Title: Effect of health education on promoting influenza vaccination health literacy among primary school students: a cluster randomized controlled trial protocol

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INTRODUCTION

The Influenza virus, known for its mutability and potent infectivity, poses a significant health risk. Recent trends indicate an escalating incidence of influenza in China, thereby posing a substantial threat to public health.[1, 2] According to national influenza surveillance data, each October marks the onset of the winter and spring influenza epidemic seasons across various regions in China.[3, 4] Currently, the most effective preventative measure against influenza is vaccination.[5] Seasonal influenza vaccinations have demonstrated efficacy in reducing the risk of influenza infection and severe complications across all age groups.[6] Seasonal influenza epidemics often precipitate outbreaks in densely populated areas such as schools, childcare institutions, and nursing homes.[6]

Health literacy, defined as an individual's capacity to acquire, comprehend, and utilize basic health information and services for informed health decisions, plays a pivotal role in vaccination uptake.[7, 8] Enhancing vaccine health literacy can potentially augment vaccination willingness and mitigate vaccination hesitancy.[9] Therefore, improving the population's awareness, attitudes, and behaviors towards influenza vaccination health literacy is integral to the successful implementation of influenza

prevention and control measures and strategy development.

While numerous studies have investigated the broader implications of health education interventions on vaccination awareness and rates, there remains a distinct lack of focused research specifically targeting primary school students, especially within the context of China.[10-12] The unique age group, characterized by their transitional cognitive abilities and susceptibility to influence, may respond differently to health literacy interventions than other age cohorts. Moreover, regional differences, cultural practices, and local health infrastructure in China might further impact the effectiveness of such interventions. Thus, this study aims to investigate the influence of health education on influenza vaccination rates and the level of influenza vaccination health literacy among fourth and fifth-grade primary school students. The methodological approach will involve a cluster randomized trial with schools serving as the unit of analysis. The findings will provide a scientific basis for future interventions.

METHODS AND ANALYSIS

Study objectives

This study seeks to explore the impact of health education interventions on vaccination and influenza vaccination awareness among senior primary school students. By evaluating the impact of health education on the seasonal influenza vaccination rate and the level of influenza vaccination health literacy, we aim to provide a scientific foundation for regional influenza prevention and control

strategies. The specific objectives of this research are: 1) To ascertain the rate of influenza infection, the status of influenza vaccination, and the level of health literacy related to influenza vaccination among primary school students in Dongguan City. 2) To compare and contrast the influenza vaccination rate and the level of influenza vaccination health literacy between the experimental and control groups, thereby evaluating the impact of health education intervention on these parameters. 3) To assess the efficacy of influenza vaccine immunization among primary school students in Dongguan City.

Study design

The proposed study is a cluster randomized controlled trial. Two administrative districts, one in the central urban area and the other in the non-central urban area of Dongguan, will be selected for this study. Within each district, ten primary schools will be randomly selected, with half designated as intervention group schools and the remaining half as control group schools. This results in a total of twenty primary schools, evenly split between the intervention and control groups.

The intervention group will receive a health education intervention focused on influenza vaccination, while the control group will continue with their routine school health education. The intervention period for this study is projected to last approximately three to four months. Data collection will conduct at the onset and conclusion of the intervention period. The primary outcomes of interest are the differences in influenza vaccination rates and influenza vaccination health literacy levels between the experimental and control groups, which will be used to evaluate

the effectiveness of the intervention. The overview of the study procedure is shown in the Figure 1.

Study sample

Study participants are primary school students in grades 4 to 5 in Dongguan City. Inclusion criteria include: 1) Primary school students within the age range of 7-12 years. 2) Students and their parents who voluntarily agree to participate in the study and provide signed informed consent. 3) Permanent residents of Dongguan City who are expected to complete the project without transferring schools during the study period. In addition, individuals with contraindications to influenza vaccination, who have recently received an influenza vaccination, diagnosed with influenza or confirmed as influenza-like cases at the commencement of the study, or unwilling to participate in the project, will be excluded.

Sampling method

The study employs a multi-stage cluster sampling method. In the first stage, one central urban area (tentatively identified as Dongcheng Street, which oversees 31 primary schools) and one non-central urban area (tentatively identified as Gaobu Town, which oversees 13 primary schools) will be randomly selected, reflecting the urban-rural structure of Dongguan City. In the second stage, ten primary schools will be randomly selected from each administrative district, with five designated as intervention group schools and the remaining five as control group schools. This results in a total of twenty primary schools, evenly split between the intervention and

control groups. In the third stage, two classes from each of the two grades (fourth and fifth grades) are randomly selected from each of the twenty selected schools using a cluster sampling method, with surveys conducted at the class level. Each school comprises a minimum of 152 students. Schools with 152 students will have one additional class randomly selected. The final estimated total sample size is projected to be 3036. Random sampling and randomized grouping are achieved using computer software to generate random numbers. The sample size is determined using the following formula:

$$n = \frac{\left\{z_{1-\alpha/2}\sqrt{2\,(m-1)\rho+2} + z_{\beta}\sqrt{(m\rho+1)}\right\}^2 * \{p_1(1-p_1)+p_2(1-p_2)\}}{(p_1-p_2)^2}$$

where: n is the desired sample size for each cohort, $z_{1-\alpha/2}$ is the value corresponding to the accepted Type I error rate (eg $z_{1-\alpha/2}$ about 1.96 for an error rate of 0.05), $z_{\beta}$is the value corresponding to the desired statistical power, e.g., for a power of 0.8, z_{β} is approximately 0.84. m is the size of each cohort, ρ is the intra-group correlation coefficient, p_1 is the expected outcome rate in the test group (ie, influenza vaccination rate), and p_2 is the expected outcome rate in the control group. Based on the assumption that the anticipated influenza vaccination rate is 80% in the intervention group and 50% in the control group, the estimated sample size, denoted as 'n', is 138 students per school.[13, 14] This implies that approximately 138 primary school students are required for each group, yielding a total sample size of 2760 individuals. To account for potential sample attrition, the sample size is expanded by 10%, resulting in a final estimated total sample size of 3036 for statistical analysis.

Intervention methods

The intervention group will receive a health education intervention focused on

influenza vaccination literacy, while the control group will continue with their standard school health education without any additional intervention. An influenza vaccination health education including topics such as the importance of influenza vaccination, benefits of vaccination, and vaccination methods, will be developed and reviewed by an expert group. The package for the intervention group will include educational activities, distribution of promotional materials, vaccination services, and distribution of vaccination souvenirs. The details are as follows:

1) Educational activities include classroom lectures and parent meetings. Medical professionals or public health experts will be invited to deliver lectures at the school, providing detailed information on the role and benefits of influenza vaccination and the risks of influenza. Teachers and relevant school staff will be trained to understand the importance of influenza vaccination, reinforcing these messages in everyday teaching. Content about influenza vaccines will be incorporated into school health education courses, facilitating student learning about influenza vaccines. In addition, Teachers will discuss the importance of the flu vaccine at parent meetings, encouraging parents to facilitate their children's vaccination.

2) Promotional materials include educational booklet, animated videos, vaccination service and vaccination souvenirs. Educational booklet will be designed and distribute to students to raise their awareness of flu vaccines. Animated videos will be created to explain the effects of flu vaccines and the benefits of vaccination in an easy-to-understand manner. These videos will be played on school TVs or computers, and students will be organized to watch them. Influenza vaccination services will be provided to students who have no contraindications to influenza vaccination, are in

good health, and are 4-6 months post their last influenza vaccination, based on the principle of informed consent, voluntariness, and self-payment. 'Epidemic Prevention Little Guards' medals will be created and distributed to vaccinated students as a commemorative incentive to encourage vaccination.

Intervention time

Staff of the affiliated street Center for Disease Prevention and Control (CDC) will visit the school in the first month to implement intervention activities using the health education intervention package. The intervention period will commence in September 2023 and conclude in February 2024, resulting in a total intervention duration of approximately three to four months. The specific intervention process is as follows: 1) At the start of the semester (early intervention stage in September 2023), initiation activities will be conducted. The investigators will introduce the study to teachers and students, and medical professionals or public health experts will be invited to deliver classroom lectures at the intervention group schools. Baseline data will be collected at this stage. 2) During the intervention period (September 2023 – January 2024), the intervention group will follow the health education intervention toolkit to conduct intervention activities. 3) At the conclusion of the semester (February 2024), follow-up data will be collected. The intervention timeline is shown in the Figure 2.

Data collection and analysis

Questionnaire surveys will be administered to students and parents before and after

the intervention, using self-completion. The questionnaire design, which is informed by similar research literature (Appendix 1 & 2), will undergo evaluations for reliability and validity. The questionnaire will include the following content: 1) Socio-demographic characteristics (name, age, sex, class, residential address, parents' educational level, occupation, family income); 2) Personal history (basic disease history, allergy history, and personal history); 3) Influenza vaccination health literacy level. The health literacy level concerning influenza vaccination will be assessed across four dimensions: knowledge, attitude, behavior, and skills related to influenza vaccination. Details of these four dimensions include knowledge of basic facts about the influenza vaccine (such as its efficacy, vaccination frequency, and side effects), attitudes towards the influenza vaccine (including perceptions of its efficacy and safety), behavioral characteristics related to influenza vaccination (such as willingness to be vaccinated, vaccination status, and timing of vaccination), and sources of information about the influenza vaccine.

Confirmation of influenza and surveillance of influenza-like cases

Influenza cases are characterized by initial symptoms such as fever, headache, myalgia, and general malaise, with body temperatures potentially reaching 39-40°C. Patients may experience chills, muscle and joint pain, fatigue, loss of appetite, nasal congestion, runny nose, substernal discomfort, facial flushing, and conjunctival hyperemia. Confirmed cases must have one or more of the following positive pathogenic test results: influenza virus nucleic acid test, influenza antigen test, influenza virus culture isolation, and a four-fold or greater increase in the level of influenza virus-specific IgG antibody in the convalescent and recovery period double sera compared to the acute stage.

Confirmed cases of influenza will primarily be identified through the municipal CDC influenza surveillance network. Furthermore, influenza-like illness (ILI) is defined as instances of fever (body temperature ≥ 38°C) accompanied by either a cough or sore throat, with epidemiological evidence or a positive influenza rapid antigen test, and excluding other diseases that cause influenza-like symptoms. The fever should occur within the current acute febrile illness period. Body temperature identification includes self-measurement by patients and temperature detection by medical institutions. Identification of ILI cases can be achieved through establishment of a case reporting system in schools or student or parent self-report. The case reporting system in schools involves training school medical staff and teachers to understand the definition and reporting methods for ILI cases. When students exhibit influenza-like symptoms (such as fever, cough, sore throat, or other symptoms), the school's medical staff or teachers will report these cases. Concurrently, a morning inspection and registration system for illness-related absenteeism will be implemented. Cases identified through the student or parent self-report will be obtained by questionnaires, telephone calls, emails, or online platform reports.

Study outcomes

Primary outcomes include the influenza vaccination rate and the influenza vaccination health literacy level. The influenza vaccination rate will be calculated as the number of vaccinated individuals divided by the total number of individuals, multiplied by 100%. Regarding the influenza vaccination health literacy level, each correct answer for the scale will be scored as one point, with incorrect answers receiving no points. Based on the scores, health literacy levels will be categorized as low, medium, or

high.

Secondary outcomes include influenza incidence, the ILI incidence and the influenza vaccine protection rate. The influenza incidence will be calculated as the number of individuals diagnosed with influenza divided by the total number of individuals, multiplied by 100%, The ILI incidence will be calculated as the number of ILI cases divided by the total number of participants, multiplied by 100%. The influenza vaccine protection rate will be calculated as the difference between the incidence rate in unvaccinated individuals and the incidence rate in vaccinated individuals, divided by the incidence rate in unvaccinated individuals, multiplied by 100%.

Statistical analysis plan

Continuous variables will be described using means ± standard deviation or median (interquartile range), and comparisons will be made using two independent samples t-tests or Wilcoxon rank-sum tests. Categorical variables will be described using frequency and composition ratios, and rate comparisons will be conducted using Chi-square tests or Fisher's exact probability method. The association between the level of influenza vaccination health literacy and vaccination willingness will be analyzed using multivariate logistic regression.

Quality control

Quality Control will be conducted in accordance with the requisite quality control standards, with dedicated on-site quality control personnel assigned to oversee investigation and evaluation. These personnel should be proficient in various testing technical requirements and quality control points, and familiar with the on-site

organizational process and division of responsibilities. Their primary responsibilities include: on-site inspection of various investigation and evaluation operational processes, immediate correction of identified issues; on-site review and re-testing of collected information, with rectification based on re-test results; collection, summarization, and analysis of investigation and evaluation quality control issues, with timely reporting and sharing of these issues.

Patient and public involvement

Students and their parents, teachers, and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

ETHICS AND DISSEMINATION

This study follows the Declaration of Helsinki and the Chinese clinical trial research ethics and regulations. Before the commencement of the project, ethical approval has been sought from the Ethics Committee of the School of Public Health, Sun Yat-sen University. The research process respects the autonomy of students and schools. The primary schools selected for this study have an equal probability of being assigned to either the intervention or control group, ensuring the impartiality and fairness of the research. Prior to the initiation of the study, the lead researcher provided an overview of the study's purpose, procedures, and potential risks. Comprehensive informed consent forms, detailing the study's intent, processes, and potential risks, will be handed to both students and their guardians, and participation is strictly voluntary. Data confidentiality is ensured through anonymization and restricted access, with only the core study team able to view raw data. Provisions are also in place to address any adverse reactions or events related to the study or vaccination.

Findings from the study will be made accessible to both the scientific community and the public. Results are slated for submission to peer-reviewed journals, ensuring validation and broader reach within the research community. Beyond academic circles, outcomes will be relayed to key stakeholders, including school officials, health departments, and community leaders, fostering informed decisions at the grassroots level. Additionally, feedback sessions, online postings, and conference presentations are avenues being considered to ensure widespread dissemination and awareness.

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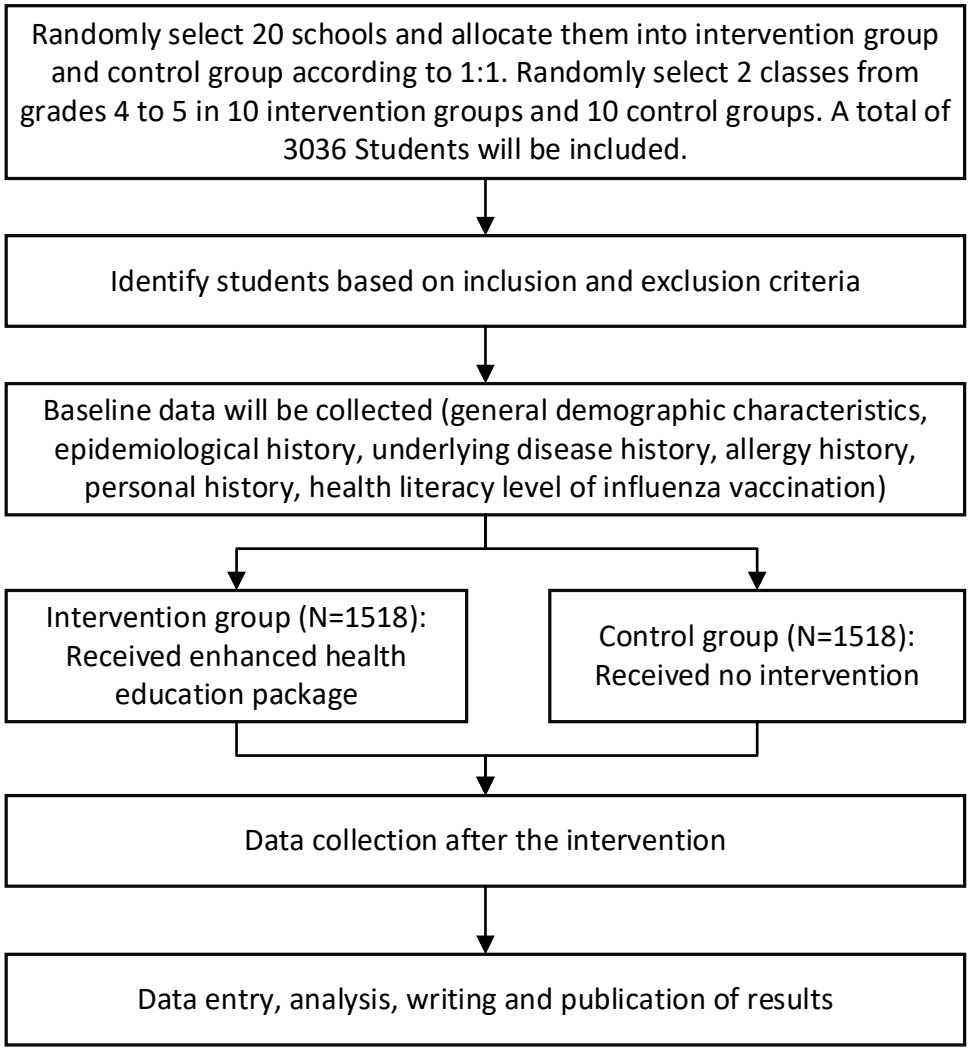

Figure 1 Overview of the study

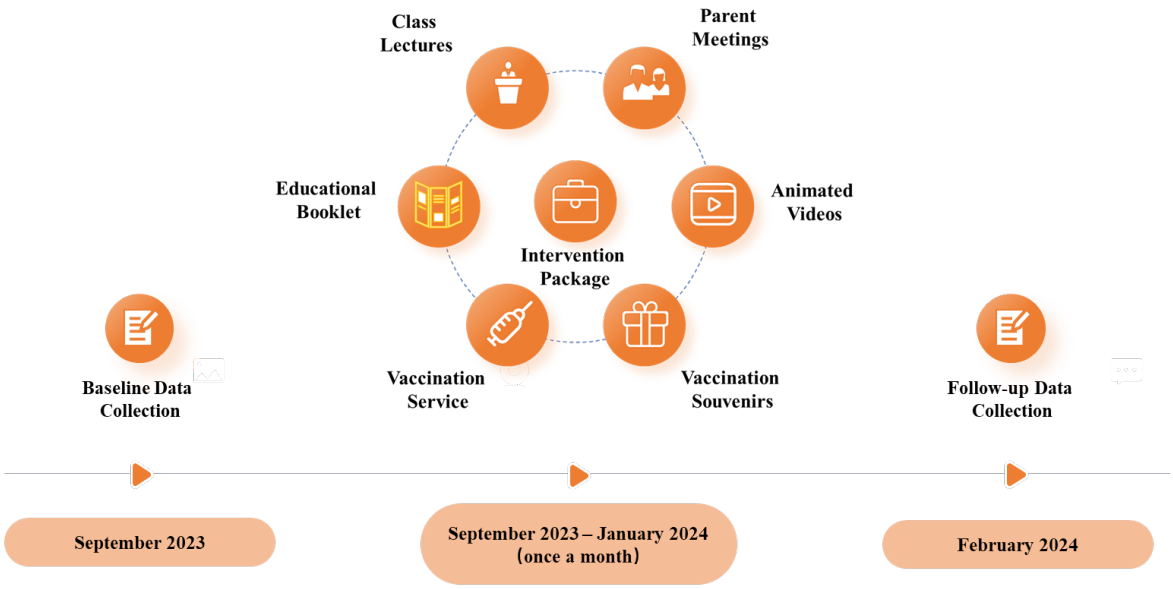

Figure 2 Intervention timeline

Appendix

Appendix I Health Literacy Research Questionnaire (Parent Version)

Appendix II Health Literacy Research Questionnaire (Student Version)

Appendix III Registration Form of Influenza-like Cases in the School Clinic

Appendix IV SPIRIT 2013 Checklist

Appendix I Questionnaire for the Health Literacy Study of Influenza Vaccination among Primary School Students in Dongguan City (Parent Version)

	Question
Basic information	
	The street where your child’s school belong is?
	Your child’s school?
	Your child’s ID type?
	Your child’s ID number?
	Your phone number?
	Are you the child's father, mother or?
	Do you currently live with your children?
	Your age?
	Your spouse's age?
	Your highest level of education?
	Your spouse’s highest level of education?
	Your occupation?
	Your spouse’s occupation?
	Your home address?
	Your household income?
	How many children do you currently have?
	How is your child's health?
Knowledge questions	
	Do you know what the symptoms of flu are?
	Do you know when is the flu season in Dongguan?
	Do you know how the flu is transmitted?
	Do you think the flu is an infectious disease?
	Do you know what the flu vaccine is?
	Have you heard of the flu vaccine?
	Do you know the minimum age for children to receive their first

	flu vaccination?
	Do you think it's appropriate to get the flu vaccine during a flu epidemic?
	Do you know the contraindications of flu vaccination?
	Do you know what the possible side effects of the flu vaccine are?
Attitude Questions	
	Do you think the flu is just a cold?
	Do you think you need to be quarantined at home after getting the flu?
	Do you think your family and friends are likely to get the flu during the pandemic season?
	If you or your child gets the flu, there is a high risk of transmitting it to others around you?
	Do you think that getting the flu can cause serious consequences or complications?
	If you or a family member gets the flu, it can have a serious impact on your or your family's health?
	Do you think the flu vaccination is the most effective preventive measure against influenza?
	Do you think the flu vaccination is effective in reducing the risk of spreading the influenza virus?
	Do you think the flu vaccination will reduce the risk of your family getting the flu?
	Do you think the flu vaccination will reduce the symptoms of influenza in your family?
	Do you think children are a priority and recommended population for the flu vaccination?
	Do you think the flu vaccine needs to be given every year to

prevent the flu?

Do you think getting a flu vaccine is good for you and your child's health?

Do you think it is necessary to get a flu vaccine?

Are you confident that the flu vaccine is safe?

Behavioral questions

Within the last year, have you ever had influenza (or had a sudden onset of illness with a high fever ≥38°C accompanied by flu-like symptoms such as generalised malaise, myalgia, sore throat, etc.)?

If yes, when was the last time you had influenza (or had a sudden onset of illness with high fever ≥38°C accompanied by influenza-like symptoms such as generalised malaise, myalgia, sore throat, etc.)?

Has your child had influenza (or had a sudden onset of illness with high fever ≥38°C, accompanied by flu-like symptoms such as generalised weakness, myalgia, sore throat, etc.) within the last year?

If yes, when was the last time your child had influenza (or had a sudden onset of illness with a high fever ≥38°C accompanied by influenza-like symptoms such as generalised malaise, myalgia and sore throat)?

Have you taken your child for a flu vaccination between 2020 and 2022?

Have you or your spouse been vaccinated against flu in 2023?

If you have been vaccinated against flu, when did you or your spouse get the flu vaccine this year?

Has your child been vaccinated against flu in 2023?

If your child has been vaccinated against flu, when did your

	child get the flu vaccine this year?
	If your child has been vaccinated against flu, why did you decide to take your child for a flu vaccination this year?
	If your child hasn't been vaccinated against flu, why did you decide not to take your child for a flu vaccination this year?
	If your child has not had a flu vaccination this year, are you currently willing to take your child to get one?
	Would you be willing to take your child for a flu vaccination in the future?
	Would you like to recommend that others get the flu vaccine?
Skill Questions	
	Do you know how to schedule your flu vaccine?
	Do you take an active interest in information about flu vaccinations?
	Where do you get information about flu vaccinations?

Appendix II Questionnaire for Health Literacy Study of Influenza Vaccination among Primary School Students in Dongguan City (Student Version)

	Question
Basic information	
	Your class?
	Your gender?
	How old are you?
knowledge questions	
	Have you heard of the influenza or flu?
	Do you know what the symptoms of having the flu are?
	Do you think you can spread the flu to other people when you get it?
	Do you think you can go to class after getting the flu?
	Have you heard of the flu vaccine?
	Do you know what the flu vaccine does?
	Do you know how the flu vaccine works? (For example, it helps our body learn how to beat the flu virus)
Attitude Questions	
	Do you think getting a flu vaccine is a good thing or a bad thing?
	Are you afraid of getting the flu vaccine? Why?
Behavioral questions	
	Within the last year, have you had the flu (or had flu-like symptoms such as sudden high fever, temperature over 38°C, general lack of energy, headache, sore throat, etc.)?
	If yes, when was the last time you had influenza (or had a sudden onset of illness with high fever ≥38°C accompanied by influenza-like symptoms such as generalised malaise, myalgia, sore throat, etc.)?
	Have you been vaccinated against flu in 2023?

	If you have been vaccinated, when did you get your flu vaccine in 2023?
	Would you like your parents to take you for a flu vaccination?
Skill Questions	
	Where do you get information about flu vaccinations?
	Who do you ask if you have questions about the flu vaccine?

Appendix III Registration Form of Influenza-like illness Cases in the School Clinic

School:_____

Serial No.	See a doctor	Date	Name	Gender	Age	Body temperature	Symptom		Remark
							Sore throat	Cough	

Note: (1) Influenza-like illness refers to patients exhibiting a body temperature of ≥ 38℃, accompanied by either a cough or sore throat.

(1) Symptom Column: Please mark a '√' under the appropriate item to indicate the presence of a symptom.

(2) This form should be completed by the school doctors.

(3) If there is a history of exposure to live poultry or a live poultry market, please provide this information in the 'Remarks' column.

Filler:_____

Appendix IV SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	N/A

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10, Figure2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12, Appendix I-II

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14-15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14-15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14-15

	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14-15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	20-26
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.