Optimizing vaccine introduction

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Version Number: 0.8

April 12, 2019

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List of Abbreviations

CDC	Centers for Disease Control and Prevention
PI	Principal Investigator
WHO	World Health Organization

Protocol Summary

Title:	Optimizing vaccine introduction
Population:	1,000 Parents of children or adolescents in Shanghai (objectives 1-3) 120 vaccination providers (objective 4)
Number of Sites:	40 immunization clinics Several elementary, middle, and high schools
Study Duration:	First wave (summer 2019): 3 months Second wave (summer 2022): 3 months
Study Design:	Experiment
Objectives:	
Primary Objective:	To determine how the framing of the HPV vaccination across several dimensions affects short-term willingness to receive it
Secondary Objective:	To determine how the framing of the HPV vaccination across several dimensions affects sustained willingness to receive it
Tertiary Objective:	To determine how the framing of the HPV vaccination across several dimensions affects actual uptake of vaccine
Quaternary Objective:	To understand what factors providers think are important when promoting the HPV vaccine

1 Key Roles

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2 Background Information and Scientific Rationale

2.1 Background Information

Since 2000, the US has licensed ten new vaccines (Plotkin & Plotkin, 2013), but research on vaccine hesitancy has not kept pace with vaccine development. HPV's faltering rollout in the US is a cautionary tale about how not to inform the public about a vaccine. Prior to vaccine introduction, awareness of HPV was low (Friedman & Shepeard, 2007). The Advisory Committee on Immunization Practices (ACIP) published its first set of recommendations in 2006 (Markowitz et al., 2007, 2014); early reports focused on the relation between vaccination and sexual intercourse (Clark, 2007b, 2007a). The vaccine was not recommended for routine use in males until 2011. Parents have remained concerned about the HPV vaccine's impact on their child's sexual behaviors (Brewer & Fazekas, 2007), and uptake remains low—37% for girls and 13% for boys in 2014 (Lancet, 2016). Programs that have attempted to promote HPV vaccination since its introduction in the US have met with mixed success (Walling et al., 2016). In contrast, the hepatitis B vaccine—which protects against an infection largely spread through injection drug use or sexual intercourse—has not had such a pushback from the public, likely because it was marketed as vaccine that protects against the development of chronic infection in young infants (Hardt et al., 2016). The scientific premise of this study is that the period when a vaccine is adopted into the national immunization program is the critical window for shaping public discourse about and uptake of the vaccine. As more vaccines are formulated, it is critical that we determine how to best promote these vaccines to the public.

2.2 Scientific Rationale

This grant proposal will be carried out in China so I can focus on changes in attitudes toward vaccines as new vaccines are added to the national immunization schedule. I will focus on HPV—a sexually transmitted disease that causes cancer. Only 14.5% of Chinese have heard of HPV (Li et al., 2009). This proposal represents a substantial contribution to the field by evaluating the best methods for introducing a new vaccine to market These findings can help increase vaccine uptake and prevent disease.

2.3 Potential Risks and Benefits

The main risk associated with this study would be loss of confidentiality – where someone would be able to identify participants and discover how they responded.

Participants will not directly benefit from study, although others might benefit. This is because we may be able to improve vaccination coverage rates in the future with our findings about what characteristics about vaccines are or are not important to emphasize.

3 Objectives

Primary Objective
To determine how the framing of the HPV vaccination across several dimensions affects short-term willingness to receive it

Primary Outcome Measures
At the end of the survey, parents will respond to a series of statements about their willingness to get their child vaccinated (which will be assessed on a 5-point scale from “strongly willing” to “not at all willing”). In the analysis, this outcome can be analyzed either as a continuous/ordinal outcome or as a dichotomized outcome (agree vs disagree).

Secondary Objective
To determine how the framing of the HPV vaccination across several dimensions affects sustained willingness to receive it

Secondary Outcome Measures
Same as primary outcome measure (but asked 3 years after initial intervention).

Tertiary Objective
To determine how the framing of the HPV vaccination across several dimensions affects actual uptake of vaccine

Tertiary Outcome Measures
Uptake of HPV vaccination, as recorded in the electronic immunization registry (four years after initial intervention).

Quaternary Objective
To understand what factors providers think are important when promoting the HPV vaccine

Quatenary Outcome Measures
We will enroll vaccination providers from all clinics to complete a simple questionnaire about HPV vaccination.

4 Study Design

Participants will be randomized into two groups to receive information about the HPV vaccine. This information will be depicted on a sheet of paper using graphs and words. For one group, they will receive information similar to how it was historically presented in the US (as a sexually transmitted disease). The other group will receive modified messaging that downplays both the "gendered" nature of the disease and the role of sexual transmission and emphasizes that HPV is a cancer. The exact messaging will be developed in consultation with a mentor, Dr. Zikmund-Fisher, and after taking related coursework (as part of training goal 1). Although I believe this latter method will result in higher acceptance of HPV, the former method of presenting the information is still ethical because it will replicate materials from the WHO (World Health Organization, 2014). We will also collect demographic and socioeconomic data, along with measures of exposure to various information sources, including traditional media, social media, and messaging from hospitals and doctors.

Parents will provide information at three different stages. For wave 1 (this protocol), they will spend 30 minutes at a clinic filling out a paper questionnaire. For wave 2 (a separate protocol to be developed in the future), they will be re-contacted by phone and asked if they want to come to the clinic again to participate in another study. The third stage of data collection involves us linking their questionnaire data to their child's vaccination records; we notify them about this in the informed consent document, but since we will also collect their child's vaccination record number at the time of wave 1, we will not need to recontact them in the future in order to access the electronic immunization registry.

5 Study Population

5.1 Selection of the Study Population

Participants may be sampled from several locations. There is a two-stage selection procedure. Townships have already been sampled (through a random selection procedure, stratified by district within the city) based on the population of their surrounding township according to the 2010 Census.

The primary location would be immunization clinics. Parents could be selected as a convenience sample (from parents already at the clinic for vaccination appointments), or they could be sampled randomly from population registers at the clinic.

For the first wave of data collection, a convenience sample within each clinic will be taken of parents of children. On days of data collection, we (i.e., the PI or a master's student) will go to the clinic in the morning and explain the study. As the vaccine providers vaccinate children throughout the day, they will direct parents of children into a private room, where we can explain the study more, ask for informed consent, and give the parent-participant a questionnaire.

Another potential study location will be middle schools or high schools in Shanghai. We will attempt to go to schools within the townships that we have already selected, but the extent to which we use schools will be dependent on their availability. At schools, teachers will send questionnaires and informed consent forms to students, and students will bring these documents home to their parents to fill out.

We will enroll 120 vaccination providers from all clinics (an average of 3 per clinic) to complete a simple questionnaire about HPV vaccination.

5.2 Inclusion and Exclusion Criteria

Participants can be included if they are parents of children 2-18 years old.

All vaccination providers at a clinic which offers an HPV vaccine are eligible.

6 Data and Safety Monitoring Plan

6.1 Study Procedures

Oversight responsibilities
Oversight of the trial is provided by the Principal Investigator (PI), Dr. Wagner and his mentors on the study: Drs. Matthew Boulton, Brian Zikmund-Fisher, and Xiaodong Sun.

Monitoring procedures
Dr. Wagner assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. The research protocol will be reviewed by the University of Michigan IRB and the Shanghai CDC ethical review committee (collectively referred to as the "IRBs").

Study data are accessible at all times for the PI and mentors to review. The PI and mentors will review study protocol prior to each period of data collection, and will review study conduct, drop-outs, and protocol deviations one month and two months after the beginning of each data collection period. The PI will review AEs and SAEs individually in real-time and aggregate on a weekly bases (see the "AE Management" and "Data analysis plans" sections below). The PI ensures all protocol deviations, AEs, and SAEs are reported to the NIH and IRBs according to the applicable regulatory requirements.

6.2 Expected Adverse Events

Expected AEs
Because we are not testing any therapy, are not taking any biological samples, and are only engaging in an educational/behavioral intervention, we do not expect any "physical" AE to occur. However, we potentially could change someone's attitude about the HPV vaccine for the worse. Because our goal in this study is to identify ways in which we can improve acceptance of HPV vaccination, if it turns out that we are in fact making people more vaccine hesitant, that would be a behavioral/attitudinal AE.

Although no previous study in China has replicated exactly what we will plan to do, observational studies have found a variation in acceptability of HPV vaccine. One study in Hong Kong found "the prevalence of parental acceptability of HPV vaccination for the index son and daughter were: […] 51.6% and 63.0% (free vaccination)" (Wang et al., 2018). Another study from Jinan found that "female students were more willing to take the HPV vaccine than male students (76.7% vs 58.6%)" (Xue et al., 2017).

If, from preliminary analyses (see below), we find that acceptability of the vaccine is less than 40% (about 10% to 20% less than acceptability of what was found in previous studies – we are using a lower number to account for variability in the study population characteristics), we will stop data collection (enrollment of new participants), notify the IRBs, and identify ways to change the protocol prior to re-starting data collection.

AE Management

If we found someone with a low attitude towards vaccines, we do not believe that it would be appropriate to try to change their attitude, since (1) further interaction with someone who had a negative experience with us is unlikely to make their experience more positive, and (2) we do not know for sure if this attitude was related to their participation in this study. However, we can provide materials from a neutral party (like pamphlets on HPV from the National CDC) to the study site locations, so that individuals can have a different perspective on the medical issue.

Of course, if a participant participates some physical adverse event, we are unsure how it could be linked to our study, but all study procedures will occur at an immunization clinic (which are co-located with larger medical facilities), and so the individual should be able to receive timely and appropriate care.

6.3 Data analysis and management

Data analysis plans
As data are being collected and entered into a database, we will tabulate our endpoint – vaccine acceptability, which we will dichotomize from a Likert scale – on a weekly basis. And if these numbers fall below a certain threshold, we will follow the procedures as outlined in the "Expected AEs" section above.

Reporting of AEs
All physical AEs will be reported according to the two IRBs' AE reporting guidelines. In addition, aggregate statistics about behavioral/attitudinal AEs will be reported if they cross the threshold listed in this document.

Plan for data management
Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

Confidentiality throughout the trial is maintained by keeping informed consent forms and questionnaires in separate locations, and destroying the questionnaires after they have been input into an electronic database. Informed consent forms will be kept for a period of time designated by the IRBs. The informed consent forms and questionnaires will be in a locked locker, in a locked room, at the Shanghai CDC, which is a complex of buildings with guards at each entrance.

The data will initially be stored in a secure online platform – such as Box – which is HIPAA compliant and which the University of Michigan supports. While the data are being collected, and while some personally identifiable information may be present in the database, this folder will be password-locked and only available to study team members.

We will also keep a record linking the participants' ID number to their vaccination record number. This linkage file will be kept separate from the questionnaires, and it will be on the hard drive of a computer at the Shanghai CDC. The computer will be password-locked and will only be accessible to study team members.

Data sharing

Reproducibility and replicability of studies are both extremely important. Therefore, we plan to upload a final dataset (along with code detailing my statistical analysis) to a public repository, such as figshare.com. This dataset will have personally identifiable information removed – and the clinic location will be coded by a number (not the name of the location) to prevent individuals being able to locate members of the study and identify them.

7 Statistical Considerations

7.1 Study Outcome Measures

At the end of the survey, parents will respond to the statement, “I am willing to vaccinate my child against HPV,” using a five-point Likert scale from “strongly willing” to “not at all willing”. In the analysis, this outcome can be analyzed either as a continuous/ordinal outcome or as a dichotomized outcome (agree vs disagree).

7.2 Sample Size Considerations

Based on previous results, we are powering to detect a difference between 70% and 80% in the outcome between the two groups (see explanation below). This would require a simple random sample of 588 or an effective sample size of 994 based on a design effect of 1.69. The enrollment of parents will be in immunization clinics.

This sample size of providers is limited by the number of clinics (n=40), but because we are sampling few providers from each clinic, the design effect is negligible, and we should be able to provide an estimate of risk perception with a confidence interval of 8 percentage points (assuming an outcome proportion of 80%). The outcome is the proportion of individuals who respond “somewhat important” or “very important” to questions on a 5-point Likert scale.

7.3 Participant Enrollment and Follow-Up

I estimate the follow-up rate to be 80%, given figures in recently published studies from China: 86.1% (Lau, Gross, Wu, Cheng, & Lau, 2017), 83% (Choi, Steward, Miège, Hudes, & Gregorich, 2016), 80.3% (Xu, Byles, Shi, McElduff, & Hall, 2016), 79.8% (Guo et al., 2017).

Participants from previous waves will be contacted by phone and asked to come to the immunization clinic for an additional survey. The person contacting past participants by phone would be me, a master’s student, or staff from the vaccination clinic.

7.4 Analysis Plan

We will use standard regression methods to compare this outcome between the main study arms. To account for the complex survey design, all models will use survey procedures, including weights, clustering, and Taylor series estimation of variance.

8 Subject Confidentiality

Confidentiality throughout the trial is maintained by keeping informed consent forms and questionnaires in separate locations, and destroying the questionnaires after they have been input into an electronic database. Informed consent forms will be kept for a period of time designated by the IRBs. The informed consent forms and questionnaires will be in a locked locker, in a locked room, at the Shanghai CDC, which is a complex of buildings with guards at each entrance.

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8.1 Future Use of Stored Specimens

This study does not include any biological specimens.

Although participant information will be de-identified from the main dataset, a separate linkage file will show their name, their study ID, their vaccination record ID, and their contact information. We will use this information to contact them in the future and to obtain their vaccination records.

9 Informed Consent Process

Many parents and children visit vaccination clinics every day in China to receive mandatory vaccines. They wait in line until they are called to visit with a nurse (“vaccination provider”), who discusses vaccination options with them, and then directs them to another nurse who will obtain the vaccines they need and administer the dose(s) required. Afterward, the parents and children are supposed to wait at clinics for 30 minutes after vaccination to see if there is any adverse reaction to the vaccine. A large age range of children come into the clinic, and so we will notify the vaccination providers what are required age range is (2-18 years), and parents of those children will then be told by the nurses about our study. The nurses will mention to parents whose children fall into the age category (2-18 years) that a study is taking place about their attitudes towards vaccination. Vaccination providers will then direct parents to come into a private room to learn more about the study. Of course, some parents may be uninterested at this point and we would never see them. At the end of our time at each clinic, we will ask the nurses how many parents did not come and see us (so we can tally up our response rate).

Clinics have a few private rooms for conducting meetings which are out of the way from where other parents are waiting (before and after vaccinations). Within such a room we will ask parents the screening question (is their child between 2-18 years), and if they answer affirmatively, give the parents the informed consent form and ask if they want to voluntarily participate in this study. We will give them time to read through the document and sign and ask any questions to study staff.

Similarly, for parents sampled at schools, the forms (questionnaire, enrollment log, and informed consent form) will be sent by the teacher to the child’s home. The teacher will be responsible for collecting these documents and handing them back to the study team.

If they sign the informed consent, we will file it in a separate location from the questionnaires. This questionnaire is something that the parents can fill out themselves, and study staff will be available to answer any questions.

Any follow-up survey (i.e., 3 years later) will involve the parents being re-consented.

10 Literature References

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Supplements and Appendices

None