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 the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women (V503-055)".

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 Nov 2023. 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 LLC.

Dec 2023

PASS INFORMATION

Title	Post-Marketing surveillance for the safety of GARDASIL® in a cohort of Chinese women
Version identifier of the final study report	GARDASIL® Final Study Report V503-055, VERSION 1.0
Date of last version of the final study report	N/A
EU PAS register number	EUPAS36132
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
Research question and objectives	To monitor the occurrence of new onset of 7 pre-specified autoimmune disorders and adverse pregnancy outcomes in a cohort of Chinese women who received G4.
Country(-ies) of study	China
Author	Prof. PPD Peking University Health Science Center, China
Merck Final Repository (REDS) Date	Nov 29, 2023

MARKETING AUTHORISATION HOLDER(S)

Marketing authorization holder(s)	Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. 126 East Lincoln Ave, P.O. Box 2000, Rahway, NJ 07065, US
MAH contact person	PPD

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXES

1 ABSTRACT

Title

Post-Marketing surveillance for the safety of GARDASIL® in a cohort of Chinese women

Keywords

GARDASIL®; Post-Marketing Surveillance; HPV; Autoimmune Disorder; Pregnancy Outcome

Rationale and background

Upon licensure of GARDASIL® (G4) in 2017 and GARDASIL®9 (G9) in 2018 CCI [redacted] CCI [redacted] CCI [redacted]. This final study report presents the study results for women who were vaccinated with G4. The results for women vaccinated with G9 (including for those who received mixed G4/G9 regimens) were presented in a separate study report, submitted to CDE in May 2022.

Research question and objectives

To monitor the occurrence of new onset of 7 pre-specified AIs and adverse pregnancy outcomes in a cohort of Chinese women who received G4.

Study design

Surveillance within a database system in the Ningbo Regional Health Information Platform (NRHIP); observational design.

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.

Subjects and study size, including dropouts

Women between ages of 20 and 45 years old during the study period (i.e., age-eligible for vaccination with G4) who were residents of Ningbo, whose medical care information was available in the NRHIP, and who received at least one dose of G4 as part of routine health care. Ningbo has a population of approximately 2.8 million local female residents between the ages of 16-45 years old.

For the pregnancy surveillance, the study population includes women who had pregnancy exposure to G4, and their infants.

This is a descriptive study, and no sample size calculation and no hypothesis testing were done.

Variables and data sources

Exposure:

For AIs surveillance: Receipt of at least one dose of G4 during the study period.

For pregnancy surveillance: Receipt of at least one dose of G4 during the study period, up to 30 days prior to conception or anytime during pregnancy.

Outcomes:

For AIs surveillance: Pre-specified new-onset of 7 AIs (systemic lupus erythematosus, Graves' disease, Hashimoto's disease, type 1 diabetes, multiple sclerosis, optic neuritis, and uveitis) diagnosed in the study population within 6 months after each dose of G4.

For pregnancy surveillance: Stillbirth and major congenital anomaly in infants of women in the study population with G4 vaccination up to 30 days prior to conception or during pregnancy.

The pre-specified AIs and pregnancy outcomes were identified from the NRHIP using study-specific case identification methods.

Results

A total of 195,593 doses of G4 were administered to 76,212 women aged 20 to 45 years old who had received no other HPV vaccine before they were vaccinated with G4 in Ningbo over the study period from 9 January 2018 to 31 March 2021.

A total of 113 women were diagnosed with a new-onset case of pre-specified AIs, including 24 cases of Graves' disease (44.21 per 100,000 person-years), 71 cases of Hashimoto's disease (130.84 per 100,000 person-years), 1 case of optic neuritis (1.84 per 100,000 person-years), and 17 cases of uveitis (31.31 per 100,000 person-years) within 6 months of receipt of a dose of G4.

A total of 168 women had received G4 during their pregnancy or within 30 days before conception. Among these women, no stillbirth was observed. Five of the infants born to a mother with pregnancy exposure to G4 were diagnosed with congenital heart diseases during the observation period of 3 months from birth.

Discussion

In this large database study, 113 new-onset cases of 7 pre-specified AIs within 6 months of receipt of a dose of G4, as well as 5 adverse pregnancy outcomes in 168 women exposed to G4 during their pregnancy or 30 days before pregnancy, were identified in 76,212 women who received a total of 195,593 doses of G4. This study used a broad case identification method, and rigorous review and case validation were conducted by clinical experts following pre-specified procedures.

CCI

[redacted]

CCI

[redacted]

Marketing Authorization Holder(s)

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

1 Merck Drive, P.O. Box 100, Whitehouse Station, NJ08899, US

Names and affiliations of principal investigators

Prof. PPD, Peking University Health Science Center, China

2 LIST OF ABBREVIATIONS

AE	Adverse Event
AEFI	Adverse Events Following Immunization
AIs	Autoimmune Disorder
CDC	Center for Disease Control and Prevention
CDE	Center for Drug Evaluation
CI	Confidence Interval
EMR	Electronic Medical Record
G4	GARDASIL®
G9	GARDASIL®9
GPP	Good Pharmacoepidemiology Practice
HGRAC	Human Genetic Resource Administration of China
HPV	Human Papillomavirus
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
PSUR	Periodic Safety Update Report
PQC	Product Quality Complaint
SAR	Serious Adverse Reaction
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
SQI	Significant Quality Issue
SRC	Safety Review Committee

T1DM	Type 1 Diabetes

3 INVESTIGATORS

Principal investigator	Prof. 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	Prof. PPD , Peking University Health Science Center, China
Investigators	Prof. PPD Peking University Health Science Center Dr. PPD , Peking University Health Science Center

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
Safety Review Committee (SRC) chairman	PPD
SRC member	
SRC member	
SRC member	
SRC member	
SRC member	
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	Due to HGRAC new requirement of database preservation licensing and onsite visit delay for COVID-19
Database lock	Approximately 1 month prior to compilation of study report.	09-Sep-2022	
Final report of study results	Prior to license renewal	27-Nov-2023	Delay was due to travel restriction to Ningbo because of the COVID-19 outbreak in 2022

6 RATIONALE AND BACKGROUND

6.1 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 deaths in Chinese women {085DS5}. 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. Cervical cancer is 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. Over the past decade, the Chinese government has initiated activities to reduce the burden of cervical cancer in Chinese women.

As a measure of primary prevention of cervical cancer, the Chinese government has approved bivalent, quadrivalent, and nonavalent HPV 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 the nonavalent vaccine (GARDASIL®9). GARDASIL® (G4) targets HPV types 6, 11, 16, and 18 and was approved in China for 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. In November 2020, the age indication for G4 in China was expanded for use in women 9 to 45 years and for G9 in August 2022.

6.2 Rationale

While a favorable safety profile for G4 has been seen in the pre- and post-marketing setting, the safety of these vaccines administered to Chinese women as part of routine health care has not been studied. CCI [redacted] CCI [redacted] MSD conducted a surveillance of pregnancy and autoimmune outcomes following routine vaccination of Chinese women 16-45 years old. This database surveillance used a regional health information platform in Ningbo

(Ningbo Regional Health Information Platform, NRHIP) to monitor safety of G4 and G9 vaccination in Chinese women.

This final study report presents the study results for women who were vaccinated with G4. The results for women vaccinated with G9 (including for those who received mixed G4/G9 regimens) were presented in a separate study report, which was submitted to CDE in May 2022.

7 RESEARCH QUESTION AND OBJECTIVES

- ✓ To monitor within the NRHIP the diagnosis of 7 pre-specified new-onset AIs diagnosed within a period of up to 6 months after each dose of G4 in Chinese women who were age-eligible for vaccination at any time during the study period, based on data from the NRHIP.
- ✓ To monitor within the NRHIP the occurrence of stillbirth and major congenital anomaly in infants of Chinese women who were age-eligible for vaccination at any time during the study period and who were inadvertently vaccinated with G4 up to 30 days prior to conception or anytime during pregnancy, based on data from the NRHIP.

8 AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
NA				

9 RESEARCH METHODS

9.1 Study design

This database study was designed for the safety surveillance of G4 vaccination in Chinese women. This study was conducted using the existing computerized databases and infrastructure at the NRHIP {089XW8, 089YJW}. There are two components in this surveillance: AIs safety and pregnancy safety, described below.

9.1.1 AIs surveillance

In consultation with national and local experts and CDE (experts consultation meeting on December 20, 2018 and CDE consultation meeting on June 12, 2019), there was alignment that safety research within the NRHIP is possible, but that accurate endpoint assessment (i.e., disease diagnosis) is critical, because establishing vaccine safety requires high quality data on both the vaccination status and the disease outcome under surveillance. There was also alignment that this is an area in which the NRHIP requires further, ongoing development. High-level surveillance (i.e., broad but not specific case identification methods) of a multitude of AIs at this stage in the development of the NRHIP for research purposes was not considered appropriate. Rather, focused and rigorous identification of specific disease outcomes is needed. Therefore, careful identification and validation (within the context of the data available in this platform) of AIs has been undertaken, to identify new-onset diagnoses within 6 months (considered as AI risk window in this study) after any dose of G4.

The AIs can be broadly classified into 3 categories: rheumatologic, endocrine, and neurological disorders. The following aspects were considered when selecting AIs, 1) from each of these 3 categories, 1 to 3 relatively common AIs were selected because these conditions have established diagnostic criteria and treatment options, 2) have been identified in the NRHIP within the general population of women 16-45 years old, and are 3) commonly studied in other studies of G4 or G9 safety (though there is no evidence of the association between vaccination with G4 or G9 and new onset of any of these conditions). These conditions were selected in alignment with CDE and defined in the study protocol and include: systemic lupus erythematosus

(rheumatologic); Graves' disease, Hashimoto's disease and type 1 diabetes (endocrine); and multiple sclerosis, optic neuritis and uveitis (neurologic). Uveitis and optic neuritis have been implicated as early conditions that could be associated with development of demyelinating disorders, and therefore were included in the "neurologic" category in this instance {089YJ5, 089YJD}.

9.1.2 Pregnancy outcome surveillance

Women in the vaccinated cohort who received at least one dose of G4 up to 30 days prior to conception or anytime during pregnancy and their infants were eligible for the pregnancy outcomes surveillance. Congenital anomalies under surveillance in this study are selected according to the National Maternal and Child Health Surveillance Manual 2013, and included anencephaly, spina bifida, encephalocele, congenital hydrocephalus, cleft palate, cleft lip, cleft palate with cleft lip, microtia/anotia, other malformations of outer ear, esophageal atresia or stenosis, rectoanal atresia or stenosis, hypospadias, exstrophy of urinary bladder, talipes equinovarus, polydactyly, syndactyly, limb reductions, congenital diaphragmatic hernia, exomphalos, gastroschisis, conjoined twins, Down syndrome, congenital heart diseases {089ZCY}.

9.2 Setting

Study 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 Zhejiang province, in the eastern 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. Vaccination record for the first dose of G4 and G9 became available in Ningbo on 9 January 2018 and 25 January 2019, respectively.

The NRHIP is one of the best regional health information systems in China. The NRHIP collects healthcare information from a variety of sources within Ningbo, thereby providing a comprehensive and centralized structure to store healthcare data, including age, gender, disease diagnosis, treatment, drug prescription and dispensing,

and laboratory testing results. Electronic medical records of outpatient visits, emergency room visits and hospitalizations from local hospitals have been integrated into the NRHIP. The vaccine register system in the NRHIP contains information on vaccines administered in Ningbo.

A cohort of G4 vaccinated women was identified from the Ningbo Vaccine Register within the NRHIP and their safety outcomes of interest after vaccination were surveilled based on information within the NRHIP.

Study period: The surveillance period for G4 was from 9 January 2018 to 31 March 2021.

9.3 Subjects

Women who received G4 vaccination were eligible for study participation. Vaccinated women were identified from the vaccine register within the NRHIP.

The AIs surveillance inclusion criteria and exclusion criteria were:

Inclusion criteria

- ✓ Female residents registered in the NRHIP;
- ✓ Age-eligible for vaccination during the study period (between 20 to 45 years old at the initiation of G4 vaccination during the study period);
- ✓ Received at least 1 dose of G4;
- ✓ Received only G4 and no other HPV vaccine (as initial HPV vaccine);
- ✓ Received G4 vaccination in Ningbo;

Exclusion criteria

- ✓ Women who received any HPV vaccine other than G4 will be censored at the date of the first HPV vaccination other than G4;
- ✓ Women with prior diagnosis or clear symptom onset of a pre-specified AI before G4 vaccination initiation.

The pregnancy outcome surveillance inclusion and exclusion criteria were:

Inclusion criteria

- ✓ Female residents registered in the NRHIP;
- ✓ Age-eligible for vaccination during the study period (between 20 to 45 years old at the initiation of G4 vaccination during the study period);

- ✓ Received at least one dose of G4 vaccine up to 30 days prior to conception or anytime during pregnancy (criterion is based on the data available within the antenatal care and childbirth EMRs within the NRHIP for this surveillance);
- ✓ Received only G4 and no other HPV vaccine (as initial HPV vaccine);
- ✓ Received G4 vaccination in Ningbo;
- ✓ Delivered at a gestational age of 28 weeks or above, or gave birth to a baby with birthweight no less than 1000g (if the gestational age at delivery is unknown) at the index pregnancy (this criterion based on availability of records included in the NRHIP).

Exclusion criteria

- ✓ Women who received any HPV vaccine other than G4 were censored at the date of the first HPV vaccination other than G4.

To capture as many G4 vaccinated women as possible, those who received G4 at first (initial HPV vaccine), and then received other HPV vaccines were included and censored at the date of receipt of other HPV vaccines. However, those who received other HPV vaccines at first dose (initial HPV vaccine), and then received G4 were not included in this surveillance.

9.4 Variables

9.4.1 Exposure

Exposure for AIs surveillance was defined as receipt of at least one dose of G4 in women who were age-eligible for vaccination at any time during the study period. The surveillance period ended 6 months after each dose or at the time of vaccination of a subsequent dose, whichever occurred earlier.

Exposure for pregnancy surveillance was defined as receipt of at least one dose of G4 up to 30 days prior to conception or anytime during pregnancy among women who were age-eligible for vaccination at any time during the study period.

Case identification of pregnancy exposure

Information on pregnancy was extracted from the maternal specific program data in the NRHIP. G4 vaccination data for women was extracted from the vaccine register in the NRHIP. Data from the maternal specific program and G4 vaccination data were

linked. The vaccination dates of each dose of G4 were compared with the relevant pregnancy data to identify cases with potential maternal G4 exposure.

A potential pregnancy exposure window to identify pregnancy exposure of 50 weeks (started from a maximum of 60 days before last menstrual period), which is wider than the range of 30 days before conception until 40 weeks of gestational age at delivery was used to increase the sensitivity to identify cases with maternal exposure and to ensure that all cases with potential maternal exposure were detected, including those with longer pregnancy duration or unclear conception dates. This study did not differentiate between last menstrual period and conception date. Cases with potential maternal exposure were then linked to medical information in the EMR (testing, diagnosis, prescription, surgical intervention, etc.) to collect all medical records of the cases for the validation of cases with potential maternal exposure.

Validation of cases with maternal exposure

The determination of the conception date is important in this study because it is determinant to identify whether a female was exposed to G4 or not during her pregnancy. The validation process included case profile form development, EMR data extraction, determination of the date of conception and validation of cases with maternal exposure. Details of this validation process are described in the study data management plan.

9.4.2 Outcome

9.4.2.1 AIs surveillance

The following 7 conditions were included in the AIs surveillance part of this study: Graves' disease, Hashimoto's disease, SLE, type 1 diabetes, multiple sclerosis, optic neuritis and uveitis. The outcome of interest for each of these conditions was new-onset and diagnosis within 6 months after each dose of G4.

AIs diagnoses were captured using available outpatient, emergency room, and inpatient diagnosis codes and free text in the NRHIP. The case identification method of each AI included in the surveillance was developed in consultation with the NRHIP experts and local clinicians with expertise in the conditions of interest. Case

validation was undertaken by clinicians with proper training for these activities. Details of case identification and validation are included in the data management plan.

Step 1: Development of a case identification method for selected AIs

Broad case identification methods of AIs based on relevant ICD-10 codes and key words of diagnosis were used for the case identification. Local clinicians reviewed and revised these pre-identified ICD codes and key words to ensure the reliability of the case capture. In addition, this method was reviewed by the SRC to ensure that it was applicable to identify potential cases in the NRHIP.

Step 2: Case identification of selected AIs

Vaccination data and AI data were extracted from various databases in NRHIP and linked. AI case identification methods were applied to extract the relevant information of the diagnosis of the selected AIs (diagnosis name, ICD code, date) in the total population to identify selected AI cases. G4 vaccination data were extracted from the vaccine register in the NRHIP. Then, selected AI cases identified in the general population and G4 vaccination data were linked, and dates of AIs onset and vaccination date were compared to identify potential AI cases with onset in the 6 months following G4 vaccination. Medical information was linked for these potential AI cases to collect all medical records for potential AI case validation.

Step 3: Case validation of selected AIs

Case validation was conducted for all potential AI cases identified in G4 risk window. For each AI, all medical information available in the NRHIP was collected and validated by two independent clinicians. A third clinician was assigned to review the cases if the diagnosis of the two clinicians was not consistent. For each confirmed AI case, a short narrative (typically less than 200 Chinese characters) was prepared by one of the clinicians responsible for the case validation.

9.4.2.2 Adverse pregnancy outcome surveillance

For the pregnancy surveillance, stillbirth and congenital anomalies in infants with G4 maternal exposure during pregnancy were the outcomes of interest. Major congenital anomalies included anencephaly, spina bifida, encephalocele, congenital hydrocephalus, cleft palate, cleft lip, cleft palate with cleft lip, microtia/anotia, other

malformations of outer ear, esophageal atresia or stenosis, rectoanal atresia or stenosis, hypospadias, exstrophy of urinary bladder, talipes equinovarus, polydactyly, syndactyly, limb reductions, congenital diaphragmatic hernia, exomphalos, gastroschisis, conjoined twins, down syndrome and congenital heart diseases.

The case identification methods of pregnancy outcomes included in the surveillance were also developed in consultation with the NRHIP experts and local clinicians with relevant expertise. Case validation was undertaken by clinicians who had received specific training for these activities. Details of case identification and validation are included in the data management plan.

Step 1: Case identification of pregnancy outcomes

Stillbirth cases were identified from maternal EMR using stillbirth-related ICD-10 codes (Z37, Outcome of delivery) and diagnosis key words (stillbirth/死产). Stillbirth cases were linked to their vaccination status to identify potential stillbirth cases that occurred in the G4 potential pregnancy exposure window.

Diagnosis related information (diagnosis name, ICD codes and diagnosis date) was extracted from the NRHIP infant EMR using pre-defined congenital anomaly related ICD-10 codes and diagnosis key words, to identify selected congenital anomaly cases in newborns. Data of newborn was extracted from the NRHIP neonatal specific program. Maternal exposure and neonatal specific program data were linked to identify the infants with congenital anomalies whose mothers were vaccinated. Vaccination and conception dates of the mother-infant pairs were compared to identify infants with conception dates in the G4 potential pregnancy exposure window. Then, other medical information was extracted from the infant EMR to acquire all medical records that are needed for the case validation of the potential congenital anomaly cases.

Step 2: Case validation of pregnancy outcomes

All potential stillbirth cases and potential congenital anomaly cases occurring in the G4 potential pregnancy exposure window underwent case validation. Steps included pregnancy outcome case profile form development, EMR data extraction, case validation and narrative writing.

An SRC, composed of external experts with expertise in autoimmune disorders, obstetrics, pharmacoepidemiology, epidemiology, statistics and vaccine observational research, was assembled. The SRC reviewed the data management plan and the statistical analysis plan. It also reviewed the final analysis results and the study report.

9.4.3 Covariates

As a health information platform, the NRHIP stores extensive health data, whereas a more limited amount of socioeconomic data is available in the NRHIP. Covariates that could potentially have an impact on HPV vaccination exposure and the pre-specified AIs or pregnancy outcomes were extracted and analyzed. For AI outcomes, the covariates included factors such as age at first dose, residence region, marital status, occupation, diagnosis time, age at diagnosis, days between last vaccination dose before diagnosis and diagnosis. For pregnancy outcomes, the covariates included age at first dose, residence region, education, occupation, cigarette smoking status, alcohol drinking status, gravidity and parity. The finalized list of covariates was compiled in consultation with NHRIP experts and was described within the statistical analysis plan for this surveillance.

9.5 Data sources and measurement

This is a database surveillance and data from the NRHIP was used for vaccination safety analyses.

The NRHIP is one of the most advanced regional health information system platforms in China and 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. The NRHIP contains three main data sources: hospital information system, maternal and child healthcare information system and CDC (Center for Disease Control and Prevention) information system. The hospital information system collects information on outpatient visits, emergency room visits and hospitalizations, including demographic characters, diagnosis, treatment, drug prescription and dispensing and laboratory examination results. The Ningbo CDC

information system mainly collects, reports and manages information pertaining to vaccination information, communicable diseases, chronic diseases, death certification, foodborne diseases, vector-borne diseases, and similar factors. The data from the CDC, hospital, and maternal and children health information systems are integrated, verified, stored, exchanged, and shared in the NRHIP. Different datasets are linkable using personal identification variables and database-specific unique index variables.

Vaccine register system

The vaccine register system in Ningbo collects information on vaccine cold chain management, migrating children management, and digital vaccination clinics. The information system provides services such as responses to inquiries on vaccination information and immunization records and ability to make appointments for vaccination, informed consent, payment and some consultation and to monitor 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 on individual ID, 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) has been mandatory.

Electronic medical records (EMR)

The NRHIP covers all 221 public hospitals and 28 large private hospitals in Ningbo city except for some specialized hospitals or private clinics, such as eye hospitals and dental hospitals. These specialized hospitals and private clinics generally lack capability for diagnosis or treatment of AIs and birth defects diseases. The NRHIP collects information on outpatient visits, emergency room visits, hospitalization, disease diagnosis (International Classification of Disease (ICD) 10 code, Ningbo-specific and hospital-specific diagnostic codes, and free text), laboratory test results, drug prescription and dispensing, surgeries, and body check-ups since 2015. Therefore, both HPV vaccination and information regarding AIs and pregnancy outcomes are collected in the NRHIP, and the data are linkable using personal ID number at individual level at the NRHIP in Ningbo. Health information of Ningbo

residents who receive care outside Ningbo is not available in the NRHIP for most conditions, including those pertinent to this surveillance.

Maternal and children health management system

In total, there are 12 maternal and children health hospitals in Ningbo, including 1 municipal maternal and child health hospital and 11 county-level maternal and child health hospitals. The maternal and child health management system is part of the NRHIP, and it collects information on antenatal care and childbirth from all hospitals that provide maternal healthcare services in Ningbo. The system can capture almost all pregnancies and childbirths in local residents.

9.5.1 Study Procedures

This study was approved by the Institutional Review Board (IRB) of Peking University Health Science Center. The study was based on a secondary analysis of data that was routinely collected in Ningbo and preserved in the NRHIP. Therefore, no recruitment and no informed consent were needed in this study. Permission of waiver of informed consent for this study was granted. The electronic health 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 Peking University study personnel had access to these data. All analyses performed 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 bias, including selection bias and information bias. In order to reduce the selection bias in this study, all eligible women vaccinated with G4 were monitored for outcomes of interest within the NRHIP. The surveillance covered all potential cases in NRHIP of pre-specified AIs in eligible women after vaccination and pregnancy outcomes in women with potential maternal vaccine exposure during the observational period. In addition, information on

vaccination exposure and outcomes was extracted from the NRHIP, reducing the risk of recall biases.

As this is a database study, outcomes of interest were identified from the NRHIP relying on the physician-assigned diagnosis and relevant information recorded. To reduce the detection bias related to the diagnosis of AIs and pregnancy outcomes in the vaccinated women, case identification methods were developed for the identification of potential cases that improved the outcome measurement accuracy. In addition, case validation was conducted to confirm the diagnosis among the potential cases.

9.7 Study size

In this database study, all women in the NRHIP who were vaccinated with at least one dose of G4 during the study period in Ningbo and who met the study inclusion criteria were included in the analysis. This is a descriptive study, and no sample size calculation was done given that no hypothesis testing was performed.

9.8 Data management

In this study, data management procedures included seven steps: data extraction, data cleaning, data linkage, de-identification, case validation, database lock, and data analysis. Ningbo CDC was responsible for coding, data extraction, data cleaning, data linkage, and de-identification. PKU was responsible for providing technical support and quality control. PKU was also responsible for developing and executing programming codes after de-identification, case validation, database lock, and data analysis.

All data management activities were undertaken under the supervision of the Peking University and Ningbo CDC, and followed all procedures detailed in a separate “Data Management Plan”.

9.9 Statistical methods

9.9.1 Main summary measures

A separate detailed statistical analysis plan was developed and finalized prior to any analyses in this study.

Demographic characteristics of women vaccinated with G4 were described as frequencies and percentages, with mean (±standard deviation (SD)), or median values (interquartile range (IQR)), based on the data available within the NRHIP. Descriptive analysis of information available within the NRHIP pertaining to G4 vaccination was undertaken.

A descriptive analysis of the outcomes of interest was performed. The number of women who had an onset of the prespecified autoimmune diseases within 6 months after any dose of G4 was provided. Additionally, numbers of stillbirths and congenital anomalies in infants born to women who received at least one dose of G4 up to 30 days prior to conception or anytime during pregnancy were provided. The trimester of pregnancy at vaccination and maternal age was reported.

As the study is based on secondary data, causal nature of associations cannot be evaluated.

9.9.2 Main statistical methods

Not applicable as only descriptive analyses were conducted in this study.

9.9.3 Missing values

In case of missing values related to exposure and outcomes, the records with these missing values were excluded from the analyses. In case of missing values related to covariates, these missing values were summarized in an independent category as “unknown”.

9.9.4 Sensitivity analyses

No sensitivity analyses were performed in this study.

9.9.5 Amendments to the statistical analysis plan

Not applicable in this study.

9.10 Quality control

By signing the protocol, all parties followed applicable standard operating procedures (SOPs) for non-interventional study. All parties also agreed to train the study personnel appropriately to ensure that the study was conducted and data were generated, documented, and reported in compliance with the protocol and Good Pharmacoepidemiology Practice (GPP). All parties maintained transparency and open communication in order to effectively manage the study and proactively mitigate any risks. The study protocol, the statistical analysis plan and the data management plan were finalized before any actual data analyses.

The Sponsor met with Peking University on a weekly base, reviewed the data management plan and statistical analysis plan, conducted audit visits and assembled the SRC to ensure that the study was conducted 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. A 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.

9.10.1 Quality of data linkage

The data from the CDC (vaccine register system), the hospital (electronic medical records), and the maternal and children health information systems are integrated, verified, stored, exchanged, and shared in the NRHIP.

HPV vaccination and outcome information (including AIs diagnoses and pregnancy outcomes) were collected in the NRHIP, and the data was linked at individual level in the NRHIP in Ningbo. Personal identification variables and database-specific unique index variables were used for the linkage of the subjects across different datasets in the NRHIP to allow for each person's vaccination status to be combined with autoimmune diseases of interest and pregnancy outcomes.

In the NRHIP, ID variables were missing for a small proportion of women in the different data sources. Multiple linkage steps were applied to minimize the loss of data and to help ensure accurate linkage of subjects across various data sources in the platform. The dataset linkage steps were described in the study data management plan.

9.10.2 Standardization of autoimmune and pregnancy outcome diagnoses

Seven selected AIs and pregnancy outcomes after exposure to G4 vaccination have been monitored in this study. Key variables and information relevant to outcomes of interest were identified and extracted from the NRHIP to develop study-specific analysis datasets. Key variables included, medical diagnosis code, prescription medication, clinical characteristics, lab test results, medical follow-ups, etc. The format of these key variables from different data sources was standardized and clearly defined in the data management plan.

Case identification methods were developed to identify potential AI cases and pregnancy outcomes in the NRHIP. Diagnosis codes and key words of diagnosis in the EMRs of outpatient visits, emergency room visits, and hospitalizations that were pertinent to the outcomes of interest were included in these case identification methods. Study-specific clinical definitions of the 7 selected AIs and pregnancy outcomes were clearly described in the statistical analysis plan for this study. Physicians and experts in the area of autoimmune disease, maternal and child health were consulted when the case definitions were developed. The case validation of potential cases was conducted as described in the data management plan. All clinical experts in this study were trained in the case validation process prior to review.

9.10.3 Information integrity

Vaccination register, EMR data, maternal and child healthcare information system in the NRHIP are set up and managed strictly following the local health authority's requirements and regulations. Data integrity had previously been assessed in a preliminary 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 all collected in the system. All vaccination records of

adults in Ningbo city have been collected in the system since 2017 without missing IDs.

The 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 separate analyst (validation analyst). For all data processing steps, the validation analyst reviewed the program along with input and output datasets.

10 RESULTS

10.1 Participants

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

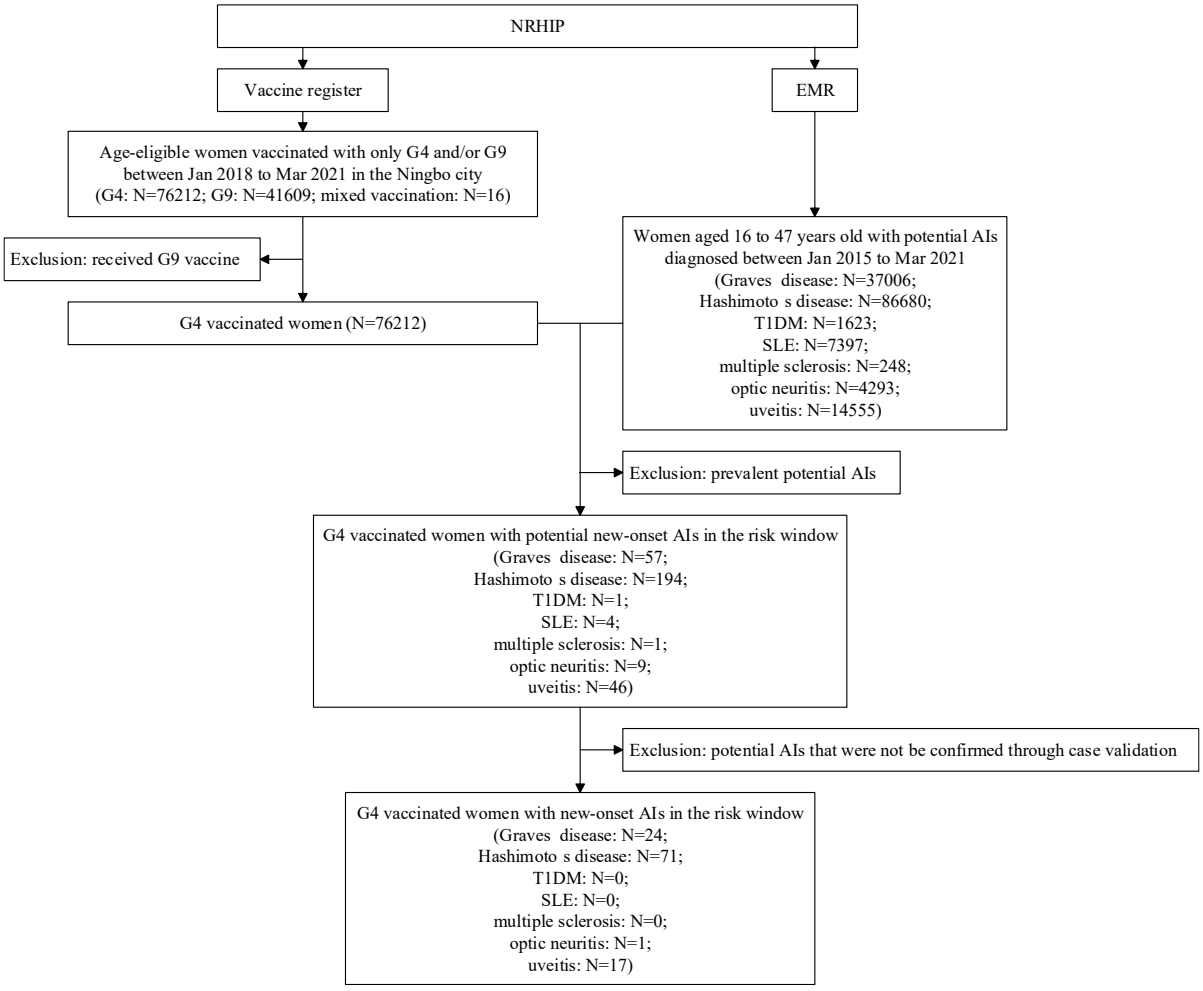

Figure 1. Flowchart of autoimmune disorder surveillance

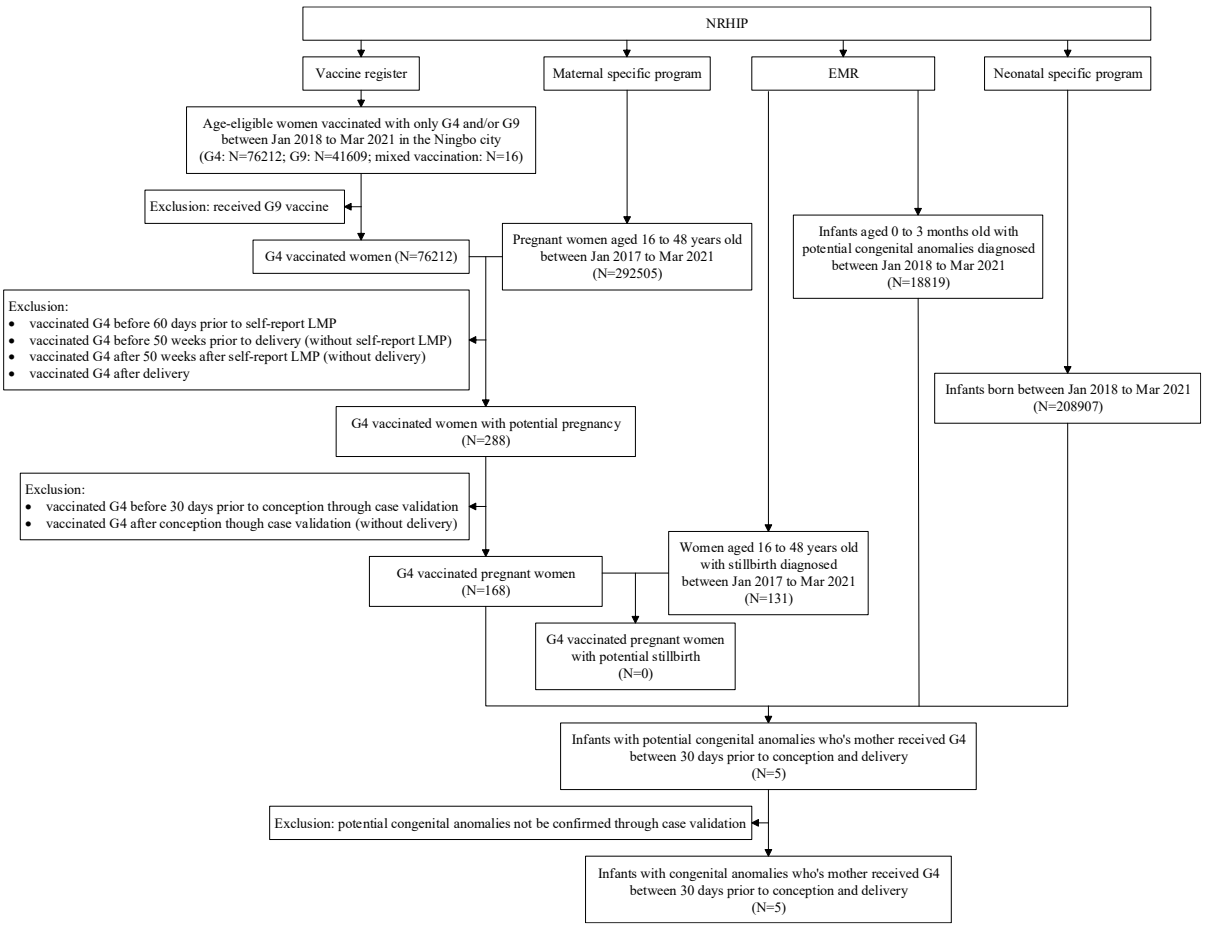

Figure 2. Flowchart of adverse pregnancy outcome surveillance

Confidential

10.1.1 Protection of Human Subjects

This is a database surveillance activity that focuses on 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 Ningbo and up to the data extraction cut-off on 31 March 2021, a total of 195,593 doses of G4 were administered in Ningbo. Overall, a total of 76,212 women were vaccinated with at least one dose of G4. The number of women who received their first dose of G4 increased from 12,030 in 2018 to 40,263 in 2020. During the first quarter of 2021, 9,738 women in Ningbo received a first dose of G4. The mean age at first dose of G4 was 33.87 (SD=5.28) years. 43.96% and 40.65% of these women were from urban areas and rural areas, respectively, for the remaining women the residence region was unknown. As of 31 March 2021, 11.22%, 20.92% and 67.86% of women had received 1, 2 and 3 doses of G4, respectively. Two women received more than 3 doses of G4. The mean time interval between dose 1 and 2, dose 2 and 3 were 2.27 (SD=0.26) and 4.35 (SD=0.33) months, respectively (Table 1).

Confidential

Table 1. Characteristics of women vaccinated with G4 between 9 Jan 2018 and 31 Mar 2021 in the NRHIP

Variables	
Total number of women vaccinated*	76,212
Age at first dose (years), mean±SD	33.87±5.28
20-25 years, n (%)	4,492 (5.89)
26-30 years, n (%)	19,882 (26.09)
31-35 years, n (%)	24,589 (32.26)
36-40 years, n (%)	18,691 (24.53)
41-45 years, n (%)	8,558 (11.23)
Residence region, n (%)††	
Urban	33,499 (43.95)
Rural	30,978 (40.65)
Unknown	11,735 (15.40)
Year of first dose, n (%)	
2018	12,030 (15.78)
2019	14,181 (18.61)
2020	40,263 (52.83)
2021†	9,738 (12.78)
Number of doses received, mean±SD, median (IQR), range	2.57±0.69, 3 (1), 1-5
1 dose, n (%)§	8,553 (11.22)
2 doses, n (%)§	15,940 (20.92)
3 doses, n (%)§	51,717 (67.86)
>3 doses, n (%)§	2 (0.00)
Time interval between doses (months), mean±SD, median (IQR), range	
Dose 1 and dose 2 (n=67,595)	2.27±0.73, 2.07 (0.26), 0.07-36.01
Dose 2 and dose 3 (n=51,745)	4.35±0.81, 4.14 (0.33), 1.15-26.81

* At least 1 dose of G4
† 2021 data collection cut-off: Mar 31st
§ Number and percentage of women who had received 1 dose, 2 doses, 3 doses or >3 doses of G4 as of the cut-off date
†† Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

10.3 Outcome data

Between 9 January 2018 and 31 March 2021, a total of 314 potential new onset AI cases were identified for women vaccinated with at least one dose of G4, including 57 cases of Graves' disease, 194 cases of Hashimoto's disease, 2 cases of T1DM, 4 cases of SLE, 2 cases of multiple sclerosis, 9 cases of optic neuritis, and 46 cases of uveitis. After the exclusion of 2 cases with onset prior to G4 vaccination or with inconsistent diagnosis records, 314 potential AI cases (99.36%) were reviewed by clinicians for case validation. Finally, 113 AI cases (35.99% of all potential cases) were confirmed, including 24 cases of Graves' disease, 71 cases of Hashimoto's disease, 1 case of optic neuritis, and 17 cases of uveitis (Table 2).

A total number of 24 new-onset cases of Graves' disease were identified in women vaccinated with G4. The mean age of these women at their first dose of G4 was 31.49 (SD=6.57) years. Five women received their first dose in 2018, 5 in 2019, and 14 in 2020. The women had received a mean of 2.92 (SD=0.28) doses, and therefore, the vast majority (22 women) had completed their 3rd dose of vaccination. Eight of these women were from urban areas, 8 women were from rural areas, and the residence region of 8 women was unknown. The number of women with new-onset Graves' disease diagnosed after dose 1, dose 2 and dose 3 of G4 was 13, 10 and 1, respectively. The mean time interval between the last dose of G4 and the date of diagnosis was 53.83 (SD=35.44) days (Table 3).

A total of 71 women vaccinated with G4 were identified with new-onset Hashimoto's disease. The mean age of these women at their first dose of G4 was 34.37 (SD=5.12) years. Nearly half of them (34 women) were from urban areas. Most of these women (51 women) received their first dose in 2020, 10 women received their first dose in 2018 and 10 in 2019. The vast majority of these women (91.55%) had completed all 3 doses of vaccination. Twenty-three women were diagnosed with new-onset Hashimoto's disease after dose 1, 47 women were diagnosed after dose 2, and 1 woman was diagnosed after dose 3. The mean time interval between the last dose of G4 and the date of diagnosis was 68.25 (SD=35.92) days (Table 4).

One woman was diagnosed with new-onset optic neuritis. She was from an urban area and PPD PPD when she was vaccinated with her first dose of G4. She received the first two doses

in 2020, and the third dose in 2021. This woman was diagnosed with new-onset optic neuritis after she had received dose 1. The time interval between the date of the first dose and the date of diagnosis was 24 days.

A total of 17 women vaccinated with G4 were identified with new-onset uveitis. The mean age of these women at their first dose of G4 was 34.70 (SD=6.07) years. More than half of them (10 women) were from urban areas. Three women received their first dose in 2018 and 5 in 2019, and 9 women received their first dose in 2020. A proportion of 88.24% of women had completed their 3rd dose of vaccination during the study period. The women received a mean of 2.88 (SD=0.33) doses. Most women (70.59%) were diagnosed with new-onset uveitis after dose 1, and 29.41% of women were diagnosed after dose 2. The mean time interval between the last dose of vaccination and the date of diagnosis was 53.06 (SD=36.09) days (Table 5).

A total of 288 women with potential pregnancy and G4 exposure were extracted, and their data were reviewed by clinicians for validation of their pregnancy. One hundred and twenty women were not included because the G4 exposure was not during pregnancy or 30 days prior to the date of conception. For 168 of these women (58.33% of 288 women with potential maternal exposure) the G4 exposure during pregnancy or 30 days prior to the date of conception was confirmed. The number of women who received G4 30 days before conception or during pregnancy was 70, 63 and 35 in 2018, 2019 and 2020, respectively. In the first quarter of 2021, no pregnant women in Ningbo received G4. Forty-five, 38 and 85 of these women had received respectively 1, 2 and 3 doses during the study period. The mean age at first dose of G4 was 30.07 (SD=3.98) years. 44.05% of the women were from urban areas, 42.26% were from rural areas, and for 13.69% of the women the residence region was unknown. Most of them (84.52%) had at least a university degree. Their occupational status was very diverse and not specified or known for almost half of them. Almost all women (99.4%) were recorded as non-smokers or non-alcohol-drinkers. The median numbers of gravidities (all pregnancies) and parities (previous births) were 1 (IQR=1) and 0 (IQR=0), respectively and therefore most of these women had their first pregnancy and delivery during the study period. A similar proportion of women had their conception before dose 1, after dose 1, after dose 2, and after dose 3. Among these women, 42.86% received the first dose of

G4 within 30 days prior to conception, more than half (54.17%) in the first trimester of their pregnancy, 2.00% during the second trimester and 2.38% in the third trimester (Table 6).

Among the 168 women with maternal G4 exposure, no stillbirth case was identified. Five potential cases of congenital heart diseases were identified and confirmed in infants with maternal G4 exposure (Table 7). For these infants, the mean age at diagnosis was 1.33 (SD=0.86) months. Three infants were PPD. All these infants were PPD. The mean age of their mothers was 31.45 (SD=6.30) years old. Most of these women (80.00%) were from rural areas and had bachelor's degrees. None of them was a current smoker or a regular alcohol drinker. For three women, it was the first pregnancy. For the other two women, it was the second and the sixth pregnancy, respectively. Only one woman had a history of one delivery. The mean gestation age was 38.40 (SD=1.14) weeks. The number of women who had received their first dose of G4 in 2018, 2019, and 2020 was similar. No woman had received the first dose in 2021. Three women had completed their 3rd dose of vaccination. The numbers of women who were pregnant before dose 1, after dose 1, and after dose 2 was 1, 2, and 2, respectively. No woman was pregnant after dose 3. One woman received G4 within 30 days prior to conception and four women received it in the first trimester of their pregnancy. One woman delivered after vaccination of dose 1, three after dose 2, and one after dose 3 (Table 8).

Table 2. Autoimmune disorder cases in women with G4 exposure*

	Potential cases identified, N	Cases reviewed by clinicians for case validation, n1 (n1/N%)	Confirmed cases, n2 (n2/N%)
Total autoimmune disorder†	314	312 (99.36)	113 (35.99)
Graves' disease	57	57 (100)	24 (42.11)
Hashimoto's disease	194	194 (100)	71 (36.60)
T1DM	2	1 (50.00)	0 (0)
SLE	4	4 (100)	0 (0)
Multiple sclerosis	2	1 (50.00)	0 (0)
Optic neuritis	9	9 (100)	1 (11.11)
Uveitis	46	46 (100)	17 (36.96)

* New-onset autoimmune disorder cases within 6 months after any dose of G4 in women who received at least one dose of G4 and no other HPV vaccine.
† This category is not mutually exclusive, i.e., one woman may have more than one autoimmune disorder.

Table 3. Characteristics of women with G4 exposure who had new onset Graves' disease

Variables	G4
Total	24
Age at first dose (years), mean±SD	31.49±6.57
20-25 years, n (%)	6 (25.00)
26-30 years, n (%)	4 (16.67)
31-35 years, n (%)	7 (29.17)
36-40 years, n (%)	5 (20.83)
41-45 years, n (%)	2 (8.33)
Year at first dose, n (%)	
2018	5 (20.83)
2019	5 (20.83)
2020	14 (58.33)
2021[†]	0 (0)
Number of doses received, mean±SD, median (IQR), range	2.92±0.28, 3 (0), 2-3
Only 1 dose, n (%)[§]	0 (0)
2 doses, n (%)[§]	2 (8.33)
3 doses, n (%)[§]	22 (91.67)
Residence region, n (%)	
Urban	8 (33.33)
Rural	8 (33.33)
Unknown	8 (33.33)
Marital status, n (%)	
Unmarried	2 (8.33)
Married	0 (0)
Divorced	0 (0)
Widowed	0 (0)
Unknown	22 (91.67)
Diagnosis time, n (%)	
After dose 1	13 (54.17)
After dose 2	10 (41.67)
After dose 3	1 (4.17)
Time interval between last dose of vaccination before diagnosis and diagnosis (day), mean±SD, median (IQR), range	53.83±35.44, 48.50 (50.00), 0-118

[*] At least 1 dose of G4
[†] 2021 data collection cut-off: Mar 31st
[§] Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G4 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

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Table 4. Characteristics of women with G4 exposure who had new onset Hashimoto's disease

Variables	G4
Total *	71
Age at first dose (years), mean±SD	34.37±5.12
20-25 years, n (%)	1 (1.41)
26-30 years, n (%)	21 (29.58)
31-35 years, n (%)	20 (28.17)
36-40 years, n (%)	20 (28.17)
41-45 years, n (%)	9 (12.68)
Year at first dose, n (%)	
2018	10 (14.08)
2019	10 (14.08)
2020	51 (71.83)
2021†	0 (0)
Number of doses received, mean±SD, median (IQR), range	2.92±0.28, 3 (0), 2-3
Only 1 dose, n (%)§	0 (0)
2 doses, n (%)§	6 (8.45)
3 doses, n (%)§	65 (91.55)
Residence region, n (%)	
Urban	34 (47.89)
Rural	25 (35.21)
Unknown	12 (16.90)
Marital status, n (%)	
Unmarried	5 (7.04)
Married	29 (40.85)
Divorced	0 (0)
Widowed	0 (0)
Unknown	37 (52.11)
Diagnosis time, n (%)	
After dose 1	23 (32.39)
After dose 2	47 (66.20)
After dose 3	1 (1.41)
Time interval between last dose of vaccination before diagnosis and diagnosis (day), mean±SD, median (IQR), range	68.25±35.92, 63 (61), 0-145

* At least 1 dose of G4
† 2021 data collection cut-off: Mar 31st
§ Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G4 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

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Table 5. Characteristics of women with G4 exposure who had new onset uveitis

Variables	G4
Total *	17
Age at first dose (years), mean±SD	34.70±6.07
20-25 years, n (%)	1 (5.88)
26-30 years, n (%)	3 (17.65)
31-35 years, n (%)	8 (47.06)
36-40 years, n (%)	1 (5.88)
41-45 years, n (%)	4 (23.53)
Year at first dose, n (%)	
2018	3 (17.65)
2019	5 (29.41)
2020	9 (52.94)
2021†	0 (0)
Number of doses received, mean±SD, median (IQR), range	2.88±0.33, 3 (0), 2-3
Only 1 dose, n (%)§	0 (0)
2 doses, n (%)§	2 (11.76)
3 doses, n (%)§	15 (88.24)
Residence region, n (%)	
Urban	10 (58.82)
Rural	6 (35.29)
Unknown	1 (5.88)
Marital status, n (%)	
Unmarried	4 (23.53)
Married	0 (0)
Divorced	0 (0)
Widowed	0 (0)
Unknown	13 (76.47)
Diagnosis time, n (%)	
After dose 1	12 (70.59)
After dose 2	5 (29.41)
After dose 3	0 (0)
Time interval between last dose of vaccination and diagnosis (day), mean±SD, median (IQR), range	53.06±36.09, 47 (30), 6-119

* At least 1 dose of G4

† 2021 data collection cut-off: Mar 31st

§ Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G4 as of the cut-off date

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

Table 6. Characteristics of women with maternal G4 exposure*

Variables	G4
Total†	168
Age at first dose (years), mean±SD	30.07±3.98
20-25 years, n (%)	27 (16.07)
26-30 years, n (%)	74 (44.05)
31-35 years, n (%)	51 (30.36)
36-40 years, n (%)	15 (8.93)
41-45 years, n (%)	1 (0.60)
Residence region, n (%)	
Urban	74 (44.05)
Rural	71 (42.26)
Unknown	23 (13.69)
Education, n (%)	
University and above	142 (84.52)
Senior high school	16 (9.52)
Junior school and below	8(4.76)
Unknown	2 (1.19)
Occupation, n (%)	
Factory worker	31 (18.45)
Agriculture worker	10 (5.95)
Administrator / manager / professional / technical	44 (26.19)
Service worker	16 (9.52)
Other	61 (36.31)
Unknown	6 (3.57)
Cigarette smoking status, n (%)	
Non-smoker	167 (99.40)
Smoker	1 (0.60)
Unknown	0 (0)
Alcohol drinking status, n (%)	
Non-drinker	167 (99.40)
Drinker	1 (0.60)
Unknown	0 (0)
Gravidity, mean±SD, median (IQR), range	1.79±1.29, 1 (1), 1-7
1, n (%)	105 (62.50)
2, n (%)	27 (16.07)
≥3, n (%)	36 (21.43)
Parity, mean±SD, median (IQR), range	0.21±0.41, 0 (0), 0-1
0, n (%)	129 (78.66)
1, n (%)	1 (21.34)
2, n (%)	0 (0)
≥3, n (%)	0 (0)
Year at first dose, n (%)	
2018	70 (41.67)
2019	63 (37.50)
2020	35 (20.83)
2021 §	0 (0)
Number of doses received, mean±SD, median (IQR), range	2.24±0.85, 3 (2), 1-3
1 dose, n (%) ‖	45 (26.79)

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Variables	G4
2 doses, n (%) [‖]	38 (22.62)
3 doses, n (%) [‖]	85 (50.60)
Conception time, n (%)	
Before dose 1	40 (23.81)
After dose 1	42 (25.00)
After dose 2	59 (35.12)
After dose 3	27 (16.07)
Vaccination time of the first dose in risk windows, n (%)	
Within 30 days prior to conception	72 (42.86)
In the 1st trimester (0-12 weeks)	91 (54.17)
In the 2nd trimester (13-28 weeks)	1 (0.60)
In the 3rd trimester (29-40 weeks or above)	4 (2.38)

[*] Only women with maternal vaccination exposure and who delivered at 28 gestational weeks or above or gave birth to a baby with birthweight no less than 1000g (if the gestational age at delivery is unknown) are included in the analysis.
[†] At least 1 dose of G4
[§] 2021 data collection cut-off: Mar 31st
[‖] Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G4 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

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Table 7. Adverse pregnancy outcomes in infants of women with maternal G4 exposure*

Adverse pregnancy outcome	Potential cases identified, n	Cases reviewed by clinicians in case validation, n	Confirmed cases, n
Stillbirth	0	0	0
Anencephaly	0	0	0
Spina bifida	0	0	0
Encephalocele	0	0	0
Congenital hydrocephalus	0	0	0
Cleft palate	0	0	0
Cleft lip	0	0	0
Cleft palate with cleft lip	0	0	0
Microtia/anotia	0	0	0
Other malformations of outer ear	0	0	0
Esophageal atresia or stenosis	0	0	0
Rectoanal atresia or stenosis	0	0	0
Hypospadias	0	0	0
Exstrophy of urinary bladder	0	0	0
Talipes equinovarus	0	0	0
Polydactyly	0	0	0
Syndactyly	0	0	0
Limb reductions	0	0	0
Congenital diaphragmatic hernia	0	0	0
Exomphalos	0	0	0
Gastroschisis	0	0	0
Conjoined twins	0	0	0
Down syndrome	0	0	0
Congenital heart diseases	5	5	5

* Only women with maternal vaccination exposure and who delivered at 28 gestational weeks or above or gave birth to a baby with birthweight no less than 1000g (if the gestational age at delivery is unknown) are included in the analysis.

Table 8. Characteristics of infants with congenital anomalies born to women with maternal G4 exposure and their mothers

Variables	G4
Infants	
Total number of infants with congenital anomalies born to women with maternal G4 exposure*	5
Age at diagnosis (months), mean±SD	1.33±0.86
Male, n (%)	3 (60.00)
Congenital anomalies, n (%)	
Congenital heart diseases	5 (100)
Mother	
Total number of women with maternal G4 exposure who gave births to infants with congenital anomalies*	5
Age at first dose (years), mean±SD	31.45±6.30
20-25 years, n (%)	1 (20.00)
26-30 years, n (%)	2 (40.00)
31-35 years, n (%)	1 (20.00)
36-40 years, n (%)	0 (0.00)
41-45 years, n (%)	1 (20.00)
Year at first dose, n (%)	
2018	2 (40.00)
2019	1 (20.00)
2020	2 (40.00)
2021†	0 (0)
Residence region, n (%)	
Urban	1 (20.00)
Rural	4 (80.00)
Unknown	0 (0)
Education, n (%)	
University and above	4 (80.00)
Senior high school	0 (0)
Junior school and below	0 (0)
Unknown	1 (20.00)
Occupation, n (%)	
Factory worker	0 (0)
Agriculture worker	0 (0)
Administrator / manager / professional / technical	0 (0)
Service worker	0 (0)
Other	0 (0)
Unknown	5 (100)
Cigarette smoking status, n (%)	
Non-smoker	5 (100)
Smoker	0 (0)
Unknown	0 (0)
Alcohol drinking status, n (%)	
Non-drinker	5 (100)
Drinker	0 (0)
Unknown	0 (0)

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Variables	G4
Gravidity, mean±SD/median (IQR), range	2.20±2.17, 1 (1), 1-6
1, n (%)	3 (60.00)
2, n (%)	1 (20.00)
≥3, n (%)	1 (20.00)
Parity, mean±SD/median (IQR), range	0.20±0.45, 0 (0), 0-1
0, n (%)	4 (80.00)
1, n (%)	1 (20.00)
2, n (%)	0 (0)
≥3, n (%)	0 (0)
Gestation age at delivery (weeks), mean±SD/median (IQR), range	38.40±1.14, 38 (1), 37-40
Multiple pregnancies, n (%)	
Singleton	5 (100)
Twins	0 (0)
>2 fetus	0 (0)
Total doses received, median (IQR), range	2.40±0.89, 3 (1), 1-3
Only 1 dose, n (%)[§]	1 (20.00)
2 doses, n (%)[§]	1 (20.00)
3 doses, n (%)[§]	3 (60.00)
Conception time, n (%)	
Before dose 1	1 (20.00)
After dose 1	2 (40.00)
After dose 2	2 (40.00)
After dose 3	0 (0.00)
Vaccine time, n (%)	
Vaccination within 30 days prior to conception	1 (20.00)
Vaccination in the 1st trimester (0-12weeks)	4 (80.00)
Vaccination in the 2nd trimester (13-28 weeks)	0 (0)
Vaccination in the 3rd trimester (29-40 weeks or above)	0 (0)
Delivery time, n (%)	
After dose 1	1 (20.00)
After dose 2	3 (60.00)
After dose 3	1 (20.00)

[*] At least 1 dose of G4
[†] 2021 data collection cut-off: Mar 31st
[§] The number and percentage of women who received only 1 dose, 2 doses, and 3 doses of G4 during follow-up.

10.4 Main results

A total of 195,593 doses of G4 were administered to 76,212 women aged 20 to 45 years who had received no other HPV vaccine before they were vaccinated with G4 in Ningbo over the study period from 9 January 2018 to 31 March 2021.

Among the women who were exclusively vaccinated with G4, a total of 113 women were diagnosed with a new-onset of pre-specified AIs, including 24 cases of Graves' disease, 71 cases of Hashimoto's disease, 1 case of optic neuritis, and 17 cases of uveitis.

A total of 168 women had received G4 during their pregnancy or within 30 days before conception. Among these women, no stillbirth was observed. Five infants born to mothers with pregnancy exposure to G4 were diagnosed with congenital heart diseases during the observation period of 3 months from birth.

10.5 Other analyses

CCI [redacted] on the G9 report, the proportion and incidence density of AIs in women received G4 were calculated. Person-time for G4 vaccinated women was calculated, starting at the date when the women received their first dose of G4. The follow-up time ended at the date when a pre-specified AIs was detected, six months after a last dose of G4 that a woman received or on 31March 2021, whatever came first.

The mean follow-up time of the 76,212 women vaccinated with G4 was 0.71 year, with an overall follow-up time of 54300.63 person-years. A total of 24 cases of Graves' disease, 71 cases of Hashimoto's disease, 1 case of optic neuritis, and 17 cases of uveitis were identified during the follow-up period, corresponding to an incidence density of respectively 44.21 cases per 100,000 person-years (95%CI: 29.63-65.96), 130.84 cases per 100,000 person-years (95%CI: 103.69-165.11), 1.84 cases per 100,000 person-years (95% CI: 0.26-13.07), and 31.31 cases per 100,000 person-years (95% CI: 19.47-50.37). The respective proportions were 31.49 per 100,000 persons (95% CI: 21.11-46.98) for Graves' disease, 93.16 per 100,000 persons (95% CI: 73.83-117.54) for Hashimoto's disease, 1.31 per 100,000 persons (95% CI: 0.19-9.31) for optic neuritis, and 22.31 per 100,000 persons (95% CI: 13.87-35.88) for uveitis (Table 9).

Table 9. AIs disease occurrence among 76,212 women vaccinated with G4*

	Number of cases	Proportion (/100,000), 95% CI	Incidence density (/100,000 person-year), 95% CI
Graves' disease	24	31.49 (21.11, 46.98)	44.21 (29.63, 65.96)
Hashimoto's disease	71	93.16 (73.83, 117.54)	130.84 (103.69, 165.11)
Optic neuritis	1	1.31 (0.19, 9.31)	1.84 (0.26, 13.07)
Uveitis	17	22.31 (13.87, 35.88)	31.31 (19.47, 50.37)

* New-onset of 7 pre-specified AI cases within 6 months after any dose of G4 in women who received at least one dose of G4 and no other HPV vaccine.

10.6 Adverse events/adverse reactions

This is a surveillance study based on a secondary analysis of data that were routinely collected in Ningbo and preserved in the NRHIP. Specific case identification methods were applied to identify pre-specified AIs and adverse pregnancy outcomes (stillbirth and major congenital anomaly) in NRHIP. Medical care information in NRHIP was extracted and reviewed based on the pre-specified methods. Adverse events (AEs) and product quality complaints (PQCs) were not actively solicited in this study according to the study design, however, during review of medical records or physician notes (paper or electronic) to collect data as required by the protocol, the SAR/NSAR and other events which meet criteria were to be reported.

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[redacted]

11 DISCUSSION

11.1 Limitations

The NRHIP is designed for routine health care management, rather than for research purposes. This surveillance occurred within the NRHIP, which is a cloud-based health information platform that has not been tested or used for surveillance of vaccine safety before. Conditions and diseases diagnosed and treated outside Ningbo city are not captured in the NRHIP. Also, while medical records are routinely entered into the NRHIP, some factors such as diagnostic codes may vary among institutions (e.g., hospitals) that report data to the NRHIP. To address this issue, study-specific case identification methods were developed and included a variety of source data terminology, such as diagnosis codes and free text of diagnosis in EMRs in the NRHIP. In addition, expert administrators of the NRHIP, as well as experts familiar with clinical practice and medical coding in Ningbo, were consulted for their input as case identification methods were developed. In addition, case validation in this surveillance relied on the decisions made by clinical experts based on the medical records available in NRHIP, which might not be complete.

Currently, the NRHIP is only accessible to qualified technicians of Ningbo CDC. Downloading data from the NRHIP is prohibited. However, with the appropriate approvals, study investigators from Peking University could access de-identified data and perform analyses for research purposes.

Linkage of vaccination data with AI cases (to identify AI cases among vaccinated women) and pregnant women (to identify women exposed to vaccine during or shortly before pregnancy) was critical in this study. In an analysis of feasibility of using the NRHIP to conduct this surveillance, the proportion of identifiers for women aged 16 to 45 years old in 2017 that could not be linked with AIs was relatively small, suggesting that this may not impact study findings to an important degree.

After review of the study report, it has been recommended by SRC to conduct comparative studies between vaccinated and unvaccinated population over the same period in the future. This is a surveillance study to monitor the occurrence of new onset AIs and adverse pregnancy outcomes in women who received G4, and the occurrence of AIs among

unvaccinated women was not assessed in this study. As vaccination with G4 is driven by women's willingness to be vaccinated and doses of G4 are paid out-of-pocket, vaccinated women are expected to be different from unvaccinated women in many ways, that would result in potential biases and confounding for comparative studies. Differences in the socioeconomic status leads to unequal uptake of the vaccine and vaccinated women are more likely to receive preventive health care services and may result in a detection bias of study outcomes. Due to the database design of this study, these variables could not be collected and analyzed in this study. Therefore, a comparison between vaccinated and unvaccinated groups would not have been appropriate in this study.

Another limitation of the study is that for some AIs, the onset date can precede the actual diagnosis date. This study adapted the diagnosis date which was used as a proxy for AIs onset. Also, for the determination of pregnancy outcome following maternal exposure, spontaneous abortions and elective termination (for any reason) could not be reported as these are considered sensitive data in Ningbo. Therefore, the adverse pregnancy outcome surveillance in this study is limited to stillbirth and 23 pre-defined congenital anomalies following live births.

11.2 Interpretation

11.2.1 Autoimmune disorders

A total of 113 women were diagnosed with a new-onset case of pre-specified AIs among the study population of 76,212 women aged 20 to 45 years old who had received no other HPV vaccine before they were vaccinated with G4 in Ningbo over the study period from 9 January 2018 to 31 March 2021. Among these 113 women, there were 24 women who had Graves' disease, 71 women with Hashimoto's disease, 1 woman with optic neuritis, and 17 women with uveitis. No new-onset cases of T1DM, SLE, or multiple sclerosis were identified among the study population.

We did not assess the occurrence of new-onset AI cases among unvaccinated women or in the general population. However, the results can be put into context using data from published literature. As recommended by SRC, the measurement units of data from the

literature and this study were harmonized, and key information from literature including characteristics of subjects was added to help interpret the study results.

In a prospective cohort study that examined the effect of regional differences in iodine intake on the incidence of thyroid diseases among more than 3,000 participants in northeastern China between 1999 and 2004, the 5-year cumulative incidence of Graves' disease ranged from 0.6% (600 per 100,000 persons) to 0.8% (800 per 100,000 persons), and the incidence of Hashimoto's thyroiditis ranged between 0.0% (0 per 100,000 persons) and 0.5% (500 per 100,000 persons) in the different regions {089XWB}. The prevalence of Graves' disease decreased over the two decades. Based on a cross-sectional survey conducted in China among a representative sample of 78,470 participants between 2015 to 2017, the female-specific prevalence of Graves' disease was 0.69% (95% CI: 0.58%-0.82%) (690 cases per 100,000 persons, 95% CI: 580-820 cases per 100,000 persons) and the prevalence was 0.55%, 0.57% and 0.59% (550, 570, and 590 cases per 100,000 persons) among the total population aged 18 to 29, 30-39, and 40-49 years, respectively. As a subtype of lymphocytic thyroiditis, the main symptom of Hashimoto's disease is overt hypothyroidism. The prevalence of Hashimoto's thyroiditis was not estimated in that survey, but the prevalence of overt hypothyroidism was 1.53% (95% CI: 1.33%-1.75%) (1,530 cases per 100,000 persons, 95% CI: 1,330–1,750 cases per 100,000 persons) in women. The prevalence increased with age from 0.45% (450 cases per 100,000 persons) in the 18-29 age group to 2.09% (2,090 cases per 100,000 persons) in the ≥70 age group. The prevalence was 0.70% (700 cases per 100,000 persons) and 1.26% (1,260 cases per 100,000 persons) in the age groups 30 to 39 years and 40 to 49 years, respectively {089XWF}. In a cross-sectional study in Zhejiang province conducted in 2011 (in which Ningbo city is located), the proportions of Graves' disease and lymphocytic thyroiditis were 0.2% (200 cases per 100,000 persons) and 0.3% (300 cases per 100,000 persons) among adult women, respectively and proportions of Graves' disease and lymphocytic thyroiditis were 0.2% (200 cases per 100,000 persons) and 0.3% (300 cases per 100,000 persons) in people aged 18 to 44 years, respectively {089XWH}. A previous systematic review was conducted to review HPV vaccine post-marketing safety studies and to summarize risk estimates of autoimmune diseases {07YQYT}. The results of this study suggested that there were no increased risks of Graves'

disease, T1DM, SLE, multiple sclerosis, and optic neuritis associated with G4 vaccination. But this study found a higher risk of Hashimoto's disease after G4 vaccination (OR=1.25, 95% CI: 1.09–1.44). However, the higher risk of Hashimoto's disease is mainly driven by one study, in which after further evaluation, the researchers demonstrated that most of the new onset cases were likely preexisting cases and no consistent evidence for a safety signal for autoimmune thyroid conditions in general was observed among vaccinated subjects {03RTZF}. In our study, 24 women were diagnosed with new-onset Graves' disease and 71 women were diagnosed with Hashimoto's disease within 6 months after G4 vaccination among 76,212 women who received G4 between January 2018 and March 2021. The incidence densities of Graves' disease and Hashimoto's disease after G4 vaccination were 44.21 (95% CI: 29.63-65.96) cases per 100,000 person-years and 130.84 (95% CI: 103.69-165.11) cases per 100,000 person-years, respectively.

We did not identify any published study that reported the incidence or prevalence of optic neuritis in mainland China, but one study had been conducted in Taiwan. In this 5-year longitudinal, nationwide, population-based study, 191,761 subjects were involved, and the 5-year cumulative incidence rates were 1.24 cases per 1000 persons (124 cases per 100,000 persons) and 2.94 cases per 1000 persons (294 cases per 100,000 persons) in women aged 20-39 years and 40-59 years from 2000 to 2004 {089YJF}. One G4 vaccinated woman was diagnosed with new-onset optic neuritis in our study. The incidence density was 1.84 (95% CI: 0.26-13.07) cases per 100,000 person-years, and the proportion was 1.31 (95% CI: 0.19-9.31) per 100,000 persons.

There is limited data on the epidemiology of uveitis in China. In a community-based survey, conducted among 10,500 participants in the Guangdong province, the prevalence of uveitis was 0.140% (140 cases per 100,000 persons) in women {089YK0}. In a population-based cohort study using medical claims data in Taiwan between 2003 to 2008, the incidence density was 99.6 cases per 100,000 person-years in women and increased with age. The incidence was respectively 79.7, 105.2, and 125.9 cases per 100,000 person-years among subjects aged 16-25, 26-35, and 36-45 years {089XRY}. The epidemiology of uveitis varies worldwide with an incidence ranging from 17 to 52 cases per 100,000 person-years, and a prevalence from 38 to 714 cases per 100,000 persons {089XF9}. The majority of this data is

from developed countries, and the frequency might be different in China due to genetic and environmental factors. Our study identified 17 new-onset cases of uveitis among 76,212 women aged 20 to 45 years who had received G4 between 9 January 2018 and 31 March 2021. The incidence density was 31.31 (95% CI: 19.47-50.37) cases per 100,000 person-years, as well as the proportion was 22.31 (95% CI: 13.87-35.88) per 100,000 persons.

In our study, no new-onset cases of T1DM, SLE, and multiple sclerosis were observed in women who received G4 during the study period. All these diseases are rare in the general population. According to a population-based surveillance conducted in 505 hospitals across China using national registration system during 2010-2013, the incidence density of T1DM was 0.93 cases per 100,000 person-years in women. And the incidence decreased with age from 2.68 cases per 100,000 person-years in the 10-14 age group to 0.37 cases per 100,000 person-years in the ≥75 age group. The incidence was 1.11, 1.19, 1.02, 0.73, 0.54, and 0.54 case per 100,000 person-years among subjects aged respectively 20-24, 25-29, 30-34, 35-39, 40-44, and 45-49 years {089XFB}. Currently, the epidemiology of SLE has only been assessed regionally in China. In a population-based epidemiological investigation conducted in Beijing, a community-based survey was carried out using a screening questionnaire among 14,642 individuals, and the prevalence of SLE was 0.06% (60 cases per 100,000 persons) among females {089XFD}. In another a population-based case–control study conducted in Anhui province, the age-standardized prevalence of SLE was 36.03 cases per 100,000 persons with a female-specific prevalence of 70.28 cases per 100,000 persons. The prevalence increased with age, reaching a peak in the age group from 40 to 49 years. The prevalence was 83.73, 109.94, and 173.54 per 100,000 persons among women aged respectively 20-29, 30-39, and 40-49 years {089XFF}. For multiple sclerosis, according to the data from Basic Medical Insurance for Urban Employee from 6 provinces in China, the prevalence was 2.44 cases per 100,000 persons from 2012 to 2016. The prevalence in women was highest among those from 30 to 34 years old, and the prevalence was 3.44, 5.55, 4.90, 4.34, and 4.19 per 100,000 persons in the 20-29, 30-34, 35-39, 40-44, 45-49 years old age groups, respectively {089XFH}.

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Table 10. AIs disease occurrence among general population from published literatures

	Study period	Region	Sex	Age (year)	Indicator	Estimation (95% CI)
Graves' disease	1999-2004	Northeast of China	F/M	All ages	5-year cumulative incidence	0.6%-0.8%
	2011	Zhejiang Province	F	⩾18	proportion	0.20%
			F/M	19~44		0.20%
	2015-2015	China	F	All ages	prevalence	0.69% (0.58%-0.82%)
			F/M	18~29		0.55%
				30~39		0.57%
				40~49		0.59%
Hashimoto's disease	1999-2004	Northeast of China	F/M	All ages	5-year cumulative incidence	0.0%-0.5%
	2011	Zhejiang Province	F	⩾18	proportion	0.30%
			F/M	19~44		0.30%
	2015-2015	China	F	All ages	prevalence	1.53% (1.33%-1.75%)
			F/M	18~29		0.45%
				30~39		0.70%
				40~49		1.26%
Optic neuritis	2000-2004	Taiwan Province	F	20-39	5-year cumulative incidence	1.24/1,000 persons
				40-59		2.94/1,000 persons
Uveitis	2002	Guangdong Province	F	All ages	prevalence	0.14%
	2003-2008	Taiwan Province	F	All ages	incidence density	99.6/100,000 PY
			F/M	16-25		79.7/100,000 PY
				26-35		105.2/100,000 PY
				36-45		125.9/100,000 PY

11.2.2 Adverse pregnancy outcomes

A total of 168 women received G4 during their pregnancy or within 30 days before conception. Among these 168 women, no stillbirth was observed. Five of the infants born to a mother with pregnancy exposure to G4 were diagnosed with congenital heart diseases within 3 months after birth. A number of factors may confound this association as information including medications taken during pregnancy, occupational exposures, health history of the mother or family disease history that are not available in the database.

Although G4 are not indicated for use during pregnancy, sometimes the vaccines are inadvertently administered during pregnancy. To date, no unfavorable pregnancy outcomes associated with vaccination during pregnancy have been identified. Pregnancy exposure has been studied in a pregnancy registry for G4, and results have been published {046L2P}. Several cohort studies have also reported on pregnancy safety. In a cohort of all women in Denmark who had a pregnancy between 2006 and 2013, no significant differences in adverse pregnancy outcomes (spontaneous abortion, stillbirth, major birth defect, small size for gestational age, low birth weight, and preterm birth) were found in infants of vaccinated women, compared to women who had not received G4 or G9 during their pregnancy {04W257}. Other population-based observational studies (from Scandinavia and California) had similar findings {083KQR, 04W256, 04W258}. A systematic review published in 2020 suggested that inadvertent G4 vaccination during pregnancy was not associated with significantly greater risks of adverse pregnancy outcomes, including spontaneous abortion, stillbirth, small for gestational age, preterm birth, and birth defects {089XS2}.

Data on the epidemiology of congenital heart diseases in China shows an increasing trend in recent years. As reported in a comprehensive systematic review of the birth prevalence of congenital heart diseases in China in 2020, the total birth prevalence increased continuously over time in the past decades {089XS5}. In a large-scale hospital-based multicenter study conducted in Zhejiang province, where Ningbo is located, the incidence of congenital heart disease was reported to be much higher than in other parts of China {089XS8}. In a retrospective analysis on congenital anomaly using maternal and neonatal specific program data in Ningbo, the most common congenital anomalies were congenital heart diseases.

Between September 2011 and August 2014, a total of 4,175 infants were diagnosed with congenital heart diseases among 256,504 new births. The proportion of congenital heart diseases was 162.8 cases per 10,000 newborns, with a sharp increasing trend raising from 135.9/10,000 to 212.1/10,000 during the study period {089XSD}. Another study in Zhejiang Province also reported this increasing trend and the birth prevalence of congenital heart disease was highest in 2015 with a rate of 309.5/10,000 in 2015 and was stable in 2016 at a rate of 304.7/10,000 {089ZCZ}. In our study, 5 infants born to mothers who had received G4 during their pregnancy or within 30 days before conception were diagnosed with congenital heart diseases within 3 months after birth. All of the 5 cases out of 168 vaccinated mothers (298/10,000) were validated by clinicians according to Chinese congenital anomaly guidelines {089ZCY}.

11.3 Generalizability

This is a database study based on NRHIP, and all eligible subjects 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. The socioeconomic status of the Ningbo female population might be higher compared to 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 where the socioeconomic level is lower. These geographical and socioeconomic factors need to be considered when extrapolating the results from Ningbo to other regions in China.

12 OTHER INFORMATION

Not applicable in this report.

13 CONCLUSION

Between 9 January 2018 and 31 March 2021, a total of 195,593 doses of G4 were administered to 76,212 women who 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.

During the study period, a total of 113 women who had received at least one dose of G4, were diagnosed with a new-onset case of pre-specified AIs, including 24 cases of Graves' disease, 71 cases of Hashimoto's disease, 1 case of optic neuritis, and 17 cases of uveitis. No cases of T1DM, SLE, or MS were identified among the study population. A total of 168 women had received G4 during their pregnancy or within 30 days before conception. Among these 168 women, no stillbirth was observed. Among the infants born to a mother with G4 pregnancy exposure, 5 were diagnosed with congenital heart diseases within 3 months after birth.

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In our study, no new safety concerns were identified.

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Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	V503-055/Version 2.0	21-May-2020	Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women
2	V503-055/DMP Version 3.0	18-Jan-2022	Data Management Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women
	V503-055/SAP Version 1.1	11-Feb-2022	Statistical Analysis Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

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Annex 2Study Protocol

Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

2. Annex 2 HPV
HPV PMC safety s

Confidential

Annex 3Study Data Management Plan

Data Management Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

Annex 3 HPV
PMC safety study

Annex 4Study Statistical Analysis Plan

Statistical Analysis Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

4. Annex 4 HPV PMC safety study

PASS INFORMATION

Title	Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women
Version identifier of the final study report	GARDASIL ®9 Final Study Report V503-055, VERSION 1.0
Date of last version of the final study report	N/A
EU PAS register number	EUPAS36132
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, 60µg 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
Research question and objectives	To monitor the occurrence of new onset of 7 pre-specified autoimmune disorders and adverse pregnancy outcomes in a cohort of Chinese women who received G4 or G9
Country(-ies) of study	China
Author	Prof. 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

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXES

1 ABSTRACT

Title

Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

Keywords

GARDASIL®, GARDASIL®9; Post-Marketing Surveillance; HPV; Autoimmune Disorder; Pregnancy Outcome

Rationale and background

Upon licensure of GARDASIL® (G4) in 2017 and GARDASIL®9 (G9) in 2018 in China, [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.

Research question and objectives

To monitor the occurrence of new onset of 7 pre-specified AIs and adverse pregnancy outcomes in a cohort of Chinese women who received G4 or G9.

Study design

Surveillance within a database system in the Ningbo Regional Health Information Platform (NRHIP); observational design.

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.

Subjects and study size, including dropouts

Women between ages of 16 and 45 years old during the study period (i.e., age-eligible for vaccination with G4 and/or G9) who were residents of Ningbo, whose medical care information was available in the NRHIP, and who received at least one dose of G4 or G9 as part of routine health care. Ningbo has a population of approximately 2.8 million local female residents between the ages of 16-45 years old.

For the pregnancy surveillance, the study population includes women who had pregnancy exposure to G4 or G9, and their infants.

This is a descriptive study, no sample size calculation and no hypothesis testing were done.

Variables and data sources

Exposure:

For AIs surveillance: Receipt of at least one dose of G4 or G9 during the study period.

For pregnancy surveillance: Receipt of at least one dose of G4 or G9 during the study period, up to 30 days prior to conception or anytime during pregnancy.

Outcomes:

For AIs surveillance: Pre-specified new-onset of 7 AIs (systemic lupus erythematosus, Graves' disease, Hashimoto's disease, type 1 diabetes, multiple sclerosis, optic neuritis and uveitis) diagnosed in the study population within 6 months after each dose of G4 or G9.

For pregnancy surveillance: Stillbirth and major congenital anomaly in infants of women in the study population with G4 or G9 vaccination up to 30 days prior to conception or during pregnancy.

The pre-specified AIs and pregnancy outcomes were identified from the NRHIP using study-specific case identification methods.

Results

A total of 102,670 doses of G9 were administered to 41,609 women aged 16 to 26 years old who had received no other HPV vaccine in Ningbo over the study period from 25 January 2019 to 31 March 2021. Sixteen women had received a mixed G4/G9 regimen representing a total of 55 doses of G4 and G9.

A total of 36 women were diagnosed with a new-onset case of pre-specified AIs, including 11 cases of Graves' disease, 21 cases of Hashimoto's disease, and 4 cases of uveitis within 6 months of receipt of a dose of G9.

A total of 50 women had received G9 during their pregnancy or within 30 days before conception. Among these 50 women, no stillbirth was observed. One of the infants born to a mother with pregnancy exposure was diagnosed with microtia during the observation period of 3 months from birth.

Discussion

In this large database study, 36 new-onset cases of 7 pre-specified AIs within 6 months of receipt of a dose of G9 as well as 1 adverse pregnancy outcome in women exposed to G9 during their pregnancy or 30 days before pregnancy were identified in 41,609 women who received a total of 102,670 doses of G9. This study used a broad case identification method, and rigorous review and case validation was conducted by clinical experts following pre-specified procedures.

[redacted]

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[redacted]

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

Names and affiliations of principal investigators

Prof. PPD Peking University Health Science Center, China

2 LIST OF ABBREVIATIONS

AE	Adverse Event
AEFI	Adverse Events Following Immunization
AIs	Autoimmune Disorder
CDC	Center for Disease Control and Prevention
CDE	Center for Drug Evaluation
CI	Confidence Interval
EMR	Electronic Medical Record
G4	GARDASIL®
G9	GARDASIL®9
GPP	Good Pharmacoepidemiology Practice
HGRAC	Human Genetic Resource Administration of China
HPV	Human Papillomavirus
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
PSUR	Periodic Safety Update Report
SAR	Serious Adverse Reaction
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
SQI	Significant Quality Issue
SRC	Safety Review Committee
T1DM	Type 1 Diabetes

3 INVESTIGATORS

Principal investigator	Prof. 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	Prof. PPD Peking University Health Science Center, China
Investigators	Prof. PPD, Peking University Health Science Center Dr. PPD, Peking University Health Science Center

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
Safety Review Committee (SRC) chairman	PPD
SRC member	
SRC member	
SRC member	
SRC member	
SRC member	
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	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-Mar-2022	
Final report of study results	Prior to license renewal	21-Apr-2022	

6 RATIONALE AND BACKGROUND

6.1 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 deaths 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]. Cervical cancer is 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.

As a measure of primary prevention of cervical cancer, the Chinese government has approved bivalent, quadrivalent, and nonavalent HPV 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 the nonavalent vaccine (GARDASIL®9). GARDASIL® (G4) targets HPV types 6, 11, 16, and 18 and was approved in China for 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.

6.2 Rationale

While a favorable safety profile for G4 and G9 has been seen in the pre- and post-marketing setting, the safety of these vaccines administered to Chinese women as part of routine health care has not been studied. [redacted] MSD conducted a surveillance of pregnancy and autoimmune outcomes following routine vaccination of Chinese women 16-45 years old. This database surveillance

used a regional health information platform in Ningbo (Ningbo Regional Health Information Platform, NRHIP) to monitor safety of G4 and G9 vaccination in Chinese women.

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

7 RESEARCH QUESTION AND OBJECTIVES

- ✓ To monitor within the NRHIP the diagnosis of 7 pre-specified new-onset AIs diagnosed within a period of up to 6 months after each dose of G4 or G9 in Chinese women who were age-eligible for vaccination at any time during the study period, based on data from the NRHIP.
- ✓ To monitor within the NRHIP the occurrence of stillbirth and major congenital anomaly in infants of Chinese women who were age-eligible for vaccination at any time during the study period and who were inadvertently vaccinated with G4 or G9 up to 30 days prior to conception or anytime during pregnancy, based on data from the NRHIP.

8 AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
NA				

9 RESEARCH METHODS

9.1 Study design

This database study was designed for the safety surveillance of G4 or G9 vaccination in Chinese women. This study was conducted using the existing computerized databases and infrastructure at the NRHIP [2]. There are two components in this surveillance: AIs safety and pregnancy safety, described below.

9.1.1 AIs surveillance

In consultation with national and local experts and China Center for Drug Evaluation (CDE) (experts consultation meeting on December 20, 2018 and CDE consultation meeting on June 12, 2019), there was alignment that safety research within the NRHIP is possible, but that accurate endpoint assessment (i.e., disease diagnosis) is critical, because establishing vaccine safety requires high quality data on both the vaccination status and the disease outcome under surveillance. There was also alignment that this is an area in which the NRHIP requires further, ongoing development. High-level surveillance (i.e., broad but not specific case identification methods) of a multitude of AIs at this stage in the development of the NRHIP for research purposes was not considered appropriate. Rather, focused and rigorous identification of specific disease outcomes is needed. Therefore, careful identification and validation (within the context of the data available in this platform) of AIs has been undertaken, to identify new-onset diagnoses within 6 months (considered as AI risk window in this study) after any dose of G4 or G9.

The AIs can be broadly classified into 3 categories: rheumatologic, endocrine, and neurological disorders. The following aspects were considered when selecting AIs, 1) from each of these 3 categories, 1 to 3 relatively common AIs were selected because these conditions have established diagnostic criteria and treatment options, 2) have been identified in the NRHIP within the general population of women 16-45 years old, and are 3) commonly studied in other studies of G4 or G9 safety (though there is no evidence of the association between vaccination with G4 or G9 and new onset of any of these conditions). These conditions were selected in alignment with CDE and defined in the study protocol and

include: systemic lupus erythematosus (rheumatologic); Graves' disease, Hashimoto's disease and type 1 diabetes (endocrine); and multiple sclerosis, optic neuritis and uveitis (neurologic). Uveitis and optic neuritis have been implicated as early conditions that could be associated with development of demyelinating disorders, and therefore were included in the "neurologic" category in this instance [3, 4].

9.1.2 Pregnancy outcome surveillance

Women in the vaccinated cohort who received at least one dose of G9 up to 30 days prior to conception or anytime during pregnancy and their infants were eligible for the pregnancy outcomes surveillance. Congenital anomalies under surveillance in this study are selected according to the National Maternal and Child Health Surveillance Manual 2013, and included anencephaly, spina bifida, encephalocele, congenital hydrocephalus, cleft palate, cleft lip, cleft palate with cleft lip, microtia/anotia, other malformations of outer ear, esophageal atresia or stenosis, rectoanal atresia or stenosis, hypospadias, exstrophy of urinary bladder, talipes equinovarus, polydactyly, syndactyly, limb reductions, congenital diaphragmatic hernia, exomphalos, gastroschisis, conjoined twins, Down syndrome, congenital heart diseases.

9.2 Setting

Study 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 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. Vaccination record for the first dose of G4 and G9 became available in Ningbo on 9 January 2018 and 25 January 2019, respectively.

The NRHIP is one of the best regional health information systems in China. The NRHIP collects healthcare information from a variety of sources within Ningbo, thereby providing a

comprehensive and centralized structure to store healthcare data, including age, gender, disease diagnosis, treatment, drug prescription and dispensing, and laboratory testing results. Electronic medical records of outpatient visits, emergency room visits and hospitalizations from local hospitals have been integrated into the NRHIP. The vaccine register system in the NRHIP contains information on vaccines administered in Ningbo.

A cohort of G4 or G9 vaccinated women was identified from the Ningbo Vaccine Register within the NRHIP and their safety outcomes of interest after vaccination were surveilled based on information within the NRHIP.

Study period: The surveillance period for G9 was from 25 January 2019 to 31 March 2021.

9.3 Subjects

Women who received G9 vaccination (including mixed G4/G9 regimens) were eligible for study participation. Vaccinated women were identified from the vaccine register within the NRHIP.

The AIs surveillance inclusion criteria and exclusion criteria were:

Inclusion criteria

- ✓ Female residents registered in the NRHIP;
- ✓ Age-eligible for vaccination during the study period (between 16 to 26 years old at the initiation of G9 vaccination during the study period);
- ✓ Received at least 1 dose of G9;
- ✓ Received only G4 or G9 and no other HPV vaccine (as initial HPV vaccine);
- ✓ Received G9 vaccination in Ningbo;

Exclusion criteria

- ✓ Women who received any HPV vaccine other than G4 or G9 will be censored at the date of the first HPV vaccination other than G4 or G9;

- ✓ Women with prior diagnosis or clear symptom onset of a pre-specified AI before G9 vaccination initiation.

The pregnancy outcome surveillance inclusion and exclusion criteria were:

Inclusion criteria

- ✓ Female residents registered in the NRHIP;
- ✓ Age-eligible for vaccination during the study period (between 16 to 26 years old at the initiation of G9 vaccination during the study period);
- ✓ Received at least one dose of G9 vaccine up to 30 days prior to conception or anytime during pregnancy (criterion is based on the data available within the antenatal care and childbirth EMRs within the NRHIP for this surveillance);
- ✓ Received only G4 or G9 and no other HPV vaccine(as initial HPV vaccine);
- ✓ Received G9 vaccination in Ningbo;
- ✓ Delivered at a gestational age of 28 weeks or above, or gave birth to a baby with birthweight no less than 1000g (if the gestational age at delivery is unknown) at the index pregnancy (this criterion based on availability of records included in the NRHIP).

Exclusion criteria

- ✓ Women who received any HPV vaccine other than G4 or G9 were censored at the date of the first HPV vaccination other than G4 or G9.

To capture as many G4 and G9 vaccinated women as possible, those who received G4/G9 at first (initial HPV vaccine), and then received other HPV vaccines were included and censored at the date of receipt of other HPV vaccines. However, those who received other HPV vaccines at first dose (initial HPV vaccine), and then received G4 or G9 were not included in this surveillance.

9.4 Variables

9.4.1 Exposure

Exposure for AIs surveillance was defined as receipt of at least one dose of G9 in women who were age-eligible for vaccination at any time during the study period. The surveillance period ended 6 months after each dose or at the time of vaccination of a subsequent dose, whichever occurred earlier.

Exposure for pregnancy surveillance was defined as receipt of at least one dose of G9 up to 30 days prior to conception or anytime during pregnancy among women who were age-eligible for vaccination at any time during the study period.

Case identification of pregnancy exposure

Information on pregnancy was extracted from the maternal specific program data in the NRHIP. G9 vaccination data for women was extracted from the vaccine register in the NRHIP. Data from the maternal specific program and G9 vaccination data were linked. The vaccination dates of each dose of G9 were compared with the relevant pregnancy data to identify cases with potential maternal G9 exposure.

A potential pregnancy exposure window to identify pregnancy exposure of 50 weeks (started from a maximum of 60 days before last menstrual period), which is wider than the range of 30 days before conception until 40 weeks of gestational age at delivery was used to increase the sensitivity to identify cases with maternal exposure and to ensure that all cases with potential maternal exposure were detected, including those with longer pregnancy duration or unclear conception dates. This study did not differentiate between last menstrual period and conception date. Cases with potential maternal exposure were then linked to medical information in the EMR (testing, diagnosis, prescription, surgical intervention, etc.) to collect all medical records of the cases for the validation of cases with potential maternal exposure.

Validation of cases with maternal exposure

The determination of the conception date is important in this study because it is determinant to identify whether a female was exposed to G9 or not during her pregnancy. The validation

process included case profile form development, EMR data extraction, determination of the date of conception and validation of cases with maternal exposure. Details of this validation process are described in the study data management plan.

9.4.2 Outcome

9.4.2.1 AIs surveillance

The following 7 conditions were included in the AIs surveillance part of this study: Graves' disease, Hashimoto's disease, SLE, type 1 diabetes, multiple sclerosis, optic neuritis and uveitis. The outcome of interest for each of these conditions was new-onset and diagnosis within 6 months after each dose of G4 or G9.

AIs diagnoses were captured using available outpatient, emergency room, and inpatient diagnosis codes and free text in the NRHIP. The case identification method of each AI included in the surveillance was developed in consultation with the NRHIP experts and local clinicians with expertise in the conditions of interest. Case validation was undertaken by clinicians with proper training for these activities. Details of case identification and validation are included in the data management plan.

Step 1: Development of a case identification method for selected AIs

Broad case identification methods of AIs based on relevant ICD-10 codes and key words of diagnosis were used for the case identification. Local clinicians reviewed and revised these pre-identified ICD codes and key words to ensure the reliability of the case capture. In addition, this method was reviewed by the SRC to ensure that it was applicable to identify potential cases in the NRHIP.

Step 2: Case identification of selected AIs

Vaccination data and AI data were extracted from various databases in NRHIP and linked. AIs case identification methods were applied to extract the relevant information of the diagnosis of the selected AIs (diagnosis name, ICD code, date) in the total population to identify selected AI cases. G9 vaccination data were extracted from the vaccine register in the NRHIP. Then, selected AI cases identified in the general population and G9 vaccination

data were linked and dates of AI onset and vaccination date were compared to identify potential AI cases with onset in the 6 months following G9 vaccination. Medical information was linked for these potential AI cases to collect all medical records for potential AI case validation.

Step 3: Case validation of selected AIs

Case validation was conducted for all potential AI cases identified in G4/G9 risk window. For each AI, all medical information available in the NRHIP was collected and validated by two independent clinicians. A third clinician was assigned to review the cases if the diagnosis of the two clinicians was not consistent. For each confirmed AI case , a short narrative (typically less than 200 Chinese characters) was prepared by one of the clinicians responsible for the case validation.

9.4.2.2 Adverse pregnancy outcome surveillance

For the pregnancy surveillance, stillbirth and congenital anomalies in infants with maternal G9 exposure during pregnancy were the outcomes of interest. Major congenital anomalies included anencephaly, spina bifida, encephalocele, congenital hydrocephalus, cleft palate, cleft lip, cleft palate with cleft lip, microtia/anotia, other malformations of outer ear, esophageal atresia or stenosis, rectoanal atresia or stenosis, hypospadias, exstrophy of urinary bladder, talipes equinovarus, polydactyly, syndactyly, limb reductions, congenital diaphragmatic hernia, exomphalos, gastroschisis, conjoined twins, down syndrome and congenital heart diseases.

The case identification methods of pregnancy outcomes included in the surveillance were also developed in consultation with the NRHIP experts and local clinicians with relevant expertise. Case validation was undertaken by clinicians who had received specific training for these activities. Details of case identification and validation are included in the data management plan.

Step 1: Case identification of pregnancy outcomes

Stillbirth cases were identified from maternal EMR using stillbirth-related ICD-10 codes (Z37, Outcome of delivery) and diagnosis key words (stillbirth/死产). Stillbirth cases were linked to their vaccination status to identify potential stillbirth cases that occurred in the G9 potential pregnancy exposure window.

Diagnosis related information (diagnosis name, ICD codes and diagnosis date) was extracted from the NRHIP infant EMR using pre-defined congenital anomaly related ICD-10 codes and diagnosis key words, to identify selected congenital anomaly cases in newborns. Data of newborn was extracted from the NRHIP neonatal specific program. Maternal exposure and neonatal specific program data were linked to identify the infants with congenital anomalies whose mothers were vaccinated. Vaccination and conception dates of the mother-infant pairs were compared to identify infants with conception dates in the G9 potential pregnancy exposure window. Then, other medical information was extracted from the infant EMR to acquire all medical records that are needed for the case validation of the potential congenital anomaly cases.

Step 2: Case validation of pregnancy outcomes

All potential stillbirth cases and potential congenital anomaly cases occurring in the G9 potential pregnancy exposure window underwent case validation. Steps included pregnancy outcome case profile form development, EMR data extraction, case validation and narrative writing.

An SRC, composed of external experts with expertise in autoimmune disorders, obstetrics, pharmacoepidemiology, epidemiology, statistics and vaccine observational research, was assembled. The SRC reviewed the data management plan and the statistical analysis plan. It also reviewed the final analysis results and the study report.

9.4.3 Covariates

As a health information platform, the NRHIP stores extensive health data, whereas a more limited amount of socioeconomic data is available in the NRHIP. Covariates that could potentially have an impact on HPV vaccination exposure and the pre-specified AIs or pregnancy outcomes were extracted and analyzed. For autoimmune outcomes, the covariates

included factors such as age at first dose, residence region, marital status, occupation, diagnosis time, age at diagnosis, days between last vaccination dose before diagnosis and diagnosis. For pregnancy outcomes, the covariates included age at first dose, residence region, education, occupation, cigarette smoking status, alcohol drinking status, gravidity and parity. The finalized list of covariates was compiled in consultation with NHRIP experts and was described within the statistical analysis plan for this surveillance.

9.5 Data sources and measurement

This is a database surveillance and data from the NRHIP was used for vaccination safety analyses.

The NRHIP is one of the most advanced regional health information system platforms in China and 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. The NRHIP contains three main data sources: hospital information system, maternal and child healthcare information system and CDC (Center for Disease Control and Prevention) information system. The hospital information system collects information on outpatient visits, emergency room visits and hospitalizations, including demographic characters, diagnosis, treatment, drug prescription and dispensing and laboratory examination results. The Ningbo CDC information system mainly collects, reports and manages information pertaining to vaccination information, communicable diseases, chronic diseases, death certification, foodborne diseases, vector-borne diseases, and similar factors. The data from the CDC, hospital, and maternal and children health information systems are integrated, verified, stored, exchanged, and shared in the NRHIP. Different datasets are linkable using personal identification variables and database-specific unique index variables.

Vaccine register system

The vaccine register system in Ningbo collects information on vaccine cold chain management, migrating children management, and digital vaccination clinics. The

information system provides services such as responses to inquiries on vaccination information and immunization records and ability to make appointments for vaccination, informed consent, payment and some consultation and to monitor 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 on individual ID, 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 been mandatory.

Electronic medical records (EMR)

The NRHIP covers all 221 public hospitals and 28 large private hospitals in Ningbo city except for some specialized hospitals or private clinics, such as eye hospitals and dental hospitals. These specialized hospitals and private clinics generally lack capability for diagnosis or treatment of AIs and birth defects diseases. The NRHIP collects information on outpatient visits, emergency room visits, hospitalization, disease diagnosis (International Classification of Disease (ICD) 10 code, Ningbo-specific and hospital-specific diagnostic codes, and free text), laboratory test results, drug prescription and dispensing, surgeries, and body check-ups since 2015. Therefore, both HPV vaccination and information regarding AIs and pregnancy outcomes are collected in the NRHIP, and the data are linkable using personal ID number at individual level at the NRHIP in Ningbo. Health information of Ningbo residents who receive care outside Ningbo is not available in the NRHIP for most conditions, including those pertinent to this surveillance.

Maternal and children health management system

In total, there are 12 maternal and children health hospitals in Ningbo, including 1 municipal maternal and child health hospital and 11 county-level maternal and child health hospitals. The maternal and child health management system is part of the NRHIP and it collects information on antenatal care and childbirth from all hospitals that provide maternal healthcare services in Ningbo. The system can capture almost all pregnancies and childbirths in local residents.

9.5.1 Study Procedures

This study was approved by the Institutional Review Board (IRB) of Peking University Health Science Center. The study was based on a secondary analysis of data that was routinely collected in Ningbo and preserved in the NRHIP. Therefore, no recruitment and no informed consent were needed in this study. Permission of waiver of informed consent for this study was granted. The electronic health 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 Peking University study personnel had access to these data. All analyses performed 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 bias, including selection bias and information bias. In order to reduce the selection bias in this study, all eligible women vaccinated with G9 were monitored for outcomes of interest within the NRHIP. The surveillance covered all potential cases in NRHIP of pre-specified AIs in eligible women after vaccination and pregnancy outcomes in women with potential maternal vaccine exposure during the observational period. In addition, information on vaccination exposure and outcomes was extracted from the NRHIP, reducing the risk of recall biases.

As this is a database study, outcomes of interest were identified from the NRHIP relying on the physician-assigned diagnosis and relevant information recorded. To reduce the detection bias related to the diagnosis of AIs and pregnancy outcomes in the vaccinated women, case identification methods were developed for the identification of potential cases that improved the outcome measurement accuracy. In addition, case validation was conducted to confirm the diagnosis among the potential cases.

9.7 Study size

In this database study, all women in the NRHIP who were vaccinated with at least one dose of G9 during the study period in Ningbo and who met the study inclusion criteria were included in the analysis. This is a descriptive study and no sample size calculation was done given that no hypothesis testing was performed.

9.8 Data management

In this study, data management procedures included seven steps: data extraction, data cleaning, data linkage, de-identification, case validation, database lock, and data analysis. Ningbo CDC was responsible for coding, data extraction, data cleaning, data linkage and de-identification. PKU was responsible for providing technical support and quality control. PKU was also responsible for developing and executing programming codes after de-identification, the case validation, database lock and data analysis.

All data management activities were undertaken under the supervision of the Peking University and Ningbo CDC, and followed all procedures detailed in a separate “Data Management Plan”.

9.9 Statistical methods

9.9.1 Main summary measures

A separate detailed data analysis plan was developed and finalized prior to any analyses in this study.

Demographic characteristics of women vaccinated with G9 were described as frequencies and percentages, with mean (±standard deviation (SD)), or median values (interquartile range (IQR)), based on the data available within the NRHIP. Descriptive analysis of information available within the NRHIP pertaining to G9 vaccination was undertaken.

A descriptive analysis of the outcomes of interest was performed. The number of women who had an onset of the prespecified autoimmune diseases within 6 months after any dose of G9 was provided. Additionally, numbers of stillbirths and congenital anomalies in infants born to women who received at least one dose of G9 up to 30 days prior to conception or anytime during pregnancy were provided. The trimester of pregnancy at vaccination and maternal age was reported.

As the study is based on secondary data, causal nature of associations cannot be evaluated.

9.9.2 Main statistical methods

Not applicable as only descriptive analyses were conducted in this study.

9.9.3 Missing values

In case of missing values related to exposure and outcomes, the records with these missing values were excluded from the analyses. In case of missing values related to covariates, these missing values were summarized in an independent category as “unknown”.

9.9.4 Sensitivity analyses

No sensitivity analyses were performed in this study.

9.9.5 Amendments to the statistical analysis plan

Not applicable in this study.

9.10 Quality control

By signing the protocol, all parties followed applicable standard operating procedures (SOPs) for non-interventional study. All parties also agreed to train the study personnel appropriately to ensure that the study was conducted and data were generated, documented, and reported in compliance with the protocol and Good Pharmacoepidemiology Practice (GPP). All parties maintained transparency and open communication in order to effectively manage the study and proactively mitigate any risks. The study protocol, the statistical analysis plan and the data management plan were finalized before any actual data analyses.

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

The Sponsor met with Peking University on a weekly base, reviewed the data management plan and statistical analysis plan, conducted audit visits and assembled the SRC to ensure that the study was conducted 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. A 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.

Quality of data linkage

The data from the CDC (vaccine register system), the hospital (electronic medical records), and the maternal and children health information systems are integrated, verified, stored, exchanged, and shared in the NRHIP.

HPV vaccination and outcome information (including AI diagnoses and pregnancy outcomes) were collected in the NRHIP, and the data was linked at individual level in the NRHIP in Ningbo. Personal identification variables and database-specific unique index variables were used for the linkage of the subjects across different datasets in the NRHIP to allow for each person's vaccination status to be combined with autoimmune diseases of interest and pregnancy outcomes.

In the NRHIP, ID variables were missing for a small proportion of women in the different data sources. Multiple linkage steps were applied to minimize the loss of data and to help ensure accurate linkage of subjects across various data sources in the platform. The dataset linkage steps were described in the study data management plan.

Standardization of autoimmune and pregnancy outcome diagnoses

Seven selected AIs and pregnancy outcomes after exposure to G9 vaccination have been monitored in this study. Key variables and information relevant to outcomes of interest were identified and extracted from the NRHIP to develop study-specific analysis datasets. Key variables included, medical diagnosis code, prescription medication, clinical characteristics,

lab test results, medical follow-ups, etc. The format of these key variables from different data sources was standardized and clearly defined in the data management plan.

Case identification methods were developed to identify potential AI cases and pregnancy outcomes in the NRHIP. Diagnosis codes and key words of diagnosis in the EMRs of outpatient visits, emergency room visits, and hospitalizations that were pertinent to the outcomes of interest were included in these case identification methods. Study-specific clinical definitions of the 7 selected AIs and pregnancy outcomes were clearly described in the statistical analysis plan for this study. Physicians and experts in the area of autoimmune disease, maternal and child health were consulted when the case definitions were developed. The case validation of potential cases was conducted as described in the data management plan. All clinical experts in this study were trained in the case validation process prior to review.

Information integrity

Vaccination register, EMR data, maternal and the child healthcare information system in the NRHIP are set up and managed strictly following the local health authority's requirements and regulations. Data integrity had previously been assessed in a preliminary 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 all collected in the system. All vaccination records of adults in Ningbo city have been collected in the system since 2017 without missing IDs.

The 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 separate analyst (validation analyst). For all data processing steps, the validation analyst reviewed the program along with input and output datasets.

10 RESULTS

10.1 Participants

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

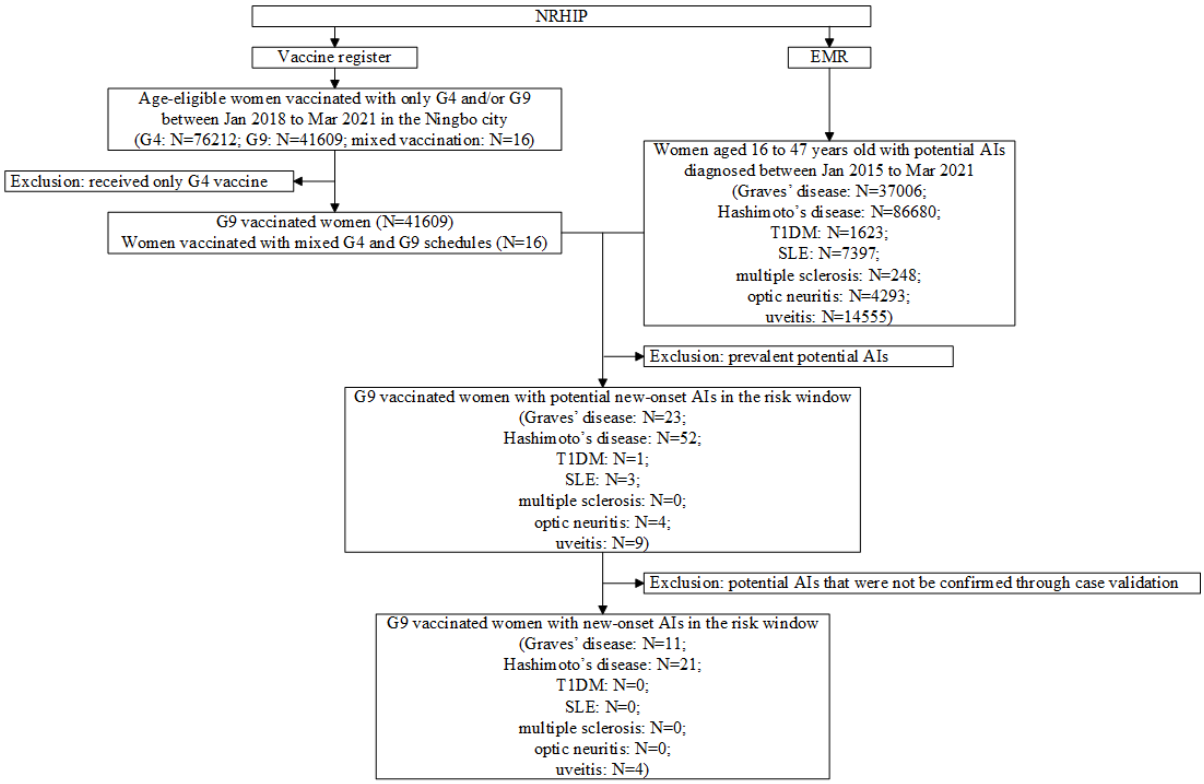

Figure 1. Flowchart of autoimmune disorder surveillance

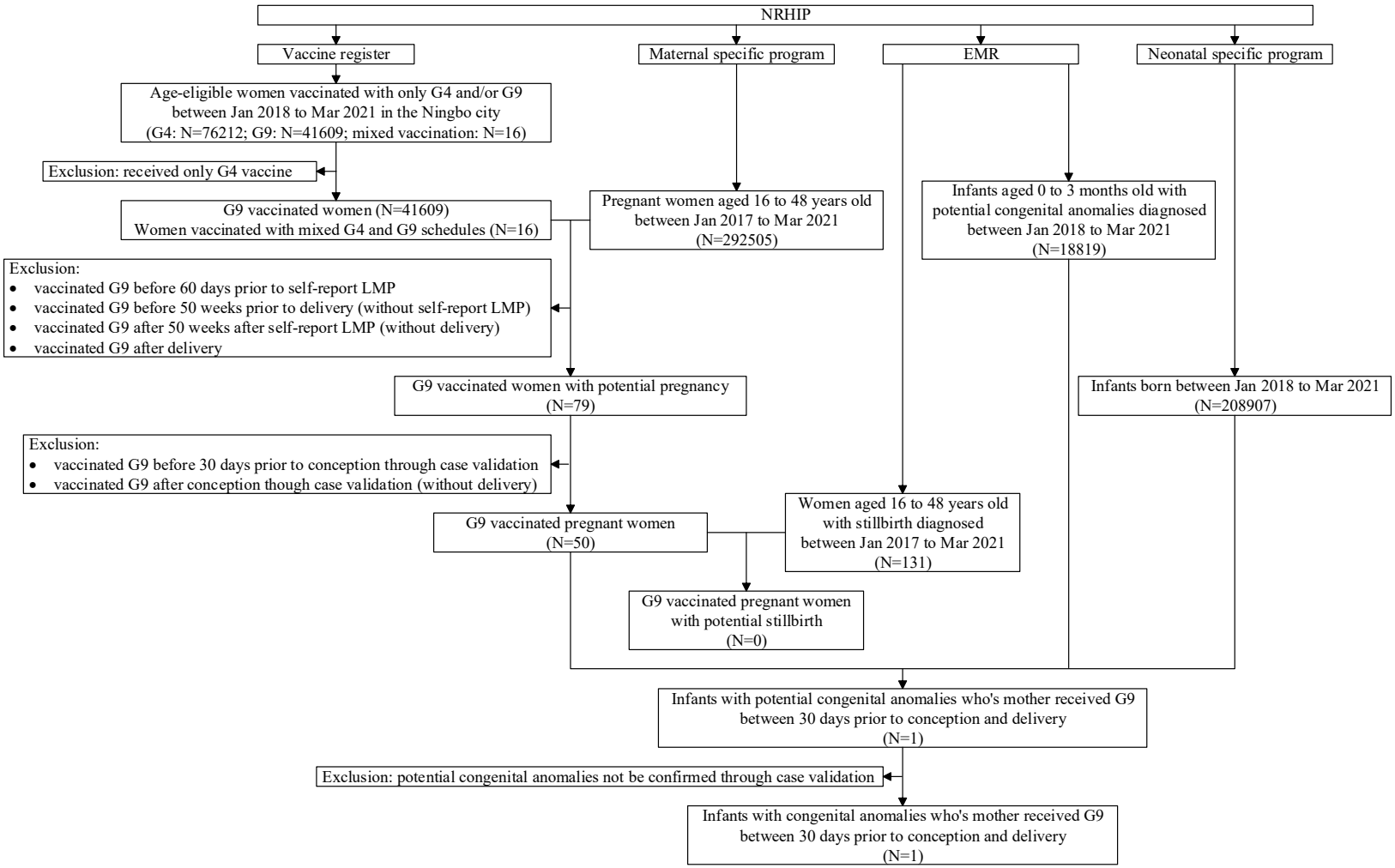

Figure 2: Flowchart of adverse pregnancy outcome surveillance

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

10.1.1 Protection of Human Subjects

This is a database surveillance activity that focuses on 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 Cooperation Study.

10.2 Descriptive data

Since 25 January 2019 when G9 vaccination records have become available in Ningbo and up to the data extraction cut-off on 31 March 2021, a total of 102,670 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. The mean age at first dose was 22.81 (SD=2.44) years, and most of the women (78.44%) initiated vaccination at age 21 to 26 years. 36.49% and 44.92% of these women were from urban areas and rural areas, respectively, for the remaining women the residence region was unknown. As of 31 March 2021, 13.65%, 25.96% and 60.40% of women had received 1, 2 and 3 doses of G9, respectively. The mean time interval between dose 1 and 2, and dose 2 and 3 were 2.20 and 4.31months, respectively, with low standard deviation (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. Sixteen women received a G4/G9 mixed regimen. The mean age at first dose was 23.8 years (SD=1.5), slightly higher than for the exclusively G9 vaccinated women (mean age=22.81 years old) and most of them (14 women) received the first dose at age 21-26 years, consistent with the G9 vaccinated women. An equal number of women were from urban and rural areas. Seven women received a mixed regimen in each of the years 2019 and 2020 and 2

women were vaccinated in the first quarter of 2021. The majority of these women (N=9) 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 [5] (Table 2).

Table 1. Characteristics of women vaccinated with G9 only between 25th Jan 2019 and 31st Mar 2021 in the NRHIP

Variables	G9
Total number of women vaccinated*	41,609
Age at first dose (years), mean±SD	22.81±2.44
16-20 years, n (%)	8,972 (21.56)
21-26 years, n (%)	32,637 (78.44)
Residence region, n (%)	
Urban	15,183 (36.49)
Rural	18,691 (44.92)
Unknown	7,735 (18.59)
Year of first dose, n (%)	
2019	10,615 (25.51)
2020	23,258 (55.90)
2021†	7,736 (18.59)
Number of doses received, mean±SD, median (IQR), range	2.47±0.72, 3 (1), 1-3
1 dose, n (%)§	5,678 (13.65)
2 doses, n (%)§	10,801 (25.96)
3 doses, n (%)§	25,130 (60.40)
Time interval between doses (months), mean±SD, median (IQR), range	
Dose 1 and dose 2 (n=35,883)	2.20±0.45, 2.07 (0.16), 1.02-16
Dose 2 and dose 3 (n=25,175)	4.31±0.66, 4.14 (0.33), 1.84-21.42

* At least 1 dose of G9 and no other HPV vaccine
† 2021 data collection cut-off: Mar 31st
§ Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G9 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

Table 2. Characteristics of women vaccinated with mixed G4 and G9 regimens between 9th Jan 2018 and 31st Mar 2021 in the NRHIP

Variables	Mixed G4/G9
Total number of women vaccinated*	16
Age at first dose (years), mean±SD	23.75±1.53
16-20 years, n (%)	2 (12.50)
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)
Residence region, n (%)	
Urban	8 (50.00)
Rural	8 (50.00)
Unknown	0 (0)
Year at first dose, n (%)	
2019	7 (43.75)
2020	7 (43.75)
2021†	2 (12.50)
Number of doses received, mean±SD, median (IQR), range	3.44±0.73, 4 (1), 2-4
2 doses, n (%)§	2 (12.50)
3 doses, n (%)§	5 (31.25)
> 3 doses, n (%)§	9 (56.25)
Time interval between each dose (months), mean±SD, median (IQR), range	
Dose 1 and dose 2 (n=14)	2.28±0.54, 2.12 (0.26), 1.22-3.32
Dose 2 and dose 3 (n=11)	4.25±1.06, 4.14 (0.29), 2.53-7.06
Dose 3 and the last dose (n=4)	6.70±6.33, 4.07 (6.83), 2.53-16.13

* At least 1 dose of G4 and at least 1 dose of G9
† 2021 data collection cut-off: Mar 31st
§ Number and percentage of women who had received 2 dose, 3 doses or > 3 doses of G4 and G9 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

10.3 Outcome data

Between 25 January 2019 and 31 March 2021, 92 potential new onset AI cases were identified for women vaccinated with at least one dose of G9 and no other HPV vaccine, including 23 cases of Graves' disease, 52 cases of Hashimoto's disease, 1 case of T1DM, 3 cases of SLE, 4 cases of optic neuritis, and 9 cases of uveitis. No potential new onset cases of multiple sclerosis were identified. After exclusion of 4 cases with onset prior to G9 vaccination or with inconsistent diagnosis records, 88 potential AI cases (95.65%) were reviewed by clinicians for case validation. Finally, 36 cases (39.13% of all potential cases) were confirmed, including 11 cases of Graves' disease, 21 cases of Hashimoto's disease and 4 cases of uveitis. (Table 3). No potential AI cases were identified in women who had received mixed G4/G9 regimens.

A total number of 11 new onset cases of Graves' disease were identified in women vaccinated with G9. The mean age of these women at their first dose of G9 was 23.33 (SD=2.20) years. Three women received their first dose in 2019 and 8 in 2020. The number of women with new-onset Graves' disease diagnosed after dose 1 and dose 2 of G9 was 6 and 5 women, respectively. No new-onset cases were diagnosed after dose 3. The women had received a mean of 2.91 (SD=0.30) doses, and therefore, the vast majority (10 women) had completed their 3rd dose of vaccination. More than half of them (6 women) were from urban areas. The mean time interval between the last dose of vaccination before diagnosis and the date of diagnosis was 57.91 (SD=33.67) days (Table 4).

A total of 21 women vaccinated with G9 were identified with new-onset Hashimoto's disease. The mean age of these women at their first dose of G9 was 23.82 (SD=1.81) years. Seven of these women received their first dose of G9 in 2019, and 13 in 2020. During the first quarter of 2021, only 1 woman received her first dose of G9. Hashimoto's disease was diagnosed after dose 1 among 9 women and after dose 2 among 12 women. No new-onset cases were observed after dose 3.The mean number of doses received was 2.90 (SD=0.30). The vast majority (19 women) received all 3 doses of G9. Nearly half of them (42.86%) were from urban areas. The mean time interval between the last dose of vaccination before diagnosis and the date of diagnosis was 59.92 (SD=37.17) days (Table 5).

Four women were diagnosed with new-onset uveitis. The mean age of these women at their first dose of G9 was 23.14 (SD=3.65) years. Two women received their first dose in 2019, and the others received it in 2020. One woman had received only two doses of G9 during the study period, the three others had been vaccinated with all three doses. Half of them were from urban areas. One woman was diagnosed with new-onset uveitis after she had received dose 1, and the others were diagnosed after dose 2. No woman was diagnosed after dose 3. The range of the time interval between the date of the last dose of vaccination before diagnosis and the date of diagnosis was 13 to 44 days.

A total of 79 women with potential pregnancy and G9 exposure were extracted and their data were reviewed by clinicians for validation of their pregnancy. Twenty nine women were not included because the G9 exposure was not during pregnancy or 30 days prior to the date of conception. For 50 of these women (63.29%) the G9 exposure during pregnancy or 30 days prior to the date of conception was confirmed. The number of women who received G9 30 days before conception or during pregnancy was 40 in 2019 and 10 in 2020. In the first quarter of 2021, no pregnant women in Ningbo received G9. Eleven of these women had received a total of 1 and 2 doses during the study period, respectively and 28 had received 3 doses of G9 during the study periodThe mean age at first dose of G9 was 24.56 (SD=0.93) years. old. Twenty-five women were from rural areas, and most of them (n=43) had at least a university degree. Their occupational status was very diverse and not specified or known for almost half of them. All of these women were non-smokers and they did not drink alcohol. The median numbers of gravidities (all pregnancies) and parities (previous births) were 1 (IQR=0) and 0 (IQR=0), respectively and therefore most of these women had their first pregnancy and delivery during the study period. A similar proportion of women had their conception before dose 1, after dose 1, after dose 2, and after dose 3. More than half (56.00%) of these women received the first dose of G9 in the first trimester of their pregnancy, 36% within 30 days prior to conception and 6% in the second trimester. Only 1 (2.00%) woman had received her first dose of G9 during the third trimester (Table 6). No pregnancies were identified among women with mixed G4 and G9 exposure.

Among the 50 women with maternal G9 exposure, no stillbirth case was identified. One potential microtia case was identified in an infant born to one of the exposed women. This

woman had received all three doses of G9 in 2019, and the last dose was given in the first trimester (estimated dates approximately 6 days after conception). The time between the last dose of G9 and delivery was 272 days.

This microtia case was reviewed and confirmed by clinicians. (Table 7). This congenital anomaly was reported in a PPD infant and was diagnosed at age one month. PPD mother was PPD when she received her first dose of G9. PPD PPD she delivered at a gestational age of 39 weeks.

Table 3. Autoimmune disorder cases in women with G9 exposure*

	Potential cases identified, N	Cases reviewed by clinicians for case validation, n1 (n1/N%)	Confirmed cases, n2 (n2/N%)
Total autoimmune disorder†	92	88 (95.65)	36 (39.13)
Graves' disease	23	23 (100)	11 (47.83)
Hashimoto's disease	52	52 (100)	21 (40.38)
T1DM	1	0 (0)	0 (0)
SLE	3	2 (66.67)	0 (0)
Multiple sclerosis	0	0 (--)	0 (--)
Optic neuritis	4	4 (100)	0 (0)
Uveitis	9	7 (77.78)	4 (44.44)

* New-onset autoimmune disorder cases within 6 months after any dose of G9 in women who received at least one dose of G9 and no other HPV vaccine.
† This category is not mutually exclusive, i.e., one woman may have more than one autoimmune disorder.

Table 4. Characteristics of women with G9 exposure who had new onset Graves' disease

Variables	G9
Total	11
Age at first dose (years), mean±SD	23.33±2.20
16-20 years, n (%)	3 (27.27)
20-26 years, n (%)	8 (72.73)
Year at first dose, n (%)	
2019	3 (27.27)
2020	8 (72.73)
2021[†]	0 (0)
Number of doses received, mean±SD, median (IQR), range	2.91±0.30, 3 (0), 2-3
Only 1 dose, n (%)[§]	0 (0)
2 doses, n (%)[§]	1 (9.09)
3 doses, n (%)[§]	10 (90.91)
Residence region, n (%)	
Urban	6 (54.55)
Rural	4 (36.36)
Unknown	1 (9.09)
Marital status, n (%)	
Unmarried	2 (18.18)
Married	0 (0)
Divorced	0 (0)
Widowed	0 (0)
Unknown	9 (81.82)
Diagnosis time, n (%)	
After dose 1	6 (54.55)
After dose 2	5 (45.45)
After dose 3	0 (0)
Time interval between last dose of vaccination before diagnosis and diagnosis (day), mean±SD, median (IQR), range	57.91±33.67, 56 (53), 25-121

[*] At least 1 dose of G9
[†] 2021 data collection cut-off: Mar 31st
[§] Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G9 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

Table 5. Characteristics of women with G9 exposure who had new onset Hashimoto's disease

Variables	G9
Total *	21
Age at first dose (years), mean±SD	23.82±1.81
16-20 years, n (%)	2 (9.52)
20-26 years, n (%)	19 (90.48)
Year at first dose, n (%)	
2019	7 (33.33)
2020	13 (61.90)
2021†	1 (4.76)
Number of doses received, mean±SD, median (IQR), range	2.90±0.30, 3 (0), 2-3
Only 1 dose, n (%)§	0 (0)
2 doses, n (%)§	2 (9.52)
3 doses, n (%)§	19 (90.48)
Residence region, n (%)	
Urban	9 (42.86)
Rural	8 (38.10)
Unknown	4 (19.05)
Marital status, n (%)	
Unmarried	1 (4.76)
Married	1 (4.76)
Divorced	0 (0)
Widowed	0 (0)
Unknown	19 (90.48)
Diagnosis time, n (%)	
After dose 1	9 (42.86)
After dose 2	12 (57.14)
After dose 3	0 (0)
Time interval between last dose of vaccination before diagnosis and diagnosis (day), mean±SD, median (IQR), range	59.29±37.17, 61 (65), 4-125

* At least 1 dose of G9
† 2021 data collection cut-off: Mar 31st
§ Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G9 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

Table 6. Characteristics of women with maternal G9 exposure*

Variables	G9
Total†	50
Age at first dose (years), mean±SD	24.56±0.93
16-20 years, n (%)	0 (0.00)
20-26 years, n (%)	50 (100.00)
Residence region, n (%)	
Urban	14 (28.00)
Rural	25 (50.00)
Unknown	11 (22.00)
Education, n (%)	
University and above	43 (86.00)
Senior high school	6 (12.00)
Junior school and below	1 (2.00)
Unknown	0 (0.00)
Occupation, n (%)	
Factory worker	9 (18.00)
Agriculture worker	5 (10.00)
Administrator / manager / professional / technical	10 (20.00)
Service worker	3 (6.00)
Other	22 (44.00)
Unknown	1 (2.00)
Cigarette smoking status, n (%)	
Non-smoker	50 (100.00)
Smoker	0 (0.00)
Unknown	0 (0.00)
Alcohol drinking status, n (%)	
Non-drinker	50 (100.00)
Drinker	0 (0.00)
Unknown	0 (0.00)
Gravidity, mean±SD, median (IQR), range	1.28±0.73, 1 (0), 1-4
1, n (%)	42 (84.00)
2, n (%)	4 (8.00)
⩾3, n (%)	4 (8.00)
Parity, mean±SD, median (IQR), range	0.02±0.14, 0 (0), 0-1
0, n (%)	49 (98.00)
1, n (%)	1 (2.00)
2, n (%)	0 (0.00)
⩾3, n (%)	0 (0.00)
Year at first dose, n (%)	
2019	40 (80.00)
2020	10 (20.00)
2021 §	0 (0.00)
Number of doses received, mean±SD, median (IQR), range	2.34±0.82, 3 (1), 1-3
1 dose, n (%) ‖	11 (22.00)

Variables	G9
2 doses, n (%) ‖	11 (22.00)
3 doses, n (%) ‖	28 (56.00)
Conception time, n (%)	
Before dose 1	15 (30.00)
After dose 1	12 (24.00)
After dose 2	13 (26.00)
After dose 3	10 (20.00)
Vaccination time of the first dose in risk windows, n (%)	
Within 30 days prior to conception	18 (36.00)
In the 1st trimester (0-12 weeks)	28 (56.00)
In the 2nd trimester (13-28 weeks)	3 (6.00)
In the 3rd trimester (29-40 weeks or above)	1 (2.00)

* Only women with maternal vaccination exposure and who delivered at 28 gestational weeks or above or gave birth to a baby with birthweight no less than 1000g (if the gestational age at delivery is unknown) are included in the analysis.
† At least 1 dose of G9
§ 2021 data collection cut-off: Mar 31st
‖ Number and percentage of women who had received 1 dose, 2 doses or 3 doses of G9 as of the cut-off date
Urban area includes Haishu, Jiangbei, Beilun, Zhenhai, Yinzhou, Fenghua; rural area includes Yuyao, Cixi, Xiangshan, Ninghai.

Table 7. Adverse pregnancy outcomes in infants of women with maternal G9 exposure*

Adverse pregnancy outcome	Potential cases identified, n	Cases reviewed by clinicians in case validation, n	Confirmed cases, n
Stillbirth	0	0	0
Anencephaly	0	0	0
Spina bifida	0	0	0
Encephalocele	0	0	0
Congenital hydrocephalus	0	0	0
Cleft palate	0	0	0
Cleft lip	0	0	0
Cleft palate with cleft lip	0	0	0
Microtia/anotia	1	1	1
Other malformations of outer ear	0	0	0
Esophageal atresia or stenosis	0	0	0
Rectoanal atresia or stenosis	0	0	0
Hypospadias	0	0	0
Exstrophy of urinary bladder	0	0	0
Talipes equinovarus	0	0	0
Polydactyly	0	0	0
Syndactyly	0	0	0
Limb reductions	0	0	0
Congenital diaphragmatic hernia	0	0	0
Exomphalos	0	0	0
Gastroschisis	0	0	0
Conjoined twins	0	0	0
Down syndrome	0	0	0
Congenital heart diseases	0	0	0

* Only women with maternal vaccination exposure and who delivered at 28 gestational weeks or above or gave birth to a baby with birthweight no less than 1000g (if the gestational age at delivery is unknown) are included in the analysis.

10.4 Main results

A total of 102,670 doses of G9 were administered to 41,609 women aged 16 to 26 years old who had received no other HPV vaccines in Ningbo over the study period from 25 January 2019 to 31 March 2021. Sixteen women had received mixed G4 and G9 regimens representing a total of 55 doses of G4 and G9.

Among the women who were exclusively vaccinated with G9, a total of 36 women were diagnosed with a new-onset of pre-specified AIs, including 11 cases of Graves' disease, 21 cases of Hashimoto's disease, and 4 cases of uveitis.

A total of 50 women had received G9 during their pregnancy or within 30 days before conception. Among these 50 women, no stillbirth was observed. One of the infants born to a mother with pregnancy exposure to G9 was diagnosed with microtia during the observation period of 3 months from birth.

No cases of AIs and no pregnancies were observed among the women who had received a mixed G4/G9 regimen.

10.5 Other analyses

[redacted], the proportion and incidence density were calculated. Person-time for G9 vaccinated women was calculated, starting at the date when the women received their first dose of G9. The follow-up time ended at the date when a pre-specified AIs was detected, six months after a last dose of G9 that a woman received or on 31 March 2021, whatever came first.

The mean follow-up time of the 41,609 women vaccinated with G9 was 0.64 year, with an overall follow-up time of 26,629.76 person-years. Eleven cases of Graves' disease, 21 cases of Hashimoto's disease, and 4 cases of uveitis were identified during the follow-up period, corresponding to an incidence density of respectively 41.34 cases per 100,000 person-years (95%CI: 22.89-74,65), 78.94 cases per 100,000 person-years (95%CI: 51.47-121.08) and 15.03 cases per 100,000 person-years (95%CI: 5.64-40.05). The respective proportions were 26.44 per 100,000 persons (95%CI: 13.20-47.30) for Graves' disease, 50.47 per 100,000 persons (95%CI: 31.24-77.14) for Hashimoto's disease and 9.61 per 100,000 persons (95%CI: 2.62-24.61) for uveitis (Table 8).

Table 8. AIs disease occurrence among 41,609 women, vaccinated with G9*

	Number of cases	Proportion (/100,000) and 95%CI	Incidence density (/100,000 person-year), 95%CI
Graves' disease	11	26.44 (13.20, 47.30)	41.34 (22.89, 74,65)
Hashimoto's disease	21	50.47 (31.24, 77.14)	78.94 (51.47, 121.08)
Uveitis	4	9.61 (2.62, 24.61)	15.03 (5.64, 40.05)

* New-onset of 7 pre-specified AI cases within 6 months after any dose of G9 in women who received at least one dose of G9 and no other HPV vaccine.

10.6 Adverse events/adverse reactions

This is a surveillance study based on a secondary analysis of data that were routinely collected in Ningbo and preserved in the NRHIP. Specific case identification methods were applied to identify pre-specified AIs and adverse pregnancy outcomes (stillbirth and major congenital anomaly) in NRHIP. Medical care information in NRHIP was extracted and reviewed based on the pre-specified methods. Adverse events (AEs) and product quality complaints (PQCs) were not actively solicited in this study according to the study design, however, during review of medical records or phy-sician notes (paper or electronic) to collect data as required by the protocol, the SAR/NSAR and other events which meet criteria were to be reported.

11 DISCUSSION

11.1 Limitations

The NRHIP is designed for routine health care management, rather than for research purposes. This surveillance occurred within the NRHIP, which is a cloud-based health information platform that has not been tested or used for surveillance of vaccine safety before. Conditions and diseases diagnosed and treated outside Ningbo city are not captured in the NRHIP. Also, while medical records are routinely entered into the NRHIP, some factors such as diagnostic codes may vary among institutions (e.g., hospitals) that report data to the NRHIP. To address this issue, study-specific case identification methods were developed and included a variety of source data terminology, such as diagnosis codes and free text of diagnosis in EMRs in the NRHIP. In addition, expert administrators of the NRHIP, as well as experts familiar with clinical practice and medical coding in Ningbo, were consulted for their input as case identification methods were developed. In addition, case validation in this surveillance relied on the decisions made by clinical experts based on the medical records available in NRHIP, which might not be complete.

Currently, the NRHIP is only accessible to qualified technicians of Ningbo CDC. Downloading data from the NRHIP is prohibited. However, with the appropriate approvals, study investigators from Peking University could access de-identified data and perform analyses for research purposes.

Linkage of vaccination data with AI cases (to identify AI cases among vaccinated women) and pregnant women (to identify women exposed to vaccine during or shortly before pregnancy) was critical in this study. In an analysis of feasibility of using the NRHIP to conduct this surveillance, the proportion of identifiers for women aged 16 to 45 years old in 2017 that could not be linked with AIs was relatively small, suggesting that this may not impact study findings to an important degree.

Since this is a surveillance study to monitor the occurrence of new onset AIs and adverse pregnancy outcomes in women who received G9, general population (unvaccinated women) wasn’t included in this survaillence. Vaccinated women who self-pay for vaccination and

may have unique health-seeking or other behaviors may be very different from unvaccinated women. Therefore, a comparison between vaccinated and unvaccinated groups wasn't applicable in this study.

Another limitation of the study is that for some AIs, the onset date can precede the actual diagnosis date. This study adapted the diagnosis date which was used as a proxy for AI onset. Also for the determination of pregnancy outcome following maternal exposure, spontaneous abortions and elective termination (for any reason) could not be reported as these are considered sensitive data in Ningbo. Therefore, the adverse pregnancy outcome surveillance in this study is limited to stillbirth and 23 pre-defined congenital anomalies following live births.

11.2 Interpretation

A total of 36 women were diagnosed with a new-onset case of pre-specified AIs among the study population of 41,609 women aged 16 to 26 years old who had received at least one dose of G9 and no other HPV vaccine in Ningbo over the study period from 25 January 2019 to 31 March 2021. Among these 36 women, there were 11 subjects who had Graves' disease, 21 subjects with Hashimoto's disease, and 4 subjects with uveitis. No cases of T1DM, SLE, MS or optic neuritis were identified among the study population.

We did not assess the occurrence of new onset AI cases among unvaccinated women or in the general population. However the results can be put into context using data from published literature:

In a prospective cohort study that examined the effect of regional differences in iodine intake on the incidence of thyroid diseases among more than 3000 participants in northeastern China between 1999 and 2004, the 5-year cumulative incidence of Graves' disease ranged from 0.6% to 0.8%, and the prevalence from 1.1% to 1.4%. In the same study, the incidence of Hashimoto's thyroiditis ranged between 0.0% and 0.5%, and the prevalence between 0.4% and 1.5% in the different regions. The prevalence of Graves' disease decreased over the two decades [6]. Based on a cross-sectional survey conducted in China among a representative sample of 78,470 participants between 2015 to 2017, the prevalence of Graves' disease was

0.53% in the total population. Prevalence in women and men was 0.69% and 0.38%, respectively. The prevalence was 0.55% among those aged 18 to 29 years. As a subtype of lymphocytic thyroiditis, the main symptom of Hashimoto's disease is overt hypothyroidism. The prevalence of Hashimoto's thyroiditis was not estimated in that survey, but the prevalence of overt hypothyroidism was 1.02%. Women had a higher prevalence (1.53%) than men (0.53%), and prevalence increased with age from 0.45% in the 18-29 age group to 2.09% in the ≥70 age group. The prevalence was 0.45% in the age group 18 to 29 years [7]. In a cross-sectional study in Zhejiang province conducted in 2011 (in which Ningbo city is located), proportion of Graves' diseases and lymphocytic thyroiditis was 0.2% and 0.3% among those over 6 years old, respectively. This study found no difference in the proportion of the two thyroid diseases between women and men. The proportion of Graves' disease decreased with age from 0.2% in the 6-17 age group to 0.1% in the ≥45 age group, while lymphocytic thyroiditis increased with age from 0.2% in the 6-17 age group to 0.3% in the ≥45 age group [8]. In our study, 11 women were diagnosed with Graves' disease within 6 months after G9 vaccination among 41,609 women who received G9 between January 2019 and March 2021. In addition, 21 women were diagnosed with Hashimoto's thyroiditis in our study. When comparing the results of these two thyroid diseases from our study to the published data, no increase in the occurrence after vaccination with G9 was detected, even if direct comparison was not possible.

The epidemiology of uveitis varies worldwide with an incidence ranging from 17 to 52 cases per 100,000 person-years, and a prevalence from 38 to 714 cases per 100,000 persons [9]. The majority of this data is from developed countries, and the frequency might be different in China due to genetic and environmental factors. There is limited data on the epidemiology of uveitis in China. In a community-based survey, conducted among 10,500 participants in the Guangdong province, the prevalence of uveitis was 0.152%. The prevalence was higher among males (0.167%) compared to females (0.140%) [10]. In Taiwan between 2003 to 2008, the prevalence ranged between 102.2 and 122.0 per 100,000 persons, and the incidence density was 111.3 cases per 100,000 person-years. The incidence density was lower among women (99.6 per 100,000 person-years) compared to men (122.8 per 100,000 person-years) and increased with age. The incidence was 79.7 per 100,000 person-years among subjects aged 16 to 25 years old. The annual cumulative prevalence ranged from 318.8 to 622.7 cases

per 100,000 persons [11]. In this study, 4 women were diagnosed with new-onset uveitis among 41,609 women aged 16 to 26 years who had received G9 between 25 January 2019 and 31 March 2021. Even if direct comparison is not possible, the results from our study did not suggest an increased risk of uveitis in women after vaccination with G9.

In our study, no new-onset cases of T1DM, SLE, multiple sclerosis, and optic neuritis were observed in women who received G9 during the study period. All these diseases are rare in the general population. According to a surveillance conducted in 505 hospitals across China during 2010-2013, the incidence density of T1DM was 0.93 cases per 100,000 person-years. The incidence density among females was lower (0.81 case per 100,000 person-years) compared to men (0.95 per 100,000 person years) and decreased with age from 2.68 cases per 100,000 person-years in the 10-14 age group to 0.37 case per 100,000 person-years in the ≥75 age group. Among subjects aged 15 to 29 years, the incidence density was 1.02 cases per 100,000 person-years [12]. Currently, the epidemiology of SLE has only been assessed regionally in China. In Beijing, the prevalence of SLE was 0.03% overall, and 0.06% among females [13]. In the Anhui province, the prevalence of SLE was 36.03 cases per 100,000 persons with a female-specific prevalence of 70.28 cases per 100,000 persons. The prevalence increased with age, reaching a peak in the age group from 40 to 49 years. The prevalence was 28.69 per 100,000 persons and 83.73 per 100,000 persons respectively among subjects 10 to 19 years and 20 to 29 years [14]. Prevalence of SLE was higher in women in both studies in Beijing and in Anhui. For multiple sclerosis, according to the data from Basic Medical Insurance for Urban Employee from 6 provinces in China, the prevalence was 2.44 cases per 100,000 persons from 2012 to 2016. The prevalence in women and men was 3.48 and 1.56 per 100,000 persons, respectively. The prevalence in women was highest among 30 to 34 year-olds, and the prevalence was 0.48 and 2.06 per 100,000 persons in the 10 to 19 and in the 20 to 29-year-old age group, respectively [15]. We did not identify any published study that reported the incidence or prevalence of optic neuritis in mainland China, but one study had been conducted in Taiwan. In this study, the 5-year cumulative incidence rate was 1.33 cases per 1000 person-years from 2000 to 2004. Compared to men (1.00 case per 1000 person-years), women had a higher incidence (1.67 cases per 1000 person-years). The incidence increased with age,and was 0.36 and 1.24 cases per 1000 person-years among women aged 0 to 19 years and 20 to 39 years, respectively [16].

A total of 50 women received G9 during their pregnancy or within 30 days before conception. Among these 50 women, no stillbirth was observed. In one infant born to a G9 exposed mother a case of microtia was diagnosed within 3 months after birth. A number of factors may confound this association as information including medications taken during pregnancy, occupational exposures, health history of the mother or family disease history is not available in the database.Data on the epidemiology of microtia in China is limited. In studies conducted in China and worldwide, microtia was reported in approximately 1 to 5 per 10,000 births [17-19].

Although G4 and G9 are not indicated for use during pregnancy, sometimes the vaccines are inadvertently administered during pregnancy. To date, no unfavorable pregnancy outcomes associated with vaccination during pregnancy have been identified. Pregnancy exposure has been studied in a pregnancy registry for G4, and results have been published [20].A pregnancy registry for G9 is currently ongoing. Several cohort studies have also reported on pregnancy safety. For example, in a cohort of all women in Denmark who had a pregnancy between 2006 and 2013, no significant differences in adverse pregnancy outcomes (spontaneous abortion, stillbirth, major birth defect, small size for gestational age, low birth weight, and preterm birth) were found in infants of vaccinated women, compared to women who had not received G4 or G9 during their pregnancy [21]. Other population-based observational studies (from Scandinavia and California) had similar findings [22-24].

11.3 Generalisability

This is a database study based on NRHIP, and all eligible subjects 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. The socioeconomic status of the Ningbo female population might be higher compared to that in other regions of China. As G4/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. These geographical and socioeconomic factors need to be considered when extrapolating the results from Ningbo to other regions in China.

12 OTHER INFORMATION

Not applicable in this report.

13 CONCLUSION

Between 25 January 2019 and 31 March 2021, a total of 102,670 doses of G9 were administered to 41,609 women who 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.

During the study period, a total of 36 women who had received at least one dose of G9, were diagnosed with a new-onset case of pre-specified AIs, including 11 cases of Graves' disease, 21 cases of Hashimoto's disease and 4 cases of uveitis. No cases of T1DM, SLE, MS or optic neuritis were identified among the study population. A total of 50 women had received G9 during their pregnancy or within 30 days before conception. Among these 50 women, no stillbirth was observed. In the infants born to a G9 exposed mother, a case of microtia was diagnosed within 3 months after birth.

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Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	V503-055/Version 2.0	21-May-2020	Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women
2	V503-055/DMP Version 3.0	18-Jan-2022	Data Management Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women
	V503-055/SAP Version 1.1	11-Feb-2022	Statistical Analysis Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

Annex 2 Study Protocol

Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

2. Annex 2 HPV
HPV PMC safety s

Annex 3 Study Data Management Plan

Data Management Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

Annex 3 HPV
PMC safety study

Annex 4 Study Statistical Analysis Plan

Statistical Analysis Plan for Post-Marketing surveillance for the safety of GARDASIL® and GARDASIL®9 in a cohort of Chinese women

4. Annex 4 HPV PMC safety study