Improving influenza vaccine uptake in pregnant women: a randomised controlled trial

Study Protocol

1. General information

Protocol Number:	IVPWRCT-002: 20230705
Protocol Title:	Improving influenza vaccine uptake in pregnant women: a randomised controlled trial
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Project site:	Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong Department of Obstetrics and Gynaecology, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong
Compliance:	This study will be conducted in compliance with Declaration of Helsinki, ICH-GCP and standard CONSORT 2010 statement.

2. Background information

Influenza is a major cause of infection globally with an annual attack rate estimated at 20%-30% in children and 5%-10% in adults (1). A higher risk of complications from influenza-induced pneumonia in pregnant women and increased mortality in the third trimester were first reported in the influenza pandemic of 1916-1918 (2). In Hong Kong, 1 in 160 children younger than 2 months old and 1 in 57 children aged from 2 months to under 6 months are hospitalised in Hong Kong public hospitals due to influenza (3).

Influenza vaccination is one of the most effective interventions to prevent influenza infection and associated complications. Inactivated influenza vaccines (IIVs) are recommended for use in people aged 6 months and above, including pregnant women (4). IIVs were 64%-68% effective in preventing influenza-associated hospitalisation in children aged from 6 months to under 6 years during 2015-2016 (5). Influenza vaccine protects both pregnant women (6) and their newborns below 6 months of age (1). Thus pregnant women are in the highest priority group recommended by both World Health Organization (1) and the Scientific Committee on Vaccine Preventable Diseases, the Centre for Health Protection (CHP) (7). Since 2016/17, they have been provided with free or subsidised influenza vaccination by the Hong Kong Government (8). Pregnant women who are Hong Kong residents can receive subsidised influenza vaccine from private practitioners registered in the Vaccination Subsidy Scheme (VSS).

Despite the influenza vaccination recommendations and reports of its safety during pregnancy (9), the uptake of influenza vaccine in pregnant women is still low in Hong Kong. Before the Government's subsidy scheme became available, the influenza vaccine uptake in pregnant women was 1.7%-6.2% (10-13). Previous local studies showed that determinants of influenza vaccination among pregnant women include better knowledge and more positive attitudes in relation to influenza vaccine, being recommended by healthcare professionals, previously vaccinated with influenza vaccine (either mothers themselves or their family members), awareness of vaccination recommendation, having university degree and longer gestation week (10;11;13). It has anticipated that the COVID-19 pandemic may impact on the acceptance of influenza vaccine but data is lacking.

There is no provision for influenza vaccination in pregnant women to be given as part of standard antenatal care. Wong and colleagues (14) conducted a randomised controlled trial (RCT) to promote maternal influenza vaccination with one-to-one education as the intervention and showed that the intervention could increase the uptake from 10% to 21.1%. Our team has previously developed an intervention package which was proved effective in increasing influenza vaccine uptake in young children aged from 6 months to 2 years from 13% to 38% (12). The intervention package included: (i) a concise information sheet about the risk of influenza and benefits of influenza vaccination; (ii) semi-completed forms to utilise the Government's subsidy; (iii) contact details of nearby VSS registered clinics that do not charge above the subsidy; and (iv) vaccination reminders. This proposed study will compare influenza vaccine uptake in three groups of pregnant women: (i) a group offered a multi-component intervention package to encourage uptake of influenza vaccine through the VSS; (ii) a group offered the same package and free influenza vaccination as part of routine antenatal care; and (iii), a control group receiving current standard care.

3. Hypotheses and objectives

Hypotheses:

The uptake of seasonal influenza vaccine in pregnant women can be improved by providing mothers with either a multi-component intervention package to encourage influenza vaccine through the VSS or to offer free influenza vaccine as part of routine antenatal care.

Aims:

1. To determine whether influenza vaccine uptake in pregnant women can be increased with a multiple component intervention package and with influenza vaccine offered as part of routine antenatal care at no charge
2. To improve mothers' knowledge of maternal influenza vaccination
3. To explore whether influenza vaccine uptake in children at approximately 1 year old would be increased with the intervention

4. Study design

This is a prospective RCT of two interventions designed to improve influenza vaccine uptake in pregnant women. The study will be conducted in compliance with Declaration of Heisinki, ICH-GCP and standard CONSORT 2010 statement (15).

Subjects

Pregnant women will be recruited antenatally in two public hospitals (Prince of Wales Hospital and Pamela Youde Nethersole Eastern Hospital). A convenience sample of eligible mothers coming for antenatal check-up will be invited to participate in this proposed study. The inclusion criteria to subject selection includes: pregnant women in any trimester; at least 18 years old; Cantonese speaking and able to read Chinese; no serious obstetrical complications; no mental or psychosocial problem that might affect their interpretation of study questionnaires; not yet received influenza vaccine during this pregnancy; have plans to continue most antenatal follow-up at the study hospitals; have plans to remain in Hong Kong after delivery for at least one month; have smart phones; and can provide signed informed consent. Those cannot meet the inclusion criteria will be excluded. There is no withdrawal criterion of this study. Subjects enrolled in the study who later do not wish to be contacted anymore will be regarded as withdrawal.

After enrolment and consenting, all participants will be randomly allocated into either control or intervention groups using block randomisation (16). Three groups will have similar numbers of participants. We will use statistical software R (version 3.5.2) to randomly generate the treatment allocation in random block sizes of 6 to 12 with block size kept unknown to the research assistants carrying out recruitment and interviews. The treatment assignments will be placed in sealed and opaque envelopes with sequential numbers on the covers. Research assistants who will be responsible for study outcomes assessment, will be blinded to treatment allocation, i.e., not generating treatment allocation and not delivering treatments. Also, the principal investigator and partcipants will also be blinded to treatment allocation, i.e., not knowing the grouping of participants.

As a token of appreciation, we will offer cash or supermarket coupons with equivalent value of HKD200 (USD26) to subjects on completion of the study by registered mail, in consonance with local experience and international practice. Upon receiving the incentive, participants will be asked to sign on a form of acknowledgement of receipt (attachment I). Dates of incentive sent and received and the return of the acknowledgement of receipt will be recorded on a study log sheet as a governance system which will adequately monitor the disbursement of incentives to ensure accountability and traceability.

Interventions

Control Group

Subjects in the control group will receive the standard information about the VSS that is available from the CHP through text message in smart phones (https://www.chp.gov.hk/en/features/46107.html) (attachment II: Sample of VSS leaflet in 2020/21).

Intervention Group 1

Subjects in the intervention group 1 will receive an intervention package through text messages containing the following:

1. the same standard information about the VSS by CHP (https://www.chp.gov.hk/en/features/46107.html) as the control-subjects; and

2. additional interventions which include: a concise information sheet designed by our research team specifically for this study including (i) highlight of the risks of influenza in pregnant women and infants and the benefits of influenza vaccination to them (attachment III: Draft of concise information for intervention group 1), (ii) a hyperlink to the forms required for the VSS, if necessary, with guidelines to complete (attachment IV: Sample of VSS consent 2001/2021), and (iii) a hyperlink of Department of Health (DH)'s website to search for VSS registered clinics that do not charge additional fees for influenza vaccination above the subsidy.

When vaccination is possible, they will receive text message reminders for vaccination (also contain the concise information sheet) with a further reminder one to two months later.

Intervention Group 2

Subjects in the intervention group 2 will receive the same standard information about the VSS by CHP (https://www.chp.gov.hk/en/features/46107.html) as the control-subjects and the same multiple interventions as the intervention group 1 through text message. In addition the subjects will be informed that should they prefer they can receive free influenza vaccine during future antenatal follow-up visit once the vaccine is available.

Methods

The study will recruit subjects before and during the influenza vaccine available in 2023 according to the gestation of pregnancy, i.e., pregnant women who will be eligible for influenza vaccine when vaccines are available. Research staff will recruit subjects from antenatal clinics at the study sites. An informed consent form will be verbally explained by the research staff and written consent sought (attachment V). In the

consent form, an option will be provided for participants to decide whether they are willing to be followed up at their children's age of approximately 1 year. Enrolled subjects will complete a simple questionnaire to collect key demographic information, assess baseline knowledge and attitudes towards influenza vaccine and obtain contact information. Subjects will be informed that they will be sent further details within the following 1-2-week periods. Randomisation will be carried out to determine which package will be sent to subjects.

Subjects in the intervention group 1 will be sent the following information: (i) details about the risks of influenza in pregnant women and infants and the benefits of influenza vaccination highlighted in a concise information sheet, (ii) a hyperlink to the forms required for the VSS, if necessary, with guidelines to complete, (iii) a hyperlink of DH's website to search for VSS registered clinics that do not charge additional fees for influenza vaccination above the subsidy. Text message reminders for vaccination, together with the concise information sheet again, will be sent when vaccination is possible with a further reminder one to two months later.

Subjects in intervention group 2 will receive the same intervention package as intervention group 1. In addition, subjects will be offered free influenza vaccination at the subsequent antenatal clinic visit. The details of getting the free influenza vaccine will be listed on the concise information (attachment VI: Draft of concise information for intervention group 2), which will be included in the intervention package. If the subject wish to be vaccinated, they could send the research staff a text message about their intention. Research staff will inform the subject when the free influenza vaccine is available (from October to the following April) and will arrange the vaccination at one of the subject's subsequent antenatal check-ups. Subjects wishing to receive influenza vaccine at a subsequent clinic visit will get the vaccine from a research nurse attending the antenatal clinics.

The concise intervention information will provide correct information in the areas of misconception about influenza and influenza vaccine during pregnancy. Focus group discussions/individual interviews with approximately 10-45 pregnant women (until data saturation) will be conducted to understand their knowledge and attitudes in relation to influenza and its vaccine. Pregnant women coming to PWH or PYNEH for antenatal check-up will be invited to join the focus group discussion/individual interviews. An informed consent form will be verbally explained by the research staff and written consent will be sought (attachment X). After signing the informed consent form, the subject will complete a short survey on their demographic background (attachment XI). Focus group discussions/individual interviews will be conducted face-to-face or virtually through ZOOM and follow on a guide systematically (attachment XII). The concise intervention information will then be updated according to the findings from the qualitative interviews.

All participants will be followed up first by text message at three to four weeks after their expected date of delivery by research staff who will be blinded to treatment group allocation. After confirming delivery, an online self-administered questionnaire will be completed by the participants. If the participants cannot complete the questionnaires online, hardcopy of the questionnaires with stamped and addressed return envelopes will be sent to their home. Follow-up by phone will be the last resort. Attachment VII shows the logistic flow of the proposed study.

Participants who agree to be followed up at children's age of approximately 1 year will receive text messages around the time for vaccination information.

Data collection

Data will be collected at two to three time-points: at enrolment and at three to four weeks after the expected date of delivery; and optionally at children's approximately 1 year old. All questionnaires will be self-administered (attachment VIII). The following information will be collected at each time point:

1. At enrolment
    - Demographic information
        - Age/ year of birth, place of birth, highest educational level attained, occupation, marital status, household members and income, cigarettes and alcohol consumptions, and receiving CSSA or not
        - Personal identifies such as contact numbers, postal and residential address will be recorded in a separate logbook and linked only to the study number
    - Maternal health information
        - Expected date of delivery, gravidity and parity, pregnancy related health problems, and disease history (17)
    - Vaccination information
        - Heard of influenza vaccine, awareness of influenza vaccination recommendations in priority groups (pregnant women, persons aged 50 years or above, and children aged from 6 months and less than 12 years), and awareness and understanding of VSS in priority groups
        - Influenza vaccination history of mothers and family members in the same household
        - Vaccination status during this and previous pregnancies
    - Knowledge and attitudes in relation to influenza disease and influenza vaccine
2. At three to four weeks after the expected date of delivery
    - Influenza vaccination information during pregnancy
        - Vaccination status of mothers and family members in the same household
        - Reasons of receiving or not receiving influenza vaccine
        - Recommendations of receiving or not receiving influenza vaccine
    - Maternal health status during pregnancy
        - Perceived health status during pregnancy, pregnancy related health problems, and respiratory illnesses and symptoms (17)
    - Infant's information
        - Sex, date of birth, gestational age, method of delivery, and birth weight
    - Caregiver and decision maker on infant's vaccination
    - Infant feeding intension or practice
    - Knowledge and attitudes in relation to influenza disease and influenza vaccine
    - Whether they read the information provided by the research team
    - Perception on change of behaviour because of the control/intervention packages

3. At approximately children's age of 1 year
    - Vaccination information of mothers and children
        - Influenza vaccination status of mothers
        - Any vaccination status of children
        - Reasons of receiving or not receiving influenza vaccine
        - Recommendations of receiving or not receiving influenza vaccine
    - Influenza infection history of mothers and children

Maternal knowledge and attitudes towards influenza and its vaccine will be assessed by a self-administered questionnaire based on the Health Belief Model (HBM). The HBM is a simple, widely used framework to explain human health decision-making and behaviour (18;19). It contains six constructs to predict how humans make decisions, including perceived susceptibility and severity of illnesses, perceived benefits and barriers of interventions, cues to action and self-efficacy. The questionnaire will be based on the questionnaire from a previous study (12), and refined through further pilot testing. The same set of questions will be asked at the two data collection time-points.

5. Selection of subjects

A previous Hong Kong RCT showed that the influenza vaccine uptake in pregnant women was 4.3% in 2014-2015 (12). Three other local studies showed 3.9% in 2005/06 (10), 6.2% in 2009/10 (13) and 1.7% in 2010/11 (11). Following the COVID-19 pandemic we anticipate that there will be greater awareness and acceptance of influenza vaccines. In a local RCT to promote maternal influenza vaccine uptake conducted by Wong and colleagues in 2013-2015 (14), the uptakes in the control and intervention groups were 10% and 21.1% respectively. They reported that the higher-than-expected vaccination rate in the control group might indicate the study itself increased the knowledge or awareness of influenza vaccination in the control subjects. To ensure we will have enough sample to prove the hypothesis, we assume a baseline uptake of 10% in the sample size calculation. A similar intervention package was effective in increasing influenza vaccine uptake in children aged from 6 months to 2 years by 25 percentage points (12). We expect the improvement in uptake would be more difficult in pregnant women (conservatively around 20 percentage points increase). Because of the different settings and policies in the two study sites, analysis will be stratified by study sites. Based on a required power of 80% and a significance level of 0.05, by using G*Power (version 3.1.9.4), the sample size required in each group is 69, and thus 414 in total in two study sites. Taking into account participants who do not complete the study (about 20% from past experience), the sample size required is 522 in total and 261 in one study site.

6. Study tools

The intervention will include: (i) standard information about the VSS that is available from the CHP through text message in smart phones (same as that for the controls); (ii) key information including highlight of the risks of influenza in pregnant women and infants and the benefits of influenza vaccination to them, a hyperlink to the forms required for the VSS, if necessary, with guidelines to complete, and a hyperlink of DH's website to search for VSS registered clinics that do not charge additional fees for influenza vaccination above the subsidy; (iii) text message reminders for vaccination; (iv) and being

informed that should they prefer they can receive free influenza vaccine during future antenatal follow-up visit once the vaccine is available.

7. Safety

Not applicable as this research does not involve any safety issue. Common side effects of influenza vaccination include soreness, redness and swelling where the vaccine was given, mild headache, fever, muscle aches and fatigue.

8. Statistics

Exposures

Intervention Group 1: Type of intervention given: (i) concise information, (ii) provision of and guidance on completing documentation to utilise vaccination subsidy, (iii) a hyperlink of DH's website to search for VSS registered clinics, and (iv) vaccination reminders.

Intervention Group 2: Access to free influenza vaccination at an antenatal clinic follow up visit.

Outcome measures

Primary Outcome measure
Influenza vaccine uptake rate in pregnant women

Secondary Outcome measure
Knowledge and attitudes of mothers in relation to influenza disease and influenza vaccine before and after receiving intervention information

Statistical analysis

DMP Tool will be used to prepare a formal data management plan. To ensure data quality, data will be double-entered and validated using EpiData. Intention-to-treat analysis (20) will be used and any missing influenza vaccination status will be taken as no vaccination. Demographic and maternal health factors will be compared between intervention- and control-subjects. Wilcoxon rank-sum tests will be used for continuous variables and chi-square tests for categorical variables. Chi-square tests will be performed to examine the effectiveness of the intervention package in improving influenza vaccination uptake in pregnant women. Each HBM attitude statement will be scored from 1 to 4 (from strongly disagree to strongly agree). Cronbach's alpha (21) will be used to measure internal consistency of HBM constructs. Permutation tests (22) will be used to examine any paired difference in attitude scores before and after intervention delivery. All statistical analyses will be performed using statistical software R (version 3.6.1) and a two-tailed p-value < 0.05 will be taken as statistically significant.

9. Access to data

All personal information will be kept confidential and the use of the data collected will only be restricted in the office of the Department of Paediatrics of The Chinese University of Hong Kong. Access to data is only limited to authorised members of research team under the direction of the principal investigator.

10. Quality control and quality assurance

Face-to-face interviews will be conducted in Prince of Wales Hospital and Pamela Youde Nethersole Eastern Hospital. Telephone follow-ups and data analysis will be carried out in the Department of Paediatrics of The Chinese University of Hong Kong using their office space. Principal investigator and co-investigators will supervise the project to ensure it progresses appropriately.

11. Ethics

Written informed consent will be sought from each participant and they will be informed of the potential risks and benefits clearly before signing the informed consent from. To protect participants' privacy, all research data would be handled in line with Hospital Authority / Hospital's policy in handling / storage / destruction of patients' medical records. Research data will be locked in cabinets where the department or ward keeps patients' confidential information. Electronic data will be saved in a secured computer of the hospital or university with restricted access.

12. Data handling

All data collected will be locked, held in anonymous files and analysed within the Department of Paediatrics of The Chinese University of Hong Kong.

13. Insurance

Not applicable.

14. Publication policy

Papers approved by the study team will be published in appropriate peer reviewed journals.

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