Title: Pilot of a Cohort of Households for Influenza Monitoring and Evaluation in Seattle (pCHIMES)

Home-based testing and administration of baloxavir within 48 hours of influenza diagnosis in Seattle, WA

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The funders and sponsors had no role in design of this study.

Summary

Background: Households represent an important location for transmission of influenza. Rapid delivery of antiviral may reduce household exposures to influenza among susceptible individuals.
Design: This study is a pilot study of a home-based approach to influenza infection control, utilizing self-test kits and rapid home delivery of baloxavir (BXM).
Population: Households with at least 3 individuals residing there at least 4 days a week, including at least 2 household members that are eligible to take BXM, will be monitored throughout the influenza season for the onset of a cough.
Study size and duration: This study will be conducted in 250 households in the Seattle, WA area for one influenza season, beginning November 1, 2019 and ending May 1, 2020.
Intervention: Household will self-monitor for onset of a cough or 2 or more respiratory symptoms throughout the influenza season. When symptoms develop in a study participant, the participant will self-test for influenza infection using a prepositioned home-testing kit, as well as collect a separate nasal swab specimen at Study Day 0. Additionally, if eligible, the sick participant will connect with a healthcare provider via the 98point6 app on their smartphone to discuss their respiratory symptoms, and the provider will determine whether antiviral treatment is appropriate. If determined to be a probable influenza illness, the individual will receive a rapid home delivery of BXM, and the ill participant will provide a self-collected nasal swab specimen Study Day 2-3 and Study Day 5-7. For all illness episodes, the ill individual will complete a questionnaire regarding symptom duration and severity, as well as behavioral changes due to illness.
Primary aim: Determine the percentage of drug-eligible, individuals with a diagnosed influenza infection who initiate antiviral therapy within 48 hours of symptom onset.
Secondary arm: Determine the social and technical infrastructure that would be required to rapidly detect and interrupt influenza transmission at the household level; determine whether a home-based self-test and antiviral delivery strategy would be feasible in the context of a pandemic; and assess the prevalence of antiviral resistance in post-treatment nasal swab specimens.

I. Background

Acute respiratory infections (ARIs) are a major cause of morbidity worldwide.[1] In the United States, the estimated annual economic burden of influenza to the healthcare system and society is $11.2 billion ($6.3-$25.3 billion), and the Centers for Disease Control and Prevention (CDC) estimates that influenza has resulted in 140,000-960,000 hospitalizations and 12,000-79,000 deaths annually since 2010.[2,3] Current influenza prevention and treatment options available to the general population include seasonal vaccination and antivirals for both treatment and prophylaxis. Despite these options, lack of durable immunity and variable influenza vaccine effectiveness contribute to large-scale epidemics each season.[4-6] This highlights a need for additional evidence-based prevention and treatment strategies to increase preparedness.

Current Antiviral Receipt Process: Traditionally, influenza infection is diagnosed during a clinic visit and if antiviral treatment is prescribed, a subsequent visit to a pharmacy to receive the antivirals is required. This multi-step process leads to delays in receipt of antivirals and potentially exposes other individuals in clinics and pharmacies to influenza. This practice is problematic since viral shedding occurs during this time frame, and it is well-established that antiviral therapy is most effective when started within 48 hours of symptom onset.[7-12] Additionally, this process may deter individuals from seeking care and thus further the spread of influenza within households and communities.

Household Transmission: Households play a key role in the overall spread of influenza because the frequency and intensity of contacts between household members are greater than contacts that occur within the broader community.[13] Historically, household studies aimed to provide information on age-specific incidence and characteristics of respiratory infections; however, newer laboratory methods make it possible to define illness etiology and better understand household transmission dynamics.[14-17] It is estimated that approximately 1/3 of all influenza transmissions occur within households.[14] Therefore, the household represents an important point for intervention or control strategies to decrease influenza spread, particularly during a pandemic.

Previous studies that focused on the use of antivirals like zanamivir and oseltamivir to block influenza transmission between household members found this strategy efficacious or effective, though efficacy and effectiveness varied by study design, type of antiviral used, and time from symptom onset to start of antiviral therapy.[18-23] A small number of studies report insignificant results for antiviral use in stopping secondary influenza transmission, though these studies had small sample sizes and may have lacked the statistical power necessary to identify an effect on transmission.[24,25] Additionally, the randomized controlled trials conducted in households for zanamivir and oseltamivir are limited in that antivirals were used for treatment and prophylaxis or just prophylaxis, making it difficult to clearly define to role of antiviral use in ill individuals.[18-21] Furthermore, this combined strategy for treatment and prophylaxis may contribute to increased levels of antiviral resistance and may not be practical in pandemic situations when drug supplies are limited.

Antiviral Treatment: Home-based influenza self-testing and subsequent rapid treatment with antivirals has not been previously evaluated in antiviral clinical trials. Home-based start of antivirals has the potential to decrease exposure risk in the community and decrease time from symptom start to initiation of therapy, thereby decreasing illness duration and risk of transmission to other household members. Current advances in technology, including tele-medicine services (tele-health) and rapid 1-2 hour delivery services (Amazon Now, Uber, Lyft, FedEx), make this strategy feasible to study.

Baloxavir (BXM) is a single dose oral agent licensed for treatment of influenza for individuals aged 12 years and older. Unlike oseltamivir, a neuraminidase inhibitor, BXM functions as a cap-dependent endonuclease inhibitor and prevents influenza genome synthesis. In a phase III randomized controlled trial, BXM showed equivalence to oseltamivir in time to alleviation of influenza symptoms.[26] Additionally, BXM was associated with significantly lower infectious viral titer one day after initiation as well as reductions in viral RNA loads and shorter median duration of virus detection compared to both oseltamivir and placebo. Furthermore, initial findings from a phase IIIb clinical efficacy study report that household contacts of index patients who were given BXM were significantly less likely to develop influenza relative to household contacts of index patients who were given placebo (1.9% vs 13.6%), despite a wide-range of times to initiation of therapy.[27] Therefore, in contrast to other antiviral medications, BXM may be better suited to stop person-to-person transmission.

The present study seeks to use a home-based approach to influenza infection, utilizing self-testing and rapid household delivery of BXM within 48 hours of symptom onset to treat cases of probable influenza. We aim to study the feasibility of this strategy to better understand the social and technical infrastructure required to rapidly detect and interrupt influenza transmission at the household level to increase pandemic preparedness.

Equipoise: There remain important unanswered questions regarding the usability of influenza self-tests, transmission dynamics, and antiviral resistance in households. It is established that the likelihood of infection following an exposure in the household is greater than the likelihood of infection following an exposure in the community due to differences in the frequency and intensity of contacts.[13] However, the feasibility of a home-based strategy where individuals self-test and rapidly receive antiviral therapy within 48 hours of symptom onset remains unknown. Likewise, the impact of this strategy on community transmission dynamics is unknown, but it is anticipated that this study will provide valuable knowledge and insights for citywide pandemic preparedness given that the current process for antiviral receipt remains problematic. Therefore, there is an unmet need to evaluate the feasibility of home-based approach to influenza infection.

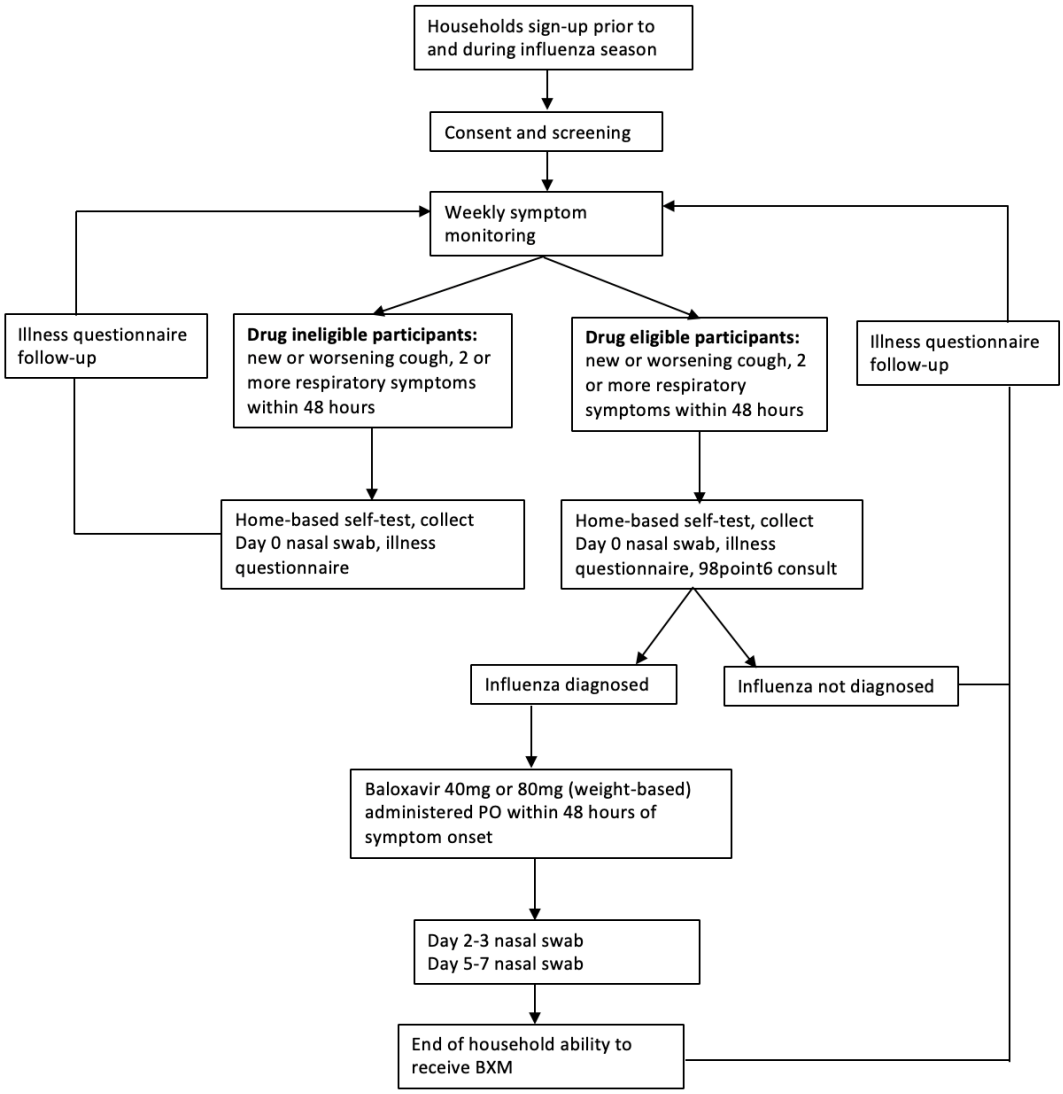
II. Study design

This is a pilot study that will evaluate the feasibility of a home-based approach to influenza infection for households in the Seattle, WA area, utilizing an influenza self-test, followed by telehealth consultation for diagnosis and rapid home delivery of antivirals. Households with 3 or more of the same members at least 4 days per calendar week will be eligible to enroll, as long as there are at least 2 members in household eligible to take BXM. Individuals 12 years or older, weighing at least 40 kg, will eligible to take BXM, and thus, are able to enroll as drug eligible participants. Individuals that are not able to take BXM will be able to enroll in the study as drug ineligible participants. Individuals within an eligible household will be enrolled prior to or during the annual influenza season and monitored throughout the influenza season for the development of a cough or 2 or more respiratory symptoms. If a drug ineligible study participant, meaning a household member who does not meet BXM criteria, develops symptoms, they will use an influenza self-test; however, regardless of the result, they will not be able to receive BXM. Nevertheless, the drug ineligible study participant will provide one self-collected or parent/permanent legal guardian-collected nasal swab specimen that will be mailed back to the laboratory for further testing.

If a drug eligible study participant in the household develops a cough or 2 or more respiratory symptoms, he/she will use a prepositioned influenza self-test kit as soon as possible. Additionally, the individual will connect with a healthcare provider through the 98point6 app to

review the participant's medical information and provide an influenza diagnosis based on clinical judgement. If probable influenza is diagnosed, the 98point6 provider will confirm that antiviral treatment is appropriate. If appropriate, drug eligible study participant will subsequently receive a single dose of BXM delivered to their household via rapid delivery service for therapy initiation within 48 hours of symptom onset. Concurrently, the ill individual will collect a Study Day 0 nasal swab sample that will be mailed back to the laboratory for further testing. Additional nasal swabs will be collected at Study Day 2-3 and Study Day 5-7. If influenza is not diagnosed, the ill individual will provide one self-collected or parent/permanent legal guardian-collected nasal swab specimen that will be mailed back to the laboratory for further testing, and the household will remain enrolled and all study participants in the household will continue to self-monitor for presence of symptoms. Once an eligible study participant receives BXM, no additional household members will be eligible to receive BXM; the household will be able to continue monitoring for onset of symptoms, as well as self-testing and swabbing when symptoms develops, but the household will no longer be able to receive BXM delivery.

Figure 1. Study schema



Symptom Table

Feeling Feverish	Muscle or Body Aches
Headache	Rash
Sore Throat or Itchy/Scratchy Nose	Runny/stuffy nose
Feeling More Tired Than Usual	Muscle or body aches
Nausea or Vomiting	Increased trouble with breathing
Ear Pain or Ear Discharge	Diarrhea

The study is being conducted in the Seattle, WA area over one influenza season. The goal is to have 250 households comply with full study procedures. Of these, 25% are estimated to have an individual in the household diagnosed with influenza based on estimates from previous household studies.[23, 28-29]
A table for influenza attack rates by household size is provided below.

Household attack rate	**Total households enrolled**	**Primary cases**	**Secondary cases** (mean household size 5)	**Secondary cases** (mean household size 4)	**Secondary cases** (mean household size 3)
25%	250	63	45-96	34-72	23-48
20%	250	50	36-76	27-57	18-38
10%	250	25	18-38	14-29	9-19
Mean household size includes case.					
Secondary attack rate 18-38%, secondary cases presented as a range based on these high and low bounds.[30-32]					

The University of Washington is the sponsor of the study which is supported by an anonymous funder who does not have any ownership over the management and conduct of the study, the data, or the rights to publish.

III. Objectives

The objective of the study is to measure the proportion of individuals who are initiated on antiviral therapy within 48 hours of symptom onset using a home-based self-test, followed by a telehealth consultation to diagnose influenza and home delivery of antivirals

Primary Outcome Measures

The primary outcome measure will be the proportion of eligible individuals who initiate antiviral therapy at home within 48 hours of symptom onset utilizing a home-based test and the tele-health app for influenza diagnosis and rapid home-delivery of antivirals. It will be calculated using binomial regression with log link, where the number of drug eligible influenza-diagnosed individuals, defined as the number of individuals eligible to receive BXM with both self-test positive influenza and laboratory-confirmed influenza, reporting administration of the study drug within 48 hours of symptom onset is divided by the total number of drug eligible individuals with both self-test positive influenza and laboratory-confirmed influenza.

Secondary endpoints:

- Proportion of individuals who test positive for influenza using the home-based test within 48 hours of symptom onset
- Proportion of individuals with a positive home-based influenza self-test who have a positive test confirmed by the central laboratory
- Sensitivity and specificity of a self-test compared to a laboratory-based molecular influenza test
- Proportion of individuals who are delivered antivirals within 48 hours of symptom onset
- Proportion of individuals who self-report administration antiviral therapy within 48 hours of symptom onset
- Symptom duration and severity among drug eligible and drug ineligible influenza-positive individuals
- Proportion of families with influenza infection diagnosed within 7 days of an index case (another influenza-positive household member)
- Viral quantity and duration of viral RNA detection among drug eligible and drug ineligible influenza-positive participants
- Proportion of drug ineligible study participants seeking medical care for respiratory illness symptoms
- Proportion of individuals who choose to take a self-test among those who are eligible to take a self-test
- Within-host variation in influenza strains between the first and the third viral swab
- Cost effectiveness, assessed using health resource utilization (visit to clinic, hospital, pharmacy, emergency department) and school and work absenteeism
- Proportion with antiviral resistance, assessed by genetic sequencing of influenza strains from the drug eligible and drug ineligible study participants

Hypothesis

Primary hypothesis:

- A home-based approach to influenza infection control will result in a large percentage of drug eligible individuals diagnosed with influenza initiating antiviral therapy within 48 hours of symptom onset.

Secondary hypotheses:

- Home-based approach to influenza infection control and rapid delivery of antiviral therapy will decrease symptom severity in the drug eligible individuals diagnosed with influenza that administer antiviral therapy within 48 hours of symptom onset compared to drug eligible, influenza-infected individuals that administer antiviral therapy greater than 48 hours after symptom onset.
- Home-based approach to influenza infection control and rapid delivery of antiviral therapy will decrease the duration of viral RNA detection in the drug eligible, influenza-infected individuals that administer antiviral therapy within 48 hours of symptom onset compared to drug eligible, influenza-infected individuals that administer antiviral therapy greater than 48 hours after symptom onset.

IV. Study Population

The study will be conducted in households with at least 3 members, where at least 2 of these members must be eligible to receive BXM, in the Seattle area. Participants aged 12 years or older, weighing at least 40 kg, will be drug eligible. Participants of any age that reside in the same household as the case at least 4 days per calendar week will be drug ineligible study participants. Drug eligible study participants will receive baloxavir intervention when appropriate,

and all drug eligible and drug ineligible participants will receive a 7-day follow-up from the study team per illness episode.

Study size
The study is being conducted in the Seattle, WA area over one influenza season. The goal is to enroll 250 households, with enrollment occurring prior to and during the annual influenza season.

Household enrollment criteria
The household must meet all the following enrollment criteria:

Household inclusion criteria
- Group of at least 3 individuals of any ages defined as at least 3 persons residing at the same address for at least 4 days per calendar week
- Household group utilizes common household areas
- At least 2 household members meeting all individual inclusion/exclusion criteria listed below and willing to participate (e.g. at least two members of the household are 12 years of age or older)
- At least one member of the household has a smartphone

Household exclusion criteria
Within eligible households, individuals meeting any of the following criteria will be excluded:
- Previous documentation of an influenza infection prior to or during the annual influenza season in any household member prior to enrollment

Study participants
Inclusion criteria for eligible study participants include:

Inclusion criteria for drug eligible study participants:
- Resident of a household with 3 or more members (including eligible cases) for 4 or more days a calendar week
- Age 12 years or older weighing at least 40 kg (greater than 88 pounds)
- Willing and able to take study medication
- Willing to comply with all study procedures
- English-speaking
- Able to provide written, informed consent and/or assent (if applicable)
- Permanent mailing address that is available for study staff to mail necessary materials

Inclusion criteria for drug ineligible study participants:
- Resident of a household with 3 or more members (including eligible cases) for 4 or more days a calendar week
- Willing to comply with all study procedures
- English-speaking
- Able to provide written, informed consent and/or assent (if applicable)

Exclusion criteria
Individuals meeting any of the following criteria will be excluded from being drug-eligible, but may still participate in the study by submitting swabs:

- Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration
- Individuals with hypersensitivity to baloxavir
- Any individual that has one or more of the following conditions:
    - Pregnant
    - Currently lactating
    - Immunosuppressed or immunocompromised (by disease or medication)
    - Cancer
    - Liver disease
    - Kidney disease

Individuals meeting the following criteria will be excluded from being drug-eligible, and will not participate in submitting swabs:

- Age younger than 3 months

Withdrawal criteria

All household members and/or their parent or permanent legal guardians are free to withdraw from the study at any time. Household members can also withdraw from sample collection but allow continued collection of symptom data. Additionally, it is within the rights of the PI to withdraw any participant or household from participation in this study without their consent at her discretion.

Additional consent concerns

Staff enrolling households will verbally summarize the consent form for any participant who requests it either in-person or via telephone. If ability to provide consent or assent is a concern for any staffer when engaging a household member, the staff member will not enroll that individual.

V. Study procedures

Study Timeline

The study will be conducted during one influenza season, defined in this study as November 1 to May 1. Households will be eligible to enroll in the study prior to the start of the influenza season. Additionally, households that have not had a previously documented case of influenza during the season of proposed enrollment will be eligible to enroll during the annual influenza season.

Recruitment and screening

Recruitment of households will be conducted via media advertising campaigns directed at households with children. Strategies will include but are not limited to:

- Web-based marketing (positioning of advertising on childcare sites such as care.com or WebMD.com)
- Recruitment materials through an online portal on the overall Seattle Flu Study website (seattleflu.org)
- Targeted recruitment materials sent by mail to households with children
- Use of geolocation to target social messaging advertisements via Facebook or other sites to individuals at locations frequented by households with children (e.g. community centers, libraries, the zoo and aquarium)
- Post flyers at public locations including community centers, libraries, and childcare facilities

Households will be screened for eligibility through a web-based portal via a standardized screening questionnaire to ensure that all individual and household inclusion and exclusion criteria are met. An additional screening over the phone or an in-person meeting with a member of the study team will also occur to ensure all individual and household inclusion and exclusion criteria are met.

Obtaining Consent
Consent will be obtained from an individual and their household members at time of enrollment by study staff only after a full explanation has been given, and time allowed for consideration and questions. This process will mainly occur over the phone with individuals consenting via REDCap questionnaires. Though for families unable or not willing to consent via REDCap, and in-person consent visit with the study team can be scheduled. Individuals under 18 years of age will have consent provided by their parent or legal guardian. In addition to consent by their legal guardian, study staff will attempt to obtain assent from individuals 7 to18 years of age when applicable. Following the consent process, all household members will receive a paper or electronic copy of the consent form.

All subjects who consent to participate will also be asked to approve the storage of their biospecimens (nasal swabs). Persons who consent to the study, but who do not want their biospecimens stored may still participate in the study. Their biospecimens will be tested as per protocol, but the remaining aliquots will be destroyed once test results of sufficient quality are reported.

Study Personnel
Given the scale of this project and the necessity to collect data of the highest quality, an extensive organizational structure is necessary to ensure that adequate supervision is provided at all levels of organization. For this study, the organizational structure will fall into five categories:

- **Enrollment and Follow-up team:** This team will be responsible for completing the screening and obtaining consent from all study participants. This team will be comprised of study staff who will be directly supervised by the research lead team. All members of the enrollment team will receive extensive training in the specifics of this protocol prior to the start of participant enrollment. Members of this group will be responsible creating the participant trainings (excluding the Ellume home-testing video) for this study. Additionally, members of this group will be responsible for going to the households when in-person training is requested. This team will also be responsible for sending the weekly reminders to households (see Weekly Monitoring section), and reviewing adverse event questionnaires to determine whether there is evidence of short-term reaction to the study drug.

- **Data management team:** This team will be primarily responsible for checking the completeness and quality of the data being reported by study participants. This team will be comprised of study staff who have relevant data management experience and will be directly supervised by the research lead team. The additional responsibilities for this team include sending participant gift cards electronically, tracking the study drug, and maintaining the log of study drug delivery.

- **Research Lead team:** This team will be responsible for overseeing the enrollment and follow-up team and the data management team. The primary responsibilities for this team include overseeing the day to day operations of the study, working with the enrollment and follow-up team and the data management team, and answering questions from participants regarding the study. Additionally, this team will act as troubleshooters for any minor problems that come along during the course of the study. This team will also function as the daily supervisors for the study and will act as a link between the previous two teams and the medical expert team.

- **The Bedford team**: Located at Fred Hutchinson Cancer Research Center, will contribute to the analysis of the data from this study through development and maintenance of a database to store study data (both survey and lab data), the production of this data into a "flu-map" of Seattle, which displays current influenza prevalence based on census tract, and a phylogenetic analysis of samples collected through the study (including genome assembly). As part of this, the Bedford team will have access to PHI such as participant address.

- **Medical expert team:** This team will be composed of a study research nurse, as well as the principal investigator, co-principal investigators, and the study Safety Officer. This team will act as overall supervisors for the study, and as troubleshooters for any major problem that comes along during the course of the project. They will be responsible for dissemination of data to study partners, and will participate in the interviewing and hiring of personnel at all levels below them.

All members of the study staff or research team have completed institution approved human subjects training. Additionally, for staff or research team members that interact directly with participants, Good Clinical Practice (GCP) training has been complete. This training as well as project-specific training will be required for any newly hired staff. This will involve presentations and discussions on the importance of voluntary participation, informed consent, confidentiality, data security, and sensitivity to the participants in the research. Quality control procedures will also be emphasized during the project-specific training and this training will be reviewed on a regular basis by study investigators.

Individual and Household Enrollment Process

1. **Check eligibility:** Individuals will be screened for eligibility over the phone, in-person, or through a web-based portal via a standard screening questionnaire to ensure that all individual and household inclusion criteria are met. Individuals or households that meet any of the exclusion criteria will not be eligible to participate in this study (See IV. Study Population section).

2. **Consent:** If eligible, all household members will provide informed consent at the time of enrollment. For children, consent will be provided by their parent or permanent legal guardian and assent will be obtained by study staff as applicable. This process can also be done electronically (e-consent) (See Obtaining consent section).

3. **Enrollment Questionnaire:** The household will then complete a REDCap survey that will collect information about the participants or household that is not expected to change for the duration of the study. Data collected on the enrollment questionnaire may include, but are not limited to, information about address and living situation, birthdate, past

medical history, health insurance, household structure, the preferred method of communication for the participant, and socioeconomic status.

4. **Participant Training:** Following consent and completion of enrollment, all enrolled household members will watch informational videos or receive informational pamphlets regarding how to properly complete study tasks. These videos will be created by the study staff and will be available to participants via the Seattle Flu Study website during the study. However, households will have the option to request an in-person training by study staff on how to properly complete these tasks. Study participants will also be provided with a phone number and email address for the study where additional questions can be directed. A comprehensive list of the trainings each household must complete prior to being enrolled is provided below.

    - Nasal self-swab collection – pamphlet
    - Symptom monitoring logs – pamphlet
    - Illness questionnaire – pamphlet
    - Study drug information and risks – pamphlet
    - Ellume home-testing – video
    - tele-health app access – pamphlet

    During this time, households will also receive information regarding how and when they will receive their thank you gift cards.

5. **Receipt of standardized nasal swab kit and completion of baseline nasal swab kit:** Via a delivery service, all enrolled households will receive two types of standardized nasal swab kits, one type that will be used to establish baseline health and the other type will be stored in their home until nasal swab collection is needed. For the standardized nasal swab kits that will be used following the onset of an acute cough or two or more respiratory symptoms. These kits will contain nasal swabs and standard 5 mL tubes for the nasal swabs that contain universal transport media (UTM). The swabs will be collected via self-swab or parent/permanent legal guardian-swab. The number of swabs and tubes sent to each household will vary depending on the size of the household, but all kits will contain enough of these materials for non-drug-eligible study participants to collect a nasal swab following the development of an acute cough or two or more respiratory symptoms, for drug-eligible study participants to collect a nasal swab following an when influenza infection is not diagnosed, and for drug-eligible participants to collect a nasal swab specimens at Study day 0, Study day 2-3, and Study day 5-7 when influenza is diagnosed. Additionally, each kit will contain biohazard bags for packaging of each individual tube, larger plastic bags as well as absorbent sleeves for collective packaging of all nasal swab specimens at each time point. The standardized nasal swab kits will also contain pre-paid shipping labels and return boxes, which will allow the participants to mail the nasal swab specimens back to the laboratory the day of or the day after collection (as soon as possible). The baseline nasal swab kit will contain all the same materials as the standardized nasal swab kit but in a quantity of one.

    After completing the required study trainings, all household members, regardless of whether they are drug eligible, will provide a nasal swab sample, which will be collected by self-swab or parent/legal guardian-swab. These swabs will then be packaged and returned to the laboratory for storage and eventual testing. This process will be done as a trial run to ensure that participants will be able to successfully collect and return nasal swabs following a positive influenza self-test result and may help determine baseline

viral and bacterial nasal carriage for each participant.

6. **Receipt of a thermometer:** Via a delivery service, all enrolled households will receive a standard digital thermometer as well as a supply of corresponding plastic probes, which can be used to orally measure participant body temperature throughout the study.

7. **Receipt of home-based influenza test:** Via a delivery service, all enrolled households will receive influenza home-testing kits. The number of testing kits sent to the household will vary depending on the size of the household. The household will store these tests until the onset of a cough or two or more respiratory symptoms. All households will have access to the contact information for the study team, via phone number or email, which they will contact if they are in need of additional home-testing kits.

8. **Tele-health app access:** All drug eligible study participants will download the tele-health app onto their smartphone. Next, drug eligible participants will register for an account with tele-health. Upon completing the enrollment questionnaire, the data management team will share participant information necessary for a tele-health account via a HIPAA compliant transfer method. This information includes participant and household study ID number, name, birthdate, age, sex, last four digits of social security number (SSN) for drug eligible adults, and address. This process will be done to ensure only drug eligible participants can register for a tele-health account. After registering for an account, drug eligible participants will follow the steps provided in the tele-health training pamphlet to ensure they understand how to connect with a tele-health provider. Drug eligible study participants will be able to use their tele-health account until 30 days after the conclusion of the study.

Weekly Monitoring

At the start of influenza season, defined in this study as November 1, pre-enrolled households will receive weekly reminders via text message, email, or phone call to complete their symptom monitoring logs regarding the presence or absence of cough or 2 or more respiratory symptoms. Additionally, households will be reminded to self-test for influenza as soon as symptoms develop in a member of the household. The household will complete a symptom monitoring log via REDCap online or text-message, regardless of age, for the duration of the influenza season (November 1-May 1). Once a household has a drug eligible participant who is diagnosed with probable influenza by a telehealth provider and that participant has received and administered BXM, weekly monitoring will still occur, but the household is no longer eligible to receive BXM delivery.

For households that enroll during the influenza season, they will receive weekly reminders via text message, email, or phone call to complete their symptom monitoring logs starting the day of enrollment. These reminders will be identical to the reminders the pre-enrolled household receive. The household will complete a weekly symptom monitoring log via REDCap online or text-message, regardless of age, for the duration of the influenza season (November 1-May 1). Once a household has a drug eligible participant who is diagnosed with probable influenza by a telehealth provider and that participant has received and administered BXM, weekly monitoring will still occur, but the household is no longer eligible to receive BXM delivery.

Onset of Symptoms

Immediately following the onset of an acute cough or 2 or more respiratory symptoms in a drug ineligible participant, the following procedures will occur:

1. The participant will self-test for influenza using the prepositioned home-testing kit as long as the following criteria are met:
    - Symptom duration <48 hours
    - Cough present or 2 or more respiratory symptoms present
2. The individual will provide a nasal swab specimen collected via self-swab or parent/permanent legal guardian-swab, which will be mailed back to the laboratory for testing and further characterization (See VI. Laboratory Procedures section).
3. Next, the ill individual will complete day 0 of the illness questionnaire in REDCap, which will ask information about respiratory and systemic symptoms, recent travel history, and absenteeism.
4. Additionally, one week later, the ill individual will complete day 7 of the illness questionnaire, which will ask information about respiratory and systemic symptoms, recent travel history, and absenteeism in 7 calendar days following the onset of a cough in the ill participant.

Immediately following the onset of an acute cough or 2 or more respiratory symptoms in a drug eligible participant, the following procedures will occur:

1. The person will self-test for influenza using the prepositioned home-testing kit as long as the following criteria are met:
    - Symptom duration <48 hours
    - Cough present or 2 or more respiratory symptoms present
        i. Qualification for receipt of study drug will be determined based on a review of medical information with the tele-health provider. If the individual meets the required criteria (symptom duration <48 hours) and is diagnosed with probable influenza by a healthcare provider, this will trigger subsequent delivery of the intervention, if deemed appropriate.
2. Next, the ill individual will collect a nasal swab sample via self-swab or parent/legal guardian-swab as soon as possible. These specimens will then be packaged and shipping back to the laboratory via a delivery service for testing and further characterization. Additionally, the ill individual will complete day 0 of illness questionnaire in REDCap, which will ask information about respiratory and systemic symptoms, recent travel history, and absenteeism.
3. Concurrently, the participant will connect with a provider via the tele-health app previously downloaded on their smartphone. The provider will review the participant's symptoms and determine whether influenza infection is likely to be the underlying cause of the symptoms. If probable influenza is diagnosed, the tele-health provider will prescribe a weight-based dose of BXM. If antiviral treatment is not deemed appropriate by the tele-health provider, this information will be documented in the post-visit Care Plan for the study participant and subsequently shared with the study team.
4. Next, the study pharmacy will be notified that the participant is being prescribed BXM.
5. Following the prescription, the study pharmacist will dispense and package the BXM. Additionally, an informational hand out regarding the BXM dosing instructions will be included in this package. Furthermore, the individual will receive a post-visit Care Plan through the tele-health app, which will include reminders about the next steps for the study.
6. Following packaging of the study drug, a rapid delivery service will be notified that the intervention is available for delivery.

7. Next, rapid delivery service will pick up the study drug and deliver it in-person to the household of the case.
8. After delivery, the case will take the study drug and record the time of ingestion in the illness questionnaire in REDCap.

Follow-up
Following drug receipt, individuals will be screened 48 hours later to determine whether there is evidence of short-term reaction to the drug. Any short-term evidence reaction to the drug will be treated promptly by consultation with a member of the study medical expert team. In addition, the household will receive the contact information for a medical professional for follow-up questions after initiation of the intervention. Furthermore, the drug eligible participant will also be able to direct drug related questions to a tele-health provider via the tele-health app.

All sick individuals, meaning those drug eligible and those drug ineligible, will complete an illness questionnaire in REDCap 7 days after they report the illness. This questionnaire will collect information on the presence or absence of respiratory and systemic symptoms during the 7 days after reporting the illness. Data will also be collected on childcare, school, and work absenteeism, and subsequent visits to health care providers. Additionally, the influenza-diagnosed individual will provide nasal swab specimens collected via self-swab or parent/legal guardian-swab at Study day 2-3 and Study day 5-7. These swabs will be returned to the laboratory via a delivery services the day of or the day after collection (See VI. Laboratory Procedures section). In addition to the illness questionnaire, the drug eligible, influenza infected participant will complete a standard questionnaire at 7 and 14 days following study drug receipt to monitor for the occurrence of adverse events (AEs) or serious adverse events (SAEs). These questionnaires will be monitored by a member of the study team. Additionally, any provider consultations with tele-health following drug administration will be reported to the study team to monitor for the occurrence of adverse events (AEs) or (SAEs). Any reported adverse events will be assessed to determine if related to drug treatment and whether unexpected or not and subsequently reported to the IRB using a standardized AE and SAE form. After the self-collected nasal swabs have been tested in the laboratory, the case will have to ability to view the results of their swab on the Seattle Flu Study website.

For all individuals that provide nasal swab specimens for testing and further characterization, they will have the ability to view whether influenza or respiratory syncytial virus (RSV) was detected from their swab(s) on the Seattle Flu Study website (See VI. Laboratory Procedures).

Data collection
Data will be collected electronically in REDCap online via a computer or mobile device or through a text-message accessible app. The major data collection activities will occur at the following times (See Table 1).

- **At household enrollment**, which can occur prior to and during the influenza season, the household will submit an enrollment questionnaire. This questionnaire will collect information that is not expected to change through the duration of the influenza season. Questions in the enrollment questionnaire may include information about address and living situation, birthdate, past medical history, health insurance, household structure, the preferred method of communication, and socioeconomic status. Additionally, at this time, informed consent will be obtained from each household participant willing to take part in the study, and the household will complete the required study training (see V. Study Procedures section). All eligible study participants in the household will also provide a baseline nasal swab specimen.

- **On a weekly basis during the influenza season**, the household will complete a symptom log where they will report on the occurrence of a cough or 2 or more respiratory symptoms in enrolled participants for that week in order to monitor for onset of new or worsening cough or two or more respiratory symptoms among study participants.
- **Monthly during the influenza season,** the household will complete a questionnaire where they will report any changes to household structure or changes in influenza vaccine status for participating household members.
- **Following the onset of a cough or two or more respiratory symptoms**, the ill participant, regardless of whether they are drug eligible or not, will use an prepositioned influenza self-test.
    - For drug ineligible participants, they will provide one nasal swab specimen collected via self-swab or parent/permanent legal guardian-swab, which will be mailed back to the laboratory. Additionally, the ill participant will complete an illness questionnaire at day 0, then again at day 7. The household will remain enrolled and continue to monitor for the development of a cough or 2 or more respiratory symptoms via the weekly symptom monitoring log.
    - **If the ill participant is drug eligible**, they connect with a telehealth provider using their smartphone as soon as possible.
        - **If influenza is not diagnosed**, the sick participant will provide one nasal swab collected via self-swab or parent/permanent legal guardian-swab, which will be mailed back to the laboratory. Additionally, the ill participant will complete an illness questionnaire at Study day 0, then again at Study day 7. The household will remain enrolled and continue to monitor for the development of a cough or 2 or more respiratory symptoms via the weekly symptom monitoring log.
        - **If influenza is diagnosed,** ill participant will provide a nasal swab sample collected via self-swab or parent/legal guardian-swab. Also, following a positive test result, the ill participant will complete Study day 0 of the illness questionnaire. This questionnaire will collect information regarding the presence, duration, and severity of respiratory and systemic symptoms in the ill participant. Additional information such as recent travel history, childcare, school, or work absenteeism as well as data on subsequent medical care will be collected on the questionnaire. Additionally, the 98point6 provider will confirm antiviral treatment is appropriate, and write a BXM prescription. Next, BXM will be delivered home of the case within 6 hours via a rapid delivery service.
- **Following delivery and therapy initiation**, the case will document the time of consumption.
- **At Study day 2-3 and Study day 5-7 after a positive test result**, the drug eligible, influenza-infected participant will provide nasal swab samples collected via self-swab or parent/legal guardian-swab. All nasal swabs will be mailed back to the laboratory for further testing the same day or the day following collection (see VI. Laboratory Procedures section). Also, the ill participant will complete an illness questionnaire 7 days after antiviral treatment. This questionnaire will collect information regarding the presence, duration, and severity of respiratory and systemic symptoms. Additional information such as recent travel history, childcare, school, or work absenteeism as well as data on subsequent medical care will be collected through the questionnaire.
- **Within 48 hours after drug receipt**, individuals will be screened for evidence of reaction to the drug using a standardized questionnaire in REDCap.

- **7 days and 14 days after drug receipt,** individuals will be screened for evidence of reaction to the drug using a standardized questionnaire.

Table 1. Timing of Data Collection

Data Items	**Enrollment**	**Weekly during Influenza Season**	**Monthly during Influenza Season**	**Influenza not diagnosed, drug eligble group**	**Influenza diagnosed, drug eligible group**	**Sick, drug ineligible group**
Informed consent	X					
Baseline health and demographic data collected	X					
Baseline nasal swab collection	X					
Self-monitor cough or 2 or more respiratory symptoms		X				
Report changes in household structure or influenza vaccine status			X			
Nasal swab collection (Study day 0)				X	X	X
Nasal swab collection (Study day 2-3)					X	
Nasal swab collection (Study day 5-7)					X	
Illness questionnaire (Study day 0, Study day 7)				X	X	X

Record timing of drug receipt					X	
Standard questionnaire for AEs and SEAs (48 hours , 7 &14 days post-treatment)					X	

Medication management

Baloxavir (BXM)
Drug eligible, influenza-infected study participants will receive a one-time oral dose of baloxavir (Xofluza) based on weight. For individuals weighing 80kg or more, they will receive 80mg of BXM. For individuals weighing 40-80kg, they will receive 40mg of BXM (See Table 2). The drug will be delivered to the individual's home within 2-6 hours of an influenza diagnosis. The case will be instructed to take the medication immediately on receipt and record the time of ingestion using the REDCap app or by text message. The description of the antiviral from the product monograph is as follows:

> *XOFLUZA™ is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.*
> *Limitations of Use: Influenza viruses change over time, and factors such as the virus type or subtype, emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use XOFLUZA.*

Medication storage and packing
BXM blister packs will be provided to the study team prior to the start of the influenza season by the drug manufacturer or purchased from the manufacturer. According to the manufacturer, baloxavir should be stored in its blister package at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Additional storage recommendations are provided below.

- 20 mg white to light yellow, oblong shaped film-coated tablets debossed with "Θ772" on one side and "20" on the other side available as:
    - 2 x 20 mg tablets per blister card in secondary packaging: NDC 50242-828-02
    - 4 x 20 mg tablets per blister card in secondary packaging: NDC 50242-828-02
- 40 mg white to light yellow, oblong shaped film-cated tablets debossed with "BXM40" on one side available as:
    - 1 x 40 mg tablet per blister card in secondary package: NDC 50242-860-01
    - 2 x 40 mg tablets per blister card in secondary packaging: NDC 50242-860-02

Upon receiving a prescription for antiviral medication from a tele-health provider, a study pharmacist will pull the blister pack or packs from the correct weight bin, which will be organized prior to the start of the influenza season, and dispense the medication.

Following the packaging and labeling of the intervention, an informational hand out about the study drug will be included in this packaging along with the contact information for a licensed medical professional associated with the study who is available to answer any follow-up questions the participant may have regarding the intervention. Furthermore, the drug eligible participant will also be able to direct drug related questions to a 98point provider via the tele-health app.

Medication delivery and counseling

After the intervention is dispensed, the rapid delivery service will be notified that the study drug is available for delivery. Next, the rapid delivery service will pick up the intervention and deliver the package to the household of the case within 2-6 hours of an influenza diagnosis . Once the medication leaves the storage facility, delivery tracking will be performed by a member of the study staff and a log recording successful medication delivery will be kept as additional quality assurance measure.

Upon enrollment in the study, all eligible study participants in the enrolled household will receive information regarding the potential risks of the study drug as well as information regarding prohibited medications/treatments. Once the medication is received by the case, there will also be an informational hand out included in the delivery package as well as the contact information for a licensed medical professional associated with the study who is available to answer any follow-up questions the participant may have regarding the intervention. Finally, after reviewing this information and administering the medication, cases will record the time of medication administration via REDCap.

Prohibited medications/treatments

Prohibited medications/treatments during the study include concurrent use of any anti-influenza medication. The concurrent use of BXM with the intranasal live attenuated influenza vaccine (LAIV) has not been evaluated; concurrent administration may inhibit viral replication of LAIV and thereby decrease the effectiveness of LAIV vaccination. Co-administration with polyvalent cation-containing products may decrease plasma concentrations of BXM which may reduce efficacy. Medications containing calcium, magnesium, iron, selenium, or zinc, such as Tums, are not to be taken within 2 hours of taking BXM. Additionally, participants should avoid co-administration with dairy products, calcium-fortified beverages, polyvalent-cation containing laxatives or antacids. This information will be given to the participant at enrollment, and will be provided in the informational handout with the medication.

Table 2. Medication Information

Patient Body Weight (kg)	Recommended Oral Dose
40 kg to less than 80 kg	Single dose of 40 mg
At least 80 kg	Single dose of 80 mg

Compensation

Households that participate in this study will not receive compensation; however, as a thank you gift for the time spent completing study tasks households will receive with a $20 gift card for enrollment. In addition, households will receive a $5 gift card for completion of study participant training (See V. Study Procedures section), and a $5 gift card for completion of a baseline nasal swab kit from eligible cases. Furthermore, enrolled households will receive a $5 gift card per household for completion of each weekly symptom monitoring log for the duration of the influenza season and a $10 gift card for using the influenza self-test. For drug eligible, influenza-infected cases, they will also receive an additional $30 for study drug receipt. Participants will also receive $5 per follow-up nasal swab sequence collected and successfully returned to the laboratory. Gift cards, with summed amounts, will be sent electronically to each household and to each household member (when applicable) twice a month, with the first gift card being processed within the first two weeks of the month and the second gift card being processes within the last two weeks of the month. A log of previously sent and currently owed gift card amounts will be kept on a password protected network (See VIII. Data management section), and member of the study staff will update this log on a weekly basis. An overview of thank you gifts for this study is shown below (Table 3).

Table 3. Overview of participant thank you gifts

	Study Enrollment	**Completion of training and baseline swab kit**	**Completion of weekly symptom log**	**Completion of self-test for influenza**	**Receipt of study drug**	**Completion and return of nasal swab specimens**
Individual	-	-	-	$10	$30	$5
Household	$20	$10	$5	-	-	-
Frequency	Once	Once	Per week	Per illness	Once	Per swab sequence

VI. Laboratory Procedures

Ellume Home-Test: Following the onset of a cough or two or more respiratory symptoms, the individual will unpack their prepositioned home-testing kit and follow the in-box instructions to perform the test. The general process for completion of this test is as follows:

1. The participant will self-collect a nasal swab.
2. The nasal swab will be placed into a dropper that already contains media.
3. The participant will then connect the test strip to their smartphone via Bluetooth.
4. Once connected, the participant will drop the media that has been mixed with the nasal swab sample from the dropper onto the target area of the test strip.

Additional nasal swabs, from a standardized nasal swab kit, will be collected from the participants. For drug ineligible and for drug eligible, participants not diagnosed with influenza, only one nasal swab will be collected at Study day 0 via self-swab or parent/legal guardian-swab. For drug eligible, participants diagnosed with influenza nasal swab specimens will be collected at Study day 0, Study day 2-3, and Study day 5-7 via self-swab or parent/legal guardian-swab following an influenza diagnosis from the telehealth provider. After collection, the swab will be placed directly into a 5 mL tube containing universal transport media (UTM) that is included in the standardized nasal swab kit, and a barcode unique to the participant will be placed on the outside of the tube. Next, the tube will be enclosed in a biohazard bag, then packaged with an absorbent sleeve and placed into one of the provided return shipping boxes, with an attached pre-paid shipping labels. Previous testing has demonstrated that respiratory

viral RNA is stable at room temperature in UTM for up to one week. Nevertheless, these specimens will be placed into the mail as soon as possible so that the nasal swabs can be returned to the laboratory via delivery services the day of or the day after collection for testing and further characterization. This same process for specimen return will occur at Study day 2-3 and Study day 5-7.

Initial Results: Once delivered to the laboratory, the boxes will be unpackaged and any errors that occurred during specimen return will be noted during this time in a spreadsheet accessible to all study staff. Next, the barcode for each specimen as well as a testing cartridge will be scanned into the multiplex PCR instrument (Cepheid) used for detection of influenza A/B or RSV in order to link testing results to each participant. Then, for each specimen, 300 μL of UTM will be transferred to the testing cartridge and run on the Cepheid instrument. On the computer attached to the instrument, testing results are displayed in the GeneXpert Dx System qualitatively as a positive or negative for the three respiratory targets (influenza A, influenza B, and RSV), and quantitatively as Ct values. These results will then be manually entered into a centralized laboratory database, which can later be linked to clinical data for analysis.

Further Characterization: The remaining UTM for each nasal swab sample will be aliquoted under a sterile hood into three matrix 1.0 mL tubes, with each tube containing 650 μL of UTM. A log of the sample information such as collection date, test status, and aliquot date is kept in an excel sheet in a password protected network, which links this information to each participant. One tube will remain in the freezer as backup sample for the duration of the trial (See Future Use in VIII. Data Management section). Another tube will be sent an off-site archive for deep storage. Next, using standard aseptic techniques, 200 μL from the non-storage tube will be transferred to a cartridge to undergo standard viral RNA extraction via the MagNA Pure 96 System using the MagNA Pure 96 DNA and Viral NA Small Volume Kit 2.0. This extraction process will occur in batches, with 94 samples being processed per batch. The output plate will contain 50 μL of purified nucleic acid per sample. Following standard laboratory procedures, the extracted nucleic acid samples will be added to a PreAmp reaction master mix containing TaqPath 1-Step RT-qPCR Master Mix CG, TaqMan PreAmp pool respiratory tract microbiota, and TaqMan Universal Xeno RT control (ThermoFisher). RT-PCR (TaqMan Open Array) cycling conditions will be according to the manufacturer's recommendations for a total of 40 cycles. Positive and negative controls will be included in each extraction and PCR run. Samples will be considered positive if they meet a priori criteria for paired Crt, Cq, and amplification scores (initially set by ThermoFisher). Pathogen detection results will be TaqMan Open Array, which will be uploaded to a central data capture system and subsequently stored in the password protected network. These results can later be linked to clinical data for analysis. (See **SFS Protocol** for full laboratory details).

Return of Results: Some of these results, such as whether the nasal specimens test positive for the following viral respiratory pathogens: Influenza A and B, and RSV, will be available to the participant after initial laboratory testing via the Cepheid on the Seattle Flu Study website. Results will be reported in easy-to-understand language explaining in lay terms the name of the virus, usual symptoms, and basic advice about preventing the spread of infection. Additionally, participants will be able to see where their sample is located on a phylogenetic tree specific to the respiratory viruses their specimen was positive for. Participants will be able to access these results by entering the barcode present on their Study Day 0 nasal swab into the results section of the Seattle Flu Study website, which will show their specific results page.

VII. Risks and Benefits

Study participants will benefit from the receipt of a thermometer. Additionally, influenza-infected participants that receive baloxavir may benefit from a reduction in the duration and severity of their respiratory and systematic symptoms.

Nasal swab collection is a minimal risk event; it may be uncomfortable and may cause watery eyes or sneezing; in rare cases, it may cause slight bleeding of the nose (<1:4,000). Given that participants will be self-swabbing, a nose bleed is very unlikely to occur. However, the information on the proper steps for how to treat a nose bleed (i.e. pressure applied to the septal area continuously for 5 to 20 minutes) will be provided to the participants during the self-swab training video.

Incidences of adverse events occurring in ≥1% of subjects receiving **BXM** in prior randomized controlled trials of acute, uncomplicated influenza in adults and adolescents have included:

- Diarrhea
- Bronchitis
- Nausea
- Nasopharyngitis
- Headache

There is minimal risk of breach of confidentiality in this study. This risk is minimal because there are multiple safeguards in place (see VIII. Data Management section) to ensure participant confidentiality is protected.

There are very few risks to others who are not study subjects. Nevertheless, it should be noted that there is the potential for the transmission of BXM resistant influenza strains from person-to-person, though there are not currently enough data available to determine the likelihood of this event.[33] Non-study subjects that reside in enrolled households may benefit from a reduced risk of secondary transmission of influenza by cases that receive BXM. Similarly, non-study subjects that are part of the social network of household where the case receives BXM may benefit from reduced risk of secondary influenza transmission. All risks and benefits of the intervention will be clearly communicated during the consent process to all study participants prior to enrollment.

Cost of participation

There is no cost to subjects for participation in this study.

Payment for Participation

There is no payment for participation in this study.

VIII. Data Management

Data security and privacy

All information from the study subjects will be kept confidential. All forms and specimens will have a participant identification number, given to the participant upon enrollment in the study, that will be used in the place of names whenever possible. Data will be collected electronically in REDCap either online or through a text-message accessible app. REDCap's survey app is Title 21 CFR Part 11 compliant, password protected and auditable database. The list linking the participant to the ID number will be stored separately from the REDCap database. Access to identifiable information will be limited to the study staff and the study pharmacist (for drug dispensing and delivery purposes); their grounds for employment regarding this study will be

contingent on maintaining the security of study records and any identifiable information. Electronic files will be secured via logon password protection for study accounts. Any datasets that include identifiable information will be stored on in a HIPAA-compliant manner. No identifying information will be included on any data sent to the broader study team or any other data-sharing repositories. All data files transferred for the purpose of this study will be transferred via encrypted software and the original files will be kept on our server.

Identifiable numbers will be kept on biospecimens (nasal swabs) while the laboratory processing occurs. All subjects who consent to participate will also be asked to approve the storage of their biospecimens (nasal swabs). Backup aliquots will be kept until we are sure all laboratory assays are completed with adequate quality control. Persons who consent to the trial, but who do not want their biospecimens stored may still participate in the trial. Their biospecimens will be tested as per protocol, but the remaining aliquots will be destroyed.

Identifiers will be kept on all data files until the study is closed out. Primary data collection sources will be kept for at least 5 years following the publication of the primary result from this study. Once this time elapses and the electronic data files are fully cleaned, any paper forms will be destroyed.

Data quality
Data will be checked for missing or unusual values and checked for consistency within individual participants and households by study staff in the centralized data capture system. Computerized checks will be conducted weekly to identify missing, inconsistent or out of range data. Any suspect data will be raised as data queries. Examples of suspect data (while not an exhaustive list) will include:

- Invalid or improbable dates of birth (e.g. dates in the future, dates greater than 100 years in the past)
- Unlikely changes in symptom reporting (e.g. a participant reports experiencing 5 symptoms one day and then no symptoms the following day)
- Unusual or unlikely household variation (e.g. participants in the same household reporting different household structures)

The study coordinator will investigate data queries to provide an explanation and possible resolution of discrepancies on a weekly basis using the data quality module overview on REDCap. The study coordinator will raise queries and share them with the study staff who are involved in the household enrollment process or are involved in data collection and management. The study staff will contact participants via their preferred method of communication to clarify instances of suspect data. Following this communication, the data items will be marked as “verified,” and an additional review will be conducted by the study coordinator then the query will be closed. When there are no longer any open queries on a survey it can be locked by the study coordinator. See the **SFS Data Management Plan (DMP)** for full details.

Protection against risks
All identifying data will be stored at the University of Washington using standard security techniques. Hard copies of data collection materials that have identifiers will be locked in the office of the study PI or a room with limited access by specific individuals. When possible, redacted (de-identified) versions of the data will be used for coding and data analysis. Personal identifiers will be stored in the database on a password protected network that is HIPAA-compliant, and only accessible to specific individuals. Transfer or storage on portable devices

(e.g., laptops, flashdrives) will be encrypted. The devices on which this information is stored will be accessible only to individuals who need access to the data.

The project will be approved by the Institutional Review Board (IRB) at the University of Washington. This study will be conducted according to Good Clinical Practice (GCP) guidelines at that are appropriate for use of already approved drugs. We will appoint an independent Safety Officer who is not involved in this study.

To reduce distress, study participants will be given the opportunity to skip any questions that they are not comfortable answering. Additionally, all participants will be reminded that participating in research is always optional, and they may terminate their participation at any time without consequences. All members of the research team will be required to complete the Good Clinical Practice (GCP) and the Protecting Human Research Participants training offered before enrollment of participants begins. Only those research team members with login credentials and passwords will be granted access to the centralized data capture system, where data are stored and audited. As previously stated, to mask participant identity, participants will be assigned unique study identifiers (participant ID numbers) at the time of enrollment. Only specific members of the study team and the study pharmacist (for cases) will be able to link to the participant ID to the participant's name.

Future Use

As the genome of influenza viruses (and other respiratory viruses) can change even within a season, it is critical that backup samples be kept that can be used with the latest primers to account for this drift. The samples will be held in a freezer at the University of Washington to serve as this backup.

Nasal swab specimens will be provided by the case following an illness. Following self-collection, specimens will be shipped back to the laboratory the day of or the day after collection via delivery services. Aliquots from consenting participants, will be held in freezers at the University of Washington for potential other, new influenza assays that may be used in the study, if they prove to be less expensive, easier to do and are accurate. We will amend this application if such opportunity presents itself.

We do not currently expect to share specimens with outside investigators, but if compelling opportunities arise that will advance the overall objectives of this research, the Executive Committee (See IX. Data Safety and Monitoring section) of the study will consider such requests. They alone have the authority to make such decisions.

All biospecimens (nasal swabs) will be coded and identifiable through the study's main database. Any specimens shared with external investigators (if deemed appropriate by the Executive Committee) will have identifiers removed prior to sharing.

IX. Data Safety and Monitoring

There are three standing committees that will provide organizational structure for this project. These are the Executive Committee, the Operations Committee, and the Data and Safety Monitoring Board.

Executive Committee: The Executive Committee has overall scientific and administrative responsibility for the conduct of the project. The other two committees will report their recommendations to the Executive Committee where final decisions will be made. All changes

or alterations to the protocol, or issues related to financing or administrative conduct of the study must be approved by the Executive Committee. The Executive Committee will also serve as the Publications Review Committee and all publicity, presentations, or manuscripts from the study must receive approval at this level. The Executive Committee will meet on a regular basis; the frequency will be decided based on the needs of the study.

Operations Committee: The Operations Committee will have primary responsibility for the implementation of the study protocol under the direction of the Executive Committee. They will develop and test all necessary study forms and procedures and produce a Manal of Operations that will document all procedures and methodology for the project. This committee will make recommendations to the Executive Committee regarding any proposed additions or alterations to the study protocol. The Operations Committee will meet on a regular basis, the schedule will be determined by the requirements of the study.

Data and Safety Monitoring Board: The purpose of the Data and Safety Monitoring Board (DSMB) is to provide external, objective advice to the Executive Committee regarding the safety and efficacy of the intervention being evaluated. This committee will be responsible for reviewing the data from the study on a regular basis, summarizing their conclusions and advice in a written set of minutes, and communicating this information to the Executive Committee. The PI will then forward these minutes to the Institutional Review Board at the University of Washington. The DSBM has specific responsibility to determine if there are problems relating to the safety of the intervention, to the degree the study should be stropped, and to determine if the study should be stopped early because the benefit of the interventions has proved to be stronger than originally anticipated. The Data and Safety Monitoring Board will meet just prior to the pre-season enrollment of households to review the final protocol, and after the conclusion of the influenza season. Voting membership on the Data and Safety Monitoring Board is limited to persons external to the investigative team. Senior members of the investigative team will serve as ex-officio members without voting rights. In addition to the voting members of the DSMB, study investigators will act as resources to the DSMB in a non-voting capacity.

Plan for reporting unanticipated problems/adverse events:
Serious Adverse Events: Serious adverse events (SAEs) under Good Clinical Practice (GCP) guidelines include death, a life-threatening reaction the study drug (or placebo) or other study procedure, hospitalization, or significant or persistent disability or impairment. Other events may also be considered a serious adverse event if, based on medical judgement, the event jeopardized the patient to the point of requiring medical or surgical intervention to

Other Adverse Events: This will include any untoward medical event that occurs in a participant, any unfavorable sign or symptom disease temporally associated with the provision of the intervention, or any noxious or unintended response to the study drug. These other adverse events can be anticipated based on what we know about reactions to antiviral medications, or unanticipated. Examples of anticipated adverse events include (but are not limited to) instances of nausea, headache, or diarrhea.

Unanticipated adverse events are those that are either unexpected in terms of nature, severity, and frequency especially if they indicate that there is greater risk of harm than previously recognized.

Within 48 hours of taking the study drug, cases will be screened via REDCap for evidence of short-term reaction. Additionally, drug eligible, influenza-positive study participants will be

monitored at 7 and 14 days after receipt of the intervention using a standardized questionnaire. Any potential AE or SAE based on post-drug tele-health consultation will be reported to the study team as soon as possible, which will be entered into the standardized questionnaire. These questionnaires will be monitored by the data management team, such that adverse events will be reported as soon as possible. All SAEs (regardless of causality), and any grade 3 and 4 AEs which are deemed related or possibly related to the study drug, will be logged in AE database and reported using an official Adverse Event Report Form to the designated principal investigator (Dr. Helen Chu) for review within 48 hours. This review will determine if there is any indication for the event being related to the study intervention or procedures. The medical expert team will review the file and make a determination regarding attribution to study procedures or the intervention.

If the adverse event is considered by the medical expert team to be minor in severity, it will be logged in the centralized data capture system and a summary of such events will be reported to the DSMB. If the severity of the adverse event is considered to be moderate or severe by Principal and Co-Principal Investigators, it should be reported to the safety officer (DSMB) and the cognizant IRB immediately. All study-related SAEs will be reported to the IRB within 14 days.

The following are a list of anticipated and unanticipated adverse events we expect to be attributable to the study procedures or the intervention:

Anticipated Events: Mild-moderate systemic reactions, these include diarrhea, bronchitis, nausea, nasopharyngitis, and headache.

Unanticipated Events: By definition these are unexpected in terms of their nature, (see above for anticipated events) severity, and frequency, especially if they indicate that there may be greater risk of harm than previously recognized.

X. Definitions

Acute Respiratory Illness/infection (ARI): We will use the CDC definition of ARI that includes disease that typically involves the airways within the nose and throat and may or may not include fever. ARI is generally defined by the presence of two or more symptoms such as fever, cough, runny nose or nasal congestion, or sore throat. ARI is more sensitive (broader) than ILI to describe illness consistent with influenza because fever/feverishness are not required.

Drug eligible, influenza-infected study participant: A drug eligible study participant in the household that is diagnosed with influenza from a 98point6 provider based on a clinical review of the sick participant's symptoms.

Drug ineligible participant: A study participant in the household that is not able to receive BXM.

Influenza-like Illness in Adults and Adolescents (ILI): We will use the CDC definition of ILI that requires reported or measured fever (>37.8°C) plus either cough or sore throat on one or more days preceding consultation with a tele-health physician.

Laboratory-confirmed influenza infection: We will use the CDC definition that is an individual who tests positive for influenza via an approved laboratory test, which will be the multiplex PCR (Cepheid) in this study.

Person-to-person transmission: We will use the CDC definition for influenza transmission that refers to the ability of an influenza virus to spread from one person to another, most commonly through large or small droplets containing influenza virus that are expelled when a sick person is coughing or sneezing.

XI. Statistical Analyses

The primary objective is to precisely estimate the proportion of drug eligible individuals with an influenza diagnosis who initiate treatment within 48 hours. We define precision in terms of the width of a 95% confidence interval. The width of a 95% CI will be less than or equal to ±1.96*.5/sqrt(n) where n is the number of individuals who test positive for flu. With 250 households participating and an attack rate of 25% we expect 63 individuals with confirmed influenza infection. This will give a 95% CI for the proportion initiating treatment of ±0.12 or less.

The proportion of drug eligible individuals receiving the drug and initiating treatment within 48 hours of symptom onset using home-based self-test and delivery methods will be estimated. Binomial regression with log link will be used to calculate the relative risk of receiving and initiating treatment within 48 hours by demographic and clinical factors, including age, sex, race/ethnicity, symptom types, symptom severity, and duration of symptoms. The RR, 95% confidence intervals and p-values will be reported.

For the secondary endpoints of symptom duration and severity, drug eligible and drug ineligible participants will be analyzed separately. Symptom severity will be measured on a 4-point scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) for each influenza-associated symptom the participant reports experiencing. Influenza-associated symptoms the participant does not report as experiencing will be coded as 0. An additional analysis will be conducted comparing secondary endpoints for drug eligible, influenza-infected study participants that received and initiated treatment within 48 hours of symptom onset and those that initiated treatment later than 48 hours. Kaplan-Meier curves will be used to present and analyze time to resolution of symptoms, defined as the time when the influenza-positive participant reports experiencing no respiratory or systemic symptoms. For study participants who received BXM, a Cox proportional hazards model will be used to calculate the hazard ratio, 95% confidence interval, and p-value for symptom duration by group (therapy within 48 hours of symptom onset, and therapy after 48 hours of symptom onset). The analysis of drug ineligible study participants will use a similar approach but will cluster by household and use a robust variance for computing confidence intervals and p-values. For BXM recipients, symptom severity will be compared between groups (therapy within 48 hours of symptom onset, and therapy after 48 hours of symptom onset) using proportions for categorical measures of severity and Pearson's chi-square test, as well as using ordinal regression. As above, the analysis using ordinal regression of drug ineligible study participants will cluster by household and use a robust variance for computing confidence intervals and p-values.

For the secondary endpoints of maximum viral titer and duration of viral RNA detection, we will use t-tests or nonparametric alternatives and linear regression to assess maximum viral titer and Kaplan-Meier curves and Cox proportional hazards models to assess duration of viral RNA detection.

Interim Analysis

This study is being conducted over the course of one influenza season. Therefore, an interim analysis will not be performed.

Antiviral resistance analysis
The secondary outcome data regarding emergence of BXM resistance will be reviewed at the end of the influenza season via genome sequencing of the viral RNA.

Health economic analysis
The economic analysis will include a 'within-study' cost-effectiveness analysis to compare the costs and health outcomes accrued over the follow-up period for individuals that initiated the therapy within 48 hours of symptom onset and after 48 hours of symptom onset. Results will be presented as an incremental cost-effectiveness ratio, assessed using health resource utilization and school and work absenteeism, for baloxavir treatment compared at these two time points.

Translational analysis
Samples will be sent to the central laboratory for storage and analysis. The goals of the translational research will be to determine the association between influenza infection and: (1) influenza strain (by genetic sequencing), (2) viral kinetics (maximum titer, duration viral RNA detection). It will also monitor for the emergence of antiviral resistance among strains. Additional testing and sequencing of non-influenza respiratory pathogens will also occur.

XII. End of study

The end of study is defined as when the last household has had their last data collected during the final influenza season of the study period. Active household recruitment and enrollment will take place prior to and during each annual influenza season, and the study itself will take place over the course of one influenza season: November 2019-May 2020. Overall, enrollment will begin October 2019; active participation is projected to start November 2019, and the study is projected to end in May 2020.

XIII. References

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