Summary of Protocol Changes

1. Version 1, Jan 28, 2020. This was the version submitted for an initial IRB application submission as well as for sponsorship application from LSHTM (please see attached the sponsorship letter). The initial proposed sample size of 600 was a rough estimate based on previous observational studies and for three interventions arms in two vaccination clinics (one in a developed area and one in an underdeveloped area) in Guangdong province.
2. Version 2, April 14, 2020. This was the version used for a revised LSHTM IRB application and approved by LSHTM. We started to establish connections with local community-based health organizations and vaccination sites, and tentatively decided on three study sites which included one in Guangzhou city, one in Yangshan county and one in Shenzhen city. Given Shenzhen is a city that is providing free vaccines to the two target age groups, we tentatively decided to use Shenzhen as a comparison site and recruit all participants for the free vaccination treatment in Shenzhen. The flowchart was therefore updated accordingly. We also conducted a feasibility pre-test and then calculated a sample size based on the pre-test results. We adjusted the total sample size from 600 to 300, with 100 for each arm. We added a section on sample size calculation.
3. Version 3, February 9, 2021. We expanded the sample size to 450 (50 more participants for each arm) to allow sub-analysis by study site and age group. Shenzhen study site was removed because of logistic difficulties. Instead, we confirmed availability of influenza vaccine at an alternative urban site in Guangzhou City and revised the recruitment plan of participants for free vaccine treatment at all three study sites. We added a section on intervention

development. We revised the order of recruitment for the three treatment groups as standard of care, pay-it-forward, and free vaccination. We clarified the secondary outcomes (factors associated with vaccine uptake, vaccine confidence and hesitancy, and economic evaluation), revised our hypotheses and provided more information on the data analysis plan. We added the China clinical trial number.

Research Proposal Version No.: 1

Research Proposal Version Date: Jan 28, 2020

Title: Pay-it-forward to improve influenza vaccine uptake among children and elderly people in China: A quasi-experimental study

Trial Sponsor

Name: London School of Hygiene & Tropical Medicine

Address: London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT

Tel: +44 207 927 2626

Project Summary

Despite a high burden of influenza-related mortality, China has extremely low rates of influenza vaccination among key groups including children and the elderly. Ten people die of influenza each hour in China. Individuals ≥60 years is 26 times more like to die of influenza than people < 60. Kids (≤5 years) also have extremely high influenza related death. However, only 2% of Chinese are vaccinated. Influenza vaccines cost 9-16 GBP and are not covered by national insurance programs. We propose a pay-it-forward intervention to increase influenza vaccination rates among children aged between 6 months and 8 years, as well as elderly people aged 60 or above in community-based health organizations. Pay-it-forward has one person receive a gift (e.g., a free influenza vaccination to a caregiver of a child or an old individual) and then asks them if they would like to pay-it-forward for other individuals to benefit from the same generous gift. Participants will also be able to create handwritten postcards encouraging people in the local community to pay-it-forward to the next individual and donate to the rolling finance pool. We will evaluate the intervention using a quasi-experimental study including three conditions (ie, pay-it-forward, free of charge, and pay out-of-pocket) at two community health organizations in Guangdong province, Southern China – one from a developed city

and the other one from an under-developed county. We will recruit 100 children and 100 elderly individuals (50 children and 50 elderly individuals from each community health organization) respectively during the pay-it-forward condition period. Likewise, the expected sample sizes for the other two conditions will be the same. A total of 600 participants will be recruited, including 300 children (consented by the guardian) and 300 elderly individuals. Primary outcomes are influenza vaccine uptake rates and pay-it-forward donation rate.

Background

Influenza is a viral respiratory infectious disease of global importance. Seasonal influenza epidemics cause 3 to 5 million severe cases and 290,000 to 650,000 deaths in the world each year.[1] Pregnant women, infants and children, the elderly, and patients with chronic diseases are at high risks of serious illness and death when infected. In China, about 10 people die from influenza-related illnesses each hour. [2] People older than 60 years old are 26 times more like to die from influenza than younger individuals.[2] Influenza vaccination is considered the most effective way to prevent influenza-related diseases. For example, globally, over 40% of countries have decided to provide free flu vaccine to key populations such as children and elderly individuals.

Chinese Center for Diseases Control and Prevention (China CDC) has released in 2018 a high-level guideline for influenza vaccination services provision to at-risk populations and provinces are developing piloting programs. The guideline defines several at-risk populations including pregnant women, children, family members and caregivers of infants less than 6 months of age, and people aged over 60 years old. However, the most recent pooled evidence revealed that only 11.9% of children (aged 6 months to 17 years old) and 21.7% of elderly population (aged >=60 years) were vaccinated in China.[3]

There are several reasons for low influenza vaccination rates in the country. First, influenza vaccines are not subsidized by government funding in most places due to governmental financial constraints and people need to pay around 16 pounds out-of-pocket for getting the vaccination. Second, the lack of trust in vaccines generally likely decreases demand for influenza vaccine in China. In July 2018, a massive vaccine scandal swept across China, and over 500,000 children were likely injected with faulty triple vaccines (diphtheria/pertussis/tetanus, DPT).[4] This scandal dramatically decreased trust towards vaccine programs, including influenza vaccine. In addition, pregnancy is widely considered a contraindication for influenza vaccination, and pregnant women in many places are rejected by health workers for vaccination.[5] In places where influenza vaccines are free, public awareness and vaccination rates are suboptimal compared to other countries.[6] The vast majority of the population are unaware of the vaccination and there is widespread hesitancy in safety and effectiveness of influenza vaccine, even among health workers.[7] Only 8% of health workers always recommended vaccine to patients during the influenza season.[7] Innovative strategies are needed to reduce financial burden, build up public trust and collect evidence on effective interventions to improve vaccine uptake.

Pay-it-forward is an innovative, participatory behavioral intervention. Pay-it-forward has one individual receive a free influenza vaccine who will be informed by using hand-written postcard messages co-created by participants that someone else paid for them, then ask if they would like to support a future vaccination. Figure 1 illustrates how the model works. Our previous pay-it-forward studies focused on diagnostic services uptake among marginalized populations have proven effective in increasing chlamydia and gonorrhea tests uptake by three folds, compared to the control group.[8] In addition,89% of participants donated to the rolling finance pool and the community generosity build up trust in health services.[8] Evidence also showed simple acts of kindness are contagious [9] and hold potential to be leveraged to enhance public health services delivery.

In this quasi-experimental study, we propose a pay-it-forward approach, aiming to improve public trust and influenza vaccine uptake among two key sub-groups, namely children aged between 6 months and 8 years old and the elderly aged 60 or above in Guangdong province. We determined these two sub-groups based on the disease burden and the national definition of at-risk populations. Specific objectives include 1) to examine the feasibility of applying the pay-it-forward approach in influenza vaccine research in the community setting; 2) to compare the effectiveness of three strategies, which are pay-it-forward, free of charge, and pay out-of-pocket (standard care condition), on influenza vaccine uptake among children and elderly individuals in China; 3) to investigate the donation rate and average donation amount among participants in the pay-it-forward condition.

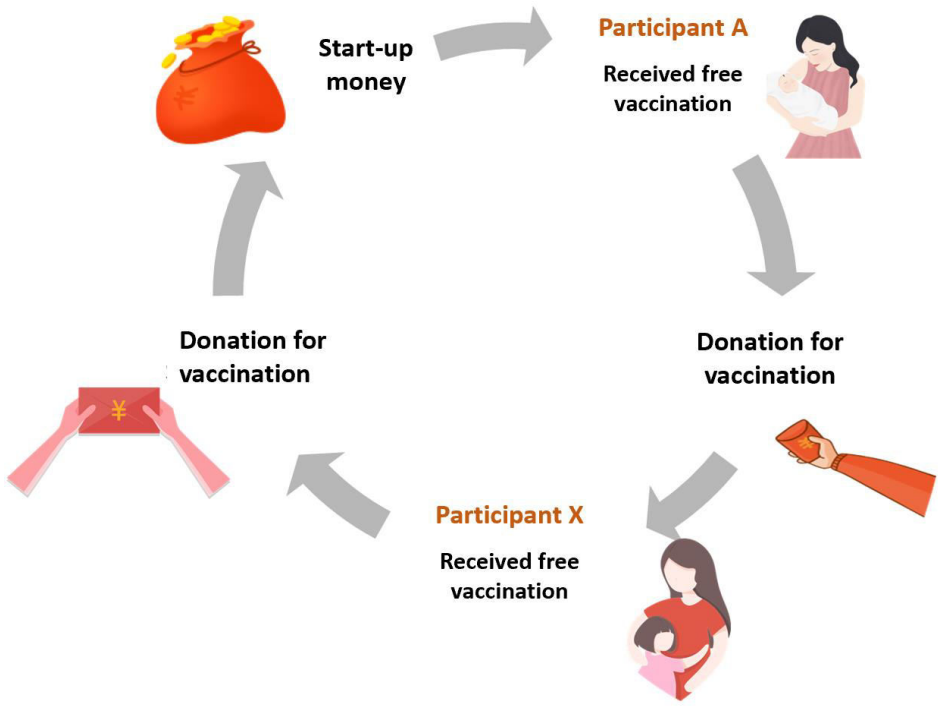

Figure 1: "Pay-it-forward" Model

Hypotheses

Based on the previous research, we conservatively estimate that compared to the standard care (out-of-pocket pay) group,

1) "pay-it-forward" model can significantly improve the influenza vaccination rate among at-risk population including children and elderly groups (30% higher than the standard care group)
2) The donation rate of participants in the "pay it forward" group can reach 50% or higher
3) The "pay it forward" donation can cover 10% of the total economic cost of influenza vaccine.

Methods

Study setting

Guangdong is a subtropical southern province with a population over 100 million in China. In southern China, influenza is prevalent throughout the year; it has a clear peak in the summer and a less pronounced peak in the winter, including Guangdong.[10] In response to the national guideline to provide influenza vaccine to at-risk populations, Guangdong Province has released relevant provincial level policies to promote influenza vaccine. Stockouts of influenza vaccines have been reported in different regions due to tighter quality control of pharmaceutical products after the national vaccine scandal in 2018.[11] Therefore, identifying study sites with sufficient vaccine supply is key to the success of the pilot study during the post-scandal transitioning period. Two batches of tetravalent influenza vaccines produced by Hualan Biology company have been issued in August, 2019; and the first 500,000 tetravalent influenza vaccines were supplied to eight provinces in China, including Guangdong. Given above factors, Guangdong province is selected as the major study location. The London School of Hygiene and Tropical Medicine (LSHTM) research team has established a local collaborative institute with

strong primary care networks in the province - Guangdong Second Provincial General Hospital.

Target population and inclusion criteria

The pilot study will focus on children and the elderly. The inclusion criteria of this study are divided into two age groups:

1） Children: i) children aged between six-month-old and eight years old, ii) no acute moderate or severe illnesses with or without fever, iii) no severe, life-threatening allergies to flu vaccine or any ingredient(s) in the vaccine., iv) a legal guardian, be it a parent or grandparent in the Chinese setting, consents to participate the study.

2） Elderly people: i) ≥ sixty years old, ii) no acute moderate or severe illnesses with or without fever, iii) no severe, life-threatening allergies to flu vaccine or any ingredient(s) in the vaccine, iv) intelligently capable of making informed decisions and consent to participate the study.

Study design

In this study, two vaccination clinics (one in developed and one in underdeveloped areas) will be selected in Guangdong Province for recruitment. The selected community health centers or vaccination clinics should have established infrastructure to provide influenza vaccination services, e.g. have sufficient influenza vaccine stock, relevant medical personnel including designated physicians and nurses for providing vaccine services. The research design is shown in Figure 2.

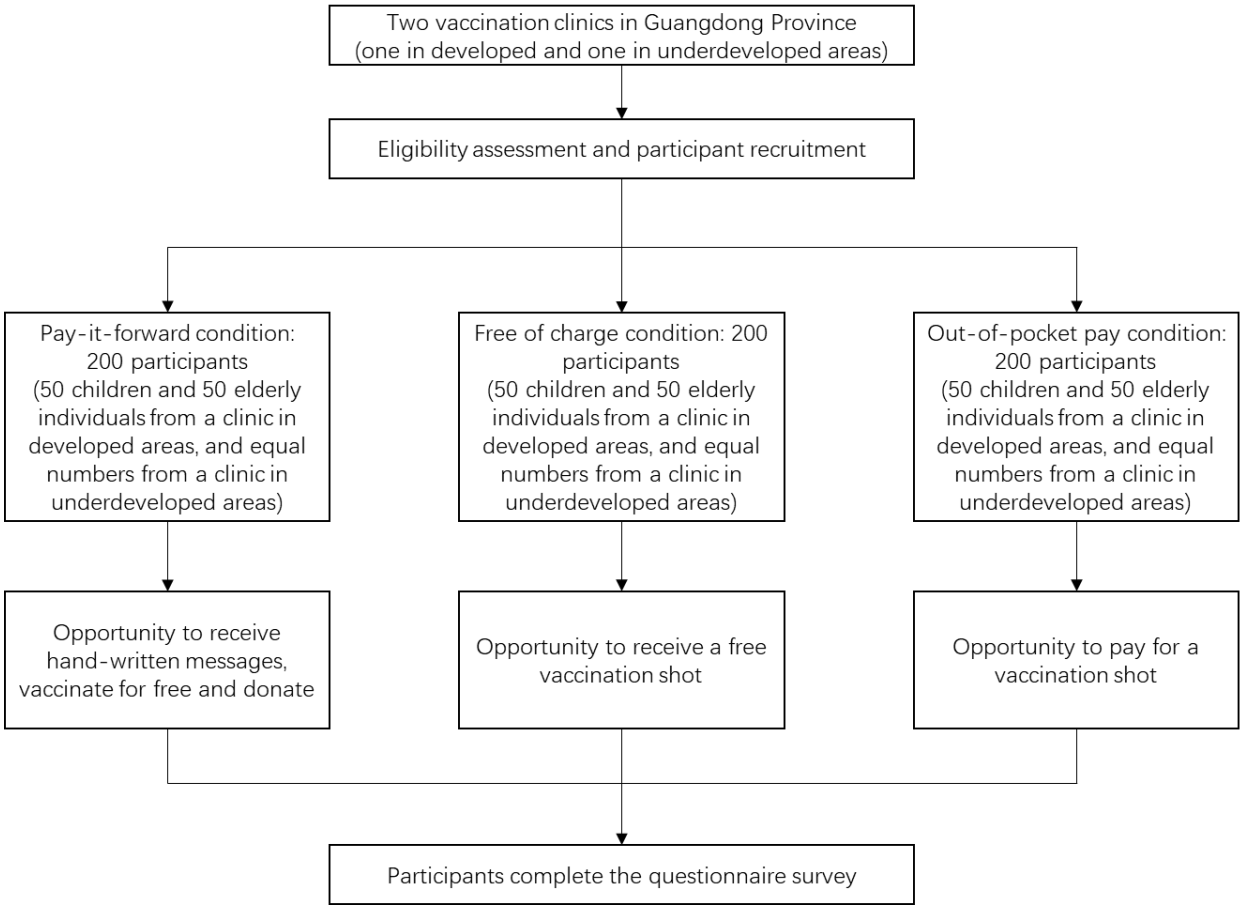

Figure.2

Sampling and recruitment

The target population will be recruited in selected vaccination clinics or community health centers. Project staff will assess eligibility based on inclusion criteria as aforementioned and provide educational information about seasonal influenza pandemics to all potential participants, ie, guardians of children and elderly people. Participants will be recruited into three conditions in chronological order, namely pay-it-forward condition, free-of-charge condition, and standard care (out-of-pocket payment) condition.

Participants recruited during the period of pay-it-forward condition will be informed about the pay-it-forward vaccination program with handwritten warm messages

co-created by participating families to enhance public trust and community cohesion (Supplementary files 1 and 2). After introducing the 'pay-it-forward' program, the project staff will provide eligible participants with the opportunity to take part, which means one eligible child or elderly individual can receive an influenza vaccination shot. The guardian or participant will then be asked whether they are willing to donate any amount of money into the pay-it-forward seed fund to support more future users to receive the same vaccination service. A donation collection box will be provided on site for those who prefer to donate cash and a WeChat QR code (a multifunctional social mobile app embedded with monetary transaction functions) will be provided to those who prefer online donation to the program. Neither the wiliness to donate nor the amount of donation will affect them receiving the influenza vaccination services for free. The microdonations will be used to support future users and usage will be publicized periodically in the vaccination clinic. Expected sample sizes for both children and elderly individuals in pay-it-forward condition are 100 respectively (50 children and 50 elderly individuals from the clinic in developed areas and equal numbers from the clinic in underdeveloped areas).

Participants recruited in the free-of-charge condition will be invited and provided a free influenza vaccination shot but they will not receive any community created messages about the pay-it-forward program. Participants recruited in the standard care condition will be asked to pay out of pocket in the event of being willing to receive the influenza vaccination shot. Participation in each condition is fully voluntary and anonymous. Access to other vaccination and medical services in the clinic will not be affected in any way due to the project. All participants will complete a short questionnaire survey to collect information about demographic backgrounds, information about participating pay-it-forward program (pay-it-forward condition only), and confidence and hesitancy in influenza vaccines.

Data collection

Written consent form will be obtained from all participants. This study will collect the following information: data recorded by the project staff using standard information tracking sheet including the number of invited and participating individuals, the number of participants who receive a vaccination shot, the number of individuals who donate and donation amount in the pay-it-forward condition, as well as survey data through the self-administered questionnaire. Those who have difficulty in reading the questionnaire survey will be assisted by the project staff on-site. A small gratitude gift worth of around 1 GBP will be given to each participant after completing the questionnaire survey.

Risk assessment and management

According to the World Health Organization reports, influenza vaccines are well tolerated, and side effects are mild and transient in general. Common adverse events include soreness, redness, and/or swelling at the vaccination site, fever, muscle pain, headache, nausea which do not require medical attention.[12] Severe threatening allergic reaction after vaccination, such as difficulty breathing, hoarseness or wheezing, swelling around the eyes or lips, hives, paleness, weakness, or a fast heart beat or dizziness, are rare. These signs most likely happen within a few minutes to a few hours after the vaccine is given. Participants who receive a vaccination shot will be required to stay at least half an hour in the vaccination clinic to be closely monitored by a designated nurse. They will be informed to self-monitor signs mentioned above for a few more hours after they leave the clinic. The contact number to a designated physician from the selected clinic will be provided to participants as emergency contact in the event of any severe adverse effects within 24 hours after the vaccination.

Withdrawal of participants

Participants can withdraw from the study at any time without giving any explanations.

Withdrawal from the study would not affect the participant's medical care or other preventive services at the clinic in any way.

Reporting of any adverse events

The local CDCs and vaccination clinics have established a strong surveillance system to monitor any adverse events associated with vaccinating patients. Each patient who receives an influenza vaccine is recorded in the clinical health information system and uploaded to the local CDCs' surveillance system. Patients with any adverse events will be dealt with by local health staff on a timely manner. The research team will leverage their existing platform for reporting any adverse events and keep a tracking record of adverse events. The research team will periodically meet with the designated health workers to make sure adverse events are properly treated.

Data management

Data will be managed according to the principles in accordance with good research practice specified by LSHTM Research Data Management Policy.[13] All data will be kept confidential and accessible only to trained study staff. All consent forms, administrative and survey data will be transformed into digital format and data in non-digital formats will be stored in a securely locked cabinet at local institutes (Guangdong Second Provincial General Hospital in Guangzhou). Paper questionnaires will be filed and stored for at least 10 years after project completion as per LSHTM's Records Retention and Disposal Schedule. Study databases will be m

anaged by a dedicated data manager (DM). All data will be checked and cleaned before being updated to the main database. The databases will be regularly backed up on the local server where back-ups are maintained in the disaster recovery room. Copies of the databases will be transferred to LSHTM using the fully encrypted (SSL) server.

The main risks to data security relate to loss of electronic data and breach of participant

confidentiality. With the acquisition of a dedicated office, all data on computers will be stored in this office which will be locked overnight. Only data entry personnel and study personnel will have access to any of the electronic data. After all checks have been completed, data will be entered into databases using desktops. The data manager will upload double entered data at the end of each day onto their computer. The Data Manager will create weekly back-ups on an external password protected hard drive. When necessary or required, and copies of this data will be securely transferred to LSHTM using encrypted files. The risks for confidential breaching are minimal since most data will use anonymized IDs unique to each participant. We will ensure that all copies of the quantitative data files are password protected, with access to the password restricted to staff who need to work with the data. Also, we will report study results only at the aggregate level. To further minimize the risk of breaching confidentiality, all study staff will be trained and certified as part of MENISCUS-1 using the NIH online training course in Protecting Human Subject Research Participants and will be required to sign a staff confidentiality agreement form.

Project Outcomes

The main anticipated measurable outcomes are:

1) Influenza vaccination rate in each condition: vaccination rate of each condition will be calculated respectively through (dividing number of participants who are vaccinated by the total number of individuals invited to participate) * 100%. Statistical differences in vaccination rates of all three conditions will be examined.

2) Donation rate in the pay-it-forward condition: the donation rate of the pay-it-forward condition will be calculated through (dividing the number of participants who donate by the total number of participants who receive a vaccination shot in the pay-it-forward group) * 100%

3) Donation measurements in the pay-it-forward condition: the total donation amount as well as proportion of economic costs covered by the microdonations through dividing total donation by total economic costs of vaccines used in the pay-it-forward condition.

Data analysis

Descriptive analyses of demographic and behavioral characteristics, participation rate, vaccination rate in each condition will be conducted. We will compare the vaccination rate between the pay-it-forward model, free-of-charge, and the standard of care model using chi-squared test and logistic regression, reported as crude odds ratios (cOR) and adjusted odds ratios (aOR), by adjusting for education, employment status, and urban/rural residence. We choose these covariates because they are potential confounders. We will use descriptive statistics to report the participants' awareness, confidence and hesitancy in influenza vaccines, contributions to future participants in the pay-it-forward group, and the fraction of the total cost of vaccination covered by pay-it-forward. All data will be analysed using SPSS Version 25.

Audits and inspections

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

Insurance provision

We will purchase around 10,000 USD insurance through the LSHTM insurance team as per LSHTM sponsorship and insurance policy.

DMC/DSMB

Given the low risks associated with a quasi-experimental study to improve existing public health service uptake, we believe having the project team as well as designate a data

manager to meet periodically and monitor the data safety would suffice. DSMB will not be assembled in this particular project.

Ethics

We have submitted local ethics application to Guangdong Second Provincial General Hospital and is currently under review. The LSHTM ethics committee will review the project protocol.

Publication – section on who will write, named authors

With inputs from the entire project team including LSHTM research team and local research team in China, the project manager Dan Wu and PI Joseph Tucker will lead the manuscript writing. More specifically, potential authors will include Dan Wu, Weiming Tang, Weibin Cheng, Yafei Si, Huipeng Liao, Yewei Xie, Nina Ren, Yunhui Chen, Zhangjun Tian, Joseph Tucker

Confidentiality

Each participant will be assigned a unique ID and personal identifiable information will not be collected. Participant survey data will only be used for research purpose of this particular project. Participant survey data will be transformed into digital format and copies of the quantitative data files will be password protected. Only designated project staff will have access to this encrypted information. We will report study results only at the aggregate level which will be difficult for others to identify individual participants. Without participant permission, project team researchers will not share the information to a third party.

Project timeline

This will be an 18-month project. The proposed activities and time periods are as below.

	Proposed activities and time periods					
	Year 1				Year 2	
Quarter	Q1	Q2	Q3	Q4	Q1	Q2
Develop subcontracts and obtain ethical approval						
Recruit participants for pay-it-forward condition						
Recruit participants for free-of-charge condition						
Recruit participants for standard care condition						
Data entry and cleaning						
Data analysis						
Writing the report and disseminate findings						

Reference

1. China CDC. Technical guideline for influenza vaccination in China 2018. http://www.chinacdc.cn/jkzt/crb/bl/lxxgm/jszl_2251/201809/t20180921_194050.html (accessed 19 Nov 2019).

2. Li L, Liu Y, Wu P, et al. Influenza-associated excess respiratory mortality in China, 2010–15: a population-based study. *The Lancet Public Health* 2019; **4**(9): e473-e81.

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should also understand these. CN-Healthcare. 2018.

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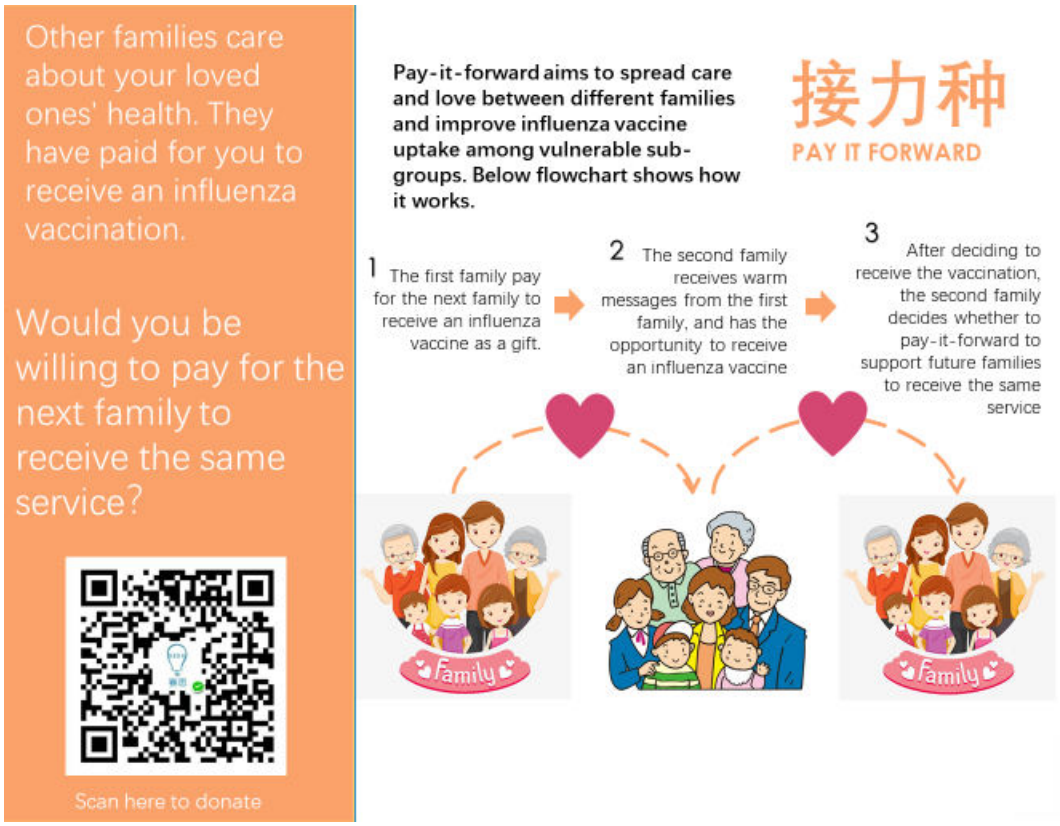
(accessed 19 Jan 2020).

13. LSHTM. Research data management policy. 2019. https://www.lshtm.ac.uk/sites/default/files/research_data_management_policy.pdf (accessed 19 Jan 2020).

Supplementary file 1: Pay-it-forward



Supplementary file 2: Examples of hand-written messages

Research Proposal Version No.: 1

Research Proposal Version Date: Jan 28, 2020

Research Proposal Version No.: 2

Research Proposal Version Date: April 14, 2020

Title: Pay-it-forward to improve influenza vaccine uptake among children and elderly people in China: A quasi-experimental study

Trial Sponsor

Name: London School of Hygiene & Tropical Medicine

Address: London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT

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health organizations in Guangdong province, Southern China – one from developed Guangzhou city, one from under-developed Yangshan county, and one from Shenzhen city where free influenza vaccination is provided to children and elderly people. We will recruit 50 children and 50 elderly individuals respectively during the pay-it-forward and standard of care treatment periods (25 children and 25 elderly individuals from each community vaccination clinic). We will recruit 50 children and 50 elderly individuals in free vaccine group in Shenzhen. In summary, a total of 300 participants will be recruited, including 150 children (consented by the guardian) and 150 elderly individuals. Primary outcomes are influenza vaccine uptake rates and pay-it-forward donation rate.

Background

Influenza is a viral respiratory infectious disease of global importance. Seasonal influenza epidemics cause 3 to 5 million severe cases and 290,000 to 650,000 deaths in the world each year.[1] Pregnant women, infants and children, the elderly, and patients with chronic diseases are at high risks of serious illness and death when infected. In China, about 10 people die from influenza-related illnesses each hour. [2] People older than 60 years old are 26 times more like to die from influenza than younger individuals.[2] Influenza vaccination is considered the most effective way to prevent influenza-related diseases. For example, globally, over 40% of countries have decided to provide free flu vaccine to key populations such as children and elderly individuals.

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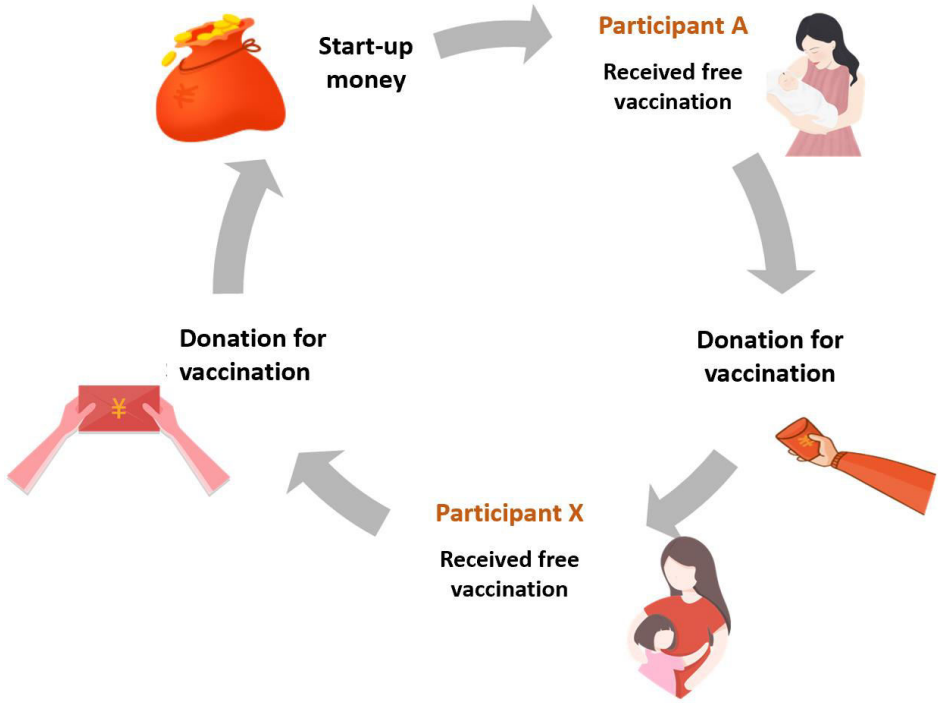

Figure 1: "Pay-it-forward" Model

Hypotheses

Based on the previous research, we conservatively estimate that compared to the standard care (out-of-pocket pay) group,

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2） Elderly people: i) ≥ sixty years old, ii) no acute moderate or severe illnesses with or without fever, iii) no severe, life-threatening allergies to flu vaccine or any ingredient(s) in the vaccine, iv) intelligently capable of making informed decisions and consent to participate the study.

Study design

In this study, three vaccination clinics – one in developed Guangzhou city, one in underdeveloped Yangshan county, and one in Shenzhen city where free influenza vaccines are provided to children and elderly people – will be selected in Guangdong Province for recruitment. The selected community health centers or vaccination clinics should have established infrastructure to provide influenza vaccination services, e.g. have sufficient influenza vaccine stock, relevant medical personnel including designated physicians and nurses for providing vaccine services. The research design is shown in Figure 2.

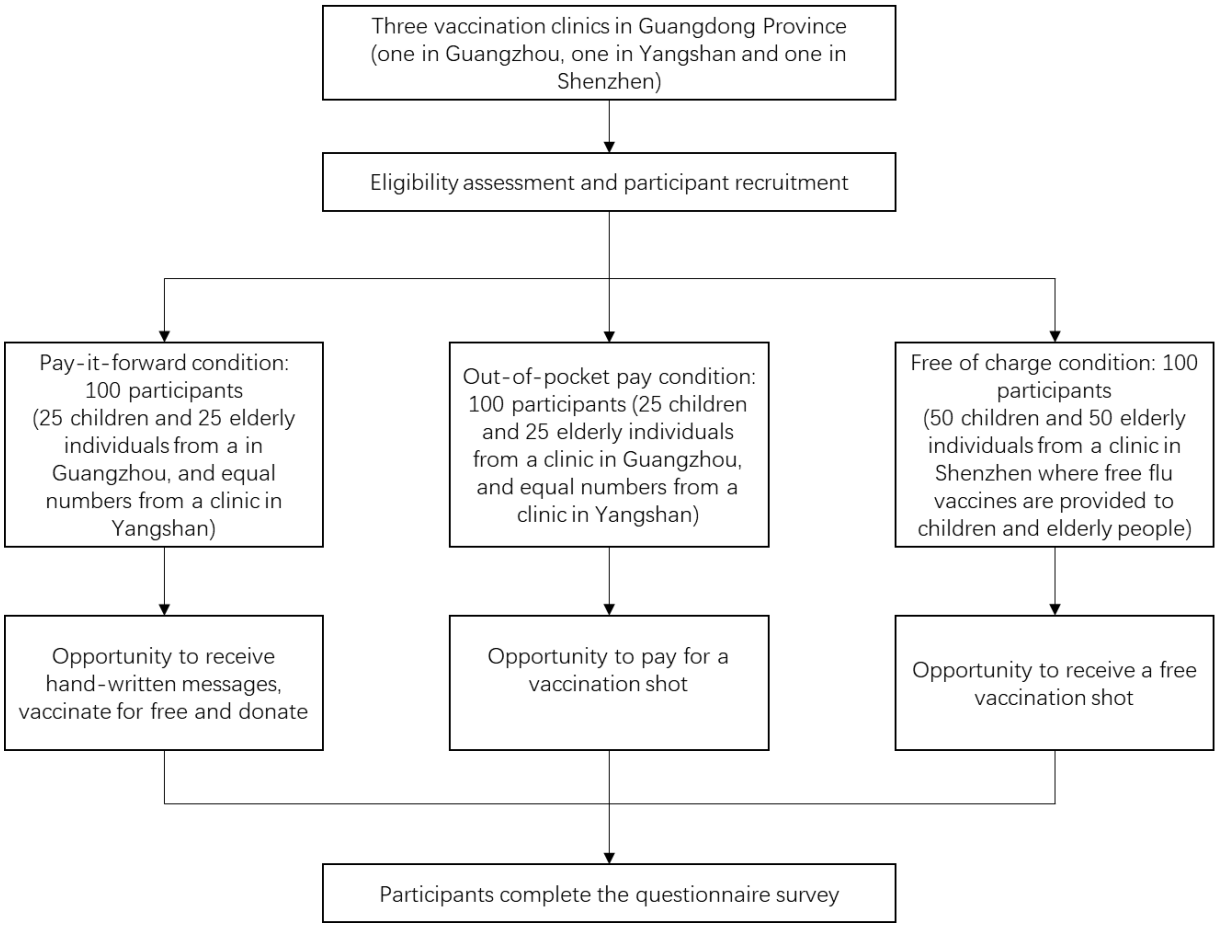

Figure.2

Sample size

Based on our previous pay-it-forward research and pilot data, we calculated the sample sizes for both children and elderly groups. The conservative estimated proportion of vaccine uptake in the standard-of-care group is 0.40. The proportion in the pay-it-forward group is assumed to be 0.5 under the null hypothesis and 0.8 under the alternative hypothesis. To achieve a 90% power to detect a difference between the pay-it-forward and standard-of-care conditions among children, 50 children are needed in the pay-it-forward group and 45 children are needed in the standard-of-care group (Figure 3). The test statistic used is the one-sided unpooled Z test. The significance level of the test is 0.025. In addition, we will have a free vaccine scenario in Shenzhen that already provides free vaccine to children and elderly groups. The estimated sample size will be 50 children and 50 elderly people for the free-of-charge condition.

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Superiority by a Margin Tests for the Difference Between Two Proportions

Numeric Results for Superiority Tests for the Difference Between Two Proportions
Test Statistic: Z-Test with Unpooled Variance
H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 = D1 > D0.

Target Power	Actual Power*	N1	N2	N	Ref. P2	P1|H0 P1.0	P1|H1 P1.1	SM Diff D0	Diff D1	Alpha
0.90	0.90106	50	45	95	0.4000	0.5000	0.8000	0.1000	0.4000	0.0250

Figure 3: Sample size calculation using PASS 15.0.5.

In summary, the total estimated samples sizes are 150 children and 150 elderly people for the pilot study (50 participants for each condition by age group).

Sampling and recruitment

The target population will be recruited in selected vaccination clinics or community health centers. Project staff will assess eligibility based on inclusion criteria as aforementioned and provide educational information about seasonal influenza to all potential participants, ie, guardians of children and elderly people. Participants will be recruited into three conditions, namely pay-it-forward condition and standard care (out-of-pocket payment) condition at the Guangzhou and Yangshan sites, and free-of-charge condition in Shenzhen study site.

Participants recruited during the period of pay-it-forward condition will be informed about the pay-it-forward vaccination program with handwritten warm messages co-created by participating families to enhance public trust and community cohesion (Supplementary files 1 and 2). After introducing the 'pay-it-forward' program, the project staff will provide eligible participants with the opportunity to take part, which means one eligible child or elderly individual can receive an influenza vaccination shot. The guardian or participant will then be asked whether they are willing to donate any amount of money into the pay-it-forward seed fund to support more future users to receive the

same vaccination service. A donation collection box will be provided on site for those who prefer to donate cash and a WeChat QR code (a multifunctional social mobile app embedded with monetary transaction functions) will be provided to those who prefer online donation to the program. Neither the willingness to donate nor the amount of donation will affect them receiving the influenza vaccination services for free. The microdonations will be used to support future users and usage will be publicized periodically in the vaccination clinic. Expected sample sizes for both children and elderly individuals in pay-it-forward condition are 50 respectively (25 children and 25 elderly individuals from the clinic in Guangzhou and equal numbers from the clinic in Yangshan) (Figure 2).

Participants for the free-of-charge condition will be recruited at a clinic in Shenzhen. They will be invited and provided a free influenza vaccination shot but they will not receive any community created messages about the pay-it-forward program. Expected sample sizes for both children and elderly individuals in free-of-charge condition are 50 respectively (Figure 2). Participants recruited in the standard care condition will be asked to pay out of pocket in the event of being willing to receive the influenza vaccination shot. Expected sample sizes for both children and elderly individuals in standard-of-care condition are 50 respectively (25 children and 25 elderly individuals from the clinic in Guangzhou and equal numbers from the clinic in Yangshan) (Figure 2). Participation in each condition is fully voluntary and anonymous. Access to other vaccination and medical services in the clinic will not be affected in any way due to the project. All participants will complete a short questionnaire survey to collect information about demographic backgrounds, information about participating pay-it-forward program (pay-it-forward condition only), and confidence and hesitancy in influenza vaccines.

Data collection

Written consent form will be obtained from all participants. This study will collect the following information: data recorded by the project staff using standard information tracking sheet including the number of invited and participating individuals, the number of participants who receive a vaccination shot, the number of individuals who donate and donation amount in the pay-it-forward condition, as well as survey data through the self-administered questionnaire. Those who have difficulty in reading the questionnaire survey will be assisted by the project staff on-site. A small gratitude gift worth of around 1 GBP will be given to each participant after completing the questionnaire survey.

Risk assessment and management

According to the World Health Organization reports, influenza vaccines are well tolerated, and side effects are mild and transient in general. Common adverse events include soreness, redness, and/or swelling at the vaccination site, fever, muscle pain, headache, nausea which do not require medical attention.[12] Severe threatening allergic reaction after vaccination, such as difficulty breathing, hoarseness or wheezing, swelling around the eyes or lips, hives, paleness, weakness, or a fast heart beat or dizziness, are rare. These signs most likely happen within a few minutes to a few hours after the vaccine is given. Participants who receive a vaccination shot will be required to stay at least half an hour in the vaccination clinic to be closely monitored by a designated nurse. They will be informed to self-monitor signs mentioned above for a few more hours after they leave the clinic. The contact number to a designated physician from the selected clinic will be provided to participants as emergency contact in the event of any severe adverse effects within 24 hours after the vaccination.

Withdrawal of participants

Participants can withdraw from the study at any time without giving any explanations. Withdrawal from the study would not affect the participant's medical care or other

preventive services at the clinic in any way.

Reporting of any adverse events

The local CDCs and vaccination clinics have established a strong surveillance system to monitor any adverse events associated with vaccinating patients. Each patient who receives an influenza vaccine is recorded in the clinical health information system and uploaded to the local CDCs' surveillance system. Patients with any adverse events will be dealt with by local health staff on a timely manner. The research team will leverage their existing platform for reporting any adverse events and keep a tracking record of adverse events. The research team will periodically meet with the designated health workers to make sure adverse events are properly treated.

Data management

Data will be managed according to the principles in accordance with good research practice specified by LSHTM Research Data Management Policy.[13] All data will be kept confidential and accessible only to trained study staff. All consent forms, administrative and survey data will be transformed into digital format and data in non-digital formats will be stored in a securely locked cabinet at local institutes (Guangdong Second Provincial General Hospital in Guangzhou). Paper questionnaires will be filed and stored for at least 10 years after project completion as per LSHTM's Records Retention and Disposal Schedule. Study databases will be m

anaged by a dedicated data manager (DM). All data will be checked and cleaned before being updated to the main database. The databases will be regularly backed up on the local server where back-ups are maintained in the disaster recovery room. Copies of the databases will be transferred to LSHTM using the fully encrypted (SSL) server.

The main risks to data security relate to loss of electronic data and breach of participant confidentiality. With the acquisition of a dedicated office, all data on computers will be

stored in this office which will be locked overnight. Only data entry personnel and study personnel will have access to any of the electronic data. After all checks have been completed, data will be entered into databases using desktops. The data manager will upload double entered data at the end of each day onto their computer. The Data Manager will create weekly back-ups on an external password protected hard drive. When necessary or required, and copies of this data will be securely transferred to LSHTM using encrypted files. The risks for confidential breaching are minimal since most data will use anonymized IDs unique to each participant. We will ensure that all copies of the quantitative data files are password protected, with access to the password restricted to staff who need to work with the data. Also, we will report study results only at the aggregate level. To further minimize the risk of breaching confidentiality, all study staff will be trained and certified as part of MENISCUS-1 using the NIH online training course in Protecting Human Subject Research Participants and will be required to sign a staff confidentiality agreement form.

Project Outcomes

The main anticipated measurable outcomes are:

1) Influenza vaccination rate in each condition: vaccination rate of each condition will be calculated respectively through (dividing number of participants who are vaccinated by the total number of individuals invited to participate) * 100%. Statistical differences in vaccination rates of all three conditions will be examined.

2) Donation rate in the pay-it-forward condition: the donation rate of the pay-it-forward condition will be calculated through (dividing the number of participants who donate by the total number of participants who receive a vaccination shot in the pay-it-forward group) * 100%

3) Donation measurements in the pay-it-forward condition: the total donation amount as

well as proportion of economic costs covered by the microdonations through dividing total donation by total economic costs of vaccines used in the pay-it-forward condition.

Data analysis

Descriptive analyses of demographic and behavioral characteristics, participation rate, vaccination rate in each condition will be conducted. We will compare the vaccination rate between the pay-it-forward model, free-of-charge, and the standard of care model using chi-squared test and logistic regression, reported as crude odds ratios (cOR) and adjusted odds ratios (aOR), by adjusting for education, employment status, and urban/rural residence. We choose these covariates because they are potential confounders. We will use descriptive statistics to report the participants' awareness, confidence and hesitancy in influenza vaccines, contributions to future participants in the pay-it-forward group, and the fraction of the total cost of vaccination covered by pay-it-forward. All data will be analysed using SPSS Version 25.

Audits and inspections

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

Insurance provision

We will purchase around 10,000 USD insurance through the LSHTM insurance team as per LSHTM sponsorship and insurance policy.

DMC/DSMB

Given the low risks associated with a quasi-experimental study to improve existing public health service uptake, we believe having the project team as well as designate a data manager to meet periodically and monitor the data safety would suffice. DSMB will not

be assembled in this particular project.

Ethics

We have submitted local ethics application to Guangdong Second Provincial General Hospital and is currently under review. The LSHTM ethics committee will review the project protocol.

Publication – section on who will write, named authors

With inputs from the entire project team including LSHTM research team and local research team in China, the project manager Dan Wu and PI Joseph Tucker will lead the manuscript writing. More specifically, potential authors will include Dan Wu, Weiming Tang, Weibin Cheng, Yafei Si, Huipeng Liao, Yewei Xie, Nina Ren, Yunhui Chen, Zhangjun Tian, Joseph Tucker

Confidentiality

Each participant will be assigned a unique ID and personal identifiable information will not be collected. Participant survey data will only be used for research purpose of this particular project. Participant survey data will be transformed into digital format and copies of the quantitative data files will be password protected. Only designated project staff will have access to this encrypted information. We will report study results only at the aggregate level which will be difficult for others to identify individual participants. Without participant permission, project team researchers will not share the information to a third party.

Project timeline

This will be an 18-month project. The proposed activities and time periods are as below.

	Year 1				Year 2	
Quarter	Q1	Q2	Q3	Q4	Q1	Q2
Develop subcontracts and obtain ethical approval						
Recruit participants for pay-it-forward condition						
Recruit participants for free-of-charge condition						
Recruit participants for standard care condition						
Data entry and cleaning						
Data analysis						
Writing the report and disseminate findings						

Reference

1. China CDC. Technical guideline for influenza vaccination in China 2018. http://www.chinacdc.cn/jkzt/crb/bl/lxxgm/jszl_2251/201809/t20180921_194050.html (accessed 19 Nov 2019).

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3. Yang J, Atkins KE, Feng L, et al. Seasonal influenza vaccination in China: Landscape of diverse regional reimbursement policy, and budget impact analysis. *Vaccine* 2016; **34**(47): 5724-35.

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10. Shu Y-L, Fang L-Q, de Vlas SJ, Gao Y, Richardus JH, Cao W-C. Dual seasonal patterns for influenza, China. *Emerging infectious diseases* 2010; **16**(4): 725-6.

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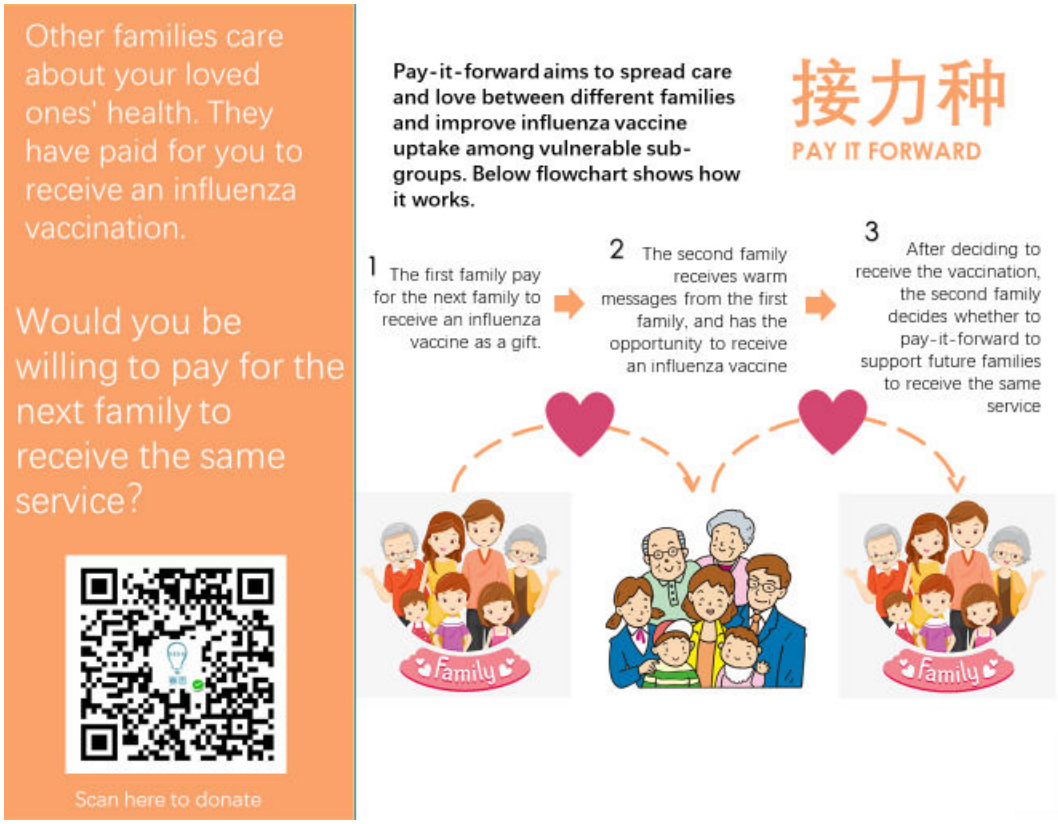
13. LSHTM. Research data management policy. 2019.

https://www.lshtm.ac.uk/sites/default/files/research_data_management_policy.pdf (accessed 19 Jan 2020).

Supplementary file 1: Pay-it-forward



Supplementary file 2: Examples of hand-written messages

Research Proposal Version No.: 2

Research Proposal Version Date: April 14, 2020

Research Proposal Version No.: 3

Research Proposal Version Date: Feb 9, 2021

Title: Pay-it-forward to improve influenza vaccine uptake among children and older adults in China: A three-arm quasi-experimental study

Trial Sponsor

Name: London School of Hygiene & Tropical Medicine

Address: London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT

Tel: +44 207 927 2626

Protocol Version 1.3

February 9, 2021

China Clinical Trials Number: ChiCTR2000040048

Project Summary

Despite a high burden of influenza-related mortality, China has low rates of influenza vaccination among key groups including children and older people. Ten people die of influenza each hour in China. However, only 2% of Chinese are vaccinated and most people in China have limited understanding of influenza vaccines. Influenza vaccines cost 9-16 GBP and are not covered by the government or employers. We propose a pay-it-forward intervention to increase influenza vaccination uptake among children and

older people in China. Pay-it-forward has one person receive a gift (e.g., a free influenza vaccination) and then asks them if they would like to pay-it-forward for other individuals to receive a free vaccine. Participants will also be able to create handwritten postcards encouraging people in the local community to pay-it-forward to the next individual and donate to the rolling finance pool. We will evaluate the intervention using a quasi-experimental study including three arms (i.e., pay-it-forward, free of charge, and pay out-of-pocket) at three sites in Guangdong province. A total of 450 participants will be recruited, including 225 parents/guardians of children and 225 older adults, with 75 per site per age group (25 per arm). The primary outcome is influenza vaccination rate as assessed by administrative records. The main comparison is influenza vaccination rates in the pay-it-forward, standard of care, and free arms.

Background

Influenza is a viral respiratory infectious disease of global importance. Seasonal influenza cause 3 to 5 million severe cases and 290,000 to 650,000 deaths in the world each year.[1] Pregnant women, infants and children, older people, and patients with chronic diseases are at high risks of serious illness and death when infected. In China, about 10 people die from influenza-related illnesses each hour. [2] People older than 60 years old are 26 times more likely to die from influenza than younger individuals.[2] Influenza vaccination is considered the most effective way to prevent influenza-related diseases. For example,

globally, over 40% of countries have policies to provide free flu vaccine to key populations.

Chinese Center for Diseases Control and Prevention (China CDC) has released a high-level guideline for influenza vaccination services provision to at-risk populations in 2018. The guideline defines several at-risk populations including pregnant women, children, family members and caregivers of infants less than 6 months of age, and people aged over 60 years old. However, the most recent pooled evidence by 2016 revealed that only 11.9% of children (aged 6 months to 17 years old) and 21.7% of older people (aged >=60 years) were vaccinated in China.[3]

There are several reasons for low influenza vaccination rates in the country. First, influenza vaccines are not subsidized by government funding in most places and people need to pay around 16 pounds out-of-pocket for getting the vaccination. Second, the lack of trust in vaccines due to a massive vaccine scandal in China is also considered to decrease demand for influenza vaccine in China.[4] In addition, pregnancy is widely considered a contraindication for influenza vaccination, and pregnant women in many places are rejected by health workers for vaccination.[5] Even in places where influenza vaccines are free, public awareness and vaccination rates are suboptimal compared to other countries.[6] The widespread hesitancy in safety and effectiveness of influenza vaccine would be the main reason for this phenomenon.[7] Innovative strategies are needed

to reduce financial burden, build up public trust and collect evidence on effective interventions to improve vaccine uptake.

Pay-it-forward is an innovative, participatory behavioral intervention. Pay-it-forward has one individual receive a free influenza vaccine who will be informed by using hand-written postcard messages co-created by participants that someone else paid for them, then ask if they would like to support a future vaccination. Figure 1 illustrates how the model works. Our previous pay-it-forward studies focused on diagnostic services uptake among marginalized populations have proven effective in increasing chlamydia and gonorrhea tests uptake by three folds, compared to the control group.[8] In addition,89% of participants donated to the rolling finance pool and the community generosity built up trust in health services.[8] Evidence also showed simple acts of kindness are contagious [9] and hold potential to be leveraged to enhance public health services delivery.

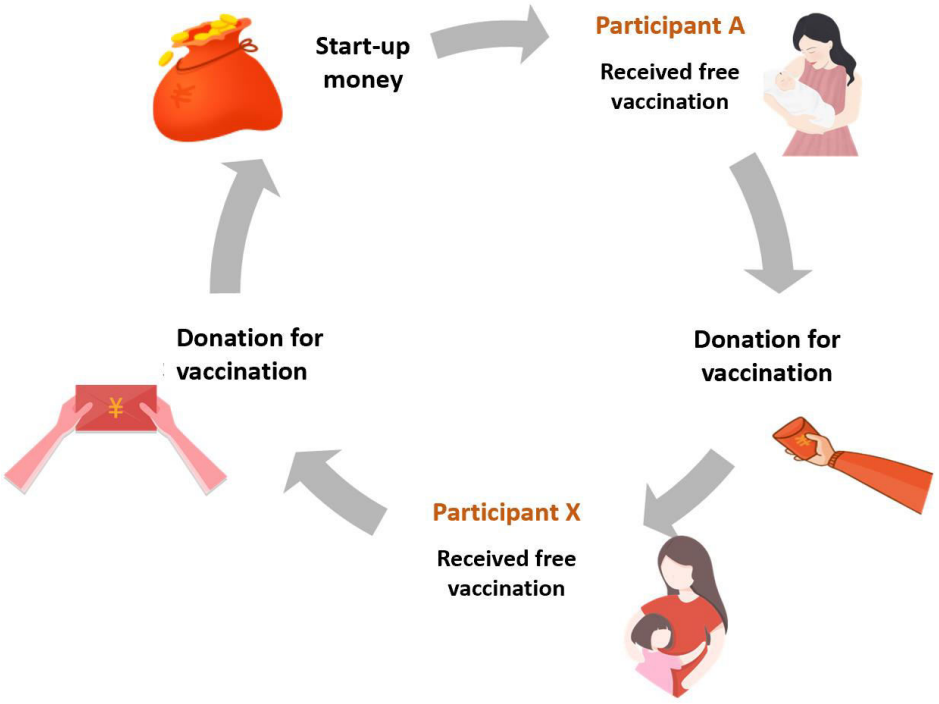


Figure 1: "Pay-it-forward" Model

In this quasi-experimental study, we propose a pay-it-forward approach, aiming to improve influenza vaccine uptake among two key sub-groups, namely children aged between 6 months and 8 years old and older adults aged 60 or above in Guangdong province of China. We determined these two sub-groups based on the disease burden, the national definition of at-risk populations and local clinical practice guidelines. Specific objectives include 1) to examine the effectiveness of pay-it-forward approach on influenza vaccine uptake among Chinese people in comparison to standard-of-care and free vaccination; 2) to conduct an economic evaluation of pay-it-forward on vaccine uptake in comparison to free vaccination and standard-of-care; and 3) to examine factors

associated with vaccine uptake, confidence/hesitancy, and other secondary outcomes.

Hypotheses

Our main hypotheses include the following:

1) Pay-it-forward can significantly improve the influenza vaccination rate among at-risk populations compared to the standard-of-care arm
2) Pay-it-forward is more cost-effective than standard-of-care in terms of cost per person vaccinated.
3) Many participants will donate money to support subsequent people to receive a free vaccine.
4) Influenza vaccine uptake in the pay-it-forward arm will be similar to that of the free vaccine arm (exploratory).

Methods

Study setting

Guangdong is a subtropical southern province in China with a population over 100 million. In southern China, influenza is prevalent throughout the year with a clear peak in the summer and a less pronounced peak in the winter.[10] In response to the national guideline to provide influenza vaccine to at-risk populations, Guangdong Province has

released relevant provincial level policies to promote influenza vaccine. Stockouts of influenza vaccines have been reported in different regions due to tighter quality control of pharmaceutical products after the national vaccine scandal in 2018.[11] We also liaised with Sanofi China office and Guangdong Second Provincial General Hospital to help identify study sites that have sufficient influenza vaccines.

Intervention development

Our team co-created messages as part of a participatory hackathon in Tanzania and a nationwide crowdsourcing open call in China. First, our team worked with diverse individuals as part of a three-day hackathon organized by the Bill and Melinda Gates Foundation and the World Food Program in Tanzania. We identified engagement strategies, including 1) inviting participants to co-create postcard messages for the pre-test (see Fig 2 for an example); 2) organizing a nationwide crowdsourcing open call to engage public in generating health messages focused on influenza and vaccines; 3) engaging local community staff in implementing the pay-it-forward pragmatic trial.

Fig 2: Postcard example

Then, our partner SESH (Social Entrepreneurship to Spur Health) led a nationwide crowdsourcing open contest to solicit messages promoting influenza vaccination. The crowdsourcing open call had five steps – organizing a steering committee to oversee the process, promoting the open call via digital and in-person methods, evaluating submissions (texts, images, videos), celebrating exceptional submissions, and sharing and implementing exceptional ideas. Due to COVID-19, the open call was transitioned to a mostly digital format. The open call website was viewed 7151 times according to analytics. We received a total of 305 submissions, including 204 texts, 90 images, and three videos. All eligible submissions were evaluated by a crowd judge panel and an expert judge panel based on pre-defined criteria (novelty, relevance, feasibility, and elaboration). Crowd judges were invited via social media platforms on a voluntary basis and each submission was judged by at least three independent crowd judges. Experts in public health research, health communication, vaccines, and infectious diseases were invited to the expert panel. Submissions were scored on a 1 to 10 scale and those ranked in the top 15% were deemed exceptional. Some of these messages were integrated into the recruitment pamphlet for the study.

Study population and inclusion criteria

The study will focus on children and older adults. The inclusion criteria of this study are divided into two age groups:

1） Parents or guardians of children between six months and eight years old. Each child needed to meet the following eligibility criteria: i) no acute moderate or severe illnesses, ii) eligible to receive an influenza vaccine based on clinical evaluation from a physician; iii) has a legal guardian (e.g. a parent or grandparent) who lives in China and consents to participate in the study; and iv) has not received an influenza vaccine in the past year.

2） Older people: i) ≥ sixty years old; ii) no acute moderate or severe illness; iii) eligible to receive an influenza vaccine based on clinical evaluation from a physician; iv) capable of making informed decisions and consenting to participate in the study; and v) have not received an influenza vaccine in the past year.

Study design

In this study, three sites –one in rural Yangshan county, one in the suburban Zengcheng district, and one in urban Guangzhou city will be selected in Guangdong Province for recruitment, to represent the three different economic conditions in Guangdong province. The selected community health centers or vaccination clinics should have established infrastructure to provide influenza vaccination services, e.g. have sufficient influenza vaccine stock, relevant medical personnel including designated physicians and nurses for providing vaccine services. The research design is shown in Figure 3.

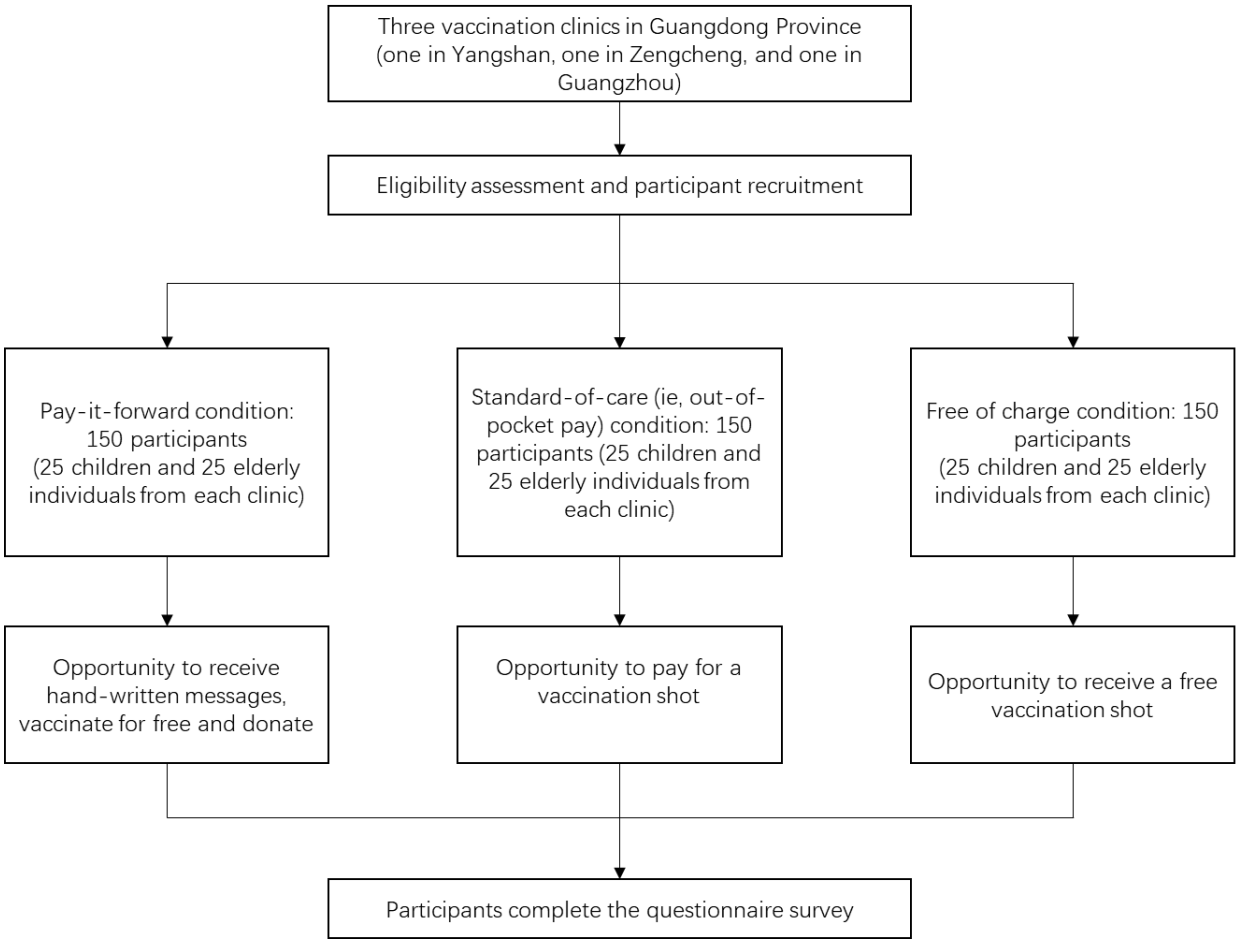


Figure 3: Flowchart of the quasi-experimental study

Sample size

Based on our previous pay-it-forward research and pre-test data, we calculated the sample sizes for both children and older groups. The conservative estimated proportion of vaccine uptake in the standard-of-care group is 0.40. The proportion in the pay-it-forward group is assumed to be 0.5 under the null hypothesis and 0.8 under the alternative hypothesis. To achieve a 90% power to detect a difference between the pay-it-forward

and standard-of-care arms among children, 50 children are needed in the pay-it-forward group and 45 children are needed in the standard-of-care group (Figure 4). The test statistic used is the one-sided unpooled Z test. The significance level of the test is 0.025. To allow sub-analysis by age group, we will recruit 25 more children and older individuals respectively for each arm as a boost sample of each age group. In addition, given free vaccination is likely the future of influenza vaccine programs in China, we add a free vaccination arm with an equal number of participants by age group. In summary, 150 participants (75 children and 75 older adults) will be recruited for each arm, totaling 450 participants for the study.

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Superiority by a Margin Tests for the Difference Between Two Proportions

Numeric Results for Superiority Tests for the Difference Between Two Proportions
Test Statistic: Z-Test with Unpooled Variance
H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 = D1 > D0.

Target Power	Actual Power*	N1	N2	N	Ref. P2	P1|H0 P1.0	P1|H1 P1.1	SM Diff D0	Diff D1	Alpha
0.90	0.90106	50	45	95	0.4000	0.5000	0.8000	0.1000	0.4000	0.0250

Figure 4: Sample size calculation using PASS 15.0.5.

Sampling and recruitment

The study participants will be recruited in selected vaccination clinics or community

health centers. Project staff will assess eligibility based on inclusion criteria as aforementioned and provide educational information about seasonal influenza to all potential participants, ie, guardians of children and older people. Participants will be recruited into three arms, namely standard-of-care (out-of-pocket payment) arm, pay-it-forward arm, and free-of-charge arm at all three sites on a time-based recruitment manner. In order to decrease the effect of temporal trends, we will minimize the time between participants receiving the standard-of-care treatment and participants receiving the pay-it-forward treatment.

Standard-of-care: Participants recruited in the standard care arm will be asked to pay out of pocket in the event of being willing to receive the influenza vaccination shot. Expected sample sizes for both children and older adults in standard-of-care arm are 75 respectively (25 children and 25 older adults from each clinic) (Figure 3).

Pay-it-forward Intervention: Participants recruited during the period of pay-it-forward arm will be informed about the pay-it-forward vaccination program with handwritten warm messages co-created by participating families to enhance public trust and community cohesion (Supplementary files 1 and 2). After introducing the 'pay-it-forward' program, the project staff will provide eligible participants with the opportunity to take part, which means one eligible child or older individual can receive an influenza vaccine. The guardian or participant will then be asked whether they are willing to donate any

amount of money into the pay-it-forward seed fund to support more future users to receive the same vaccination service. A donation collection box will be provided on site for those who prefer to donate cash and a WeChat QR code (a multifunctional social mobile app embedded with monetary transaction functions) will be provided to those who prefer online donation to the program. Neither the willingness to donate nor the amount of donation will affect them receiving the influenza vaccination services for free. The microdonations will be used to support future users and usage will be publicized periodically. Expected sample sizes for both children and older adults in pay-it-forward arm are 75 respectively (25 children and 25 older individuals from each clinic) (Figure 3).

Free-of-charge: Participants will be invited and provided a free influenza vaccine but they will not receive any community created messages about the pay-it-forward program. Expected sample sizes for both children and older adults in free-of-charge arm are 75 respectively (25 children and 25 older individuals from each clinic) (Figure 3).

Participation in each arm is fully voluntary and anonymous. Access to other vaccination and medical services in the clinic will not be affected in any way due to the project. All participants will complete a short questionnaire survey to collect information about demographic backgrounds, prior influenza vaccine history, information about participating pay-it-forward program (pay-it-forward arm only), and confidence and

hesitancy in influenza vaccines.

Data collection

Written consent form will be obtained from all participants. This study will collect the following information: data recorded by the project staff using standard information tracking sheet including the number of invited and participating individuals, the number of participants who receive a vaccine, the number of individuals who donate and donation amount in the pay-it-forward arm, as well as survey data through the self-administered online questionnaire. Those who have difficulty in reading the questionnaire survey will be assisted by the project staff on-site. A small gratitude gift worth of around 1 GBP will be given to each participant after completing the questionnaire survey.

Outcomes

The primary outcome of the study will be influenza vaccine uptake in each arm after the intervention. This will be assessed by administrative records. Secondary outcomes include costs outcomes, vaccine confidence, vaccine hesitancy, and adverse events by administrative records. The main comparison will be between the three arms – standard of care, pay-it-forward, and free vaccine. Outcomes will also be stratified by age group (children and older people) and study sites.

Data analysis

Descriptive analyses of demographic and behavioral characteristics, participation rate, vaccination rate in each arm will be conducted. We will compare the vaccination rate between standard of care, pay-it-forward, and free-of-charge arms using chi-squared test and logistic regression, reported as crude odds ratios (cOR) and adjusted odds ratios (aOR), by adjusting for education, employment status, and study sites. We choose these covariates because they are potential confounders. We will use descriptive statistics to report the participants' awareness, prior influenza vaccination history, confidence and hesitancy in influenza vaccines, contributions to future participants in the pay-it-forward arm, and the fraction of the total cost of vaccination covered by pay-it-forward.

Secondary analyses

In addition to the pre-specified comparisons above, a decision-tree model will be built to analyze the within-trial costs outcomes of pay-it-forward in comparison to standard-of-care and free vaccination. We will use a healthcare provider perspective and the time horizon of the trial. A micro-costing approach will be used for the cost collection, including the start-up costs related to the pay-it-forward arm. We will examine factors associated with vaccine uptake in the standard-of-care arm and intervention arms. We will also determine factors associated with vaccine confidence and vaccine hesitancy in the standard-of-care group and overall.

Risk assessment and management

According to the World Health Organization reports, influenza vaccines are well tolerated, and side effects are mild and transient in general. Common adverse events include soreness, redness, and/or swelling at the vaccination site, fever, muscle pain, headache, nausea which do not require medical attention.[12] Severe threatening allergic reaction after vaccination, such as difficulty breathing, hoarseness or wheezing, swelling around the eyes or lips, hives, paleness, weakness, or a fast heart beat or dizziness, are rare. These signs most likely happen within a few minutes to a few hours after the vaccine is given. Participants who receive a vaccine will be required to stay at least half an hour in the vaccination clinic to be closely monitored by a designated nurse. They will be informed to self-monitor signs mentioned above for a few more hours after they leave the clinic. The contact number to a designated physician from the selected clinic will be provided to participants as emergency contact in the event of any severe adverse effects within 24 hours after the vaccination.

Withdrawal of participants

Participants can withdraw from the study at any time without giving any explanations. Withdrawal from the study would not affect the participant's medical care or other preventive services at the clinic in any way.

Reporting of adverse events

The local CDCs and vaccination clinics have established a strong surveillance system to

monitor any adverse events associated with vaccinating patients. Each patient who receives an influenza vaccine is recorded in the clinical health information system and uploaded to the local CDCs' surveillance system. Patients with any adverse events will be dealt with by local health staff on a timely manner. The research team will leverage their existing platform for reporting any adverse events and keep a tracking record of adverse events. The research team will periodically meet with the designated health workers to make sure adverse events are properly treated.

Data management

Data will be managed according to the principles in accordance with good research practice specified by LSHTM Research Data Management Policy.[13] All data will be kept confidential and accessible only to trained study staff. All consent forms, administrative and survey data will be transformed into digital format and data in non-digital formats will be stored in a securely locked cabinet at local institutes (Guangdong Second Provincial General Hospital in Guangzhou). Paper questionnaires will be filed and stored for at least 10 years after project completion as per LSHTM's Records Retention and Disposal Schedule. Study databases will be managed by a dedicated data manager (DM). All data will be checked and cleaned before being updated to the main database. The databases will be regularly backed up on the local server where back-ups are maintained in the disaster recovery room. Copies of the databases will be transferred to LSHTM

using the fully encrypted (SSL) server.

The main risks to data security relate to loss of electronic data and breach of participant confidentiality. With the acquisition of a dedicated office, all data on computers will be stored in this office which will be locked overnight. Only data entry personnel and study personnel will have access to any of the electronic data. After all checks have been completed, data will be entered into databases using desktops. The data manager will upload double entered data at the end of each day onto their computer. The Data Manager will create weekly back-ups on an external password protected hard drive. When necessary or required, and copies of this data will be securely transferred to LSHTM using encrypted files. The risks for confidential breaching are minimal since most data will use anonymized IDs unique to each participant. We will ensure that all copies of the quantitative data files are password protected, with access to the password restricted to staff who need to work with the data. Also, we will report study results only at the aggregate level. To further minimize the risk of breaching confidentiality, all study staff will be trained and certified as part of MENISCUS-1 using the NIH online training course in Protecting Human Subject Research Participants and will be required to sign a staff confidentiality agreement form.

Audits and inspections

The study may be subject to audit by the London School of Hygiene & Tropical Medicine

under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

Insurance provision

Trial insurance is covered by the trial sponsor.

DSMB

Given the low risks associated with a quasi-experimental study to improve existing public health service uptake, we believe having the project team as well as designate a data manager to meet periodically and monitor the data safety would suffice. DSMB will not be assembled in this particular project.

Trial registration

This study was initially registered on Chinese clinical trials in September 2020. The proposal was last updated on 9 February 2021.

Ethics

We have obtained ethical approvals from Zhuhai CDC and the LSHTM ethics committee.

Publication

As per the funder's requirement, we will publish articles from this study on an open access basis.

Confidentiality

Each participant will be assigned a unique ID and personal identifiable information will not be collected. Participant survey data will only be used for research purpose of this particular project. Participant survey data will be transformed into digital format and copies of the quantitative data files will be password protected. Only designated project staff will have access to this encrypted information. We will report study results only at the aggregate level which will be difficult for others to identify individual participants. Without participant permission, project team researchers will not share the information to a third party.

Project timeline

This will be an 18-month project. The proposed activities and time periods are as below.

	Proposed activities and time periods					
	Year 1			Year 2		
Quarter	Q1	Q2	Q3	Q4	Q1	Q2
Develop subcontracts and obtain ethical approval						

Recruit participants for standard care arm

Recruit participants for pay-it-forward arm

Recruit participants for free-of-charge arm

Data entry and cleaning

Data analysis

Writing the report and disseminate findings

Reference

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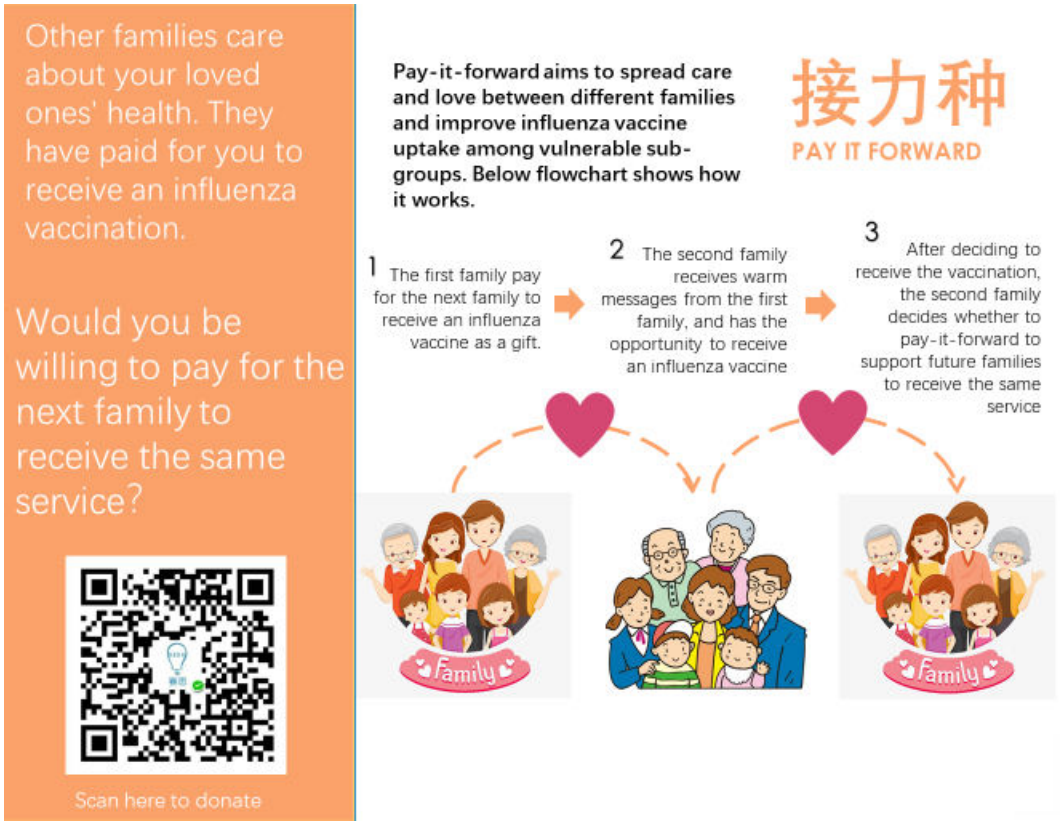
Supplementary file 1: Pay-it-forward leaflet



Supplementary file 2: Examples of hand-written messages

Research Proposal Version No.: 3

Research Proposal Version Date: Feb 9, 2021