25 July 2024
EMA/379847/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cervarix

human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)

Procedure no: EMEA/H/C/000721/P46/101

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	29/04/2024	29/04/2024
☐	CHMP Rapporteur Assessment Report	03/06/2024	07/06/2024
☐	CHMP members comments	17/06/2024	17/06/2024
☐	Updated CHMP Rapporteur Assessment Report	20/06/2024	20/06/2024
☐	Request for Supplementary Information	27/06/2024	27/06/2024
☐	Submission	02/07/2024	01/07/2024
☐	Re-start	03/07/2024	03/07/2024
☐	CHMP Rapporteur Assessment Report	10/07/2024	16/07/2024
☐	CHMP members comments	15/07/2024	19/07/2024
☐	Updated CHMP Rapporteur Assessment Report	18/07/2024	22/07/2024
☒	CHMP adoption of conclusions:	25/07/2024	25/07/2024

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1. Introduction

On 28th March 2024, the MAH submitted completed paediatric study for EPI-HPV-097 VE CN DB PMS (212381), entitled: "An observational, database study to monitor cervical cancer-related endpoints in female subjects aged between 9 and 45 years in China prior to and following GlaxoSmithKline Biologicals' SA (GSK) Cervarix vaccine launch when Cervarix vaccine is administered according to the Local Prescribing Information (PI)."

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 212381 (EPI-HPV-097 VE CN DB PMS) is a stand-alone study.

The MAH stated that Study 212381 is not part of any Paediatric Investigation Plan. An approved full waiver was obtained from Paediatric Committee (PDCO) for paediatric studies in EU.

As per the Chinese National Medical Products Administration (NMPA, former National Drug Administration of China [CNDA]) regulations, the MAH had to conduct an intensive drug monitoring (IDM) study following the launch of Cervarix in China. In addition, the Cervarix approval letter specified the following points: "set up the follow-up register system following vaccination; collect related information on immune-mediated diseases, the effect on pregnancy outcome (including neonates' birth defect) and other serious diseases related to HPV infection".

2.2. Information on the pharmaceutical formulation used in the study

Cervarix is a recombinant C-terminally truncated HPV-16 L1 and HPV-18 L1 proteins, assembled into virus-like particles (VLPs) adjuvanted with the adjuvant AS04. The HPV 16 L1 VLP and HPV 18 L1 VLP proteins constitute the active ingredient of the vaccine and are produced with a recombinant baculovirus expression system. The AS04 adjuvant is composed of an aluminium salt, Al(OH)3 and 3-O-desacyl- 4'-monophosphoryl lipid A (MPL).

Cervarix is currently approved in the United States, all European Economic Area countries, the United Kingdom, Japan and in 67 other countries.

Cervarix is approved in the European Union (EU) since 20 September 2007 via the Centralized Procedure. Cervarix is indicated for use in Europe from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types. A two dose (0.5 ml each) immunization schedule is recommended in children 9 to and including 14 years of age (the second dose is given between 5 and 13 months after the first dose) while a three dose (0.5 ml each) regimen is recommended in case of individuals from 15 years of age given at 0, 1, and 6 months.

In China, Cervarix was approved by National Medical Products Administration (NMPA) in July 2016, for use in a 3-dose schedule at 0, 1, 6 months in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1), cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ caused by high risk-human papillomavirus (HR-HPV) types 16 and 18. In May 2018, Cervarix was also approved for use in females up to 45 years of age.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study number 212381 entitled: An observational, database study to monitor cervical cancer-related endpoints in female subjects aged between 9 and 45 years in China prior to and following GlaxoSmithKline Biologicals' SA (GSK) Cervarix vaccine launch when Cervarix vaccine is administered according to the Local Prescribing Information (PI).

2.3.2. Clinical study

An observational, database study to monitor cervical cancer-related endpoints in female subjects aged between 9 and 45 years in China prior to and following GlaxoSmithKline Biologicals' SA (GSK) Cervarix vaccine launch when Cervarix vaccine is administered according to the Local Prescribing Information (PI) (Study number 212381)

In addition to studies conducted outside of China, the safety, immunogenicity and efficacy of Cervarix was also assessed in five clinical trials involving over 8000 Chinese females between 9 through 45 years of age. The results of the Phase 2/3 study (HPV-039) that assessed vaccine efficacy in more than 6000 women aged 18-25 years, showed high and sustained vaccine efficacy against all virological, cytological and histopathological efficacy endpoints associated with HPV-16/18. There was no sign of waning efficacy at the end of the study (up to Month 72). The Cervarix vaccine was generally well tolerated in Chinese women aged 18-25 years.

Study 212381 was designed to address the following NMPA's request to evaluate Cervarix impact in China: "Set up the follow-up register system following vaccination and collect related information on immune mediated diseases, the effect on pregnancy outcome (including neonates birth defect, etc) and other serious diseases related to HPV infection."

While the Phase 3 studies in China were conducted in clinical research settings, the purpose of such an observational study would be to monitor the real life effect of Cervarix on cervical cancer-related endpoints in the population in China.

To perform such evaluation, the Yinzhou Regional Health Information Platform (YRHIP) was identified by GSK following literature review, expert opinion, outsourced feasibility assessment and consultation meetings with local CDC in 2018. Yinzhou is a district in south of Shanghai, China. In 2016, Yinzhou had a total population of 1.24 million people, including 800 000 permanent residents. Since its creation, this database platform has been gradually expanding to cover all information sources, from information on public health surveillance, population screening, disease management, health information system in hospitals and other healthcare services and including HPV vaccinations (from October 2017 onwards). Since 2009, this regional system covers nearly all health-related activities of residents from birth to death. In 2018, more than 95% of permanent residents in Yinzhou were registered in the health information system with a valid healthcare identifier.

The aim of this study is to assess cervical cancer-related endpoints in female population following Cervarix vaccination in accordance to local PI using a sequential approach. In a first step, an assessment of YRHIP database performance for the detection of endpoints of interest (cervical HPV infection, cervical lesions such as cervical intraepithelial neoplasia grade 1 (CIN1), grade 2 (CIN2), CIN grade 3 (CIN3) and cervical cancer, with/without HPV type) based on pre-launch data will be performed. In the second step, baseline incidence rates of cervical cancer-related endpoints and vaccination rates will be computed. Cervical cancer screening practices during pre- and post-launch period will also be evaluated. Then, in a third step, the pre-and post-launch rates of the effectiveness

endpoints of interest will be assessed. Finally, provided that pre-defined criteria are met, the probability of occurrence of effectiveness endpoints of interest among vaccinated and unvaccinated subjects during post-launch period will be assessed. Comparative analysis for cervical cancer-related endpoints will be performed conditional upon a pre-defined number of subjects that have been vaccinated and screened in a reasonable period of time following vaccination during the study observation period.

This stepwise approach proposed for assessment of vaccine effect on cervical cancer-related endpoints was used to ensure mitigation of the limitations inherent to real-world evidence study. There were various limitations that may prevent hypothesis testing in this study including suboptimal rate of cervical screening (although according to CDC China, screening coverage for women aged 35 to 64 years, the targeted range of China's national screening program has raised overtime from about 25% in 2010, 27% in 2013, 31% in 2015, up to 37% in 2018-2019), unpredictable Cervarix uptake (an online cross-sectional survey of female students from 136 Chinese universities in 2019, only 11% of participants reported to have received the vaccine. A lower vaccination level [3.6% among females, 1.9% among males] was found in another survey among students in 2019) and the uncertain rates of cervical cancer-related endpoints. Therefore, the study aimed at assessing those factors and delivering rates of cervical cancer-related endpoints in vaccinated and unvaccinated cohorts. The sequential approach developed in the current study enabled adaption of the study design based on the results generated in the initial steps e.g., case identification validation and prevalence rates.

Methods

Design of the study

This study was an observational database study to monitor the cervical cancer-related endpoints in female participants aged between 9 and 70 years in Yinzhou, China prior to and following *Cervarix* launch.

The overview of the study design is provided in Figure 1.

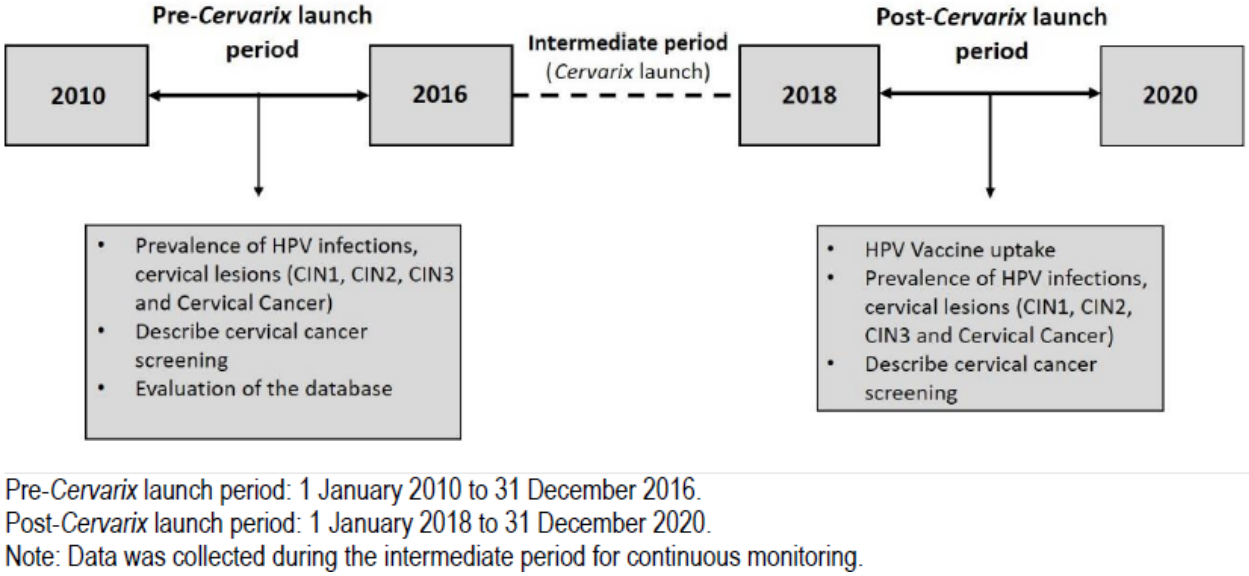


Figure 1. Study design overview (Figure 6.1 CSR)

- Type of study and design: An observational database study (Retrospective cohort study design).
- General study aspects:

- Participant level data were retrieved from the database.
- Study initiation date: 10 September 2021, Study completion date: 26 October 2023, End of study date: 26 October 2023, Data lock point (date of database freeze): 28 April 2023, Date of report: Final, 13 December 2023.
- All subjects will be followed from the index date to the end of the study. Patients will be followed until death, last visit before loss to follow-up, or last visit prior to the end of the study period (December 31, 2020), whichever comes first.

- Study period:
  - Pre-Cervarix launch period: 1 January 2010 to 31 December 2016. First Cervarix doses were sold from July 2017 onwards in China and earlier elsewhere. This might bias slightly the pre-Cervarix launch area computation as potential vaccinated participants may be underestimated.
  - Post-Cervarix launch period: 1 January 2018 to 31 December 2020.
  - For Cervarix vaccine uptake: From first Cervarix vaccination record to 31 December 2020.
  - Intermediate period: 1 January 2017 to 31 December 2017. This period was to ensure no over or under estimation in pre- and post-Cervarix launch period due to few vaccinated participants. As the number of HPV vaccinated participants in that period was negligible, this period was merged with the pre-Cervarix launch period.

  Note: *Cervarix* was approved in China on 12 July 2016 and first available in 2017.

Study population

The population-wide monitoring cohort for HPV vaccines included all female permanent residents aged 9–70 years in Yinzhou District, with immunization data included from the YRHIP.

Due to an administrative adjustment dividing Yinzhou District in 2016, the index date for patients who belonged to Yinzhou District before 2016 is the later date between their registration date in the YRHIP and January 1, 2010; and the index date for patients assigned to Yinzhou District after 2016, it is the later date between their registration date in the YRHIP and January 1, 2017.

Regarding inclusion and exclusion criteria, subjects should have ≥12 months of continuous registration in the YRHIP during the study period, defined by ≥2 observations recorded in YRHIP ≥12 months apart. Baseline period will be used to assess HPV status, using HPV screening results from pre-index date to earliest available data available.

Data Sources

The Yinzhou District CDC has linked different administrative databases of general demographic characteristics, health check information, inpatient and outpatient EMRs, disease management, death certificates, and the immunization program. These databases are inherently linked to each other by a unique and encoded identifier for each individual. By end November 2018, the system integrated 33 hospitals in Yinzhou District, including 7 general hospitals, 2 specialized hospitals, 1 maternal and child health hospital, and 24 community health service centres/township health centres and 287 community health service stations. Another specific feature of this system is that all health-related outcomes, should they be diagnostic outcomes or procedures are coded in accordance to the International Classification of Diseases (ICD). Follow-up is continuous in the health information system meaning that update of important information such as vital status, clinical outcomes and claims data for all cohort members annually from the administrative databases is updated real time.

The General population will include all permanent residents aged between 9 and 70 years registered in the YRHIP from 1 January 2010 to 31 December 2020.

Objectives of the study

The aim of this study was to assess cervical cancer-related endpoints in female population following *Cervarix* vaccination in accordance to local PI using a sequential approach.

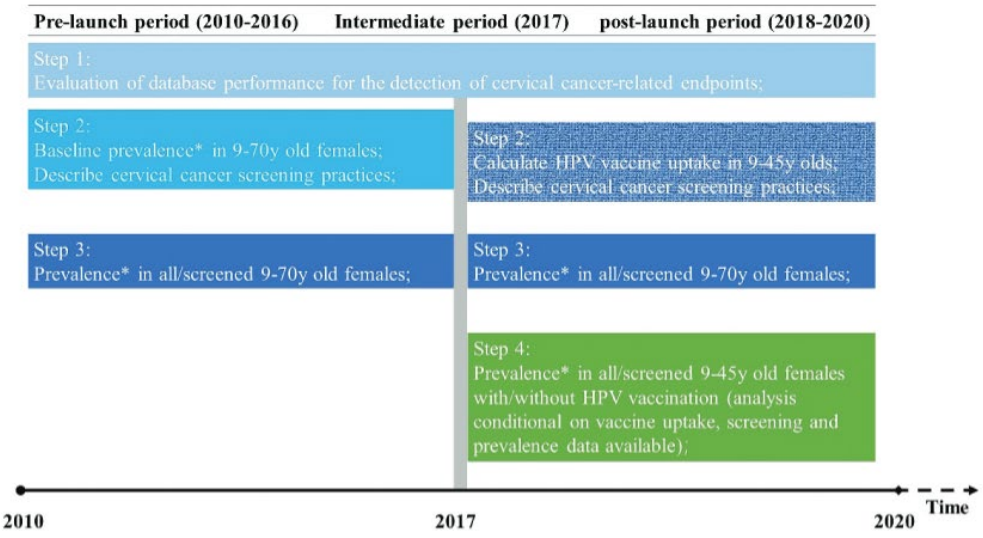


Figure 1. Study design. HPV, human papillomavirus; y, years.
*Prevalence includes prevalence of HPV infections, CIN1, CIN2, CIN3, and cervical cancer cases.

Figure 2. Timeframe and main elements for study design (Deng et al. 2023)

Step 1: Assessment of database performance on cervical cancer-related endpoints (Secondary objective)

- To assess the performance of case identification method for the detection of cervical HPV infection, cervical lesions CIN1, CIN2, CIN3 and cervical cancer, with/without HPV type.

Step 2: Baseline analyses (Secondary objectives)

- To assess background prevalence of cervical HPV infection, cervical lesions CIN1, CIN2, CIN3 and cervical cancer, with/without HPV type, among female participants aged 9 to 70 years during pre-*Cervarix* launch period, overall and by age, per calendar year.
- To assess *Cervarix* vaccination uptake among female participants aged 9 to 45 years, overall and by age, per calendar year.
- To describe cervical cancer screening practices among female participants aged 9 to 70 years, overall and by age, per calendar year per program (governmental or not) during pre- and post-*Cervarix* launch period.

Step 3: Main analysis (Primary objectives)

- To describe the prevalence of cervical cancer-related endpoints of interest* with/without HPV type, among female participants aged 9 to 70 years, overall and by vaccination status, by age, per calendar year during pre- and post-*Cervarix* launch period.

**Cervical cancer-related endpoints of interest, defined as effectiveness endpoint e.g. cervical HPV infection, cervical lesions CIN1, CIN2, CIN3 or cervical cancer, for which case ascertainment and proper case counting in the database can be performed.*

- To describe the prevalence of cervical cancer-related endpoints of interest with/without HPV type, among female participants aged 9 to 70 years screened as per local practice, overall and by vaccination status, by age, per calendar year during pre- and post-*Cervarix* launch period.

Step 4: Conditional analysis (Secondary objectives)

- To assess the probability of occurrence of cervical cancer-related endpoints of interest with/without HPV type, among female participants aged 9 to 45 years, overall and by vaccination status, by age, per calendar year during pre- and post-*Cervarix* launch period conditional on vaccine uptake, cervical cancer screening examinations and observed prevalence within each of the compared study cohorts.
- To assess the probability of occurrence of cervical cancer-related endpoints of interest with/without HPV type, among female participants aged 9 to 45 years screened as per local practice, overall and by vaccination status, by age, per calendar year during pre- and post-*Cervarix* launch period conditional on vaccine uptake, cervical cancer screening examinations and observed prevalence within each of the compared study cohorts.

Endpoints of the study

Step 1:

- Occurrence of cervical cancer-related endpoints defined by ICD-10 codes, symptoms, diagnostic tests/procedures, prescriptions, and/or case narratives when available among female participants (aged 9 to 70 years per calendar year).

Step 2:

- Occurrence of HPV infection, cervical lesions CIN1, CIN2, CIN3 and cervical cancer with/without HPV type.
- Number of participants with at least one dose of HPV vaccine administered, per type of vaccine and per number of administered doses.
- Occurrence of cervical cancer screening examinations.

Step 3-4:

- Occurrence of cervical cancer-related endpoints of interest with/without HPV type.
- Occurrence of cervical cancer-related endpoints of interests with/without HPV type within screened population.

Case definition

In this study for case identification, a list of ICD-10 codes will be used for the extraction. However, endpoint definitions in an electronic medical health records database can be a challenge. Therefore, case validation will be performed based on ICD-10 codes and a combination of disease terms in Chinese, examination, medications and/or procedures, as well as narratives, either alone or in combination to define outcomes of interest.

Cervical cancer-related endpoints will include (amongst others):

- Cervical HPV infection defined as detection of HPV with or without genotype in the cervical sample - ICD-10 code R87.81
- Cervical intraepithelial neoplasia grade 1 - ICD-10 code N87.0
- Cervical intraepithelial neoplasia grade 2 (i.e. moderate cervical dysplasia) - ICD-10 code N87.1
- Cervical intraepithelial neoplasia grade 3 (i.e. severe cervical dysplasia carcinoma in situ of cervix uteri) - ICD-10 code D06
- Cervical cancer (e.g. malignant neoplasm of cervix uteri) - ICD-10 code C53

Challenges in determining clearance or progressions of cervical cancer-related endpoints can be a potential limitation, and therefore cervical cancer-related endpoints of interest will be determined depending on case definition and frequencies based on ICD10 codes (above) or diagnostic test outcomes including HPV type (below).

Cervical cancer screening / diagnostic procedures:

- HPV testing for high-risk HPV types for validation of HPV infection
- Conventional (Pap test) and liquid-based cytology for validation of CIN1, CIN2, CIN3
- Visual inspection with acetic acid (VIA) for validation of CIN1, CIN2, CIN3
- Histopathology of the uterine cervix in Colposcope for validation of CIN+
- Biopsy of uterine cervix for validation of CIN+

Assessor's comment

The traditional method to screen women for cervical cancer has been cytology (the Papanicolaou test, also known as the Pap smear or smear test). When cytology results are positive, the diagnosis is confirmed by colposcopy, and appropriate treatment is informed by biopsy of suspicious lesions for histological diagnosis. Newer screening tests introduced in the last 15 years include visual inspection with acetic acid (VIA), and molecular tests, mainly high-risk HPV DNA-based tests, which are suitable for use in all settings.

The potential cases of each endpoint in YRHIP database will be identify by the ICD-10-based algorithm. And their specific screening / diagnostic procedures will be retrieved directly from the database. If the total number of the cases identifying by the algorithm in the study is more than 200, and then 200 cases will be selected randomly to validate.

Judication process: According to the cervical cancer screening guidelines or China's clinical diagnostic standards, two relevant experts will review the anonymous histopathological results of subjects independently to confirm the diagnosis status (without the original diagnosis and blinded by vaccine history), any disagreements will be resolved by discussion with a third expert.

Assessment of identification Algorithms: Given the low prevalence of the cervical cancer related outcomes, in order to ensure the feasibility of judication, only the cases identified by ICD-10-based algorithms will be validated. Therefore, the positive predictive value (PPV) (together with exact 95% confidence interval [CI]) will be calculated for the determination of best algorithms.

		Judication results		
		Disease	No disease	Total
Algorithm	Disease	A (True cases correctly identified by algorithm)	B (Non-cases wrongly identified as cases by algorithm)	A+B
	No disease	C (True cases not identified by algorithm)	D (true non-cases correctly identified by algorithm)	C+D
	Total	A+C	B+D	A+B+C+D

$$PPV = A/(A + B);$$

Comparing with the results of adjudication committee as "gold standards", a best performance of algorithm with PPV ≥ 70% at least will be applied to further analysis.

If PPV of the ICD-10-based algorithm is found to be low (<70%), case identification method will be further fine-tuned to include, on top of ICD-10 codes, other data sources such as results of gynaecological examination, results of HPV examination, results of cytological examination, etc.

Event and episode definition and counting rules:

An event is defined as an occurrence of an endpoint defined by ICD10 code in a subject. The event date is the date of diagnosis i.e. HPV testing results for HPV infections or histopathological results for CIN, cervical cancer; or, if this is not available, by medical diagnosis in ICD codes related to clinical status or disease.

For a given subject multiple records from various data sources will be merged and concatenated at subject level and the following definitions will apply as:

- One episode – based on temporal relationship and, if available, consistency of HPV testing i.e. the same HPV type(s). In case of progression from HPV infection to CIN1, CIN2, or from CIN1 to CIN2, etc. the events will be counted as an episode for respective endpoints with respective diagnosis date of such endpoint.
- New episode – if there is a proof of recovery from infection/ lesion/ cancer after last event; or if a new HPV type is identified. The start date of new episode is the date of diagnosis after recovery or date of new HPV type identification.
- The same episode – if not meeting criteria of a new episode.

Statistical methods

Sets for analyses

Total set included all eligible participants.

Vaccination Set included all female participants aged 9 to 45 years from the Total Set with at least one dose of any HPV vaccine received during the study period administered.

The **Analysis Set for cervical cancer-related endpoints** included all female participants aged 9 to 70 years from the Total Set during 1 January 2010 to 31 December 2020, who received no HPV vaccine (non-vaccinated) or who received at least one dose of *Cervarix*.

Analysis Screening Women Set for uptake included all female participants from the date first cervical cancer related screening from 1 January 2010, who received no HPV vaccine (non-vaccinated) or who received at least one dose of *Cervarix*. Currently, cervical cancer screening in Yinzhou includes female participants aged 9 to 70 years from governmental program or not governmental program.

Analysis of the objectives

Step 1: Assessment of database performance on cervical cancer-related endpoints (Total set)

Case identification method for cervical cancer-related endpoints (cervical HPV infection, cervical lesions CIN1, CIN2, CIN3 and cervical cancer, with/without HPV type) will be defined using ICD-10 codes available in YRHIP.

For cervical cancer-related endpoints (cervical HPV infection, cervical lesions CIN1, CIN2, CIN3 and cervical cancer, with/without HPV type), PPV of the case identification method will be assessed as follows:

- Case identification method for extraction of cervical cancer-related endpoints will make use of ICD-10 codes.
- For cervical cancer-related endpoints, performance of these ICD-10 based case identification method will be assessed against case identification method using other source data (Chinese disease terms, specify medications and/or examination, and/or procedures, and/or narratives), the latter being considered as a benchmark. In turn, PPV (together with exact 95% confidence interval [CI]) of the ICD-10 based case identification method will be computed. The proportion of confirmed cases (together with exact 95% CI) will be calculated as the number of confirmed cases divided by the total number of cases identified by case identification method.
- If performance of the ICD-10 based case identification method is found to be low, case identification method will be further fine-tuned to include, on top of ICD-10 codes, other data sources such as procedures, lab results, medication, etc.

Step 2: Baseline analysis (Total set)

Annual background prevalence of cervical cancer-related endpoints during prelaunch period: For each cervical cancer-related endpoint, background prevalence (expressed as the number and the percentage of persons with exact 95% CI) during pre-launch period will be calculated among female subjects aged 9-70 years overall and by age, for each calendar year.

Annual vaccine uptake of Cervarix and other HPV vaccine(s): Vaccine uptake of *Cervarix* or other HPV vaccine(s) (expressed as number and the percentage of persons vaccinated with at least one dose of HPV vaccine, together with exact 95% CI) among female subjects aged 9-45 years will be calculated during postlaunch period. Vaccine uptake will be calculated, by vaccine type, per number of administered doses, by the age and overall, per calendar year.

Annual frequency of cervical cancer screening during pre- and post-launch period: Cervical cancer screening frequency and practices per screening program among female subjects aged 9-70 years will be tabulated, overall and by method, by age, for each calendar year during pre- and post-launch period.

Based on the above, the cervical cancer-related endpoints of interest will be defined.

Step 3: Main analysis (Analysis set)

Annual prevalence of cervical cancer-related endpoints of interest per vaccination status during pre- and post-launch period: For cervical cancer-related endpoints of interest (based on pre-launch data

analysis), prevalence (expressed as the proportion of cases, together with exact 95% CIs) during pre and post-launch period will be calculated among female subjects aged 9-70 years overall and separately by vaccination status (at least 1 dose of Cervarix vaccine versus no HPV vaccination, complete vaccination schedule vs no vaccination), by vaccine type, by age for each calendar year.

Annual prevalence of cervical cancer-related endpoints of interest during pre- and post-launch period among female subjects screened for HPV: For cervical cancer-related endpoints of interest (based on pre-launch data analysis), prevalence (expressed as the proportion of cases, together with exact 95% CIs) during pre- and post-launch period will be calculated among female subjects aged 9-70 years who were screened for HPV as per local practice, overall and by vaccination status (at least one dose of Cervarix vaccine versus no HPV vaccination), by vaccine type, by age for each calendar year.

Step 4: Conditional analysis (Analysis set)

Conditional on a minimum number of vaccinated subjects and observed prevalence of cervical cancer-related endpoints, the probability of cervical cancer-related endpoints of intertest may be assessed in the age cohorts where vaccination uptake together with endpoints assessment occurred and/or prevalence of cervical cancer-related endpoint is the highest.

The probability of cervical cancer-related endpoints may be compared between vaccinated and unvaccinated subjects using a Poisson regression adjusted for age and other possible covariates (e.g. calendar year).

The probability of cervical cancer-related endpoints amongst screened women may be compared between vaccinated and unvaccinated subjects, using a Poisson regression adjusted for age and other possible covariates (e.g. calendar year).

Interpretation of analyses

The study is descriptive, and no hypothesis testing will be performed.

Assessor's comment

Cervical cancer screening / diagnostic procedures

Women with Cervical intraepithelial neoplasia grade CIN2 and CIN3 are at high risk for developing invasive cancer, although the average time for progression is still several years. Therefore, women with CIN2/3 should receive treatment. Exceptions to this recommendation are women in the 20 to 24 year age group and pregnant women.
Since a certain percentage of low-grade squamous intraepithelial lesions (LGSIL) on pap smear will have CIN2 or 3, it makes sense that these pap smears still require colposcopy and biopsy in most cases. The same holds for older women with atypical squamous cells of undetermined significance (ASCUS) pap smears who also have a high-risk HPV.
Cytology is the screening test, but histologic characteristics of a tissue biopsy make the diagnosis. Colposcopy with directed biopsy is the preferred method for evaluation of an abnormal pap smear result. "Co-testing" combines cytology and HPV testing for high-risk types, but is still considered screening.
If suspicious lesions are identified during colposcopy, a biopsy may be performed. A small tissue sample is collected from the affected area for further examination during a cervical biopsy. The biopsy results can confirm and validate the presence and grade of CIN of suggestive cellular and histological signs via direct examination. Therefore, the diagnosis of CIN lesions ultimately requires biopsy of the uterine cervix with tissue sampling.

Any prevalence estimates for CIN lesions need to be based on tissue sampling performed under colposcopy with directed biopsy. Case ascertainment/validation based on other types of methods such as HPV testing or Pap smear is not appropriate.

In this study, the cervical cancer diagnostic procedures to validate CIN1/2/3 will include conventional (pap test), liquid-based cytology, visual inspection with acetic acid (VIA) or histopathology of the uterine cervix by colposcopy. The limitations in the availability of appropriate diagnostic tools for detection and characterization of HPV-related infection and CIN lesions may have an impact on outcome identification. The limitations in the case validation/ascertainment process may as well suffer of appropriate case validation for HPV-related infection and CIN lesions. Hence, the estimates of the cervical cancer-related endpoints of interest could be underestimated and/or must be interpreted with caution.

Other important limitations are the suboptimal rate of cervical screening (China achieved national coverage of 36.8% in the year 2018-2019). Also, lack of completeness or inefficiencies in the correct identification of vaccination status could happen.

Results

Participants disposition

The overall disposition of the participants with reasons for exclusion from different analysis set are provided in the Figure 3.

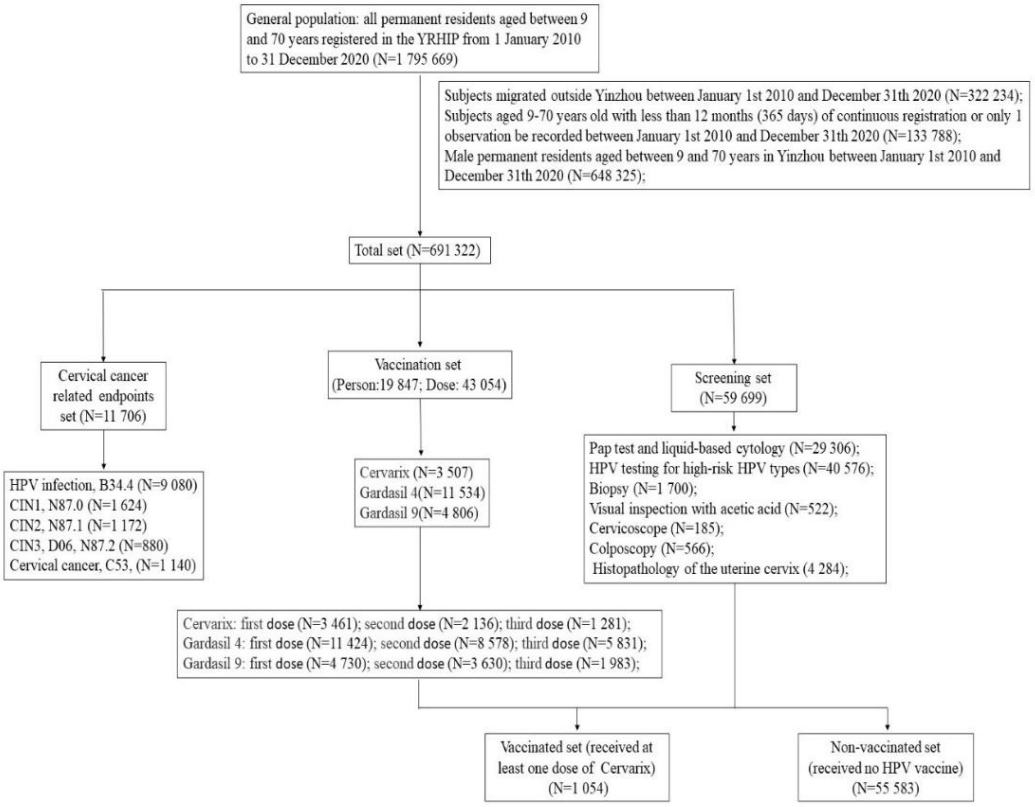


Figure 3. Participants disposition (Figure 11.1 CSR)

The data of a total of 1 795 669 participants were extracted from the database. Out of which, 691 322 eligible participants were included in the Total set. Within the Total set, the following subsets were considered.

The Cervical cancer related endpoints set consisted of 11 706 participants. Out of which, 9080 participants were infected with HPV infection. The number of participants who developed CIN1, CIN2 and CIN3 lesions were 1624, 1172 and 880, respectively. Also, there were 1140 participants who ultimately developed cervical cancer.

The Vaccination set consisted of 19 847 participants (who received at least one dose of the vaccines). Out of which, 3507 participants received *Cervarix*, 11 534 received Gardasil 4 and 4806 received Gardasil 9. Also refer to Table 1 below.

The Screening set consisted of 59 699 participants. Out of which, 29 306 participants were tested using Pap test and liquid based cytology, 40 576 participants were tested using HPV testing for high-risk HPV types, 1700 participants were tested using biopsy, 522 participants were tested using visual inspection with acetic acid, 185 participants were tested using cervicoscope, 566 participants were tested using colposcopy and 4284 participants were tested using histopathology of the uterine cervix. Also refer to Table 2 and Table 3 below.

The vaccinated set was based on the status of vaccine uptake and totalized 1054 participants who received at least one dose of Cervarix There were 55 583 participants who didn't receive any HPV vaccine and were categorized as unvaccinated set.

Table 1. Vaccine uptake rate during study period by age strata, calendar year and number of administered doses – Vaccination set (extract of Table 14.1.5.1., CSR)

Type of vaccine	Variables	Age group	Calendar year, (Cases n / N per 1000)															
			Overall				2018				2019				2020			
			n	N	rate	95%CI	n	N	rate	95%CI	n	N	rate	95%CI	n	N	rate	95%CI
Cervarix	Age at the first dose of vaccination	9-45Y	3461	326934	10.59	(10.24-10.94)	652	322794	2.02	(1.87-2.18)	1178	331322	3.56	(3.36-3.76)	1445	335462	4.31	(4.09-4.53)
		9-17Y	118	31085	3.8	(3.14-4.54)	35	30108	1.16	(0.81-1.62)	54	31298	1.73	(1.3-2.25)	5	32275	0.15	(0.05-0.36)
		18-24Y	369	53889	6.85	(6.17-7.58)	143	53957	2.65	(2.23-3.12)	76	54403	1.4	(1.1-1.75)	38	54335	0.7	(0.49-0.96)
		25-29Y	443	62536	7.08	(6.44-7.77)	90	61255	1.47	(1.18-1.81)	163	64113	2.54	(2.17-2.96)	149	65394	2.28	(1.93-2.67)
		30-34Y	926	59175	15.65	(14.66-16.68)	133	57765	2.3	(1.93-2.73)	326	60313	5.41	(4.84-6.02)	465	61723	7.53	(6.87-8.25)
		35-39Y	926	55012	16.83	(15.77-17.94)	125	54507	2.29	(1.91-2.73)	338	55540	6.09	(5.46-6.77)	460	56045	8.21	(7.48-8.99)
		40-45Y	653	65240	10.01	(9.26-10.8)	117	65204	1.79	(1.48-2.15)	210	65655	3.2	(2.78-3.66)	326	65691	4.96	(4.44-5.53)
	Vaccination doses	1	3461	326934	10.59	(10.24-10.94)	652	322794	2.02	(1.87-2.18)	1178	331322	3.56	(3.36-3.76)	1445	335462	4.31	(4.09-4.53)
		2	2136	326934	6.53	(6.26-6.82)	338	322794	1.05	(0.94-1.16)	665	331322	2.01	(1.86-2.17)	1010	335462	3.01	(2.83-3.2)
		3	1281	326934	3.92	(3.71-4.14)	218	322794	0.68	(0.59-0.77)	541	331322	1.63	(1.5-1.78)	522	335462	1.56	(1.43-1.7)

Table 2. Prevalence of cervical cancer screening item during study period by age strata, program, calendar year and overall –Screening set (extract Table 14.2.2.69.a, CSR)

Year	Age	Prevalence (Cases n / N per 1000, 95%CI)															
		HPV testing				Pap test and liquid-based cytology				Cervicoscope				Colposcopy			
		n	*N*	prevalence	95%CI	n	*N*	prevalence	95%CI	n	*N*	prevalence	95%CI	n	*N*	prevalence	95%CI
2018	9-70Y	9625	475555	20.24	(19.84-20.64)	5161	475555	10.85	(10.56-11.15)	49	475555	0.1	(0.08-0.14)	136	475555	0.29	(0.24-0.34)
	9-17Y	3	29504	0.1	(0.02-0.3)	0	29504	0	(0-0.13)	0	29504	0	(0-0.13)	1	29504	0.03	(0-0.19)
	18-24Y	186	51484	3.61	(3.11-4.17)	45	51484	0.87	(0.64-1.17)	1	51484	0.02	(0-0.11)	3	51484	0.06	(0.01-0.17)
	25-29Y	998	59462	16.78	(15.77-17.85)	484	59462	8.14	(7.43-8.89)	6	59462	0.1	(0.04-0.22)	17	59462	0.29	(0.17-0.46)
	30-34Y	1652	59022	27.99	(26.67-29.35)	908	59022	15.38	(14.41-16.41)	8	59022	0.14	(0.06-0.27)	16	59022	0.27	(0.15-0.44)
	35-39Y	1791	54185	33.05	(31.56-34.59)	1033	54185	19.06	(17.93-20.25)	11	54185	0.2	(0.1-0.36)	20	54185	0.37	(0.23-0.57)
	40-45Y	1858	65529	28.35	(27.1-29.65)	1085	65529	16.56	(15.59-17.56)	7	65529	0.11	(0.04-0.22)	20	65529	0.31	(0.19-0.47)
	46-50Y	1470	44650	32.92	(31.29-34.62)	813	44650	18.21	(16.99-19.49)	9	44650	0.2	(0.09-0.38)	31	44650	0.69	(0.47-0.99)
	51-55Y	948	37437	25.32	(23.75-26.96)	419	37437	11.19	(10.15-12.31)	5	37437	0.13	(0.04-0.31)	11	37437	0.29	(0.15-0.53)
	56-60Y	407	32719	12.44	(11.27-13.7)	166	32719	5.07	(4.33-5.9)	2	32719	0.06	(0.01-0.22)	7	32719	0.21	(0.09-0.44)
	61-65Y	278	25965	10.71	(9.49-12.03)	155	25965	5.97	(5.07-6.98)	0	25965	0	(0-0.14)	9	25965	0.35	(0.16-0.66)
	66-70Y	91	15601	5.83	(4.7-7.16)	67	15601	4.29	(3.33-5.45)	0	15601	0	(0-0.24)	2	15601	0.13	(0.02-0.46)
2019	9-70Y	10873	485519	22.39	(21.98-22.81)	5701	485519	11.74	(11.44-12.05)	40	485519	0.08	(0.06-0.11)	136	485519	0.28	(0.24-0.33)
	9-17Y	2	30782	0.06	(0.01-0.23)	0	30782	0	(0-0.12)	0	30782	0	(0-0.12)	0	30782	0	(0-0.12)
	18-24Y	192	51806	3.71	(3.2-4.27)	53	51806	1.02	(0.77-1.34)	1	51806	0.02	(0-0.11)	1	51806	0.02	(0-0.11)
	25-29Y	1053	62096	16.96	(15.96-18)	425	62096	6.84	(6.21-7.52)	5	62096	0.08	(0.03-0.19)	11	62096	0.18	(0.09-0.32)
	30-34Y	2138	61755	34.62	(33.19-36.09)	1055	61755	17.08	(16.08-18.14)	6	61755	0.1	(0.04-0.21)	19	61755	0.31	(0.19-0.48)
	35-39Y	2114	55314	38.22	(36.64-39.85)	1164	55314	21.04	(19.86-22.27)	13	55314	0.24	(0.13-0.4)	21	55314	0.38	(0.24-0.58)
	40-45Y	1968	66006	29.82	(28.53-31.14)	1163	66006	17.62	(16.63-18.65)	9	66006	0.14	(0.06-0.26)	28	66006	0.42	(0.28-0.61)
	46-50Y	1620	45167	35.87	(34.17-37.62)	940	45167	20.81	(19.51-22.17)	6	45167	0.13	(0.05-0.29)	25	45167	0.55	(0.36-0.82)
	51-55Y	959	37909	25.3	(23.74-26.93)	460	37909	12.13	(11.06-13.29)	0	37909	0	(0-0.1)	18	37909	0.47	(0.28-0.75)
	56-60Y	490	33010	14.84	(13.57-16.21)	246	33010	7.45	(6.55-8.44)	0	33010	0	(0-0.11)	6	33010	0.18	(0.07-0.4)
	61-65Y	264	26089	10.12	(8.94-11.41)	137	26089	5.25	(4.41-6.2)	0	26089	0	(0-0.14)	3	26089	0.11	(0.02-0.34)
	66-70Y	122	15588	7.83	(6.5-9.34)	73	15588	4.68	(3.67-5.88)	0	15588	0	(0-0.24)	5	15588	0.32	(0.1-0.75)
2020	9-70Y	10740	489514	21.94	(21.53-22.35)	4954	489514	10.12	(9.84-10.4)	4	489514	0.01	(0-0.02)	57	489514	0.12	(0.09-0.15)
	9-17Y	2	31830	0.06	(0.01-0.23)	0	31830	0	(0-0.12)	0	31830	0	(0-0.12)	0	31830	0	(0-0.12)
	18-24Y	160	51696	3.1	(2.63-3.61)	36	51696	0.7	(0.49-0.96)	0	51696	0	(0-0.07)	0	51696	0	(0-0.07)
	25-29Y	812	63221	12.84	(11.98-13.75)	302	63221	4.78	(4.25-5.35)	0	63221	0	(0-0.06)	5	63221	0.08	(0.03-0.18)
	30-34Y	2046	63270	32.34	(30.97-33.75)	921	63270	14.56	(13.64-15.52)	1	63270	0.02	(0-0.09)	7	63270	0.11	(0.04-0.23)
	35-39Y	1943	55882	34.77	(33.27-36.32)	1039	55882	18.59	(17.49-19.75)	0	55882	0	(0-0.07)	14	55882	0.25	(0.14-0.42)
	40-45Y	1927	66067	29.17	(27.9-30.48)	1041	66067	15.76	(14.82-16.74)	3	66067	0.05	(0.01-0.13)	6	66067	0.09	(0.03-0.2)
	46-50Y	1574	45325	34.73	(33.06-36.45)	784	45325	17.3	(16.12-18.54)	0	45325	0	(0-0.08)	11	45325	0.24	(0.12-0.43)
	51-55Y	1145	38034	30.1	(28.41-31.87)	454	38034	11.94	(10.87-13.08)	0	38034	0	(0-0.1)	6	38034	0.16	(0.06-0.34)
	56-60Y	666	33005	20.18	(18.69-21.75)	223	33005	6.76	(5.9-7.7)	0	33005	0	(0-0.11)	3	33005	0.09	(0.02-0.27)
	61-65Y	342	25844	13.23	(11.88-14.7)	96	25844	3.71	(3.01-4.53)	0	25844	0	(0-0.14)	3	25844	0.12	(0.02-0.34)
	66-70Y	165	15343	10.75	(9.18-12.51)	67	15343	4.37	(3.39-5.54)	0	15343	0	(0-0.24)	2	15343	0.13	(0.02-0.47)

95%CI: Exact 95% Poisson CIs was calculated

* All of these cervical cancer screening items arenon-governmental

** Cervicoscope is an examination method, which can be used to observe the shape of the uterine cavity, the development of the uterine cavity, the condition of the endometrium, and the pathological changes in the uterine cavity. It can also be used to biopsy the tissues in the cervix.*

** Colposcopy is a test that can be used to check the tissue changes in the cervix and vagina. During colposcopy, visual inspection with acetic acid can be used for testing cervical cancer related disease, as well as biopsy sampling.*

Table 3. Prevalence of cervical cancer screening item during study period by age strata, program, calendar year and overall –Screening set (extract Table 14.2.2.69.b, CSR)

Year	Age	Prevalence (Cases n / N per 1000, 95%CI)											
		Visual inspection with acetic acid				Biopsy				Histopathology			
		n	*N*	prevalence	95%CI	n	*N*	prevalence	95%CI	n	*N*	prevalence	95%CI
2018	9-70Y	133	475555	0.28	(0.23-0.33)	515	475555	1.08	(0.99-1.18)	696	475555	1.46	(1.36-1.58)
	9-17Y	1	29504	0.03	(0-0.19)	0	29504	0	(0-0.13)	0	29504	0	(0-0.13)
	18-24Y	3	51484	0.06	(0.01-0.17)	3	51484	0.06	(0.01-0.17)	5	51484	0.1	(0.03-0.23)
	25-29Y	17	59462	0.29	(0.17-0.46)	46	59462	0.77	(0.57-1.03)	49	59462	0.82	(0.61-1.09)
	30-34Y	16	59022	0.27	(0.15-0.44)	91	59022	1.54	(1.24-1.89)	101	59022	1.71	(1.39-2.08)
	35-39Y	19	54185	0.35	(0.21-0.55)	107	54185	1.97	(1.62-2.39)	130	54185	2.4	(2-2.85)
	40-45Y	20	65529	0.31	(0.19-0.47)	84	65529	1.28	(1.02-1.59)	127	65529	1.94	(1.62-2.31)
	46-50Y	30	44650	0.67	(0.45-0.96)	57	44650	1.28	(0.97-1.65)	100	44650	2.24	(1.82-2.72)
	51-55Y	10	37437	0.27	(0.13-0.49)	46	37437	1.23	(0.9-1.64)	77	37437	2.06	(1.62-2.57)
	56-60Y	7	32719	0.21	(0.09-0.44)	44	32719	1.34	(0.98-1.8)	60	32719	1.83	(1.4-2.36)
	61-65Y	9	25965	0.35	(0.16-0.66)	30	25965	1.16	(0.78-1.65)	39	25965	1.5	(1.07-2.05)
	66-70Y	2	15601	0.13	(0.02-0.46)	7	15601	0.45	(0.18-0.92)	10	15601	0.64	(0.31-1.18)
2019	9-70Y	130	485519	0.27	(0.22-0.32)	502	485519	1.03	(0.95-1.13)	707	485519	1.46	(1.35-1.57)
	9-17Y	0	30782	0	(0-0.12)	0	30782	0	(0-0.12)	0	30782	0	(0-0.12)
	18-24Y	1	51806	0.02	(0-0.11)	8	51806	0.15	(0.07-0.3)	8	51806	0.15	(0.07-0.3)
	25-29Y	11	62096	0.18	(0.09-0.32)	40	62096	0.64	(0.46-0.88)	43	62096	0.69	(0.5-0.93)
	30-34Y	19	61755	0.31	(0.19-0.48)	65	61755	1.05	(0.81-1.34)	91	61755	1.47	(1.19-1.81)
	35-39Y	21	55314	0.38	(0.24-0.58)	108	55314	1.95	(1.6-2.36)	144	55314	2.6	(2.2-3.06)
	40-45Y	26	66006	0.39	(0.26-0.58)	68	66006	1.03	(0.8-1.31)	116	66006	1.76	(1.45-2.11)
	46-50Y	22	45167	0.49	(0.31-0.74)	77	45167	1.7	(1.35-2.13)	132	45167	2.92	(2.45-3.46)
	51-55Y	18	37909	0.47	(0.28-0.75)	62	37909	1.64	(1.25-2.1)	79	37909	2.08	(1.65-2.6)
	56-60Y	5	33010	0.15	(0.05-0.35)	43	33010	1.3	(0.94-1.75)	56	33010	1.7	(1.28-2.2)
	61-65Y	3	26089	0.11	(0.02-0.34)	33	26089	1.26	(0.87-1.78)	39	26089	1.49	(1.06-2.04)
	66-70Y	5	15588	0.32	(0.1-0.75)	1	15588	0.06	(0-0.36)	4	15588	0.26	(0.07-0.66)
2020	9-70Y	46	489514	0.09	(0.07-0.13)	423	489514	0.86	(0.78-0.95)	549	489514	1.12	(1.03-1.22)
	9-17Y	0	31830	0	(0-0.12)	0	31830	0	(0-0.12)	0	31830	0	(0-0.12)
	18-24Y	0	51696	0	(0-0.07)	4	51696	0.08	(0.02-0.2)	4	51696	0.08	(0.02-0.2)
	25-29Y	3	63221	0.05	(0.01-0.14)	17	63221	0.27	(0.16-0.43)	17	63221	0.27	(0.16-0.43)
	30-34Y	7	63270	0.11	(0.04-0.23)	49	63270	0.77	(0.57-1.02)	57	63270	0.9	(0.68-1.17)
	35-39Y	10	55882	0.18	(0.09-0.33)	56	55882	1	(0.76-1.3)	78	55882	1.4	(1.1-1.74)
	40-45Y	5	66067	0.08	(0.02-0.18)	50	66067	0.76	(0.56-1)	81	66067	1.23	(0.97-1.52)
	46-50Y	10	45325	0.22	(0.11-0.41)	68	45325	1.5	(1.17-1.9)	93	45325	2.05	(1.66-2.51)
	51-55Y	5	38034	0.13	(0.04-0.31)	72	38034	1.89	(1.48-2.38)	97	38034	2.55	(2.07-3.11)
	56-60Y	2	33005	0.06	(0.01-0.22)	55	33005	1.67	(1.26-2.17)	62	33005	1.88	(1.44-2.41)
	61-65Y	3	25844	0.12	(0.02-0.34)	45	25844	1.74	(1.27-2.33)	50	25844	1.93	(1.44-2.55)
	66-70Y	1	15343	0.07	(0-0.36)	8	15343	0.52	(0.23-1.03)	11	15343	0.72	(0.36-1.28)

95%CI: Exact 95% Poisson CIs was calculated

* All of these cervical cancer screening items have been non-governmenta

Assessor's comment

Number of vaccinated subjects

The total number of vaccinated female participants, aged between 9 and 70 yoa, with at least one dose of Cervarix was 3507. The total number of vaccinated that received the first dose, the second dose and the third dose of Cervarix in the Yinzhou district were 3461, 2136 and 1281 respectively. The total number of vaccinated participants that received the first dose of Cervarix in the Yinzhou district (n=3461) is slightly smaller than the total number of participants vaccinated with at least one dose of Cervarix (n=3507) because some participants may have received their first dose of Cervarix in another geographic area, and be included in the study. Of these participants 843 were vaccinated by 2018, 2048 by 2019 and 3507 by 2020.

Vaccine uptake

The vaccine uptake was 10.59 per 1000 for Cervarix (at least 1 dose) for the pooled age group of 9 to 45 years and cumulative of the year 2018-2020. Vaccine uptake since 2018 has increased up to 2020 with 2.02 for 2018, 3.56 for 2019 and 4.31 for 2020.

This vaccine uptake is lower than the already low HPV vaccination rate in China (24%). This constitutes a significant limitation of this retrospective observational study. In order to reach an adequate sample size for robust estimates, it is expected that more than 3 years follow-up period foreseen in the study design will be needed. Indeed, the overall assessment showed that given the current vaccine coverage for *Cervarix*, attaining the adequate sample size for vaccine effectiveness calculation would demand a considerable amount of time, and this may constitute a significant limitation of the study[1].

The MAH also mentioned a possible lack of completeness or inefficiencies in the correct identification of vaccination status may have happened, and limit the study result interpretation.

Although it would have been valuable to continue monitoring cervical HPV-related diseases and cancer in the YRHIP database, the MAH is not planning it. This is because of insufficient number of Cervarix-vaccinated participants and consequently insufficient statistical power cannot be achieved as to assess the outcomes of interest.

Screening rates and rates of detection of HPV infections

Between 2010 and 2020, a total 59699 female subjects were screened for HPV, representing 8.6% of the Total set. Most of them (40576) tested using HPV testing for high-risk HPV types and using Pap test and liquid based cytology (29 306). Only 1700 participants were tested using biopsy, 522 participants were tested using visual inspection with acetic acid, 185 participants were tested using cervicoscope, 566 participants were tested using colposcopy and 4284 participants were tested using histopathology of the uterine cervix.

The total number of vaccinated with at least one dose of Cervarix that underwent screening methods was 1054 on a total of 3507 (30%) vaccinated subjects with at least one dose. The total number of unvaccinated that underwent screening methods was 55 583 with a screening rate less than 10% which differs from the vaccinated set. The differences in overall screening rates between the vaccinated versus unvaccinated set is a limitation of this study. This is probably due to the higher awareness of the importance of screening in the vaccinated set. Of note, according to the CSR, China achieved overall national screening coverage of 36.8% in the year 2018-2019. The suboptimal rate of cervical screening is an important limitation of this study.

[1] Yin X, Zhang M, Wang F, et al. A national cross-sectional study on the influencing factors of low HPV vaccination coverage in mainland China. *Front Public Health*. 2023;10:1-8.

The screening detection rate for any types of HPV infections in the vaccinated set vs the unvaccinated set was different with a higher rate in the vaccinated set (278.76 vs 182.13 for the post-Cervarix launch period 2018-2020, refer to CSR Table 14.2.2.7). This was also observed for the detection rate of CIN1 and to a minor extent for CIN2 and CIN3 (refer to CSR tables 11.9, 11.10 and 11.11). This suggests that the vaccinated set had a different seeking behavior for screening than the unvaccinated and might be explained by better awareness of the importance of screening.

Screening performance for CIN lesions

There are limitations related to the availability of appropriate diagnostic tools for the detection and the characterization of CIN lesions that may have had an impact on outcome validation of CIN lesions. Indeed, only tissue sampling of the cervix by colposcopy or cervicoscopy with microscopic preparation for histopathology examination can validate/confirm CIN lesions and their grade. HPV testing and Pap smear cannot confirm or validate CIN lesions. Case ascertainment for CIN lesions using these screening results is not considered a valid diagnostic tool but only a screening method. Hence, the suboptimal rate of appropriate diagnostic procedures is an important limitation of this study.

Furthermore, all the cervical cancer screening methods mentioned in the protocol (including HPV testing and Pap tests) were not part of governmental screening program in the specific region district that was investigated which is an important limitation as this could lead to underestimates of the prevalences in the vaccinated as well as the unvaccinated sets related to financial constraints of the subjects. Biopsy sampling rate via colposcopy within the screening set (and/or to a minor extent during cervicoscopy) was very low (<0.1%).

Therefore, the values of the cervical cancer related endpoints of interests must be interpreted with caution and cannot provide reliable conclusions.

Demographics

The demographic and baseline characteristics for the participants in various analysis data sets are provided in Table 4.

Table 4. Demographic characteristics (Table 11.1 CSR)

		Total set	Vaccination set	Screening set	Cervical cancer-related endpoints set
	N	691 322	19 847	59 699	11 706
Age of registration	Mean	38.64	24.79	36.46	40.60
	SD	14.44	8.18	10.15	11.69
	Median	38.00	26.00	36.00	40.00
	Minimum and Maximum	9-70	9-59	9-70	9-70
Age of event (diagnosis/vaccination /screening)	Mean	-	31.47	41.87	46.47
	SD	-	7.15	10.07	11.58
	Median	-	32.00	41.00	46.00
	Minimum and Maximum	-	10-67	14-80	14-80
Age group of registration, n(%)	9-17Y	45 989 (6.65)	4 968 (25.03)	940 (1.57)	201 (1.72)
	18-24Y	75 506 (10.92)	4 317 (21.75)	6 318 (10.58)	1 023 (8.74)
	25-29Y	85 876 (12.42)	4 304 (21.69)	9 581 (16.05)	1 571 (13.42)
	30-34Y	85 046 (12.30)	4 087 (20.59)	10 394 (17.41)	1 933 (16.51)
	35-39Y	78 402 (11.34)	1 695 (8.54)	10 148 (17.00)	1 848 (15.79)
	40-45Y	97 333 (14.08)	461 (2.32)	11 144 (18.76)	2 220 (18.96)
	46-50Y	64 335 (9.31)	9 (0.05)	5 401 (9.05)	1 296 (11.07)
	51-55Y	53 227 (7.70)	4 (0.02)	2 885 (4.83)	864 (7.38)
	56-60Y	47 516 (6.87)	2 (0.01)	1 693 (2.84)	448 (3.83)
	61-65Y	36 786 (5.32)	0 (0.00)	844 (1.41)	228 (1.95)
	66-70Y	21 306 (3.08)	0 (0.00)	351 (0.59)	74 (0.63)
Age group of event (diagnosis/vaccination /screening), n(%)	9-17Y	-	224 (1.13)	10 (0.02)	3 (0.03)
	18-24Y	-	4 243 (21.38)	1 167 (1.95)	225 (1.92)
	25-29Y	-	3 843 (19.36)	6 068 (10.16)	958 (8.18)
	30-34Y	-	4 950 (24.94)	10 876 (18.22)	1 704 (14.56)

		Total set	Vaccination set	Screening set	Cervical cancer-related endpoints set
	35-39Y	-	4 564 (23.00)	11 403 (19.10)	2 000 (17.09)
	40-45Y	-	2 947 (14.85)	13 240 (22.18)	2 331 (19.91)
	46-50Y	-	106 (0.53)	10 566 (17.70)	2 008 (17.15)
	51-55Y	-	16 (0.08)	6 102 (10.22)	1 446 (12.35)
	56-60Y	-	2 (0.01)	3 219 (5.39)	995 (8.50)
	61-65Y	-	2 (0.01)	2 006 (3.36)	700 (5.98)
	66-70Y	-	1 (0.01)	896 (1.50)	275 (2.35)
Age group of diagnosis, n(%)	9-17Y	-	-	-	3 (0.03)
	18-24Y	-	-	-	225 (1.92)
	25-29Y	-	-	-	958 (8.18)
	30-34Y	-	-	-	1 704 (14.56)
	35-39Y	-	-	-	2 000 (17.09)
	40-45Y	-	-	-	2 331 (19.91)
	46-50Y	-	-	-	2 008 (17.15)
	51-55Y	-	-	-	1 446 (12.35)
	56-60Y	-	-	-	995 (8.50)
	61-65Y	-	-	-	700 (5.98)
	66-70Y	-	-	-	275 (2.35)
Education level, n(%)	Illiterate and semi-illiterate	85 655 (12.39)	1 537 (7.74)	5 357 (8.97)	1 157 (9.88)
	Primary school and junior high school	377 678 (54.63)	3 960 (19.95)	28 136 (47.13)	6 067 (51.83)
	Senior high school/technical school	95 854 (13.87)	3 412 (17.19)	9 593 (16.07)	1 785 (15.25)
	Junior College or above degree	117 065 (16.93)	10 734 (54.08)	15 744 (26.37)	2 516 (21.49)
	Unknown	15 081 (2.18)	204 (1.03)	869 (1.46)	181 (1.55)
Married status, n(%)	Unmarried	87 006 (12.59)	1 078 (5.43)	3 569 (5.98)	674 (5.76)
	Married	531 738 (76.92)	11 883 (59.87)	51 172 (85.72)	9 949 (84.99)
	Divorced/widowed	16 941 (2.45)	70 (0.35)	911 (1.53)	277 (2.37)
	Unknown	55 637 (8.05)	1 078 (5.43)	4 047 (6.78)	806 (6.89)

N = total number of participants
n = number of Participants with at least one record in the specified category
% = 100*n/N
SD = standard deviation
Source: Table 14.1.3.2

- Amongst the 691 322 participants in the Total set, the highest number of participants (n=97 333) were concentrated among the age group of registration 40 to 45 years, followed by age group of registration 25 to 29 years (n=85 876). Majority of participants were married (n=531 738) with the most common educational qualification as primary school and junior high school (n=377 678).
- Amongst the 11 706 participants in the Cervical cancer related endpoints set, the highest number of participants (n=2220) were concentrated among the age group of registration 40 to 45 years and maximum number of events (diagnosis) reported (n=2331). Majority of the

participants were married (n=9949) with the most common educational qualification as primary school and junior high school (n=6067).

- Amongst the 19 847 participants in the Vaccination set, the highest number of participants (n=4968) were concentrated among the age group of registration 9 to 17 years and the age group of registration 30 to 34 years experienced the maximum number of events (n=4950). Majority of the participants were married (n=11 883) with the most common educational qualification as junior college or above degree (n=10 734).
- Amongst the 59 699 participants in the Screening set, the highest number of participants (n=11 144) were concentrated among the age group of registration 40 to 45 years and the maximum number of events experienced (n=13 240). Majority of the participants were married (n=51 172) with the most common educational qualification as primary school and junior high school (n=28 136).

Assessor's comment

Mean age of participants included in the Vaccination set (24.8 [SD 8.2]) was lower than mean age of Total set (38.6 [SD 14.4]), Screening set (36.5 [SD 10.1]) and Cervical cancer-related endpoints set (40.6 [SD 11.7]).

Similarly the mean age of event of participants included in the Vaccination set (31.5 [SD 7.1]) was lower than mean age of Screening set (41.9 [SD 10.1]) and Cervical cancer-related endpoints set (46.5 [SD 11.6]).

The vaccinated set had a lower marital status and a higher education background when compared to screening set. Thus, the vaccinated set seems to be quiet different when compared to the screening set, any result comparisons will need to be interpreted with caution. In addition, demographics correspond to the whole vaccinated set, i.e. not restricted to the Cervarix vaccinated set.

According to Table 1, only 4 % of the Cervarix vaccinated participants were dosed between 9-17 years of age. Around 11% of the vaccinated participants were dosed between 18-24 years of age, 13% between 25-29 years of age and 27% between 30-34 and 35-39 years of age. Around 19% of the vaccinated participants were dosed between 40-45 years of age.

Event was diagnosed in only 1.1% of the 9-17 years of age of the vaccinated participants, while around 20-25% of events were diagnosed in each age category of 25-29, 30-34, 35-39 years of age. Around 15% of events were diagnosed in the 40-45 years of age category. Less than 1% of the events were diagnosed between age of 46-70 years.

Only 1.6% of the participants of the screening set were 9-17 years of age, 10% were 18-24 years of age and around 16-19% were in of each age category of 25-29, 30-34, 35-39, 40-45 years of age.

Results of main primary objectives

Detection rate of each type of HPV infection during pre-Cervarix launch period (2010-2017).

The detection rate of each type of HPV infection during pre-Cervarix launch period (2010-2017) are provided in the Table 11.2 and Table 11.3 of the CSR.

- Overall (pooled age groups, cumulative of the year 2010-2017), the detection rate (per 1000 population) was maximum for all types of HPV infection (198.07; 95% CI=191.90, 204.34) in the pooled age group of 9 to 70 years. The detection rate was maximum in the age group 9 to 17 years (333.33; 95% CI=8.40, 905.70) followed by the age group 56 to 60 years (263.31; 95% CI=230.91, 297.73) for all types of HPV infection.

- The detection rate (per 1000 population) for HPV-16 infection was 10.92 (95% CI=9.37, 12.66) in the pooled age group of 9 to 70 years. The detection rate was maximum in the age group 18 to 24 years (27.71; 95% CI=13.91, 49.04) followed by the age group 66 to 70 years (26.85; 95% CI=7.36, 67.31) for HPV-16 infection.
- The detection rate (per 1000 population) for HPV-18 infection was 4.08 (95% CI=3.15, 5.20) in the pooled age group of 9 to 70 years. The detection rate was maximum in the age group 18 to 24 years (7.56; 95% CI=1.56, 21.92) followed by the age group 30 to 34 years (6.30; 95% CI=3.67, 10.06) for HPV-18 infection.

Prevalence of each type of HPV infection during pre-Cervarix launch period (2010-2017).

Prevalence of each type of HPV infection during pre-Cervarix launch period (2010-2017) are provided in the Table 11.4 and Table 11.5 of the CSR.

- Overall (pooled age groups, cumulative of the year 2010-2017), the prevalence (per 100 000 population) was maximum for all types of HPV infection (913.58; 95% CI=882.12, 945.87) in the pooled age group of 9 to 70 years. The prevalence was maximum in the age group 46 to 50 years (1510.12; 95% CI=1384.31, 1644.15) followed by the age group 35 to 39 years (1452.01; 95% CI=1332.68, 1579.04) for all types of HPV infection.
- The prevalence (per 100 000 population) for HPV-16 infection was 50.38 (95% CI=43.18, 58.45) in the pooled age group of 9 to 70 years. The prevalence was maximum in the age group 35 to 39 years (91.76; 95% CI=63.56, 128.21) followed by the age group 46 to 50 years (77.96; 95% CI=51.38, 113.41) for HPV-16 infection.
- The prevalence (per 100 000 population) for HPV-18 infection was 18.82 (95% CI=14.53, 23.99) in the pooled age group of 9 to 70 years. The prevalence was maximum in the age group 30 to 34 years (47.05; 95% CI=27.41, 75.32) followed by the age group 35 to 39 years (32.39; 95% CI=16.74, 56.57) for HPV-18 infection.

Detection rate of each type of HPV infection during post-Cervarix launch period (2018-2020)

The detection rate of each type of HPV infection during post-Cervarix launch period (2018-2020) are provided in Table 11.6 of the CSR.

- Overall (pooled age groups, cumulative of the year 2018-2020), the detection rate (per 1000 population) was maximum for all types of HPV infection (178.93; 95% CI=174.40, 183.53) in the pooled age group of 9 to 70 years. The detection rate was maximum in the age group 9 to 17 years (285.71; 95% CI=36.69, 709.58) followed by the age group 61 to 65 years (276.07; 95% CI=245.62, 308.15) for all types of HPV infection.
- The detection rate (per 1000 population) for HPV-16 infection was 12.13 (95% CI=10.86, 13.50) in the pooled age group of 9 to 70 years. The detection rate was maximum in the age group 66 to 70 years (30.30; 95% CI=15.22-53.57) followed by the age group 61 to 65 years (18.40; 95% CI=10.34, 30.17) for HPV-16 infection.
- The detection rate (per 1000 population) for HPV-18 infection was 5.42 (95% CI=4.59, 6.37) in the pooled age group of 9 to 70 years. The detection rate was maximum in the age group 56 to 60 years (8.46; 95% CI=4.38, 14.74) followed by the age group 66 to 70 years (8.26; 95% CI=1.71, 23.96) for HPV-18 infection.
- The detection rate was maximum for all types of HPV infection for the vaccinated (278.76; 95% CI=221.34, 342.09) and the unvaccinated (182.13; 95% CI=177.53, 186.8) population.

- The detection rate for HPV-16 infection was 4.42 (95% CI=0.11, 24.41) for the vaccinated and 12.27 (95% CI=10.99, 13.66) for the unvaccinated population.
- The detection rate for HPV-18 infection was 0 (95% CI=0, 16.19) for the vaccinated and 5.48 (95% CI=4.63, 6.44) for the unvaccinated population.

Prevalence of each type of HPV infection during post-Cervarix launch period (2018-2020)

The prevalence of each HPV infection type during post-Cervarix launch period (2018-2022) are provided in Table 11.7 of the CSR.

- Overall (pooled age groups, cumulative of the year 2018-2020), the prevalence (per 100 000 population) was maximum for all types of HPV infection (1018.45; 95% CI=990.23, 1047.27) in the pooled age group of 9 to 70 years. The prevalence was maximum in the age group 35 to 39 years (1634.61; 95% CI=1530.06, 1744.34) followed by the age group 51 to 55 years (1496.19; 95% CI=1375.85, 1624.12) for all types of HPV infection.
- The prevalence (per 100 000 population) for HPV-16 infection was 69.02 (95% CI=61.79-76.87) in the pooled age group of 9 to 70 years. The prevalence was maximum in the age group 46 to 50 years (107.12; 95% CI=78.99, 142.01) followed by the age group 51 to 55 years (98.50; 95% CI=69.36, 135.75) for HPV-16 infection.
- The prevalence (per 100 000 population) for HPV-18 infection was 30.86 (95% CI=26.09-36.25) in the pooled age group of 9 to 70 years. The prevalence was maximum in the age group 35 to 39 years (58.44; 95% CI=39.98, 82.50) followed by the age group 51 to 55 years (47.92; 95% CI=28.40, 75.72) for HPV-18 infection.
- The prevalence was maximum for all types of HPV infection for the vaccinated (1796.41; 95% CI=1383.10, 2292.60) and the unvaccinated (1039.87; 95% CI=1011.05, 1069.29) population.
- The prevalence for HPV-16 infection was 28.51 (95% CI=0.72, 158.77) for the vaccinated and 70.05 (95% CI=62.69, 78.04) for the unvaccinated population.
- The prevalence for HPV-18 infection was 0 (95% CI=0, 105.13) for the vaccinated and 31.3 (95% CI=26.44, 36.79) for the unvaccinated population.

Assessor's comment

Detection rate

The detection rate (per 1000 population) was 198.07 (95% CI: 191.90, 204.34) and 178.93 (95% CI: 174.40, 183.53) for all types of HPV infection in the pooled age group of 9 to 70 years during the pre- and post-Cervarix launch period, respectively.

During the pre-Cervarix launch period, the detection rate (per 1000 population) for HPV-16 infection was 10.92 (95% CI: 9.37, 12.66) and for HPV-18 infection was 4.08 (95% CI: 3.15, 5.20) in the pooled age group of 9 to 70 years.

During the post-Cervarix launch period, the detection rate (per 1000 population) for HPV-16 infection was 12.13 (95% CI: 10.86, 13.50) and for HPV-18 infection was 5.42 (95% CI:4.59, 6.37) in the pooled age group of 9 to 70 years.

Noteworthy, the detection rate for HPV-16 infection was 4.42 (95% CI: 0.11, 24.41) for the vaccinated while it was 12.27 (95% CI: 10.99, 13.66) for the unvaccinated population. The detection rate for HPV-18 infection was 0 (95% CI: 0, 16.19) for the vaccinated while it was 5.48 (95% CI: 4.63, 6.44) for the unvaccinated population.

Prevalence

The prevalence (per 100 000 population) was 913.58 (95% CI: 882.12, 945.87) and 1018.45 (95% CI: 990.23, 1047.27) for all types of HPV infection in the pooled age group of 9 to 70 years during the pre- and post-Cervarix launch period, respectively.

During the pre-Cervarix launch period, the prevalence (per 100 000 population) for HPV-16 infection was 50.38 (95% CI: 43.18, 58.45) and for HPV-18 infection was 18.82 (95% CI: 14.53, 23.99) in the pooled age group of 9 to 70 years.

During the post-Cervarix launch period, the prevalence (per 100 000 population) for HPV-16 infection was 69.02 (95% CI: 61.79-76.87) and for HPV-18 infection was 30.86 (95% CI: 26.09-36.25 in the pooled age group of 9 to 70 years.

The number of vaccinated individuals who were positive for any HPV types for the complete post-Cervarix launch period is very limited (total N= 72).

The overall prevalence for all types of HPV infection were not lower for the vaccinated (1796.41; 95% CI=1383.10, 2292.60) versus the unvaccinated (1039.87; 95% CI=1011.05, 1069.29) population during the whole post-Cervarix launch period (2018-2020).

A trend for lower prevalence for HPV-16 and HPV-18 infection was observed in vaccinated individuals versus unvaccinated individuals for the whole post-Cervarix launch period; the prevalence for HPV-16 was 28.51 (95% CI: 0.72, 158.77) for the vaccinated and 70.05 (95% CI: 62.69, 78.04) for the unvaccinated population. The prevalence for HPV-18 infection was 0 (95% CI: 0, 105.13) for the vaccinated and 31.3 (95% CI: 26.44, 36.79) for the unvaccinated population.

The prevalence of selected type of HPV infection during the post-Cervarix launch period, per year, is summarized in the table below:

Prevalence of each type of HPV infection during post-*Cervarix* launch period (2018-2020) - Total set and Cervical cancer related endpoints set (per 100, 000) (from Table 1.4, CSR)

	2018		2019		2020	
	Vaccinated N=843	Unvaccinated N=474688	Vaccinated N=2048	Unvaccinated N=481020	Vaccinated N=3507	Unvaccinated N=476008
All HPV types	593.12 (5)	296.19 (1406)	1171.88 (24)	360.48 (1734)	1226.12 (43)	457.14 (2176)
HPV 16	0 (0)	21.49 (102)	48.83 (1)	27.86 (134)	0 (0)	24.37 (116)
HPV 18	0 (0)	9.9 (47)	0 (0)	11.85 (57)	0 (0)	10.5 (50)
HPV 16/18/31/33/45	0 (0)	445.5 (216)	146.48 (3)	61.12 (294)	57.03 (2)	53.36 (254)

Although a trend for lower cases of HPV-16 and HPV-18 is observed in the vaccinated individuals versus the non-vaccinated individuals, conclusion cannot be drawn.

Prevalence and associated 95% CI of other cervical cancer related diseases (including CIN1, CIN2, CIN3 and cervical cancer) per calendar year by HPV type and age strata during the post-Cervarix launch period.

Prevalence per calendar year of **CIN1** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN1 (overall population) in the pooled age group of 9 to 70 years.

- The prevalence in the year 2018 was 237.25 (95% CI=28.74, 854.37) for the vaccinated population and 66.99 (95% CI=59.83, 74.77) for the non-vaccinated population.
- The prevalence in the year 2019 was 146.48 (95% CI=30.22, 427.49) for the vaccinated population and 67.98 (95% CI=60.81, 75.76) for the non-vaccinated population.
- The prevalence in the year 2020 was 285.14 (95% CI=136.82, 523.76) for the vaccinated population and 69.12 (95% CI=61.85, 77) for the non-vaccinated population.

Prevalence per calendar year of **CIN2** among overall population during the entire study period.

The prevalence (per 100 000 population) of CIN2 (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 30.76 (95% CI=25.97, 36.17) for the non-vaccinated population.
- The prevalence in the year 2019 was 146.48 (95% CI=30.22, 427.49) for the vaccinated population and 34.51 (95% CI=29.46, 40.18) for the non-vaccinated population.
- The prevalence in the year 2020 was 114.06 (95% CI=31.09, 291.77) for the vaccinated population and 31.72 (95% CI=26.86, 37.2) for the non-vaccinated population.

Prevalence per calendar year of **CIN3** among overall population during the entire study period.

The prevalence (per 100 000 population) of CIN3 (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 23.59 (95% CI=19.43, 28.39) for the non-vaccinated population.
- The prevalence in the year 2019 was 48.83 (95% CI=1.24, 271.75) for the vaccinated population and 30.77 (95% CI=26.01, 36.14) for the non-vaccinated population.
- The prevalence in the year 2020 was 28.51 (95% CI=0.72, 158.77) for the vaccinated population and 28.78 (95% CI=24.16, 34.02) for the non-vaccinated population.

Prevalence per calendar year of **cervical cancer** among overall population during the entire study period.

The prevalence (per 100 000 population) of cervical cancer (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 58.99 (95% CI=52.28, 66.31) for the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 73.18 (95% CI=65.73, 81.23) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 72.27 (95% CI=64.83, 80.32) for the non-vaccinated population.

Prevalence per calendar year of **CIN1 with HPV-16 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN1 with HPV-16 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 0.63 (95% CI=0.13, 1.85) for the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 1.04 (95% CI=0.34, 2.43) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.45) for the non-vaccinated population.

Prevalence per calendar year of **CIN1 with HPV-18 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN1 with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 0.63 (95% CI=0.13, 1.85) for the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.42 (95% CI=0.05, 1.50) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.45) for the non-vaccinated population.

Prevalence per calendar year of **CIN2 with HPV-16 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN2 with HPV-16 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 0.84 (95% CI=0.23, 2.16) for the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 1.87 (95% CI=0.86, 3.55) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.45) for the non-vaccinated population.

Prevalence per calendar year of **CIN2 with HPV-18 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN2 with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.21 (95% CI=0.01, 1.16) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the non-vaccinated population.

Prevalence per calendar year of **CIN3 with HPV-16 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN3 with HPV-16 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.46) for the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 1.46 (95% CI=0.59, 3.00) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.68 (95% CI=0.73, 3.31) for the non-vaccinated population.

Prevalence per calendar year of **CIN3 with HPV-18 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN3 with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.21 (95% CI=0.01, 1.16) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the non-vaccinated population.

Prevalence per calendar year of **cervical cancer with HPV-16 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of cervical cancer with HPV-16 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 0.84 (95% CI=0.23, 2.16) for the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 1.87 (95% CI=0.86, 3.55) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.45) for the non-vaccinated population.

Prevalence per calendar year of **cervical cancer with HPV-18 type** among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of cervical cancer with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

- There were no cases reported in the year 2018 for the vaccinated population and the non-vaccinated population.
- There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.42 (95% CI=0.05, 1.50) for the non-vaccinated population.
- There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 0.63 (95% CI=0.13, 1.84) for the non-vaccinated population.

Prevalence of HPV infection (all types of HPV) during the entire study period (2010-2020)

The prevalence of HPV infection (all types of HPV) during the entire study period (2010-2020) is provided in the Table 11.8 of the CSR.

Prevalence of CIN1, CIN2, CIN3 and Cervical cancer during the entire study period (2010-2020)

The Prevalence of CIN1, CIN2, CIN3 and Cervical cancer during the entire study period are provided in the Table 11.9, Table 11.10, Table 11.11, and Table 11.12 of the CSR, respectively.

Prevalence and associated 95% CI of other cervical cancer related diseases (including CIN1, CIN2, CIN3 and cervical cancer) per calendar year by HPV type and age strata.

Prevalence per calendar year of CIN1, CIN2, CIN3, cervical cancer among overall population and among participants who underwent cervical cancer related screening during the entire study period by age strata are provided in the Table 11.13 to 30 and in Figures 11.2 to 11.11 of the CSR.

Assessor's comment

These main results showed a higher prevalence in the post-Cervarix launch period (2018-2020) of HPV infections, CIN1, CIN2 and CIN3 in the vaccinated set versus the unvaccinated set.

Prevalence of HPV infections, CIN1, CIN2, CIN3 and cervical cancer during the post-Cervarix launch period per vaccination status and per year are summarized in the table below (total set, per 100 000 population):

	2018		2019		2020	
	Vaccinated N= 843	Unvaccinated N= 474688	Vaccinated N= 2048	Unvaccinated N= 481020	Vaccinated N= 3507	Unvaccinated N= 476008
HPV infections	711.74 (6) [261.63, 1542.69]	311.99 (1481) [296.33, 328.27]	1171.88 (24) [752.25, 1738.67]	373.17 (1795) [356.13, 390.8]	1796.41 (63) [1383.1, 2292.6]	681.08 (3242) [657.91, 704.85]
CIN1	237.25 (2) [28.74, 854.37]	66.99 (318) [59.83, 74.77]	146.48 (3) [30.22, 427.49]	67.98 (327) [60.81, 75.76]	285.14 (10) [136.82, 523.76]	69.12 (329) [61.85, 77]
CIN2	0 (0) [0, 436.63]	30.76 (146) [25.97, 36.17]	146.48 (3) [30.22, 427.49]	34.51 (166) [29.46, 40.18]	114.06 (4) [31.09, 291.77]	31.72 (151) [26.86, 37.2]
CIN3	0 (0) [0, 436.63]	23.59 (112) [19.43, 28.39]	48.83 (1) [1.24, 271.75]	30.77 (148) [26.01, 36.14]	28.51 (1) [0.72, 158.77]	28.78 (137) [24.16, 34.02]
Invasive CC	0 (0) [0, 436.63]	58.99 (280) [52.28, 66.31]	0 (0) [0, 179.96]	73.18 (352) [65.73, 81.23]	0 (0) [0, 105.13]	72.27 (344) [64.83, 80.32]

During the post-Cervarix launch period, the prevalences (per 100 000) for the following endpoints in the vaccinated versus unvaccinated subjects were for:

HPV infections : 711.74 vs 311.99 in 2018, 1171.88 vs 373.17 in 2019 and 1796.41 vs 681.08 in 2020

CIN1 : 237.25 vs 66.99 in 2018, 146.48 vs 67.98 in 2019 and 285.14 vs 69.12 in 2020

CIN2 : 0 vs 30.76 in 2018, 146.48 vs 34.51 in 2019 and 114.06 vs 31.72 in 2020

CIN3 : 0 vs 23.59 in 2018, 48.83 vs 30.77 in 2019, 28.51 vs 28.78 in 2020

ICC : 0 vs 58.99 in 2018, 0 vs 73.18 in 2019 and 0 vs 72.27 in 2020

Cervical intraepithelial neoplasia results from HPV infection within cervical cells. These changes, especially in young women, commonly revert to normal cells due to an intact immune response and rapid turnover of cells on the cervix. About 60% of CIN1 will regress to normal after 1 year. The time interval between the acquisition of HPV infection and progression to CIN2/CIN3 and invasive carcinoma may take several years.

Surprisingly in this study, overall, the data revealed a higher prevalence in the vaccinated compared to the unvaccinated individuals for HPV infection, CIN1, CIN2 and CIN3. Results show an apparent higher prevalence in HPV infections and CIN1 lesions for the vaccinated cohort compared to the unvaccinated population between 2018 and 2020. No cases were reported for CIN2/CIN3 and ICC for the year 2018 but higher prevalences were observed for CIN2 and CIN3 for the vaccinated cohort compared to the unvaccinated population in the years 2019 and 2020. No cases were reported for ICC in the vaccinated individuals between 2018 and 2020.

There were no cases of CIN1, CIN2, CIN3 and cervical cancer with HPV-16 and HPV-18 types in the vaccinated individuals during the post-Cervarix launch period. Cases of CIN1, CIN2, CIN3 and cervical cancer with HPV-16 and HPV-18 types were detected only in a very low number of non-vaccinated participants (<10 and <5 per year for HPV-16 and HPV-18 type, respectively).

Overall, the prevalence in the vaccinated and unvaccinated cohort was very low for the HPV infections and overall CIN lesions suggesting that the registry database has significant limitations (case ascertainment related) and/or that the screening rates were insufficient at the time of the study. Moreover, the study design covered only a 3 year period post-launch of Cervarix vaccination. Therefore, the follow-up period of this study was insufficient to detect a measurable impact of the vaccination on cervical cancer-related endpoints of interest on this specific population.

These limitations imply caution in the interpretation of the prevalence observed for the cervical cancer related endpoints of interests in the vaccinated versus unvaccinated individuals. No conclusions can be made on the data observed.

Results of secondary objectives

Algorithm 4 output of each HPV infection type after inclusion date among the Total set.

Algorithm 4 identified confirmed cases of each HPV type infection in the Yinzhou database, and the higher prevalence was seen for HPV-52 (n=946), 58 (n=561) and 16 (n=497) type.

Note: Note: Algorithm 1 consisted of Chinese terms, Algorithm 2 was ICD-10 codes, Algorithm 3 was Algorithm 1 or 2 and Algorithm 4 consisted of the result of HPV testing.

Table 5: Identification of Algorithm 4 output of each HPV infection type after inclusion date among the total set

HPV type	Confirmed cases(n) *
HPV-16	497
HPV-18	210
HPV-31	146
HPV-33	200
HPV-35	71
HPV-39	266
HPV-45	59
HPV-51	345
HPV-52	946
HPV-56	173
HPV-58	561
HPV-59	133
HPV-66	180
HPV-68	246
HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68**	4232
Irrespective of HPV type	7797

* In this study, we found that very few diagnoses involving HPV infection included genotyping results. Therefore, we used the result of HPV testing to identify the genotype of HPV infection. In this case, because the algorithm we use to determine genotype is the reference that we chose to determine the confirmed cases (for example, the specific HPV test such as HPV-16, and their result shown as "positive (阳性)" or "+" or "virus load > 500") in the protocol (the reference source against which we confirm as true case the data extracted by the algorithms).

Algorithm's performance validation of other cervical cancer related diseases after inclusion date among the Total set.

Based on the algorithm's performance, algorithm 3 or manual check confirmed cases of algorithm 4 was used as the final algorithms.

The PPV of final algorithms was 99.41%, 89.47%, 79.26%, 85.88% and 78.18% for HPV infection, CIN1, CIN2, CIN3 and cervical cancer, respectively.

Note: Algorithm 4 consisted of the result of HPV testing.

Occurrence of cervical cancer related endpoints identified by different algorithms.

The number of occurrences amongst different age groups increased over the period of 10 years, from 2010 to 2020 for the pooled age group 9 to 70 years.

Final algorithm (algorithm 3+manual check confirmed cases of algorithm 4) identified 174 occurrences in the year 2010 which increased to 4014 occurrences in the year 2020.

Occurrence of cervical cancer related endpoints with/without HPV type within screened population identified by different algorithms.

The number of occurrences increased over the period of 10 years, from 2010 to 2020 for the pooled age group 9 to 70 years.

Final algorithm (algorithm 3 + manual check confirmed cases of algorithm 4) identified 93 occurrences in the year 2010 which increased to 3025 occurrences in the year 2020.

Vaccine uptake rate and time interval during two adjacent vaccinations during 2018 to 2020 for different vaccines.

Vaccine uptake was 10.59 per 1000 for Cervarix for the pooled age group of 9 to 45 years and cumulative of the year 2018-2020, 2.02 for 2018, 3.56 for 2019 and 4.31 for 2020.

Also refer to participant disposition.

Prevalence of cervical cancer screening item by program, per calendar year by age strata, and overall

The prevalence of cervical cancer screening item tested using HPV testing, Pap test and liquid-based cytology, Cervicoscope, Colposcopy, Visual inspection with acetic acid, Biopsy and Histopathology are presented in Table 1.9 and Table 1.10 of the CSR.

Also refer to participant disposition.

Prevalence and prevalence ratio of cervical cancer related endpoints in vaccinated and unvaccinated cohorts.

The conditional analysis is not conducted for the study, as the sample size required to conduct the conditional analysis was not met. As per the sample size calculation the required sample size was supposed to be 1955 participants. However, the actual sample size for the study included 1793 participants which was lower than the required sample size to conduct a sound statistically powered analysis, hence the conditional analysis was not performed.

Assessor's comment

The sample size required to conduct the conditional analysis was not met. The prevalence ratio of cervical cancer related endpoints in vaccinated and unvaccinated cohorts was not calculated. The required sample size was supposed to be 1955 participants. The number of 1955 was justified in the SAP to give estimates of vaccine effectiveness with 80% statistical power. However, because of the many limitations of the study, including the low uptake of Cervarix and the sub-optimal detection of cervical cancer related disease, this issue is not pursued for the limited period of follow-up post-Cervarix launch from 2018 to 2020.

Also refer to assessments above.

2.3.3. Discussion on clinical aspects

Cervarix was approved by the National Medical Products Administration (NMPA) in July 2016, for use in a 3-dose schedule at 0, 1, 6 months in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1)grade 2 (CIN2), grade 3 (CIN3) and adenocarcinoma in situ caused by high risk-human papillomavirus (HR-HPV) types 16 and 18. In May 2018, *Cervarix* was also approved for use in females up to 45 years of age. First Cervarix doses were sold from July 2017 onwards in China.

Study 212381 is an observational, database study to monitor cervical cancer-related endpoints in female subjects aged between 9 and 45 years in China prior to and following Cervarix vaccine launch when Cervarix vaccine is administered according to the Local Prescribing Information. This study was requested by the Chinese authorities and was conducted based on the recent YRHIP population

databased registry in the Chinese district Yinzhou with a population of more than one million inhabitants.

The study was initiated the 10 September 2021 and terminated on 26 October 2023. The main aim of this retrospective observational, registry database, study was to assess cervical cancer-related endpoints of interest (in terms of cervical HPV infection, cervical lesions CIN1, CIN2, CIN3 or cervical cancer) in female subjects aged between 9 and 70 years in China during the pre-*Cervarix* launch period (1 January 2010 to 31 December 2016) and post-*Cervarix* launch period (1 January 2018 to 31 December 2020). The study design used a sequential approach comprising 4 steps :

1. Assessment of Yinzhou Regional Health Information Platform (YRHIP) database performance for the detection of endpoints of interest (cervical HPV infection, cervical lesions such as CIN1, CIN2, CIN3 and cervical cancer, with/without HPV type) based on pre-*Cervarix* launch data.
2. Computation of baseline prevalence of cervical cancer-related endpoints and vaccination rates. Evaluation of cervical cancer screening practices during pre- and post-*Cervarix* launch period.
3. Assessment of the pre-and post-*Cervarix* launch rates of the effectiveness endpoints of interest. This was the main analysis and primary objective.
4. Upon pre-defined criteria are met, assessment of the probability of occurrence of effectiveness endpoints of interest among vaccinated and unvaccinated participants during post-*Cervarix* launch period.

A total of 691 322 eligible participants were included in the Total set. A total 59 699 were screened for HPV, representing 8.6% of the Total set. Most of them (40 576) tested using HPV testing for high-risk HPV types and using Pap test and liquid based cytology (29 306). Only 1700 participants were tested using biopsy, including only 566 participants using colposcopy, which is required for final diagnosis of CIN lesions. An additional 522 participants were tested using visual inspection with acetic acid, 185 participants were tested using cervicoscope, and 4284 participants were tested using histopathology exam of the cervix.

The total number of vaccinated female participants, aged between 9 and 70 yoa, with at least one dose of Cervarix was 3507.

The vaccine uptake rate was 10.59 per 1000 for Cervarix (at least 1 dose) for the pooled age group of 9 to 45 years and cumulative of the year 2018-2020. This vaccine uptake is lower than the already low HPV vaccination rate in China (24%). Only 4 % of the Cervarix vaccinated participants were dosed between 9-17 years of age.

The total number of vaccinated with at least one dose of Cervarix that underwent screening methods was 1054, representing 30% of the Cervarix vaccinated individuals. The total number of non-vaccinated with at least one dose of Cervarix that underwent screening methods was 55 583, i.e. 10% of the non-vaccinated set. The overall screening rate is lower than the overall national screening coverage of 36.8% achieved in the year 2018-2019 in China.

During the post-Cervarix launch period (2018-2020), an overall higher prevalence (per 100 000) in HPV infection, CIN1, CIN2 and CIN3 for the vaccinated cohort (i.e. vaccinated with at least one dose of Cervarix administered from 9 up to 45 years of age) compared to the unvaccinated population was observed. Prevalences were for:

- HPV infections : 711.74 vs 311.99 in 2018, 1171.88 vs 373.17 in 2019 and 1796.41 vs 681.08 in 2020
- CIN1 : 237. 25 vs 66.99 in 2018, 146.48 vs 67.98 in 2019 and 285.14 vs 69.12 in 2020

- CIN2 : 0 vs 30.76 in 2018, 146.48 vs 34.51 in 2019 and 114.06 vs 31.72 in 2020
- CIN3 : 0 vs 23.59 in 2018, 48.83 vs 30.77 in 2019, 28.51 vs 28.78 in 2020

There were no cases of ICC in the Cervarix vaccinated individuals during the 2018-2020 period.

Noteworthy, there were no cases of CIN1, CIN2, CIN3 and cervical cancer with HPV-16 and HPV-18 types in the vaccinated individuals. However, cases of CIN1, CIN2, CIN3 and cervical cancer with HPV-16 and HPV-18 types were detected only in a very low number of non-vaccinated participants (<10 and <5 per year for HPV-16 and HPV-18 type, respectively).

This unexpected higher prevalence in HPV infections among the vaccinated population might be due to different factors such as the limited vaccine coverage, limited screening rate, limitations in the availability of appropriate diagnostic tools for detection and characterization of HPV-related infection and diseases, potential incorrect vaccination status, and limited study period post-Cervarix launch. In addition, most of the vaccinated women were dosed after 18 years of age. Vaccine efficacy is higher in HPV naïve women (i.e., before the sexual debut because the current paradigm of HPV acquisition is sexual activity), and declines with age at first vaccination assuming that the older the woman is more likely to have been exposed to HPV.

Additional factors such as health care seeking behaviour (both for vaccination and HPV screening) have potentially biased the results.

All these limitations imply caution in the interpretation of the prevalences observed for the cervical cancer related endpoints of interests in the vaccinated and unvaccinated individuals. No conclusions can be made on the data observed.

The MAH is not planning to continue monitoring cervical HPV-related diseases and cancer in the YRHIP database due to insufficient number of Cervarix-vaccinated participants and consequently insufficient statistical power cannot be achieved as to assess the outcomes of interest.

Because of the many limitations of the study, it is agreed with the MAH that results of study 212381 do not impact the PI for Cervarix and no update of the SmPC is needed.

3. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Question 1

The different values provided regarding the number of vaccinated individuals with Cervarix are not consistent. The Applicant should clarify how many female subjects were vaccinated with Cervarix for each year (2018 to 2020) with the number of doses in the given year.

Question 2

It is requested to the MAH to communicate the further planned monitoring of the occurrences in cervical cancer related endpoints of interests and surveillance of vaccine effect on prevention of HPV-related disease in China using real-world data from YRHIP database.

The timetable is a 30 day response timetable without clock stop.

MAH responses to Request for supplementary information

Question 1

The different values provided regarding the number of vaccinated individuals with Cervarix are not consistent. The Applicant should clarify how many female subjects were vaccinated with Cervarix for each year (2018 to 2020) with the number of doses in the given year.

Applicant answer

The Company would like to clarify the different numbers of vaccinated subjects in the Clinical Study Report (CSR) questioned by the assessors in their comments in the assessment report.

Assessor comment 1: In Figure 11.1 Participants Disposition (given below) (p. 107 of CSR) the total number of vaccinated with at least one dose of Cervarix was N =3507. The total number of vaccinated that received one dose, 2 doses and 3 doses were N=3461, N=2136 and, N=1281 respectively.

Company answer 1: In the Participants Disposition flowchart (Figure 11.1), the text box that includes "Cervarix N=3507" participants corresponds to the total number of participants in the dataset that received at least one dose of Cervarix. The correct interpretation of the text box which includes "Cervarix first dose (N=3461); second dose (N=2136); third dose (N=1281)" is the first dose, second dose, and third dose respectively, and not "one dose, second dose, or third dose". These data are consistent with the participants that received their first, second, or third dose of Cervarix in the Yinzhou district and hence, registered in the database as having received the vaccine in the Yinzhou area. Some participants may have received their first dose of Cervarix in another geographic area. Therefore, the total number of participants vaccinated with at least one dose of Cervarix was N =3507, while the total number of vaccinated participants that received the first dose of Cervarix in the Yinzhou district was slightly smaller, i.e., N= 3461.

Assessor comment 2: In Table 1.5, total number of vaccinated with at least one dose of Cervarix in the female population aged between 9 and 70 yoa was N=843, N=2048, and N=3507 in the given year 2018, 2019 and 2020, respectively.

Company answer 2: In Table 1.5, the number represents the cumulative total of participants vaccinated up to that year. For example, N=3507 for the year 2020 refers to the fact that 3507 participants had been vaccinated by 2020, not that all 3507 participants were vaccinated in 2020. Similarly, N=2048 for 2019 means that 2048 participants had been vaccinated by 2019, and 843 participants were vaccinated by 2018.

Assessor comment 3: According to Template 16 p. 477 of the CSR, a total of N=853, N=1496, and N=1793 individuals had been vaccinated with Cervarix in 2018, 2019 and 2020, respectively.

Company answer 3: Template 16 displays the total number of participants vaccinated in every calendar year, as opposed to Table 1.5 that represents the cumulative number of participants vaccinated up to every calendar year. However, as the purpose of the feasibility assessment was to roughly determine the possibility to conduct the conditional analysis with sufficient statistical power, the Company did not limit the age or gender of the participants when extracting the data for this purpose. Therefore, Template 16 may also contain males or people beyond the 9-70 years of age group, who are not subject of the study. Additionally, participants can be counted multiple times. The numbers shown for every calendar year correspond to people who received the vaccine in each calendar year. However, a participant may have been vaccinated multiple times (multiple doses) in different years, and therefore can be repeatedly counted. For these reasons, the numbers in Template 16 are not aligned with those displayed in the Participants disposition flowchart, or in Table 1.5.

Rapporteur's assessment

The MAH clarified the different number of vaccinated subjects (first, second and third dose) presented in Figure 11.1, Table 1.5 and Template 16 as requested.

Issue resolved.

Question 2

It is requested to the MAH to communicate the further planned monitoring of the occurrences in cervical cancer related endpoints of interests and surveillance of vaccine effect on prevention of HPV-related disease in China using real-world data from YRHIP database.

Applicant answer

As the Cervarix vaccination coverage in the area was not expected to increase since this analysis' latest timepoint (2020) until today and in the future due to the presence of several HPV vaccines on the Chinese market, sufficient number of Cervarix-vaccinated participants and consequently sufficient statistical power cannot be achieved as to assess the outcomes of interest. the company is not planning to continue monitoring cervical HPV-related diseases and cancer in the YRHIP database.

Nevertheless, the efficacy and safety of Cervarix in China has been demonstrated in clinical trials involving over 8000 Chinese females between 9 through 45 years of age [Zhu, 2011; Zhu, 2014a, Zhu, 2014b; Zhu, 2017; Zhu, 2019] showing high and sustained vaccine efficacy against all virological, cytological, and histopathological efficacy endpoints associated with HPV-16/18. Cervarix vaccine was generally well tolerated in Chinese women aged 18-25 years [Zhu, 2019]. A ten-year follow-up Cervarix study of 6051 women aged 18-25 years at vaccination in China, unveiled a vaccine efficacy against incident HPV-16/18 infection and CIN2+ of 80.8% (95%CI, 72.4%-87.0%), and 90.5% (95%CI, 34.6%–99.8%), respectively [Zhao, 2023], adding evidence of the long-term protection of Cervarix against advanced premalignant cervical lesions and cancer.

Additionally, relevant data are becoming available from long-term follow-up observational studies and surveillance of implementation of Cervarix in National Immunisation Programmes worldwide. For instance, a recent publication from Scotland showed that there were no cases of invasive cancer recorded in females vaccinated with Cervarix at 12 or 13 years of age irrespective of the number of doses [Palmer, 2024]. Similarly in England, data from a total of 13·7 million-years of follow-up of females aged 20 years to younger than 30 years unveiled a reduction of cervical cancer of 87% (95% CI, 72%-94%) for adolescents vaccinated with Cervarix at age 12-13 years, compared with the reference unvaccinated cohort [Falcaro, 2021]. In the Netherlands, ten years post-vaccination with Cervarix of girls 13-16 years of age, vaccine effectiveness against 12-month persistent infection with vaccine types (HPV16/18) was 95.8% (95%CI, 86.6%–98.7%). Cross-protective 12-month persistent infection (HPV31/33/45) vaccine effectiveness was 64.6% (95%CI, 37.6%–79.9%). There were no indications of waning of protection over time [Hoes, 2023]. Therefore, there is sound evidence of long-term high vaccine effectiveness of Cervarix.

Rapporteur's assessment

The MAH is not planning to continue monitoring cervical HPV-related diseases and cancer in the YRHIP database due to sufficient number of Cervarix-vaccinated participants and consequently insufficient statistical power cannot be achieved as to assess the outcomes of interest.

This is acknowledged.

4. CHMP overall conclusion and recommendation

Taking into account all the significant and potential limitations, the databased registry results of this study imply caution in the interpretation of the findings and preclude any robust conclusions. No changes to the SmPC for Cervarix are considered necessary.

☒ Fulfilled:

No regulatory action required.

APPENDIX … SUPPLEMENTARY DATA

Prevalence and associated 95% CI of other cervical cancer related diseases (including CIN1, CIN2, CIN3 and cervical cancer) per calendar year by HPV type and age strata during the post-*Cervarix* launch period.

The prevalence (per 100 000 population) of CIN1 (overall population) in the pooled age group of 9 to 70 years.

CIN1

Prevalence per calendar year of CIN1 among overall population during the entire study period by age strata.

- 2018 : 237.25 (95% CI=28.74, 854.37) vs 66.99 (95% CI=59.83, 74.77)
- 2019 : 146.48 (95% CI=30.22, 427.49) vs 67.98 (95% CI=60.81, 75.76)
- 2020 : 285.14 (95% CI=136.82, 523.76) vs 69.12 (95% CI=61.85, 77)

CIN2

Prevalence per calendar year of CIN2 among overall population during the entire study period.

- 2018 : no cases reported vs 30.76 (95% CI=25.97, 36.17)
- 2019 : **146.48 (95% CI=30.22, 427.49**) vs **34.51 (95% CI=29.46, 40.18)**
- 2020 : **114.06 (95% CI=31.09, 291.77**) vs **31.72 (95% CI=26.86, 37.2)**

CIN3

Prevalence per calendar year of CIN3 among overall population during the entire study period.

- 2018 : no cases reported vs 23.59 (95% CI=19.43, 28.39)
- 2019 : **48.83 (95% CI=1.24, 271.75)** vs **30.77 (95% CI=26.01, 36.14)**
- 2020 : **28.51 (95% CI=0.72, 158.77)** vs **28.78 (95% CI=24.16, 34.02)**

Prevalence per calendar year of CIN3 among participants who underwent cervical cancer related screening during the entire study period by age strata.

- 2018 : no cases reported vs 0.46 (95% CI=0.35, 0.59)
- 2019 : **71 (95% CI=0.02, 3.89)** vs 0.58 (95% CI=0.47, 0.72)
- 2020 : **0.60 (95% CI=0.02, 3.29)** vs 0.58 (95% CI=0.47, 0.72)

Prevalence per calendar year of CIN3 with HPV type among overall population during the entire study period by age strata.
The prevalence (per 100 000 population) of CIN3 with HPV type (overall population) in the pooled age group of 9 to 70 years.

- 2018 : cases reported vs 6.53 (95% CI=4.44, 9.27)
- 2019 : **48.83 (95% CI=1.24, 271.75)** vs 6.03 (95% CI=4.04, 8.66)
- 2020 : **28.51 (95% CI=0.72, 158.77)** vs 12.18 (95% CI=9.25, 15.75)

Prevalence (per 100) per calendar year of CIN3 with HPV type among participants who underwent cervical cancer related screening during the entire study period.
The prevalence (per 100 population) of CIN3 with HPV type (cervical cancer related screening population) in the pooled age group of 9 to 70 years.

- 2018 : no cases reported vs 0.20 (95% CI=0.13, 0.29)
- 2019 : 0.71 (95% CI=0.02, 3.89) vs 0.19 (95% CI=0.13, 0.27)
- 2020 : 0.60 (95% CI=0.02, 3.29) vs 0.38 (95% CI=0.29, 0.50)

CERVICAL CANCER

Prevalence per calendar year of cervical cancer among overall population during the entire study period.

- 2018 : no cases reported vs 58.99 (95% CI=52.28, 66.31)
- 2019 : no cases reported vs 73.18 (95% CI=65.73, 81.23)
- 2020 : no cases reported vs 72.27 (95% CI=64.83, 80.32)

Prevalence (per 100) per calendar year of cervical cancer among participants who underwent cervical cancer related screening during the entire study period by age strata.

- 2018 : no cases reported vs 0.97 (95% CI=0.81, 1.15)
- 2019 : no cases reported vs 1.17 (95% CI=1.00, 1.35)
- 2020 : no cases reported vs 1.19 (95% CI=1.02, 1.38)

Prevalence per calendar year of CIN1, CIN2, CIN3 or CERVICAL CANCER with HPV-16 or HPV-18 type among overall population during the entire study period by age strata.

Prevalence per calendar year of CIN1 with HPV-16 type among overall population during the entire study period by age strata.
The prevalence (per 100 000 population) of CIN1 with HPV-16 type (overall population) in the pooled age group of 9 to 70 years.

- 2018 : no cases reported vs 0.63 (95% CI=0.13, 1.85)
- 2019 : no cases reported vs 1.04 (95% CI=0.34, 2.43)
- 2020 : no cases reported vs 1.05 (95% CI=0.34, 2.45)

Prevalence per calendar year of CIN1 with HPV-18 type among overall population during the entire study period by age strata.
The prevalence (per 100 000 population) of CIN1 with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

2018 : no cases reported in the year 2018 for the vaccinated population and the prevalence was 0.63 (95% CI=0.13, 1.85) for the non-vaccinated population.
2019 : no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.42 (95% CI=0.05, 1.50) for the non-vaccinated population.

2020 : no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.45) for the non-vaccinated population.

Prevalence per calendar year of CIN2 with HPV-16 type among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN2 with HPV-16 type (overall population) in the pooled age group of 9 to 70 years.

- 2018 : no cases reported in the year 2018 for the vaccinated population and the prevalence was 0.84 (95% CI=0.23, 2.16) for the non-vaccinated population.
- 2019 : no cases reported in the year 2019 for the vaccinated population and the prevalence was 1.87 (95% CI=0.86, 3.55) for the non-vaccinated population.
- 2020 : no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.45) for the non-vaccinated population.

Prevalence per calendar year of CIN2 with HPV-18 type among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN2 with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

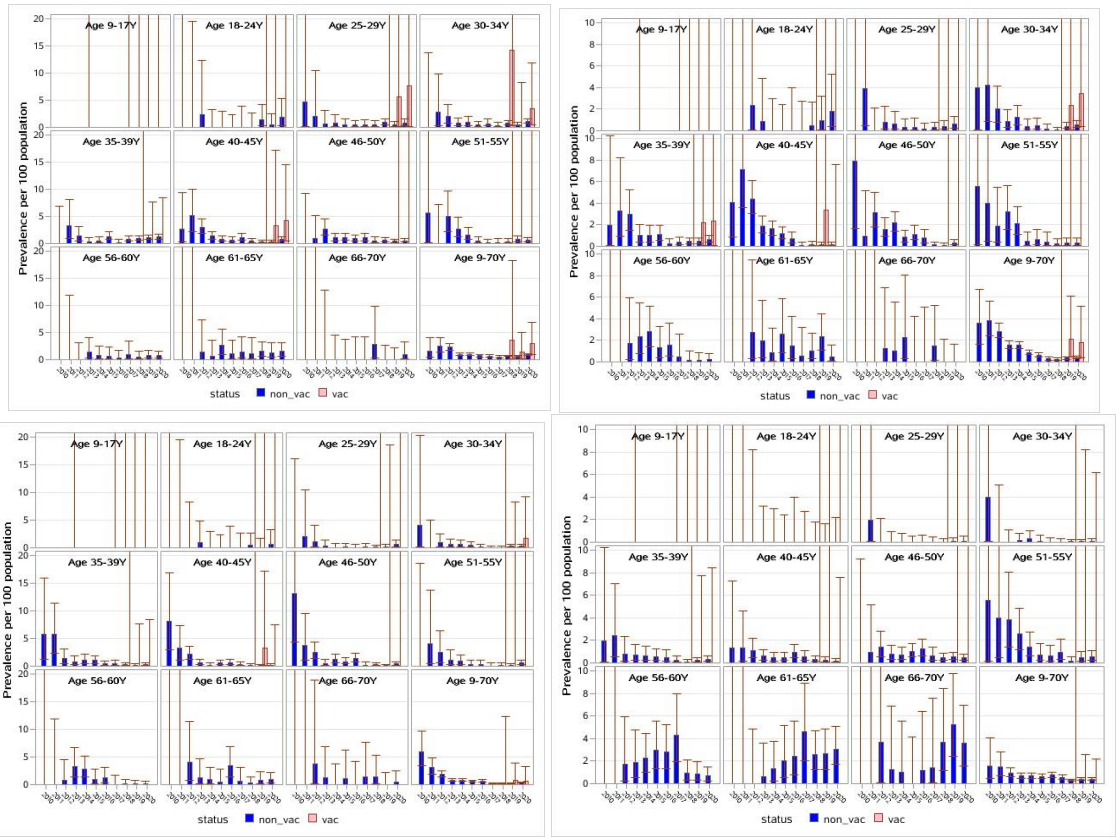
- 2018 : no cases reported in the year 2018 for the vaccinated population and the non-vaccinated population.
- 2019 : no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.21 (95% CI=0.01, 1.16) for the non-vaccinated population.
- 2020 : no cases reported in the year 2020 for the vaccinated population and the non-vaccinated population.

Prevalence per calendar year of CIN3 with HPV-16 type among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN3 with HPV-16 type (overall population) in the pooled age group of 9 to 70 years

- 2018 : no cases reported in the year 2018 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.46) for the non-vaccinated population.
- 2019 : no cases reported in the year 2019 for the vaccinated population and the prevalence was 1.46 (95% CI=0.59, 3.00) for the non-vaccinated population.
- 2020 : no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.68 (95% CI=0.73, 3.31) for the non-vaccinated population.

Prevalence per calendar year of CIN1 /2/3/AIS with HPV-16 type among participants who underwent cervical cancer related screening - Screening Set



Due to the small denominators in some subgroups, the confidence intervals are too wide, exceeding the maximum value set for the y-axis. Therefore, for aesthetic purposes, the full confidence intervals for these subgroups are not shown completely in the figure.

Prevalence per calendar year of CIN3 with HPV-18 type among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of CIN3 with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

☐ There were no cases reported in the year 2018 for the vaccinated population and the non-vaccinated population. ☐ There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.21 (95% CI=0.01, 1.16) for the non-vaccinated population. ☐ There were no cases reported in the year 2020 for the vaccinated population and the non-vaccinated population.

Prevalence per calendar year of cervical cancer with HPV-16 type among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of cervical cancer with HPV-16 type (overall population) in the pooled age group of 9 to 70 years.

☐ There were no cases reported in the year 2018 for the vaccinated population and the prevalence was 0.84 (95% CI=0.23, 2.16) for the non-vaccinated population. ☐ There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 1.87 (95% CI=0.86, 3.55) for the non-vaccinated population. ☐ There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 1.05 (95% CI=0.34, 2.45) for the non-vaccinated population.

Prevalence per calendar year of cervical cancer with HPV-18 type among overall population during the entire study period by age strata.

The prevalence (per 100 000 population) of cervical cancer with HPV-18 type (overall population) in the pooled age group of 9 to 70 years.

☐ There were no cases reported in the year 2018 for the vaccinated population and the non-vaccinated population. ☐ There were no cases reported in the year 2019 for the vaccinated population and the prevalence was 0.42 (95% CI=0.05, 1.50) for the non-vaccinated population. ☐ There were no cases reported in the year 2020 for the vaccinated population and the prevalence was 0.63 (95% CI=0.13, 1.84) for the non-vaccinated population