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Diagnostic accuracy of an app-guided, self-administered test for influenza among individuals presenting to general practice with influenza-like illness: Study protocol

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ABSTRACT

Introduction: Diagnostic tests for influenza in Australia are currently only authorized for use in clinical settings. At-home diagnostic testing for influenza could reduce the need for patient contact with health care services, which potentially could contribute to symptomatic improvement and reduced spread of influenza. We aim to determine the accuracy of an app-guided nasal self-swab combined with a lateral flow immunoassay for influenza conducted by individuals with influenza-like illness (ILI).

Methods and analysis: Adults (>=18 yr) presenting with ILI will be recruited by general practitioners(GP) participating in Australian Sentinel Practices Research Network (ASPREN). Eligible participants will have a nasal swab obtained by their GP for verification of influenza A/B status using RT-PCR at an accredited laboratory. Participants will receive an influenza test kit and will download an app that collects self-reported symptoms and influenza risk factors, then instructs them in obtaining a low-nasal self-swab, running a customized QuickVue influenza A+B lateral flow immunoassay (Quidel Corporation), and interpreting the results. Participants will also interpret an enhanced image of the test strip in the app. The primary outcome will be the accuracy of participants' test interpretation compared to the laboratory RT-PCR reference standard. Secondary analyses will include accuracy of the enhanced test strip image, accuracy of an automatic test strip reader algorithm, and validation of prediction rules for influenza based on self-reported symptoms. A post-test survey will be used to obtain participant feedback of self-test procedures.

Ethics and dissemination: The study was approved by the Human Research and Ethic Committee (HREC) at the University of Adelaide (H-2019-116). Protocol details and any amendments will be reported to https://www.tga.gov.au/. Results will be published in the peer reviewed literature, and shared with stakeholders in the primary care and diagnostics communities.

Universal Trial Number (UTN): U1111-1237-0688, registered on the Australia New Zealand Clinical Trial Registry: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619001087145

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Accuracy of nasal self-testing for influenza using a customized version of the QuickVue Influenza A+B assay will be compared to reference standard of nasal or nasopharyngeal swab obtained by a GP and tested using RT-PCR.
- Recruitment will be nested within an ongoing Australian Surveillance Practices Research Network recruiting patients presenting to general practice with influenza-like illness (ILI)

- Patients attending primary care with ILI may differ in terms of disease spectrum compared to individuals with ILI at home, which is the population where the self-test is intended to be used.
- Self-swabbing of the nose, and conducting a lateral flow test unsupervised and guided by an app may select individuals with greater smartphone experience, manual dexterity, and/or sociodemographic status.
- Self-report of ILI symptoms using an app may differ from symptoms obtained from GP consultations or from research staff, limiting the ability to validate clinical prediction rules for influenza

INTRODUCTION

Seasonal influenza occurs annually, causing disease with substantial morbidity and mortality worldwide, especially in the elderly and those with chronic disease.[1] Despite the availability of the influenza vaccine, repeated influenza infections are common throughout life, and result in a considerable healthcare burden. In Australia, it is estimated that each year influenza causes an average 310,000 general practitioner (GP) consultations, 18,000 hospital admissions, and 378 deaths.[2,3] Influenza places particular burden on primary care services during the winter months, contributing to high consultation rates for acute respiratory tract infections. Detection of influenza is thought to provide value clinically by identifying patients who may be at higher risk of complications, and also to potentially inform use of antivirals and efforts to reduce transmission.[4]

GPs generally diagnose influenza based on a combination of symptoms and risk factors present in each patient, and diagnostic confirmation requires a laboratory test.[4] Multiple tests are available for influenza, including immunoassays and molecular tests with varying levels of sophistication and cost, that can be used in different clinical settings.[5] While some point-of-care tests are approved for, and suitable in primary care settings, others can only be conducted in formal laboratory facilities.

Because there is considerable overlap in symptoms caused by influenza and other respiratory pathogens, many patients who are tested for influenza receive flu-negative results. To reduce the number of unnecessary tests that are requested by GPs, clinical prediction rules have been derived to stratify individuals more accurately than individual symptoms into those with various likelihood of influenza infection.[6] Currently there are no diagnostic tests for influenza that are approved for use by individuals outside of clinical settings in Australia or the United States. The ability to accurately test individuals at home for influenza could provide several potential advantages over current practice. One advantage for patients would be convenience by reducing the need for primary care consultations. Home-testing may also facilitate the earlier use of antivirals when they are most likely to provide beneficial effects on symptom resolution and reduce transmission, and help identify individuals at higher risk of complications compared to those with other causes of influenza-like illness (ILI). [7]

The aim of the current study is to determine the accuracy of a test for influenza that involves individuals self-swabbing their nose and conducting an immunoassay lateral flow test with guidance from a mobile app. We also aimed to explore additional methods for reading the test strip, and validating existing clinical prediction rules for influenza.

METHODS

Study Design

A prospective observational study of the comparative accuracy of a patient-run, mobile app-guided (see Appendix A), lateral flow test for influenza (a customized version of the QuickVue Influenza A + B assay test, from Quidel Corporation) using a low nasal self-swab (referred to in this protocol as 'flu@home'), compared to clinician-collected nasal or nasopharyngeal swab for influenza detected by a commercial RT-PCR. The Universal Trial Number (UTN) is U1111-1237-0688, registered on 6/08/2019. (See Figure 1).

Study population

A consecutive sample of adult patients with ILI presenting to general practices participating in the Australia Sentinel Practices Research Network (ASPREN). (See Appendix B for ASPREN protocol).

Inclusion and exclusion criteria

Inclusion criteria are: 1) age >= 18 years, 2) presenting to ASPREN clinic sites [8] with fever, cough, and fatigue, 3) agree to have their GP/nurse practitioner obtain a nasal or nasopharyngeal swab for surveillance purposes, and 4) have their own Android or iOS smartphone or tablet. Exclusion criteria will be non-English speakers, people who are incarcerated, people highly dependent on medical care who may be unable to give consent, and people with a cognitive impairment, an intellectual disability or mental illness.

Recruitment

Each clinic will recruit the first three adult patients presenting with ILI symptoms each week during the data collection period. Clinics will also recruit every ILI patient aged 65 years and older. Numbers of patients recruited will be monitored during the course of the study in order to determine whether this recruitment rate is sufficient fulfill study objectives, and increased if needed.

Clinical setting

Study participants will be recruited from practices participating in ASPREN, which is a network of sentinel GPs who report de-identified information on ILI as well as other infectious disease conditions.[8] The de-identified information will include date of symptom onset, influenza vaccination history, comorbidities related to influenza, and whether the patient is a health care worker. Data from ASPREN are used by State and Commonwealth Departments of Health for infectious disease surveillance and vaccine effectiveness estimates.[9] ASPREN data contribute

to the Global Influenza Vaccine Effectiveness Movement and the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO-CCRRI).

Outcome measurements

Primary outcome

- Accuracy of detection of influenza A/B infection based on self-reading of the flu@home test compared to laboratory RT-PCR testing.

Secondary outcomes

- Accuracy of detection of influenza A/B infection based on self-reading of an enhanced high contrast image of the flu@home test strip compared to laboratory RT-PCR testing.
- Accuracy of detection of influenza A/B infection based on the app's automatic interpretation algorithm of the flu@home test strip image compared to laboratory PCR testing.
- Accuracy of clinical prediction rules including the Flu Score [6] based on individual and combinations of presenting symptoms obtained from the app and/or the patient's GP compared to laboratory PCR testing.
- Satisfaction and experience of users interacting with the flu@home app.

Other variables

The app will collect information on demographics (age, sex, race), household composition, influenza vaccination history, risk factors for influenza infection, presence and duration of ILI symptoms (e.g., cough, fever, fatigue, chills or sweats), (see Appendix C).

Study procedures

Patients who participate in the ASPREN study will be invited to participate in the flu@home self-testing study from July 2019 until all 2300 kits are distributed, no later than March 2020. Each participating GP will be provided with a set number of test kits, based on the numbers of ILI patients encountered in previous flu seasons, and the number of ILI patients swabbed during the current 2019 flu season. Participating GPs will be asked to recruit all patients who meet study eligibility criteria. After completing the standard ASPREN protocol (see Appendix B) will ask participants if they would like to participate in the flu@home study. Once participants consent, GPs will hand them the test kit and instructions for downloading the free app, and the patient will be asked to conduct the remainder of the study procedures at home on that day or the following day. A post-test survey will be sent to participants via the app 24-48 after they complete the test procedure.

Influenza testing methods

Home/self-testing

Patients will be provided with a self-test kit by their GP containing a customized version of the Quidel QuickVue Influenza A+B lateral flow test, and asked to download the free flu@home app [10] to their personal iOS or Android smartphone or tablet. Each test kit includes a unique 8-digit study ID number that will be linked to reference test results, but cannot be used to personally identify participants. The app collects the variables noted above through a questionnaire, and guides the patient through the self-swabbing and testing procedure. They will be instructed to

obtain a low nasal swab using a single foam-tipped swab inserted into each nostril, and then perform the steps to conduct the lateral flow test.

Having completed the test steps, the app guides the patient to read their test strip by first asking them whether they see a blue line (control line) and any pink lines (1st interpretation). A pink line above the blue line indicates influenza A, and a pink line below the blue control line indicates influenza B. If the patient indicates they do not see the blue control line, they are informed that they have a defective test strip and interpretation guidance is not provided. For patients who indicate they see a blue control line, the app guides the patient to obtain a photo of their test strip using their smartphone camera. During this process the app provides a guided test strip image capture, including on-screen feedback to the participant to ensure proper alignment, lighting, positioning, scale, and rotation of the test strip prior to taking a photo. Once a photo of the strip is captured, the user is presented with a high-contrast image of their test strip and asked to reinterpret the test results by indicating how many lines they now see on the strip (2nd interpretation). Presenting a high-contrast image to the patient may help them see lines on the test strip that may have previously been too faint to easily identify. Initially, the app uses the patient's direct observation of the strip to inform the patient whether it is likely their test result was positive for influenza. During the study we may adjust this process to inform the patient of their likely test result based on auto-interpretation of the images captured.

While the test strip differentiates between influenza A and B, we will not ask individuals to make this determination. If the guided test strip image capture is not successful, the app requests the patient to manually take a normal photo of their test strip using their smartphone for later analysis. The app uses the patient's observations to inform the patient of their likely test result.

Patients will be given links to publicly-available information on influenza from healthdirect [11] and provided with usual care recommendations in the app depending on their test results (from either the 1st or 2nd interpretation).

Reference testing

Influenza will be detected using RT-PCR on the swabs obtained by the GP at ASPREN clinical sites. Samples will be sent to SA Pathology in Adelaide, South Australia, via Australia Post's Express post system, allowing for next-day delivery from all capital cities.[12] Results of the laboratory PCR test, home self-test kit, and survey data from the app will be linked by the 8-digit number available on the test kit and PCR sample.

Post-test survey

A link to a reflective online survey created in Qualtrics© will be delivered to participants who complete the test procedure. The request to complete the survey will be delivered via participants' smartphone or tablet 24-48 hours after completing their self-test.The survey will solicit responses regarding the respondent's a) health behaviors and attitudes, b) perceptions of their experience and usability of the self-test impact, c) perceived value of self-testing, and d) intention to act on self-test results. Survey items will be close-ended and, generally, call for a

response to a five-point Likert scale with anchors ranging from strongly agree to strongly disagree (see Appendix D for follow-up survey items categorized by construct, i.e., focal topic).

Participant discontinuation
Individuals who start the app, provide consent, but fail to complete all steps of the test procedure will be excluded from the primary comparative accuracy analysis. If any participants who were swabbed by their GP as part of ASPREN surveillance test positive for flu, they will be contacted by their general practice clinic to discuss further clinical management; this will not be affected by failure to complete the flu@home procedure.

Data analysis

We will conduct a descriptive analysis of demographics, presenting symptoms, and baseline variables such as household composition, vaccination status, and general health questions. Prevalence of influenza will be obtained from positivity rate of PCR laboratory testing. Sensitivity, specificity, positive and negative predictive values (with 95% confidence intervals) will be calculated for the presence of influenza based on patient interpretation of self-test results compared to the reference standard PCR result. Accuracy will also be calculated for participants' interpretation of the enhanced high-contrast photo of the test strip, as well as the automatic test strip interpretation algorithm, compared to the reference standard PCR result. We will also measure the accuracy of clinical prediction rules based on individual and combinations of ILI symptoms based on Flu Score [6] and other prediction rules, compared to the reference standard PCR result. Subgroup analyses will explore test accuracy based on age, symptom profile, duration of illness, and influenza type (A/B).

We will conduct a descriptive analysis of post-test survey results related to demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived value of self-testing, and intention to act on self-test results. In addition, we will conduct Multivariate Analysis of Variance (MANOVA) to determine if statistically significant differences exist among various subpopulations (e.g., age group, gender) regarding their responses to survey items related to variables associated with experience and usability of the self-test and and impact and perceived value of self-testing. MANOVA analysis permits simultaneous testing of the variables associated with one construct, e.g., experience and usability of the self-test, simultaneously to arrive at a holistic assessment and recognizes the potential correlation related to these variables. Analysis of Variance (ANOVA) will be used to determine if statistically significant differences exist among the responses from various subpopulations (e.g., age group, gender) to survey items related to intention to act on self-test results. We will also use Partial Least Squares Regression (PLS) to construct predictive models to assess relationships among demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived value of self-testing, and intention to act on self-test results.

Sample size calculation

The sample size required for this study was determined based on i) expected completion rate of the home test kit, ii) flu positivity rate, iii) availability of test kit materials, and iv) number of flu-positive test results which are typically provided in FDA submissions for regulatory approval of

rapid flu diagnostic tests. The expected completion rate of the home testing procedure is based on a USA-based pilot study that found that 60% of individuals completed the flu@home test kit when it was mailed to them. In the current study, we expect a higher completion rate given that participants will be recruited by their GP rather than online. The flu positivity rate among patients presenting with ILI to ASPREN clinics is based on data from previous years, which indicated a 20% positivity rate among recruited adults (of all ages) in the July – December period. Assuming that 60% of the 2300 self-test kits distributed to GPs are completed (1380), we expect 20% (276) to be influenza positive. This absolute number of flu positive specimens exceeds that required by FDA in regulatory submissions, which is typically 120.[13]

Indirect Patient and Public involvement

The flu@home app has undergone several iterations of usability and user acceptance testing with a diverse population in the United States. This included usability testing conducted during a pilot phase in the USA using an independent user research firm, which provided input on app usability, time to conduct questionnaire, and the appearance and design of the app. There has not been any prior testing of the app in Australia.

Ethics and dissemination

The study procedures will follow Australian clinical and ethical standards as outlined by the University of Adelaide Human Research Ethics Committee (HREC). All activities will follow the Code of Good Practice in Clinical Research. Participants will provide informed consent for the flu@home study within the app that is downloaded. The study was approved by the Human Research and Ethics Committee at the University of Adelaide. The authors will seek approval for any protocol modifications, which will also be reported to the clinical trials registration site. Results of this study will be reported using the STARD guidelines for reporting diagnostic accuracy studies, and published in the peer-reviewed scientific literature.[14]

Confidentiality and data management

All study data collected are non-identifiable. No participant names, addresses, or private information are collected for the purposes of the study. Samples from the ASPREN survey and app data are linked via a unique barcode. The researchers cannot link the barcode to identifiable patient details such as name, address, or other private information. ASPREN surveillance data will be stored on University of Adelaide computers, which can only be accessed by authorized representatives. All data will be non-identifiable. All data collected by the flu@home app will be protected with industry-standard encryption on systems hosted through Amazon Web Services and the Google Cloud Platform, which are only accessible by authorized representatives of the app development organization, Audere. Audere is a non-profit application development organization that runs the flu@home application. During data analysis non-identifiable data will be transferred to a University of Washington approved data storage location, which is only accessible to authorized parties, and the University of Adelaide drives for analysis.

DISCUSSION

Influenza is a common infection that occurs annually in the southern and northern hemispheres. Consultations for respiratory tract illnesses are one of the most common reasons for presentation in primary care settings in Australia and most other high- and middle-income countries.[2] Differentiating etiology of respiratory tract infection based on symptoms alone is limited, and current confirmatory diagnosis of respiratory pathogens involves laboratory testing.[13] Diagnostic tests for influenza are commonly used in laboratory settings, and in many countries are used in primary care or pharmacy settings.[15–17] Regulatory approval varies between countries, but typically tests approved for primary care involve simple point of care assays that do not require laboratory technician expertise.

The potential for individuals to test themselves for influenza follows a pathway for home-based testing that has revolutionized pregnancy testing with commonly available lateral flow assays, glucose testing using home-based monitors, as well as electronic devices for measuring blood pressure. While there is strong evidence that individuals are able to obtain swabs themselves from the nose or throat [18–20], there is no evidence currently for the accuracy of individuals performing a diagnostic test on self-obtained samples for influenza.

The potential value of a self-test for influenza could lead to changes in practice and behavior, assuming the test has sufficient accuracy. For individuals in the community, this could lead to faster diagnosis, improved access to diagnostic testing, improved diagnostic certainty, and reduced need to contact health care services. For primary health care services, it could reduce the burden of consultations for ILI and facilitate more rapid or targeted use of antivirals. In terms of public health, self-testing could also influence infection control and transmission reduction strategies at the community level. Combining a diagnostic test with a smartphone where the user's steps are process-controlled (e.g. embedded timers ensure the patient adheres to the test procedure) may both facilitate support for the user, and potentially allow enhanced interpretation of test results using the existing camera and software found in current devices. A downside to home/self-based testing for influenza is that easier access to testing could lead to the diagnosis of mild cases of influenza where antiviral treatment is not indicated. Increased access to self-testing include has financial implications including added costs to individuals who might have to purchase the tests, and to the healthcare system that might need to need to interpret, repeat or act on test results. Inaccurate tests could further cause harm through false negative and/or false positive results.

LIMITATIONS OF STUDY

The study has several potential limitations. First, recruitment of participants will not be entirely consecutive, although this follows the procedures that the participating clinics use for ongoing surveillance activities. Limiting this study to general practices means that some patients with ILI are excluded, such as those attending hospitals and emergency departments, receiving medical care from locum doctors or not seeking any medical treatment for ILI. The spectrum of individuals presenting with ILI to GPs may be different to that expected in the community, with higher influenza prevalence, more severe symptoms, and/or longer time since onset of infection. The time point at which individuals present to their GP with influenza may have a critical impact on test sensitivity, as there is strong evidence that the sensitivity of rapid antigen influenza tests

declines markedly beyond the initial 48-72 hours of illness.[21,22] The performance of the nasal swab, and conduct of the lateral flow test is unsupervised, and therefore we will not be able to determine the impact of these factors on test accuracy. Conduct of the test may vary with participant characteristics, such as age or limitations in ability to handle smartphones, and their ability to visualize lines on the test strip. We will explore these using subgroup analyses (based on age), and user feedback from follow up surveys. Differences in performance of the lateral flow test as well as the interpretation of the enhanced image may depend on the technical capabilities of individuals' smartphones.

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APPENDIX

Appendix A: App design and operation

The flu@home app can be used on an iPhone, iPad, Android smartphone, or Android tablet. The app is available in English for the study. However, the app supports development and release of other languages as needed. The entire app experience uses a touch-sensitive dynamic interface on the device. The app ensures the proper test procedure is followed through clear instructions and timers that prevent the participant from moving forward in the test process (e.g., when the test strip must remain in the test fluid for ten minutes to be certain the strip has enough time to process before reading the result). The app attempts to keep participants engaged during wait times by providing flu-related informational facts (during an initial one-minute timer when the nasal swab is processing in the RDT vial) and asking the participant to answer a set of demographic and illness-related survey questions (during the ten-minute timer). Field-level validation is employed to ensure participants answer specific required questions in the survey.

The app was built using React Native, a JavaScript framework used to create mobile applications for iOS and Android. The app communicates with the Google Cloud Platform (Firebase) to queue survey data and Firebase storage to queue images captured from the RDT flow. These are pulled by a NodeJS service into a PostgreSQL database hosted on an AWS Relational Database Service (RDS), which allows for operation and scale of a relational database in the cloud.

App data is stored in Amazon Web Services (AWS S3 and AWS RDS). Amazon Simple Store Service (S3) provides a straightforward web services interface that is used to store and retrieve data, such as PCR data from the swab taken as part of the ASPREN study and used for comparison to the RDT test results. Access to S3 requires user authentication. From the time data leaves the client, all data is encrypted both at rest and over communication links. We use AWS Key Management Service (KMS) to encrypt data at rest in AWS, and Google Cloud Platform automatically encrypts its data using Advanced Encryption Standard (AES). All connections to the app occur over Secure Sockets Layer (SSL), a standard security technology that establishes an encrypted link between a web server and browser, ensuring all data traversing the web server and browser remains private.

For near real-time reporting, Metabase is run in an Elastic Container Service (ECS) in the same AWS project referencing the same app data.

The app uses Firebase caching and analytics to track each participant page view, including a timestamp for each page view. Firebase is also used to track changed answers if a participant navigates back in the app flow.

Appendix B: Australia Sentinel Practices Research Network (ASPREN) Protocol

ASPREN clinical sites will sample the first three ILI patients each week during flu season (July – October 2019 inclusive), and the first ILI patient of the week from November 2019– March 2020 inclusive. Participating clinical sites will obtain a nasal or nasopharyngeal swab which will be transported to SA Pathology, Adelaide, South Australia for testing using RT-PCR for influenza A, influenza B, as well as RSV, enterovirus, adenovirus, mycopneumoniae, human metapneumovirus, parainfluenza 1, 2, 3 and pertussis. Samples positive for influenza A will be further subtyped. All original clinical samples testing positive for influenza will be referred to the WHO-CCRRI (Melbourne, Australia) for antigenic and phylogenetic characterization. For clinical sites in tropical regions, due to the decreased seasonality of influenza, the systematic sample involves the first three ILI patients of each week, all year round. In addition to this, in all sites all ILI patients ages 65 years and over are tested all year round.

Appendix C: Flu@home Participant Questionnaire

Symptom Survey
*Questions marked with an * are required.*

Symptom	*Which of the following were present during your illness?	*How long ago did symptoms start? (Select the time frame that best applies)	*Were these symptoms present in the last 48 hours?	*How severe were your symptoms? (Select the level of discomfort you felt at the worst point)
Fever	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Cough	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Feeling more tired than usual	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Chills or sweats	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Sore throat	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Headache	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Muscle or body aches	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Runny or stuffy nose	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Shortness of breath	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Vomiting	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe

General exposure
In the next section, the questions are going to be about being **in contact** with people who seemed to have a cold or the flu. **In contact** means being within two meters of them for at least two minutes or physical contact for any amount of time.

For reference, two meters is about the distance between you and someone sitting two rows ahead of you on the bus.

In the past week, have you been in contact with a person who seemed to have a cold or flu?

- Yes
- No
- Don't know

[If YES] Were they coughing or sneezing?

- Yes
- No
- Don't know

In the past week, have you been in contact with any children under five years old for over an hour?

- No contact with children under 5 yrs
- 1 child
- 2-5 children
- More than 5 children
- Don't know

Are there any children under 18 years old in your household?

- Yes
- No
- Don't know

[If YES] Do any children in your household attend a school, childcare setting, or play group with at least three other children for a total of three or more hours per week?

- Yes
- No
- Don't know

How many people live in your household (including you)?

- 1-2
- 3-4
- 5-7
- 8+

How many bedrooms are in your home?

- 0-1
- 2
- 3
- 4
- 5+

Influenza vaccination

We would like to ask you some questions about your influenza vaccination history. This information will be used to determine how effective the vaccine is.

Did you receive an influenza vaccination this year (2019)?

- Yes
- No
- Do not know
- I've never received an influenza vaccination.

[If YES] what was the approximate date of your influenza vaccination?

- Choose month and year starting from January 2019 up to the current month

[If YES] Did you receive a free influenza vaccination under the National Immunisation Program in 2019?

- Yes
- No
- Do not know

[If YES] What medical condition(s) do you have that made you eligible for a free influenza vaccination?

- Free text field

[If Answer to above is something other than: "I've never received an influenza vaccination"] Did you receive an influenza vaccination last year (2018)?

- Yes
- No
- Do not know

General health

Next we'd like to ask you some questions about your overall health:

Have you ever been told by a doctor that you have one of the following medical conditions? (SELECT ALL THAT APPLY)

- Asthma
- COPD/emphysema
- Diabetes
- Heart disease
- None of these
- Do not know

Are you a healthcare (or aged care) worker (i.e. do you directly work with patients/aged care residents in your job)?

- Yes
- No
- Do not know

Do you smoke tobacco?

- Yes
- No

Does anyone in your household smoke tobacco?
- Yes
- No

Is your illness preventing you from going to work or school, going to social events, or exercising/working out?
- Yes
- No

***Are you currently taking antibiotics (e.g. Amoxil, penicillin, azithromycin, co-trimoxazole (Bactrim), co-amoxiclav (Augmentin)) or antivirals (e.g. Tamiflu, Xofluza, Relenza) prescribed by a doctor (GP or hospital) for this illness?**
- Yes
- No
- Do not know

How old are you?
- 18 to 19
- 20 to 24
- 25 to 29
- 30 to 34
- 35 to 39
- 40 to 44
- 45 to 49
- 50 to 54
- 55 to 59
- 60 to 64
- 65 to 69
- 70 to 74
- 75 to 79
- 80 to 84
- 85 to 89
- 90 and older

What is the sex on your medical records?
- Male
- Female
- Indeterminate/Other
- Prefer not to say

How would you describe your race? Please select all that apply.
- Aboriginal
- Torres Strait Islander
- Pacific Islander
- North or East Asian
- African
- European
- White Australian

- South or Central American
- Middle East/North African
- Indian subcontinent
- Other

[The next question is asked after the flu rapid test is complete]

Nice job! Do you feel you performed all of the steps in the flu test correctly? Select the most applicable option

- It was easy to follow and I think I completed the test correctly
- It was a little confusing but I think I did the test correctly
- It was very confusing and I'm not sure I completed the test correctly
- During the test, I realized I did something incorrectly

Appendix D: Follow-Up Survey Variables

Category	Questions asked
Health behaviors and attitudes	I believe taking an active role in my own care is the most important factor in determining my health.*
	I am confident that I can identify when it is necessary to get medical care versus when I can handle the problem myself.*
	I often think carefully about whether health information makes sense in my particular situation.*
	I acknowledge that I have a key role in the day-to-day management of my health.*
	I often need someone to help me when I receive written information from my GP, nurse or pharmacist.*
	In general, I believe the state of my health is:**
	I am confident that I can tell my GP concerns I have even when he/she does not ask about them.*
	I like to find out a lot of information about health online.*
	I am confident that I can follow through on medical treatments I need to do at home.*
	I value my health more than anything else.*
	My health needs are always met from available healthcare resources.*
	As well as seeing my GP, I regularly monitor (check for) changes in my health.*
	I do what is necessary to keep myself healthy.*
	My GP and I work together to make decisions about what's best for my health.***
Experience/	The purpose of using flu@home was to: Yes No

usability	Test for flu	○	○
	Give me information about flu and medicine	○	○
	Test different flu medicines	○	○
	Participate in a research study about the flu	○	○
	I am satisfied with how easy it was to use flu@home (nasal swab test and app).*		
	I had the skills needed to perform swab testing using flu@home.*		
	I was able to understand the results from the flu@home app.*		
	The instructions for using flu@home were helpful in providing me with what I needed to perform the test.*		
	Using flu@home **app** was:****		
	Doing the flu@home **nasal swab test** was:****		
	Entering my information into the flu@home app was: ****		
Impact/ perceived value	I would recommend flu@home to a friend or family member.*		
	My GP was very supportive of me using flu@home.*		
	It saves time to do a home-based test like flu@home before visiting a healthcare provider.*		
	I feel that flu@home could help me better manage my illness.*		
Intention to Act	If flu@home testing indicated you had the flu, which of the following would you consider doing as next steps?		
		I would consider	
		Yes	No
	A virtual consultation with a provider (telemedicine visit)	○	○
	Sharing my results anonymously with a national flu tracking system	○	○

	Reading flu@home tips on how to prevent flu spread	○	○
	Encouraging others in my household to use flu@home for testing	○	○
	I would use the flu@home kit in the future if I have symptoms.*		
	I would do the flu@home test if I could purchase the test kit online to send to my home, rather than see my healthcare provider for diagnosis.*		

* Responses on Likert scale anchored with ‘Strongly Disagree’ and ‘Strongly Agree’
** Responses on Likert scale anchored with ‘Very Poor’ and ‘Excellent’
*** Responses on Likert scale anchored with ‘Never’ and ‘Always’
**** Responses on Likert scale anchored with ‘Very Easy’ and ‘Very Difficult’

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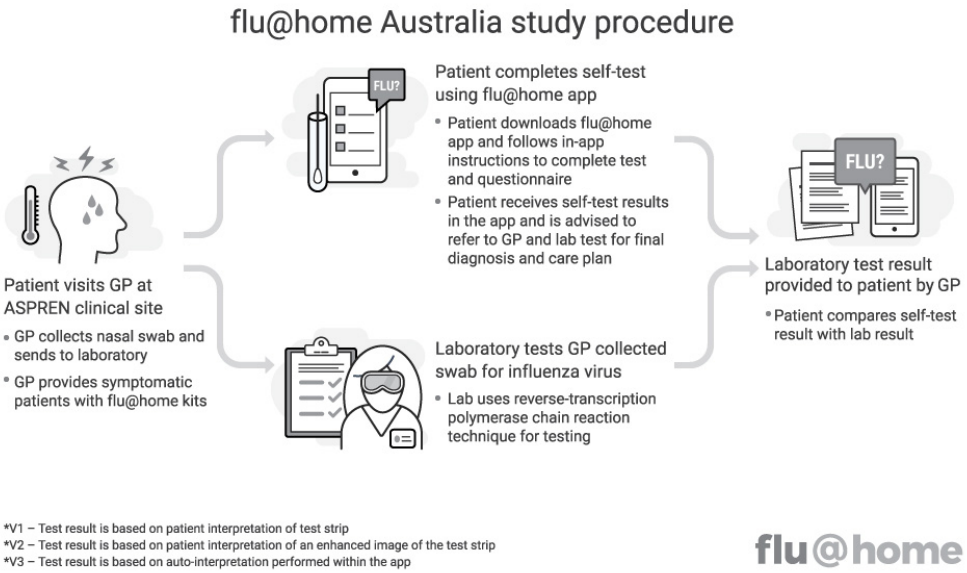

Figure 1: flu@home study procedure

243x148mm (100 x 100 DPI)

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Diagnostic accuracy of an app-guided, self-administered test for influenza among individuals presenting to general practice with influenza-like illness: Study protocol

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Diagnostic accuracy of an app-guided, self-administered test for influenza among individuals presenting to general practice with influenza-like illness: Study protocol

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ABSTRACT

Introduction: Diagnostic tests for influenza in Australia are currently only authorized for use in clinical settings. At-home diagnostic testing for influenza could reduce the need for patient contact with health care services, which potentially could contribute to symptomatic improvement and reduced spread of influenza. We aim to determine the accuracy of an app-guided nasal self-swab combined with a lateral flow immunoassay for influenza conducted by individuals with influenza-like illness (ILI).

Methods and analysis: Adults (>=18 yr) presenting with ILI will be recruited by general practitioners(GP) participating in Australian Sentinel Practices Research Network (ASPREN). Eligible participants will have a nasal swab obtained by their GP for verification of influenza A/B status using RT-PCR at an accredited laboratory. Participants will receive an influenza test kit and will download an app that collects self-reported symptoms and influenza risk factors, then instructs them in obtaining a low-nasal self-swab, running a QuickVue influenza A+B lateral flow immunoassay (Quidel Corporation), and interpreting the results. Participants will also interpret an enhanced image of the test strip in the app. The primary outcome will be the accuracy of participants' test interpretation compared to the laboratory RT-PCR reference standard. Secondary analyses will include accuracy of the enhanced test strip image, accuracy of an automatic test strip reader algorithm, and validation of prediction rules for influenza based on self-reported symptoms. A post-test survey will be used to obtain participant feedback of self-test procedures.

Ethics and dissemination: The study was approved by the Human Research and Ethic Committee (HREC) at the University of Adelaide (H-2019-116). Protocol details and any amendments will be reported to https://www.tga.gov.au/. Results will be published in the peer reviewed literature, and shared with stakeholders in the primary care and diagnostics communities.

Universal Trial Number (UTN): U1111-1237-0688, registered on the Australia New Zealand Clinical Trial Registry: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619001087145

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Accuracy of nasal self-testing for influenza using the QuickVue Influenza A+B assay will be compared to reference standard of nasal or nasopharyngeal swab obtained by a GP and tested using RT-PCR.
- Recruitment will be nested within an ongoing Australian Surveillance Practices Research Network recruiting patients presenting to general practice with influenza-like illness (ILI)

- Patients attending primary care with ILI may differ in terms of disease spectrum compared to individuals with ILI at home, which is the population where the self-test is intended to be used.
- Self-swabbing of the nose and conducting a lateral flow test unsupervised and guided by an app may select individuals with greater smartphone experience, manual dexterity, and/or sociodemographic status.
- Self-report of ILI symptoms using an app may differ from symptoms obtained from GP consultations or from research staff, limiting the ability to validate clinical prediction rules for influenza.

INTRODUCTION

Seasonal influenza occurs annually, causing disease with substantial morbidity and mortality worldwide, especially in the elderly and those with chronic disease.[1] Despite the availability of the influenza vaccine, repeated influenza infections are common throughout life, and result in a considerable healthcare burden. In Australia, it is estimated that each year influenza causes an average 310,000 general practitioner (GP) consultations, 18,000 hospital admissions, and 1,500 to 3000 deaths.[2-4] Influenza places particular burden on primary care services during the winter months, contributing to high consultation rates for acute respiratory tract infections. Detection of influenza is thought to provide value clinically by identifying patients who may be at higher risk of complications, and also to potentially inform use of antivirals and efforts to reduce transmission.[5]

GPs generally diagnose influenza based on a combination of symptoms and risk factors present in each patient, and diagnostic confirmation requires a laboratory test.[5] Multiple tests are available for influenza, including immunoassays and molecular tests with varying levels of sophistication and cost, that can be used in different clinical settings.[6] While some point-of-care tests are approved for, and suitable in primary care settings, others can only be conducted in formal laboratory facilities.

Because there is considerable overlap in symptoms caused by influenza and other respiratory pathogens, many patients who are tested for influenza receive flu-negative results. To reduce the number of unnecessary tests that are requested by GPs, clinical prediction rules have been derived to stratify individuals more accurately than individual symptoms into those with various likelihood of influenza infection.[7] Currently there are no diagnostic tests for influenza that are approved for use by individuals outside of clinical settings in Australia or the United States. The ability to accurately test individuals at home for influenza could provide several potential advantages over current practice. One advantage for patients would be convenience by reducing the need for primary care consultations. Home-testing may also facilitate the earlier use of antivirals when they are most likely to provide beneficial effects on symptom resolution and reduce transmission, and help identify individuals at higher risk of complications compared to those with other causes of influenza-like illness (ILI).[8]

The primary aim of the current study is to determine the accuracy of a self-test for influenza that involves individuals self-swabbing their nose and conducting an immunoassay lateral flow test guided by a mobile app, compared to the gold standard RT-PCR influenza test obtained by their GP. Several studies have already demonstrated the feasibility of collecting patient-reported ILI symptoms.[9-13] This study expands on this field by leveraging smartphone mobile app to instruct participants through conducting a rapid diagnostic test (RDT). We also aimed to explore additional methods for reading the test strip, and validating existing clinical prediction rules for influenza.

METHODS

Study Design

A prospective observational study of the comparative accuracy of a patient-run, mobile app-guided (see Appendix A), lateral flow test for influenza (QuickVue Influenza A + B assay test, from Quidel Corporation) using a low nasal self-swab (referred to in this protocol as 'flu@home'), compared to clinician-collected nasal or nasopharyngeal swab for influenza detected by a commercial RT-PCR. The Universal Trial Number (UTN) is U1111-1237-0688, registered on 6/08/2019. (See Figure 1).

Study population

A systematic sample of adult patients with ILI presenting to general practices participating in the Australia Sentinel Practices Research Network (ASPREN), which is a network of over 350 general providers from over 200 sentinel sites throughout Australia. GPs in the network participate in routine surveillance studies of respiratory infections by the Commonwealth. [14,15] (See Appendix B for ASPREN protocol).

Inclusion and exclusion criteria

Inclusion criteria are: 1) age >= 18 years, 2) presenting to ASPREN clinic sites [16] with fever, cough, and fatigue, 3) agree to have their GP/nurse practitioner obtain a nasal or nasopharyngeal swab for surveillance purposes, and 4) have their own Android or iOS smartphone or tablet. Exclusion criteria will be non-English speakers, people who are incarcerated, people highly dependent on medical care who may be unable to give consent, and people with a cognitive impairment, an intellectual disability or mental illness. We did not exclude people with physical disabilities or impaired vision, but rather left the decision to recruit a patient up to their GP at the time of their visit.

Recruitment

Each clinic will recruit any patient presenting with an ILI who is 18 years and older, has a smartphone and agreeds to participate in the study.

Clinical setting

Study participants will be recruited from practices participating in ASPREN, which is a network of sentinel GPs who report de-identified information on ILI as well as other infectious disease conditions.[16] The de-identified information will include date of symptom onset, influenza vaccination history, comorbidities related to influenza, and whether the patient is a health care worker. Data from ASPREN are used by State and Commonwealth Departments of Health for infectious disease surveillance and vaccine effectiveness estimates.[17] ASPREN data contribute to the Global Influenza Vaccine Effectiveness Movement and the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO-CCRRI).

Outcome measurements

Primary outcome

- Accuracy of detection of influenza A/B infection based on self-reading of the flu@home test compared to laboratory RT-PCR testing.

Secondary outcomes

- Accuracy of detection of influenza A/B infection based on self-reading of an enhanced high contrast image of the flu@home test strip compared to laboratory RT-PCR testing.
- Accuracy of detection of influenza A/B infection based on the app's automatic interpretation algorithm of the flu@home test strip image compared to laboratory PCR testing.
- Accuracy of clinical prediction rules including the Flu Score [7] based on individual and combinations of presenting symptoms obtained from the app and/or the patient's GP compared to laboratory PCR testing.
- Satisfaction and experience of patients interacting with the flu@home app.

Other variables

The app will collect information on demographics (age, sex, race), household composition, influenza vaccination history, risk factors for influenza infection, presence and duration of ILI symptoms (e.g., cough, fever, fatigue, chills or sweats), (see Appendix C). These variables will be used to facilitate interpretation of test results in terms of these various participant characteristics.

Study procedures

Patients who participate in the ASPREN study will be invited to participate in the flu@home self-testing study from July 2019 until all 2300 kits are distributed, no later than December 2020. Each participating GP will be provided with a set number of test kits, based on the numbers of ILI patients encountered in previous flu seasons, and the number of ILI patients swabbed during the current 2019 flu season. Participating GPs will be asked to recruit all patients who meet study eligibility criteria. After completing the standard ASPREN protocol (see Appendix B), a GP will ask the participant if they would like to participate in the flu@home study. Once the participant consents, the GP will hand them the test kit and instructions for downloading the free app, and the patient will be asked to conduct the remainder of the study procedures at home on that day or the following day. A post-test survey will be sent to participants via the app 24-48 after they complete the test procedure.

Influenza testing methods

Home/self-testing

Patients will be provided with a self-test kit by their GP containing a Quidel QuickVue Influenza A+B lateral flow test (rebranded as the flu@home kit for research purposes), and asked to download the free flu@home app [18] to their personal iOS or Android smartphone or tablet. Each test kit includes a unique 8-digit study ID number that will be linked to reference test results, but cannot be used to personally identify participants. The app collects the variables noted above through a questionnaire, and guides the patient through the self-swabbing and testing procedure. They will be instructed to obtain a low nasal swab using a single foam-tipped swab inserted into each nostril, and then perform the steps to conduct the lateral flow test.

Having completed the test steps, the app guides the patient to read their test strip by first asking them whether they see a blue line (control line) and any pink lines (1st interpretation). A pink line above the blue line indicates influenza A, and a pink line below the blue control line indicates influenza B. If the patient indicates they do not see the blue control line, they are informed that they have a defective test strip and interpretation guidance is not provided. For patients who indicate they see a blue control line, the app guides the patient to obtain a photo of their test strip using their smartphone camera. During this process the app provides a guided test strip image capture, including on-screen feedback to the participant to ensure proper alignment, lighting, positioning, scale, and rotation of the test strip prior to taking a photo. Once a photo of the strip is captured, the user is presented with a high-contrast image of their test strip and asked to reinterpret the test results by indicating how many lines they now see on the strip (2nd interpretation). Presenting a high-contrast image to the patient may help them see lines on the test strip that may have previously been too faint to easily identify. Initially, the app uses the patient's direct observation of the strip to inform the patient whether it is likely their test result was positive for influenza. During the study we may adjust this process to inform the patient of their likely test result based on auto-interpretation of the images captured.

While the test strip differentiates between influenza A and B, we will not ask individuals to make this determination. If the guided test strip image capture is not successful, the app requests the patient to manually take a normal photo of their test strip using their smartphone for later analysis. The app uses the patient's observations to inform the patient of their likely test result.

Patients will be given links to publicly-available information on influenza from healthdirect [19] and provided with usual care recommendations in the app depending on their test results (from either the 1st or 2nd interpretation).The app includes a medical disclaimer indicating "The interpretation of your result may differ from a medical test conducted in a clinical lab environment. In no circumstances should the results of this test be relied upon without independent consideration and confirmation by a qualified medical practitioner." [20] Patients will be notified of the results of the reference test by their GP, who will provide standard care based on the RT-PCR results. Participants whose results are discordant with those of their GP will be asked to contact their GP for any clinical management decisions or changes that their GP would recommend.

Reference testing

Influenza and other respiratory pathogens will be detected using RT-PCR on the swabs obtained by the GP at ASPREN clinical sites. (See Appendix B for list of pathogens tested). Samples will be sent to SA Pathology in Adelaide, South Australia, via Australia Post's Express post system, allowing for next-day delivery from all capital cities.[21] Results of the laboratory PCR test, home self-test kit, and survey data from the app will be linked by the 8-digit number available on the test kit and PCR sample.

Post-test survey

A link to a reflective online survey created in Qualtrics© will be delivered to participants who complete the test procedure. The request to complete the survey will be delivered via participants' smartphone or tablet 24-48 hours after completing their self-test.The survey will solicit responses regarding the respondent's a) health behaviors and attitudes, b) perceptions of their experience and usability of the self-test impact, c) perceived value of self-testing, and d) intention to act on self-test results. Survey items will be close-ended and, generally, call for a response to a five-point Likert scale with anchors ranging from strongly agree to strongly disagree (see Appendix D for follow-up survey items categorized by construct, i.e., focal topic).

Participant discontinuation

Individuals who start the app, provide consent, but fail to complete all steps of the test procedure will be excluded from the primary comparative accuracy analysis. If any participants who were swabbed by their GP as part of ASPREN surveillance test positive for flu, they will be contacted by their general practice clinic to discuss further clinical management; this will not be affected by failure to complete the flu@home procedure.

Data analysis

We will conduct a descriptive analysis of demographics, presenting symptoms, and baseline variables such as household composition, vaccination status, and general health questions. Prevalence of influenza will be obtained from positivity rate of PCR laboratory testing. Sensitivity, specificity, positive and negative predictive values (with 95% confidence intervals) will be calculated for the presence of influenza based on patient interpretation of self-test results compared to the reference standard PCR result. Accuracy will also be calculated for participants' interpretation of the enhanced high-contrast photo of the test strip, as well as the automatic test strip interpretation algorithm, compared to the reference standard PCR result. We will also measure the accuracy of clinical prediction rules based on individual and combinations of ILI symptoms based on Flu Score [7] and other prediction rules, compared to the reference standard PCR result. Subgroup analyses will explore test accuracy based on age, symptom profile, duration of illness, and influenza type (A/B).

We will conduct a descriptive analysis of post-test survey results related to demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived value of self-testing, and intention to act on self-test results. In addition, we will conduct Multivariate Analysis of Variance (MANOVA) to determine if statistically significant differences

exist among various subpopulations (e.g., age group, gender) regarding their responses to survey items related to variables associated with experience and usability of the self-test and impact and perceived value of self-testing. MANOVA analysis permits simultaneous testing of the variables associated with one construct, e.g., experience and usability of the self-test, simultaneously to arrive at a holistic assessment and recognizes the potential correlation related to these variables. Analysis of Variance (ANOVA) will be used to determine if statistically significant differences exist among the responses from various subpopulations (e.g., age group, gender) to survey items related to intention to act on self-test results. We will also use Partial Least Squares Regression (PLS) to construct predictive models to assess relationships among demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived value of self-testing, and intention to act on self-test results.

Sample size calculation

The sample size required for this study was determined based on i) expected completion rate of the home test kit, ii) flu positivity rate, iii) availability of test kit materials, and iv) number of flu-positive test results which are typically provided in FDA submissions for regulatory approval of rapid flu diagnostic tests. The expected completion rate of the home testing procedure is based on a USA-based pilot study that found that 60% of individuals completed the flu@home test kit when it was mailed to them. In the current study, we expect a higher completion rate given that participants will be recruited by their GP rather than online. The flu positivity rate among patients presenting with ILI to ASPREN clinics is based on data from previous years, which indicated a 20% positivity rate among recruited adults (of all ages) in the July – December period. Assuming that 60% of the 2300 self-test kits distributed to GPs are completed (1380), we expect 20% (276) to be influenza positive. This absolute number of flu positive specimens exceeds that required by FDA in regulatory submissions to evaluate the accuracy of new tests designed for clinical settings, which is typically 120.[22] There are not currently any recommendations for sample sizes needed for evaluation of the accuracy of home based tests for influenza.

Indirect Patient and Public involvement

The flu@home app has undergone several iterations of usability and user acceptance testing with a diverse population in the United States. This included usability testing conducted during a pilot phase in the USA using an independent user research firm, which provided input on app usability, time to conduct questionnaire, and the appearance and design of the app. There has not been any prior testing of the app in Australia, however, the research study members from Australia reviewed the app prior to launch to ensure the language in the app was appropriate for the Australian context.

Ethics and dissemination

The study procedures will follow Australian clinical and ethical standards as outlined by the University of Adelaide Human Research Ethics Committee (HREC). All activities will follow the Code of Good Practice in Clinical Research. Participants will provide informed consent for the flu@home study within the app that is downloaded. The study was approved by the Human Research and Ethics Committee at the University of Adelaide. The authors will seek approval for any protocol modifications, which will also be reported to the clinical trials registration site.

Results of this study will be reported using the STARD guidelines for reporting diagnostic accuracy studies, and published in the peer-reviewed scientific literature.[23]

Confidentiality and data management

All study data collected are non-identifiable. No participant names, addresses, or private information are collected for the purposes of the study. Samples from the ASPREN survey and app data are linked via a unique barcode. The researchers cannot link the barcode to identifiable patient details such as name, address, or other private information. ASPREN surveillance data will be stored on University of Adelaide computers, which can only be accessed by authorized representatives. All data will be non-identifiable. All data collected by the flu@home app will be protected with industry-standard encryption on systems hosted through Amazon Web Services and the Google Cloud Platform, which are only accessible by authorized representatives of the app development organization, Audere. Audere is a non-profit application development organization that runs the flu@home application. During data analysis non-identifiable data will be transferred to a University of Washington approved data storage location, which is only accessible to authorized parties, and the University of Adelaide drives for analysis. Further information about confidentiality and data management in the mobile app can be found in Appendix A.

DISCUSSION

Influenza is a common infection that occurs annually in the southern and northern hemispheres. Consultations for respiratory tract illnesses are one of the most common reasons for presentation in primary care settings in Australia and most other high- and middle-income countries.(2) In Australia influenza season occurs between the months of May to October.[24] Differentiating etiology of respiratory tract infection based on symptoms alone is limited, and current confirmatory diagnosis of respiratory pathogens involves laboratory testing.[22] Diagnostic tests for influenza are commonly used in laboratory settings, and in many countries are used in primary care or pharmacy settings.[25–27] Regulatory approval varies between countries, but typically tests approved for primary care involve simple point of care assays that do not require laboratory technician expertise.

We will use an existing rapid diagnostic test for influenza A and B that has been been approved in the United States for use in primary care clinics since 2004 (QuickVue Influenza A + B assay test, from Quidel Corporation)[28]. This test has adequate performance as demonstrated by regulatory approval in the US, with a 2017-18 clinical study comparing this test to an FDA cleared A+B molecular test, showing sensitivity of 94% for Type A and 70% for Type B, and specificity of 90% for Type A and 97% for Type B[29,30]. However, we note that additional evaluations of this test (and similar lateral flow tests) for influenza show lower test accuracy in further clinical evaluations. A a 2017 meta-analysis of 162 studies of rapid tests for infuenza found noted that the pooled sensitivity of stuch tests favored industry-sponsored studies by 6.2 to 34.0%. [31]

The potential for individuals to test themselves for influenza follows a pathway for home-based testing that has revolutionized pregnancy testing with commonly available lateral flow assays,

glucose testing using home-based monitors, as well as electronic devices for measuring blood pressure. While there is strong evidence that individuals are able to obtain swabs themselves from the nose or throat [32–34], there is no evidence currently for the accuracy of individuals performing a diagnostic test on self-obtained samples for influenza.

The potential value of a self-test for influenza could lead to changes in practice and behavior, assuming the test has sufficient accuracy. For individuals in the community, this could lead to faster diagnosis, improved access to diagnostic testing, improved diagnostic certainty, and reduced need to contact health care services. For primary health care services, it could reduce the burden of consultations for ILI and facilitate more rapid or targeted use of antivirals if these can be prescribed remotely (by telephone, or telemedicine consultations). In terms of public health, self-testing could also influence infection control and transmission reduction strategies at the community level. Combining a diagnostic test with a smartphone where the user's steps are process-controlled (e.g. embedded timers ensure the patient adheres to the test procedure) may both facilitate support for the user, and potentially allow enhanced interpretation of test results using the existing camera and software found in current devices. A downside to home/self-based testing for influenza is that easier access to testing could lead to the diagnosis of mild cases of influenza where antiviral treatment is not indicated. Increased access to self-testing include has financial implications including added costs to individuals who might have to purchase the tests, and to the healthcare system that might need to interpret, repeat or act on test results. Inaccurate tests could further cause harm through false negative and/or false positive results.

LIMITATIONS OF STUDY

The study has several potential limitations. First, recruitment of participants will not be entirely consecutive, although this follows the procedures that the participating clinics use for ongoing surveillance activities. Limiting this study to general practices means that some patients with ILI are excluded, such as those attending hospitals and emergency departments, receiving medical care from locum doctors or not seeking any medical treatment for ILI. Second, the spectrum of individuals presenting with ILI to GPs may be different to that expected in the community, with higher influenza prevalence, more severe symptoms, and/or longer time since onset of infection. The time point at which individuals present to their GP with influenza may have a critical impact on test sensitivity, as there is strong evidence that the sensitivity of rapid antigen influenza tests declines markedly beyond the initial 48-72 hours of illness.[35,36] Third, the performance of the nasal swab, and conduct of the lateral flow test is unsupervised, and therefore we will not be able to determine the impact of these factors on test accuracy. There is robust evidence that individuals are able to collect mid turbinate and low nasal swabs with similar performance to health care professionals for influenza, but we will not be able to further verify this in the current study. [37] Fourth, conduct of the test may vary with participant characteristics, such as age or limitations in ability to handle smartphones, and their ability to visualize lines on the test strip. We will explore these using subgroup analyses (based on age), and user feedback from follow up surveys. Fifth, differences in interpretation of the enhanced image may depend on the technical capabilities of individuals' smartphones. Sixth, technical aspects of the flu@home app may need additional validation before being implemented into more complex human studies or

being used with a commercial device. Finally, we will not be able to evaluate comparative costs of the flu@home test compared to usual care within this study.

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Figure Legend

Figure 1. flu@home Australia study procedure

Contributorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Additionally, each author certifies that this material or similar material has not been and will not be submitted to publication before its appearance in BMJ Open.

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Guarantors: Barry Lutz, Matthew Thompson

Competing Interests

The authors do not have any competing interests.

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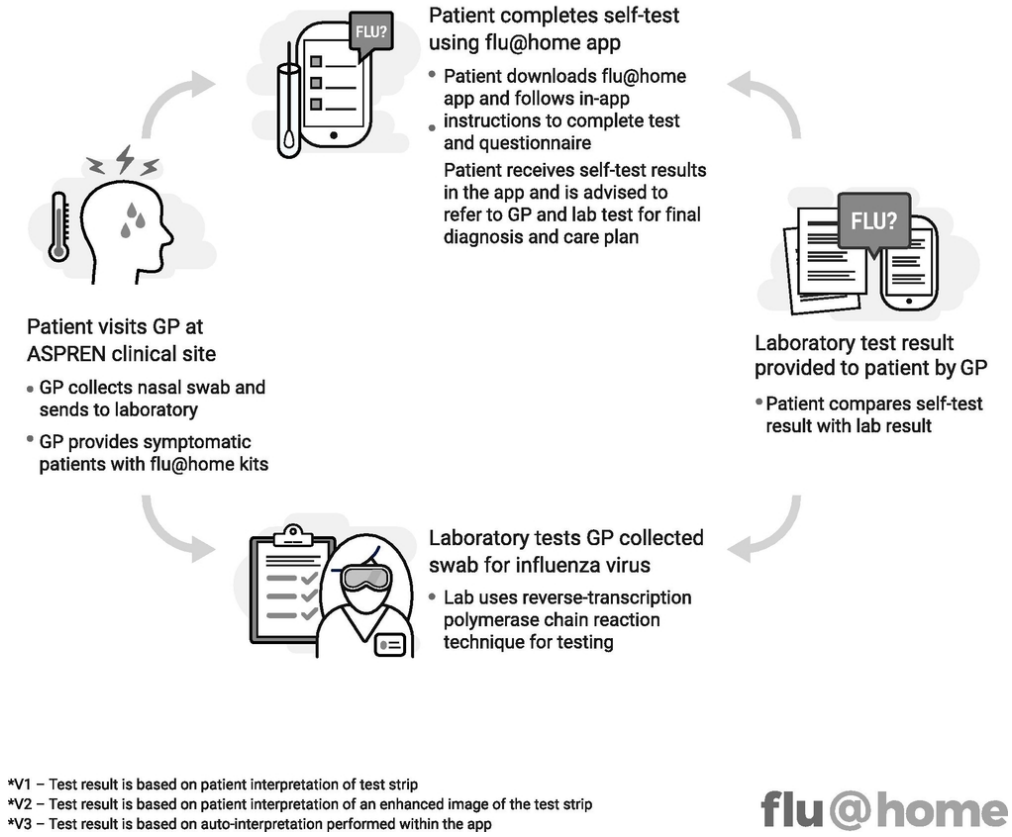

flu@home Australia study procedure

85x81mm (300 x 300 DPI)

APPENDIX

Appendix A: App design and operation

The flu@home app can be used on an iPhone, iPad, Android smartphone, or Android tablet. The app is available in English for the study. However, the app supports development and release of other languages as needed. The entire app experience uses a touch-sensitive dynamic interface on the device. The app ensures the proper test procedure is followed through clear instructions and timers that prevent the participant from moving forward in the test process (e.g., when the test strip must remain in the test fluid for ten minutes to be certain the strip has enough time to process before reading the result). The app attempts to keep participants engaged during wait times by providing flu-related informational facts (during an initial one-minute timer when the nasal swab is processing in the RDT vial) and asking the participant to answer a set of demographic and illness-related survey questions (during the ten-minute timer). Field-level validation is employed to ensure participants answer specific required questions in the survey.

The app was built using React Native, a JavaScript framework used to create mobile applications for iOS and Android. The app communicates with the Google Cloud Platform (Firebase) to queue survey data and Firebase storage to queue images captured from the RDT flow. These are pulled by a NodeJS service into a PostgreSQL database hosted on an AWS Relational Database Service (RDS), which allows for operation and scale of a relational database in the cloud.

The flu@home Australia app is available for personal devices which are expected to be under control of an individual who uses a passcode to access the device. All supported devices use encryption to protect app data resident on the device. This encryption is afforded by the device itself, not a specific application. In the event that a device is stolen, the device's onboard locking feature is the front-line defense against access to data on the device. The flu@home application does not collect the user's name, email, or other key identifiable information in the app. It focuses on data collection of symptoms, disease presentation, and demographics. The level of data protection offered by the flu@home app is the same level of protection afforded to most other health applications, email, messaging, etc. available on a mobile device.

App data is stored in Amazon Web Services (AWS S3 and AWS RDS). Amazon Simple Store Service (S3) provides a straightforward web services interface that is used to store and retrieve data, such as PCR data from the swab taken as part of the ASPREN study and used for comparison to the RDT test results. Access to S3 requires user authentication. From the time data leaves the client, all data is encrypted both at rest and over communication links. We use AWS Key Management Service (KMS) to encrypt data at rest in AWS, and Google Cloud Platform automatically encrypts its data using Advanced Encryption Standard (AES). All connections to the app occur over Secure Sockets Layer (SSL), a standard security technology that establishes an encrypted link between a web server and browser, ensuring all data traversing the web server and browser remains private.

For near real-time reporting, Metabase is run in an Elastic Container Service (ECS) in the same AWS project referencing the same app data.

The app uses Firebase caching and analytics to track each participant page view, including a timestamp for each page view. Firebase is also used to track changed answers if a participant navigates back in the app flow.

Appendix B: Australia Sentinel Practices Research Network (ASPREN) Protocol

The protocol for ASPREN clinical sites requires GPs to sample the first three ILI patients each week during flu season (May – October 2019 inclusive), and the first ILI patient of the week from November 2019– April 2020 inclusive. For the flu@home study, GPs will be allowed to recruit all adult patients presenting to the clinic with ILI symptoms, in order to meet recruitment goals. Participating clinical sites will obtain a nasal or nasopharyngeal swab which will be transported to SA Pathology, Adelaide, South Australia for testing using RT-PCR for influenza A, influenza B, as well as RSV, enterovirus, adenovirus, mycopneumoniae, human metapneumovirus, parainfluenza 1, 2, 3 and pertussis. Samples positive for influenza A will be further subtyped. All original clinical samples testing positive for influenza will be referred to the WHO-CCRRI (Melbourne, Australia) for antigenic and phylogenetic characterization. For clinical sites in tropical regions, due to the decreased seasonality of influenza, the systematic sample involves the first three ILI patients of each week, all year round. In addition to this, in all sites all ILI patients ages 65 years and over are tested all year round.

Appendix C: Flu@home Participant Questionnaire

Symptom Survey
*Questions marked with an * are required.*

Symptom	*Which of the following were present during your illness?	*How long ago did symptoms start? (Select the time frame that best applies)	*Were these symptoms present in the last 48 hours?	*How severe were your symptoms? (Select the level of discomfort you felt at the worst point)
Fever	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Cough	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Feeling more tired than usual	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Chills or sweats	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Sore throat	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Headache	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Muscle or body aches	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Runny or stuffy nose	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Shortness of breath	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Vomiting	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe

General exposure
In the next section, the questions are going to be about being **in contact** with people who seemed to have a cold or the flu. **In contact** means being within two meters of them for at least two minutes or physical contact for any amount of time.

For reference, two meters is about the distance between you and someone sitting two rows ahead of you on the bus.

In the past week, have you been in contact with a person who seemed to have a cold or flu?

- Yes
- No
- Don't know

[If YES] Were they coughing or sneezing?

- Yes
- No
- Don't know

In the past week, have you been in contact with any children under five years old for over an hour?

- No contact with children under 5 yrs
- 1 child
- 2-5 children
- More than 5 children
- Don't know

Are there any children under 18 years old in your household?

- Yes
- No
- Don't know

[If YES] Do any children in your household attend a school, childcare setting, or play group with at least three other children for a total of three or more hours per week?

- Yes
- No
- Don't know

How many people live in your household (including you)?

- 1-2
- 3-4
- 5-7
- 8+

How many bedrooms are in your home?

- 0-1
- 2
- 3
- 4
- 5+

Influenza vaccination

We would like to ask you some questions about your influenza vaccination history. This information will be used to determine how effective the vaccine is.

Did you receive an influenza vaccination this year (2019*)?

- Yes
- No
- Do not know
- I've never received an influenza vaccination.

[If YES] what was the approximate date of your influenza vaccination?

- Choose month and year starting from January 2019* up to the current month

[If YES] Did you receive a free influenza vaccination under the National Immunisation Program in 2019*?

- Yes
- No
- Do not know

[If YES] What medical condition(s) do you have that made you eligible for a free influenza vaccination?

- Free text field

[If Answer to above is something other than: "I've never received an influenza vaccination"] Did you receive an influenza vaccination last year (2018*)?

- Yes
- No
- Do not know

General health

Next we'd like to ask you some questions about your overall health:

Have you ever been told by a doctor that you have one of the following medical conditions? (SELECT ALL THAT APPLY)

- Asthma
- COPD/emphysema
- Diabetes
- Heart disease
- None of these
- Do not know

Are you a healthcare (or aged care) worker (i.e. do you directly work with patients/aged care residents in your job)?

- Yes
- No
- Do not know

Do you smoke tobacco?

- Yes
- No

Does anyone in your household smoke tobacco?

- Yes
- No

Is your illness preventing you from going to work or school, going to social events, or exercising/working out?

- Yes
- No

Are you currently taking antibiotics (e.g. Amoxil, penicillin, azithromycin, co-trimoxazole (Bactrim), co-amoxiclav (Augmentin)) or antivirals (e.g. Tamiflu, Xofluza, Relenza) prescribed by a doctor (GP or hospital) for this illness?

- Yes
- No
- Do not know

How old are you?

- 18 to 19
- 20 to 24
- 25 to 29
- 30 to 34
- 35 to 39
- 40 to 44
- 45 to 49
- 50 to 54
- 55 to 59
- 60 to 64
- 65 to 69
- 70 to 74
- 75 to 79
- 80 to 84
- 85 to 89
- 90 and older

What is the sex on your medical records?

- Male
- Female
- Indeterminate/Other
- Prefer not to say

How would you describe your race? Please select all that apply.

- Aboriginal
- Torres Strait Islander
- Pacific Islander
- North or East Asian
- African
- European
- White Australian

- South or Central American
- Middle East/North African
- Indian subcontinent
- Other

[The next question is asked after the flu rapid test is complete]

Nice job! Do you feel you performed all of the steps in the flu test correctly? Select the most applicable option

- It was easy to follow and I think I completed the test correctly
- It was a little confusing but I think I did the test correctly
- It was very confusing and I'm not sure I completed the test correctly
- During the test, I realized I did something incorrectly

** All questions with an asterisk listed by the year will be updated in the mobile app in January 2020 (i.e. questions referring to "this year" will list 2020 instead of 2019.)*

Appendix D: Follow-Up Survey Variables

Category	Questions asked
Health behaviors and attitudes	I believe taking an active role in my own care is the most important factor in determining my health.*
	I am confident that I can identify when it is necessary to get medical care versus when I can handle the problem myself.*
	I often think carefully about whether health information makes sense in my particular situation.*
	I acknowledge that I have a key role in the day-to-day management of my health.*
	I often need someone to help me when I receive written information from my GP, nurse or pharmacist.*
	In general, I believe the state of my health is:**
	I am confident that I can tell my GP concerns I have even when he/she does not ask about them.*
	I like to find out a lot of information about health online.*
	I am confident that I can follow through on medical treatments I need to do at home.*
	I value my health more than anything else.*
	My health needs are always met from available healthcare resources.*
	As well as seeing my GP, I regularly monitor (check for) changes in my health.*
	I do what is necessary to keep myself healthy.*
	My GP and I work together to make decisions about what's best for my health.***
Experience/	The purpose of using flu@home was to: Yes No

usability	Test for flu	○	○
	Give me information about flu and medicine	○	○
	Test different flu medicines	○	○
	Participate in a research study about the flu	○	○
	I am satisfied with how easy it was to use flu@home (nasal swab test and app).*		
	I had the skills needed to perform swab testing using flu@home.*		
	I was able to understand the results from the flu@home app.*		
	The instructions for using flu@home were helpful in providing me with what I needed to perform the test.*		
	Using flu@home **app** was:****		
	Doing the flu@home **nasal swab test** was:****		
	Entering my information into the flu@home app was: ****		
Impact/ perceived value	I would recommend flu@home to a friend or family member.*		
	My GP was very supportive of me using flu@home.*		
	It saves time to do a home-based test like flu@home before visiting a healthcare provider.*		
	I feel that flu@home could help me better manage my illness.*		
Intention to Act	If flu@home testing indicated you had the flu, which of the following would you consider doing as next steps?		
		I would consider	
		Yes	No
	A virtual consultation with a provider (telemedicine visit)	○	○
	Sharing my results anonymously with a national flu tracking system	○	○

	Reading flu@home tips on how to prevent flu spread	○	○
	Encouraging others in my household to use flu@home for testing	○	○
	I would use the flu@home kit in the future if I have symptoms.*		
	I would do the flu@home test if I could purchase the test kit online to send to my home, rather than see my healthcare provider for diagnosis.*		

* Responses on Likert scale anchored with ‘Strongly Disagree’ and ‘Strongly Agree’
** Responses on Likert scale anchored with ‘Very Poor’ and ‘Excellent’
*** Responses on Likert scale anchored with ‘Never’ and ‘Always’
**** Responses on Likert scale anchored with ‘Very Easy’ and ‘Very Difficult’

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Diagnostic accuracy of an app-guided, self-administered test for influenza among individuals presenting to general practice with influenza-like illness: Study protocol

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Diagnostic accuracy of an app-guided, self-administered test for influenza among individuals presenting to general practice with influenza-like illness: Study protocol

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ABSTRACT

Introduction: Diagnostic tests for influenza in Australia are currently only authorized for use in clinical settings. At-home diagnostic testing for influenza could reduce the need for patient contact with health care services, which potentially could contribute to symptomatic improvement and reduced spread of influenza. We aim to determine the accuracy of an app-guided nasal self-swab combined with a lateral flow immunoassay for influenza conducted by individuals with influenza-like illness (ILI).

Methods and analysis: Adults (>=18 yr) presenting with ILI will be recruited by general practitioners(GP) participating in Australian Sentinel Practices Research Network (ASPREN). Eligible participants will have a nasal swab obtained by their GP for verification of influenza A/B status using RT-PCR at an accredited laboratory. Participants will receive an influenza test kit and will download an app that collects self-reported symptoms and influenza risk factors, then instructs them in obtaining a low-nasal self-swab, running a QuickVue influenza A+B lateral flow immunoassay (Quidel Corporation), and interpreting the results. Participants will also interpret an enhanced image of the test strip in the app. The primary outcome will be the accuracy of participants' test interpretation compared to the laboratory RT-PCR reference standard. Secondary analyses will include accuracy of the enhanced test strip image, accuracy of an automatic test strip reader algorithm, and validation of prediction rules for influenza based on self-reported symptoms. A post-test survey will be used to obtain participant feedback of self-test procedures.

Ethics and dissemination: The study was approved by the Human Research and Ethic Committee (HREC) at the University of Adelaide (H-2019-116). Protocol details and any amendments will be reported to https://www.tga.gov.au/. Results will be published in the peer reviewed literature, and shared with stakeholders in the primary care and diagnostics communities.

Universal Trial Number (UTN): U1111-1237-0688, registered on the Australia New Zealand Clinical Trial Registry: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619001087145

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Accuracy of nasal self-testing for influenza using the QuickVue Influenza A+B assay will be compared to reference standard of nasal or nasopharyngeal swab obtained by a GP and tested using RT-PCR.
- Recruitment will be nested within an ongoing Australian Surveillance Practices Research Network recruiting patients presenting to general practice with influenza-like illness (ILI)

- Patients attending primary care with ILI may differ in terms of disease spectrum compared to individuals with ILI at home, which is the population where the self-test is intended to be used.
- Self-swabbing of the nose and conducting a lateral flow test unsupervised and guided by an app may select individuals with greater smartphone experience, manual dexterity, and/or sociodemographic status.
- Self-report of ILI symptoms using an app may differ from symptoms obtained from GP consultations or from research staff, limiting the ability to validate clinical prediction rules for influenza.

INTRODUCTION

Seasonal influenza occurs annually, causing disease with substantial morbidity and mortality worldwide, especially in the elderly and those with chronic disease.[1] Despite the availability of the influenza vaccine, repeated influenza infections are common throughout life, and result in a considerable healthcare burden. In Australia, it is estimated that each year influenza causes an average 310,000 general practitioner (GP) consultations, 18,000 hospital admissions, and 1,500 to 3000 deaths.[2-4] Influenza places particular burden on primary care services during the winter months, contributing to high consultation rates for acute respiratory tract infections. Detection of influenza is thought to provide value clinically by identifying patients who may be at higher risk of complications, and also to potentially inform use of antivirals and efforts to reduce transmission.[5]

GPs generally diagnose influenza based on a combination of symptoms and risk factors present in each patient, and diagnostic confirmation requires a laboratory test.[5] Multiple tests are available for influenza, including immunoassays and molecular tests with varying levels of sophistication and cost, that can be used in different clinical settings.[6] While some point-of-care tests are approved for, and suitable in primary care settings, others can only be conducted in formal laboratory facilities.

Because there is considerable overlap in symptoms caused by influenza and other respiratory pathogens, many patients who are tested for influenza receive flu-negative results. To reduce the number of unnecessary tests that are requested by GPs, clinical prediction rules have been derived to stratify individuals more accurately than individual symptoms into those with various likelihood of influenza infection.[7] Currently there are no diagnostic tests for influenza that are approved for use by individuals outside of clinical settings in Australia or the United States. The ability to accurately test individuals at home for influenza could provide several potential advantages over current practice. One advantage for patients would be convenience by reducing the need for primary care consultations. Home-testing may also facilitate the earlier use of antivirals when they are most likely to provide beneficial effects on symptom resolution and reduce transmission, and help identify individuals at higher risk of complications compared to those with other causes of influenza-like illness (ILI).[8]

The primary aim of the current study is to determine the accuracy of a self-test for influenza that involves individuals self-swabbing their nose and conducting an immunoassay lateral flow test guided by a mobile app, compared to the gold standard RT-PCR influenza test obtained by their GP. Several studies have already demonstrated the feasibility of collecting patient-reported ILI symptoms.[9-13] This study expands on this field by leveraging smartphone mobile app to instruct participants through conducting a rapid diagnostic test (RDT). We also aimed to explore additional methods for reading the test strip, and validating existing clinical prediction rules for influenza.

METHODS

Study Design

A prospective observational study of the comparative accuracy of a patient-run, mobile app-guided (see Appendix A), lateral flow test for influenza (QuickVue Influenza A + B assay test, from Quidel Corporation) using a low nasal self-swab (referred to in this protocol as 'flu@home'), compared to clinician-collected nasal or nasopharyngeal swab for influenza detected by a commercial RT-PCR. The Universal Trial Number (UTN) is U1111-1237-0688, registered on 6/08/2019. (See Figure 1).

Study population

A systematic sample of adult patients with ILI presenting to general practices participating in the Australia Sentinel Practices Research Network (ASPREN), which is a network of over 350 general providers from over 200 sentinel sites throughout Australia. GPs in the network participate in routine surveillance studies of respiratory infections by the Commonwealth. [14,15] (See Appendix B for ASPREN protocol).

Inclusion and exclusion criteria

Inclusion criteria are: 1) age >= 18 years, 2) presenting to ASPREN clinic sites [16] with fever, cough, and fatigue, 3) agree to have their GP/nurse practitioner obtain a nasal or nasopharyngeal swab for surveillance purposes, and 4) have their own Android or iOS smartphone or tablet. Exclusion criteria will be non-English speakers, people who are incarcerated, people highly dependent on medical care who may be unable to give consent, and people with a cognitive impairment, an intellectual disability or mental illness. We did not exclude people with physical disabilities or impaired vision, but rather left the decision to recruit a patient up to their GP at the time of their visit.

Recruitment

Each clinic will recruit any patient presenting with an ILI who is 18 years and older, has a smartphone and agreeds to participate in the study.

Clinical setting

Study participants will be recruited from practices participating in ASPREN, which is a network of sentinel GPs who report de-identified information on ILI as well as other infectious disease conditions.[16] The de-identified information will include date of symptom onset, influenza vaccination history, comorbidities related to influenza, and whether the patient is a health care worker. Data from ASPREN are used by State and Commonwealth Departments of Health for infectious disease surveillance and vaccine effectiveness estimates.[17] ASPREN data contribute to the Global Influenza Vaccine Effectiveness Movement and the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO-CCRRI).

Outcome measurements

Primary outcome

- Accuracy of detection of influenza A/B infection based on self-reading of the flu@home test compared to laboratory RT-PCR testing.

Secondary outcomes

- Accuracy of detection of influenza A/B infection based on self-reading of an enhanced high contrast image of the flu@home test strip compared to laboratory RT-PCR testing.
- Accuracy of detection of influenza A/B infection based on the app's automatic interpretation algorithm of the flu@home test strip image compared to laboratory PCR testing.
- Accuracy of clinical prediction rules including the Flu Score [7] based on individual and combinations of presenting symptoms obtained from the app and/or the patient's GP compared to laboratory PCR testing.
- Satisfaction and experience of patients interacting with the flu@home app.

Other variables

The app will collect information on demographics (age, sex, race), household composition, influenza vaccination history, risk factors for influenza infection, presence and duration of ILI symptoms (e.g., cough, fever, fatigue, chills or sweats), (see Appendix C). These variables will be used to facilitate interpretation of test results in terms of these various participant characteristics.

Study procedures

Patients who participate in the ASPREN study will be invited to participate in the flu@home self-testing study from July 2019 until all 2300 kits are distributed, no later than December 2020. Each participating GP will be provided with a set number of test kits, based on the numbers of ILI patients encountered in previous flu seasons, and the number of ILI patients swabbed during the current 2019 flu season. Participating GPs will be asked to recruit all patients who meet study eligibility criteria. After completing the standard ASPREN protocol (see Appendix B), a GP will ask the participant if they would like to participate in the flu@home study. Once the participant consents, the GP will hand them the test kit and instructions for downloading the free app, and the patient will be asked to conduct the remainder of the study procedures at home on that day or the following day. A post-test survey will be sent to participants via the app 24-48 after they complete the test procedure.

Influenza testing methods

Home/self-testing

Patients will be provided with a self-test kit by their GP containing a Quidel QuickVue Influenza A+B lateral flow test (rebranded as the flu@home kit for research purposes), and asked to download the free flu@home app [18] to their personal iOS or Android smartphone or tablet. Each test kit includes a unique 8-digit study ID number that will be linked to reference test results, but cannot be used to personally identify participants. The app collects the variables noted above through a questionnaire, and guides the patient through the self-swabbing and testing procedure. They will be instructed to obtain a low nasal swab using a single foam-tipped swab inserted into each nostril, and then perform the steps to conduct the lateral flow test.

Having completed the test steps, the app guides the patient to read their test strip by first asking them whether they see a blue line (control line) and any pink lines (1st interpretation). A pink line above the blue line indicates influenza A, and a pink line below the blue control line indicates influenza B. If the patient indicates they do not see the blue control line, they are informed that they have a defective test strip and interpretation guidance is not provided. For patients who indicate they see a blue control line, the app guides the patient to obtain a photo of their test strip using their smartphone camera. During this process the app provides a guided test strip image capture, including on-screen feedback to the participant to ensure proper alignment, lighting, positioning, scale, and rotation of the test strip prior to taking a photo. Once a photo of the strip is captured, the user is presented with a high-contrast image of their test strip and asked to reinterpret the test results by indicating how many lines they now see on the strip (2nd interpretation). Presenting a high-contrast image to the patient may help them see lines on the test strip that may have previously been too faint to easily identify. Initially, the app uses the patient's direct observation of the strip to inform the patient whether it is likely their test result was positive for influenza. During the study we may adjust this process to inform the patient of their likely test result based on auto-interpretation of the images captured.

While the test strip differentiates between influenza A and B, we will not ask individuals to make this determination. If the guided test strip image capture is not successful, the app requests the patient to manually take a normal photo of their test strip using their smartphone for later analysis. The app uses the patient's observations to inform the patient of their likely test result.

Patients will be given links to publicly-available information on influenza from healthdirect [19] and provided with usual care recommendations in the app depending on their test results (from either the 1st or 2nd interpretation).The app includes a medical disclaimer indicating "The interpretation of your result may differ from a medical test conducted in a clinical lab environment. In no circumstances should the results of this test be relied upon without independent consideration and confirmation by a qualified medical practitioner." [20] Patients will be notified of the results of the reference test by their GP, who will provide standard care based on the RT-PCR results. Study materials will clearly indicate that the flu@home test is an experimental research test, and participants should trust the reference test results provided by their GP. Participants whose flu@home results are discordant with those of their GP will be

asked to contact their GP for any clinical management decisions or changes that their GP would recommend.

Reference testing
Influenza and other respiratory pathogens will be detected using RT-PCR on the swabs obtained by the GP at ASPREN clinical sites. (See Appendix B for list of pathogens tested). Samples will be sent to SA Pathology in Adelaide, South Australia, via Australia Post's Express post system, allowing for next-day delivery from all capital cities.[21] Results of the laboratory PCR test, home self-test kit, and survey data from the app will be linked by the 8-digit number available on the test kit and PCR sample.

Post-test survey
A link to a reflective online survey created in Qualtrics© will be delivered to participants who complete the test procedure. The request to complete the survey will be delivered via participants' smartphone or tablet 24-48 hours after completing their self-test.The survey will solicit responses regarding the respondent's a) health behaviors and attitudes, b) perceptions of their experience and usability of the self-test impact, c) perceived value of self-testing, and d) intention to act on self-test results. Survey items will be close-ended and, generally, call for a response to a five-point Likert scale with anchors ranging from strongly agree to strongly disagree (see Appendix D for follow-up survey items categorized by construct, i.e., focal topic).

Participant discontinuation
Individuals who start the app, provide consent, but fail to complete all steps of the test procedure will be excluded from the primary comparative accuracy analysis. If any participants who were swabbed by their GP as part of ASPREN surveillance test positive for flu, they will be contacted by their general practice clinic to discuss further clinical management; this will not be affected by failure to complete the flu@home procedure.

Data analysis
We will conduct a descriptive analysis of demographics, presenting symptoms, and baseline variables such as household composition, vaccination status, and general health questions. Prevalence of influenza will be obtained from positivity rate of PCR laboratory testing. Sensitivity, specificity, positive and negative predictive values (with 95% confidence intervals) will be calculated for the presence of influenza based on patient interpretation of self-test results compared to the reference standard PCR result. Accuracy will also be calculated for participants' interpretation of the enhanced high-contrast photo of the test strip, as well as the automatic test strip interpretation algorithm, compared to the reference standard PCR result. We will also measure the accuracy of clinical prediction rules based on individual and combinations of ILI symptoms based on Flu Score [7] and other prediction rules, compared to the reference standard PCR result. Subgroup analyses will explore test accuracy based on age, symptom profile, duration of illness, and influenza type (A/B).

We will conduct a descriptive analysis of post-test survey results related to demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived

value of self-testing, and intention to act on self-test results. In addition, we will conduct Multivariate Analysis of Variance (MANOVA) to determine if statistically significant differences exist among various subpopulations (e.g., age group, gender) regarding their responses to survey items related to variables associated with experience and usability of the self-test and impact and perceived value of self-testing. MANOVA analysis permits simultaneous testing of the variables associated with one construct, e.g., experience and usability of the self-test, simultaneously to arrive at a holistic assessment and recognizes the potential correlation related to these variables. Analysis of Variance (ANOVA) will be used to determine if statistically significant differences exist among the responses from various subpopulations (e.g., age group, gender) to survey items related to intention to act on self-test results. We will also use Partial Least Squares Regression (PLS) to construct predictive models to assess relationships among demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived value of self-testing, and intention to act on self-test results.

Sample size calculation

The sample size required for this study was determined based on i) expected completion rate of the home test kit, ii) flu positivity rate, iii) availability of test kit materials, and iv) number of flu-positive test results which are typically provided in FDA submissions for regulatory approval of rapid flu diagnostic tests. To our knowledge, there have been no other comparative accuracy studies of a smartphone-enabled respiratory illness diagnostic test conducted in Australia. Therefore, the expected completion rate of the home testing procedure is based on a USA-based pilot study that found that 60% of individuals completed the flu@home test kit when it was mailed to them. In the current study, we expect a higher completion rate given that participants will be recruited by their GP rather than online. The flu positivity rate among patients presenting with ILI to ASPREN clinics is based on data from previous years, which indicated a 20% positivity rate among recruited adults (of all ages) in the July – December period. Assuming that 60% of the 2300 self-test kits distributed to GPs are completed (1380), we expect 20% (276) to be influenza positive. This absolute number of flu positive specimens exceeds that required by FDA in regulatory submissions to evaluate the accuracy of new tests designed for clinical settings, which is typically 120.[22] There are not currently any recommendations for sample sizes needed for evaluation of the accuracy of home-based tests for influenza.

Indirect Patient and Public involvement

The flu@home app has undergone several iterations of usability and user acceptance testing with a diverse population in the United States. This included usability testing conducted during a pilot phase in the USA using an independent user research firm, which provided input on app usability, time to conduct questionnaire, and the appearance and design of the app. There has not been any prior testing of the app in Australia, however, the research study members from Australia reviewed the app prior to launch to ensure the language in the app was appropriate for the Australian context.

Ethics and dissemination

The study procedures will follow Australian clinical and ethical standards as outlined by the University of Adelaide Human Research Ethics Committee (HREC). All activities will follow the

Code of Good Practice in Clinical Research. Participants will provide informed consent for the flu@home study within the app that is downloaded. The study was approved by the Human Research and Ethics Committee at the University of Adelaide (HREC Number: H-2019-116). The authors will seek approval for any protocol modifications, which will also be reported to the clinical trials registration site. Results of this study will be reported using the STARD guidelines for reporting diagnostic accuracy studies, and published in the peer-reviewed scientific literature.[23]

Confidentiality and data management

All study data collected are non-identifiable. No participant names, addresses, or private information are collected for the purposes of the study. Samples from the ASPREN survey and app data are linked via a unique barcode. The researchers cannot link the barcode to identifiable patient details such as name, address, or other private information. ASPREN surveillance data will be stored on University of Adelaide computers, which can only be accessed by authorized representatives. All data will be non-identifiable. All data collected by the flu@home app will be protected with industry-standard encryption on systems hosted through Amazon Web Services and the Google Cloud Platform, which are only accessible by authorized representatives of the app development organization, Audere. Audere is a non-profit application development organization that runs the flu@home application. During data analysis non-identifiable data will be transferred to a University of Washington approved data storage location, which is only accessible to authorized parties, and the University of Adelaide drives for analysis. Further information about confidentiality and data management in the mobile app can be found in Appendix A.

DISCUSSION

Influenza is a common infection that occurs annually in the southern and northern hemispheres. Consultations for respiratory tract illnesses are one of the most common reasons for presentation in primary care settings in Australia and most other high- and middle-income countries.(2) In Australia influenza season occurs between the months of May to October.[24] Differentiating etiology of respiratory tract infection based on symptoms alone is limited, and current confirmatory diagnosis of respiratory pathogens involves laboratory testing.[22] Diagnostic tests for influenza are commonly used in laboratory settings, and in many countries are used in primary care or pharmacy settings.[25–27] Regulatory approval varies between countries, but typically tests approved for primary care involve simple point of care assays that do not require laboratory technician expertise.

We will use an existing rapid diagnostic test for influenza A and B that has been been approved in the United States for use in primary care clinics since 2004 (QuickVue Influenza A + B assay test, from Quidel Corporation)[28]. This test has adequate performance as demonstrated by regulatory approval in the US, with a 2017-18 clinical study comparing this test to an FDA cleared A+B molecular test, showing sensitivity of 94% for Type A and 70% for Type B, and specificity of 90% for Type A and 97% for Type B[29,30]. However, we note that additional evaluations of this test (and similar lateral flow tests) for influenza show lower test accuracy in further clinical evaluations. A a 2017 meta-analysis of 162 studies of rapid tests for infuenza

found noted that the pooled sensitivity of stuch tests favored industry-sponsored studies by 6.2 to 34.0%. [31]

The potential for individuals to test themselves for influenza follows a pathway for home-based testing that has revolutionized pregnancy testing with commonly available lateral flow assays, glucose testing using home-based monitors, as well as electronic devices for measuring blood pressure. While there is strong evidence that individuals are able to obtain swabs themselves from the nose or throat [32–34], there is no evidence currently for the accuracy of individuals performing a diagnostic test on self-obtained samples for influenza.

The potential value of a self-test for influenza could lead to changes in practice and behavior, assuming the test has sufficient accuracy. For individuals in the community, this could lead to faster diagnosis, improved access to diagnostic testing, improved diagnostic certainty, and reduced need to contact health care services. For primary health care services, it could reduce the burden of consultations for ILI and facilitate more rapid or targeted use of antivirals if these can be prescribed remotely (by telephone, or telemedicine consultations). In terms of public health, self-testing could also influence infection control and transmission reduction strategies at the community level. Combining a diagnostic test with a smartphone where the user's steps are process-controlled (e.g. embedded timers ensure the patient adheres to the test procedure) may both facilitate support for the user, and potentially allow enhanced interpretation of test results using the existing camera and software found in current devices. A downside to home/self-based testing for influenza is that easier access to testing could lead to the diagnosis of mild cases of influenza where antiviral treatment is not indicated. Increased access to self-testing include has financial implications including added costs to individuals who might have to purchase the tests, and to the healthcare system that might need to interpret, repeat or act on test results. Inaccurate tests could further cause harm through false negative and/or false positive results.

LIMITATIONS OF STUDY

The study has several potential limitations. First, recruitment of participants will not be entirely consecutive, although this follows the procedures that the participating clinics use for ongoing surveillance activities. Limiting this study to general practices means that some patients with ILI are excluded, such as those attending hospitals and emergency departments, receiving medical care from locum doctors or not seeking any medical treatment for ILI. Second, the spectrum of individuals presenting with ILI to GPs may be different to that expected in the community, with higher influenza prevalence, more severe symptoms, and/or longer time since onset of infection. The time point at which individuals present to their GP with influenza may have a critical impact on test sensitivity, as there is strong evidence that the sensitivity of rapid antigen influenza tests declines markedly beyond the initial 48-72 hours of illness.[35,36] Third, the performance of the nasal swab, and conduct of the lateral flow test is unsupervised, and therefore we will not be able to determine the impact of these factors on test accuracy. There is robust evidence that individuals are able to collect mid turbinate and low nasal swabs with similar performance to health care professionals for influenza, but we will not be able to further verify this in the current study. [37] Fourth, conduct of the test may vary with participant characteristics, such as age or

limitations in ability to handle smartphones, and their ability to visualize lines on the test strip. We will explore these using subgroup analyses (based on age), and user feedback from follow up surveys. Fifth, differences in interpretation of the enhanced image may depend on the technical capabilities of individuals' smartphones. Sixth, we are aware that the flu@home app has not been validated in this population and setting, and may need additional validation before being implementedor being used with a commercial device. Finally, while we do ask study participants about multiple aspects of their experience with the home-based influenza test, we will not ask specifically about their feelings regarding testing positive for influenza using a home-based test. Understanding the emotional impact of receiving a positive result using a self-test is out of scope for this study. Additionally, we will not be able to evaluate comparative costs of the flu@home test compared to usual care within this study.

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Figure Legend

Figure 1. flu@home Australia study procedure

Contributorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Additionally, each author certifies that this material or similar material has not been and will not be submitted to publication before its appearance in BMJ Open.

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Competing Interests

The authors do not have any competing interests.

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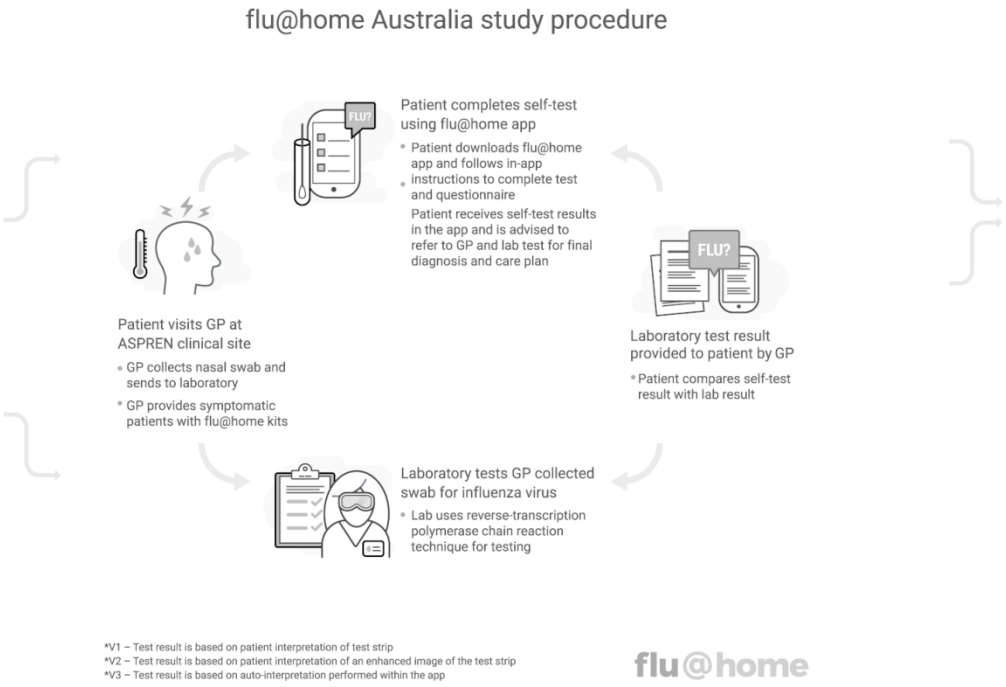

flu@home Australia study procedure

121x81mm (300 x 300 DPI)

APPENDIX

Appendix A: App design and operation

The flu@home app can be used on an iPhone, iPad, Android smartphone, or Android tablet. The app is available in English for the study. However, the app supports development and release of other languages as needed. The entire app experience uses a touch-sensitive dynamic interface on the device. The app ensures the proper test procedure is followed through clear instructions and timers that prevent the participant from moving forward in the test process (e.g., when the test strip must remain in the test fluid for ten minutes to be certain the strip has enough time to process before reading the result). The app attempts to keep participants engaged during wait times by providing flu-related informational facts (during an initial one-minute timer when the nasal swab is processing in the RDT vial) and asking the participant to answer a set of demographic and illness-related survey questions (during the ten-minute timer). Field-level validation is employed to ensure participants answer specific required questions in the survey.

The app was built using React Native, a JavaScript framework used to create mobile applications for iOS and Android. The app communicates with the Google Cloud Platform (Firebase) to queue survey data and Firebase storage to queue images captured from the RDT flow. These are pulled by a NodeJS service into a PostgreSQL database hosted on an AWS Relational Database Service (RDS), which allows for operation and scale of a relational database in the cloud.

The flu@home Australia app is available for personal devices which are expected to be under control of an individual who uses a passcode to access the device. All supported devices use encryption to protect app data resident on the device. This encryption is afforded by the device itself, not a specific application. In the event that a device is stolen, the device's onboard locking feature is the front-line defense against access to data on the device. The flu@home application does not collect the user's name, email, or other key identifiable information in the app. It focuses on data collection of symptoms, disease presentation, and demographics. The level of data protection offered by the flu@home app is the same level of protection afforded to most other health applications, email, messaging, etc. available on a mobile device.

App data is stored in Amazon Web Services (AWS S3 and AWS RDS). Amazon Simple Store Service (S3) provides a straightforward web services interface that is used to store and retrieve data, such as PCR data from the swab taken as part of the ASPREN study and used for comparison to the RDT test results. Access to S3 requires user authentication. From the time data leaves the client, all data is encrypted both at rest and over communication links. We use AWS Key Management Service (KMS) to encrypt data at rest in AWS, and Google Cloud Platform automatically encrypts its data using Advanced Encryption Standard (AES). All connections to the app occur over Secure Sockets Layer (SSL), a standard security technology that establishes an encrypted link between a web server and browser, ensuring all data traversing the web server and browser remains private.

For near real-time reporting, Metabase is run in an Elastic Container Service (ECS) in the same AWS project referencing the same app data.

The app uses Firebase caching and analytics to track each participant page view, including a timestamp for each page view. Firebase is also used to track changed answers if a participant navigates back in the app flow.

Appendix B: Australia Sentinel Practices Research Network (ASPREN) Protocol

The protocol for ASPREN clinical sites requires GPs to sample the first three ILI patients each week during flu season (May – October 2019 inclusive), and the first ILI patient of the week from November 2019– April 2020 inclusive. For the flu@home study, GPs will be allowed to recruit all adult patients presenting to the clinic with ILI symptoms, in order to meet recruitment goals. Participating clinical sites will obtain a nasal or nasopharyngeal swab which will be transported to SA Pathology, Adelaide, South Australia for testing using RT-PCR for influenza A, influenza B, as well as RSV, enterovirus, adenovirus, mycopneumoniae, human metapneumovirus, parainfluenza 1, 2, 3 and pertussis. Samples positive for influenza A will be further subtyped. All original clinical samples testing positive for influenza will be referred to the WHO-CCRRI (Melbourne, Australia) for antigenic and phylogenetic characterization. For clinical sites in tropical regions, due to the decreased seasonality of influenza, the systematic sample involves the first three ILI patients of each week, all year round. In addition to this, in all sites all ILI patients ages 65 years and over are tested all year round.

Appendix C: Flu@home Participant Questionnaire

Symptom Survey
*Questions marked with an * are required.*

Symptom	*Which of the following were present during your illness?	*How long ago did symptoms start? (Select the time frame that best applies)	*Were these symptoms present in the last 48 hours?	*How severe were your symptoms? (Select the level of discomfort you felt at the worst point)
Fever	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Cough	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Feeling more tired than usual	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Chills or sweats	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Sore throat	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Headache	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Muscle or body aches	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Runny or stuffy nose	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Shortness of breath	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Vomiting	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe

General exposure
In the next section, the questions are going to be about being **in contact** with people who seemed to have a cold or the flu. **In contact** means being within two meters of them for at least two minutes or physical contact for any amount of time.

For reference, two meters is about the distance between you and someone sitting two rows ahead of you on the bus.

In the past week, have you been in contact with a person who seemed to have a cold or flu?

- Yes
- No
- Don't know

[If YES] Were they coughing or sneezing?

- Yes
- No
- Don't know

In the past week, have you been in contact with any children under five years old for over an hour?

- No contact with children under 5 yrs
- 1 child
- 2-5 children
- More than 5 children
- Don't know

Are there any children under 18 years old in your household?

- Yes
- No
- Don't know

[If YES] Do any children in your household attend a school, childcare setting, or play group with at least three other children for a total of three or more hours per week?

- Yes
- No
- Don't know

How many people live in your household (including you)?

- 1-2
- 3-4
- 5-7
- 8+

How many bedrooms are in your home?

- 0-1
- 2
- 3
- 4
- 5+

Influenza vaccination

We would like to ask you some questions about your influenza vaccination history. This information will be used to determine how effective the vaccine is.

Did you receive an influenza vaccination this year (2019*)?

- Yes
- No
- Do not know
- I've never received an influenza vaccination.

[If YES] what was the approximate date of your influenza vaccination?

- Choose month and year starting from January 2019* up to the current month

[If YES] Did you receive a free influenza vaccination under the National Immunisation Program in 2019*?

- Yes
- No
- Do not know

[If YES] What medical condition(s) do you have that made you eligible for a free influenza vaccination?

- Free text field

[If Answer to above is something other than: "I've never received an influenza vaccination"] Did you receive an influenza vaccination last year (2018*)?

- Yes
- No
- Do not know

General health

Next we'd like to ask you some questions about your overall health:

Have you ever been told by a doctor that you have one of the following medical conditions? (SELECT ALL THAT APPLY)

- Asthma
- COPD/emphysema
- Diabetes
- Heart disease
- None of these
- Do not know

Are you a healthcare (or aged care) worker (i.e. do you directly work with patients/aged care residents in your job)?

- Yes
- No
- Do not know

Do you smoke tobacco?

- Yes
- No

Does anyone in your household smoke tobacco?

- Yes
- No

Is your illness preventing you from going to work or school, going to social events, or exercising/working out?

- Yes
- No

Are you currently taking antibiotics (e.g. Amoxil, penicillin, azithromycin, co-trimoxazole (Bactrim), co-amoxiclav (Augmentin)) or antivirals (e.g. Tamiflu, Xofluza, Relenza) prescribed by a doctor (GP or hospital) for this illness?

- Yes
- No
- Do not know

How old are you?

- 18 to 19
- 20 to 24
- 25 to 29
- 30 to 34
- 35 to 39
- 40 to 44
- 45 to 49
- 50 to 54
- 55 to 59
- 60 to 64
- 65 to 69
- 70 to 74
- 75 to 79
- 80 to 84
- 85 to 89
- 90 and older

What is the sex on your medical records?

- Male
- Female
- Indeterminate/Other
- Prefer not to say

How would you describe your race? Please select all that apply.

- Aboriginal
- Torres Strait Islander
- Pacific Islander
- North or East Asian
- African
- European
- White Australian

- South or Central American
- Middle East/North African
- Indian subcontinent
- Other

[The next question is asked after the flu rapid test is complete]

Nice job! Do you feel you performed all of the steps in the flu test correctly? Select the most applicable option

- It was easy to follow and I think I completed the test correctly
- It was a little confusing but I think I did the test correctly
- It was very confusing and I'm not sure I completed the test correctly
- During the test, I realized I did something incorrectly

** All questions with an asterisk listed by the year will be updated in the mobile app in January 2020 (i.e. questions referring to "this year" will list 2020 instead of 2019.)*

Appendix D: Follow-Up Survey Variables

Category	Questions asked
Health behaviors and attitudes	I believe taking an active role in my own care is the most important factor in determining my health.*
	I am confident that I can identify when it is necessary to get medical care versus when I can handle the problem myself.*
	I often think carefully about whether health information makes sense in my particular situation.*
	I acknowledge that I have a key role in the day-to-day management of my health.*
	I often need someone to help me when I receive written information from my GP, nurse or pharmacist.*
	In general, I believe the state of my health is:**
	I am confident that I can tell my GP concerns I have even when he/she does not ask about them.*
	I like to find out a lot of information about health online.*
	I am confident that I can follow through on medical treatments I need to do at home.*
	I value my health more than anything else.*
	My health needs are always met from available healthcare resources.*
	As well as seeing my GP, I regularly monitor (check for) changes in my health.*
	I do what is necessary to keep myself healthy.*
	My GP and I work together to make decisions about what's best for my health.***
Experience/	The purpose of using flu@home was to: Yes No

usability	Test for flu	○	○
	Give me information about flu and medicine	○	○
	Test different flu medicines	○	○
	Participate in a research study about the flu	○	○
	I am satisfied with how easy it was to use flu@home (nasal swab test and app).*		
	I had the skills needed to perform swab testing using flu@home.*		
	I was able to understand the results from the flu@home app.*		
	The instructions for using flu@home were helpful in providing me with what I needed to perform the test.*		
	Using flu@home **app** was:****		
	Doing the flu@home **nasal swab test** was:****		
	Entering my information into the flu@home app was: ****		
Impact/ perceived value	I would recommend flu@home to a friend or family member.*		
	My GP was very supportive of me using flu@home.*		
	It saves time to do a home-based test like flu@home before visiting a healthcare provider.*		
	I feel that flu@home could help me better manage my illness.*		
Intention to Act	If flu@home testing indicated you had the flu, which of the following would you consider doing as next steps?		
		I would consider	
		Yes	No
	A virtual consultation with a provider (telemedicine visit)	○	○
	Sharing my results anonymously with a national flu tracking system	○	○

	Reading flu@home tips on how to prevent flu spread	○	○
	Encouraging others in my household to use flu@home for testing	○	○
	I would use the flu@home kit in the future if I have symptoms.*		
	I would do the flu@home test if I could purchase the test kit online to send to my home, rather than see my healthcare provider for diagnosis.*		

* Responses on Likert scale anchored with ‘Strongly Disagree’ and ‘Strongly Agree’
** Responses on Likert scale anchored with ‘Very Poor’ and ‘Excellent’
*** Responses on Likert scale anchored with ‘Never’ and ‘Always’
**** Responses on Likert scale anchored with ‘Very Easy’ and ‘Very Difficult’

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Diagnostic accuracy of an app-guided, self-administered test for influenza among individuals presenting to general practice with influenza-like illness: Study protocol

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Diagnostic accuracy of an app-guided, self-administered test for influenza among individuals presenting to general practice with influenza-like illness: Study protocol

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ABSTRACT

Introduction: Diagnostic tests for influenza in Australia are currently only authorized for use in clinical settings. At-home diagnostic testing for influenza could reduce the need for patient contact with health care services, which potentially could contribute to symptomatic improvement and reduced spread of influenza. We aim to determine the accuracy of an app-guided nasal self-swab combined with a lateral flow immunoassay for influenza conducted by individuals with influenza-like illness (ILI).

Methods and analysis: Adults (>=18 yr) presenting with ILI will be recruited by general practitioners(GP) participating in Australian Sentinel Practices Research Network (ASPREN). Eligible participants will have a nasal swab obtained by their GP for verification of influenza A/B status using RT-PCR at an accredited laboratory. Participants will receive an influenza test kit and will download an app that collects self-reported symptoms and influenza risk factors, then instructs them in obtaining a low-nasal self-swab, running a QuickVue influenza A+B lateral flow immunoassay (Quidel Corporation), and interpreting the results. Participants will also interpret an enhanced image of the test strip in the app. The primary outcome will be the accuracy of participants' test interpretation compared to the laboratory RT-PCR reference standard. Secondary analyses will include accuracy of the enhanced test strip image, accuracy of an automatic test strip reader algorithm, and validation of prediction rules for influenza based on self-reported symptoms. A post-test survey will be used to obtain participant feedback of self-test procedures.

Ethics and dissemination: The study was approved by the Human Research and Ethic Committee (HREC) at the University of Adelaide (H-2019-116). Protocol details and any amendments will be reported to https://www.tga.gov.au/. Results will be published in the peer reviewed literature, and shared with stakeholders in the primary care and diagnostics communities.

Universal Trial Number (UTN): U1111-1237-0688, registered on the Australia New Zealand Clinical Trial Registry: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619001087145

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Accuracy of nasal self-testing for influenza using the QuickVue Influenza A+B assay will be compared to reference standard of nasal or nasopharyngeal swab obtained by a GP and tested using RT-PCR.
- Recruitment will be nested within an ongoing Australian Surveillance Practices Research Network recruiting patients presenting to general practice with influenza-like illness (ILI)

- Patients attending primary care with ILI may differ in terms of disease spectrum compared to individuals with ILI at home, which is the population where the self-test is intended to be used.
- Self-swabbing of the nose and conducting a lateral flow test unsupervised and guided by an app may select individuals with greater smartphone experience, manual dexterity, and/or sociodemographic status.
- Self-report of ILI symptoms using an app may differ from symptoms obtained from GP consultations or from research staff, limiting the ability to validate clinical prediction rules for influenza.
- The mobile app was validated in the United States, but was not adapted or validated for the Australian context.

INTRODUCTION

Seasonal influenza occurs annually, causing disease with substantial morbidity and mortality worldwide, especially in the elderly and those with chronic disease.[1] Despite the availability of the influenza vaccine, repeated influenza infections are common throughout life, and result in a considerable healthcare burden. In Australia, it is estimated that each year influenza causes an average 310,000 general practitioner (GP) consultations, 18,000 hospital admissions, and 1,500 to 3000 deaths.[2-4] Influenza places particular burden on primary care services during the winter months, contributing to high consultation rates for acute respiratory tract infections. Detection of influenza is thought to provide value clinically by identifying patients who may be at higher risk of complications, and also to potentially inform use of antivirals and efforts to reduce transmission.[5]

GPs generally diagnose influenza based on a combination of symptoms and risk factors present in each patient, and diagnostic confirmation requires a laboratory test.[5] Multiple tests are available for influenza, including immunoassays and molecular tests with varying levels of sophistication and cost, that can be used in different clinical settings.[6] While some point-of-care tests are approved for, and suitable in primary care settings, others can only be conducted in formal laboratory facilities.

Because there is considerable overlap in symptoms caused by influenza and other respiratory pathogens, many patients who are tested for influenza receive flu-negative results. To reduce the number of unnecessary tests that are requested by GPs, clinical prediction rules have been derived to stratify individuals more accurately than individual symptoms into those with various likelihood of influenza infection.[7] Currently there are no diagnostic tests for influenza that are approved for use by individuals outside of clinical settings in Australia or the United States. The ability to accurately test individuals at home for influenza could provide several potential advantages over current practice. One advantage for patients would be convenience by reducing the need for primary care consultations. Home-testing may also facilitate the earlier use of antivirals when they are most likely to provide beneficial effects on symptom resolution and reduce transmission, and help identify individuals at higher risk of complications compared to those with other causes of influenza-like illness (ILI).[8]

The primary aim of the current study is to determine the accuracy of a self-test for influenza that involves individuals self-swabbing their nose and conducting an immunoassay lateral flow test guided by a mobile app, compared to the gold standard RT-PCR influenza test obtained by their GP. Several studies have already demonstrated the feasibility of collecting patient-reported ILI symptoms.[9-13] This study expands on this field by leveraging smartphone mobile app to instruct participants through conducting a rapid diagnostic test (RDT). We also aimed to explore additional methods for reading the test strip, and validating existing clinical prediction rules for influenza.

METHODS

Study Design

A prospective observational study of the comparative accuracy of a patient-run, mobile app-guided (see Appendix A), lateral flow test for influenza (QuickVue Influenza A + B assay test, from Quidel Corporation) using a low nasal self-swab (referred to in this protocol as 'flu@home'), compared to clinician-collected nasal or nasopharyngeal swab for influenza detected by a commercial RT-PCR. The Universal Trial Number (UTN) is U1111-1237-0688, registered on 6/08/2019. (See Figure 1).

Study population

A systematic sample of adult patients with ILI presenting to general practices participating in the Australia Sentinel Practices Research Network (ASPREN), which is a network of over 350 general providers from over 200 sentinel sites throughout Australia. GPs in the network participate in routine surveillance studies of respiratory infections by the Commonwealth. [14,15] (See Appendix B for ASPREN protocol).

Inclusion and exclusion criteria

Inclusion criteria are: 1) age >= 18 years, 2) presenting to ASPREN clinic sites [16] with fever, cough, and fatigue, 3) agree to have their GP/nurse practitioner obtain a nasal or nasopharyngeal swab for surveillance purposes, and 4) have their own Android or iOS smartphone or tablet. Exclusion criteria will be non-English speakers, people who are incarcerated, people highly dependent on medical care who may be unable to give consent, and people with a cognitive impairment, an intellectual disability or mental illness. We did not exclude people with physical disabilities or impaired vision, but rather left the decision to recruit a patient up to their GP at the time of their visit.

Recruitment

Each clinic will recruit any patient presenting with an ILI who is 18 years and older, has a smartphone and agreeds to participate in the study.

Clinical setting

Study participants will be recruited from practices participating in ASPREN, which is a network of sentinel GPs who report de-identified information on ILI as well as other infectious disease conditions.[16] The de-identified information will include date of symptom onset, influenza vaccination history, comorbidities related to influenza, and whether the patient is a health care worker. Data from ASPREN are used by State and Commonwealth Departments of Health for infectious disease surveillance and vaccine effectiveness estimates.[17] ASPREN data contribute to the Global Influenza Vaccine Effectiveness Movement and the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO-CCRRI).

Outcome measurements

Primary outcome

- Accuracy of detection of influenza A/B infection based on self-reading of the flu@home test compared to laboratory RT-PCR testing.

Secondary outcomes

- Accuracy of detection of influenza A/B infection based on self-reading of an enhanced high contrast image of the flu@home test strip compared to laboratory RT-PCR testing.
- Accuracy of detection of influenza A/B infection based on the app's automatic interpretation algorithm of the flu@home test strip image compared to laboratory PCR testing.
- Accuracy of clinical prediction rules including the Flu Score [7] based on individual and combinations of presenting symptoms obtained from the app and/or the patient's GP compared to laboratory PCR testing.
- Satisfaction and experience of patients interacting with the flu@home app.

Other variables

The app will collect information on demographics (age, sex, race), household composition, influenza vaccination history, risk factors for influenza infection, presence and duration of ILI symptoms (e.g., cough, fever, fatigue, chills or sweats), (see Appendix C). These variables will be used to facilitate interpretation of test results in terms of these various participant characteristics.

Study procedures

Patients who participate in the ASPREN study will be invited to participate in the flu@home self-testing study from July 2019 until all 2300 kits are distributed, no later than December 2020. Each participating GP will be provided with a set number of test kits, based on the numbers of ILI patients encountered in previous flu seasons, and the number of ILI patients swabbed during the current 2019 flu season. Participating GPs will be asked to recruit all patients who meet study eligibility criteria. After completing the standard ASPREN protocol (see Appendix B), a GP will ask the participant if they would like to participate in the flu@home study. Once the participant consents, the GP will hand them the test kit and instructions for downloading the free app, and the patient will be asked to conduct the remainder of the study procedures at home on that day or the following day. A post-test survey will be sent to participants via the app 24-48 after they complete the test procedure.

Influenza testing methods

Home/self-testing

Patients will be provided with a self-test kit by their GP containing a Quidel QuickVue Influenza A+B lateral flow test (rebranded as the flu@home kit for research purposes), and asked to download the free flu@home app [18] to their personal iOS or Android smartphone or tablet. Each test kit includes a unique 8-digit study ID number that will be linked to reference test results, but cannot be used to personally identify participants. The app collects the variables noted above through a questionnaire, and guides the patient through the self-swabbing and testing procedure. They will be instructed to obtain a low nasal swab using a single foam-tipped swab inserted into each nostril, and then perform the steps to conduct the lateral flow test.

Having completed the test steps, the app guides the patient to read their test strip by first asking them whether they see a blue line (control line) and any pink lines (1st interpretation). A pink line above the blue line indicates influenza A, and a pink line below the blue control line indicates influenza B. If the patient indicates they do not see the blue control line, they are informed that they have a defective test strip and interpretation guidance is not provided. For patients who indicate they see a blue control line, the app guides the patient to obtain a photo of their test strip using their smartphone camera. During this process the app provides a guided test strip image capture, including on-screen feedback to the participant to ensure proper alignment, lighting, positioning, scale, and rotation of the test strip prior to taking a photo. Once a photo of the strip is captured, the user is presented with a high-contrast image of their test strip and asked to reinterpret the test results by indicating how many lines they now see on the strip (2nd interpretation). Presenting a high-contrast image to the patient may help them see lines on the test strip that may have previously been too faint to easily identify. Initially, the app uses the patient's direct observation of the strip to inform the patient whether it is likely their test result was positive for influenza. During the study we may adjust this process to inform the patient of their likely test result based on auto-interpretation of the images captured.

While the test strip differentiates between influenza A and B, we will not ask individuals to make this determination. If the guided test strip image capture is not successful, the app requests the patient to manually take a normal photo of their test strip using their smartphone for later analysis. The app uses the patient's observations to inform the patient of their likely test result.

Patients will be given links to publicly-available information on influenza from healthdirect [19] and provided with usual care recommendations in the app depending on their test results (from either the 1st or 2nd interpretation).The app includes a medical disclaimer indicating "The interpretation of your result may differ from a medical test conducted in a clinical lab environment. In no circumstances should the results of this test be relied upon without independent consideration and confirmation by a qualified medical practitioner." [20] Patients will be notified of the results of the reference test by their GP, who will provide standard care based on the RT-PCR results. Study materials will clearly indicate that the flu@home test is an experimental research test, and participants should trust the reference test results provided by their GP. Participants whose flu@home results are discordant with those of their GP will be

asked to contact their GP for any clinical management decisions or changes that their GP would recommend.

Reference testing
Influenza and other respiratory pathogens will be detected using RT-PCR on the swabs obtained by the GP at ASPREN clinical sites. (See Appendix B for list of pathogens tested). Samples will be sent to SA Pathology in Adelaide, South Australia, via Australia Post's Express post system, allowing for next-day delivery from all capital cities.[21] Results of the laboratory PCR test, home self-test kit, and survey data from the app will be linked by the 8-digit number available on the test kit and PCR sample.

Post-test survey
A link to a reflective online survey created in Qualtrics© will be delivered to participants who complete the test procedure. The request to complete the survey will be delivered via participants' smartphone or tablet 24-48 hours after completing their self-test.The survey will solicit responses regarding the respondent's a) health behaviors and attitudes, b) perceptions of their experience and usability of the self-test impact, c) perceived value of self-testing, and d) intention to act on self-test results. Survey items will be close-ended and, generally, call for a response to a five-point Likert scale with anchors ranging from strongly agree to strongly disagree (see Appendix D for follow-up survey items categorized by construct, i.e., focal topic).

Participant discontinuation
Individuals who start the app, provide consent, but fail to complete all steps of the test procedure will be excluded from the primary comparative accuracy analysis. If any participants who were swabbed by their GP as part of ASPREN surveillance test positive for flu, they will be contacted by their general practice clinic to discuss further clinical management; this will not be affected by failure to complete the flu@home procedure.

Data analysis
We will conduct a descriptive analysis of demographics, presenting symptoms, and baseline variables such as household composition, vaccination status, and general health questions. Prevalence of influenza will be obtained from positivity rate of PCR laboratory testing. Sensitivity, specificity, positive and negative predictive values (with 95% confidence intervals) will be calculated for the presence of influenza based on patient interpretation of self-test results compared to the reference standard PCR result. Accuracy will also be calculated for participants' interpretation of the enhanced high-contrast photo of the test strip, as well as the automatic test strip interpretation algorithm, compared to the reference standard PCR result. We will also measure the accuracy of clinical prediction rules based on individual and combinations of ILI symptoms based on Flu Score [7] and other prediction rules, compared to the reference standard PCR result. Subgroup analyses will explore test accuracy based on age, symptom profile, duration of illness, and influenza type (A/B).

We will conduct a descriptive analysis of post-test survey results related to demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived

value of self-testing, and intention to act on self-test results. In addition, we will conduct Multivariate Analysis of Variance (MANOVA) to determine if statistically significant differences exist among various subpopulations (e.g., age group, gender) regarding their responses to survey items related to variables associated with experience and usability of the self-test and impact and perceived value of self-testing. MANOVA analysis permits simultaneous testing of the variables associated with one construct, e.g., experience and usability of the self-test, simultaneously to arrive at a holistic assessment and recognizes the potential correlation related to these variables. Analysis of Variance (ANOVA) will be used to determine if statistically significant differences exist among the responses from various subpopulations (e.g., age group, gender) to survey items related to intention to act on self-test results. We will also use Partial Least Squares Regression (PLS) to construct predictive models to assess relationships among demographics, health behaviors and attitudes, experience and usability of the self-test, impact and perceived value of self-testing, and intention to act on self-test results.

Sample size calculation

The sample size required for this study was determined based on i) expected completion rate of the home test kit, ii) flu positivity rate, iii) availability of test kit materials, and iv) number of flu-positive test results which are typically provided in FDA submissions for regulatory approval of rapid flu diagnostic tests. To our knowledge, there have been no other comparative accuracy studies of a smartphone-enabled respiratory illness diagnostic test conducted in Australia. Therefore, the expected completion rate of the home testing procedure is based on a USA-based pilot study that found that 60% of individuals completed the flu@home test kit when it was mailed to them. In the current study, we expect a higher completion rate given that participants will be recruited by their GP rather than online. The flu positivity rate among patients presenting with ILI to ASPREN clinics is based on data from previous years, which indicated a 20% positivity rate among recruited adults (of all ages) in the July – December period. Assuming that 60% of the 2300 self-test kits distributed to GPs are completed (1380), we expect 20% (276) to be influenza positive. This absolute number of flu positive specimens exceeds that required by FDA in regulatory submissions to evaluate the accuracy of new tests designed for clinical settings, which is typically 120.[22] There are not currently any recommendations for sample sizes needed for evaluation of the accuracy of home-based tests for influenza.

Patient and Public involvement

The flu@home app has undergone several iterations of usability and user acceptance testing with a diverse population in the United States. This included usability testing conducted during a pilot phase in the USA using an independent user research firm, which provided input on app usability, time to conduct questionnaire, and the appearance and design of the app. There has not been any prior testing of the app in Australia, however, the research study members from Australia reviewed the app prior to launch to ensure the language in the app was appropriate for the Australian context.

Ethics and dissemination

The study procedures will follow Australian clinical and ethical standards as outlined by the University of Adelaide Human Research Ethics Committee (HREC). All activities will follow the

Code of Good Practice in Clinical Research. Participants will provide informed consent for the flu@home study within the app that is downloaded. The study was approved by the Human Research and Ethics Committee at the University of Adelaide (HREC Number: H-2019-116). The authors will seek approval for any protocol modifications, which will also be reported to the clinical trials registration site. Results of this study will be reported using the STARD guidelines for reporting diagnostic accuracy studies, and published in the peer-reviewed scientific literature.[23]

Confidentiality and data management

All study data collected are non-identifiable. No participant names, addresses, or private information are collected for the purposes of the study. Samples from the ASPREN survey and app data are linked via a unique barcode. The researchers cannot link the barcode to identifiable patient details such as name, address, or other private information. ASPREN surveillance data will be stored on University of Adelaide computers, which can only be accessed by authorized representatives. All data will be non-identifiable. All data collected by the flu@home app will be protected with industry-standard encryption on systems hosted through Amazon Web Services and the Google Cloud Platform, which are only accessible by authorized representatives of the app development organization, Audere. Audere is a non-profit application development organization that runs the flu@home application. During data analysis non-identifiable data will be transferred to a University of Washington approved data storage location, which is only accessible to authorized parties, and the University of Adelaide drives for analysis. Further information about confidentiality and data management in the mobile app can be found in Appendix A.

DISCUSSION

Influenza is a common infection that occurs annually in the southern and northern hemispheres. Consultations for respiratory tract illnesses are one of the most common reasons for presentation in primary care settings in Australia and most other high- and middle-income countries.(2) In Australia influenza season occurs between the months of May to October.[24] Differentiating etiology of respiratory tract infection based on symptoms alone is limited, and current confirmatory diagnosis of respiratory pathogens involves laboratory testing.[22] Diagnostic tests for influenza are commonly used in laboratory settings, and in many countries are used in primary care or pharmacy settings.[25–27] Regulatory approval varies between countries, but typically tests approved for primary care involve simple point of care assays that do not require laboratory technician expertise.

We will use an existing rapid diagnostic test for influenza A and B that has been been approved in the United States for use in primary care clinics since 2004 (QuickVue Influenza A + B assay test, from Quidel Corporation)[28]. This test has adequate performance as demonstrated by regulatory approval in the US, with a 2017-18 clinical study comparing this test to an FDA cleared A+B molecular test, showing sensitivity of 94% for Type A and 70% for Type B, and specificity of 90% for Type A and 97% for Type B[29,30]. However, we note that additional evaluations of this test (and similar lateral flow tests) for influenza show lower test accuracy in further clinical evaluations. A a 2017 meta-analysis of 162 studies of rapid tests for infuenza

found noted that the pooled sensitivity of stuch tests favored industry-sponsored studies by 6.2 to 34.0%. [31]

The potential for individuals to test themselves for influenza follows a pathway for home-based testing that has revolutionized pregnancy testing with commonly available lateral flow assays, glucose testing using home-based monitors, as well as electronic devices for measuring blood pressure. While there is strong evidence that individuals are able to obtain swabs themselves from the nose or throat [32–34], there is no evidence currently for the accuracy of individuals performing a diagnostic test on self-obtained samples for influenza.

The potential value of a self-test for influenza could lead to changes in practice and behavior, assuming the test has sufficient accuracy. For individuals in the community, this could lead to faster diagnosis, improved access to diagnostic testing, improved diagnostic certainty, and reduced need to contact health care services. For primary health care services, it could reduce the burden of consultations for ILI and facilitate more rapid or targeted use of antivirals if these can be prescribed remotely (by telephone, or telemedicine consultations). In terms of public health, self-testing could also influence infection control and transmission reduction strategies at the community level. Combining a diagnostic test with a smartphone where the user's steps are process-controlled (e.g. embedded timers ensure the patient adheres to the test procedure) may both facilitate support for the user, and potentially allow enhanced interpretation of test results using the existing camera and software found in current devices. A downside to home/self-based testing for influenza is that easier access to testing could lead to the diagnosis of mild cases of influenza where antiviral treatment is not indicated. Increased access to self-testing include has financial implications including added costs to individuals who might have to purchase the tests, and to the healthcare system that might need to interpret, repeat or act on test results. Inaccurate tests could further cause harm through false negative and/or false positive results.

LIMITATIONS OF STUDY

The study has several potential limitations. First, recruitment of participants will not be entirely consecutive, although this follows the procedures that the participating clinics use for ongoing surveillance activities. Limiting this study to general practices means that some patients with ILI are excluded, such as those attending hospitals and emergency departments, receiving medical care from locum doctors or not seeking any medical treatment for ILI. Second, the spectrum of individuals presenting with ILI to GPs may be different to that expected in the community, with higher influenza prevalence, more severe symptoms, and/or longer time since onset of infection. The time point at which individuals present to their GP with influenza may have a critical impact on test sensitivity, as there is strong evidence that the sensitivity of rapid antigen influenza tests declines markedly beyond the initial 48-72 hours of illness.[35,36] Third, the performance of the nasal swab, and conduct of the lateral flow test is unsupervised, and therefore we will not be able to determine the impact of these factors on test accuracy. There is robust evidence that individuals are able to collect mid turbinate and low nasal swabs with similar performance to health care professionals for influenza, but we will not be able to further verify this in the current study. [37] Fourth, conduct of the test may vary with participant characteristics, such as age or

limitations in ability to handle smartphones, and their ability to visualize lines on the test strip. We will explore these using subgroup analyses (based on age), and user feedback from follow up surveys. Fifth, differences in interpretation of the enhanced image may depend on the technical capabilities of individuals' smartphones. Sixth, we are aware that the flu@home app has not been validated in this population and setting, and may need additional validation before being implementedor being used with a commercial device. Finally, while we do ask study participants about multiple aspects of their experience with the home-based influenza test, we will not ask specifically about their feelings regarding testing positive for influenza using a home-based test. Understanding the emotional impact of receiving a positive result using a self-test is out of scope for this study. Additionally, we will not be able to evaluate comparative costs of the flu@home test compared to usual care within this study.

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Figure Legend

Figure 1. flu@home Australia study procedure

Contributorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Additionally, each author certifies that this material or similar material has not been and will not be submitted to publication before its appearance in BMJ Open.

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Competing Interests

The authors do not have any competing interests.

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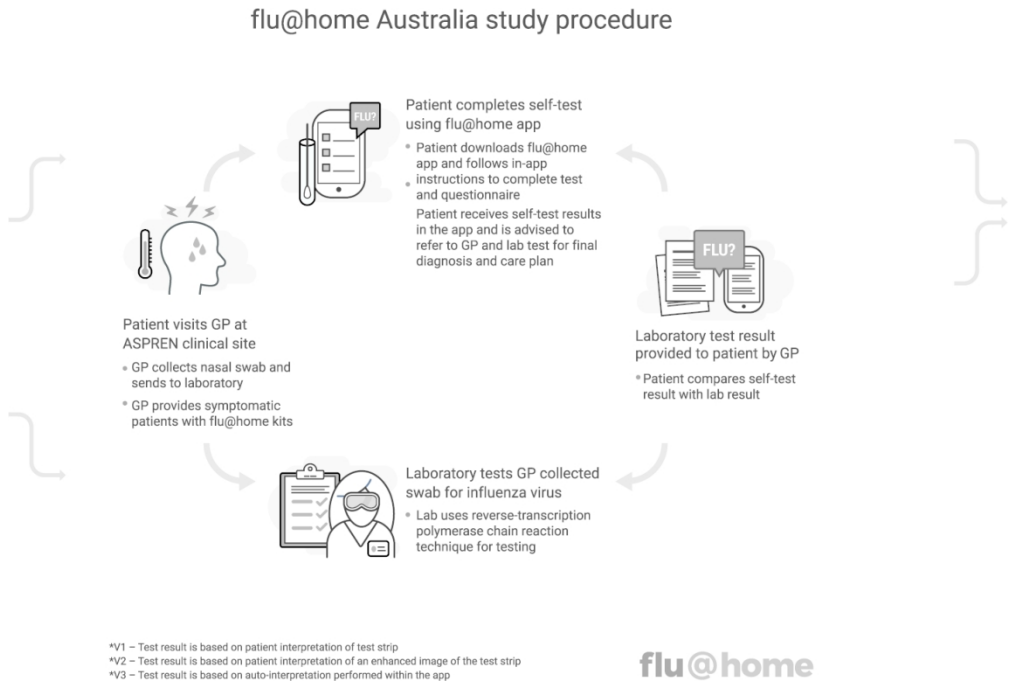

Figure 1
flu@home Australia study procedure

121x81mm (300 x 300 DPI)

APPENDIX

Appendix A: App design and operation

The flu@home app can be used on an iPhone, iPad, Android smartphone, or Android tablet. The app is available in English for the study. However, the app supports development and release of other languages as needed. The entire app experience uses a touch-sensitive dynamic interface on the device. The app ensures the proper test procedure is followed through clear instructions and timers that prevent the participant from moving forward in the test process (e.g., when the test strip must remain in the test fluid for ten minutes to be certain the strip has enough time to process before reading the result). The app attempts to keep participants engaged during wait times by providing flu-related informational facts (during an initial one-minute timer when the nasal swab is processing in the RDT vial) and asking the participant to answer a set of demographic and illness-related survey questions (during the ten-minute timer). Field-level validation is employed to ensure participants answer specific required questions in the survey.

The app was built using React Native, a JavaScript framework used to create mobile applications for iOS and Android. The app communicates with the Google Cloud Platform (Firebase) to queue survey data and Firebase storage to queue images captured from the RDT flow. These are pulled by a NodeJS service into a PostgreSQL database hosted on an AWS Relational Database Service (RDS), which allows for operation and scale of a relational database in the cloud.

The flu@home Australia app is available for personal devices which are expected to be under control of an individual who uses a passcode to access the device. All supported devices use encryption to protect app data resident on the device. This encryption is afforded by the device itself, not a specific application. In the event that a device is stolen, the device's onboard locking feature is the front-line defense against access to data on the device. The flu@home application does not collect the user's name, email, or other key identifiable information in the app. It focuses on data collection of symptoms, disease presentation, and demographics. The level of data protection offered by the flu@home app is the same level of protection afforded to most other health applications, email, messaging, etc. available on a mobile device.

App data is stored in Amazon Web Services (AWS S3 and AWS RDS). Amazon Simple Store Service (S3) provides a straightforward web services interface that is used to store and retrieve data, such as PCR data from the swab taken as part of the ASPREN study and used for comparison to the RDT test results. Access to S3 requires user authentication. From the time data leaves the client, all data is encrypted both at rest and over communication links. We use AWS Key Management Service (KMS) to encrypt data at rest in AWS, and Google Cloud Platform automatically encrypts its data using Advanced Encryption Standard (AES). All connections to the app occur over Secure Sockets Layer (SSL), a standard security technology that establishes an encrypted link between a web server and browser, ensuring all data traversing the web server and browser remains private.

For near real-time reporting, Metabase is run in an Elastic Container Service (ECS) in the same AWS project referencing the same app data.

The app uses Firebase caching and analytics to track each participant page view, including a timestamp for each page view. Firebase is also used to track changed answers if a participant navigates back in the app flow.

Appendix B: Australia Sentinel Practices Research Network (ASPREN) Protocol

The protocol for ASPREN clinical sites requires GPs to sample the first three ILI patients each week during flu season (May – October 2019 inclusive), and the first ILI patient of the week from November 2019– April 2020 inclusive. For the flu@home study, GPs will be allowed to recruit all adult patients presenting to the clinic with ILI symptoms, in order to meet recruitment goals. Participating clinical sites will obtain a nasal or nasopharyngeal swab which will be transported to SA Pathology, Adelaide, South Australia for testing using RT-PCR for influenza A, influenza B, as well as RSV, enterovirus, adenovirus, mycopneumoniae, human metapneumovirus, parainfluenza 1, 2, 3 and pertussis. Samples positive for influenza A will be further subtyped. All original clinical samples testing positive for influenza will be referred to the WHO-CCRRI (Melbourne, Australia) for antigenic and phylogenetic characterization. For clinical sites in tropical regions, due to the decreased seasonality of influenza, the systematic sample involves the first three ILI patients of each week, all year round. In addition to this, in all sites all ILI patients ages 65 years and over are tested all year round.

Appendix C: Flu@home Participant Questionnaire

Symptom Survey
*Questions marked with an * are required.*

Symptom	*Which of the following were present during your illness?	*How long ago did symptoms start? (Select the time frame that best applies)	*Were these symptoms present in the last 48 hours?	*How severe were your symptoms? (Select the level of discomfort you felt at the worst point)
Fever	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Cough	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Feeling more tired than usual	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Chills or sweats	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Sore throat	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Headache	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Muscle or body aches	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Runny or stuffy nose	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Shortness of breath	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe
Vomiting	YES/NO	1 day, 2 days, 3 days, 4+ days	YES/NO	mild, moderate, severe

General exposure
In the next section, the questions are going to be about being **in contact** with people who seemed to have a cold or the flu. **In contact** means being within two meters of them for at least two minutes or physical contact for any amount of time.

For reference, two meters is about the distance between you and someone sitting two rows ahead of you on the bus.

In the past week, have you been in contact with a person who seemed to have a cold or flu?

- Yes
- No
- Don't know

[If YES] Were they coughing or sneezing?

- Yes
- No
- Don't know

In the past week, have you been in contact with any children under five years old for over an hour?

- No contact with children under 5 yrs
- 1 child
- 2-5 children
- More than 5 children
- Don't know

Are there any children under 18 years old in your household?

- Yes
- No
- Don't know

[If YES] Do any children in your household attend a school, childcare setting, or play group with at least three other children for a total of three or more hours per week?

- Yes
- No
- Don't know

How many people live in your household (including you)?

- 1-2
- 3-4
- 5-7
- 8+

How many bedrooms are in your home?

- 0-1
- 2
- 3
- 4
- 5+

Influenza vaccination

We would like to ask you some questions about your influenza vaccination history. This information will be used to determine how effective the vaccine is.

Did you receive an influenza vaccination this year (2019*)?

- Yes
- No
- Do not know
- I've never received an influenza vaccination.

[If YES] what was the approximate date of your influenza vaccination?

- Choose month and year starting from January 2019* up to the current month

[If YES] Did you receive a free influenza vaccination under the National Immunisation Program in 2019*?

- Yes
- No
- Do not know

[If YES] What medical condition(s) do you have that made you eligible for a free influenza vaccination?

- Free text field

[If Answer to above is something other than: "I've never received an influenza vaccination"] Did you receive an influenza vaccination last year (2018*)?

- Yes
- No
- Do not know

General health

Next we'd like to ask you some questions about your overall health:

Have you ever been told by a doctor that you have one of the following medical conditions? (SELECT ALL THAT APPLY)

- Asthma
- COPD/emphysema
- Diabetes
- Heart disease
- None of these
- Do not know

Are you a healthcare (or aged care) worker (i.e. do you directly work with patients/aged care residents in your job)?

- Yes
- No
- Do not know

Do you smoke tobacco?

- Yes
- No

Does anyone in your household smoke tobacco?

- Yes
- No

Is your illness preventing you from going to work or school, going to social events, or exercising/working out?

- Yes
- No

Are you currently taking antibiotics (e.g. Amoxil, penicillin, azithromycin, co-trimoxazole (Bactrim), co-amoxiclav (Augmentin)) or antivirals (e.g. Tamiflu, Xofluza, Relenza) prescribed by a doctor (GP or hospital) for this illness?

- Yes
- No
- Do not know

How old are you?

- 18 to 19
- 20 to 24
- 25 to 29
- 30 to 34
- 35 to 39
- 40 to 44
- 45 to 49
- 50 to 54
- 55 to 59
- 60 to 64
- 65 to 69
- 70 to 74
- 75 to 79
- 80 to 84
- 85 to 89
- 90 and older

What is the sex on your medical records?

- Male
- Female
- Indeterminate/Other
- Prefer not to say

How would you describe your race? Please select all that apply.

- Aboriginal
- Torres Strait Islander
- Pacific Islander
- North or East Asian
- African
- European
- White Australian

- South or Central American
- Middle East/North African
- Indian subcontinent
- Other

[The next question is asked after the flu rapid test is complete]

Nice job! Do you feel you performed all of the steps in the flu test correctly? Select the most applicable option

- It was easy to follow and I think I completed the test correctly
- It was a little confusing but I think I did the test correctly
- It was very confusing and I'm not sure I completed the test correctly
- During the test, I realized I did something incorrectly

** All questions with an asterisk listed by the year will be updated in the mobile app in January 2020 (i.e. questions referring to "this year" will list 2020 instead of 2019.)*

Appendix D: Follow-Up Survey Variables

Category	Questions asked
Health behaviors and attitudes	I believe taking an active role in my own care is the most important factor in determining my health.*
	I am confident that I can identify when it is necessary to get medical care versus when I can handle the problem myself.*
	I often think carefully about whether health information makes sense in my particular situation.*
	I acknowledge that I have a key role in the day-to-day management of my health.*
	I often need someone to help me when I receive written information from my GP, nurse or pharmacist.*
	In general, I believe the state of my health is:**
	I am confident that I can tell my GP concerns I have even when he/she does not ask about them.*
	I like to find out a lot of information about health online.*
	I am confident that I can follow through on medical treatments I need to do at home.*
	I value my health more than anything else.*
	My health needs are always met from available healthcare resources.*
	As well as seeing my GP, I regularly monitor (check for) changes in my health.*
	I do what is necessary to keep myself healthy.*
	My GP and I work together to make decisions about what's best for my health.***
Experience/	The purpose of using flu@home was to: Yes No

usability	Test for flu	○	○
	Give me information about flu and medicine	○	○
	Test different flu medicines	○	○
	Participate in a research study about the flu	○	○
	I am satisfied with how easy it was to use flu@home (nasal swab test and app).*		
	I had the skills needed to perform swab testing using flu@home.*		
	I was able to understand the results from the flu@home app.*		
	The instructions for using flu@home were helpful in providing me with what I needed to perform the test.*		
	Using flu@home **app** was:****		
	Doing the flu@home **nasal swab test** was:****		
	Entering my information into the flu@home app was: ****		
Impact/ perceived value	I would recommend flu@home to a friend or family member.*		
	My GP was very supportive of me using flu@home.*		
	It saves time to do a home-based test like flu@home before visiting a healthcare provider.*		
	I feel that flu@home could help me better manage my illness.*		
Intention to Act	If flu@home testing indicated you had the flu, which of the following would you consider doing as next steps?		
		I would consider	
		Yes	No
	A virtual consultation with a provider (telemedicine visit)	○	○
	Sharing my results anonymously with a national flu tracking system	○	○

	Reading flu@home tips on how to prevent flu spread	○	○
	Encouraging others in my household to use flu@home for testing	○	○
	I would use the flu@home kit in the future if I have symptoms.*		
	I would do the flu@home test if I could purchase the test kit online to send to my home, rather than see my healthcare provider for diagnosis.*		

* Responses on Likert scale anchored with ‘Strongly Disagree’ and ‘Strongly Agree’
** Responses on Likert scale anchored with ‘Very Poor’ and ‘Excellent’
*** Responses on Likert scale anchored with ‘Never’ and ‘Always’
**** Responses on Likert scale anchored with ‘Very Easy’ and ‘Very Difficult’