Point of care testing using FebriDx ® to improve antibiotic use for respiratory tract infections in primary care: a mixed methods feasibility study (PREFIX)

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1. Synopsis

Short title	The PREFIX study
Full title	Point of care testing using FebriDx ® to improve antibiotic use for respiratory tract infections in primary care: a mixed methods feasibility study
Population	Patients aged 1 year and over attending primary care with a suspected lower respiratory tract infection (LRTI) who would be likely be prescribed antibiotics in the absence of further diagnostic testing
Intervention	1) FebriDx ® testing FebriDx ® (Lumos Diagnostics) is a CE-marked point-of-care device that tests for viral and bacterial host response using a dual-marker lateral flow immunoassay design. https://www.FebriDx ®.com/Home/Europe.
Aims and Objectives	AIMS 1) Explore the potential clinical utility and facilitators/barriers to using FebriDx ® to safely reduce the use of antibiotics for LRTI in primary care. 2) Explore the feasibility of conducting a future trial assessing the clinical impact, safety and cost-effectiveness of FebriDx ® to guide antibiotic use for LRTIs in UK primary care OBJECTIVES 1) Describe how clinicians use FebriDx ® in the assessment of patients with LRTI in routine primary care including the rate at which it was used by each clinician/practice and a description of the patient population (demographics and clinical features) in whom the test was used. 2) Provide preliminary estimates that will help inform a future trial, including the proportion of participants with different test results (on FebriDx ® and viral PCR), changes in clinicians perceptions of the need for antibiotics from before- to after-testing (on likert scales), the proportion of participants where the clinician stated that they avoided use of antibiotics as a result of use of the test, patient outcomes with 30-days (re-consultation rate, subsequent use of antibiotics for the same condition, hospitalisation, and adverse events), and process measures (such as rating of ease-of-use, training requirements, time to result and number of invalid results). 3) Explore the real-world diagnostic accuracy of FebriDx ® in the primary care setting, by taking nasopharyngeal swabs at the time of recruitment, for later viral analysis by multiplex polymerase chain reaction (PCR). 4) Describe the views of primary care staff and patients who have had the opportunity to use FebriDx ® to guide antibiotic treatment decisions for LRTI in primary care about how easy or difficult the test was to use, barriers and facilitators to implementation, and perceived value of the test in clinical decision making.

	5) Describe the views of primary care clinicians and patients who have had the opportunity to use FebriDx ® to guide antibiotic treatment decisions for LRTI in primary care about the value of conducting a trial of using FebriDx ® to guide antibiotic prescribing for LRTI in primary care, and the potential barriers and facilitators to conducting such a trial.
Rationale	Data from secondary care suggests that FebriDx ® may help clinicians better differentiate between bacterial and viral respiratory tract infections, and better guide subsequent management decisions regarding antibiotic use. In order to inform an application for funding to carry out a fully-powered randomised controlled trial of use of FebriDx ® in UK primary care, we aim to undertake a mixed-methods feasibility study to explore its potential clinical impact, as well as identify facilitators and barriers to its use.
Study design	STAGE ONE (quantitative data collection) Patients presenting with a LRTI (defined below) will be invited to participate and undergo FebriDx ® testing if the participating clinician judges that they would be likely to prescribe antibiotics in the absence of further diagnostic testing. Patient data will be collected via online case-report forms, completed before and after FebriDx ® testing. An initial CRF will collect data on details of symptoms, initial clinical impression, and reported likelihood of prescribing antibiotics (immediate or delayed) in the absence of further diagnostic testing. A subsequent CRF completed post-FebriDx ® testing will collect data on the result of the FebriDx ® test, users' views on its validity, time-to-result, and the subsequent use of antibiotics. Further data collection will include user-recorded ease-of-use scores, follow-up data on subsequent antibiotic use and complications, practices data on reasons for non-participation, and practice-level data on the number of patients with LRTI seen before/during/after the recruitment period, and the proportion prescribed antibiotics. *STAGE TWO (semi-structured interviews)* We will conduct semi-structured interviews with primary care staff and patients (10-20 of each) to explore their views on the acceptability and potential clinical impact of FebriDx ®, and the design of a larger future study.
Sample size	STAGE ONE We will recruit up to ten GP practices, with up to 300 devices to be used in total for both training and recruitment purposes (an overall recruitment target of 156 participants). STAGE TWO 10-20 patients and 10-20 primary care staff
Setting	STAGE ONE - GP practices STAGE TWO – Interviews via remote video-call

2. Background and rationale

Acute lower respiratory tract infections (LRTI) are one of the commonest reasons for primary care consultation and antibiotic prescription, despite the fact that approximately 70% are viral in aetiology, and the majority are self-limiting (1) (2). Unfortunately, both bacterial and viral LRTIs clinically present similarly, and approximately 50% of patients receive an antibiotic prescription, many of these inappropriately (3) (4).

Reducing unnecessary antibiotic prescriptions in primary care is well-acknowledged as a key component of tackling the impending crisis of antibiotic resistance globally (5). Antibiotics also carry a substantial risk of adverse effects, and it is increasingly recognised that antibiotics can have negative effects on the gut microbiota (6) (7). This may in turn promote antibiotic-resistance at the individual level, and increase the risk of gastrointestinal, immunological and neurocognitive conditions (7). Furthermore, prescribing antibiotics has been shown to reinforce patients' belief in the need for antibiotics, and increases the chance of re-attendance to primary care in the future (8). There has therefore been an increasing drive to develop tools which can help clinicians better distinguish between bacterial and viral LRTIs.

A promising area of current research is rapid diagnostic testing at the initial point of patient contact, so-called "point-of-care testing" (POCT). The majority of devices studied in primary care have been designed to measure a single marker, typically c-reactive protein (CRP), an acute phase reactant that generally increases to higher levels with bacterial compared to viral infections (9), or to detect the presence of a specific pathogen, such as influenza (10). Previous studies have shown that POCT in primary care has the potential to safely reduce use of antibiotics (as well as informing use of antivirals), as well as managing patients' expectations and facilitating patient education, and informing infection-control strategies (9) (10) (11,12).

These studies have also overall demonstrated good acceptability amongst clinicians, however, concerns have been raised by primary care clinicians regarding the accuracy of results compared to laboratory testing, and how single biomarkers should be interpreted and/or acted upon (9,11,12). Furthermore, the majority of devices require an additional 'desktop' analyser to be used. This significantly increases up-front capital costs, as well as maintenance requirements, quality control issues, and infection control concerns (13). It also significantly impedes their portability and ease-of-use (especially in the primary care setting), limiting their adoption into in everyday clinical practice (9,11,12).

FebriDx ® (Lumos Diagnostics) is a CE marked point-of-care device that tests for viral and bacterial host response using a dual-marker lateral flow immunoassay design (14). https://www.FebriDx ®.com/Home/Europe. It is designed to quickly identify immune responses associated with both bacterial and viral infections using a fingerstick of human blood, and gives a result in 10 minutes. It provides a point-of-care measurement of both CRP and myxovirus resistance protein A (MxA), a derivative of interferon α/β which is associated with viral infection. The UK's National Institute of Health and Care Excellence (NICE) published a medtech innovation briefing (MIB) for FebriDx ® on 26/08/2022 (available at: https://www.nice.org.uk/advice/mib224)

What are the potential advantages of FebriDx ® over other point-of-care CRP tests?
FebriDx ® is a single-use, hand-held device, and does not require an additional desktop analyser. This device may therefore offer improved ease-of-use over other POCT devices, especially in the primary care setting, where clinicians may predominantly work in individual rooms (15). Furthermore, as a dual-marker device simultaneously measuring both viral and bacterial host response, this offers increased specificity over single-measurement devices. This may therefore help clinicians better differentiate between bacterial and viral respiratory tract infections (including COVID-19), and better guide subsequent management decisions. At around £12.75 per test, the overall cost is similar to POCT using CRP alone, and does not require the high up-front and ongoing maintenance costs associated with a desktop analyser (13).

Studies exploring the diagnostic accuracy of FebriDx ® have shown good agreement with reference-standard Polymerase Chain Reaction (PCR) (16–18). These include a prospective, multi-centre study of adults and children presenting with LRTIs to emergency care in the US. For bacterial detection, agreement between FebriDx ® and PCR was 91.7% (sensitivity 80%, specificity 93%) and for viral detection agreement was 84% (sensitivity 87%, specificity 83%). Furthermore, FebriDx ® was shown to have high diagnostic accuracy for the identification of COVID-19 in hospitalised adults (sensitivity 93%, specificity 86%) in a recent UK study conducted during the first wave of the COVID-19 pandemic (19).

Studies exploring the impact of FebriDx ® in UK primary care are, however, limited to a single small retrospective observational study at one GP practice which reported good ease-of-use and cost-effectiveness (15). It is important that FebriDx ® is evaluated further in the primary care setting, especially as data from secondary care cannot necessarily be extrapolated as the sensitivity of a test may vary by disease severity (spectrum bias) (20). Furthermore, there is little follow-up evidence exploring the impact of the test on antibiotic use.

Further UK primary care studies are therefore needed to establish the acceptability, ease-of-use, real-world clinical impact, safety and cost-effectiveness of using FebriDx ® to guide appropriate antibiotic prescribing in this setting. In order to inform an application for funding to carry out a fully-powered randomised controlled trial of use of FebriDx ®in UK primary care, we aim to undertake a mixed-methods feasibility study to explore its potential clinical impact, as well as identify facilitators and barriers to its use.

3. Aims

1) Explore the potential clinical utility and facilitators/barriers to using FebriDx ® to safely reduce the use of antibiotics for LRTI in primary care.

2) Explore the feasibility of conducting a future trial assessing the clinical impact, safety and cost-effectiveness of FebriDx ® to guide antibiotic use for LRTIs in UK primary care

Objectives

3) Describe how clinicians use FebriDx ® in the assessment of patients with LRTI in routine primary care including the rate at which it was used by each clinician/practice and a description of the patient population (demographics and clinical features) in whom the test was used.

4) Provide preliminary estimates that will help inform a future trial, including the proportion of participants with different test results (on FebriDx ® and viral PCR), changes in clinicians perceptions of the need for antibiotics from before- to after-testing (on likert scales), the proportion of participants where the clinician stated that they avoided use of antibiotics as a result of use of the test, patient outcomes with 30-days (re-consultation rate, subsequent use of antibiotics for the same condition, hospitalisation, and adverse events), and process measures (such as rating of ease-of-use, training requirements, time to result and number of invalid results).

5) Explore the real-world diagnostic accuracy of FebriDx ® in the primary care setting, by taking nasopharyngeal swabs at the time of recruitment, for later viral analysis by multiplex polymerase chain reaction (PCR).

6) Describe the views of primary care staff and patients who have had the opportunity to use FebriDx ® to guide antibiotic treatment decisions for LRTI in primary care about how easy or difficult the test was to use, barriers and facilitators to implementation, and perceived value of the test in clinical decision making.

7) Describe the views of primary care staff and patients who have had the opportunity to use FebriDx ® to guide antibiotic treatment decisions for LRTI in primary care about the value of conducting a trial of using FebriDx ® to guide antibiotic prescribing for LRTI in primary care, and the potential barriers and facilitators to conducting such a trial.

Study design

Overview

This is a mixed-methods, multi-centre, non-randomised feasibility study. Formal advice and peer-review with regards to study design was sought from the Southampton Research Design Service (RDS), the NIHR CRN Wessex, and patient contributors during the development of the grant application. Lumos Diagnostics had no role in the design of the study. We will recruit up to ten GP practices, with up to 300 devices to be used in total for both training and recruitment purposes (an overall recruitment target of 156 participants). A sequential explanatory approach to data collection will be taken (21), with quantitative data analysis in stage one, followed by qualitative interviews with the study's practice participants in stage two.

Stage one (quantitative data collection)

Patients presenting with a LRTI (defined below) will be invited to participate and undergo FebriDx ® testing if the participating clinician judges that they would be likely to prescribe antibiotics in the absence of further diagnostic testing. Patient data will be collected via two online case-report forms, completed before and after FebriDx ® testing. An initial CRF will collect data on details of symptoms, initial clinical impression, and reported likelihood of prescribing antibiotics (immediate or delayed) in the absence of further diagnostic testing. A subsequent CRF completed post-FebriDx ® testing will collect data on the result of the FebriDx ®test, users' views on its validity, time-to-result, and the subsequent use of antibiotics. Further data collection will include user-recorded ease-of-use scores, follow-up data on subsequent antibiotic use and complications, practices data on reasons for non-participation, and practice-level data on the number of patients with LRTI seen before/during/after the recruitment period, and the proportion prescribed antibiotics.

Stage two (semi-structured interviews)

We will conduct semi-structured interviews with practice staff and patients (10-20 of each) to explore their views on the acceptability and potential clinical impact of FebriDx ®, and the design of a larger future study.

Stage one (quantitative data collection)

We plan to recruit up to ten GP practices. Recruiting clinicians may be any primary care clinician who is qualified to prescribe, including GPs, GP trainees, and nurse practitioners. Any healthcare professional (including prescribing clinicians, paramedics, healthcare assistants, and nurses) may perform FebriDx ® testing as part of the study. We may use an initial stakeholder meeting to help inform the development of brief training in how to use the device (including patient selection, where in patient pathway to introduce test, how to interpret results). This will be supplemented with formal training on the technical aspects of using the devices. Additional training on use of the device may be provided by Lumos Diagnostics (who otherwise have no input into the study). Participating practice staff will be able to conduct up to four tests

on a volunteer (such as another member of staff) during a 'run-in' period, to allow participants to gain initial familiarity with the FebriDx ® equipment.

Inclusion criteria

- Adults or children (aged 1 year or more) presenting in primary care with symptoms suggestive of a lower respiratory tract infection (defined as in previous studies as an acute cough as the predominant symptom, judged by the GP to be infective in origin, lasting <21 days, and with other symptoms or signs localising to the lower respiratory tract (shortness of breath, sputum, chest pain). This is a definition which we have used in previous studies (22)
- The clinician has decided that they are likely to prescribe antibiotics in the absence of further diagnostic testing
- The patient is at the surgery or willing to attend the surgery to undergo FebriDx ® testing
- The patient (or their parent or legal guardian) can follow the study procedures and is willing to provide informed consent

Exclusion criteria

- Patients who have taken antibiotics within the last 30 days
- Participant (or their parent/guardian) unable to provide informed consent

Justification for proposed sample size

Since this a feasibility study, a formal sample size calculation is not required (23). Up to 300 devices in total will be available. We plan to recruit up to 10 GP practices. If nine GP practices were recruited, up to 144 tests would be used during the 'run-in period' (based on four users per-practice), leaving 156 tests for inclusion in the analysis. Based on previous research and clinical experience of FebriDx ®, we anticipate that this number of devices would allow users to become competent in their use and provide sufficient descriptive quantitative data on their use in clinical practice, and the types of patients in which they can provide useful information in order to inform subsequent management strategies. We will report the proportion of patients who are prescribed antibiotics after FebriDx ®. In terms of the estimate of effect, based on a 95% confidence interval, 156 participants would allow us to describe 50% (7.8%), 60% (7.7%), 70% (7.2%), 80% (6.3%), and 90% (4.7%). Given that these will be patients who would have been likely to be prescribed antibiotics prior to use of FebriDx ®, this would represent reductions in antibiotic prescribing of around 10-50%.

GP practice recruitment

GP surgeries will be recruited to the study through various means. We will be applying for NIHR portfolio adoption in order to facilitate the support of CRN Wessex, who have already indicated that they would be willing to provide study support and assist with the identification and recruitment of suitable GP practices to this study

We will identify and approach suitable GP practices through CRN Wessex, and our own local networks. We have already established links with GP practices potentially interested in participating. Potential practices will be sent detailed information about the study, and those interested will be invited to contact the study team by email, phone or text message to express their interest, check eligibility and discuss availability. Within the limits of recruiting research-active practices, and the small number of practices we plan to recruit, we will attempt to recruit practices which cover a range of patient demographics if possible (including areas of higher deprivation or mixed cultural backgrounds).

Patient recruitment and consent

Patients contacting their GP practice with a suspected lower respiratory tract infection will be individually consented and recruited to the study, following clinical assessment (either remotely or face-to-face). Access

to potential participant's GP practice medical records prior to study involvement will only ever be undertaken by those in their direct healthcare team.

Clinicians participating in the study will identify potential participants, and provide them with verbal information about the study, as well as a participant information sheet (PIS) in either paper or online form. Potential participants will be given additional time that day (if wished) to consider whether or not to take part, unless urgent treatment is deemed clinically necessary, in which case the clinician may decide to proceed with 'usual care' only if the participant feels they would need more time to decide.

Participants who are still interested in taking part will undergo screening by the clinician to confirm eligibility, before asking them to complete a consent form (either online or paper), and taking part in the study. In the case of written consent, a copy of the signed consent form will be given to the participant and a copy kept in the investigator file.

Participants will be encouraged to have a nasopharyngeal swab, but this will not be a requirement for participation.

Patients recruited to stage one will also be asked to express interest in taking part in a follow-up interview (stage two) and provide consent for their contact details to be shared with the research team by recording them onto a secure online GDPR-compliant database, which will then be used to transfer the details to a secure password-protected University of Southampton server.

Data collection process

Data will be collected via online CRFs. Minor amendments may be made to these following initial trialling. In total, we anticipate that patients will be involved for approximately 20 minutes following completion of the consent form.

1. *Completion of initial CRF (5 minutes)*
   Participating clinicians will be asked to record basic data for each participant using an initial online case report form prior to conducting FebriDx ® testing. This data will include patient demographics, clinical features of the presenting illness, their rationale for considering use of antibiotics, and their perceived likelihood of prescribing antibiotics prior to conducting the test.

2. *FebriDx ® testing +/- optional n*asopharyngeal swab collection *(3-4 minutes)*
   Testing using FebriDx ® will be performed. Any invalid tests may increase the length of time required, but we expect based on prior experience that the majority of tests will be valid. Additionally, a nasopharyngeal swab will also be taken from participants who agree to this optional component. These may be performed by either the study team, or the patient themselves via self-swabbing (at the time of recruitment or later that day). Samples may be transported to the laboratory in Southampton General Hospital either via post or via courier (with the GP practice's routine clinical samples).

3. *Wait for FebriDx ® result (10-minutes)*

4. *Communication of result and completion of second CRF (5 minutes)*
   Following completion of the FebriDx ® test, GP practice staff will be asked to record further data on a second online CRF. This will include the test result, their views on the validity of the test result, time to result, their subsequent management, and the reasons for prescribing or not. The CRF will also have an open-text box available for staff to record any additional data and/or comments they feel pertinent. For external validation-purposes, practice staff may additionally be asked to photograph

the FebriDx ® test result and send this to the study team via email with details of the patient's study ID and collection date/time (no patient-identifying information).

During initial study training we will provide clinicians with a summary of NICE guidance and links to antimicrobial stewardship tools, including evidence-based materials for patients. This is to ensure that patients who are not prescribed antibiotics, who might otherwise have been prescribed antibiotics, are provided with adequate information and advice on symptomatic treatment strategies and safety netting advice. This was specifically raised as an important aspect of the consultation by our PPI team.

Additional data collection and follow-up
Patients will be asked to consent to allowing access to their medical records, and at the end of the study we will ask participating practices to review the medical records of participants and document subsequent healthcare contacts (general practice in-hours, out of hours, A&E, walk-in centres, and hospital admissions) use of antibiotics, and serious complications such as sepsis or death. We will also ask practices to collect anonymous data on reasons for clinicians not recruiting patients who met the inclusion criteria, reasons for non-participation, and to provide practice medical record search results about the number of patients with LRTI seen during the recruitment period, and the proportion prescribed antibiotics.

Formal ease of use scoring will also be undertaken, such as the validated 'System Usability Score', or alternative modified ease-of-use scoring (previously used in POCT studies conducted by co-investigator TW (24)) completed by the study team and/or GP practice staff involved in the study.

Contact details for the study team (including both telephone and email address) will be provided to participants in order to allow them to seek further information at a later stage if desired.

Laboratory procedures
Nasopharyngeal viral swabs will be transported to the microbiology laboratory in Southampton General Hospital either via post, or via courier (as per routine clinical samples). These will be frozen for later viral analysis by multiplex polymerase chain reaction (PCR) at an accredited laboratory at Southampton General Hospital.

Data analysis
We will use descriptive statistics to report data collected from the case report forms, including recruitment rates, patient characteristics, FebriDx ® results, reliability (test failure rate), ease-of-use score (modified Clinical Laboratory Improvement Amendments (CLIA) categorisation criteria (24)), antibiotic prescribing rates (presented with 95% confidence intervals), subsequent healthcare contacts and serious complications (within 30-days). We will also use descriptive statistics to report practice-level data on the overall attendance to the practice with LRTI during the recruitment period, as well as antibiotic prescribing rates. The results of the viral analysis of nasopharyngeal swabs will be compared to participant's FebriDx ® results and presenting clinical features, to allow us to explore the real-world diagnostic accuracy (sensitivity and specificity) of FebriDx ® in the primary care setting. Our study statisticians are experienced study statisticians with experience of clinical studies in primary care, and will provide senior oversight for the quantitative data analysis.

Stage two (qualitative data collection)

Following completion of the quantitative phase of the study, qualitative data on the use of FebriDx ® during stage one of the study will be collected by performing semi-structured interviews.

These will be conducted with

1) 10-20 practice staff who were actively involved in the study
2) 10-15 patients who took part in stage one and expressed interest in taking part in a follow-up qualitative interview.

Justification for proposed sample size
Based on previous studies carried out by our research group, for the qualitative interviews we believe that our proposed sample size will provide enough information power to allow us to gain sufficient insight into the usability of the FebriDx ® devices and the barriers/facilitators to their adoption into routine clinical practice.

Primary care staff recruitment and consent
Primary care staff actively involved in stage one will be directly invited to participate in the follow-up interviews. Those who express interest in participating will be emailed written information in the form of a patient information sheet (PIS). Interested participants will be invited to contact the study team by email, phone or text message to express their interest, check eligibility and discuss availability. Participant consent will be provided by audio-recording consent at the start of the interview (with audio-recorded agreement to each statement on the consent form), and after the participant has been given the opportunity to have any questions answered.

Patient recruitment
Patients recruited to stage one will be asked to express interest in taking part in a follow-up interview during recruitment to stage one. Contact details for those interested will be collected by the primary care clinicians. A separate PIS for Stage Two will be shared, and consent taken, via the same process as above for primary care staff.

Data collection
Interviews will be semi-structured using pre-developed interview topic guides to explore participants' views on use of the FebriDx ® devices. Interview guides will be drafted; however these may be further developed iteratively depending on the responses to previous interviews. Questions will focus on the perceived ease-of-use of FebriDx ®, and their views on the feasibility for this technology to be integrated into UK primary care, including the barriers and facilitators. Finally, we will also ask for their views on the design of future larger research studies to establish the clinical benefit and cost-effectiveness of FebriDx ®. We believe that semi-structured interviews are preferable over questionnaires due to the richer qualitative data they provide, opportunity to explore additional themes as indicated, and the relatively small number of primary care staff members involved in the study. The interviews themselves may be in-person or remote (Microsoft Teams), depending on preferences and feasibility. Interviews will predominantly be conducted by a qualitative research fellow, in addition to co-PI Dr Christopher Wilcox. We may also involve University of Southampton undergraduate medical students in Stage Two as part of their BMedSci research project in year three of their course, with appropriate senior supervision and Good Clinical Practice (GCP) training.

Data analysis
Qualitative interviews will be audio-recorded and downloaded onto the University of Southampton secure server immediately after the interview and transcribed verbatim. Transcripts will also be stored on a secure server. Video and audio recordings will be deleted once they have been transcribed. Transcribing will be undertaken by a University-approved professional transcription service, with appropriate confidentiality agreements in place.

Analysis will take place using thematic analysis (25), and will include reading and familiarisation with the transcripts, noting and recording initial themes and then conducting systematic and detailed open coding using NVivo software. The coding of the first set of interviews will generate an initial coding framework, which will be discussed with the members of the research team (including PPI members). This will be further developed and refined as analysis proceeds. The research team will also critically discuss the categories and

themes emerging from the data, to ensure trustworthiness and increase rigour. Senior oversight for the qualitative data analysis will be provided by co-applicant Dr Ingrid Muller, an experienced primary care academic health psychologist.

Patient and Public (PPI) involvement

Public contributors will play a key role in the design/conduct/analysis/write-up/dissemination of this study. The PPI contributors on the funding grant application were very supportive of the study, and have agreed to stay on as members of the PPI panel for this study. They felt this was a very important area to explore, especially in the face of impending antibiotic resistance. In particular, the group felt that this device could be a useful tool for helping clinicians decide when antibiotics are, and are not, indicated for chest infections. They also felt the additional time required for recruitment into this study (and conducting the test itself) was acceptable for patients in all age groups. We will be undertaking regular study meetings with the PPI team, and have costed for this accordingly (allowing for additional pre-reading of study documents).

Anticipated Risks

Clinical risks

The clinical risks of undertaking the single-use FebriDx ® test itself is extremely low. A 'fingerprick' quantity of blood is taken and therefore risks of subsequent bleeding or infection are extremely low. Furthermore, the test is virtually painless, and has been well-tolerated by both adults and young children in previous studies (15–19).

There is a possibility that participants undergoing FebriDx ® testing may not be subsequently prescribed antibiotics by their primary care clinician, when they otherwise would have done. There is currently equipoise regarding the risks and benefits of this. Antibiotics cause harms as well as potentially causing benefits in those with susceptible infections. Numerous previous studies have shown that it is safe to reduce antibiotic use through CRP point-of-care testing (9), and previous studies exploring the diagnostic accuracy of FebriDx ® have shown good agreement with reference-standard Polymerase Chain Reaction (PCR) (16–18). Furthermore, it has been shown in recent large randomised controlled trials (RCTs) of both children and adults in primary care (26) (22) that antibiotics are unlikely to make a clinically important difference to the symptom burden for uncomplicated LRTIs - both overall, and for the key clinical subgroups where antibiotic prescribing is most common.

Furthermore, during initial study training we will provide clinicians with a summary of NICE guidance and links to antimicrobial stewardship tools, including evidence-based materials for patients. This is to ensure that patients are provided with adequate information and advice on symptomatic treatment strategies and safety-netting advice. This was specifically raised as an important aspect of the consultation by our PPI team.

Other potential risks

Steps will be taken to ensure confidentiality is maintained in both stages of the study, unless there are exceptional circumstances with regards to serious concerns about patient safety (see full details in confidentiality section). We will adhere to GPDR guidance and all data will be pseudonymised. Any personal identifiable data (such as contact details) will be stored separately to research data to protect anonymity.

Patients will be asked to consent for access to their medical records, and at the end of the study we will ask participating practices to review the medical records of participants and document subsequent healthcare

contacts (general practice in-hours, out of hours, A&E, walk-in centres, and hospital admissions) use of antibiotics, and serious complications such as sepsis or death.

Patients who express interest in taking part in Stage Two (interviews) will also be asked to consent to have their contact details shared with members of the study team. Taking part in interviews themselves will have very low risk to participants and questions asked will not include any sensitive topics. Personal details will not be shared, and any quotes will be completely anonymised.

Regulatory and Ethical considerations

FebriDx ® was CE-marked as an in vitro diagnostic device in September 2014. This was updated in October 2018. This study does not meet the criteria of a Clinical Trial of an Investigational Medicinal Product (CTIMP).

Study sponsorship

University of Southampton will act as sponsor for study.

Declaration of Helsinki

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives as well as ICH E6.

ICH Guidelines for Good Clinical Practice

The Investigators will ensure that this study is conducted in full conformity to the guidelines for GCP (CPMP/ICH/135/95) July 1996. This Good Clinical Practices document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, and sponsors.

Informed consent process

Each patient's consent to participate in the study will be obtained after a full explanation of the study. Discussion of objectives, risks and inconveniences of the study and the conditions under which it is to be conducted are to be provided to the patient by appropriately delegated staff with knowledge in obtaining informed consent with reference to the patient information leaflet. This information will emphasise that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and for any reason. The patient will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

Young people aged 16-17 years will be presumed to be capable of giving consent on their own behalf to participate.

Most children/young people under the age of 16 years will not be able to consent for themselves and we will seek consent from an informed person with parental responsibility. However, we will aim to give the child / young person information about the study which is understandable to them and which explains what is involved and the potential risks and benefits. If the child or young person is capable of assessing the information provided, their wishes will be considered. An assent form has been created for the purposes of this study. The recruiting healthcare professional will be advised that, whenever practical and appropriate, a

child's assent should be sought before including them in the research. This will obviously be inappropriate for very young children.

For children/young people under the age of 16 years who may be capable of consenting for themselves, we will first seek permission from a person with parental responsibility for approaching the child/young person. With the parent's permission, the recruiting clinician will assess whether the child/young person is able to consent for themselves using the principles of 'Gillick competence'. If the parent has given permission to approach the child/young person and have been assessed as being Gillick competent, then we will only obtain informed consent from the Gillick competent young person.

Confidentiality

Details surrounding maintenance of confidentiality will be described in the participant information sheet, and when taking informed consent. The investigators will take necessary steps to preserve the confidentiality of participants in the study. Only in exceptional circumstances we may be required to break confidentiality. This would only be the case if there was disclosure or evidence of significant abuse/maltreatment/poor care of patients. In these circumstances, we would discuss the concerns raised amongst appropriately qualified team members and, if necessary, notify the appropriate authorities.

For stage one, pseudo-anonymous electronic data will be collected on online case report forms via secure University of Southampton-approved online databases, including 'ALEA' and 'Qualtrics'. The data collected will be stored on fire-walled University of Southampton servers. Files will be password protected and only accessible to researchers responsible for the running of the study. We will adhere to GPDR guidance and all data will be pseudonymised. On CRFs patients will only be identified by trial ID code. The information will be available to the study team, safety monitors, sponsor, and external monitors who can ask to audit or monitor the study. The site will retain a patient identification code list which is only available to site staff.

Contact details will be stored securely on a separate database from any other participant data collected to ensure anonymity is maintained. This information will only be accessed by relevant members of the study team. Any written study information will be stored securely in a locked room at study sites, or in electronic form on a secure server. Trial documents will be retained in a secure location during and after the trial has finished. The PIs or delegate will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. All written study documents generated will be kept in the Trial Master File, kept in a secure locked room at each study site. All online data will be retained on a secure online server hosted by the university of Southampton. All source documents and pseudo-anonymous research data will be retained for a period of 10 years following the end of the trial, as per University of Southampton policy.

For stage two, qualitative interviews will be audio-recorded and downloaded onto the University of Southampton secure server immediately after the interview. Transcribing will be undertaken by a University-approved professional transcription service, with appropriate confidentiality agreements in place. Transcripts will also be stored on the secure server. Video and audio recordings will be deleted once they have been transcribed. Personal details will not be shared at any time, and any quotes from participants published in the final study report will be completely anonymised.

Research Ethics Committee

A copy of the protocol, proposed informed consent form, other written participant information and the proposed advertising material will be submitted to the Research Ethics Committee for written approval, using the UK Integrated Research Application System.

Health Research Authority

As this study involves NHS sites, the investigator will seek Health Research Authority (HRA) approval. A copy of the protocol, proposed informed consent form, other written participant information and the proposed advertising material will be submitted to the HRA for written approval, using the UK Integrated Research Application System. The investigator will notify deviations from the protocol, urgent safety measures or SAEs occurring at the site to the sponsor and will notify the HRA and MHRA of these if necessary in accordance with procedures.

Study amendments

The investigator will submit and, where necessary, obtain approval from the University of Southampton Research Governance Office and the HRA for all subsequent amendments to the protocol and associated trial documents as per REC, MHRA and HRA requirements: http://www.hra.nhs.uk/resources/after-you-apply/amendments/. The investigator is responsible for ensuring that changes to the approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subjects.

End of study

The end of study is considered the date of the last patient recruited into the study has completed the study and data analysis (including laboratory samples) has been completed.

Monitoring

Monitoring and auditing may be undertaken at any time by the Sponsor institution (University of Southampton) or the National Institute for Health Research SPCR as the funding organisation.

Financing and insurance

Financing

The study will be funded by the School for Primary Care Research (SPCR) administered by the National Institute for Health Research by means of a research grant to the Primary Care Research Centre, University of Southampton. The research funding will be administered by the University of Southampton. In addition to this funding, FebriDx ® devices and quality assurance materials have been funded through internal award from the Southampton NIHR Biomedical Research Centre (BRC). Additional funding will be obtained from the BRC to pay for the postage and analysis of laboratory supplies (including consumables and staff costs). Finally, internal NIHR research capability funding will be obtained for further research fellow salary support costs.

Insurance

The University of Southampton has a specialist insurance policy in place, which would operate in the event of any participant suffering harm as a result of their involvement in the research.

Participant compensation

For stage two, participants in the qualitative interviews (both staff and patients) will receive £40 as a thank you for their time

PPI compensation

PPI members will receive £50 for attending each one-hour meeting (plus pre-reading as appropriate). The exception to this will be Professor John McGavin (an Emeritus professor of English from the University of Southampton) who is one of the lead Primary Care public contributors for the University of Southampton and has kindly stated that he does NOT wish to be financially reimbursed for any involvement as a PPI study team member.

Publication and dissemination strategy

We intend to publish the results of this study in scientific journals and present the results at scientific meetings. All results in journals and presentations will be anonymous. A summary of findings will be provided to participants, and study progress and results will be made available via appropriate websites (e.g. SCPR) and social media feeds. Further avenues for output may also be explored after consultation with PPI members.

Anticipated impact

The results of this mixed-methods study will provide us with useful data on the feasibility for this technology to be implemented into UK primary care (provided that subsequent large randomised trials demonstrate clinical benefit and cost-effectiveness). Importantly, this study will provide useful insights into the perceived acceptability and usability of this technology amongst primary care clinicians, as well as an insight into the possible implementation 'models' within general practice. Furthermore (from both the quantitative and qualitative stages of the study) these data will provide initial insights into how the technology might alter antibiotic/antiviral prescribing by clinicians, as well as other subsequent management decisions/infection control strategies (including its potential use as a COVID-19 screening tool).

These data will support a future grant application for an adequately powered trial of FebriDx ® use in UK primary care. A future trial will be fully-powered to detect impact on antibiotic/antiviral prescribing rates, subsequent patient outcomes (using patient-completed symptom diaries and clinical notes-review) and the real-world diagnostic accuracy of FebriDx ® (by taking throat swabs for PCR alongside FebriDx ® testing). These are likely to include programs such as a NIHR Programme for Applied Health Research or NIHR Health Technology Assessment Programme.

If we are able to demonstrate that FebriDx ® is feasible to implement, and randomised trials demonstrate that this technology and safely and cost-effectively reduce antibiotic prescribing rates amongst patients presenting to primary care with acute respiratory tract infection (for whom the majority of antibiotics in primary care are prescribed), then we will have identified an important tool in the fight against antibiotic resistance. There is also potential for this technology to be a useful screening tool, such as for COVID-19 in general practice.

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