Study on HPV Vaccination Behavior and Comprehensive Intervention in Adolescent Female Adolescents Based on the Biopsychosocial Medical Model: A Multicenter Randomized Controlled Trial

Study Protocol

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1 Research Background

1) The pivotal role of HPV vaccines in cervical cancer prevention and control and the current status of vaccine hesitancy

Human papillomavirus (HPV) infection is a major pathogenic factor for cervical cancer and its precancerous lesions [1 – 4]. The World Health Organization (WHO) has designated cervical cancer elimination as one of its global public health objectives and released the Global Strategy to Accelerate the Elimination of Cervical Cancer in 2020, proposing the "90-70-90" target to significantly increase cervical cancer screening rates and HPV vaccination coverage, thereby achieving primary prevention of cervical cancer [2]. HPV vaccination has been proven to significantly reduce the incidence risks of cervical cancer and high-grade cervical intraepithelial neoplasia, making it one of the key interventions for cervical cancer prevention today [3 – 5].

In recent years, with the gradual introduction of bivalent, quadrivalent, and nonavalent HPV vaccines in China, the domestic HPV vaccination coverage rate has shown some improvement. However, the overall level remains lower than that of certain high-income countries, with significant disparities observed between regions and urban-rural areas [6,7]. Among the key recommended vaccination population of adolescent females aged 9 – 14 years in China, the vaccine initiation rate and full vaccination completion rate remain generally low. Some families and caregivers still harbor concerns regarding the safety, efficacy, and necessity of vaccination, exhibiting varying degrees of "vaccine hesitancy" [8 – 10].

2) Multilayered Physiological-Psychological-Social Influencing Factors and the Necessity of Comprehensive Intervention

HPV vaccination behavior is influenced by a multifaceted combination of factors, including individuals 'risk perception of HPV/cervical cancer, vaccine trust, general anxiety levels and health beliefs, family decision-making patterns and parent-child communication, physician-patient interaction quality, as well as healthcare service accessibility and policy environments [8 – 10,14,15]. This process fundamentally

represents the result of interactions among biological, psychological, and social dimensions, which aligns closely with Engel's biopsychosocial (BPS) medical model [16,17]. From a BPS perspective, single-dimensional interventions (e.g., adolescent classroom education only, parental distribution of promotional materials only, or one-time physician training only) are unlikely to adequately address the multiple needs of families in real decision-making contexts. Existing evidence indicates that reliance on passive health education, one-off knowledge lectures, or single-message dissemination (e.g., SMS reminders) as "single-factor" interventions often only achieve short-term improvements in cognition or intention in complex real-world scenarios, with limited sustained effects on actual vaccination behavior [6,11 − 13]. Furthermore, multiple systematic reviews and intervention trials have progressively demonstrated that multi-component/multilevel intervention packages integrating multiple strategies and acting on multiple levels are more likely to achieve stable and replicable effects in improving HPV vaccination initiation rates and full course completion rates compared to single-component interventions [6,11-13,18,19].

Specifically, the multi-level intervention trial conducted by Paskett et al. in a U.S. community setting integrated various approaches such as parent education materials, physician reminders, and performance feedback. The results demonstrated that multi-level interventions could improve HPV vaccination rates among adolescent girls aged 9 − 17, but overall levels still had room for improvement, suggesting that "package-style" comprehensive measures are needed in real-world settings to achieve significant effects [13]. The PrevHPV national cluster randomized trial conducted by Thilly et al. in France combined multiple strategies including school health education, healthcare provider support, and on-campus vaccination. The results revealed that providing free on-campus vaccination as a key component of this comprehensive intervention package significantly increased adolescent vaccination rates [18]. Although school-based vaccination models have shown remarkable efficacy in Western countries and some nations, in regions like mainland China with uneven distribution of medical resources and incomplete implementation of free school

vaccination programs, outpatient clinics remain the primary channel for vaccine access. Some online practice studies also indicate that implementing multi-level, package-style interventions—including parent communication, healthcare provider training, appointment reminders, and process optimization—simultaneously in outpatient settings can improve HPV vaccination initiation and completion rates, whereas the effects of individual interventions alone are often limited [6,13,19]. These studies demonstrate that integrating complementary measures into a "comprehensive intervention package" better aligns with the practical needs of real-world health service systems to enhance vaccination rates.

The World Health Organization Strategic Advisory Group of Experts on Immunization (SAGE) also emphasized in the Vaccine Hesitation Report that effective interventions for vaccine-hesitant populations often require a combination of strategies such as information communication, healthcare worker training, and improved service accessibility, rather than relying on "single-point" interventions [11]. In the areas of routine childhood immunization and HPV vaccine promotion, systematic reviews similarly suggest that multi-component combination interventions demonstrate greater advantages in improving vaccination coverage rates [6,12,13,19]. However, existing multi-level interventions predominantly focus on school-community or home-vaccination site settings. For the unique context of pediatric/child health clinics, there remains a lack of systematic theoretical frameworks and prospective evidence for designing integrated comprehensive intervention strategies that account for biological, psychological, and social factors, based on the tripartite interaction among adolescents, caregivers, and healthcare workers.

3) Comprehensive Intervention Design Based on the Biopsychosocial Medical Model

The BPS medical model proposed by Engel emphasizes the holistic understanding and intervention of biological factors, psychological states, and social contexts in disease prevention and health promotion [16,17]. In the context of adolescent HPV

vaccination, this means not only providing scientific information about the virus and vaccine but also addressing family emotional responses in risk communication, adolescents' gradually increasing autonomy and decision-making participation, as well as the accessibility and experience of outpatient visits and vaccination procedures [8 – 10,14,15]. From a methodological perspective, integrating the BPS model into HPV vaccination and pre-integrating an intervention package that covers health information, risk communication, family co-decision-making, and emotional support into a single study—rather than isolating the effects of individual components—more closely aligns with the actual delivery of public health and clinical services. This approach also helps address the critical question of whether "integrative service models that can be implemented in real-world settings are truly effective" [11,13,18,19].

China and other Asian countries have conducted preliminary explorations in HPV vaccine promotion. Domestic school-based health education programs and online education initiatives have demonstrated improvements in adolescents 'and college students' knowledge levels regarding HPV and vaccination intentions, as well as vaccination willingness, although their impact on long-term vaccination behaviors remains limited [20,21]. Regions such as Hong Kong and Malaysia have promoted HPV vaccination through school-based or national programs, achieving relatively high coverage rates in some areas. However, scalable models tailored to diverse socio-cultural and healthcare system contexts still require further comparative analysis and optimization [22-25]. Overall, existing studies predominantly involve single-component or partial-intervention approaches. While some designs employ multi-level interventions, they lack prospective randomized controlled evidence with clear theoretical foundations, targeted at adolescents and caregivers, or embedded in specific settings such as pediatric/child health clinics.

Therefore, this study aims to conduct an international multicenter prospective randomized controlled trial in mainland China, Hong Kong, China, and Malaysia, based on the BPS medical model as the theoretical foundation. Targeting adolescent

females aged 9-17 and their caregivers, it designs a multi-level comprehensive intervention package implementable in pediatric/child health clinics, integrating age-appropriate health education, risk communication, family co-decision support, and necessary emotional and psychological support. The overall impact on HPV vaccination initiation rates, full completion rates, and related psychosocial outcomes will be evaluated in real clinical and public health service settings. By adopting this "integrated intervention package" design rather than single-component trials, it better aligns with practical and scalable service models in public health practice, providing evidence-based support with external validity for improving adolescent HPV vaccination rates in pediatric settings.

2 Purpose of research

Primary objective ：

In pediatric/child healthcare settings, evaluate the impact of a comprehensive HPV vaccination intervention program based on the biopsychosocial medical model on the HPV vaccination initiation rate (proportion of first dose completed) among adolescent females within 3 months after enrollment.

Secondary objectives:

1. Systematically explore the influencing factors of HPV vaccination behavior among adolescent females from biological, psychological, and social dimensions, and construct a BPS integrated influence framework:

1.1 Biological aspects: including prior reproductive health-related medical history, menstrual status, and history of chronic diseases;

1.2 Psychological aspects: including vaccine hesitancy levels, awareness of HPV infection and cervical cancer risks, understanding of vaccine risk-benefit profiles, and general anxiety/depression levels among adolescents and caregivers;

1.3 Social dimension: including family socioeconomic status, caregiver education level, family decision-making patterns, quality of parent-child communication, peer support, and school support.

2. Evaluate the impact of comprehensive intervention on the completion rate of HPV vaccination within 6 months after enrollment.

3. Evaluate the impact of comprehensive interventions on the following psychosocial outcomes:

3.1 Knowledge level of HPV/HPV vaccine among adolescents and caregivers;

3.2 Level of vaccine hesitancy, decision conflict, and decision satisfaction among caregivers;

3.3 Psychological states such as anxiety/depression in adolescents and caregivers;

3.4 Quality of communication and level of joint decision-making between parents and children on topics related to reproductive health and vaccination.

4. Preliminary establishment of a predictive model for HPV vaccination behavior among adolescent females based on the BPS model to identify high-risk populations who have not been vaccinated or completed vaccination, providing evidence for future stratified management and precision intervention strategies.

5. Explore the feasibility and scalability of this comprehensive intervention program in pediatric/child healthcare institutions across different regions (mainland China, Hong Kong, Malaysia), to provide references for subsequent development of regional or international collaborative health promotion pathways for adolescent HPV vaccination.

3 Research technique

This study was a prospective, international multicenter, randomized, open-label, parallel-controlled, superiority trial.

Study type and design: Interventional clinical study with superiority trial design, aimed at comparing the superiority of "BPS comprehensive intervention + routine education" versus "routine education" in improving HPV vaccination initiation rates, while exploring its impact on vaccination rates and psychosocial outcomes.

Research Center: Led by Children's Hospital affiliated with Zhejiang University School of Medicine, this initiative involves collaboration with one pediatric/child

health care institution in Hong Kong, China, and one pediatric/maternal and child health care institution in Malaysia, totaling three centers.

Subject allocation: Eligible participants who signed the informed consent/informed consent form were randomly assigned in a 1:1 ratio to either the comprehensive intervention group (trial group) or the conventional education group (control group).

Blind level: Due to the characteristics of health education and communication method interventions, this study adopted an open-label design, where both the study physicians and participants were aware of the grouping assignments. Objective records could be made for primary behavioral outcomes during outcome evaluation (e.g., verification of vaccination records), and blind processing of scale score data entry and statistical analysis was implemented for data analysts whenever possible.

Study duration: Each participant was followed up for 6 months from enrollment. Considering the participant recruitment timeline, the total implementation period of this study is estimated to be approximately 3 years, including phases such as protocol preparation and ethical approval, center launch and training, participant recruitment and intervention implementation, follow-up, as well as data cleaning and analysis.

Sample size estimation: The primary outcome of this study was the first-dose HPV vaccination rate within 6 months after enrollment. Based on the superiority trial design, the estimation was performed using the formula for rate comparison between two independent samples.

Hypothesis and parameter settings

Type I error (α): Set at 0.05 (two-tailed test);

The test power ($1-\beta$): set to 0.80, indicating an allowable 20% Type II error rate.

The vaccination initiation rate in the control group (conventional education) within 6 months was estimated as follows: Based on previous literature and preliminary survey data from our center, while accounting for potential heterogeneity in baseline levels across different sub-centers (Mainland China, Hong Kong,

Malaysia), the weighted vaccination initiation rate for the control group was estimated to be approximately 30%.

Expected vaccination initiation rate in the intervention group (BPS comprehensive intervention): Assuming that BPS comprehensive intervention can achieve clinically significant improvements. Referring to the effect sizes of similar multi-level intervention studies, the expected vaccination rate in the intervention group can be increased to 45% (0.45).

Type of test: Comparison of rates between two independent samples (efficacy trial).

Sample size calculation formula

The classic formula for comparing two group proportions was adopted:

$$n = \frac{\left[Z_{\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + Z_{\beta}\sqrt{p_c(1-p_c) + p_t(1-p_t)}\right]^2}{(p_t - p_c)^2}$$

among：

- $\bar{p} = (p_c + p_t)/2$
- $Z_{\alpha/2} = 1.96$ (two-tailed α =0.05)
- $Z_{\beta} = 0.84$ (corresponding to a test power of 0.80)

Substitute the parameters: $p_c = 0.30$, $p_t = 0.45$, $\bar{p} = 0.40$

The calculation shows that the required sample size for each group is approximately 118 cases.

Consider loss to follow-up and adherence

Considering a 10% – 15% rate of loss to follow-up and poor adherence (e.g., discontinuation of treatment or missing key follow-ups), the rate is adjusted for a 15% reduction:

$$n' = \frac{118}{1 - 0.15} \approx 139$$

To further control the potential central effect in multicenter studies and facilitate stratified block randomization at each sub-center, the total sample size is planned to be increased to 300 cases (150 cases in the trial group and 150 cases in the control

group). With three centers in total, considering the varying population sizes across centers, the proposed sample size is 200 cases per center (100 cases each in the trial and control groups), 50 cases at the Hong Kong, China center (25 cases each in the trial and control groups), and 50 cases at the Malaysia center (25 cases each in the trial and control groups).

If there is a slight increase or decrease in enrollment at any center during the actual recruitment process, appropriate adjustments will be made within the overall sample size control range to ensure that the total sample size remains no less than 280 cases.

Intermediate blind review:

After completing 50% of the subject enrollment, a blinded sample size reassessment will be conducted. If significant deviations are identified between the overall mixed variance or baseline rate and the estimated bias, the final sample size will be adjusted under the premise of adhering to statistical principles.

Blinding method (specific blinding measures, unblinding methods, and provisions for unblinding in emergency situations)

The intervention content of this study primarily involves health education and changes in communication methods. Due to practical operational and ethical considerations, strict blinding could not be implemented for both study physicians and participants, thus an open-label design was adopted. To minimize bias, the following measures will be implemented:

Randomization and allocation concealment

This study employed a rigorous central randomization system (IWRS). After completing baseline assessments and confirming eligibility, researchers entered participant information into the system, which automatically generated grouping results. The random sequence was generated and sealed by the lead unit's statistician, preventing on-site researchers from predicting or intervening in allocation outcomes. The system maintained complete and tamper-proof audit trails.

Blinded design

Given that this study is a behavioral intervention trial, blinding could not be implemented between participants and intervention implementers (medical staff), thus an open-label design was adopted. To minimize measurement bias and implementation bias, the study followed the PROBE (Prospective Randomized Open-label Blinded Endpoint) design principles:

Blinded outcome evaluation: An independent assessor (Independent Assessor) was designated, who was not involved in participant enrollment or intervention implementation, and solely responsible for contacting participants at follow-up nodes to collect data.

Prioritization of objective outcomes: The primary outcome (3-month HPV vaccination rate) is strictly assessed based on objective medical records such as vaccination certificates and electronic immunization records, rather than relying on participants' verbal recollections, to ensure objectivity in endpoint determination.

Data analysis blinding protocol: The data collection system (EDC) will export data with concealed group labels (replaced by Group A/B). Statistical analysts remain blinded to the specific grouping scheme until completing primary outcome analysis and finalizing results.

Intervention discontinuation and subject withdrawal/loss to follow-up (describe adverse events that may lead to study intervention discontinuation or subject withdrawal, define the criteria for subject loss to follow-up, and outline plans to reduce loss to follow-up)

This study is designed as a minimal-risk intervention study, but it is essential to clearly define potential scenarios that may lead to intervention discontinuation, subject withdrawal, or loss to follow-up, along with corresponding management protocols. For individual subjects, if severe adverse events or newly developed serious illnesses occur during the study, and the investigator comprehensively assesses that continued participation (including vaccination and follow-up) may pose risks to physical or mental health, subsequent study interventions will be terminated, and further medical consultation or referral will be recommended based on specific circumstances. Additionally, significant emotional fluctuations or exacerbation of

severe anxiety/depression induced by questionnaires or interviews during intervention or follow-up, when the investigator determines a clear correlation with the study process, will also serve as an indication for intervention discontinuation. Furthermore, major protocol violations—such as failure to receive interventions as per assigned groups, repeated refusal to cooperate with critical intervention phases resulting in ineffective implementation, or recommendations for adjustments/termination from ethics committees or regulatory authorities during study execution—may also lead to intervention discontinuation for individual subjects.

Subject withdrawal from the study primarily refers to the cessation of any study interventions and follow-up after a specified time point. Common scenarios include: voluntary withdrawal by the subject and/or caregiver due to unwillingness to continue participation; termination of participation deemed necessary by investigators due to severe adverse events or other medical reasons; inability to continue follow-up due to objective factors such as relocation or prolonged overseas stay; and termination of study participation required by ethics committees or regulatory authorities. The research team will meticulously document the withdrawal time and reasons upon subject withdrawal, and retain all collected time-point assessment data for analysis with the consent of the subject and caregiver.

Unlike "withdrawal," "lost to follow-up" refers to cases where participants did not explicitly indicate withdrawal but failed to provide critical follow-up information after multiple attempts within the scheduled follow-up window. This study defined follow-up windows as 4 weeks before and after key follow-up time points (particularly 3 months and 6 months). During these periods, participants were contacted at least twice via phone calls, text messages, or WeChat at different dates and time slots. If contact remained unestablished or the participant explicitly refused any form of communication, the time point was classified as lost to follow-up. Cases persisting beyond the study end were considered completely lost to follow-up. All lost-to-follow-up cases were labeled in the database with specific time points and methods/attempt counts for subsequent lost-to-follow-up pattern analysis and sensitivity analysis.

To minimize loss to follow-up and enhance compliance, the research team will collect at least two valid contact methods (e.g., primary caregiver's mobile number and backup contact information, WeChat ID) at baseline and record their preferred contact time. Prior to each follow-up visit, reminders will be sent via SMS or WeChat to inform participants of the follow-up method and approximate schedule. Where feasible, follow-up assessments will be integrated with participants' outpatient appointments or vaccination schedules, offering flexible follow-up options such as phone calls or online questionnaires to reduce additional time costs for families. Families completing all follow-ups on time may receive small tokens of appreciation or participation certificates under ethical guidelines to enhance engagement. Additionally, the data management team will periodically compile follow-up completion rates and loss-to-follow-up statistics across centers, conducting targeted communication and supervision for centers with high dropout rates to promptly adjust operational strategies.

4 Subject investigated

The study subjects were sourced from pediatric and adolescent gynecology clinics, vaccination clinics, adolescent health clinics, and specialized pediatric/child health clinics (e.g., endocrinology and growth development clinics) across various research centers. Eligible participants included females aged 9 – 17 years and their primary caregivers who had visited these clinics, met age and HPV vaccination criteria, and had not yet completed the full HPV vaccination regimen.

Recruitment Method: 1) Potential participants were screened on-site by trained research physicians or study coordinators through electronic medical records, outpatient registration information, and brief interviews to confirm preliminary eligibility; 2) Eligible participants and their caregivers received verbal explanations and written brochures detailing study objectives, procedures, potential benefits, and risks; 3) Written informed consent forms were obtained from caregivers, supplemented with additional consent documents tailored to adolescents' age and comprehension levels; 4) After completing baseline questionnaires and related

assessments, participants were randomized through a centralized randomization system.

Eligibility criteria (must meet all the following criteria)

(1) Female, aged 9 – 17 years (inclusive of 9 and 17 years);

(2) Patients visiting the pediatric/adolescent gynecology clinic, adolescent health care clinic, or related pediatric/child health care clinic at the research center; or those seeking vaccination at immunization clinics for non-HPV vaccines (e.g., influenza, tetanus, etc.);

(3) No doses of HPV vaccine have been administered, and there was no confirmed HPV vaccination schedule on the day of consultation (confirmed by investigator inquiry).

(4) The visit must be accompanied by at least one primary caregiver (parent or other legal guardian) who can understand the study content and is willing to participate in the collaborative decision-making intervention.

(5) The plan is to reside in the area where the research center is located for most of the next 12 months to facilitate follow-up visits.

(6) Caregivers sign a written informed consent form; adolescents themselves sign the informed consent/agreement form in accordance with local ethical requirements.

Exclusion criteria (meeting any of the following criteria will result in exclusion)

(1) Individuals who have completed previous vaccination or received any type of HPV vaccine;

(2) Individuals with a history of severe allergic reactions to any HPV vaccine or its major components, or those currently deemed unsuitable for HPV vaccination by the administering physician;

(3) Participants with severe comorbid physical illnesses (e.g., severe cardiopulmonary diseases, active malignant tumors, etc.) or severe mental disorders, who are deemed by investigators unsuitable for participation in this study or unable to complete follow-up;

(4) Participants who have engaged in other clinical studies highly related to HPV vaccination behavior interventions within the past 1 year may interfere with the evaluation of intervention efficacy in this study.

(5) Individuals who are currently undergoing treatment for HPV infection-related conditions (e.g., condyloma acuminatum) and are deemed by physicians to be temporarily unsuitable for vaccination.

(6) Patients with a history of autoimmune diseases or tumors.

(7) The researchers identified other factors that may influence study adherence or result interpretation (e.g., families with extremely high mobility).

Exit criteria (Participants may voluntarily withdraw from the study at any time for any reason. Patients will also be withdrawn if any of the following conditions occur)

(1) Participants who have been enrolled and randomly assigned may be deemed to have withdrawn from the study under the following circumstances:

(2) The subject and/or caregiver voluntarily requested to withdraw informed consent and declined to continue participating in the study;

(3) Serious adverse events or other medical conditions occur, and the investigator determines that continued participation in the study would be detrimental to the subject;

(4) Inability to continue follow-up due to relocation or prolonged overseas stay;

(5) Severe protocol violations (e.g., repeated refusal to participate in follow-ups and inability to be contacted) were determined after discussion by the research team and led to protocol exit.

(6) The reasons for withdrawal and the withdrawal time must be recorded in detail. The obtained data may be included in the corresponding analysis set upon obtaining consent from the subject/caregiver.

Termination criteria (Study termination refers to the complete cessation of clinical research before completion as per the protocol)

(1) If major safety issues occur during the study, it should be promptly discontinued.

(2) The study identified significant errors in the development of the research protocol or substantial deviations in its implementation, making it difficult to evaluate the intervention effects.

(3) The sponsor requested to terminate the study.

5 Research process

Pre-enrollment screening

Participants who meet the preset initial screening criteria but fail to complete baseline assessment and randomization prior to formal enrollment due to non-compliance with inclusion criteria/exclusion criteria or refusal to sign informed consent are defined as screening failures. Information from screening-failing subjects is used solely for statistical analysis of screening and is not included in the formal analytical dataset.

Baseline assessment

(1) Collect general demographic and biological characteristics (age, height, weight, Tanner stage of development, gynecological inflammation status, medical history, menstrual status, HPV infection status among family members, and vaccination status, etc.);

(2) Record previous vaccination history (including HPV and other routine vaccines);

(3) Assess baseline levels of HPV/vaccine-related knowledge, vaccine hesitancy, decision-making conflict, anxiety/depression, and parent-child communication;

(4) Record whether the first dose of HPV vaccine was administered on-site or at a scheduled time.

intervention study

Each center adopted a centralized, hierarchical randomization method, where statistical personnel from the lead institution generated a 1:1 allocation sequence using computer-generated random numbers. The allocation protocol was stored in the study data management system and implemented by the study coordinator after completing baseline assessment through either a network randomization system or a unified random allocation table, ensuring randomness and allocation concealment.

The control group in this study consisted of routine health education and vaccination services currently provided at each center, with the experimental group additionally receiving a BPS comprehensive intervention module.

Experimental Group: Comprehensive Intervention for HPV Vaccination Based on the BPS Model

In addition to conventional outpatient education and vaccination procedures, the following multidimensional interventions are incorporated:

Biological intervention:

1. Based on the adolescent's past medical history and menstrual status, vaccination clinics or relevant specialists shall conduct a brief assessment of reproductive health-related risks, explain in plain language the relationship between HPV infection and diseases such as cervical cancer, as well as the protective scope and vaccination schedules of different vaccine types.

2. Provide a uniformly produced structured pictorial manual, containing the following content: basic knowledge of HPV, types of HPV vaccines and vaccination procedures, common adverse reactions and management, as well as contraindications for vaccination.

Psychological intervention:

1. At baseline, use a simplified vaccine hesitancy scale (e.g., a localized version of the Parental Assessment of Childhood Vaccination [PACV]) and Decision Conflict Scale (DCS Simplified Version) to assess caregivers' vaccine hesitancy and decision conflict levels, identifying high-risk families;

2. During the outpatient vaccination consultation process, the investigator conducts approximately 5-10 minutes of face-to-face communication based on a pre-designed "Structured Collaborative Decision-Making Communication Flowchart": 1) Assessing primary concerns and information needs of adolescents and caregivers; 2) Providing targeted explanations of vaccine risk-benefit profiles; 3) Guiding participants to express value preferences (e.g., prioritizing disease prevention over short-term adverse effects); 4) Assisting in weighing the pros and cons of different options (immediate vaccination, delayed vaccination, or no vaccination).

3. For families assessed at baseline as having high vaccine hesitancy or high decision-making conflict, arrange one telephone or online (e.g., WeChat video)

follow-up within 1 – 2 months to further clarify misunderstandings, address concerns, and provide emotional support and decision-making counseling.

Social/family-level interventions:

1. Utilize platforms such as WeChat/SMS to regularly deliver reviewed HPV/vaccine-related scientific information and vaccination schedule reminders (e.g., post-first dose reminders for subsequent doses) to caregivers;

2. Distribute "Parent-Child Communication Reminder Cards" containing several concise guidelines to encourage parents to discuss the importance of HPV, sexual and reproductive health, and vaccination with adolescents while respecting their privacy and feelings, emphasizing collaborative decision-making.

3. Collect family decision-making patterns (e.g., parental dominance, collaborative decision-making, adolescent-led approaches), and encourage adolescents to have a greater voice in health-related decisions during communication, while ensuring the protection of their interests and safety.

4. All centers will undergo standardized training to ensure consistency in intervention content and procedures. The research team will monitor intervention quality through on-site supervision and random interviews (with informed consent).

Participants in the control group and their caregivers will receive routine HPV vaccination education and services currently implemented at each research center, including but not limited to: routine verbal education by outpatient vaccination physicians/nurses (explaining vaccine targets, basic protective effects, common adverse reactions, etc.); distribution of routine vaccination brochures or posted promotional posters; and appointment scheduling and vaccination arrangements according to existing procedures at each center.

The control group did not receive additional structured collaborative decision-making communication, systematic telephone/online follow-ups, regular WeChat-based science popularization information dissemination, or parent-child communication reminder cards as components of the BPS comprehensive intervention.

Follow-up evaluation

The treatment course of this study lasted for 6 months. After enrollment, participants were required to complete 2 visits, with planned follow-up time points at 3 months and 6 months.

- Follow-up visit at 1 – 3 months

1. Focus on evaluating whether the first dose of HPV vaccine has been administered (primary outcome);

2. Record the number of doses administered and the administration time for individuals who have started vaccination;

3. Re-evaluate relevant scales;

4. Record any vaccination-related adverse events and medical visits (if applicable).

- Follow-up visit at 2 – 6 months

1. Assess whether the full course of HPV vaccination has been completed (one of the secondary outcomes);

2. Collect complete vaccination records (including vaccination dates and vaccine types for different doses), and provide supporting evidence such as vaccination certificates or screenshots from electronic vaccination systems when necessary;

3. Reassess knowledge, vaccine hesitancy, psychological state, parent-child communication, and decision-making conflict/satisfaction;

4. Collect overall evaluations of the vaccination experience and intervention program.

Follow-up can be conducted through a combination of on-site outpatient evaluations and telephone/network-based follow-up questionnaires to minimize loss to follow-up. Each center should strive to use a unified electronic data collection system (EDC) for recording follow-up data.

Proposed questionnaires and scales

1. HPV/HPV vaccine knowledge questionnaire (self-designed or adapted, including multiple-choice questions/judgment questions);

2. Vaccine Hesitation Scale (e.g., localized version of PACV for caregivers);

3. Decision Conflict Scale (DCS Simplified Version);

4. Anxiety/Depression Scales: GAD-7, PHQ-9 Adolescent Applicable Version (Adolescent Self-Rating), with simplified self-rating scales available for caregivers;

5. Parent-child communication scale or simplified version of family communication questionnaire (focusing on health/reproductive health topics);

6. Brief Table of Decision Satisfaction and Intervention Satisfaction (self-designed with 5 – 10 items).

3.5 Outcomes/Evaluation Metrics (including primary outcomes/evaluation metrics and secondary outcomes/evaluation metrics, with clear clinical definitions and specified measurement time points)

6 Evaluating indicator

Primary outcome/primary endpoint

Within 3 months after enrollment, the HPV vaccination initiation rate (proportion of first dose completed): Within 3 months from the date of signing informed consent and completion of baseline assessment, adolescents received the first dose of any HPV vaccine at any qualified vaccination site, with confirmation through vaccination certificates, vaccination record systems, or vaccination vouchers. The proportion was calculated by dividing the number of subjects who completed the first dose by the total number of assessable subjects in both the trial group and control group, followed by intergroup comparison.

Secondary outcomes/secondary evaluation indicators

Full vaccination completion rate within 1.6 months: Based on the actual type of HPV vaccine administered to participants, the completion of all recommended doses (e.g., 2 or 3 doses) within 6 months after enrollment, with documented vaccination records.

2. Changes in vaccine hesitancy levels: The total score of the caregiver vaccine hesitancy scale was assessed at baseline, 3 months, and 6 months, with analysis of time-dependent and between-group variations.

3. Changes in HPV/HPV vaccine knowledge level: Trend and intergroup differences in knowledge questionnaire scores at various follow-up time points.

4. Changes in psychological states such as anxiety/depression: Changes in scores of scales like GAD-7 and PHQ-9 among adolescents and caregivers, comparing intra-group changes over different time points and inter-group differences.

5. Changes in parent-child communication quality: Changes in scores on the Parent-Child Communication Scale, with particular focus on communication frequency related to reproductive health/vaccines, openness, and conflict levels.

6. Decision conflict and decision satisfaction: Temporal changes and intergroup differences in DCS scores and decision satisfaction scale scores.

7. Intervention feasibility and acceptability indicators (test group): Utilization rate of intervention materials (manuals/videos/WeChat push notifications, etc.) and self-rated usefulness; Completion rate of structured collaborative decision-making interviews; Completion rate and satisfaction with telephone/online follow-ups.

8. Safety and vaccination-related visits: Record the visitation status of adverse events related to HPV vaccination, severe adverse events (if any), and subjective safety evaluations of vaccination, and perform descriptive analysis.

7 Risk Prevention and Management

Although the core interventions of this study were health education and communication method optimization, which inherently carried minimal risk, systematic management of adverse events (AEs) and serious adverse events (SAEs) was still required due to the study involving HPV vaccination, a routine medical procedure. Any adverse medical events occurring during the study period (from the date of informed consent signing to the end of the last follow-up) were classified as

AEs, including new or aggravated symptoms, signs, or laboratory abnormalities in participants, regardless of whether they had a causal relationship with the study intervention or vaccination. The study specifically focused on local reactions associated with HPV vaccination (e.g., redness, swelling, pain, or induration at the injection site), systemic reactions (e.g., fever, headache, fatigue), and allergic reactions. Adverse events were defined as SAEs if they met any of the following criteria: causing death, life-threatening conditions, requiring hospitalization or prolonged hospital stay, resulting in persistent/significant functional impairment or disability, leading to congenital malformations/birth defects, or being deemed clinically significant by investigators.

For all adverse events, the study physicians will evaluate their severity and correlation with HPV vaccination or study interventions. Severity can be classified based on clinical impact into mild (minor symptoms with minimal impact on daily activities), moderate (notable discomfort partially affecting study participation requiring general treatment or short-term management), and severe (significant impact on daily life necessitating hospitalization or active medical intervention). Correlation assessment integrates factors such as temporal relationship between event occurrence and vaccination/intervention timing, prior similar medical history, changes after continued or discontinued vaccination, and other potential etiologies, categorizing events as definitively associated, highly probable associated, possibly associated, unlikely associated, unrelated, or indeterminate. Additionally, vaccine package inserts and historical safety data will be referenced to differentiate between expected and unexpected adverse events. Unexpected and severe events will receive heightened attention and prompt reporting. Where regional regulatory authorities have specific requirements such as "suspected accidental severe adverse reactions," corresponding reports will be supplemented according to local guidelines during implementation phases.

General non-serious adverse events were primarily collected at various follow-up time points through questionnaires or face-to-face interviews, uniformly entered into electronic case report forms, and documented with start/end dates, clinical

manifestations, management measures, and outcomes. For serious adverse events, researchers promptly notified the center director orally upon awareness and submitted standardized SAE report forms to the lead institution and institutional ethics committee within 24 – 72 hours. If the event was suspected to be highly related to HPV vaccination, adverse drug reaction reporting was conducted in accordance with national and regional drug regulatory authorities' regulations. The lead institution was responsible for consolidating adverse events and serious adverse events reported by all centers, regularly analyzing event types and incidence frequencies, and jointly evaluating with participating centers when necessary whether to adjust the study protocol, update informed consent content, or implement additional safety measures.

The management of adverse events was conducted in accordance with the routine clinical practices of each center. Mild to moderate local or systemic reactions could generally be alleviated through symptomatic measures such as local cold compresses and oral antipyretic analgesics. In cases of suspected moderate to severe allergic reactions or other serious vaccination-related events, immediate emergency response measures and specialist consultations should be implemented, with careful consideration given to subsequent vaccination schedules. Under all circumstances, the safety and interests of participants were prioritized. During severe adverse event management, study interventions could be terminated or adjusted at any time. The decision to continue participation was jointly determined by investigators after thorough communication with participants and their caregivers, with documentation submitted to the ethics committee for record-keeping.

8 Adverse Event Recording and Reporting

During the study period, investigators should closely monitor the occurrence of adverse events. Upon the occurrence of an adverse event (including major adverse events), investigators must analyze the causes, make judgments, and track and record the time of onset, symptoms, severity, duration, management measures, and outcomes of the adverse event, while evaluating its relevance to the trial. All relevant medical

documentation, including laboratory test result reports, should be recorded in the original files.

In the event of a serious adverse event, immediate protective measures must be implemented for the subject. The investigator must promptly complete the "Serious Adverse Event Form" and report it to the ethics committee within 24 hours. The subject experiencing the serious adverse event shall be followed up and recorded until clinical improvement or death occurs.

9 Data Management

In terms of data management, this study will adopt a unified Electronic Case Report Form (eCRF) and Electronic Data Collection System (EDC). All research centers will enter and manage data on the same platform using authorized accounts. Each participant will be assigned a unique study number upon enrollment for data entry and analysis, with personal identifiers such as names not appearing in the analytical database. Informed consent forms and corresponding coding tables will be stored separately in paper or encrypted electronic formats to ensure a balance between anonymization and traceability. The EDC system imposes mandatory fields and logical validation rules for key variables, such as requiring vaccination dates to be later than enrollment dates and limiting scale scores within reasonable ranges, thereby minimizing technical errors and omissions. Study data will be regularly backed up on secure servers to prevent data loss due to system failures or human errors.

To ensure data quality and subject compliance, the research team will establish standardized operating procedures (SOPs) covering the entire process from subject screening, enrollment, intervention implementation, follow-up evaluation, to data entry. Prior to project initiation, the lead institution will conduct unified training for research physicians, coordinators, and data entry personnel at each center to familiarize them with the study protocol, inclusion/exclusion criteria, scale administration guidelines, and Electronic Data Capture (EDC) usage. During study implementation, the project coordination team will regularly monitor enrollment progress, follow-up completion rates, and missing rates of key variables at each center.

Identified issues will be promptly communicated to respective centers via "questionnaire forms," with follow-up tracking of corrective actions. Additionally, multi-channel communication, flexible follow-up schedules, and appropriate engagement incentives will be implemented to enhance subjects' understanding and cooperation, thereby improving data integrity and follow-up quality at the source.

Given that this project is an international multicenter study, ensuring consistency in implementation across centers is a critical aspect of quality control. To this end, on one hand, multicenter kick-off meetings and centralized training sessions are organized at the study initiation stage to provide detailed explanations of the research protocol and intervention content. Unified educational materials, videos, reminder cards, and assessment scales are distributed. For collaborating centers such as Hong Kong and Malaysia, where language or cultural differences may necessitate minor adjustments to certain expressions, the process follows the "translate first, conduct localized pilot testing, then review and confirm by the lead institution" approach to ensure consistency in core content. On the other hand, during the project implementation, the lead institution regularly reports key quality indicators from each center (e.g., enrollment numbers, follow-up completion rates, missing rate of key variables, adverse event reporting rates). Centers showing significant deviations from expected outcomes undergo remote or necessary on-site monitoring, including random checks of informed consent forms, consistency between source data and electronic case reports (eCRFs), and intervention execution records. This dynamic process enables continuous calibration and optimization of implementation quality across all centers.

10 Statistical analysis technique

This study will establish a detailed statistical analysis plan in advance, with standardized procedures focusing on data set definition and selection, missing data handling strategies, and statistical methods for primary and secondary outcomes. Regarding the overall analysis, three datasets will be utilized: 1) The Full Analysis Set (FAS), also known as the Intent-to-Treat (ITT) set, comprising all participants who

underwent randomization and completed at least one baseline assessment, strictly categorized according to randomization groups for primary efficacy analysis; 2) The Per-Protocol Set (PPS), derived from the FAS by excluding major protocol violations (e.g., failure to receive assigned intervention groups or missing critical follow-up data), for sensitivity analysis of primary outcomes; 3) The Safety Analysis Set (SS), including all participants who actually received at least one study-related intervention (whether comprehensive interventions or routine education), for adverse event and safety analysis.

Regarding missing data handling, considering the sensitivity of behavioral outcomes to public health interpretation, this study adopted a relatively conservative strategy in the ITT analysis of primary behavioral outcomes (completion of first dose within 3 months): if reliable vaccination records or household confirmation could not be obtained within the predetermined time window, cases were principally treated as "unvaccinated," supplemented by sensitivity analyses using methods such as multiple imputation. Similar principles were applied to the indicator of completion of full vaccination within 6 months. For continuous variables such as scale scores, linear mixed models were utilized to estimate values based on "available data" whenever possible, avoiding sample size loss caused by simple deletion of missing cases. When necessary, multiple imputation techniques could be employed according to missing pattern patterns to minimize estimation bias.

In terms of statistical methods, descriptive analysis was first conducted on baseline general characteristics of the two study groups. Continuous variables were expressed as mean ± standard deviation or median and quartiles, with intergroup comparisons performed using t-tests or nonparametric rank-sum tests based on distribution characteristics. Categorical variables were described by frequency and percentage, with χ^2 tests or Fisher's exact test employed for comparison. The primary outcome, "completion rate of first HPV vaccine dose within 3 months," was compared between groups using χ^2 tests. To account for potential confounding and multicenter effects, a generalized linear mixed model (GLMM) was further

constructed: with first-dose completion status as the dependent variable, group, age, socioeconomic status, and baseline vaccine hesitancy score (PACV score) as fixed effects, and study center as a random effect. The model estimated adjusted odds ratio (aOR) or adjusted relative risk (aRR) with 95% confidence intervals for the intervention measures. The secondary outcome, "completion rate of full vaccination within 6 months," was compared between groups and adjusted for multiple factors using a similar approach.

For secondary phenotypic indicators such as vaccine hesitancy, HPV knowledge level, anxiety/depression levels among adolescents and caregivers, parent-child communication quality, as well as decision-making conflict and decision satisfaction, score differences between the two groups will be compared at each time point. Repeated measures ANOVA or linear mixed-effects models will be employed, incorporating time, group, and their interaction terms, to examine the trajectory of intervention effects on these psychosocial outcomes over time. Indicators such as intervention feasibility and acceptability will primarily be analyzed using descriptive statistics, with χ^2 tests or rank-sum tests applied to different centers or populations as needed. Unless otherwise specified, statistical tests will be conducted using two-tailed methods with a significance level of α=0.05. P-values for primary outcomes will serve as the basis for effect determination, while exploratory analyses will be prioritized for secondary outcomes. Bonferroni or FDR methods may be employed for multiple comparison corrections for selected key secondary outcomes. Statistical analyses will utilize commonly used software (e.g., SPSS, SAS, or R), with software versions explicitly noted in formal statistical analysis plans and final reports.

11 Form of publication for research findings

Develop at least 1 – 3 high-quality academic papers and a scalable comprehensive HPV vaccination intervention protocol;

To provide replicable practice paradigms and policy recommendations for this institution and collaborative centers in adolescent vaccination prevention and family co-decision services.

12 Ethical considerations

1. Risks and Benefits

In light of the practical characteristics of this study, the direct medical risks faced by participants primarily stem from HPV vaccination itself. Since this study does not alter the routine vaccine types or vaccination protocols across centers, the risk of vaccine-related local and systemic adverse reactions is comparable to conventional immunization. Such risks are mitigated through standardized vaccination procedures, adverse event monitoring, and prompt intervention. Beyond medical risks, psychological and privacy-related concerns may also arise during the study. For instance, certain questionnaires involve topics such as health status, psychological emotions, and family communication, which may cause temporary discomfort for individual participants or caregivers. To address this, the research team will maintain neutral and respectful phrasing in inquiries, explicitly inform participants that they may skip questions they are unwilling to answer, conduct surveys in relatively quiet and private environments, and refer individuals exhibiting significant psychological distress for further medical evaluation or referral to psychiatric specialists.

In terms of implementation research, operational risks such as insufficient recruitment progress, poor follow-up and adherence rates, and multicenter execution disparities also exist. To mitigate recruitment progress risks, this study not only utilized vaccination clinics at each center but also expanded to pediatric and adolescent gynecology clinics, adolescent health clinics, and relevant pediatric/child health specialty clinics. Multiple channels were employed to broaden potential participant sources, with phased enrollment targets and early warning mechanisms established. Screening departments were expanded internally when necessary. For follow-up and adherence management, comprehensive measures including multi-channel contact collection, appointment reminders, flexible follow-up methods, and appropriate incentives were implemented. The dropout rate was continuously monitored during project implementation, with targeted interventions for high-risk centers. To address potential regulatory and technical risks in multicenter consistency and cross-regional collaboration, the study adhered to regional data protection

standards, cross-border information transmission protocols, and vaccine safety monitoring regulations prior to initiation. Essential data sharing and confidentiality agreements were signed to ensure compliant multicenter collaboration and data aggregation analysis.

2. Protection of subject privacy

Only researchers participating in this study may access the personal medical records of subjects, with confidentiality clauses included in the signed investigator declarations or confidentiality agreements. Ethics committees and regulatory authorities are authorized to review clinical trial records. Data processing will employ anonymization techniques to omit information that could identify individual subjects, and the publication of research findings will not disclose personal information of participants. Subject medical records are stored in the archival repository of Children's Hospital Affiliated to Zhejiang University School of Medicine, which implements stringent security and confidentiality measures.

3. Informed consent and signing of the informed consent form

Prior to initiating clinical research, investigators must provide participants or their legal guardians with detailed information regarding the clinical study, including the nature of the study, research objectives, potential benefits, and risks, to ensure that participants or their legal guardians fully understand the clinical study. The study subjects were minors aged 9 – 17 years. Based on the age and cognitive abilities of participants, the method of obtaining informed consent was as follows: All minor participants were required to have their legal guardians sign the Informed Consent Form (Guardian Version). Additionally, depending on the age and cognitive abilities of minor participants, the method of obtaining consent from the participants themselves was as follows:

Children and adolescents within this age group generally possess the requisite comprehension and judgment capabilities. Prior to the initiation of the study, researchers will provide comprehensive explanations regarding the study objectives, procedures, potential risks, and benefits in language that is understandable to the

participants. The participants themselves will sign the corresponding "Informed Consent Form (Minor Version)." Throughout the study, the wishes of minor participants will be fully respected. If a participant explicitly declines participation, even if their guardian has signed the informed consent form, the individual will not be included in the study. Clinical research may only commence after obtaining signed informed consent.

Each patient must provide detailed contact information including address and telephone number. Additionally, physicians should provide their own contact details to ensure patients can reach the investigators at any time.