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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Not applicable
Data analysis	SAS software (version 9.4; SAS Institute, Cary, NC, USA) Code availability All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). The SAS programs used for data processing and analysis are intrinsically linked to the individual-level raw data collected as part of the clinical trial and cannot be meaningfully interpreted or reused without access to these data. Therefore, the programs are available from the corresponding authors (wuting@xmu.edu.cn or zhangj@xmu.edu.cn) upon reasonable request, under the same access restrictions as the analyzed dataset.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The individual-level raw data in this study were collected as part of a clinical trial and are subject to confidentiality restrictions. The processed data are available under restricted access. Researchers may submit a detailed proposal for non-commercial purposes to the corresponding authors (wuting@xmu.edu.cn or zhangj@xmu.edu.cn) after publication. The corresponding authors will review the requests promptly and determine whether the data can be shared (within 2 months).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	This study was conducted exclusively in female participants.
Reporting on race, ethnicity, or other socially relevant groupings	The study population consisted entirely of participants of Chinese ethnicity. No other racial or ethnic groups were included.
Population characteristics	A total of 7372 participants were enrolled in the Phase 3 trial. Among them, 3691 received the HPV vaccine and 3681 received the control vaccine (Figure 1). After the end of the Phase 3 trial, 1648 participants consented and were enrolled in the extension study, with 806 in the vaccine group and 842 in the control group (Figure S1). The baseline characteristics were similar between the vaccine and control groups in both the trial and extension study (Table 1). In the Phase 3 trial, the mean age (SD) was 30.0 (7.4) years in the vaccine group and 29.9 (7.3) years in the control group. The median follow-up time (IQR) was 5.6 (5.5, 5.7) years for women in both the vaccine and control groups. In the extension study, the mean age (SD) was 30.2 (7.4) years in the vaccine group and 30.1 (7.4) years in the control group. The median (IQR) follow-up time for women in both groups was 10.2 years (10.2, 10.3). In both studies, the baseline prevalence rates of HR-HPV types were similar between the vaccine and control groups, with HPV-52, -16, and -51 being the most common types.
Recruitment	The analysis was based on a multicenter, double-blinded, randomized, controlled phase 3 clinical trial of the E.coli-produced HPV-16/18 bivalent vaccine and its long-term extension study. Detailed methodologies for both studies have been described previously. Briefly, 7372 eligible healthy women aged 18-45 years, who were non-pregnant, had no history of HPV vaccination or high-grade cervical lesions, and had 1-4 sexual partners, were enrolled from five sites in China. Eligible women were randomly allocated (1:1) to receive three doses of either the HPV vaccine or the control (Hepatitis E) vaccine. Following phase 3 trial completion, 1986 participants from two sites were invited to join the extension study. Participants who received at least one dose of the investigational vaccine in the phase 3 trial were eligible.
Ethics oversight	The phase 3 trial (NCT01735006) and extension study (NCT05045755, NCT04969445) were approved by independent ethics committees (Cancer Hospital Chinese Academy of Medical Sciences, Peking University People's Hospital, Jiangsu Provincial Centre for Disease Control, Guangxi Liuzhou Centre for Disease Control and Prevention and Henan Cancer Hospital) and strictly adhered to Good Clinical Practice guidelines. All participants provided written informed consent at the start of both studies.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample-size calculation was performed. The analysis was based on a multicenter, double-blinded, randomized, controlled phase 3 clinical trial of the E.coli-produced HPV-16/18 bivalent vaccine and its long-term extension study.
Data exclusions	No data were excluded arbitrarily. However, different analyses were performed in different analysis sets, which varied according to the research question (e.g., incidence, persistence, or progression analyses). For example, Participants who were negative for the corresponding HPV type at day 0, as well as those who attended at least one follow-up visit, were included in the HPV incident infection analysis set. Among them, participants who had not completed colposcopy referral were excluded from the cervical lesion analysis set. Participants who were negative for the corresponding HPV type at day 0, and attended two follow-up visits at intervals of at least 150 days (300 days), were included in the 6mPI (12mPI) analysis set.

Replication	All results in the manuscript can be replicated using the data and the same analysis methods
Randomization	Participants were originally assigned to vaccine or control groups through randomized allocation as part of the clinical trial. The present analyses used data from these randomized groups.
Blinding	During the phase 3 clinical trial and the follow-up period, all investigators were blinded to participants' vaccination status. Laboratory staff were also unaware of group assignments during specimen processing and testing.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT01735006, NCT05045755, NCT04969445
Study protocol	The study protocol has been published previously as a supplementary file(https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(25)00207-X/fulltext)
Data collection	The analysis was based on a multicenter, double-blind, randomized, controlled phase 3 clinical trial of the E. coli–produced HPV-16/18 bivalent vaccine conducted in China from 2012 to 2019 (Liuzhou City, Funing County, Yangcheng County, Xinmi City, and Fengning County), and its long-term extension study conducted from 2021 to 2024 in Funing County and Xinmi City.
Outcomes	This post hoc analysis aimed to evaluate the impact of HPV-16/18 bivalent vaccine immunization on the spectrum and natural history of high-risk HPV (HR-HPV) infections.

Plants

Seed stocks	Not applicable
Novel plant genotypes	Not applicable
Authentication	Not applicable