Title: Feasibility and impact of test-and-treat for influenza in homeless shelters

Stepped-wedge design study of point-of-care molecular testing for influenza and treatment with baloxavir for prevention of secondary transmission of influenza in homeless shelters in Seattle, WA

Protocol version: 2.8
Date updated: March 19, 2022

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Funding: Centers for Disease Control and the University of Washington

Trial Sponsor: University of Washington[1]

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

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Summary

Background: Influenza is an important but under-studied issue for residents of homeless shelters, who may be at increased risk for acquisition of and complications from influenza infection. The homeless population also may be critical for understanding regional influenza transmission.

Design: This study is a stepped-wedge cluster-randomized trial of on-site rapid testing and treatment for influenza in 9 homeless shelters within the Seattle area.

Population: Adults and children staying in participating shelters who have new acute cough or two or more acute respiratory infection (ARI) symptoms.

Study sites and size: 9 homeless shelters in the Seattle area. Approximately 3200 individuals will participate.

Study duration: Two influenza seasons, beginning October 1, 2019 and continuing until April 1, 2021.

Intervention: Initially, all participating shelters will start with routine surveillance, with sampling of individuals with new acute cough or ≥2 (ARI) symptoms with onset in the prior 7 days. Shelters will be randomized to implement a test-and-treat strategy at different months throughout flu season, treating individuals who present new acute cough or ARI symptoms within 2 days (48 hours). Shelters will continue routine surveillance until all offer the test-and-treat strategy. Eligible individuals will be tested on site with a point-of-care molecular influenza test and, if positive, offered antiviral treatment with baloxavir for those aged ≥12 years, who weigh >40kg, are not pregnant or breastfeeding, and do not have active malignancy, liver disease, or are immunocompromised. Oseltamivir will be given to those aged <12 years, as well as to those older than 12 who are immunocompromised, have liver disease, or are women who are pregnant or breastfeeding. Individuals with 3-7 days of symptoms, or who choose not to participate in the intervention strategy, will still be eligible for participation in the routine surveillance. In addition to collecting nasal swabs for testing, individuals will fill out a questionnaire at the time of enrollment on symptom duration and severity, demographic characteristics, relevant coinfections, vaccination status, and bed location in the shelter.

Primary aim: Evaluate whether this strategy reduces secondary spread of influenza in the shelter environment.

Secondary aims: Assess feasibility of test-and-treat strategy for influenza in institutional settings. Characterize the spread of influenza and other viral pathogens within the shelters under study and across the Seattle metropolitan area.

I. Background

Annual influenza epidemics are associated with high morbidity and mortality rates, especially among the elderly, those with underlying health conditions, and pregnant women.[1] The CDC estimates that influenza has resulted in between 140,000-960,000 hospitalizations and between 12,000-79,000 deaths annually since 2010.[2] Transmission of influenza viruses, as well as other respiratory pathogens, has been well-documented in residential facilities, including long-term care facilities and hospitals, yet data concerning transmission of influenza viruses within homeless shelters remains limited. Shelter residents may be at increased risk for communicable diseases due to close contact, high rates of underlying comorbidities, mixing of different age groups, low vaccine coverage for vaccine-preventable diseases, and presence of transient individuals who may introduce new pathogens into the population. Imperfect vaccine effectiveness and lack of durable immunity from annual vaccination highlight a need for additional evidence-based prevention and treatment strategies to increase preparedness. There is also a gap in the existing literature regarding the prevalence and transmission of influenza viruses in homeless populations, who may be an important risk group for pandemic influenza.

Homeless as a high-risk group: According to a 2018 report, approximately 12,000 people in Seattle are experiencing homelessness – the most per capita in the U.S. This same report estimates that 48% of these individuals are housed in a shelter.[3]Homeless individuals experience higher morbidity and mortality than the general population, mostly due to infectious diseases from lack of access to sanitation; untreated chronic medical conditions; higher rates of mental health issues; and common substance use.[4]Those in shelters may be at high risk for acquisition and transmission of influenza viruses in the shelter environment due to overcrowding, inadequate ventilation, and poor sanitary conditions.[5–7]Cancer, heart disease, and cerebrovascular disease are major causes of death in the homeless, particularly amongst older men.[8,9]Immunocompromising conditions such as diabetes in this population are also less likely to be controlled, increasing their vulnerability to infectious diseases.[10] Estimates (varying dependent on how the population is sampled) have indicated that more than 30% of individuals experiencing homelessness suffer from a serious mental illness and at least 50% abuse substances, with significant overlap between the two disorders.[11,12]

Acute Respiratory Illness (ARI) disease burden in the homeless: Past studies have described local outbreaks of influenza and other respiratory viruses in homeless shelters.[13] A cross-sectional investigation of respiratory virus prevalence conducted in French shelters detected at least one pathogen in 8.7% of participants.[6]In a study of adults hospitalized in an urban hospital in Seattle during a five year period, people experiencing homelessness accounted for one-third of individuals diagnosed with respiratory syncytial virus (RSV) but were just 10% of the overall

hospitalized population.[14] A New York-based study of three shelter clinics evaluated 4,319 charts for influenza-like-illness (ILI). The study identified 59 recorded cases, less than one fourth of which had been vaccinated. They also found that people experiencing homelessness had high rates of pneumonia and related death, suggesting higher rates of influenza as pneumonia is a common complication of influenza.[5]Another study found pneumonia or influenza-related mortality rates among a cohort of homeless adults aged 25 to 44 ranged from 11.9-36.6 per 100,000 person years (rate ratio of 1.6-6.3% when compared to the general population).[15]

Testing and antiviral therapy accessibility: Prior studies have demonstrated that early oseltamivir treatment reduces the duration of symptoms and viral shedding among children and adults with uncomplicated medically-attended influenza.[16] There is less observational evidence for its effectiveness in reducing symptoms when prescribed to patients in community settings, and few studies have investigated its effect on influenza viral shedding and on prevention of secondary infections within households or other enclosed spaces.[17]

Baloxavir is an oral agent licensed for treatment of influenza for individuals aged 12 and older. Unlike oseltamivir, a neuraminidase inhibitor, baloxavir functions as a cap-dependent endonuclease inhibitor that prevents influenza genome synthesis. It reduces viral load more quickly than oseltamivir and is taken as a single-dose regimen. Therefore, in contrast to other antiviral medications, baloxavir may be better suited to stop person-to-person transmission. This is pertinent to a population such as those experiencing homelessness who may be disproportionately transient or psychosocially unstable when compared to the general population and thus limited in their ability to adhere to longer courses of treatment.

The CDC recommends initiation of antiviral therapy in high-risk patients with suspected influenza without awaiting test results.[18] Despite a significant proportion of the homeless population qualifying as high-risk due to underlying chronic comorbidities, studies have shown that they encounter significant barriers to accessing testing and treatment services for acute infections.[19]The present study seeks to use point-of-care molecular testing for influenza and early initiation of treatment with baloxavir or oseltamivir to treat cases of influenza in homeless shelters and study the effect of this strategy on prevention of secondary cases of influenza among other shelter residents.

Equipoise: There remain important unanswered questions regarding influenza burden and transmission blockading efforts in sheltered homeless populations. While prior studies have established that homeless populations are at high risk for tuberculosis, hepatitis A, and pneumonia, there are inadequate data to conclude that they are also at increased risk for transmission of influenza and other respiratory viruses.[20] The study of hospitalized homeless

patients with RSV and influenza in Seattle was limited by the lack of a community control. The cross-sectional investigation in French shelters had a sample size of less than 300 and were unable to detect any cases of influenza during peak flu season using RT-PCR testing, indicating inadequate study power.[6]It is also unknown how a single-dose treatment with an antiviral such as baloxavir will impact incidence over the course of a season in a densely-populated community space like a shelter. Neither point-of-care testing for respiratory pathogens nor on-site pharmaceutical treatment has been evaluated as a method of infection prevention in homeless shelters. Despite evidence from past studies showing that rapid molecular influenza tests are as sensitive and specific as traditional influenza RT-PCR assays,[21]there is an unmet need to evaluate their effectiveness in a low-resource community setting.

Conducting a test-and-treat intervention in shelters will provide valuable knowledge as we prototype the social and technical infrastructure required to rapidly detect and interrupt influenza transmission citywide. It is also suggested that controlling influenza virus transmission within shelters may benefit the broader public in the same way that reducing the rates of tuberculosis among homeless persons is regarded as essential in preventing transmission to the general population.[5]

This study will assess and characterize the spread of influenza viruses and other respiratory pathogens within shelters across in the Seattle metropolitan area and the effect of daily surveillance and an early point-of-care test-and-treat strategy on reducing transmission. Individuals will be recruited for participation during the surveillance period - the local respiratory viral season - and then assessed for eligibility for intervention. Participants will be recruited prospectively from nine homeless shelters when acutely ill with a respiratory infection. Respiratory specimens, clinical metadata, and demographic data will be collected prospectively at participating shelters throughout the study.

Methods/Design

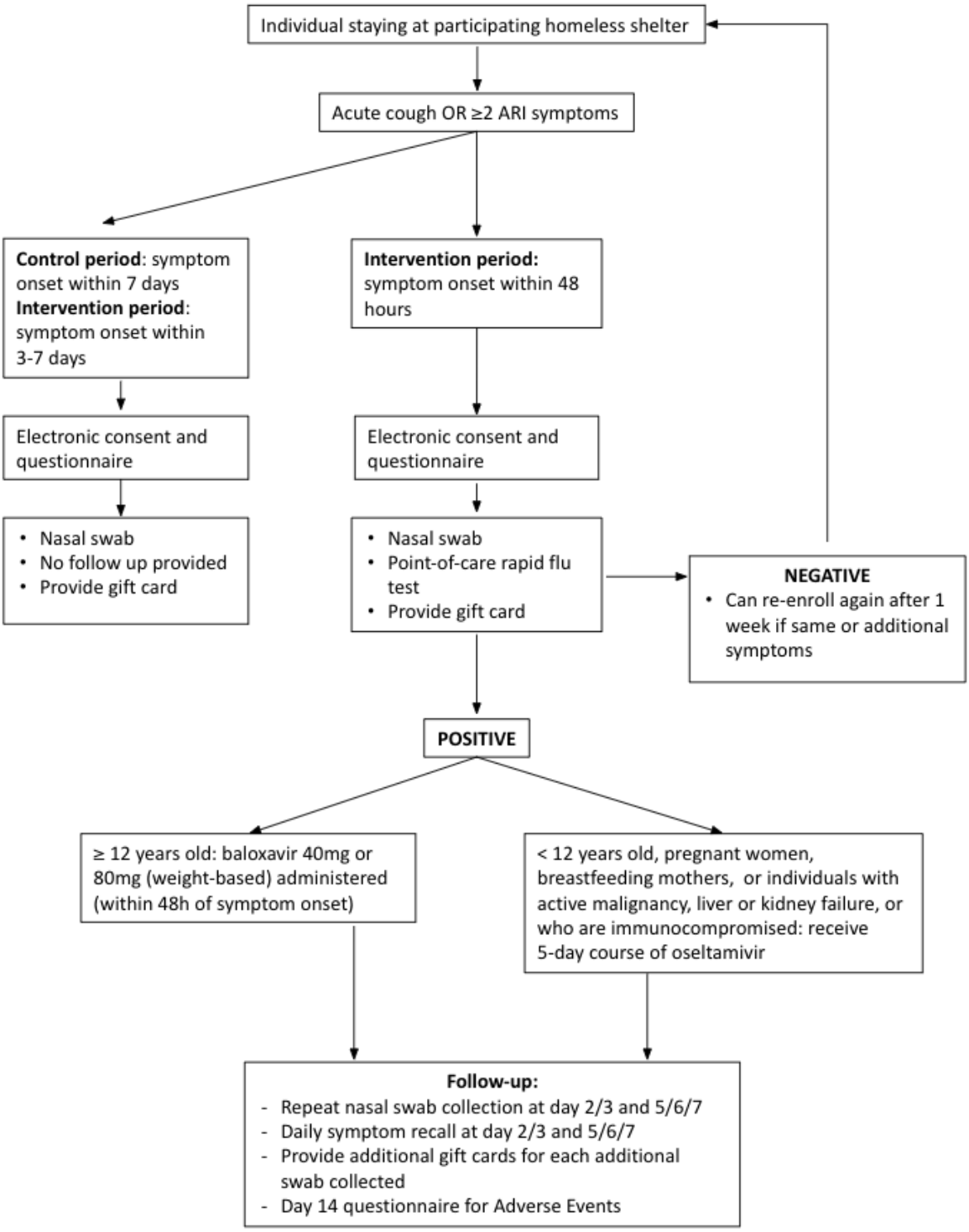
The protocol for this study is in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). A SPIRIT checklist is provided in **Additional File 1**.

II. Study Design

The trial is a stepped-wedge cluster-randomized design clustered by homeless shelter. The intervention is implementation of on-site point-of-care molecular influenza testing and treatment with a single dose of baloxavir or a 5-day course of oseltamivir for all influenza-positive cases. Homeless shelters will be randomized to begin the intervention at different times throughout flu season. Residents within shelters will be eligible to participate if they have acute cough or two or more qualifying ARI symptoms (See **Table 1** for symptom list). The

control condition is an influenza-surveillance kiosk installed in a shelter that allows participants to collect a nasal swab that is then sent to an outside lab for testing. During the intervention period, symptomatic individuals with symptom onset in the last 48 hours will be eligible for point-of-care testing at a “improved” kiosk with a molecular test for influenza and an antiviral intervention if they have not yet received antiviral treatment for their symptoms. If they test positive for influenza, they will be administered an antiviral (either baloxavir or oseltamivir) when they receive their results. All participants will receive active drug; there will be no placebo arm. During the intervention period, symptomatic individuals with symptom onset in the last 3-7 days will be eligible to participate in swab collection, but will not receive point-of-care testing or antiviral treatment. Whole genome sequencing of all influenza-positive samples detected will enable the study team to determine whether a participant has acquired and transmitted the pathogen to secondary cases within-shelter, or whether a case represents a community-acquired infection.

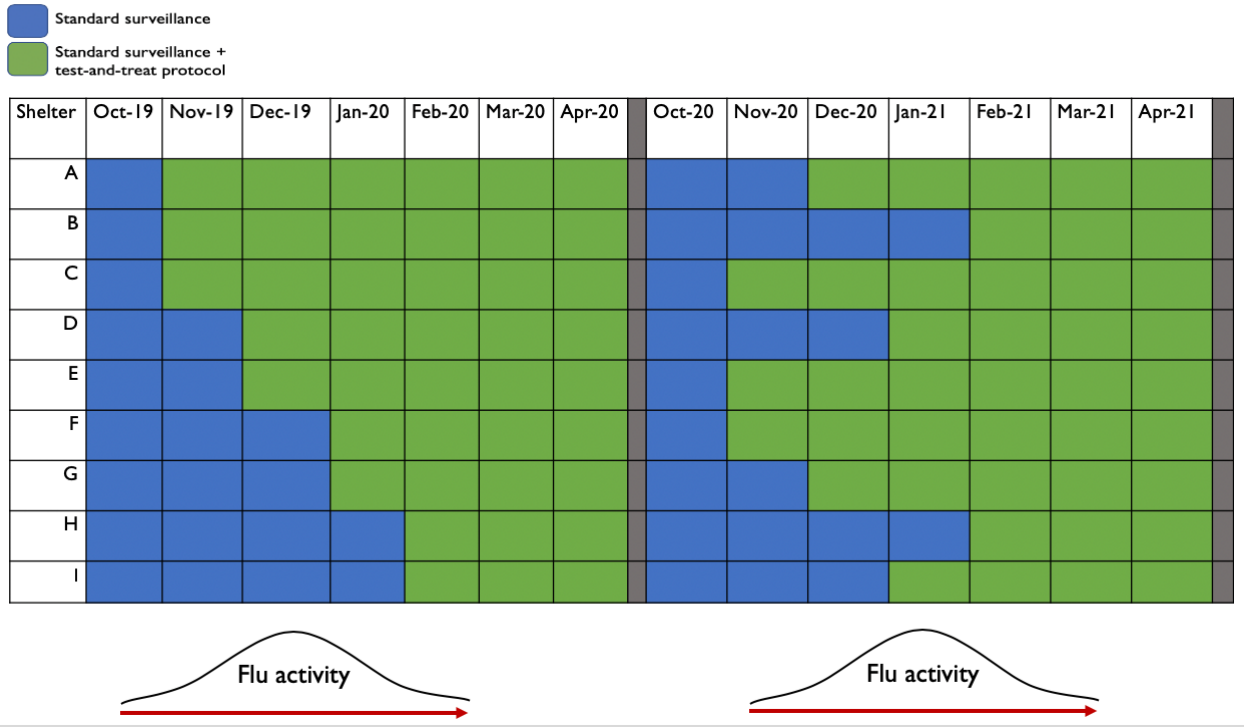
Figure 1. Trial intervention schema


Individual staying at participating homeless shelter
Acute cough OR ≥2 ARI symptoms
Control period: symptom onset within 7 days
Intervention period: symptom onset within 3-7 days
Intervention period: symptom onset within 48 hours
Electronic consent and questionnaire
Electronic consent and questionnaire
• Nasal swab
• No follow up provided
• Provide gift card
• Nasal swab
• Point-of-care rapid flu test
• Provide gift card
NEGATIVE
• Can re-enroll again after 1 week if same or additional symptoms
POSITIVE
≥ 12 years old: baloxavir 40mg or 80mg (weight-based) administered (within 48h of symptom onset)
< 12 years old, pregnant women, breastfeeding mothers, or individuals with active malignancy, liver or kidney failure, or who are immunocompromised: receive 5-day course of oseltamivir
Follow-up:
- Repeat nasal swab collection at day 2/3 and 5/6/7
- Daily symptom recall at day 2/3 and 5/6/7
- Provide additional gift cards for each additional swab collected
- Day 14 questionnaire for Adverse Events

Primary outcome measure of the trial is number of cases of influenza per person-day in the shelter during the intervention period compared to the control period.

Secondary outcomes:
- Symptom duration and severity among cases
- Viral titer and shedding duration among cases
- Feasibility of implementation
- Cost effectiveness
- Emergence of viral resistance

Figure 2. Stepped wedge design for trial



The trial is being conducted in nine homeless shelters in the Seattle, WA metropolitan area. The aim is to enroll nine shelters, each with a nightly population of between approximately 45 to 212 individuals for a total number of a maximum 1,696 individuals under surveillance each influenza season. We will conduct this trial over two influenza seasons with re-randomization of the shelters each season for timing of the intervention. The University of Washington is the sponsor of the trial 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 trial is to evaluate the efficacy of on-site testing and rapid antiviral treatment with baloxavir or oseltamivir in influenza-positive individuals for prevention of secondary cases of influenza virus infection within homeless shelters.

Primary Outcome Measure

The primary outcome measure will be the incidence of cases of influenza in shelters during the intervention period compared to the incidence of cases during the control period. It will be calculated as the number of cases of laboratory-confirmed influenza among shelter residents divided by the number of unique shelter residents tested. The incidence during intervention periods will be compared to the incidence during non-intervention periods using a generalized linear mixed model to control for clustering, differences in shelters, and time period.

Secondary Outcome Measures

Feasibility and adherence outcomes

- Feasibility of implementation of point-of-care molecular testing and treatment of influenza in shelters (time between symptom onset until diagnosis)
- Feasibility of implementation of influenza treatment in shelters (time between symptom onset until treatment)
- Proportion of participants that become lost to follow-up (after testing positive for influenza at baseline enrollment and receiving an antiviral)
- Proportion of participants that show non-compliance with study drug (only applicable to oseltamivir)

Clinical outcomes

- Symptom type, duration and severity among viral positive cases (including broken down by influenza sub-type)
- Prevalence of asymptomatic and pauci-symptomatic influenza-positive cases
- Proportion of laboratory-confirmed influenza cases that report fever
- Relationship between symptom type, duration and severity, and current seasonal influenza vaccination status

Laboratory outcomes

- Influenza viral RNA levels
- Proportion of samples with detectable influenza RNA virus at days 2/3 and days 5/6/7
- Proportion of cases in the shelter that are found via sequencing to be secondary cases, and proportion that are community-acquired
- Emergence of antiviral resistance, assessed by genetic sequencing of influenza strains

Hypothesis

Our primary hypothesis is that implementation of a point-of-care diagnostic and antiviral treatment intervention among sheltered individuals experiencing homelessness will reduce the incidence of influenza within this population over the course of an influenza season.

IV. Study Population

Participants will be any individuals staying at any of the shelters participating in the study. Participants ≥12 years of age who test positive for influenza will be given baloxavir as treatment and receive a 7-day follow-up from the study team. Participants <12 years of age, women who are pregnant or breastfeeding, those with active malignancy, liver disease, and participants who are immunocompromised (see **Table 3**) who test positive for influenza will receive a 5-day course of oseltamivir. Based on an average of 164 specimens collected per month at two shelters over one influenza season during this study's pilot year, we anticipate that enrollment numbers at an additional 7 shelters will more than triple throughout each season (on average ≥492 specimens per month collected). This is due to the increased target population (412 to 1,032) and the increased number of hours/days spent conducting participant enrollment and specimen collection at each shelter proposed in this study design.

Sample size

The study aims to demonstrate a reduction in symptomatic influenza virus infections after implementation of point-of-care molecular testing for influenza and early treatment with baloxavir or oseltamivir. Power calculations were based on an assumed 1.67% incidence rate per month, which was determined based on assumed 12% incidence rate during the flu season. The table below outlines the power based on various estimated effect sizes and number of shelters-seasons (shelters x season):

	Power (%) to detect intervention effect as a function of RR and number of shelter-seasons. Assumptions: Six month flu season, average shelter census = 200, effective control incidence rate = 1.6%/month (=2%*.8), SD(shelter) = .0028, SD(shelter*month) = .0032, SD(intervention) = 0.						
			Number of shelter-seasons				
		8	12	16	18	24	32
RR	.7	21	31	36	41	51	63
	.65	27	40	48	54	65	77
	.6	34	51	60	67	77	88
	.5	52	72	81	86	93	98

Assuming nine shelters participating for two seasons each (18 shelter-seasons), we would have an estimated 86 percent power to detect a risk ratio of 0.50 at a 0.05 two-sided significance

level, and assuming 200 participants per shelter. The incidence during intervention periods will be compared to the incidence during non-intervention periods using general estimating equation models to control for clustering, differences in shelters, and time period. Power calculation details can be found in **Additional File 2.**

Individual enrollment criteria

Participants must fulfill all of the following inclusion criteria:

- Resident for 1 or more days at a participating shelter
- 3 months or older
- Acute cough or ≥2 ARI symptoms (see **Table 1** for list)
- Willing to take study medication
- Willing to comply with all study procedures, including weekly surveillance and repeat nasal swab at day 2/3 and day 5/6/7 post-treatment.
- Able to provide written, informed consent and/or assent

Table 1 – ARI trigger symptoms (participants should have ≥2 or more of the following new symptoms for eligibility within the past 7 days during the control period and within the past 48 hours during the intervention period)

Feeling feverish	Runny or stuffy nose
Headaches	Increased trouble with breathing
Cough	Fatigue (tiredness)
Sore throat or itchy/scratchy throat	Muscle or body aches
Nausea or vomiting	Diarrhea**
Rash**	Ear pain or ear discharge**

** *Only if under 18*

Exclusion criteria

Individuals meeting any of the following criteria will be excluded:

- 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

- Inability to consent and/or comply with study protocol
- Individuals who have received oseltamivir or baloxavir within past 7 days for treatment of influenza
- Individuals with known hypersensitivity to baloxavir marboxil or oseltamivir
- Individuals with chronic kidney disease (CKD)

Withdrawal criteria

All participants are free to withdraw from the study at any time. Additionally, it is within the rights of the PI to withdraw any participant at any time during the study at her discretion.

Additional consent concerns

Study staff enrolling participants should verbally summarize the consent form for any shelter clients who request it. If ability to provide consent is a concern for any shelter kiosk staffer when engaging with a participant, the staff member will not enroll the individual.

V. Study Procedures

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 four 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 composed 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 for enrolling participants at pre-designated spaces within each shelter between 3 to 6 days per week, as well as collecting weekly environmental samples from the shelter. This team will also be responsible for sending reminders to enrolled participants to follow-up with them on day 2/3 and day 5/6/7 following initiation of an antiviral to provide a daily symptom log and additional nasal swabs (see Follow-up Period section), and contacting the participant within 24-hours to determine whether there is evidence of short-term reaction to the study drug.
- **Data management team:** This team will be primary responsible for checking the completeness and quality of the data being reported by study participants. This team will be composed 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 dispensed study drug.

- **Research Lead team:** This team will be responsible for overseeing the enrollment and 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. This team will function as the supervisors for the study and will act as a link between the previous two teams and the medical expert team.
- **Medical expert team:** This team will be composed of a study research nurse, as well as the principal investigator, and co-principal investigators. This team will act as overall supervisors for the study, and as troubleshooters for any major problem that arises 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 Good Clinical Practice (GCP) and the Protecting Human Research Participants training. 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.

Study Personnel Training

See *Seattle Flu Study Protocol* for full details concerning staff training.

Additional orientation and training for staffers working exclusively at shelter kiosks enrolling participants will take place over one day prior to the start of surveillance sample collection. Training content will include:

- Verbally conducting the questionnaire with clients (appropriate use of rephrasing and repetition techniques; eliciting responses for sensitive questions; avoiding lead phrasing of questions);
- How to conduct on-site molecular diagnostics and dispense antiviral treatment (see *On-site Molecular Testing Protocol*);
- And how to conduct environmental sampling (see *Air Filtration Environmental Sampling Protocol* and *Environmental Surface Sampling Protocol*)

Recruitment, screening, and consent

Individuals will be recruited from staffed kiosks at each homeless shelter. Study staff will screen individuals staying at the shelter to ensure eligibility based on inclusion and exclusion criteria. Study staff will obtain informed consent from the individual or legal guardian after a full explanation has been given, an informational leaflet offered, and time allowed for consideration and questions. Once the intervention has been introduced to a shelter through randomization, study staff will require the participant to consent to the testing and receipt of the treatment drug in additional to providing questionnaire responses and corresponding nasal swab. For individuals 12-17 years of age, their legal guardian will be required to consent on their behalf prior to participation, and study staff will obtain assent from the individual.

Pre-intervention period

During the pre-intervention period, kiosks will screen and enroll individuals for the Seattle Flu Study (*see SFS Protocol*). Kiosks will be staffed at regular times 6 days a week at each shelter. Individuals aged with acute cough or ≥2 ARI symptoms will be eligible for participation once every two weeks. Eligible individuals who choose to participate will have a nasal swab collected and answer demographic and clinical questions on an electronic tablet. Study staff will either read the questionnaire aloud to the participant or have them complete it themselves on a tablet. The nasal swab will be transported to and tested at University of Washington. No treatment will be offered in the shelters during the pre-intervention period. All participants will receive a $5 gift card for providing questionnaire responses and a nasal swab sample. For those that provide consent, an ROI of swabbing results will be released to their shelters' on-site providers (when applicable) for follow-up purposes.

Environmental samples (air and surface) will be collected at all shelter sites by study staff starting in the pre-intervention period and continuing through the end of the flu season. They will be tested for respiratory pathogens. Swabbing locations, schedule, and additional details can be found in the *SFS Air Filtration Environmental Sampling Protocol* and *Environmental Surface Sampling Protocol.*

Intervention period

Shelters will be randomized to different starting months for the intervention. Kiosks will continue to be staffed at regular times 6 days a week during the intervention period at each shelter. The intervention will include on-site molecular testing for influenza with the Abbott device and baloxavir (XOFLUZA) treatment for all influenza-positive individuals 12 years of age and older who weigh >40kg, are not pregnant or breastfeeding, and do not have active malignancy, liver disease, or are immunocompromised. Individuals who meet inclusion criteria will have a nasal swab collected. Individuals with positive results who are Baloxair-eligible will be provided with a one-time dose of baloxavir. As baloxavir is an FDA-approved drug for

influenza treatment and considered standard-of-care, there will be no placebo introduced to the control groups. 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.*

All influenza-positive individuals aged 3 months to 11 years, who are pregnant or breastfeeding, and adults with active malignancy, liver disease, or who are immunocompromised (Table 3) will be provided with a 5-day supply of oseltamivir. The antiviral description from the product monograph is as follows:

> *Oseltamivir (also known as the marketed product TAMIFLU ®), is an antiviral neuraminidase inhibitor used for the treatment and prophylaxis of infection with influenza viruses A (including pandemic H1N1) and B. Oseltamivir exerts its antiviral activity by inhibiting the activity of the viral neuraminidase enzyme found on the surface of the virus, which prevents budding from the host cell, viral replication, and infectivity.*

Table 3. Pre-existing conditions that necessitate oseltamivir dosage

Immunosuppression (by medication or disease)
Cancer
Liver disease

The enrollment process for participants during the intervention period is as follows:

1. **Check eligibility:** Inclusion criteria specific to the intervention period that must be met prior to performing molecular testing include (1) ARI symptom onset within the past 48 hours and (2) not having already taken an antiviral for their current symptoms. Those

with acute cough or ≥ 2 ARI symptoms with onset between 3 and 7 days prior to enrollment are not eligible for molecular testing and antiviral treatment, but they should still complete the questionnaire and provide a nasal swab according to pre-intervention protocol. Additional inclusion and exclusion criteria can be found in section IV.

2. **Consent:** If the participant has had symptom onset within the past 48 hours, they must consent to the testing, antiviral dosage, and requisite follow-up procedures at this time. See *SFS Protocol* for additional details pertaining to non-intervention consent process**.**

3. **Questionnaire:** All participants must complete a REDCap survey that will ask questions gathering demographic, clinical and health behavior questions, and questions about prescription medications. This should take between 10-15 minutes to complete. After the participant has consented, the study staff member conducting the enrollment should ask whether they would prefer to complete the questionnaire themselves on the tablet or have them read the questions out loud to them and record their responses. Shelter clients may not be capable of completing the questionnaire alone if they do not have the appropriate corrective aids (glasses, contacts) for poor vision; are unfamiliar/uncomfortable with the technology and app; or have low English-language reading level. Kiosk staff should let the participant know that any question they are not comfortable providing information for they may skip and respond "Prefer not to say" in the app instead. Translated versions of the questionnaire will be available in Spanish, Tigrinya, and Amharic. We will submit translated consent forms prior to enrolling non-English speaking subjects. Telephonic translation services will also be available for participants who are not fully literate in English or their native language.

4. **Nasal swab:** One nasal swab will be collected from each participant. This singular nasal swab will both be tested on-site using the Abbott machine and will also provide a sample to be sent to the laboratory. See *SFS Protocol* for additional details pertaining to nasal swab collection procedures.

5. **Molecular test:** *(for full instructions pertaining to the use of the Abbott test instrument, see the "SFS: On-site Molecular Testing Protocol")*
    a. There should be one Abbott machine at each shelter site that should not be moved at the end of the day by the study team. The machine will be kept on-site throughout the duration of that shelter's allocated intervention period and stored in a secure and locked location by site management staff in either the shelter clinic or administrative office. An instrument quality control test will be

conducted every time the machine is moved, every time a new staff member is running the machine, and for every new lot of cartridges

b. Staff members should ensure that all required materials to run the test are available prior to enrolling patients.
c. While the participant is completing the questionnaire, the staff member should prep the working station and UTM tube with barcode.
d. Collect nasal swab samples according to standard protocol.
e. Place the swab in a UTM tube with barcode and shake vigorously for 5 seconds. Test 200 uL of the UTM liquid using the Abbott test according to the protocol.
f. Scan barcode using the tablet to correspond with the participant's questionnaire, and place UTM tube in cooler with ice pack
g. Record the test results in the "Admin" component of the questionnaire on the tablet.

Obtaining antiviral:

1. Baloxavir or oseltamivir:
    - Participants aged 12 years and older will receive a one-time dose of baloxavir.
    - Participants between the ages of 3 months and 11 years, who are pregnant or breastfeeding, who have active malignancy, liver disease, or who are immunocompromised (Table 3) will receive a 5-day course of oseltamivir.
2. Prepared kits of both antivirals will be provided through Harborview Investigational Drug Services (IDS). There will be a coded kit number on each individual kit, with the first character designating the site/shelter, the second character designating the dose of baloxavir or oseltamivir, and the rest of the numbers designating the specific kit number.
    - Ex: B41004 = site B, 40mg baloxavir, and kit number 1004
3. Study staff will notify IDS one week in advance how many additional prepared kits are needed at the shelter sites
4. A prescription form will be completed with the participant's name, date, and signed by a licensed provider (the PI of this study, Dr. Helen Chu). Her signature will be stamped on all prescriptions by kiosk staff at the time of participant enrollment and testing on site. This form will then be returned to Harborview IDS on a biweekly basis.
5. The study drug will be kept locked safely and securely in either the administrative office or clinic room at the shelter site; depending on the site, this may also be where the participant enrollment is taking place. A temperature

probe will be kept on site to monitor and ensure the room temperature does not surpass the recommended levels.

6. All antivirals will be kept on site regularly reconciled with Harborview IDS every 2 weeks to account for the amount of drugs administered throughout this time period and to restock anticipated use in the following two weeks. A member of the research team will be responsible for picking up study drugs from IDS to bring to the respective shelter in need of restocking.
7. The prescription forms with name and date of dispensing will be sent back to IDS with a member of the research team. A chain of custody form will be filled out, signed and dated by the research member who is moving the study drug.
8. *Baloxavir storage and handling:*
   - 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).
   - 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-coated 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
9. *Oseltamivir storage and handling:*
   - Capsules should be stored at 15-25°C (59-77°F).
   - Powder for Oral Suspension: Store dry powder at 15-25°C (59-77°F). Store reconstituted suspension either:
     - At room temperature (not above 25°C or 77°F). Discard unused portion within 10 days of reconstitution, or;
     - In a refrigerator (2-8°C, or 36-46°F). Discard unused portion within 17 days of reconstitution. Do not freeze reconstituted suspension.
     - Compounded with purified water containing 0.05% w/v sodium benzoate added as preservative:
       - Room temperature storage conditions: Stable for 10 days when stored at room temperature. Do not store above 25°C (77°F).

- Refrigerated storage conditions: Stable for 49 days when stored at 2-8°C (36-46°F).

10. **Medical counseling:** Study staff will provide detailed counseling for consented, flu positive participants eligible to receive **baloxavir** as a treatment drug. Participants will be counseled and assessed on the following:

    - *Prohibited medications/treatments*-Prohibited medications/treatments during the study include concurrent use of any anti-influenza medication. The concurrent use of baloxavir 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 baloxavir which may reduce the drug's efficacy. Avoid co-administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives or antacids, or oral supplements (e.g. calcium, iron, magnesium, selenium, or zinc).
    - *Other contraindications*-Contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients

Consented, flu positive participants eligible to receive **oseltamivir** after being counseled and assessed for the following:

- *Prohibited medications/treatments*- Prohibited medications/treatments during the study include concurrent use of any anti-influenza medication. Having received LAIV within the last 5 days is also prohibited as LAIV recipients may test positive for influenza virus infection for one week post-vaccination.
- *Contraindications*- Contraindicated in patients with a history of hypersensitivity to oseltamivir or any of its ingredients. Severe allergic reactions have included anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme. Prescribed oseltamivir is not recommended for participants with end-stage renal disease not undergoing dialysis.

11. **Administer drug:**
    - **Baloxavir marboxil (XOFLUZA) -** Index cases 12 years of age and older weighing 40kg or more will receive a one-time oral dose of baloxavir based on weight within 48 hours of symptom onset. Individuals weighing 80 kg or more will receive 80 mg of baloxavir. Individuals weighing 40-80 kg, will

receive 40 mg of baloxavir. Participants will be instructed to take the medication immediately on receipt from study staff. Since baloxavir is considered standard of care, a provider does not need to be present for its dispensing and can be completed by the kiosk study staff member conducting the participant enrollment. The study staff member will observe the participant taking the dose unless the participant refuses.

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

- **Oseltamivir (TAMIFLU) -** Index cases aged 3 months through 11 years will be provided with a 5-day supply of oseltamivir in either capsule or oral suspension form. Dosing will be determined based on weight (see table below). Children will be weighed prior to receipt of the drug in order to ensure the appropriate dosage is administered. Whether the child will be provided capsule or suspension will depend on whether they are capable of swallowing pills. Juice and crackers will be provided on-site to facilitate successful capsule administration .
    - Pregnant women, breastfeeding mothers, and adults with active malignancy, liver disease, or who are immunocompromised will receive ten 75 mg capsules to be taken twice daily for 5 days, or sufficient supply of oral suspension for 12.5 mL to be taken twice daily for 5 days.
    - The participants should be advised that the treatment can be taken with or without food, but it is less likely to cause an upset stomach if it is taken with food or milk. Participants should also be advised to continue to take oseltamivir until they finish the 5-day course, even if their symptoms begin to improve. The study staff will observe the participant taking the first dose of oseltamivir.

Weight	Treatment Dosage for 5 days	Volume of Oral Suspension (6 mg/mL) for each Dose	Number of Bottles of Oral Suspension to Dispense	Number of Capsules to Dispense (Strength)
Patients 3 months to 1 year of age				
Any weight	3mg/kg twice daily	0.5mL/kg	1 bottle	N/A
Patients 1 to 12 years of age Based on Body Weight				
15 kg or less	30 mg twice daily	5 mL	1 bottle	10 capsules (30 mg)
15.1 kg to 23 kg	45 mg twice daily	7.5 mL	2 bottles	10 capsules (45 mg)
23.1 kg to 40 kg	60 mg twice daily	10 mL	2 bottles	20 capsules (30 mg)
40.1 kg or more	75 mg twice daily	12.5 mL	3 bottles	10 capsules (75 mg)

12. **Compensation**: All participants in both the surveillance and intervention component of this study will receive a $5 gift card for their time (see *SFS Protocol*). Those that are eligible and enroll in the intervention component of this study will receive a $30 gift card if tested positive and take an antiviral, with an additional $5 gift card for each questionnaire and nasal swab that they provide during the 7-day follow-up period. The gift card ID will be logged in the REDCap application.

13. **Follow-up:**
    - For any children up to age 5 who test positive for flu, we will recommend that they be seen by their pediatrician, or by an urgent care provider if they do not have a pediatrician, within 72 hours
    - Research assistants will provide parents with a referral letter

- Travel vouchers will be provided for children to allow them and their caregivers to get to and from these appointments
- Following drug receipt, participants will have prospective questionnaire data and a nasal swab collected on day 2 or 3 and day 5, 6, or 7 after diagnosis. The participant will be required to return to the kiosk at their respective shelter on these days for the study staff to complete the questionnaire and provide a specimen. All participants will receive a $30 gift card if tested positive and receive an antiviral, and an additional $5 gift card for each subsequent nasal swab sample and symptom severity log that they provide on days 2/3 and 5/6/7, which will be logged in the REDCap application. A final follow-up questionnaire will be given on day 14 to assess for any adverse events. Any common treatment side effects experienced by the participant, which will have been shared by study staff during the consenting process, will be noted in the questionnaires during this follow up period alongside notes regarding relevant symptoms and their severity. These symptom logs will be used to monitor for the occurrence of adverse events (AEs) or serious adverse events (SAEs). See **Section XI** for additional detail about AE and SAE monitoring and reporting. (See **Appendix Additional File 2**).

Taking into consideration the overall transient nature of this population, we are proposing several methods to ensure strong follow-up rates of specimen collection: firstly, through auto-generated text-message reminders for those with cell phones and secondly through-paper based appointment slips provided by kiosk study staff. In-person follow-up by study staff will also be available. See **Section VIII Data Management** for additional details.

For those that provide consent to release of information (i.e. sign an ROI form), viral swab results will be released to their shelters' on-site providers (where applicable) for treatment follow-up purposes.

COVID-19 outbreak study procedures:

While the presence of COVID-19 in the Seattle, WA area impedes certain research activities and continues to be treated as an evolving situation, our study team will temporarily halt the on-site testing and treatment for influenza intervention for the season beginning April 1, 2020. Due to the unprecedented value of data that may continue to be collected directly from shelter residents to better understand this novel pathogen, we have decided to revert all nine shelter sites to the pre-intervention period of the study as described above. Standard surveillance will be implemented at all sites three days per week, with clinical and sociodemographic data

collected via tablet-based questionnaire and mid-turbinate nasal swab or anterior nare swab collection (1 April 2020 – 31 October 2020). The core departures from study protocol details described under "Pre-intervention period" after April 1 will be the reduced number of days research assistants will be present at shelter sites to conduct enrollments, and all symptomatic enrollments receiving a referral letter for clinical providers explaining their participation in this research study and that their sample will be tested for COVID-19. Symptomatic enrollments during this time of standard surveillance will not be given barcodes to access their influenza return of results on the study website. The only results returned to a study participant would be a COVID-19 positive sample.

Our research group has been asked by PHSKC Communicable Disease Epi team to help conduct contact tracing for the shelter sites where there are positive COVID-19 cases detected. Many of the shelter sites have de-congested their shelter population and moved clients to additional sites prepared to more closely adhere to social distancing efforts in a facility-setting (see Figure 3). We have modified REDCap projects so that participant enrollments may be conducted at these new shelter sites that may be housing individuals that were previously clients at shelters participating in our intervention study. These enrollments will take place as part of contact tracing efforts if a positive COVID-19 case is identified that may have been exposed to these populations, rather than having ongoing 3x/week enrollments conducted.

We will also be allowing shelter management staff to enroll in the standard surveillance component of this study from April 1 and onward for COVID-19 surveillance purposes and will be making the necessary REDCap changes to capture their sociodemographic and clinical information. Shelter staff will not be eligible for the on-site flu intervention.

Asymptomatic enrollments:
Beginning April 1, 2020 and continuing throughout the remaining study period, participation criteria for the study will be opened to any and all asymptomatic or paucisymptomatic individuals, resident or staff members, at one of the nine shelters any time there is a Research Assistant on site (see Figure 3). During both standard surveillance (pre-intervention) and intervention periods at the participants' respective shelter, nasal swab collection will be completed with a corresponding questionnaire being conducted.
Asymptomatic/paucisymptomatic participants will receive a $5 gift card for providing a nasal swab. Return of results to asymptomatic /paucisymptomatic participants will be conducted in the same manner as for symptomatic study participants (with the exception of on-site rapid influenza test eligibility). They will not be able to access the results of their nasal swab specimen for flu or other respiratory pathogens tested for on any online platform.

Each shelter resident will be eligible for asymptomatic/paucisymptomatic study participation not more than once per week. All participants, regardless of symptom presentation or study period, that do not test positive for flu using the on-site Abbott will receive a card thanking them for study participation and reminding them to be tested again in one week's time.

Figure 3. All shelter sites where routine surveillance sample collection occurred, 1 October 2019 – 31 May 2021

Shelter	Max. capacity	Resident sex	Resident age range	Sleeping arrangements available
A	60	Female	≥ 18 years	Communal bunk beds
B	100	Mixed	≥ 18 years	Communal bunk beds
C	45	Mixed	18 - 25 years	Communal floor mats and bunks beds
D	185	Mixed	All ages (family shelter)	Private rooms / shared rooms / communal floor mats
E	70	Mixed	All ages (family shelter)	Private rooms / shared rooms / communal floor mats
F	60	Male	≥ 18 years	Communal bunk beds
G	275	Mixed	≥ 18 years	Private rooms / shared rooms
H	275	Mixed	All ages (family shelter)	Private rooms / shared rooms
I	45	Male	≥ 50 years	5 person dorms
J	34	Male	≥ 18 years	Individual open cubicles
K	75	Mixed	≥ 18 years	Individual open cubicles
L	200	Mixed	≥ 18 years	Communal bunk beds

M	212	Male	≥ 50 years	Communal floor mats
N	Unknown	Mixed	All ages (family shelter)	Private rooms / shared rooms
O	100	Mixed	All ages (family shelter)	Private rooms / shared rooms / communal floor mats

IV. VI. Laboratory Procedures

Molecular flu test: *(for full instructions pertaining to the use of the Abbott test instrument, see the "SFS: On-site Molecular Testing Protocol")*

a. There should be one Abbott machine at each shelter site that should not be moved from its address at the end of the day by the study team. The machine will be kept on-site throughout the duration of that shelter's allocated intervention period and stored in a secure and locked location by site management staff in either the shelter clinic or administrative office. An instrument quality control test will be conducted every time the machine is moved, a new staff member is running the machine and for every new lot of cartridges

1. Staff members should ensure that all required materials to run the test are available prior to enrolling patients. While the participant is working through the questionnaire, the staff member should prep the working station and VTM tube with barcode.

b. Collect nasal swab samples according to standard protocol.

c. Place the swab in a VTM tube with barcode and shake vigorously for 5 seconds. Test 200 uL of the VTM liquid using the Abbott test according to the protocol.

d. Scan barcode using the tablet to correspond with the participant's questionnaire, and place VTM tube in cooler with ice pack

e. Record the test results in the "Admin" component of the questionnaire on the tablet.

Laboratory Procedures: Nasal swabs from the ill individual will be collected at day 0, day 2/3, and day 5/6/7 (for flu-positive individuals), and day 5 and day 10 (for COVID-19 positive or inconclusive individuals) and will be returned to the laboratory for testing and further

characterization. Once received, 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, each nasal swab sample will be aliquoted under a sterile hood into three matrix 1.0 mL tubes, with each tube containing 650 mL 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 a backup sample for the duration of the trial (See Future Use in VIII. Data Management section). Another tube will be sent to an off-site archive for deep storage. Next, using standard aseptic techniques, 200 mL 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 mL 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).

A laboratory-developed test or research assay will be used to test for SARS-CoV-2 due to the onset of the pandemic. For the laboratory-developed tests, SARS-CoV-2 detection will be performed using real-time RT-PCR with a probe sets targeting Orf1b and S with FAM fluor (Life Technologies 4332079 assays # APGZJKF and APXGVC4APX) multiplexed with an RNaseP probe set with VIC or HEX fluor (Life Technologies A30064 or IDT custom) each in duplicate on a QuantStudio 6 instrument (Applied Biosystems). The research assay employs only the Orf1b and RNaseP multiplexed RT-PCR in duplicate.

VII. Risks and Benefits

Study participants in the intervention period will benefit from free testing and treatment for influenza. Study participants in the standard surveillance and intervention period will benefit from free COVID-19 testing.

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). Should a nose bleed occur, it will be treated promptly by study staff using pressure applied to the septal area continuously for 5 to 20 minutes.

Incidences of adverse events occurring in ≥ 1% of subjects receiving **baloxavir** in prior acute uncomplicated influenza trials have included:

- Diarrhea
- Bronchitis
- Nausea
- Nasopharyngitis
- Headache

Adverse reactions occurring in ≥1% of adults and adolescents less than 12 years of age in **oseltamivir** treatment and prophylaxis trials include:

- Nausea
- Vomiting
- Headache
- General disorders pain

Vomiting is the only adverse reaction reported at a frequency of ≥1% in pediatric subjects receiving oseltamivir.

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

If baloxavir resistance arises, there is a theoretical risk of transmission of resistant virus to others who are not study subjects. We believe this risk to be minimal as there have only been rare case reports of secondary transmission of resistant virus. Non-study subjects residing in the same shelters or those who are part of the same social network may benefit from a reduced risk of secondary transmission of influenza by individuals treated during the intervention period. 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.

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 pharmacists (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 in a HIPAA-compliant manner via OneDrive for Business at the University of Washington. 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.

The Bedford lab, at Fred Hutchinson, 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 flu prevalence based on census tract, and a phylogenetic analysis of samples collected through the study (including genome assembly). As part of this, Bedford team lab will have access to PHI such as participant address. Each member of the lab involved in data analysis will sign a UW confidentiality agreement.

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 trial. 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 participants and shelters by SFS staff in the centralized data capture system. Computerized checks will be conducted daily for any enrollments made 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)
- No scanned barcode/sample corresponding to a submitted questionnaire
- Inconsistent demographic data for unique ID's with multiple enrollments over the course of the study period

The shelter site coordinator will investigate data queries to provide an explanation and possible resolution of discrepancies on a daily basis using REDCap's data quality module overview. Site coordinator will raise queries and share them with the study staff who completed the respondent survey on site. The staff member will respond to the queries and mark the data item as "verified". Following additional review the manager will close the query. When there are no longer any open queries on a survey it can be locked by the site coordinator.

Full details on data management procedures are available in the *Data Management Plan.*

Intervention follow-up data collection

To follow up with enrolled influenza-positive individuals who received the study drug study staff will use a secondary REDCap survey app on the tablet with a built-in daily symptom log. The database will capture daily symptom responses recorded by the study staff member on day 2 or 3 and day 5, 6 or 7 following single-dose receipt of baloxavir and additional nasal swabs collected, as well as any adverse events experienced. These follow-up questionnaires will require retrospective recall of symptoms that the participant experienced every day following receipt of the study drug, not just days 3 and 7. This database will assign a study ID to each participant, linking nasal swabs collected and symptom log responses. Study staff are responsible for reviewing this database daily for each corresponding site once the intervention period has been introduced.

To contact enrolled participants to procure repeat swabs and symptom questionnaire responses, REDCap will automatically generate daily reports that provide study staff with the names and QR codes/unique links to the symptom logs of participants due for repeat swab collections that day. If they have one, participants will provide study staff with a cell phone

number to receive REDCap automated text messages to remind them when to return for follow-up sample collection. In addition, they will be given a paper appointment slip to remind them of when they are next due for a follow-up visit with study staff. Repeated swab collection on day 2 or 3 and 5, 6, or 7 will take place during the same hours and same location within each respective shelter to ensure participants are able to locate study staff for their follow-up appointments.

At the time of enrollment, participants will be asked to consent for release of their medical records for any hospitalization within 1 month following study enrollment.
If a participant is hospitalized within 1 month of study enrollment for any reason, will we request the records of that hospitalization and abstract them for primary and secondary causes of hospitalization. If these causes are deemed respiratory or study drug related, this information will be recorded in the centralized data capture system for the study and subsequently reported to the IRB.
If a participant dies within 1 month of study enrollment, we will request the record for any ED visit or hospitalization leading up to their death and abstract information on causes of death. If these causes are deemed respiratory or study drug related, this information will be recorded in the centralized data capture system for the study and subsequently reported to the IRB.

Table 2. Timing of Trial Data Collection

	Control	**Intervention**		
Data Items	*Enrollment*	*Enrollment (Day 0)*	*Follow-up (Day 2/3)*	*Follow-up (Day 5/6/7)*
Informed Consent	X	X		
Participant's Demographic & SES Characteristic	X	X		
Clinical Data & Health Seeking Behaviors	X	X	X	X
Nasal Swab Collection	X	X	X	X

Molecular Test		X		
Initial gift card	X	X		
IF FLU POSITIVE:				
Antiviral dispensation log	●	X		
Daily symptom questionnaire	●		X	X
Additional $30 gift card	●	X		
Additional $5 gift cards	●		X	X

Adverse event reporting

Data on adverse events will be collected from the trial participant for 14 days following drug administration, with day 2/3 and day 5/6/7 symptom logs during the 7-day post-treatment period, followed by a day-14 questionnaire filled out by the participant and follow-up prompting provided by the study committees. See section XI for more details.

Protections against risks

All the data will be 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 OneDrive, which is HIPAA-compliant, password protected, and only accessible to specific individuals. Transfer or storage on portable devices (e.g., laptops, flash-drives) is encrypted. The devices on which this information is stored are accessible only to individuals who need access to the data.

The project has been approved by the Institutional Review Board (IRB) at the University of Washington. This trial will be conducted according to Good Clinical Practice (GCP) guidelines

that are appropriate for use of already approved drugs. We will appoint an independent Safety Officer who is not involved in this trial.

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 pharmacists (for index cases) will be able to like to the participant ID to the participant's name. Neither shelter staff nor the study funder will have access to a participant's data or test results.

Return of Results

During the pre-intervention period, there will only be actionable results for COVID-19. During the intervention period, the only other clinically actionable result will be a positive on-site rapid influenza test. This is a potentially urgent result, because influenza can cause severe illness and complications in a subset of patients.

A positive test for COVID-19 may also be actionable, the actions of which will be dependent upon the public health jurisdiction's directives (i.e. contact tracing may occur, but if the outbreak expands, other public health actions may occur based on a positive result). A positive test may be urgent because it would be necessary for the participant to stay isolated.

During the intervention period, patients with a positive on-site rapid flu test result will receive their results as soon as these are available (15-30 minutes after swabbing.)

COVID-19 results, if positive or inconclusive, will be offered to subjects per the health jurisdiction's directive. If the positive or inconclusive test result is not verified on a CLIA-certified instrument, the health department may notify the participant; if the positive or inconclusive test result **is** verified on a CLIA-certified instrument, the Seattle Flu Study may notify the participant if asked to do so by the health department. Regardless of who is offering results to participants, the health department will be notified of all positive or inconclusive results. A positive or inconclusive COVID-19 result would also be offered to asymptomatic subjects.

For participants requiring individual-level results as proof of test result for primary or tertiary medical care that can be shared with their clinical provider, a standardized Return of Results form may be provided.

Participants **will not** be informed of the following results from the Taqman PCR (i.e. real-time PCR testing, for which results will be available ~≥7 days after swabbing): Strep pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumonia; measles; mumps; influenza A, B, and C; human parechovirus; enterovirus and enterovirus D68; bocavirus; adenovirus; rhinovirus; human metapneumovirus; parainfluenza; non-pandemic coronaviruses; and respiratory syncytial virus.

A negative COVID-19 test may not be reported back to the participant, as is outlined in the consent forms that participants would sign. We would report negative COVID-19 results to participants based on the health department's preferred mechanism.

Future Use

As the genome of influenza viruses (and other respiratory viruses) can change even within a season, it is critical to archive samples for testing with the latest primers to account for this drift. Samples from this study will be held in a freezer at the University of Washington for this purpose. 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 main clinical trial, if they prove to be less expensive, easier to do and are accurate. We will amend this application if such an opportunity presents itself. Otherwise within 1 year of completing this protocol, remaining aliquots will be destroyed.

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. Definitions

Influenza Like Illness in Adults (ILI): We will use the CDC definition of ILI that requires reported or measured fever (>38 °C) plus either cough or sore throat on one or more days preceding enrollment.

Influenza Like Illness in Infants: We will use a modified CDC definition of ILI for any infants (children less than 5 years of age), including reported or measured fever (>38 °C) plus cough, or runny nose, or draining ear, or nasal congestion occurring on one or more days preceding enrollment.

Episodes of influenza-like illness must be separated by 14 or more days, with day zero counted as the participant's last enrollment date.

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) definition than ILI to describe illness consistent with influenza because fever/feverishness are not required.

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.

Homelessness: We will use a truncated version of the definition provided by the U.S. Department of Housing and Urban Development that identifies people who are living in a place not meant for human habitation, in emergency shelter, in transitional housing, or are exiting an institution where they temporarily resided if they were in shelter or a place not meant for human habitation before entering the institution.

X. Statistical analyses

Due to the SARS-CoV-2 pandemic onset and corresponding methodological changes, the primary outcome measure for this study will only be calculated based on data collected from Year 1. Standard surveillance beginning on March 30, 2020 expanded to include the testing of study staff and

asymptomatic individuals 3 days per week. The primary outcome measure will be calculated excluding asymptomatic individuals and shelter staff tested as part of the modified standard surveillance methodology initiated on March 30, 2020. As shelter managers were unable to provide us with reliable daily census, we were unable to establish person-days at risk for this study population. Instead, we will use unique participants as the primary unit of analysis. Overall, data collected between November 15, 2019 and March 31, 2021 will be used for data analysis.

Primary Outcome Measure

1. **Cumulative incidence** of cases of influenza (A and B) in shelters during the intervention period compared to the control period.
    a. As daily census counts for participating shelters were not made available to the research team, person-days and therefore incidence rates will not be calculable. Cumulative incidence instead will be calculated as the number of cases of laboratory-confirmed influenza among shelter residents divided by the number of unique shelter residents tested.

Endpoint: Number of influenza-positive events in the control v. intervention periods

Statistical analysis: Shelters will be analyzed with an intent to treat analysis to preserve the advantages of randomization. The number of influenza-positive tests will be analyzed using a generalized linear mixed model following a Poisson distribution with a log link and robust variance. The model is adjusted for calendar time and an exposure time variable based on shelter capacity. It will be used to calculate the relative risk of infection during the intervention period compared to prior to intervention, 95% confidence intervals, and p-value.
This model includes symptomatic individuals who tested throughout Year 1 of the study (November 15, 2019 – March 31, 2020).

Despite operational futility, descriptive statistics (counts, proportions, and appropriate measures of dispersion) for **both years 1 and 2** will be provided for the following Secondary Outcome Measures; additional statistical models will not be run due to low influenza case counts and the impact of the SARS-CoV-2 pandemic:

1. Feasibility of implementation of point-of-care molecular testing and treatment of influenza in shelters
    a. Proportion of participant encounters with time between symptom onset until diagnosis with RT-PCR <48 hours in each study period
2. Feasibility of implementation of influenza treatment in shelters
    a. Proportion of influenza-positive participants identified through on-site molecular testing in the intervention period that were treated with an antiviral
3. Proportion of participants that drop out of study
    a. Measured as dropping out after providing consent

4. Proportion of participants that show non-compliance with study drug

    a. Only applicable to those that receive oseltamivir rather than baloxavir which is a single-dose antiviral. Measured based on self-report during follow-up visits with study research assistants.
5. Proportion of laboratory-confirmed influenza cases that report fever, or feverishness
    a. Based on self-report, not gold standard measurement
6. Influenza viral RNA levels
    a. Measured mean cycle threshold value for each laboratory-confirmed influenza-positive specimen collected at baseline enrollment
7. Proportion of samples with detectable influenza RNA virus at days 2/3 and days 5/6/7
    a. Provided subject has not become lost to follow up

XI. Data Safety and Monitoring

There are two standing committees that will provide organizational structure for this project, alongside an individual independent medical monitor. These are the Executive Committee and the Operations Committee.

Executive Committee: The Executive Committee has overall scientific and administrative responsibility for the conduct of the project. The Data Safety and Monitoring Board (DSMB) 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. The specific members of the Executive Committee are not yet finalized.

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 Manual 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 frequency will be decided based on the needs of the study. The specific members of the Operations Committee are not yet finalized.

Data Safety and Monitoring Board: The purpose of the DSMB is to provide external, objective advice to the Executive Committee regarding the safety and efficacy of the interventions 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 Boards at the University of Washington. The DSMB has specific responsibility to determine if there are problems relating to the safety of the intervention, to the degree the trial should be stopped, 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 DSMB will meet just prior to the pre-season enrollment of shelter participants to review the final protocol, and once a year after the beginning of data collection to review accumulated data. Voting membership on the DSMB is limited to persons external to the investigative team. Senior members of the investigative team will serve as ex-officio members without voting rights. The specific composition of the DSMB will include expertise in biostatistics, epidemiology, and clinical infectious diseases. In addition to the voting members of the DSMB, study investigators will act as resources to the DSMB in a non-voting capacity.

As data accumulate, the DSMB will review whether there is enough evidence such that the continuation of the study would not yield any further meaningful data on treatment effects. While we do not believe *a priori* stopping rules are an appropriate approach to decision making in clinical trials (with the exception of evidence of spread for baloxavir antiviral resistance), we recognize that the DSMB may feel differently. If stopping rules are desired by the DSMB we will use those of O'Brien and Fleming. These rules use a conditional power framework and are commonly used in clinical trials.

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 to the study drug or other study procedure, hospitalization, or significant or persistent disability or impairment.
- **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.

On days 2/3 and 5/6/7 following receipt of the study drug, all study participants will be asked to complete questionnaires pertaining to evidence of short-term reaction during their interaction with the kiosk study staff, in addition to providing additional nasal swab specimen and daily symptom logs. A final questionnaire to assess for AEs and SAEs will be administered on Day 14. These questionnaires will be monitored daily by the data management team, such that adverse events will be reported in real-time.

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 the AE database and reported electronically 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 clinical investigators will review the file and make a determination regarding attribution to study procedures or the intervention.

If the adverse event is considered by the clinical 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.

XII. End of trial

The end of trial is defined as when the last individual has had their last data collected following two subsequent flu seasons; active participant enrollment will take place over the course of two years between October 2019 and is projected to end in April 2021.

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