤12months), with at least 8 weeks (≥8weeks) between doses 1 and 2.

†† Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

Table 3. Characteristics of G4 vaccinated HPV test-negative sub-cohort and matched unvaccinated cohort

Variables	G4 vaccinated HPV test-negative sub-cohort*	Matched unvaccinated cohort
No. of participants	1,129	3,311
Cohort enrollment year, n (%)		
2018	194 (17.2)	574 (17.3)
2019	287 (25.4)	835 (25.2)
2020	648 (57.4)	1,902 (57.4)
2021 †	0 (0.0)	0 (0.0)
Age at cohort enrollment (years), mean±SD	34.7 (4.96)	34.7 (4.98)
20-25 years, n(%)	16 (1.4)	48 (1.4)
26-30 years, n(%)	194 (17.2)	568 (17.2)
31-35 years, n(%)	408 (36.1)	1,196 (36.1)
36-40 years, n(%)	302 (26.7)	881 (26.6)
41-45 years, n(%)	209 (18.5)	618 (18.7)
Residence region, n (%)††		
Urban area	888 (78.7)	2,600 (78.5)
Rural area	241 (21.3)	711 (21.5)
Cervical cytology testing after cohort enrollment, n (%)	179 (15.9)	484 (14.6)
Ethnicity, n (%)		
Han	1,006 (89.1)	2,684 (81.1)
Others	5 (0.4)	20 (0.6)
Unknown	118 (10.5)	607 (18.3)
Marital status, n (%)		
Single	203 (18.0)	497 (15.0)
Married	757 (67.1)	2,069 (62.5)
Divorced	6 (0.5)	17 (0.5)
Widowed	1 (0.1)	2 (0.1)

Unknown	162 (14.3)	726 (21.9)
Parity, n (%)		
0	82 (7.3)	196 (5.9)
1	45 (4.0)	133 (4.0)
2	4 (0.4)	12 (0.4)
≥3	0 (0.0)	0 (0.0)
Unknown	998 (88.4)	2,970 (89.7)
Health insurance status, n (%)		
Yes	991 (87.8)	2,583 (78.0)
No	12 (1.1)	50 (1.5)
Unknown	126 (11.2)	678 (20.5)

† 2021 data collection cut-off: Mar 31st

* Women from G4 vaccinated HPV test-negative sub-cohort received G4 per protocol vaccination schedule, and had HPV and cytological negative results within one year prior to cohort enrollment date

†† Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

10.3 Outcome data

CIN2/3 in the G4 vaccinated cohort, G4 vaccinated HPV test-negative sub-cohort and matched unvaccinated cohort

Twenty three of 50,051 women from G4 vaccinated cohort had an onset of histologically confirmed CIN2/3 during the study period. The mean age at cohort enrollment of these women was 35.1 years (SD=5.22), and the mean age at CIN2/3 diagnosis was 36.2 years (SD=5.30). The frequency of CIN2/3 diagnosis increased with age. No woman with CIN2/3 diagnosis was enrolled at age 20-25 years old, the percentage of women with CIN2/3 diagnosis increased from 0.03% in the 26-30-year-old age group (3 cases) to 0.07% in 41-45-year-old age group (5 cases). Eight cases were diagnosed in the year 2019 among 23,408 women, followed by 7 cases among 50,042 women in 2020 and 7 among 50,035 women in 2021. One case was diagnosed among 10,665 women in 2018. More than half of these women were from urban areas (n=14) area. Their HPV and cytological testing status at enrollment and CIN2/3 diagnosis were not known and it is therefore likely that these women were infected with HPV before G4 vaccination. The mean follow-up time of the G4 vaccinated cohort was 17.2 woman-months (SD=9.23), and the rate of CIN2/3 was 0.03 (95% CI: 0.02 - 0.04) per 1,000 woman-months (Table 4).

No woman from the G4 vaccinated HPV test-negative sub-cohort had an onset of CIN2/3. The mean follow-up time was 16.0 (SD=8.78) months, and the rate of CIN2/3 was 0 (95% CI: 0 – 0.2) per 1,000 woman-months (Table 5).

No woman from the matched unvaccinated cohort had an onset of CIN2/3. The mean follow-up time of women in the unvaccinated cohort was 16.1 (SD=8.80) months and the rate of CIN2/3 was 0 (95% CI: 0 - 0.07) per 1,000 woman-months (Table 6).

AIS and ICC in the G4 vaccinated cohort, G4 vaccinated HPV test-negative sub-cohort and matched unvaccinated cohort

One woman from the G4 vaccinated cohort had an onset of AIS during the study period. No woman from the G4 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of AIS during the study period. The rates of AIS for the three cohorts were 0.001 (95% CI: 0 - 0.006), 0 (95% CI: 0 - 0.2) and 0 (95% CI: 0 - 0.07) per 1,000 woman-months, respectively.

No woman from the G4 vaccinated cohort, the G4 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of invasive cervical carcinoma. The rates of invasive cervical carcinoma were 0 (95% CI: 0 - 0.004), 0 (95% CI: 0 - 0.2) and 0 (95% CI: 0 - 0.07) per 1,000 woman-months, respectively (Table 7, Table 8, Table 9).

Disease occurrence in the general female population

CIN2/3 occurrence in the general female population aged 20 and above was relatively stable over the observation years 2016 to 2020; it was lowest in 2017 (113.96 per million) and highest in 2018 (179.41 per million). The proportion of women with CIN2/3 was lowest in the youngest age group of 20 to 25 years, ranging from 6.98 per million in 2016 to 36.95 per million in 2020 with an increasing trend since 2019.

In 2016 and 2017, most of the CIN2/3 cases occurred in the age group 41 to 45 years (226.83 and 183.30 per million, respectively). However, from 2018 on, the peak age of CIN2/3 shifted to the 36 to 40-year-old-age group (ranging from 235.21 per million in 2019 to 243.22 per million in 2020) (Table 10).

The proportion of AIS was the lowest in 2016 (2.30 per million) and the highest in 2020 (7.93 per million) with very low numbers of cases ranging from 5 in 2016 to 21 in 2020). No case occurred in any year among 20-25-year-old-women and only very few cases in the age group 26-30 years. The number of cases showed an increasing trend with age in most of the surveillance years reaching up to 13 cases among women >45 years of age in 2020 (Table 11).

The number of ICC was highest in 2017 (96 cases, 42.74 per million) and lowest in 2019 (83 cases, 34.73 per million). The proportion of ICC cases increased with age in all surveillance years, reaching 59.92 per million among women >45 years of age in 2016. Only in 2017, the proportion of cases was highest in the 41-45-year age group with 68.74 per million women who were diagnosed with ICC. No cases were observed among the youngest age group of 20-25-year-old-women in any of the surveillance years and only sporadic cases were observed in women under 40 years of age (Table 12).

Results from 2021 are not included in the description here, because the data were not available for the full year, as data collection for 2021 ended on 31 March 2021.

Table 4. Counts and rates of CIN2/3 in the G4 vaccinated cohort ("Per-protocol" analysis)

Variables	G4 vaccinated cohort (N=50,051)		
	No. of CIN2/3, % (n/N) *	Woman-months, mean±SD	Rate per 1000 woman-months, (95% CI)
Total	0.05 (23/50,051)	17.2 (9.23)	0.03 (0.02 - 0.04)
Age at cohort enrollment (years), mean±SD	35.1 (5.22)		
20-25 years, n (%)	0.00 (0/2,504)	23.0 (9.16)	0 (0 - 0.06)
26-30 years, n (%)	0.03 (3/11,057)	16.9 (9.07)	0.02 (0.003 - 0.05)
31-35 years, n (%)	0.05 (8/16,256)	15.9 (8.72)	0.03 (0.01 - 0.06)
36-40 years, n (%)	0.06 (7/12,649)	17.5 (9.25)	0.03 (0.01 - 0.07)
41-45 years, n (%)	0.07 (5/7,585)	18.0 (9.70)	0.04 (0.01 - 0.09)
Calendar year of diagnosis†			
2018, n (%)	0.01 (1/10,665)	3.7 (2.82)	0.03 (0.0006 - 0.1)
2019, n (%)	0.03 (8/23,408)	10.9 (5.58)	0.03 (0.01 - 0.06)
2020, n (%)	0.01 (7/50,042)	14.2 (9.23)	0.01 (0.004 - 0.02)
2021, n (%)	0.01 (7/50,035)	17.2 (9.23)	0.008 (0.003 - 0.02)
Age at diagnosis (year), mean±SD	36.2 (5.30)		
Residence region, n (%)††			
Urban area	0.05 (14/29,329)	17.3 (9.41)	0.03 (0.02 - 0.05)
Rural area	0.05 (9/20,119)	16.8 (8.76)	0.03 (0.01 - 0.05)
Unknown	0.00 (0/603)	28.3 (8.96)	0 (0 - 0.2)

* CIN2+ diagnosed within one year were treated as one event. Only the highest level of lesion was counted if the women had more than one lesions

†† Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

† The denominators are the numbers of women in the G4 vaccinated cohort by the end of the year.

Table 5 Counts and rates of CIN2/3 in the G4 vaccinated HPV test-negative sub-cohort

Variables	G4 vaccinated HPV test-negative sub-cohort (N=1,129)		
	No. of CIN2/3, % (n/N) *	Woman-months, mean±SD	Rate per 1000 woman-months, (95% CI)
Total	0.00 (0/1129)	16.0 (8.78)	0 (0 - 0.2)
Age at cohort enrollment (years), mean±SD	———		
20-25 years, n (%)	0.00 (0/16)	23.5 (9.68)	0 (0 - 9.8)
26-30 years, n (%)	0.00 (0/194)	15.9 (8.71)	0 (0 - 1.2)
31-35 years, n (%)	0.00 (0/408)	14.8 (8.43)	0 (0 - 0.6)
36-40 years, n (%)	0.00 (0/302)	17.1 (8.71)	0 (0 - 0.7)
41-45 years, n (%)	0.00 (0/209)	16.6 (9.10)	0 (0 - 1.1)
Calendar year of diagnosis†			
2018, n (%)	0.00 (0/194)	3.0 (2.45)	0 (0 - 6.3)
2019, n (%)	0.00 (0/481)	10.1 (5.37)	0 (0 - 0.8)
2020, n (%)	0.00 (0/1,129)	13.0 (8.78)	0 (0 - 0.3)
2021, n (%)	0.00 (0/1,129)	16.0 (8.78)	0 (0 - 0.2)
Age at diagnosis (year), mean±SD	———		
Residence region, n (%)††			
Urban area	0.00 (0/888)	16.2 (8.92)	0 (0 - 0.3)
Rural area	0.00 (0/241)	15.4 (8.25)	0 (0 - 1)
Ethnicity, n (%)			
Han	0.00 (0/1006)	16.2 (8.81)	0 (0 - 0.2)
Others	0.00 (0/5)	12.6 (6.07)	0 (0 - 58.4)
Unknown	0.00 (0/118)	14.7 (8.54)	0 (0 - 2.1)
Marital status, n (%)			
Single	0.00 (0/203)	14.8 (8.50)	0 (0 - 1.2)
Married	0.00 (0/757)	16.5 (8.85)	0 (0 - 0.3)

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Divorced	0.00 (0/6)	21.8 (10.03)	0 (0 - 28.2)
Widowed	0.00 (0/1)	7.2 (—)	0 (0 - 514.7)
Unknown	0.00 (0/162)	15.1 (8.57)	0 (0 - 1.5)
Parity, n (%)			
0	0.00 (0/82)	10.2 (4.77)	0 (0 - 4.4)
1	0.00 (0/45)	12.1 (6.04)	0 (0 - 6.8)
2	0.00 (0/4)	18.2 (10.32)	0 (0 - 50.8)
≥3	0.00 (0)		
Unknown	0.00 (0/998)	16.7 (8.92)	0 (0 - 0.2)
Health insurance status, n (%)			
Yes	0.00 (0/991)	16.2 (8.81)	0 (0 - 0.2)
No	0.00 (0/12)	12.6 (6.65)	0 (0 - 24.5)
Unknown	0.00 (0/126)	14.8 (8.62)	0 (0 - 2)

* CIN2+ diagnosed within one year were treated as one event. Only the highest level of lesion was counted if the women had more than one lesions

†† Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

† The denominators are the number of women in the G4 vaccinated HPV test-negative sub-cohort by the end of the year.

Table 6 Counts and rates of CIN2/3 in the G4 matched unvaccinated cohort

Variables	Matched unvaccinated cohort (N=3,311)		
	No. of CIN2/3, % (n/N) *	Woman-months, mean±SD	Rate per 1000 woman-months, (95% CI)
Total	0.00 (0/3,311)	16.1 (8.80)	0 (0 - 0.07)
Age at cohort enrollment (years), mean±SD	____		
20-25 years, n (%)	0.00 (0/48)	23.5 (9.47)	0 (0 - 3.3)
26-30 years, n (%)	0.00 (0/568)	15.8 (8.68)	0 (0 - 0.4)
31-35 years, n (%)	0.00 (0/1,196)	14.8 (8.44)	0 (0 - 0.2)
36-40 years, n (%)	0.00 (0/881)	17.2 (8.73)	0 (0 - 0.2)
41-45 years, n (%)	0.00 (0/618)	16.6 (9.13)	0 (0 - 0.4)
Calendar year of diagnosis†			
2018, n (%)	0.00 (0/574)	3.0 (2.45)	0 (0 - 2.1)
2019, n (%)	0.00 (0/1,409)	10.1 (5.36)	0 (0 - 0.3)
2020, n (%)	0.00 (0/3,311)	13.1 (8.80)	0 (0 - 0.09)
2021, n (%)	0.00 (0/3,311)	16.1 (8.80)	0 (0 - 0.07)
Age at diagnosis (year), mean±SD	____		
Residence region, n (%)††			
Urban area	0.00 (0/2,600)	16.2 (8.93)	0 (0 - 0.09)
Rural area	0.00 (0/711)	15.4 (8.27)	0 (0 - 0.3)
Ethnicity, n (%)			
Han	0.00 (0/2,684)	16.1 (8.77)	0 (0 - 0.09)
Others	0.00 (0/20)	12.7 (7.04)	0 (0 - 14.5)
Unknown	0.00 (0/607)	16.1 (8.98)	0 (0 - 0.4)
Marital status, n (%)			
Single	0.00 (0/497)	14.7 (8.23)	0 (0 - 0.5)

Married	0.00 (0/2,069)	16.4 (8.86)	0 (0 - 0.1)
Divorced	0.00 (0/17)	17.4 (10.06)	0 (0 - 12.5)
Widowed	0.00 (0/2)	11.2 (0.73)	0 (0 - 164.4)
Unknown	0.00 (0/726)	16.0 (8.92)	0 (0 - 0.3)
Parity, n (%)			
0	0.00 (0/196)	13.8 (7.70)	0 (0 - 1.4)
1	0.00 (0/133)	14.4 (8.48)	0 (0 - 1.9)
2	0.00 (0/12)	15.2 (9.56)	0 (0 - 20.2)
≥3	0.00 (0)		
Unknown	0.00 (0/2,970)	16.3 (8.86)	0 (0 - 0.08)
Health insurance status, n (%)			
Yes	0.00 (0/2,583)	16.1 (8.77)	0 (0 - 0.09)
No	0.00 (0/50)	13.7 (8.06)	0 (0 - 5.4)
Unknown	0.00 (0/678)	16.1 (8.95)	0 (0 - 0.3)

Unvaccinated women were matched with women of vaccinated sub-cohort by ± 1 year

* CIN2+ diagnosed within one year were treated as one event. Only the highest level of lesion was counted if the women had more than one lesions

†† Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

† The denominators are the number of women in the G4 matched unvaccinated cohort by the end of the year.

Table 7 Counts and rates of AIS and ICC in the G4 vaccinated per protocol cohort

Variables	G4 vaccinated cohort (N=50,051)
AIS cases, % (n/N)	0.0020 (1/50,051)
Woman-month, mean±SD	17.2 (9.23)
Rate per 1000 woman-months (95% CI)	0.001 (0 - 0.006)
Invasive cervical cancer cases, % (n/N)	0.0000 (0/50,051)
Woman-month, mean±SD	17.2 (9.23)
Rate per 1000 woman-months (95% CI)	0 (0 - 0.004)

Table 8 Counts and rates of AIS and ICC in the G4 vaccinated HPV test-negative sub-cohort

Variables	G4 vaccinated sub-cohort (N=1,129)
AIS cases, % (n/N)	0.0000 (0/1,129)
Woman-month, mean±SD	16.0 (8.78)
Rate per 1000 woman-months (95% CI)	0 (0 - 0.2)
Invasive cervical cancer cases, % (n/N)	0.0000 (0/1,129)
Woman-month, mean±SD	16.0 (8.78)
Rate per 1000 woman-months (95% CI)	0 (0 - 0.2)

Table 9 Counts and rates of AIS and ICC in the matched unvaccinated cohort

Variables	G4 matched unvaccinated cohort (N=3,311)
AIS cases, % (n/N)	0.0000 (0/3,311)
Woman-month, mean±SD	16.1 (8.80)
Rate per 1000 woman-months (95% CI)	0 (0 - 0.07)
Invasive cervical cancer cases, % (n/N)	0.0000 (0/3,311)
Woman-month, mean±SD	16.1 (8.80)
Rate per 1000 woman-months (95% CI)	0 (0 - 0.07)

Table 10. CIN2/3 occurrence in the general female population

Calendar Year	CIN2/3 cases (n)*	General female population (N)	Proportion (per million)
2016	**327**	**2,176,375**	**150.25**
By age groups, yr			
20-25	1	143,329	6.98
26-30	21	225,291	93.21
31-35	39	217,364	179.42
36-40	43	214,052	200.89
41-45	51	224,834	226.83
>45	172	1,151,505	149.37
2017	**256**	**2,246,361**	**113.96**
By age groups, yr			
20-25	1	137,604	7.27
26-30	18	212,112	84.86
31-35	40	229,106	174.59
36-40	40	229,411	174.36
41-45	40	218,227	183.30
>45	117	1,219,901	95.91
2018	**412**	**2,296,435**	**179.41**
By age groups, yr			
20-25	1	128,247	7.80
26-30	14	206,462	67.81
31-35	50	239,208	209.02
36-40	56	236,399	236.89
41-45	46	214,735	214.22
>45	245	1,271,384	192.70
2019	**375**	**2,389,671**	**156.93**
By age groups, yr			

20-25	3	124,223	24.15
26-30	16	198,661	80.54
31-35	50	265,352	188.43
36-40	56	238,081	235.21
41-45	52	222,311	233.91
>45	198	1,341,043	147.65
2020	**317**	**2,648,265**	**119.70**
By age groups, yr			
20-25	5	135,316	36.95
26-30	19	219,632	86.51
31-35	42	325,823	128.90
36-40	67	275,471	243.22
41-45	50	242,238	206.41
>45	134	1,449,785	92.43
2021**	**47**	**2,662,922**	**17.65**
By age groups, yr			
20-25	1	134,295	7.45
26-30	3	219,264	13.68
31-35	7	329,134	21.27
36-40	10	278,943	35.85
41-45	4	242,960	16.46
>45	22	1,458,326	15.09

*Histologically confirmed new yearly cases.

**2021 data collection cut-off: Mar 31st

Table 11. AIS occurrence in the general female population

Calendar Year	AIS cases, (n*)	General female population, (N)	Proportion (per million)
2016	**5**	**2,176,375**	**2.30**
By age groups, yr			
20-25	0	143,329	0.00
26-30	1	225,291	4.44
31-35	0	217,364	0.00
36-40	1	214,052	4.67
41-45	2	224,834	8.90
>45	1	1,151,505	0.87
2017	**16**	**2,246,361**	**7.12**
By age groups, yr			
20-25	0	137,604	0.00
26-30	0	212,112	0.00
31-35	3	229,106	13.09
36-40	2	229,411	8.72
41-45	2	218,227	9.16
>45	9	1,219,901	7.38
2018	**8**	**2,296,435**	**3.48**
By age groups, yr			
20-25	0	128,247	0.00
26-30	0	206,462	0.00
31-35	2	239,208	8.36
36-40	2	236,399	8.46
41-45	0	214,735	0.00
>45	4	1,271,384	3.15
2019	**12**	**2,389,671**	**5.02**
By age groups, yr			

20-25	0	124,223	0.00
26-30	1	198,661	5.03
31-35	3	265,352	11.31
36-40	3	238,081	12.60
41-45	3	222,311	13.49
>45	2	1,341,043	1.49
2020	**21**	**2,648,265**	**7.93**
By age groups, yr			
20-25	0	135,316	0.00
26-30	1	219,632	4.55
31-35	2	325,823	6.14
36-40	2	275,471	7.26
41-45	3	242,238	12.38
>45	13	1,449,785	8.97
2021**	**4**	**2,662,922**	**1.50**
By age groups, yr			
20-25	0	134,295	0.00
26-30	0	219,264	0.00
31-35	2	329,134	6.08
36-40	2	278,943	7.17
41-45	0	242,960	0.00
>45	0	1,458,326	0.00

*Histologically confirmed new yearly cases.

**2021 data collection cut-off: Mar 31st

Table 12. Invasive cervical cancer occurrence in the general female population

Calendar Year	ICC cases, (n*)	General female population, (N)	Proportion (per million)
2016	**85**	**2,176,375**	**39.06**
By age groups, yr			
20-25	0	143,329	0.00
26-30	1	225,291	4.44
31-35	5	217,364	23.00
36-40	2	214,052	9.34
41-45	8	224,834	35.58
>45	69	1,151,505	59.92
2017	**96**	**2,246,361**	**42.74**
By age groups, yr			
20-25	0	137,604	0.00
26-30	0	212,112	0.00
31-35	2	229,106	8.73
36-40	7	229,411	30.51
41-45	15	218,227	68.74
>45	72	1,219,901	59.02
2018	**85**	**2,296,435**	**37.01**
By age groups, yr			
20-25	0	128,247	0.00
26-30	2	206,462	9.69
31-35	1	239,208	4.18
36-40	1	236,399	4.23
41-45	6	214,735	27.94
>45	75	1,271,384	58.99
2019	**83**	**2,389,671**	**34.73**
By age groups, yr			

20-25	0	124,223	0.00
26-30	0	198,661	0.00
31-35	5	265,352	18.84
36-40	5	238,081	21.00
41-45	9	222,311	40.48
>45	64	1,341,043	47.72
2020	**90**	**2,648,265**	**33.98**
By age groups, yr			
20-25	0	135,316	0.00
26-30	1	219,632	4.55
31-35	4	325,823	12.28
36-40	4	275,471	14.52
41-45	10	242,238	41.28
>45	71	1,449,785	48.97
2021**	**27**	**2,662,922**	**10.14**
By age groups, yr			
20-25	0	134,295	0.00
26-30	0	219,264	0.00
31-35	0	329,134	0.00
36-40	4	278,943	14.34
41-45	0	242,960	0.00
>45	23	1,458,326	15.77

*New yearly cases identified from cancer register.

**2021 data collection cut-off: Mar 31st

10.4 Main results

Limited number of cases of CIN2/3 were diagnosed in the study cohorts during the study period from 9 January 2018 to 31 March 2021.

Among 50,051 women vaccinated with G4 according to the "per protocol" vaccination schedule, twenty-three women were diagnosed with CIN2/3. The rate per 1,000 woman-months was estimated at 0.03 (95% CI: 0.02 - 0.04). Among 1,129 women from the G4 vaccinated HPV test-negative sub-cohort, no new onset CIN2/3 case was detected. The rate per 1,000 woman-months was estimated at 0 (95% CI: 0 - 0.2). Among the 3,311 women from the matched unvaccinated cohort, no new onset CIN2/3 case was detected. The rate per 1,000 woman-months was estimated at 0 (95% CI: 0 - 0.07).

Among the general female population, which included vaccinated and unvaccinated women, the occurrence of CIN2/3 cases was relatively stable over the observation years 2016 to 2020, ranging from 256 (113.96 per million) in 2017 to 412 (179.41 per million) in 2018. The proportion of women with CIN2/3 was lowest in the youngest age group of women 20 to 25 years in which however an increase of cases was observed since 2019. CIN2/3 then increased with age and reached a peak in the age group 41 to 45 years in 2016/2017 and 36 to 40 years since 2018. However, these results need to be considered with caution as the number of cases was relatively low.

During the study period, one woman from the G4 vaccinated cohort had an onset of AIS, no woman from the G4 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of AIS. Among the general female population, new onset of AIS ranged from 2.30 per million in 2016 to 7.93 per million in 2020. No cases occurred in any year among the youngest age group of 20-25-year-old-women and the number of cases increased with age in most of the surveillance years.

Additionally, no woman from the G4 vaccinated cohort, the G4 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of ICC. Among the general female population, the proportion of ICC was highest in 2017 (42.74 per million) and lowest in 2020 (33.98 per million). The proportion of ICC cases increased with age in all

surveillance years and no cases were observed among the youngest age group of 20-25-year-old-women during the study period.

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10.5 Other analyses

The proportion of women from the general population who underwent cervical cytology tests was very similar from year to year between 2015 and 2020, ranging from 1.05% in 2015 and 2016 to 1.33% in 2020 with a slightly increasing trend over the years.

The proportion of women who received a cervical cytology test increased with age in all surveillance years, reaching a peak at age 36-40 years (1.62% and 1.70%) in 2015/2016 and at age 41-45 years (1.89% to 2.15%) in the subsequent years, with a sharp increase between the age groups 20-25 (0.35% to 0.49%) and 26-30 years (1.12% to 1.41%) as well as a sharp decrease in women aged >45 (0.77% to 1.01%). Results from 2021 were not included, because the data collection for 2021 ended on 31 March 2021 (Table 13).

Cervical diseases including hysterectomy or CIN2+ treatment has been reported to NRHIP since 2015. The cumulative number of women from the general female population who had a history of cervical diseases reported prior to the calendar year 2016, 2017, 2018, 2019, 2020 and 2021 is presented in Table 14.

Table 13. Proportion of women who received cervical cytology test in the general female population

General female population by calendar year and age group		Proportion of women who received cervical cytology test, n (%)
2015	**≥20 years**	**22,328 (1.05)**
	20-25 years	549 (0.36)
	26-30 years	2,806 (1.24)
	31-35 years	3,283 (1.55)
	36-40 years	3,308 (1.62)
	41-45 years	3,724 (1.58)
	>45 years	8,658 (0.79)
2016	**≥20 years**	**22,790 (1.05)**
	20-25 years	501 (0.35)
	26-30 years	2,775 (1.23)
	31-35 years	3,509 (1.61)
	36-40 years	3,637 (1.70)
	41-45 years	3,520 (1.57)
	>45 years	8,848 (0.77)
2017	**≥20 years**	**25,165 (1.12)**
	20-25 years	491 (0.36)
	26-30 years	2,370 (1.12)
	31-35 years	3,610 (1.58)
	36-40 years	4,062 (1.77)
	41-45 years	4,116 (1.89)
	>45 years	10,516 (0.86)
2018	**≥20 years**	**28,613 (1.25)**
	20-25 years	477 (0.37)
	26-30 years	2,497 (1.21)
	31-35 years	4,083 (1.71)
	36-40 years	4,589 (1.94)
	41-45 years	4,436 (2.07)
	>45 years	12,531 (0.99)
2019	**≥20 years**	**30,105 (1.26)**
	20-25 years	511 (0.41)
	26-30 years	2,431 (1.22)
	31-35 years	4,461 (1.68)
	36-40 years	4,643 (1.95)
	41-45 years	4,720 (2.12)
	>45 years	13,339 (0.99)

2020	**≥20 years**	**35,124 (1.33)**
	20-25 years	661 (0.49)
	26-30 years	3,086 (1.41)
	31-35 years	6,114 (1.88)
	36-40 years	5,436 (1.97)
	41-45 years	5,219 (2.15)
	>45 years	14,608 (1.01)
2021*	**≥20 years**	**7,712 (0.29)**
	20-25 years	168 (0.13)
	26-30 years	763 (0.35)
	31-35 years	1,260 (0.38)
	36-40 years	1,208 (0.43)
	41-45 years	1,125 (0.46)
	>45 years	3,188 (0.22)

*2021 data collection cut-off: Mar 31st

Table 14. Number of women who have a history of cervical diseases including CIN2+ or who have undergone hysterectomy or CIN2+ treatment in the general female population (by calendar year from 2016).

Population by year	Number of women who have history of cervical diseases or undergone hysterectomy or CIN2+ treatment
General female population (2016)	18,835
General female population (2017)	25,878
General female population (2018)	33,280
General female population (2019)	43,009
General female population (2020)	55,715
General female population (2021)	65,652

*Data on NRHIP is available since 2015 and the number in this table is cumulative.

10.6 Adverse events/adverse reactions

This is a retrospective study using data from the NRHIP with the objective of assessing the occurrence of CIN2+ among women vaccinated with G4. The analysis of safety is the subject of a separate study. Although adverse events (AEs) and product quality complaints (PQCs) were not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs must be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE or PQC to G4, G9 or any other Merck product is identified, the AE/PQC must be reported. For the purpose of this study, as defined in the study protocol, the term AE includes SARs, NSARs, HOIs that meet criteria for SAR/NSAR and special situations, including exposure to product during pregnancy. Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as SARs/NSARs. During review of secondary data, causality should never be assigned retrospectively.

No adverse events were reported in this study.

11 DISCUSSION

11.1 Limitations

This surveillance occurred within the NRHIP, which is a cloud-based health information platform. The NRHIP is designed for routine health care management, rather than for research purposes. Medical care (including diagnoses and treatment) received outside of the area covered by the NRHIP is not available.

Cervical cancer screening methods (e.g., cytology, HPV testing, etc.) are not standardized across health care facilities in Ningbo, as it is the case in China overall. As recommended by the SRC and described in the guidelines of cervical cancer in China, high-grade cervical intraepithelial neoplasia cases were confirmed via histological tests from local laboratories within Ningbo. However, as for most other studies that measure the impact of HPV vaccines,

the HPV types within each lesion were not known and therefore, the proportion of lesions attributable to G4 vaccine types are not known.

CCI a matched unvaccinated cohort was set up in this study. Women from the G4 vaccinated HPV test-negative sub-cohort were matched on age at cohort enrollment and area of residence (rural/urban) to up to three women from the unvaccinated HPV test-negative sub-cohort. However, a formal comparison between the cohorts of vaccinated and matched unvaccinated women was not considered meaningful due to the short follow-up period since the introduction of vaccination with G4 and the low coverage of cervical screening services in Ningbo, especially for the younger age groups eligible for vaccination and the limited capture of data from these services in the NRHIP.

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In population-based registry studies, it is not possible to obtain information on what an individual's HPV status and HPV genotyping of cervical lesions was at the time of HPV vaccination, thereby hindering the ability to identify lesions associated with vaccine types. Acquisition of HPV following sexual debut is high and HPV vaccination does not alter the course of an ongoing HPV infection. Asymptomatic prevalent infections with high-risk HPV types, or cervical lesions caused by such types, may have been already present at the time of vaccination in the G4 vaccinated cohort. This may be reflected in endpoint diagnoses occurring after vaccination.

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In addition, no lag time between G4 vaccination and diagnoses of cervical lesions was applied in this study. Generally it is expected, that full immunity is only reached several months after vaccination with the third dose {085DJ3, 07XNWX}. In addition, the latent period from HPV infection to CIN2/3 takes several years to decades. Therefore, CIN2/3 cases that occur shortly after vaccination are unlikely to be caused by infection acquired following vaccination, i.e., not breakthrough infections.

HPV vaccination in Ningbo is opportunistic. As vaccination is driven by women's willingness and doses of G4 are paid out-of-pocket, vaccinated women may be different from unvaccinated in many ways that may also be related to their risk of high-grade cervical intraepithelial neoplasia, resulting in potential biases and confounding in the study. Differences in socioeconomic status leads to unequal uptake of the vaccine and vaccinated women are more likely to receive preventive health care services and result in a detection bias and underestimation of the impact of vaccination on high-grade cervical lesions.

There is no population-based cervical screening program in Ningbo. There is a local free cervical cancer screening program in Ningbo at the current stage. However, this local screening program is opportunistic targeting 35-64 years old rural or urban women who have no jobs. In the past years, this local cervical cancer screening program mainly targeted women aged 60-64 years old. Data of this local cervical screening program are not available in the NRHIP at the current stage. While China's cervical screening guidelines recommend screening beginning at age 25, cervical cancer screening that takes place outside of the free platform is not organized and may be offered to women starting at age 20. Rather, it is based on individual health care seeking and participation in annual body check-ups provided by employers. Cervical screening within the population who is age-eligible for vaccination is not routine in Ningbo, therefore, counts of high-grade cervical intraepithelial neoplasia

within the platform was from women who had histological cervical testing because they were symptomatic or from women undergoing opportunistic cervical screening. The underlying population from which these women come is not known. In addition, screening methods for cervical cancer in Ningbo varies across health care facilities. Some use HPV tests and cytological tests (including Pap test and TCT), and others might use visual inspection with acetic acid or visual inspection with Lugol's iodine. The sensitivity of a screening method, coupled with the proportion of the population covered, the age group covered, the frequency of screening, and colposcopy and biopsy tests are important factors in the frequency of diagnosis of high-grade cervical intraepithelial neoplasia. Even if the underlying risk factors are similar across areas, the rates of high-grade cervical intraepithelial neoplasia may not be similar if their approach to cervical screening differs widely. Moreover, as screening methods and algorithms change, so too can the rates of high-grade cervical intraepithelial neoplasia diagnoses change. The way in which cervical screening results are compiled (e.g., electronic versus paper register, dataset linkage, etc.) can also impact the proper accounting for cases within a database analysis and thereby impact the estimation of high-grade cervical intraepithelial neoplasia rates. Thus, a study of high-grade cervical intraepithelial neoplasia rates needs to also characterize the cervical screening programs and population base from which the cases arise, and to monitor changes in the programs over time, so that reasons for fluctuations in rates that may be observed can be more fully understood.

Last but not least, information on lifestyle factors, such as health care seeking behavior, sexual behaviors and other factors potentially related to risk of high-grade cervical intraepithelial neoplasia or high-grade cervical intraepithelial neoplasia diagnosis chances, were not available in the NRHIP. Vaccinated and unvaccinated women are expected to be different with respect to their risk of high-grade cervical intraepithelial neoplasia, such as demographic characteristics, socio-economic status, sexual and reproductive health behaviors etc. These factors could influence the diagnosis of high-grade cervical intraepithelial neoplasia. Due to the database study design, these factors could not be collected and analyzed in this study, though they are associated with risks of high-grade cervical intraepithelial neoplasia occurrence and could have had an impact on the effectiveness of HPV vaccination.

Rates of high-grade cervical intraepithelial neoplasia were estimated but not compared between the G4 vaccinated HPV test-negative sub-cohort and the matched unvaccinated HPV test-negative cohort due to the short follow-up time since the introduction of the vaccine and the low number of cases that were reported to NRHIP. Differences in risk factors for high-grade cervical intraepithelial neoplasia between vaccinated and unvaccinated populations cannot be excluded, and relevant information is insufficient in NRHIP to identify and control these biases. Therefore, comparison between the G4 vaccinated cohort and the unvaccinated population was not performed in this study. Available data from the NRHIP, such as age, proportion of women who had cervical cytological tests were summarized in the study report. As high-quality surveillance data on HPV infection related diseases is not available in Ningbo, women from the general population provide background information of high-grade cervical intraepithelial neoplasia in Ningbo. In addition, there is no population-based cervical cancer screening program in Ningbo currently and high-grade cervical intraepithelial neoplasia cases were identified from opportunistic cervical screening or from women who had cervical testing because they were symptomatic. Therefore, the case counts of high-grade cervical intraepithelial neoplasia in the NRHIP may be an underestimate of true disease burden in the general population.

11.2 Interpretation

Since 9 January 2018 when G4 vaccination record available on the NRHIP until the data cut-off of 31 March 2021, a total of 195,457 doses of G4 were administered and 76,118 women received at least one dose of G4 and no other HPV vaccine. The number of women who received a first dose of G4 showed an increasing trend from 2018 to 2020. 67.5 % of the women received G4 according to the per protocol definition.

No new onset CIN2/3 case was observed during the study period in the G4 vaccinated HPV test-negative sub-cohort (N=1,129) and the matched unvaccinated cohort (N=3,311) corresponding to a rate of 0 (95% CI: 0 - 0.2) and 0 (95% CI: 0 - 0.07) per 1,000 woman-months respectively for the two cohorts. Only women who had an HPV test-negative result prior to cohort enrollment were enrolled in these cohorts to ensure that women had no prevalent HPV infection prior to vaccination with G4.

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Twenty-three CIN2/3 case were observed in the larger cohort of G4 vaccinated women (N=50,051) for whom the HPV and cytological testing status at enrollment and CIN2/3 diagnosis was not known and we cannot therefore exclude the possibility that the women who were observed with CIN2/3 during the study period were infected with HPV before G4 vaccination, especially as all cases were diagnosed in women who were enrolled in the study at age 26-45 years old. Although, in a context where HPV vaccination is not reimbursed, G4 vaccinated women might have a higher healthcare seeking behavior and might be more likely to get cervical screening, and thus be diagnosed with CIN2/3 than women from the general population.

One AIS case was observed in the G4 vaccinated cohort. No AIS cases were observed in the G4 vaccinated HPV test negative sub-cohort as well as in the matched unvaccinated cohort. No ICC case was observed in any of the three cohorts.

G4 was introduced in China in 2017, and the first women in Ningbo were vaccinated with G4 in 2018. Vaccine impact generally becomes first apparent for HPV infections and genital warts, which have short incubation periods following exposure to HPV. Effects on cervical lesions, which take longer to develop, can only be observed after more extended observation periods. Cancer rates are expected to decline only in the longer term because carcinogenesis after HPV infection may require several decades to become manifest.

We monitored the occurrence of CIN2/3, AIS, and ICC cases in the general female population (including vaccinated and unvaccinated women) over the years 2016 to 2021 to identify if changes in cervical screening methods over the years may have impacted high-grade cervical intraepithelial neoplasia diagnoses. The proportion of new CIN2/3 cases reported to NRHIP in this population was relatively stable, lowest in 2017 with 113.96 cases per million (n=256) and highest in 2018 with 179.41 cases per million (n=412). It is worth noting that the proportion of women vaccinated with G4 among the general population was relatively low.

The proportion of AIS varied between 2.30 per million (5 cases) in 2016 and 7.93 per million (21 cases) in 2020 and the proportion of ICC was highest in 2017 (96 cases, 42.74 per

million) and lowest in 2019 (83 cases, 34.73 per million). The number of cases reported in 2021 was not available for the complete year and therefore the trend for 2021 cannot be determined yet.

To our knowledge, incidence of CIN2+ among the general female population from the Ningbo region that could be compared to the study results is not available in the literature.

Given the lack of organized screening in Ningbo, it is difficult to get the full picture of cervical disease. Data from opportunistic screening is not reported to NRHIP. Therefore, only women who are treated in the hospital for CIN2/3 could be identified from the NRHIP. The proportion of women from the general population who underwent cervical cytology tests, as reported to the NRHIP, was very similar from year to year between 2015 and 2020, ranging from 1.05% in 2015 and 2016 to 1.33% in 2020, with a slightly increasing trend over the years. Cytology testing increased with age in all surveillance years and reached a peak at 36-40 in 2015/2016 and at 41-45 years in the subsequent years. The percentage of women with cytology testing after cohort enrollment was generally low, presumably because those women just had a recent negative test to be eligible for enrollment in the test-negative sub-cohort vaccinated sub-cohort and the matched unvaccinated cohort. We also observed a similar proportion of women who had cervical cytology testing after cohort enrollment in the G4 vaccinated HPV test-negative sub-cohort (15.9%) compared to the matched unvaccinated cohort (14.6%). This observation is based on limited data but it indicates that vaccinated women may have a higher tendency to attend cervical screening services compared to unvaccinated women due to increased awareness and health-seeking behaviors. This observation needs to be factored into the interpretation of CIN2/3 occurrence among these two cohorts. In addition, CIN2/3 is an asymptomatic disease, and the disease burden is therefore assumed to be much higher than what we observed so far in this study.

Since G4 was introduced in China in 2017, it is still too early to observe the effect of the vaccination. Evidence will become increasingly available as the time since the introduction of the vaccine accrues.

In clinical trials worldwide, the quadrivalent HPV vaccine G4 showed high efficacy against cervical, vaginal, vulvar and anal dysplasia related to the HPV types 6, 11, 16 and 18 and against condyloma related to HPV types 6 and 11.

The impact of vaccination with G4 in real-world settings has become increasingly evident, especially among girls vaccinated before HPV exposure in countries with high vaccine uptake. Maximal reductions of approximately 90% for HPV 6, 11, 16 and 18 infection, approximately 90% for genital warts, approximately 45% for low-grade cytological cervical abnormalities, and approximately 85% for high-grade histologically proven cervical abnormalities have been reported {04HBHR}.

Recent studies performed in Sweden and Denmark also showed an effective protection of G4 against invasive cervical cancer, which was most pronounced when girls were vaccinated before 17 years of age {07XNWX, 05LZH0}. Danish investigators also recently reported a reduction in the risk of vulvar and vaginal precancer/cancer associated with G4 vaccination, which was again most prominent among females vaccinated before age 17 years {085CDZ}.

Additional studies are ongoing to evaluate the effectiveness and impact of G4 and G9 in real-world settings in various countries.

11.3 Generalisability

This is a database study based on NRHIP, and all women living in the Ningbo region whose health care data are recorded in the NRHIP were eligible to be included in the study. Ningbo is an economically developed, sizeable coastal city located on the east coastline of China. Most women identified in the vaccinated cohort were Han Chinese, which makes the results from this study generalizable for other parts of China on the ethnic level. However, the Ningbo female population's socioeconomic status might be higher than that in other regions of China. As G4 is not reimbursed by public insurance in China, women with higher socioeconomic status are assumed to have more access to the vaccine, and the vaccine coverage with G4 is assumed to be higher in Ningbo compared to other parts of China. In addition, women with higher socioeconomic status might have more access to cervical screening due to increased awareness and healthcare-seeking behavior. As CIN2/3 is an

asymptomatic disease, CIN2/3 detection is increased in case of higher screening attendance. However, the screening rate is low in Ningbo, and data from public cervical screening are not yet available in NRHIP. These factors need to be considered when extrapolating the results from a region with a higher socioeconomic level to a region with a lower socioeconomic level.

12 OTHER INFORMATION

Not applicable in this report.

13 CONCLUSION

Between 9 January 2018 and 31 March 2021, a total of 195,457 doses of G4 were administered to 76,118 women who received at least one dose of G4 and no other HPV vaccines. The number of women who received a first dose of G4 showed an increasing trend from 2018 to 2020. 67.5 % of women received G4 according to the per protocol definition.

No new onset CIN2/3 case was observed during the study period in the G4 vaccinated HPV test negative sub-cohort and the matched unvaccinated cohort corresponding to a rate of 0 (95% CI: 0 - 0.2) and 0 (95% CI: 0 - 0.07) per 1,000 woman-months respectively for the two cohorts. No AIS or ICC cases were observed in any of the two cohorts.

Twenty-three CIN2/3 cases were observed in the G4 vaccinated cohort for whom the HPV and cytological testing status at enrollment and CIN2/3 diagnosis were not known and therefore the possibility that the women were infected with HPV before G4 vaccination cannot be excluded. One AIS case and no ICC cases were observed in the G4 vaccinated cohort.

The proportion of women vaccinated with G4 among the whole local population was low. It is therefore still too early to observe an impact of the vaccination on the population level. The number of new CIN2/3 cases that were observed in the general female population was relatively stable over the observation years 2016 to 2020, ranging from 256 (113.96 per million) in 2017 to 412 (179.41 per million) in 2018.

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

The number of AIS varied between 5 (2.30 per million) in 2016 and 21 (7.93 per million) in 2020 and the number of ICC was highest in 2017 (96 cases, 42.74 per million) and lowest in 2019 (83 cases, 34.73 per million).

G4 was introduced in China in 2017, and women started to get vaccinated with G4 in Ningbo in 2018. Vaccine impact generally becomes first apparent for HPV infections and genital warts, which have short incubation periods following exposure to HPV. Effects on cervical lesions which take longer time to develop can only be observed after longer observation periods. Cancer rates are expected to decline only in the longer term, because carcinogenesis after HPV infection may require several decades to become manifest.

NRHIP covers all hospitals in Ningbo that have the ability to diagnose CIN2+. Our study demonstrates that the NRHIP can be used to monitor the occurrence of CIN2+ in vaccinated and unvaccinated women living in the Ningbo region over time. However, effects on cervical lesions can only be observed after longer observation periods since the introduction of G4 vaccination.

In addition, as there is no organized cervical screening program in Ningbo and results from opportunistic cervical screening is not recorded in the NRHIP, it might take several years before the sample size is sufficient to compare the rates of high-grade cervical intraepithelial neoplasia in the vaccinated and matched unvaccinated cohorts.

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Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	V503-056/Protocol Version 2.0	21-May-2020	Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9
2	V503-056/SAP Version 2.0	20-Dec-2021	Statistical Analysis Plan for Post-marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9

Annex 2 Study protocol

Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9

2. Annex 2 HPV PMC effectiveness

Annex 3 Statistical Analysis Plan

Statistical Analysis Plan for Post-marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9

3. Annex 3 HPV
PMC effectiveness

Title	Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9
Version identifier of the final study report	GARDASIL®9 Final Study Report V503-056, VERSION 1.0
Date of last version of the final study report	N/A
EU PAS register number	EUPAS36135
Active substance	Each dose of Quadrivalent Human Papillomavirus Recombinant Vaccine (GARDASIL®, G4) contains 20 µg HPV 6 L1 VLP, 40 µg HPV 11 L1 VLP, 40µg HPV 16 L1 VLP, and 20 µg HPV 18 L1 VLP, along with 225 µg of alum. Each dose of Nonavalent Human Papillomavirus Recombinant Vaccine (GARDASIL®9, G9) contains 30 µg HPV 6 L1 VLP, 40 µg HPV 11 L1 VLP, 60 µg HPV 16 L1 VLP, 40 µg HPV 18 L1 VLP, 20 µg HPV 31 L1 VLP, 20 µg HPV 33 L1 VLP, 20 µg HPV 45 L1 VLP, 20 µg HPV 52 L1 VLP, and 20 µg HPV 58 L1 VLP, along with 500 µg of alum.
Medicinal product	G4: Quadrivalent Human Papillomavirus Recombinant Vaccine G9: Nonavalent Human Papillomavirus Recombinant Vaccine
Joint PASS	Not applicable
Research question and objectives	The primary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women who were vaccinated with G4 or G9 in Ningbo (vaccinated cohort). The secondary objective

	is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women without HPV vaccination, who are matched to the vaccinated women on factors such as age, area of residence (rural/urban), receipt of cervical HPV/cytology testing services prior to enrollment, and other factors if appropriate in this study. Disease occurrence in Chinese women in the general population is also provided in this study.
Country(-ies) of study	China
Author	PPD, Peking University Health Science Center, China
Merck Final Repository (REDS) Date	TBD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. 1 Merck Drive, P.O. Box 100, Whitehouse Station, NJ08899, US
MAH contact person	PPD

TABLE OF CONTENTS

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXES

1 ABSTRACT

Title

Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9

Keywords

GARDASIL®; GARDASIL®9; Post-Marketing surveillance; HPV; High Grade Cervical Intraepithelial Neoplasia

Rationale and background

Upon licensure of GARDASIL® (G4) in 2017 and GARDASIL®9 (G9) in 2018 in China, one of the requirements from the approval letter was [redacted]

This final study report presents the study results for women who were vaccinated with G9 (including those who received mixed G4/G9 regimens).The results for G4 will be presented in a separate study report. This report summarizes the results for G9 vaccination surveillance.

Research question and objectives

The primary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women who were vaccinated with G4 or G9 in Ningbo (vaccinated cohort).

The secondary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women without HPV vaccination, who were matched to the vaccinated women on factors such as age, area of residence (rural/urban), receipt of cervical HPV/cytology testing services prior to enrollment, and other factors if appropriate in this study.

Cervical Intraepithelial Neoplasia grade 2 or higher (CIN2+) that occurred from 2016 to 2021 in the general population aged 20 or above was also collected in this study.

Study design

Surveillance within a database system; observational design.

Setting

Vaccination and healthcare data from a platform used for storage of healthcare data from Ningbo (i.e., Ningbo Regional Health Information Platform, "NRHIP") was used in this database surveillance.

Subjects and study size, including dropouts

A vaccinated cohort was identified from the NRHIP based on specific inclusion and exclusion criteria. All women from the vaccinated cohort who had cervical HPV negative and TCT negative results within one year prior to the cohort enrollment date in the EMRs were included in a vaccinated test-negative sub-cohort, and were matched with unvaccinated women. In addition, women from the general population (including vaccinated and unvaccinated women) were monitored.

This is a database study and all eligible women were included in the analysis. The NRHIP has a population of approximately 2.8 million female residents between the ages of 16 and 45 years. This is an observational surveillance activity. Hypothesis testing is not applicable to this study

Variables and data sources

Exposure was defined as the receipt of at least one dose of G9 (including mixed G4/G9) during the study period. The surveillance outcome for the vaccinated cohort and matched unvaccinated cohort was defined as histologically confirmed high-grade cervical intraepithelial neoplasia available in the NRHIP. In addition, for completeness, adenocarcinoma in situ (AIS) and invasive cervical cancers (ICC) diagnosed during the study period and available in the NRHIP were also reported.

Results

A total of 102,791 doses of G9 were administered and 41,609 women received at least one dose of G9 and no other HPV vaccine from 25 January 2019 to 31 March 2021. The number

of women who received a first dose of G9 showed an increasing trend from 2019 to 2020 and also to 2021 when extrapolating the data from the first quarter of 2021 to the whole year. 60.2% (25,058) of vaccinated women received G9 according to the per protocol definition.

One CIN2/3 case was observed in the G9 vaccinated cohort (N=25,017) for whom the HPV and cytological testing status at enrollment and CIN2/3 diagnosis were not known and therefore the posibility that the woman was infected with HPV before G9 vaccination cannot be excluded.

No new onset CIN2/3 cases were observed during the study period in the vaccinated HPV test-negative sub-cohort (N=160) and one case was observed in the matched unvaccinated cohort (N=466). No AIS or ICC cases were observed in the vaccinated and the matched unvaccinated cohort.

The proportion of new CIN2/3 cases that were identified from NRHIP in the general female population (including vaccinated and unvaccinated women) was relatively stable over the observation years of 2016 to 2020, from the lowest in 2017 (113.96 per million) to the highest in 2018 (179.41 per million).

The proportion of AIS ranged from the lowest in 2016 (2.30 per million) to the highest in 2020 (7.93 per million). The proportion of ICC was the highest in 2017 (42.74 per million) and the lowest in 2020 (33.98 per million).

A Safety Review Committee (SRC) reviewed and evaluated the results, and concluded that the study cohort was set up according to the study protocol, and that the surveillance of cervical precancerous lesions and cervical cancer is a good start to further evaluate the G9 effectiveness.

Discussion

No new onset CIN2/3 cases were observed during the study period in the vaccinated HPV test negative sub-cohort and one case was observed in the matched unvaccinated cohort.

Our study demonstrated that NRHIP can be used to monitor the occurrence of CIN2+ in vaccinated and unvaccinated women living in Ningbo over time.

Since G9 was introduced in China in 2018, and available in Ningbo in 2019, it is still too early to observe the impact of the vaccination on CIN2+, due to the short time since G9 introduction and low vaccination coverage.

Marketing Authorisation Holder(s)

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Names and affiliations of principal investigators

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2 LIST OF ABBREVIATIONS

AE	Adverse Event
AEFI	Adverse Events Following Immunization
AIS	Adenocarcinoma In Situ
CDC	Center for Disease Control and Prevention
CDE	Center for Drug Evaluation
CIN	Cervical Intraepithelial Neoplasia
CIN2	Cervical Intraepithelial Neoplasia grade 2
CIN3	Cervical Intraepithelial Neoplasia grade 3
CIN2/3	Cervical Intraepithelial Neoplasia grade 2/3
CIN2+	Cervical Intraepithelial Neoplasia grade 2 or higher
EMR	Electronic Medical Record
G4	GARDASIL®
G9	GARDASIL®9
GPP	Good Pharmacoepidemiology Practice
HGRAC	Human Genetic Resource Administration of China
HOI	Health Outcomes of Interest
HPV	Human Papillomavirus
ICC	Invasive Cervical Cancer
ICD	International Classification of Disease
IQR	Interquartile Range
IRB	Institutional Review Board
NRHIP	Ningbo Regional Health Information Platform
NSAR	Non-Serious Adverse Reaction
PMC	Post-Marketing Commitment
PQC	Product Quality Complaints
SAR	Serious Adverse Reaction

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

SOP	Standard Operating Procedure
SRC	Safety Review Committee
TCT	Thinprep Cytology Test

3 INVESTIGATORS

Principal investigator	PPD, Peking University Health Science Center, China
Coordinating investigator for each country in which the study is to be performed	NA
Sponsor contacts	PPD
Other contacts	
Vendor/Collaborator	Peking University Health Science Center, China
Investigators	PPD, Peking University Health Science Center PPD, Center for Data Science in Health and Medicine, Peking University

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
1. Safety Review Committee (SRC) chairman	PPD
2. SRC member	
3. SRC member	
4. SRC member	
5. SRC member	
6. SRC member	

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS register	Within 1 month after final protocol submission	10-Jul-2020	
Peking University Institutional Review Board approval	NA	09-Nov-2020	
Ningbo CDC Institutional Review Board approval	NA	08-Jan-2021	
Start of data collection	After HGRAC approval (targeted for 3Q, 2020)	15-Mar-2021	Delay was due to HGRAC new requirement of database preservation licensing and onsite visit delay for COVID-19
End of data collection	Approximately 4 months prior to compilation of study report.	14-Jan-2022	
Final report of study results	Prior to license renewal	21-Apr-2022	

6 RATIONALE AND BACKGROUND

Background

In 2018, approximately 106,430 new cervical cancer cases were diagnosed and 47,739 cervical cancer deaths occurred in China. Cervical cancer is the 6th leading cause of female cancer and the 8th leading cause of cancer death in Chinese women. In Chinese women 15 to 44 years of age, cervical cancer is the 3rd leading cause of female cancer and the 2nd leading cause of cancer death [1]. Nearly all cases of cervical cancer are caused by HPV, and consistent with observations worldwide, HPV 16 and HPV 18 are the genotypes most commonly associated with cervical cancer in China, followed by HPV 31, 33, 45, 52, 58 and 59.[1] Over the past decade, the Chinese government has initiated activities to reduce the burden of cervical cancer in Chinese women. China initiated a free cervical cancer screening program in 2009 which targeted women in rural area. The program provided the free cervical screening services to 10 million women in the first 3 years. It kept on scaling up and reached 10 million women per year during 2012-2015. The screening methods varied across the country [2, 3].

As a measure of primary prevention of cervical cancer, the Chinese government has approved bivalent, quadrivalent, and nonavalent vaccines that prevent persistent HPV infection and cervical cancers and precancers caused by the HPV types targeted in the vaccines. While there is no national HPV immunization program currently implemented in China, women can receive these vaccinations at their own expense. MSD manufactures 2 of these vaccines: the quadrivalent vaccine (GARDASIL®) and nonavalent vaccine (GARDASIL®9). GARDASIL® (G4) targets HPV types 6, 11, 16, and 18 and was approved in China for use in women 20 to 45 years old in May 2017. Shortly thereafter (April 2018), GARDASIL®9 (G9), which targets HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, was approved for use in women 16 to 26 years old in China. Subsequently, GARDASIL® (G4) was approved in China for use in girls 9 to 19 years old in November 2020.

High efficacy of G4 and G9 against multiple endpoints was consistently observed in clinical trials in women worldwide, including Chinese women. In addition, the effectiveness of vaccination against high-grade cervical intraepithelial neoplasia has been observed in women

from various areas of the world subsequent to initiation of HPV vaccination programs, with the first effectiveness reported approximately 5 years after licensure [4-6].

Rationale

Real world evidence of the impact of G4 and G9 for the prevention of high-grade cervical lesions in Chinese women is not yet available. Therefore, [redacted], MSD has conducted this post-licensure surveillance of the occurrence of high-grade cervical lesions in Chinese women. This database surveillance used Ningbo regional health information platform (NRHIP). The NRHIP integrates several electronic healthcare databases, including vaccination data and EMRs from women who receive their healthcare in Ningbo and whose medical information is available in the NRHIP.

This study report presents the study results for women who were vaccinated with G9 (including those who received mixed G4/G9 regimens).The results for G4 will be presented in a separate study report.

7 RESEARCH QUESTION AND OBJECTIVES

The primary objective is to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women who were vaccinated with G4 or G9 in Ningbo (vaccinated cohort). High-grade cervical intraepithelial neoplasia (CIN) is a composite outcome that includes CIN2 and CIN3.

The secondary objective was to monitor the occurrence of high-grade cervical intraepithelial neoplasia in a cohort of Chinese women without HPV vaccination (matched unvaccinated cohort), who were matched to the vaccinated women on factors such as age, area of residence (rural/urban), receipt of cervical HPV/cytology testing services prior to enrollment date and other factors if appropriate. A vaccinated HPV test-negative sub-cohort was identified from the vaccinated cohort and matched with unvaccinated women.

Rates of high-grade cervical intraepithelial neoplasia occurrence in the vaccinated and matched unvaccinated cohorts will be reported and compared, if methodologically feasible.

High-grade cervical intraepithelial neoplasia occurrence in the general population residing in Ningbo is also provided in this study as a background measure of high-grade cervical intraepithelial neoplasia occurrence in the general population.

Counts of adenocarcinoma in situ (AIS) and invasive cervical cancer in the vaccinated cohort, the matched unvaccinated cohort and the general population of women were monitored as well, to provide background information on the disease burden of cervical cancer in Ningbo.

This is an observational surveillance activity. Hypothesis testing is not applicable to this study design.

8 AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
None				

9 RESEARCH METHODS

9.1 Study design

This is a database, observational surveillance activity that used data from the NRHIP to identify women vaccinated with G4 or G9 and to monitor the occurrence of high-grade cervical intraepithelial neoplasia after vaccination during the study period. All women who were age-eligible for vaccination during the study period and who had received at least one dose of G9 (including those who had received mixed G4/G9 regimens but no other HPV vaccines) were extracted from the NRHIP as "vaccinated women". The G9 vaccinated cohort was derived from the vaccinated women and included all women who had received exclusively G9 according to the "per protocol" defined vaccination schedule (i.e. received all 3 doses of G9 within 12 months, with at least 8 weeks between doses 1 and 2), and who had no history of cervical diseases (including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy) prior to their first dose of G9. To ensure that women had no prevalent HPV infection prior to vaccination with G9, an HPV test-negative sub-cohort was set up. Among the vaccinated cohort, all women who had cervical HPV negative and TCT (Thinprep Cytology Test) negative test results within one year prior to the cohort enrollment date were included in the "vaccinated HPV test-negative sub-cohort", and matched to unvaccinated women (Figure 1).

The unvaccinated cohort included women who had not received any HPV vaccination and who had cervical HPV negative and TCT negative results within one year prior to the cohort enrollment date and no history of cervical diseases (including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy) prior to their enrollment date. Each vaccinated woman from the vaccinated HPV test-negative sub-cohort was matched on age at enrollment and residence (urban/rural) to a maximum of three unvaccinated women. If more than three unvaccinated women were eligible to be matched to one vaccinated woman, those whose birthdates were closest to that of the vaccinated woman were selected.

For each woman from the vaccinated cohort and vaccinated HPV test-negative sub-cohort, the date of her first vaccination with G9 as recorded in the NRHIP was considered as her

enrollment date. The enrollment date for the matched unvaccinated women was the same as the cohort enrollment date of her vaccinated counterpart.

Occurrence of histologically confirmed CIN2+ was assessed in the vaccinated cohort, the vaccinated test-negative sub-cohort and in the matched unvaccinated cohort. Counts and rates of CIN2/3, AIS and ICC were reported for the cohorts. The formal comparison of the rates of high-grade cervical intraepithelial neoplasia between the vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort was not feasible due to the short follow-up period since the introduction of vaccination with G9 and low coverage of cervical screening services in Ningbo.

In addition, women from the general population were monitored for diagnosis of high-grade cervical intraepithelial neoplasia. This data was tabulated to provide context for the study findings and also to help identify secular trends that may have impacted high-grade cervical intraepithelial neoplasia diagnoses, such as changes in cervical screening methods.

Occurrence of AIS and invasive cervical cancer in the vaccinated cohort, the vaccinated HPV test-negative sub-cohort, the matched unvaccinated cohort, and the general population were also monitored to provide additional information on the burden of cervical disease in Ningbo.

CCI

[redacted]

9.2 Setting

Vaccination and healthcare data from a platform used for storage of healthcare data from Ningbo (i.e., “NRHIP”) was used in this database surveillance. Ningbo city is located in the eastern portion of the Zhejiang province, in the southeastern part of China. Within the NRHIP catchment area, there are 4 counties (Yuyao, Cixi, Ninghai, and Xiangshan) and 6 districts (Yinzhou, Haishu, Jiangbei, Zhenhai, Beilun and Fenghua). Ningbo has a population of approximately 2.8 million local female residents between 16 and 45 years old, and its location includes large districts as well as less populated areas.

The NRHIP is one of the best regional health information platforms in China [7]. The vaccine register system in the NRHIP collects information regarding vaccination records (including vaccination with G4 or G9) in Ningbo. The NRHIP collects residents' health care information and some demographic information, including age, gender, outpatient visits, emergency room visits, hospitalizations, disease diagnoses, treatments, drug prescriptions and dispensing, laboratory testing results, etc. All local hospitals that can provide CIN2+ (CIN2, CIN3, AIS and invasive cervical cancer) diagnosis and treatment have been included in the NRHIP and CIN2+ records can be retrieved from the NRHIP.

The NRHIP has achieved the highest level in the National Information Interconnection Standardization Evaluation. In 2011, Ningbo started developing a platform to incorporate the different electronic healthcare and public health information databases. In 2015, the NRHIP was officially launched and it began to integrate various health data sources.

In this study, G9 vaccination data were extracted from the NRHIP from 25 January 2019 to 31 March 2021. Outcome of interest and covariates were extracted starting from 2015 (the first year of diagnosis available in the NRHIP) until 31 March 2021.

9.3 Subjects

The following study population and cohorts were formed:

9.3.1 Vaccinated cohort

Vaccinated women

Vaccinated women were all female residents of Ningbo who were age-eligible for G4/G9 vaccination during the study period, who received at least one dose of G4 or G9 during the study period, and whose medical care information was available in the NRHIP. The following criteria were used to identify vaccinated women.

- ✓ Female residents registered in the NRHIP;
- ✓ Health data (EMRs data) available in the NRHIP;
- ✓ Received at least 1 dose of G4 or G9 during the study period (including those with a mixed regimen of G4 and G9) but no other HPV vacccines;

- ✓ 20 to 45 years old at initiation of G4 vaccination, or 16 to 26 years old at initiation of G9 vaccination.

G9 vaccinated cohort

The G9 vaccinated cohort was derived from the vaccinated women and included all women who received exclusively G9, according to the "per protocol" defined schedule and who had no cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy prior to the first dose of G9. The definition of the "per protocol" schedule is that women received all 3 doses of G9 within 12 months (≤ 12months), with at least 8 weeks (≥8weeks) between doses 1 and 2.

Inclusion criteria:

- ✓ Vaccinated women;
- ✓ Received exclusively G9 "per protocol" schedule.

Exclusion criteria:

- ✓ Had a history of cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy prior to the first dose of G9.

Among the age-eligible women, the study population was further limited to those at least 20 years old at any time during the study period, because cervical screening (and thus high-grade cervical intraepithelial neoplasia diagnosis) typically is not available prior to age 20 years.

Vaccinated HPV test-negative sub-cohort

All women from the vaccinated cohort who had cervical HPV (any HPV test method) negative and TCT (Thinprep Cytology Test) negative results within one year prior to the cohort enrollment date in the EMRs were extracted as vaccinated sub-cohort, and were matched to unvaccinated women.

Inclusion criteria:

- ✓ Women from vaccinated cohort;
  - who had HPV negative results within one year prior to cohort enrollment date; and
  - who had TCT negative results within one year prior to the cohort enrollment date.

9.3.2 Matched unvaccinated cohort

Unvaccinated women

The unvaccinated women were comprised of eligible women who received no HPV vaccine before and during the study period. Among the age-eligible women, the study population was limited to those women with sufficient follow-up time to be at least 20 years old at any time during the study period, because cervical screening (and thus high-grade cervical intraepithelial neoplasia diagnosis) typically is not available prior to age 20 years.

Inclusion criteria:

- ✓ Female residents registered in the NRHIP;
- ✓ Health data available in the NRHIP;

Exclusion criteria:

- ✓ Women who received HPV vaccination.

Matched unvaccinated cohort

The matched unvaccinated cohort includes unvaccinated women who had cervical HPV test negative and TCT negative results within one year prior to cohort enrollment date and no cervical disease history, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy at any time prior to date of enrollment.

Inclusion criteria:

- ✓ Unvaccinated women;
  - who had HPV negative result within one year prior to cohort enrollment date;

and

- who had TCT negative result within one year prior to cohort enrollment date.

Exclusion criteria:

- ✓ Women who had a history of cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy at any time prior to cohort enrollment date.

Matching process: Each eligible vaccinated woman from the HPV test-negative sub-cohort was matched to multiple potentially eligible unvaccinated women on age at enrollment (up to +/- 1 year, depending on the number of potentially eligible unvaccinated women in the NRHIP) and area of residence (urban/rural). If there were more than one unvaccinated women that were eligible to be matched to a vaccinated woman, they were ordered by the closeness of their birthday to that of the vaccinated woman.

For each vaccinated woman, a maximum of three unvaccinated women with the closest birth dates were kept. The cohort enrollment date for the potentially matched unvaccinated woman was the same as the cohort enrollment date of her vaccinated counterpart. After determination of the enrollment date of each potentially matched unvaccinated woman, those with cervical HPV positive or TCT positive result within one year prior to the enrollment date, or those with pre-existing cervical diseases or CIN2+ treatment or hysterectomy any time before the enrollment date were excluded.

In summary, unvaccinated women who had cervical HPV negative and TCT negative results within one year prior to cohort enrollment and had no cervical diseases, including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, or CIN2+ treatment or hysterectomy prior to date of enrollment constituted the matched unvaccinated cohort.

9.3.3 General female population

Surveillance for cervical disease in the general female population was also undertaken in order to better understand the occurrence of cervical disease reported to the NRHIP. The occurrence of cervical disease in the general female population during the study period was tabulated across the entire age range available in the NRHIP. Thus, surveillance in the

general female population also included women older than age 45 years during the study period.

Inclusion criteria for the general population are:

- ✓ Female residents registered in the NRHIP;
- ✓ Health data available in the NRHIP.

In the vaccinated cohort, matched unvaccinated cohort and the general population, women with notation (EMR records) available within the NRHIP that indicates a history of cervical diseases including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia or who have undergone hysterectomy or CIN2+ treatment before cohort enrollment were reported, but were excluded from the analysis.

9.4 Variables

9.4.1 Exposure

For the vaccinated cohort, exposure was defined as receipt of G9 as part of routine health care within Ningbo, among women who were age-eligible for vaccination at any point during the study period and whose medical data were available within the NRHIP.

9.4.2 Outcome

The surveillance outcome was defined as histologically confirmed high-grade cervical intraepithelial neoplasia (i.e., CIN2 or CIN3) available in the NRHIP. In addition, adenocarcinoma in situ (AIS) and invasive cervical cancer cases diagnosed during the study period and available in the NRHIP were reported.

The diagnosis and treatment of CIN2+ occured within the hospital system and local laboratory and therefore CIN2+ cases are captured in the NRHIP. Women with high-grade pap abnormalities identified by the free cervical cancer screening program or from annual body check-ups are referred to local hospitals for diagnosis and treatment. All local hospitals that can provide services relevant to CIN2+ diagnosis and treatment are covered by the NRHIP, and these CIN2+ records could be retrieved and analyzed in our study.

Histological testing results in the EMRs of outpatient visits, emergency room visits and hospitalizations were used to identify CIN2 or CIN3 cases among the vaccinated cohort, the vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort from the NRHIP. If the case was reported with a range, i.e., CIN2/3 and the exact degree of the histology result or diagnosis was not described, the highest reported grade, CIN3 in the example, was retained for the case.

Key words of histological results were used to identify AIS cases in the EMR to ensure the accuracy of the case identification. Only cases that were confirmed by histological tests were included.

Occurrence of ICC in the vaccinated cohort, the vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort were identified from the local cancer register in the NRHIP. ICD-10 code and key words of diagnosis were used to identify ICC cases in the cancer register in NRHIP.

The history of CIN2+ diseases was identified in the vaccinated cohort, the vaccinated HPV test-negative sub-cohort, the matched unvaccinated cohort and the general female population from the NRHIP. ICD-10 codes for cervical diseases including CIN2+ (CIN2, CIN3, AIS, ICC), cervical tumors or epithelial hyperplasia, key words of CIN2+ diagnosis, CIN2+ treatment and hysterectomy were used to identify women with documented history of cervical diseases within the NRHIP (both EMR and cancer registry).

A CIN2+ case identification method was developed to identify CIN2+ cases in the NRHIP [8-11]. Gynecologists and other experts were consulted during the development of the CIN2+ case identification methods.

9.4.3 Covariates

Variables including age at first vaccine dose, residence region, cervical cytology testing status, ethnicity, marital status, parity and health insurance status were reported in this study .

9.5 Data sources and measurement

The NRHIP contains three main data sources, linkable by the use of personal identification variables: the maternal and child health care information system, the Center for Disease

Control and Prevention (CDC) information system, and the hospital information system. The maternal and child health care information system collects information on antenatal health care, childbirth, child health care. The CDC information system and the hospital systems are further described below.

Ningbo CDC information system

The Ningbo CDC information system mainly collects, reports and manages information pertaining to vaccination, communicable diseases, chronic diseases, death certification, foodborne diseases, vector-borne diseases.

The CDC information system includes the vaccine register system, which has information on vaccine cold chain management, migrating children management, and digital vaccination clinics. The information system includes services such as ability to make online inquiries on vaccination information and immunization records, ability to make vaccination appointments, provide informed consent, payment, receive some consultation, and monitoring of Adverse Events Following Immunization (AEFI). The system covers 167 vaccination clinics located in 10 hospitals and 157 community health service centers in Ningbo city. The system collects general information, such as individual identifiers, name, sex, date of birth, date of vaccination, dosage, manufacturer, etc. Collection of vaccination information for children under 12 years of age has been mandatory since 2005. Since May 2017, collection of information on adult vaccination (including G4 and G9) has also been mandatory.

The CDC information system also includes the cancer register system. The cancer register is population. The main reporting channels of the cancer register are through medical institutions. Hospitals and clinics are required to routinely submit newly diagnosed clinical records of cancer to their local cancer register. Death surveillance data, insurance records, and the funeral records of patients with cancer are additional reporting sources.

Vaccination data were collected from the CDC information system using the records of vaccination of G4, G9 or other HPV vaccines extracted from the vaccination register. HPV vaccination codes were used to identify the vaccinated women to generate the vaccinated cohort.

Electronic medical records (EMRs)

The NRHIP includes EMRs that cover all 221 public hospitals and 28 large private hospitals in Ningbo city except some specialized hospitals or private clinics, such as eye hospitals and dental hospitals. Services relevant to cervical screening, diagnosis of CIN2+, or treatment of cervical lesions are not provided by these specialized hospitals or private clinics. The NRHIP collects information on outpatient and inpatient visits, disease diagnosis (ICD 10 codes, local codes, and free text of disease diagnosis), laboratory test results, drug prescription and dispensing, surgical operations, and body check-ups since 2015. Cancer treatment and deaths outside Ningbo can be tracked and captured if they occur in Zhejiang Province. Other health information outside Ningbo is not available in the NRHIP.

9.5.1Study Procedures

The study protocol was approved by the Institutional Review Board (IRB) of Peking University Health Science Center. The study involves secondary data analysis of data from the NRHIP which was routinely collected in Ningbo. Therefore, there was no recruitment procedure and no informed consent was required in this study. Permission of waiver of informed consent for this study was granted. The electronic claim records were de-identified. The study was also approved by the Human Genetic Resources Administration of China (HGRAC) for International Coperation Study. Subject rights were not compromised in this study. Data from the NRHIP contained only encrypted identifiers. This encryption eliminated the risk associated with an unlikely breach of confidentiality. Only the NRHIP experts from Ningbo CDC and the Peking University study personnel had access to the data. All analyses were based on anonymized, untraceable coded identifiers. The study sponsor did not have access to the datasets.

9.6 Bias

Observational studies are vulnerable to a variety of biases, including selection bias and information bias. This study is a database study and the outcomes were measured relying on the diagnosis recorded in the NRHIP. A CIN2+ case identification method was developed for the identification of CIN2+ cases from the NRHIP, in order to minimize the potential detection bias related to the diagnosis. Key words were applied in histological testing results

in the EMRs of outpatient visits, emergency room visits, and hospitalizations to identify confirmed CIN2/3 and AIS cases in the NRHIP, while ICD-10 code and key words of diagnosis were used to identify ICC cases in the cancer register in NRHIP.

This study aims to monitor the occurrence of high-grade cervical intraepithelial neoplasia, AIS and invasive cervical cancer in vaccinated and unvaccinated women in the NRHIP. In order to reduce the selection bias between the vaccinated and the unvaccinated cohort, matching methods were used in this study.

In addition, in order to reduce confounding, several variables that might have a potential association with or an impact on vaccination exposure or cervical health outcomes were extracted from the NRHIP and analyzed in this study. These variables include: ethnicity, attained age, age at the initiation of G9 vaccination, marital status, parity and health insurance status.

9.7 Study size

In this database study, all women vaccinated with G9 (including women with mixed G4/G9 regimens) during the surveillance period in Ningbo and who met the inclusion criteria were included. In addition, all women from the general population (including vaccinated and unvaccinated women) whose health data were in the NRHIP and who were residents of Ningbo were followed for the identification of high-grade cervical intraepithelial neoplasia, as well as AIS and invasive cervical cancer.

9.8 Data transformation

9.8.1 Data management

All data management activities were undertaken under the supervision of Peking University and Ningbo CDC, following the procedures detailed in a separate “Data Management Plan”. The main components of the data management plan included data preparation, data linkage, data cleaning, quality description and control, database lock, analytical dataset determination, archiving and backup, training and support and data security. These procedures were intended to ensure the authenticity, integrity, and confidentiality of electronic records.

9.9 Statistical methods

9.9.1 Main summary measures

A separate detailed statistical analysis plan was developed and finalized prior to conduct of any analyses in this study, and the plan was developed using Good Pharmacoepidemiology Practice (GPP) principles for conducting observational studies.

Demographics and disease characteristics are analyzed in this study. For continuous variables, mean, standard deviation (SD), median (IQR) and range are presented. For categorical variables, the number of patients in each category and percentage were presented. Rates of CIN2/3, AIS and invasive cervical cancer in the cohorts were estimated with 95% confidential interval (95% CI).

9.9.2 Main statistical methods

Rates of CIN2/3, AIS and invasive cervical cancer in the vaccinated and matched unvaccinated cohorts were reported but not compared as it was not methodologically feasible according to the study protocol and the statistical analysis plan. As vaccine uptake is limited and the follow-up time is still short to detect an impact on CIN2+ occurrence, no power calculation to detect statistically significant differences has been conducted.

9.9.3 Missing values

For the primary and secondary objectives, analyses are carried out using the available data. A subject with missing for a given variable will be excluded from the analyses for that variable.

9.9.4 Sensitivity analyses

Not applicable in this study.

9.9.5 Amendments to the statistical analysis plan

Not applicable in this study.

9.10 Quality control

By signing the study protocol, all parties agreed to follow all applicable standard operating procedures (SOPs). All parties also agreed to ensure that the study personnel was appropriately trained to ensure that the study was conducted and data was generated, documented, and reported in compliance with the protocol and GPP. All parties maintained transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor met with Peking University on a weekly basis, reviewed the data management plan and statistical analysis plan, conducted audit visitis and set up the SRC to ensure that the oversight and conduct of the study were completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. There was no significant quality issue (SQI) identified during the conduct of the study. An SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data.

A data management plan was developed for this surveillance prior to data analysis, and it specified procedures to be followed to maintain high quality. This included programming practices and standardized, study-specific quality checking procedures. In addition, MSD conducted oversight visit and rountine management meeting to ensure that study procedures were adequately followed and documented.

Quality of the data linkage

The data from the CDC (including vaccine register system and cancer register system) and from the hospitals (electronic medical records) information systems were integrated, verified, stored, exchanged, and shared in the NRHIP. Different datasets were linked using a personal identification (ID) number and other information, including name and birth date.

In case of missing values for the ID variables in the different data sources, to minimize the loss of data for these women during the linkage process and to ensure accurate linkage of subjects across various data sources in the platform, multiple linkage steps were utilized. A Substitute ID (hereafter SID) was generated by combining ID and name for data linkage. The

SID was used as the primary index, while name and birth date were used as the secondary index when SID could not achieve data linkage.

Standardization of CIN2+ diagnoses

A CIN2+ case identification method was developed in consultation with clinical experts to identify high-grade cervical intraepithelial neoplasia cases, AIS, and cervical cancer from the NRHIP for disease history descriptions and outcomes. Diagnosis codes, key words of diagnosis from the EMRs of outpatient visits, emergency room visits and hospitalizations that were pertinent to outcomes of interest were included in these methods.

Information integrity

Vaccination register and EMR data in the NRHIP are set up and managed strictly following the local health authority's requirements and regulations. Data integrity was assessed in a preliminary study feasibility assessment using data from 2017 in the NRHIP. All vaccination clinics in Ningbo city have been included in the system. The key variables associated with vaccination are collected in the system. All vaccination records of adults in Ningbo city have been collected in the system since 2017 with no missing IDs.

All data analyses were conducted according to the study protocol and the statistical analysis plan. Programming for this project was conducted by a primary analyst and validated by a second analyst (validation analyst) independently. For all data processing steps, an independent analyst reviewed the programs as well as the input and output datasets.

10 RESULTS

10.1 Participants

A flowchart was developed based on the data management process as following.

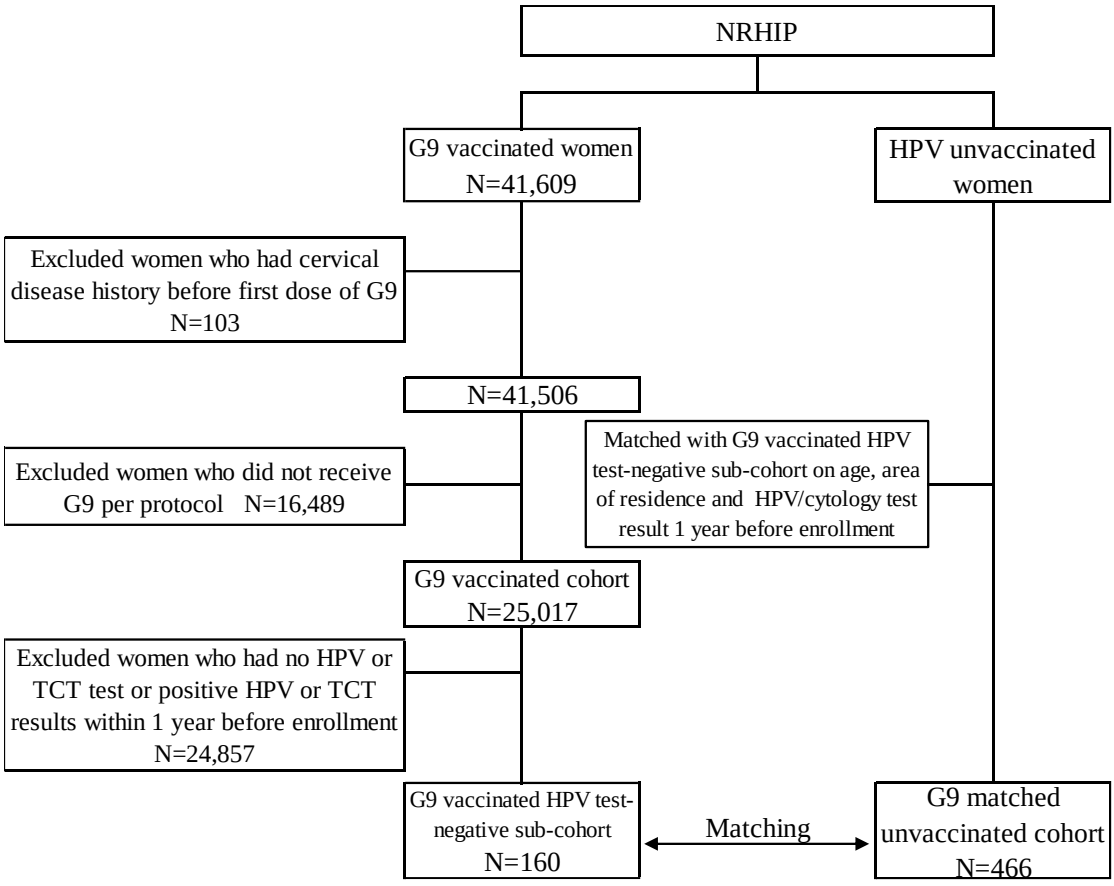

Figure 1: Flowchart of study population and cohorts

10.1.1 Protection of Human Subjects

This is a database surveillance activity that captures women who chose to receive the vaccine as part of their routine health care. No intervention was applied in this study. All participants' privacy was well-protected and database management followed local health information management requirements and local law.

The study was approved by the IRB of Peking University and Ningbo CDC with a waiver of informed concent and by the HGRAC for International Coperation Study.

10.2 Descriptive data

Since 25 January 2019 when G9 vaccination record have become available in the NRHIP and up to the data extraction cut-off on 31 March 2021, a total of 102,791 doses of G9 were

administered in Ningbo. Overall, 41,609 women were vaccinated with at least one dose of G9 and no other HPV vaccine. The number of women who received their first dose of G9 increased from 10,615 in 2019 to 23,258 in 2020. During the first quarter of 2021, 7,736 women in Ningbo received a first dose of G9. Extrapolating this number to the whole year indicates that the number of women vaccinated with G9 has further increased in 2021. Among those who received at least one dose of G9 and no other HPV vaccines, the mean age at first dose was 22.8 (SD=2.4) years, and most of the women (78.4%) initiated vaccination at age 21 to 26 years. As of 31 March 2021, 13.56%, 25.85% and 60.6% of women had received 1, 2 and 3 doses of G9, respectively. The mean time interval between dose 1 and 2, dose 2 and 3, and dose 1 and 3 were 2.2, 4.3 and 6.5 months, respectively, with low standard deviation, indicating good compliance with the recommended schedule of 0, 2 and 6 months. The vast majority of women (86.2%) received dose 1 and dose 2 with an interval of at least 8-weeks between the doses and 60.3% received the 3 doses within 12 months. Both criteria of the "per protocol" definition were met by 60.2% of the women (Table 1).

Vaccination data extraction for mixed G4/G9 regimens started on 9 January 2018, the date when G4 vaccination data became available in the NRHIP. Data cut-off was 31 March 2021. Only 16 women received a G4/G9 mixed regimen. No increasing trend was observed over the following years when 7 women received a mixed regimen in 2019 and 2020 and 2 in the first quarter of 2021. The mean age at first dose was 23.8 years (SD=1.5), slightly higher than for the exclusively G9 vaccinated women and most of them (87.5%) received the first dose at age 21-26 years, consistent with the G9 vaccinated women. Among 16 women vaccinated with the mixed regimen, 11 received more than 3 doses of G4/G9. This observation is consistent with the recommendation of an expert consensus in China, that women who initiate their vaccination with G4 and then switch to G9 should receive all 3 doses of G9 [12] (Table 2).

A total of 25,017 women (60.1% of the women who had received at least one dose of G9) were included in the G9 vaccinated cohort. Among these women, 10,318 (41.2%) were enrolled in 2019 and 14,699 (58.8%) in 2020, reflecting an increasing trend of women vaccinated with G9 since the introduction of the vaccine in China. As the time in 2021 (data cut-off on 31 March 2021) was too short for the women to get the complete 3-dose schedule

according to the "per protocol" definition, no women could be enrolled in 2021. The mean age at cohort enrollment was 22.8 years (SD=2.44). The majority of women (85.1%) were 21 to 26 years-old. The proportions of women from urban (52.9%) and rural (47.1%) areas was similar (Table 3).

The number of women enrolled in the G9 vaccinated HPV test-negative sub-cohort was 160 (corresponding to 0.4% of women who had received at least one dose of G9 and 0.6% of those who were vaccinated according to the "per protocol" schedule) and the number of the matched unvaccinated cohort was 466, reflecting a matching ratio of maximum three unvaccinated women for every vaccinated woman.

In the G9 vaccinated HPV test-negative sub-cohort, 57 (35.6%) women were enrolled in 2019 and 103 (64.4%) in 2020. Also, no woman was enrolled in 2021 because the time captured was too short for the women to get the 3 dose schedule (per protocol) before the data cut-off on 31 March 2021. The mean age at cohort enrollment was 24.0 years (SD=1.23). All women were enrolled in the cohort at 21-26 years of age. The majority of women were from urban areas (61.9%). A small percentage of women (8.8%) had cervical cytology testing after cohort enrollment. All women for whom the ethnicity was reported (85.6%) were Han Chinese. Given the relatively young age of the women in this cohort (21 to 26 years), the majority were singles (72.5%), only 11.3% were registered as married and for 16.3% the marital status was unknown. The parity status was not captured for the great majority of the women (96.9%). Most of the women (84.4%) had a health insurance (including public health insurance programs as Urban Employee Basic Medical Insurance, Urban Resident Basic Medical Insurance and Newly Cooperative Medical Scheme, but also private health insurance programs).

The proportions of women enrolled in the the matched unvaccinated cohort in 2019 and 2020 were similar to that in the vaccinated HPV test-negative sub-cohort with 36.3% of the women enrolled in 2019 and 63.7% in 2020. As for the matched unvaccinated cohort, no woman was enrolled in 2021. The mean age at cohort enrollment was 24.0 years (SD=1.23) and equal to the mean age of the women in the vaccinated HPV test-negative sub-cohort. Also, all women were enrolled at age 21-26 years. The majority of women were from the

urban area (61.6%). The proportion of women with cervical cytology test after cohort enrollment was 5.4%, lower than the 8.8% of women from the vaccinated sub-cohort. Almost all women for whom the ethnicity was reported (74.2%) were Han Chinese. The proportion of women who were reported to be single (43.1%) was lower than in the vaccinated sub-cohort and many more married women were included in this cohort (28.5%). The marital status was missing for almost 30% of women and for the great majority (85.6%) the parity status was not reported, similar to the vaccinated sub-cohort. Also in this cohort, the majority of women (65.7%), had health insurance (Table 4).

Table 1. Characteristics of women vaccinated with at least one dose of G9 and no dose of G4

Variables	G9 vaccinated women
Total number of women vaccinated with G9	41,609
Calendar year at the first dose of G9, n (%)	
2019	10,615 (25.5)
2020	23,258 (55.9)
2021 *	7,736 (18.6)
Age at the first dose of G9 (years), mean±SD	22.8 (2.4)
<16 years, n (%) †	0 (0)
16-20 years, n (%)	8,972 (21.6)
21-26 years, n (%)	32,637 (78.4)
>26 years, n (%) †	0(0)
Doses received	102,791
1 dose, n (%) ††	5,641 (13.56)
2 doses, n (%) ††	10,754 (25.85)
3 doses, n (%) ††	25,214 (60.6)
>3 doses, n (%) ††	0(0)
Time interval between each dose (months), mean±SD; median (IQR), range	
Dose 1 and dose 2 (n=35,883)	2.2 (0.5), 2.1 (0.1), 1.0-16.0
Dose 2 and dose 3 (n=25,175)	4.3 (0.7), 4.1 (0.3), 1.8-21.4
Dose 1 and dose 3 (n=25,133)	6.5 (0.8), 6.2 (0.5), 4.1-23.5
At least 8 weeks between doses 1 and 2, n (%)	
Yes	35,853 (86.2)
No	5756 (13.8)
Received 3 doses of G9 within 12 months, n (%)	
Yes	25,079 (60.3)
No	16,530 (39.7)
"Per protocol" vaccination ¶, n (%)	

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Yes	25,058 (60.2)
No	16,551 (39.8)

* 2021 data collection cut-off: Mar 31st

† Women vaccinated with a first dose of G9 <16 and >26 are not included in the study

†† Women's vaccination status at the data cut-off point (women who received 1 dose or 2 doses might receive dose 2 and/or dose 3 at a later timepoint per vaccination schedule). For women whose first dose recorded in the NRHIP was coded as dose 2 or 3, we assumed that they had received previous doses out of Ningbo

¶ "Per protocol" vaccination regimen is defined as women who received all 3 doses of G9 within 12 months, with at least 8 weeks between doses 1 and 2.

Table 2. Characteristics of women vaccinated with a mixed regimen of G4 and G9

Variables	Mixed G4/G9 vaccinated women
Total number of women vaccinated with mixed G4/G9	16
Calendar year at the first dose, n (%)	
2018	0 (0)
2019	7 (43.8)
2020	7(43.8)
2021 *	2 (12.5)
Age at the first dose (years), mean±SD	23.8 (1.5)
<16 years, n (%) †	0 (0)
16- 20 years, n (%)	2 (12.5)
21-26 years, n (%)	14 (87.5)
27-30 years, n (%)	0 (0)
31-35 years, n (%)	0 (0)
36-40 years, n (%)	0 (0)
41-45 years, n (%)	0 (0)
>45 years, n (%) †	0 (0)
Doses received	
2 doses, n (%) ††	2 (12.5)
3 doses, n (%) ††	3 (18.8)
>3 doses, n (%) ††	11 (68.8)
Time interval between each dose (months), mean±SD; median (IQR), range	
Dose 1 and dose 2 (n=14)	2.3 (0.5), 2.1 (0.3), 1.2-3.3
Dose 2 and dose 3 (n=11)	4.2 (1.1), 4.1 (0.3), 2.5-7.1
Dose 1 and dose 3 (n=11)	6.4 (1.5), 6.2 (0.3), 3.7-10.3

* 2021 data collection cut-off: Mar 31st

† Women vaccinated with a first dose of G4 or G9 <16 and >45 are not included in the study

†† Women's vaccination status at the data cut-off point (women who received 2 doses might receive dose 3 at a later timepoint per vaccination schedule). For women whose first dose recorded in the NRHIP was coded as dose 2 or 3, we assumed that they had received previous doses out of Ningbo

Table 3. Characteristics of G9 vaccinated cohort (per protocol†)

Variables	G9 vaccinated cohort
No. of participants	25,017
Cohort enrollment year, n (%)	
2019	10,318 (41.2)
2020	14,699 (58.8)
2021 *	0 (0.0)
Age at cohort enrollment (years), mean±SD	22.8 (2.44)
16-20 years, n (%)	3,718 (14.9)
21-26 years, n (%)	21,299 (85.1)
Residence region, n (%)	
Urban area	13,233 (52.9)
Rural area	11,774 (47.1)
Unknown	10 (0.0)

* 2021 data collection cut-off: Mar 31st

† The definition of the "per protocol"vaccination schedule is that women received all 3 doses of G9 within 12 months (≤12months), with at least 8 weeks (≥8weeks) between doses 1 and 2.

Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

Table 4. Characteristics of G9 vaccinated HPV test-negative sub-cohort and matched unvaccinated cohort

Variables	G9 vaccinated HPV test-negative sub-cohort*	Matched unvaccinated cohort
No. of participants	160	466
Cohort enrollment year, n (%)		
2019	57 (35.6)	169 (36.3)
2020	103 (64.4)	297 (63.7)
2021 †	0 (0.0)	0 (0.0)
Age at cohort enrollment (years), mean±SD	24.0 (1.23)	24.0 (1.23)
16-20 years, n(%)	0 (0.0)	0 (0.0)
21-26 years, n(%)	160 (100.0)	466 (100.0)
Residence region, n (%)		
Urban area	99 (61.9)	287 (61.6)
Rural area	61 (38.1)	179 (38.4)
Cervical cytology testing after cohort enrollment, n (%)	14 (8.8)	25 (5.4)
Ethnicity, n (%)		
Han	137 (85.6)	344 (73.8)
Others	0 (0.0)	2 (0.4)
Unknown	23 (14.4)	120 (25.8)
Marital status, n (%)		
Single	116 (72.5)	201 (43.1)
Married	18 (11.3)	133 (28.5)
Divorced	0 (0.0)	0 (0.0)
Widowed	0 (0.0)	0 (0.0)
Unknown	26 (16.3)	132 (28.3)
Parity, n (%)		
0	5 (3.1)	49 (10.5)
1	0 (0.0)	16 (3.4)

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

2	0 (0.0)	2 (0.4)
≥3	0 (0.0)	0 (0.0)
Unknown	155 (96.9)	399 (85.6)
Health insurance status, n (%)		
Yes	135 (84.4)	306 (65.7)
No	0 (0.0)	18 (3.9)
Unknown	25 (15.6)	142 (30.5)

† 2021 data collection cut-off: Mar 31st

*Women from G9 vaccinated HPV test-negative sub-cohort received G9 per protocol vaccination schedule, and had HPV and cytological negative results within one year prior to cohort enrollment date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

10.3 Outcome data

CIN2/3 in the vaccinated cohort, vaccinated HPV test-negative sub-cohort and matched unvaccinated cohort

One out of 25,017 women vaccinated with G9 "per protocol" had an onset of histologically confirmed CIN2/3 during the study period. The age at cohort enrollment of this women was PPD and she was diagnosed with CIN2/3 in 2020 at an age of [redacted]. PPD PPD Her HPV and cytological testing status at enrollment and CIN2/3 diagnosis was not known and it is therefore possible that the woman was infected with HPV before G9 vaccination. The mean follow-up time of the G9 vaccinated cohort was 14.4 woman-months (SD=6.54), and the rate of CIN2/3 was 0.003 (95% CI: 0.0001 - 0.02) per 1,000 woman-months (Table 5).

No women from the vaccinated HPV test-negative sub-cohort had an onset of CIN2/3. The mean follow-up time was 13.3 (SD=6.25) woman-months and the rate of CIN2/3 was 0 (95% CI: 0 – 1.7) per 1,000 woman-months (Table 6).

One woman from the matched unvaccinated cohort with an onset of CIN2/3 was identified. Her age at cohort enrollment was PPD years, and she was diagnosed with CIN2/3 in 2020 at an age of PPD .This woman was from an PPD PPD PPD The mean follow-up time of women in the unvaccinated cohort was 13.4 (SD=6.24) woman-months and the rate of CIN2/3 was 0.2 (95% CI: 0.004 - 0.9) per 1,000 woman-months (Table 7).

AIS and ICC in the vaccinated cohort, vaccinated HPV test-negative sub-cohort and matched unvaccinated cohort

No women from the G9 vaccinated cohort, the G9 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of AIS during the study period. The rates of AIS for the three cohorts were 0 (95% CI: 0 - 0.01), 0 (95% CI: 0 - 1.7) and 0 (95% CI: 0 - 0.6) per 1,000 woman-months, respectively.

Also, no woman from the G9 vaccinated cohort, the G9 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of invasive cervical carcinoma. The

rates of invasive cervical carcinoma were 0 (95% CI: 0 - 0.01), 0 (95% CI: 0 - 1.7) and 0 (95% CI: 0 - 0.6) per 1,000 woman-months, respectively (Table 8, Table 9, Table 10).

Disease occurrence in the general female population

CIN2/3 occurrence in the general female population aged 20 and above was relatively stable over the observation years 2016 to 2020, it wasthe lowest in 2017 (113.96 per million) and the highest in 2018 (179.41 per million).. The proportion of women with CIN2/3 was lowest in the youngest age group of 20 to 25 years, ranging from 6.98 per million in 2016 to 36.95 per million in 2020 with a sharp increasing trend since 2019.

In 2016 and 2017, most of the CIN2/3 cases occurred in the age group 41 to 45 years (226.83 and 183.30 per million, respectively). However from 2018 on, the peak age of CIN2/3 shifted to the 36 to 40 year-old-age group (ranging from 235.21 per million in 2019 to 243.22 per million in 2020) (Table 11).

The proportion of AIS was the lowest in 2016 (2.30 per million) and the highest in 2020 (7.93 per million) with very low numbers of cases ranging from 5 in 2016 to 21 in 2020). No case occurred in any year among 20-25 year-old-women and only very few cases in the age group 26-30 years. The number of cases showed an increasing trend with age in most of the surveillance years reaching up to 13 cases among women >45 years of age in 2020 (Table 12).

The number of ICC was highest in 2017 (96 cases, 42.74 per million) and lowest in 2019 (83 cases, 34.73 per million). The proportion of ICC cases increased with age in all surveillance years, reaching 59.92 per million among women >45 years of age in 2016. Only in 2017, the proportion of cases was highest in the 41-45 year age group with 68.74 per million women who were diagnosed with ICC. No cases were observed among the youngest age group of 20-25 year-old-women in any of the surveillance years and only sporadic cases were observed in women under 40 years of age (Table 13).

Results from 2021 are not included in the description here, because the data were not available for the full year, as data collection for 2021 ended on 31 March 2021.

Table 5. Counts and rates of CIN2/3 in the G9 vaccinated cohort ("Per-protocol" analysis)

Variables	G9 vaccinated cohort (N=25,017)		
	No. of CIN2/3, % (n/N) *	Woman-months, mean±SD	Rate per 1,000 woman-months, (95% CI)
Total	0.00 (1/25,017)	14.4 (6.54)	0.003 (0.0001 - 0.02)
Age at cohort enrollment (years), mean±SD	[redacted]		
18-20 years	0.00 (0/3,718)	14.3 (6.42)	0 (0 - 0.07)
21-26 years	0.01 (1/21,299)	14.4 (6.56)	0.003 (0.0001 - 0.02)
Calendar year of diagnosis†			
2019	0.00 (0/10,318)	6.2 (3.61)	0 (0 - 0.06)
2020	0.00 (1/25,017)	11.4 (6.54)	0.004 (0.0001 - 0.02)
2021	0.00 (0/25,016)	NA	NA
Age at diagnosis (year), mean±SD	[redacted]		
Residence region, n (%)			
Urban area	0.00 (0/13,233)	14.6 (6.67)	0 (0 - 0.02)
Rural area	[redacted]	14.2 (6.39)	0.006 (0.0002 - 0.03)
Unknown	0.00 (0/10)	15.9 (7.31)	0 (0 - 23.2)

Note: Histologically confirmed CIN2/3 outcome data was captured in and limited to women who attained 20 years or above.
* CIN2+ diagnosed within one year were treated as one event. Only the highest level of lesion was counted if the women had more than one lesions
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai
† The denominators are the numbers of women in the G9 vaccinated cohort by the end of the year.

Table 6. Counts and rates of CIN2/3 in the G9 vaccinated HPV test-negative sub-cohort

Variables	G9 vaccinated HPV test-negative sub-cohort (N=160)		
	No. of CIN2/3, % (n/N) *	Woman-months, mean±SD	Rate per 1,000 woman-months, (95% CI)
Total	0.00 (0/160)	13.3 (6.25)	0 (0 - 1.7)
Age at cohort enrollment (years), mean±SD	——	——	——
18-20 years	0.00 (0)	——	——
21-26 years	0.00 (0/160)	13.3 (6.25)	0 (0 - 1.7)
Calendar year of diagnosis†			
2019	0.00 (0/57)	5.8 (3.48)	0 (0 - 11.2)
2020	0.00 (0/160)	10.3 (6.25)	0 (0 - 2.2)
2021	0.00 (0/160)	13.3 (6.25)	0 (0 - 1.7)
Age at diagnosis (year), mean±SD	——	——	——
Residence region, n (%)			
Urban area	0.00 (0/99)	13.7 (6.21)	0 (0 - 2.7)
Rural area	0.00 (0/61)	12.7 (6.30)	0 (0 - 4.8)
Ethnicity, n (%)			
Han	0.00 (0/137)	13.5 (6.42)	0 (0 - 2)
Others	0.00 (0)	——	——
Unknown	0.00 (0/23)	12.3 (5.12)	0 (0 - 13)
Marital status, n (%)			
Single	0.00 (0/116)	12.9 (6.17)	0 (0 - 2.5)
Married	0.00 (0/18)	16.8 (7.36)	0 (0 - 12.2)
Divorced	0.00 (0)	——	——
Widowed	0.00 (0)	——	——
Unknown	0.00 (0/26)	12.7 (5.14)	0 (0 - 11.2)
Parity, n (%)			

0	0.00 (0/5)	14.2 (6.48)	0 (0 - 52)
1	0.00 (0)	——	——
2	0.00 (0)	——	——
≥3	0.00 (0)	——	——
Unknown	0.00 (0/155)	13.3 (6.26)	0 (0 - 1.8)
Health insurance status, n (%)			
Yes	0.00 (0/135)	13.3 (6.37)	0 (0 - 2.1)
No	0.00 (0)	——	——
Unknown	0.00 (0/25)	13.5 (5.67)	0 (0 - 10.9)

Note: Histologically confirmed CIN2/3 outcome data was captured in and limited to women who attained 20 years or above.

* CIN2+ diagnosed within one year were treated as one event. Only the highest level of lesion was counted if the women had more than one lesions

Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

† The denominators are the number of women in the G9 vaccinated HPV test-negative sub-cohort by the end of the year.

Table 7. Counts and rates of CIN2/3 in the G9 matched unvaccinated cohort

Variables	Matched unvaccinated cohort (N=466)		
	No. of CIN2/3, % (n/N) *	Woman-months, mean±SD	Rate per 1,000 woman-months, (95% CI)
Total	0.22 (1/466)	13.4 (6.24)	0.2 (0.004 - 0.9)
Age at cohort enrollment (years), mean±SD	[redacted]		
18-20 years	0.00 (0)	——	——
21-26 years	0.22 (1/466)	13.4 (6.24)	0.2 (0.004 - 0.9)
Calendar year of diagnosis†			
2019	0.00 (0/169)	5.7 (3.43)	0 (0 - 3.8)
2020	0.22 (1/466)	10.4 (6.23)	0.2 (0.005 - 1.2)
2021	0.00 (0/465)	NA	NA
Age at diagnosis (year), mean±SD	[redacted]		
Residence region, n (%)			
Urban area	[redacted]	13.8 (6.19)	0.3 (0.006 - 1.4)
Rural area	0.00 (0/179)	12.8 (6.29)	0 (0 - 1.6)
Ethnicity, n (%)			
Han	[redacted]	13.5 (6.26)	0.2 (0.005 - 1.2)
Others	0.00 (0/2)	20.4 (1.41)	0 (0 - 90.6)
Unknown	0.00 (0/120)	13.0 (6.20)	0 (0 - 2.4)
Marital status, n (%)			
Single	0.00 (0/201)	13.1 (6.20)	0 (0 - 1.4)
Married	[redacted]	14.2 (6.45)	0.5 (0.01 - 2.9)
Divorced	0.00 (0)	——	——
Widowed	0.00 (0)	——	——
Unknown	0.00 (0/132)	13.0 (6.07)	0 (0 - 2.1)
Parity, n (%)			

0	0.00 (0/49)	13.6 (6.77)	0 (0 - 5.6)
1	0.00 (0/16)	14.2 (6.40)	0 (0 - 16.2)
2	0.00 (0/2)	14.3 (7.14)	0 (0 - 128.8)
≥3	0.00 (0)	——	——
Unknown	[redacted]	13.3 (6.19)	0.2 (0.005 - 1)
Health insurance status, n (%)			
Yes	[redacted]	13.7 (6.41)	0.2 (0.006 - 1.3)
No	0.00 (0/18)	11.7 (5.36)	0 (0 - 17.5)
Unknown	0.00 (0/142)	12.9 (5.94)	0 (0 - 2)

Note: Histologically confirmed CIN2/3 outcome data was captured in and limited to women who attained 20 years or above.

Unvaccinated women were matched with women of vaccinated sub-cohort by ± 1 year

* CIN2+ diagnosed within one year were treated as one event. Only the highest level of lesion was counted if the women had more than one lesions

Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai

† The denominators are the number of women in the G9 matched unvaccinated cohort by the end of the year.

Table 8. Counts and rates of AIS and ICC in the G9 vaccinated cohort

Variables	G9 vaccinated cohort (N=25,017)
No. of AIS cases, % (n/N)	0.0000 (0/25,017)
Woman-months, mean±SD	14.4 (6.54)
Rate per 1,000 woman-months (95% CI)	0 (0 - 0.01)
No. of ICC cases, % (n/N)	0.0000 (0/25,017)
Woman-months, mean±SD	14.4 (6.54)
Rate per 1,000 woman-months (95% CI)	0 (0 - 0.01)

Table 9. Counts and rates of AIS and ICC in the G9 vaccinated HPV test-negative sub-cohort

Variables	G9 vaccinated sub-cohort (N=160)
No. of AIS cases, % (n/N)	0.0000 (0/160)
Woman-months, mean±SD	13.3 (6.25)
Rate per 1,000 woman-months (95% CI)	0 (0 - 1.7)
No. of ICC cases, % (n/N)	0.0000 (0/160)
Woman-months, mean±SD	13.3 (6.25)
Rate per 1,000 woman-months (95% CI)	0 (0 - 1.7)

Table 10. Counts and rates of AIS and ICC in the matched unvaccinated cohort

Variables	G9 matched unvaccinated cohort (N=466)
No. of AIS cases, % (n/N)	0.0000 (0/466)
Woman-months, mean±SD	13.4 (6.24)
Rate per 1,000 woman-months (95% CI)	0 (0 - 0.6)
No. of ICC cases, % (n/N)	0.0000 (0/466)
Woman-months, mean±SD	13.4 (6.24)
Rate per 1,000 woman-months (95% CI)	0 (0 - 0.6)

Table 11. CIN2/3 occurrence in the general female population

Calendar Year	CIN2/3 cases (n)*	General female population (N)	Proportion (per million)
2016	**327**	**2,176,375**	**150.25**
By age groups, yr			
20-25	1	143,329	6.98
26-30	21	225,291	93.21
31-35	39	217,364	179.42
36-40	43	214,052	200.89
41-45	51	224,834	226.83
>45	172	1,151,505	149.37
2017	**256**	**2,246,361**	**113.96**
By age groups, yr			
20-25	1	137,604	7.27
26-30	18	212,112	84.86
31-35	40	229,106	174.59
36-40	40	229,411	174.36
41-45	40	218,227	183.30
>45	117	1,219,901	95.91
2018	**412**	**2,296,435**	**179.41**
By age groups, yr			
20-25	1	128,247	7.80
26-30	14	206,462	67.81
31-35	50	239,208	209.02
36-40	56	236,399	236.89
41-45	46	214,735	214.22
>45	245	1,271,384	192.70
2019	**375**	**2,389,671**	**156.93**
By age groups, yr			

20-25	3	124,223	24.15
26-30	16	198,661	80.54
31-35	50	265,352	188.43
36-40	56	238,081	235.21
41-45	52	222,311	233.91
>45	198	1,341,043	147.65
2020	**317**	**2,648,265**	**119.70**
By age groups, yr			
20-25	5	135,316	36.95
26-30	19	219,632	86.51
31-35	42	325,823	128.90
36-40	67	275,471	243.22
41-45	50	242,238	206.41
>45	134	1,449,785	92.43
2021**	**47**	**2,662,922**	**17.65**
By age groups, yr			
20-25	1	134,295	7.45
26-30	3	219,264	13.68
31-35	7	329,134	21.27
36-40	10	278,943	35.85
41-45	4	242,960	16.46
>45	22	1,458,326	15.09

*Histologically confirmed new yearly cases.

**2021 data collection cut-off: Mar 31st

Table 12. AIS occurrence in the general female population

Calendar Year	AIS cases, (n*)	General female population, (N)	Proportion (per million)
2016	**5**	**2,176,375**	**2.30**
By age groups, yr			
20-25	0	143,329	0.00
26-30	1	225,291	4.44
31-35	0	217,364	0.00
36-40	1	214,052	4.67
41-45	2	224,834	8.90
>45	1	1,151,505	0.87
2017	**16**	**2,246,361**	**7.12**
By age groups, yr			
20-25	0	137,604	0.00
26-30	0	212,112	0.00
31-35	3	229,106	13.09
36-40	2	229,411	8.72
41-45	2	218,227	9.16
>45	9	1,219,901	7.38
2018	**8**	**2,296,435**	**3.48**
By age groups, yr			
20-25	0	128,247	0.00
26-30	0	206,462	0.00
31-35	2	239,208	8.36
36-40	2	236,399	8.46
41-45	0	214,735	0.00
>45	4	1,271,384	3.15
2019	**12**	**2,389,671**	**5.02**
By age groups, yr			

20-25	0	124,223	0.00
26-30	1	198,661	5.03
31-35	3	265,352	11.31
36-40	3	238,081	12.60
41-45	3	222,311	13.49
>45	2	1,341,043	1.49
2020	**21**	**2,648,265**	**7.93**
By age groups, yr			
20-25	0	135,316	0.00
26-30	1	219,632	4.55
31-35	2	325,823	6.14
36-40	2	275,471	7.26
41-45	3	242,238	12.38
>45	13	1,449,785	8.97
2021**	**4**	**2,662,922**	**1.50**
By age groups, yr			
20-25	0	134,295	0.00
26-30	0	219,264	0.00
31-35	2	329,134	6.08
36-40	2	278,943	7.17
41-45	0	242,960	0.00
>45	0	1,458,326	0.00

*Histologically confirmed new yearly cases.

**2021 data collection cut-off: Mar 31st

Table 13. Invasive cervical cancer occurrence in the general female population

Calendar Year	ICC cases, (n*)	General female population, (N)	Proportion (per million)
2016	**85**	**2,176,375**	**39.06**
By age groups, yr			
20-25	0	143,329	0.00
26-30	1	225,291	4.44
31-35	5	217,364	23.00
36-40	2	214,052	9.34
41-45	8	224,834	35.58
>45	69	1,151,505	59.92
2017	**96**	**2,246,361**	**42.74**
By age groups, yr			
20-25	0	137,604	0.00
26-30	0	212,112	0.00
31-35	2	229,106	8.73
36-40	7	229,411	30.51
41-45	15	218,227	68.74
>45	72	1,219,901	59.02
2018	**85**	**2,296,435**	**37.01**
By age groups, yr			
20-25	0	128,247	0.00
26-30	2	206,462	9.69
31-35	1	239,208	4.18
36-40	1	236,399	4.23
41-45	6	214,735	27.94
>45	75	1,271,384	58.99
2019	**83**	**2,389,671**	**34.73**
By age groups, yr			

20-25	0	124,223	0.00
26-30	0	198,661	0.00
31-35	5	265,352	18.84
36-40	5	238,081	21.00
41-45	9	222,311	40.48
>45	64	1,341,043	47.72
2020	**90**	**2,648,265**	**33.98**
By age groups, yr			
20-25	0	135,316	0.00
26-30	1	219,632	4.55
31-35	4	325,823	12.28
36-40	4	275,471	14.52
41-45	10	242,238	41.28
>45	71	1,449,785	48.97
2021**	**27**	**2,662,922**	**10.14**
By age groups, yr			
20-25	0	134,295	0.00
26-30	0	219,264	0.00
31-35	0	329,134	0.00
36-40	4	278,943	14.34
41-45	0	242,960	0.00
>45	23	1,458,326	15.77

*New yearly cases identified from cancer register.

**2021 data collection cut-off: Mar 31st

10.4 Main results

Only very few cases of CIN2/3 were diagnosed in the study cohorts during the study period from 25 January 2019 to 31 March 2021.

Among 25,017 women vaccinated with G9 according to the "per protocol" vaccination schedule, one woman was diagnosed with CIN2/3. The rate per 1,000 woman months was estimated at 0.003 (95% CI: 0.0001 - 0.02). Among 160 women from the vaccinated HPV test-negative sub-cohort, no new onset CIN2/3 case was detected. The rate per 1,000 woman-months was estimated at 0 (95% CI: 0 - 1.7). Among the 466 women from the matched unvaccinated cohort, one woman had an onset of CIN2/3. The rate per 1,000 woman-months was estimated at 0.2 (95% CI: 0.004 - 0.9).

Among the general female population, which included vaccinated and unvaccinated women, the occurrence of CIN2/3 cases was relatively stable over the observation years 2016 to 2020, ranging from 256 (113.96 per million) in 2017 to 412 (179.41 per million) in 2018. The proportion of women with CIN2/3 was lowest in the youngest age group of women 20 to 25 years in which however a sharp increase of cases was observed since 2019. CIN2/3 then increased with age and reached a peak in the age group 41 to 45 years in 2016/2017 and 36 to 40 years since 2018. However, these results need to be considered with caution as the number of cases was relatively low.

During the study period, no women from the G9 vaccinated cohort, the G9 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of AIS. Among the general female population, new onset of AIS ranged from 2.30 per million in 2016 to 7.93 per million in 2020. No cases occurred in any year among the youngest age group of 20-25 year-old-women and the number of cases increased with age in most of the surveillance years.

Additionally, no woman from the G9 vaccinated cohort, the G9 vaccinated HPV test-negative sub-cohort and the matched unvaccinated cohort had an onset of ICC. Among the general female population, the proportion of ICC was highest in 2017 (42.74 per million) and lowest in 2020 (33.98 per million). The proportion of ICC cases increased with age in all

surveillance years and no cases were observed among the youngest age group of 20-25 year-old-women during the study period.

10.5 Other analyses

The proportion of women from the general population who underwent cervical cytology tests was very similar from year to year between 2015 and 2020, ranging from 1.05% in 2015 and 2016 to 1.33% in 2020 with a slightly increasing trend over the years.

The proportion of women who received a cervical cytology test increased with age in all surveillance years, reaching a peak at age 36-40 years (1.62% and 1.70%) in 2015/2016 and at age 41-45 years (1.89% to 2.15%) in the subsequent years, with a sharp increase between the age groups 20-25 (0.35% to 0.49%) and 26-30 years (1.12% to 1.41%) as well as a sharp decrease in women aged >45 (0.77% to 1.01%). Results from 2021 were not included, because the data collection for 2021 ended on 31 March 2021 (Table 14).

Cervical diseases including hysteretomy or CIN2+ treatment has been reported to NRHIP since 2015. The cumulative number of women from the general female population who had a history of cervical diseases reported prior to the calendar year 2016, 2017, 2018, 2019, 2020 and 2021 is presented in Table 15.

Table 14. Proportion of women who received cervical cytology test in the general female population

General female population by calendar year and age group		Proportion of women who received cervical cytology test, n (%)
2015	**≥20 years**	**22,328 (1.05)**
	20-25 years	549 (0.36)
	26-30 years	2,806 (1.24)
	31-35 years	3,283 (1.55)
	36-40 years	3,308 (1.62)
	41-45 years	3,724 (1.58)
	>45 years	8,658 (0.79)
2016	**≥20 years**	**22,790 (1.05)**
	20-25 years	501 (0.35)
	26-30 years	2,775 (1.23)
	31-35 years	3,509 (1.61)
	36-40 years	3,637 (1.70)
	41-45 years	3,520 (1.57)
	>45 years	8,848 (0.77)
2017	**≥20 years**	**25,165 (1.12)**
	20-25 years	491 (0.36)
	26-30 years	2,370 (1.12)
	31-35 years	3,610 (1.58)
	36-40 years	4,062 (1.77)
	41-45 years	4,116 (1.89)
	>45 years	10,516 (0.86)
2018	**≥20 years**	**28,613 (1.25)**
	20-25 years	477 (0.37)
	26-30 years	2,497 (1.21)
	31-35 years	4,083 (1.71)
	36-40 years	4,589 (1.94)
	41-45 years	4,436 (2.07)
	>45 years	12,531 (0.99)
2019	**≥20 years**	**30,105 (1.26)**
	20-25 years	511 (0.41)
	26-30 years	2,431 (1.22)
	31-35 years	4,461 (1.68)
	36-40 years	4,643 (1.95)
	41-45 years	4,720 (2.12)
	>45 years	13,339 (0.99)

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

2020	**≥20 years**	**35,124 (1.33)**
	20-25 years	661 (0.49)
	26-30 years	3,086 (1.41)
	31-35 years	6,114 (1.88)
	36-40 years	5,436 (1.97)
	41-45 years	5,219 (2.15)
	>45 years	14,608 (1.01)
2021*	**≥20 years**	**7,712 (0.29)**
	20-25 years	168 (0.13)
	26-30 years	763 (0.35)
	31-35 years	1,260 (0.38)
	36-40 years	1,208 (0.43)
	41-45 years	1,125 (0.46)
	>45 years	3,188 (0.22)

*2021 data collection cut-off: Mar 31st

Table 15. Number of women who have a history of cervical diseases including CIN2+ or who have undergone hysterectomy or CIN2+ treatment in the general female population (by calendar year from 2016).

Population by year	Number of women who have history of cervical diseases or undergone hysterectomy or CIN2+ treatment
General female population (2016)	18,835
General female population (2017)	25,878
General female population (2018)	33,280
General female population (2019)	43,009
General female population (2020)	55,715
General female population (2021)	65,652

*Data on NRHIP is available since 2015 and the number in this table is cumulative.

10.6 Adverse events/adverse reactions

This is a retrospective study using data from the NRHIP with the objective of assessing the occurrence of CIN2+ among women vaccinated with G9 the analysis of safety is the subject of a separate study. Although adverse events (AEs) and product quality complaints (PQCs) were not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs must be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE or PQC to G4, G9 or any other Merck product is identified, the AE/PQC must be reported. For the purpose of this study, as defined in the study protocol, the term AE includes SARs, NSARs, HOIs that meet criteria for SAR/NSAR and special situations, including exposure to product during pregnancy. Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as SARs/NSARs. During review of secondary data, causality should never be assigned retrospectively.

No adverse events were reported in this study.

11 DISCUSSION

11.1 Limitations

This surveillance occured within the NRHIP, which is a cloud-based health information platform. The NRHIP is designed for routine health care management, rather than for research purposes. Medical care (including diagnoses and treatment) received outside of the area covered by the NRHIP is not available.

Cervical cancer screening methods (e.g., cytology, HPV testing, etc.) are not standardized across health care facilities in Ningbo, as it is the case in China overall. CCI [redacted] CCI [redacted] CCI [redacted]. However, as for most other studies that measaure the impact of HPV

vaccines, the HPV types within each lesion were not known and therefore, the proportion of lesions attributable to G9 vaccine types are not known.

cci [redacted], a matched unvaccinated cohort was set up in this study. Women from the vaccinated HPV test-negative sub-cohort were matched on age at cohort enrollment and area of residence (rural/urban) to up to three women from the unvaccinated HPV test-negative sub-cohort. However, a formal comparison between the cohorts of vaccinated and matched unvaccinated women was not considered meaningful due to the short follow-up period since the introduction of vaccination with G9 and the low coverage of cervical screening services in Ningbo, especially for the younger age groups eligible for vaccination and the limited capture of data from these services in the NRHIP.

cci [redacted]

In population-based registry studies, it is not possible to obtain information on what an individual's HPV status and HPV genotyping of cervical lesions was at the time of HPV vaccination, thereby hindering the ability to identify lesions associated with vaccine types. Acquisition of HPV following sexual debut is high and HPV vaccination does not alter the course of an ongoing HPV infection. Asymptomatic prevalent infections with high risk HPV types, or cervical lesions caused by such types, may have been already present at the time of vaccination in the G9 vaccinated cohort. This may be reflected in endpoint diagnoses occurring after vaccination.

In addition, no lag time was applied in this study. Generally it is expected, that full immunity is only reached several months after vaccination with the third dose [13,14]. In addition, the latent period from HPV infection to CIN2/3 takes several years to decades. Therefore, CIN2/3 cases that occur shortly after vaccination are unlikely to be caused by infection acquired following vaccination, i.e., not breakthrough infections.

HPV vaccination in Ningbo is opportunistic. As vaccination is driven by women's willingness and doses of G9 are paid out-of-pocket, vaccinated women may be different from unvaccinated in many ways that may also be related to their risk of high-grade cervical intraepithelial neoplasia, resulting in potential biases and confounding in the study. Differences in socioeconomic status leads to unequal uptake of the vaccine and vaccinated women are more likely to receive preventive health care services and result in a detection bias and underestimation of the impact of vaccination on high-grade cervical lesions.

There is no population-based cervical screening program in Ningbo. There is a local free cervical cancer screening program in Ningbo at the current stage. However, this local screening program is opportunistic-based and it targets 35-64 years old rural or urban women who have no jobs. In the past years, this local cervical cancer screening program mainly targeted women aged 60-64 years old. Data of this local cervical screening program are not available in the NRHIP at the current stage. While China's cervical screening guidelines recommend screening beginning at age 25, cervical cancer screening that takes place outside of the free platform is not organized and may be offered to women starting at age 20. Rather, it is based on individual health care seeking and participation in annual body check-ups provided by employers. Cervical screening within the population who is age-eligible for vaccination is not routine in Ningbo, therefore, counts of high-grade cervical intraepithelial neoplasia within the platform was from women who had histological cervical testing because

they were symptomatic or from women undergoing opportunistic cervical screening. The underlying population from which these women come is not known. In addition, screening methods for cervical cancer in Ningbo varies across health care facilities. Some use HPV tests and cytological tests (including Pap test and TCT), and others might use visual inspection with acetic acid or visual inspection with Lugol's iodine. The sensitivity of a screening method, coupled with the proportion of the population covered, the age group covered, the frequency of screening, and colposcopy and biopsy tests are important factors in the frequency of diagnosis of high-grade cervical intraepithelial neoplasia. Even if the underlying risk factors are similar across areas, the rates of high-grade cervical intraepithelial neoplasia may not be similar if their approach to cervical screening differs widely. Moreover, as screening methods and algorithms change, so too can the rates of high-grade cervical intraepithelial neoplasia diagnoses change. The way in which cervical screening results are compiled (e.g., electronic versus paper register, dataset linkage, etc.) can also impact the proper accounting for cases within a database analysis and thereby impact the estimation of high-grade cervical intraepithelial neoplasia rates. Thus, a study of high-grade cervical intraepithelial neoplasia rates needs to also characterize the cervical screening programs and population base from which the cases arise, and to monitor changes in the programs over time, so that reasons for fluctuations in rates that may be observed can be more fully understood.

Last but not least, information on lifestyle factors, such as health care seeking behavior, sexual behaviors and other factors potentially related to risk of high-grade cervical intraepithelial neoplasia or high-grade cervical intraepithelial neoplasia diagnosis chances, were not available in the NRHIP. Vaccinated and unvaccinated women are expected to be different with respect to their risk of high-grade cervical intraepithelial neoplasia, such as demographic characteristics, socio-economic status, sexual and reproductive health behaviors etc. These factors could influence the diagnosis of high-grade cervical intraepithelial neoplasia. Due to the database study design, these factors could not be collected and analyzed in this study, though they are associated with risks of high-grade cervical intraepithelial neoplasia occurrence and could have had an impact on the effectiveness of HPV vaccination.

Rates of high-grade cervical intraepithelial neoplasia were estimated but not compared between the vaccinated HPV test-negtive sub-cohort and the matched unvaccinated HPV test-negative cohort due to the short follow-up time since the introduction of the vaccine and the low number of cases that were reported to NRHIP. Available data from the NRHIP, such as age, proportion of women who had cervical cytological tests were summarized in the study report. As high-quality surveillance data on HPV infection related diseases is not available in Ningbo, women from the general population provide background information of high-grade cervical intraepithelial neoplasia in Ningbo. In addition, there is no population-based cervical cancer screening program in Ningbo currently and high-grade cervical intraepithelial neoplasia cases were identified from opportunistic cervical screening or from women who had cervical testing because they were symptomatic. Therefore, the case counts of high-grade cervical intraepithelial neoplasia in the NRHIP may be an underestimate of true disease burden in the general population.

11.2 Interpretation

Since 25 January 2019 when G9 vaccination record available on the NRHIP until the data cut-off of 31 March 2021, a total of 102,791 doses of G9 were administered and 41,609 women received at least one dose of G9 and no other HPV vaccine. The number of women who received a first dose of G9 showed an increasing trend from 2019 to 2020 and also to 2021 when extrapolating the data from the first quarter of 2021 to the whole year. 60.2 % of the women received G9 according to the per protocol definition.

No new onset CIN2/3 case was observed during the study period in the vaccinated HPV test negative sub-cohort (N=160) and one case was observed in the matched unvaccinated cohort (N=466) corresponding to a rate of 0.0 (95% CI: 0 -1.7) and 0.2 (95% CI: 0.004 - 0.9) per 1,000 woman-months respectively for the two cohorts. Only women who had an HPV test-negative result prior to cohort enrollment were enrolled in these cohorts to ensure that women had no prevalent HPV infection prior to vaccination with G9.

Also, only one CIN2/3 case was observed in the larger cohort of G9 vaccinated women (N=25,017) for whom the HPV and cytological testing status at enrollment and CIN2/3

diagnosis was not known and we cannot therefore exclude the possibility that the woman who was observed with CIN2/3 during the study period was infected with HPV before G9 vaccination.

No AIS or ICC cases were observed in the vaccinated cohort and the matched unvaccinated cohort.

G9 was introduced in China in 2018, and the first women were vaccinated with G9 in 2019 in Ningbo. Vaccine impact generally becomes first apparent for HPV infections and genital warts, which have short incubation periods following exposure to HPV. Effects on cervical lesions which take longer to develop, can only be observed after longer observation periods. Cancer rates are expected to decline only in the longer term, because carcinogenesis after HPV infection may require several decades to become manifest.

We monitored the occurrence of CIN2/3, AIS and ICC cases in the general female population (including vaccinated and unvaccinated women) over the years 2016 to 2021 to identify if changes in cervical screening methods over the years may have impacted high-grade cervical intraepithelial neoplasia diagnoses. The proportion of new CIN2/3 cases that were reported to NRHIP in this population was relatively stable, ranging from 113.96 per million (256 cases) in 2017 to 179.41 per million (412 cases) in 2018. It is worth noting that the proportion of women vaccinated with G9 among the general population was quite low.

The proportion of AIS varied between 2.30 per million (5 cases) in 2016 and 7.93 per million (21 cases) in 2020 and the proportion of ICC was highest in 2017 (96 cases, 42.74 per million) and lowest in 2019 (83 cases, 34.73 per million). The number of cases reported in 2021 was not available for the complete year and therefore the trend for 2021 cannot be determined yet.

To our knowledge, incidence of CIN2+ among the general female population from the Ningbo region that could be compared to the study results is not available in the literature.

Given the lack of organized screening in Ningbo, it is difficult to get the full picture of cervical disease. Data from opportunistic screening is not reported to NRHIP. Therefore, only women who are treated in the hospital for CIN2/3 could be identified from the NRHIP.

The proportion of women from the general population who underwent cervical cytology tests, as reported to the NRHIP, was very similar from year to year between 2015 and 2020, ranging from 1.05% in 2015 and 2016 to 1.33% in 2020, with a slightly increasing trend over the years. Cytology testing increased with age in all surveillance years and reached a peak at 36-40 in 2015/2016 and at 41-45 years in the subsequent years. The percentage of women with cytology testing after cohort enrollement was generally low, presumably because those women just had a recent negative test to be eligible for enrollment in the test-negative subcohort vaccinated sub-cohort and the matched unvaccinated cohort. We also observed a higher proportion of women who had cervical cytology testing after cohort enrollment in the vaccinated sub-cohort (8.8%) compared to the matched unvaccinated cohort (5.4%). This observation is based on limited data but it indicates that vaccinated women may have a higher tendency to attend cervical screening services compared to unvaccinated women due to increased awareness and health-seeking behaviours. This observation needs to be factored into the interpretation of CIN2/3 occurence among these two cohorts. In addition, CIN2/3 is an asymptomatic disease, and the disease burden is therefore assumed to be much higher than what we observed so far in this study.

Since G9 was introduced in China in 2018, it is still too early to observe the effect of the vaccination. Evidence will become increasingly available as the time since the introduction of the vaccine accrues.

In clinical trials worldwide, the quadrivalent HPV vaccine G4 showed high efficacy against cervical, vaginal, vulvar and anal dysplasia related to the HPV types 6, 11, 16 and 18 and against condyloma related to HPV types 6 and 11. In addition to the types covered by G4, G9 has also shown high efficacy in the pivotal clinical trial focusing on prevention of cervical, vaginal and vulvar diseases related to the additional 5 high-risk HPV types (HPV 31, 33, 45, 52 and 58) that are not covered by the quadrivalent HPV vaccine, G4 [15].

The impact of vaccination with G4 in real-world settings has become increasingly evident, especially among girls vaccinated before HPV exposure in countries with high vaccine uptake. Maximal reductions of approximately 90% for HPV 6, 11, 16 and 18 infection, approximately 90% for genital warts, approximately 45% for low-grade cytological cervical

abnormalities, and approximately 85% for high-grade histologically proven cervical abnormalities have been reported [16].

Recent studies performed in Sweden and Denmark also showed an effective protection of G4 against invasive cervical cancer, which was most pronounced when girls were vaccinated before 17 years of age [17,18]. Danish investigators also recently reported a reduction in the risk of vulvar and vaginal precancer/cancer associated with G4 vaccination, which was again most prominent among females vaccinated before age 17 years [19].

Additional studies are ongoing to evaluate the effectiveness and impact of G9 in real-world settings in various countries.

11.3 Generalisability

This is a database study based on NRHIP, and all women living in the Ningbo region whose health care data are recorded in the NRHIP were eligible to be included in the study. Ningbo is an economically developed large coastal city located in the east coastline of China. Most women identified in the vaccinated cohort were Han Chinese, which makes the results from this study generalizable for other parts of China on the ethnic level. However, the socioeconomic status of the Ningbo female population might be higher compared to that in other regions of China. As G9 is not reimbursed by public insurance in China, women with higher socioeconomic status are assumed to have more access to the vaccine and the vaccine coverage with G9 is assumed to be higher in Ningbo compared to other parts of China where the socioeconomic level is lower. In addition, women with higher socioeconomic status might have more access to cervical screening due to increased awareness and health care seeking behaviour. As CIN2/3 is an asymptomatic disease, CIN2/3 detection is increased in case of higher screening attendance. However, the screening rate is low in Ningbo and data from public cervical screening are not yet available in NRHIP. These factors need to be considered when extrapolating the results from a region with higher socioeconomic level to a region with lower socioeconomic level.

12 OTHER INFORMATION

Not applicable in this report.
(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

13 CONCLUSION

Between 25 January 2019 and 31 March 2021, a total of 102,791 doses of G9 were administered and 41,609 women received at least one dose of G9 and no other HPV vaccine. The number of women who received a first dose of G9 showed an increasing trend from 2019 to 2020 and also to 2021 when extrapolating the data from the first quarter of 2021 to the whole year. 60.2 % of women received G9 according to the per protocol definition.

No new onset CIN2/3 case was observed during the study period in the vaccinated HPV test negative sub-cohort and one case was observed in the matched unvaccinated cohort corresponding to a rate of 0.0 (95%CI: 0 - 1.7) and 0.2 (95%CI: 0.004 - 0.9) per 1,000 woman-months respectively for the two cohorts. No AIS or ICC case was observed in any of these cohorts.

The proportion of women vaccinated with G9 was low, so it is still too early to observe an impact of the vaccination on the population level. The number of new CIN2/3 cases that were observed in the general female population was relatively stable over the observation years 2016 to 2020, ranging from 256 (113.96 per million) in 2017 to 412 (179.41 per million) in 2018.

The number of AIS varied between 5 (2.30 per million) in 2016 and 21 (7.93 per million) in 2020 and the number of ICC was highest in 2017 (96 cases, 42.74 per million) and lowest in 2019 (83 cases, 34.73 per million).

G9 was introduced in China in 2018, and women started to get vaccinated with G9 in Ningbo in 2019. Vaccine impact generally becomes first apparent for HPV infections and genital warts, which have short incubation periods following exposure to HPV. Effects on cervical lesions which take longer time to develop can only be observed after longer observation periods. Cancer rates are expected to decline only in the longer term, because carcinogenesis after HPV infection may require several decades to become manifest.

NRHIP covers all hospitals in Ningbo that have the ability to diagnose CIN2+. Our study demonstrates that the NRHIP can be used to monitor the occurrence of CIN2+ in vaccinated and unvaccinated women living in the Ningbo region over time. However, effects on cervical

lesions can only be observed after longer observation periods since the introduction of G9 vaccination.

In addition, as there is no organized cervical screening program in Ningbo and results from opportunistic cervical screening is not recorded in the NRHIP, it might take several years before the sample size is sufficient to compare the rates of high-grade cervical intraepithelial neoplasia in the vaccinated and matched unvaccinated cohorts.

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Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	V503-056/Protocol Version 2.0	21-May-2020	Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9
2	V503-056/SAP Version 2.0	20-Dec-2021	Statistical Analysis Plan for Post-marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9

Annex 2 Study protocol

Post-Marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9

2. Annex 2 HPV PMC effectiveness

Annex 3 Statistical Analysis Plan

Statistical Analysis Plan for Post-marketing surveillance for HPV infection related serious disease in a cohort of Chinese women who received GARDASIL® and GARDASIL®9

3. Annex 3 HPV
PMC effectiveness