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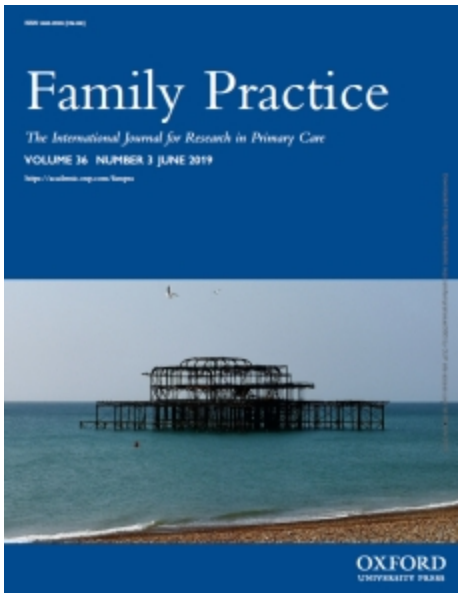

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Novel multi-virus rapid respiratory microbiological point-of-care testing in primary care: a mixed methods feasibility evaluation

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Novel multi-virus rapid respiratory microbiological point-of-care testing in primary care: a mixed methods feasibility evaluation

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Tanzeela Y Khalid*,[a] Lorna J Duncan*,[a] Hannah V Thornton,[a] Gemma Lasseter,[b] Peter Muir,[c] Zara Abigail Toney,[d] Alastair D Hay.[a,b]

Author affiliations:

a. Centre for Academic Primary Care, Bristol Medical School: Population Health Sciences, University of Bristol, UK

b. NIHR Health Protection Research Unit in Behavioural Science and Evaluation, University of Bristol, UK

c. Public Health Laboratory Bristol, National Infection Service, Public Health England, Bristol, UK

d. St George's, University of London MBBS Programme at the University of Nicosia Medical School, Nicosia, Cyprus

*Joint first authors

Correspondence to: Dr L. J. Duncan, Centre for Academic Primary Care, Bristol Medical School: Population Health Sciences, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK; Lorna.Duncan@bristol.ac.uk

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Key messages

- Respiratory point-of-care test was easy-to-use and acceptable to clinicians and patients
- At baseline, clinicians over-diagnosed bacterial infections and under-diagnosed influenza
- POCT increased diagnostic certainty, and reduced expectation of antibiotic effectiveness

ABSTRACT

Background and objectives

Rapid multi-viral respiratory microbiological point-of-care tests (POCTs) have not been evaluated in UK primary care. The aim of this study was to evaluate the use of a multi-viral microbiological POCT for suspected respiratory tract infections (RTIs).

Methods

In this observational, mixed-methods feasibility study practices were provided with a POCT machine for any patient aged ≥3 months with suspected RTI. Dual throat/nose swabs tested for 17 respiratory viruses and three atypical bacteria, 65 minutes per sample.

Results

Twenty clinicians recruited 93 patients (estimated 1:3 of all RTI cases). Patient's median age was 29, 57% female, and 44% with comorbidities. Pre-test diagnoses: upper RTI (48%); lower RTI (30%); viral/influenza like illness (18%); other (4%). Median set-up time was 2.72 minutes, with 72% swabs processed <4 hours, 90% <24 hours. Tests detected ≥1 virus in 58%, no pathogen 37%, and atypical bacteria 2% (3% inconclusive). Antibiotics were prescribed pre-test to 35% of patients with no pathogen detected and 25% with a virus. Post-test diagnoses changed in 20%, and diagnostic certainty increased (p=0.02), more so when the test was positive rather than negative (p<0.001). Clinicians predicted decreased antibiotic benefit post-test (p=0.02). Interviews revealed the POCT has clear potential, was easy to use and well-liked, but limited by time-to-result and the absence of testing for typical respiratory bacteria.

Conclusions

This POCT was acceptable and appeared to influence clinical reasoning. Clinicians wanted faster time-to-results and more information about bacteria. Randomised trials are needed to understand safety, efficacy, and patient perceptions of these POCTs.

Word count: 250

Keywords: bacterial, diagnosis, point-of-care testing, primary health care, respiratory tract infections, viral

Lay Summary

The UK government has called for the introduction of rapid diagnostics to curb overuse of antibiotics for common infections. Multi-viral respiratory 'point-of-care' tests (POCTs) are available but have not been used in UK primary care before. These POCTs use samples from the nose or back of the throat and give results quickly, to see if viruses or bacteria are there. In this study, four GP practices were given POCT machines for 6 weeks to see how they were used. Of the 93 patient samples tested, 3% were inconclusive, 37% tested negative, 58% had at least one virus, and only 2% had a bacterial infection. Clinicians were more certain of patient diagnoses after testing especially when a virus or bacterium was detected and they were also less likely to predict the patient would benefit from antibiotics. Clinical diagnoses changed in 20% of patients after testing but less than 10% were contacted to change their treatment plan. During interviews, clinicians revealed they liked the test finding it easy-to-use but wanted faster time-to-results and testing for more bacteria. Clinical trials are needed to see if these POCTs can safely and cost-effectively reduce antibiotic prescribing in primary care.

Word count: 194

INTRODUCTION

Primary care is responsible for the majority of antibiotic prescribing in the UK,[1] US,[2] and worldwide.[3] Most of this prescribing is for the treatment of acute respiratory tract infections (RTIs), despite evidence suggesting that antibiotics do not confer clinical benefit in most patients.[4 5] This overprescribing results in side effects and fuels the global health crisis of antimicrobial resistance (AMR).[6 7] Clinicians cannot easily differentiate on clinical grounds those who might be more likely to benefit from antibiotics.[8 9] The high prescribing rate is therefore often attributed to clinical uncertainty regarding microbiological diagnosis and disease prognosis.[10 11] A review on AMR commissioned by the UK Department of Health and Social Care advocated the use of rapid diagnostics to reduce unnecessary antibiotic prescribing.[7]

Rapid microbiological point-of-care testing (POCT) technology can detect a range of upper respiratory tract microbes. If diagnostic of aetiology, results could improve targeting of antibiotics to susceptible bacterial infections. These tests are being trialled and used in some UK hospitals [12 13] but have not been formally evaluated in UK primary care. The COVID-19 pandemic has seen rapid investment in POCTs and increased hospital uptake.[14] The main drawbacks of this technology which may limit use and/or uptake in primary care include run times exceeding the timespan of appointments, the limited range of microbes detected (typical bacteria are not detected), high costs, and lack of evidence regarding clinical and cost-effectiveness.

This observational, mixed-methods feasibility study provided first-hand experience of a multiplex microbiological POCT to potential users in primary care to gain an understanding of what clinicians' think of POCTs, how often they would use them, how they fit into the flow of primary care, and how they could influence management. We selected the Biofire® Filmarray® Respiratory Panel v1.7 (bioMérieux) because it requires a short hands-on time (circa 2 minutes), tests for more respiratory micro-organisms than competitor POCTs, and has a rapid turnaround time.[15]

METHODS

Design and setting

We conducted a mixed-methods prospective cohort and staff interview study from February-June 2019 in the South West of England. All 48 research active GP practices in the Bristol, North Somerset and South Gloucestershire Clinical Commissioning Group were invited to participate via the National Institute for Health Research West of England Clinical Research Network. Of the practices expressing interest, we purposefully sampled four that varied in list size and patient deprivation. The Biofire® Filmarray® v1.5 instruments (BioFire Diagnostics, Utah) were installed in each practice for six weeks, taking 50 x 40 x 46.5 cm of benchtop space in treatment rooms.

Study population and sample size

All patients age >3 months with suspected acute (≤28 days) respiratory infection, including patients with comorbidities, were eligible. Patients were excluded if unwilling to be swabbed or previously recruited. Clinicians, health care assistants (HCAs), and administrators directly involved with the study were eligible for interview.

As this is the first use of this technology in UK primary care, this evaluation is intended to describe the epidemiology and characteristics of use. Therefore, a pragmatic sample size was chosen based on recruitment rates in a previous study our team has completed in this population.[16]

Pre-test measures

After informed patient/parent consent, clinicians completed a case report form recording patient and RTI characteristics including: duration of illness (days), patient/parent perceived wellness (0 to 10), diagnosis, certainty of diagnosis (uncertain, fairly uncertain, certain, very certain), perceived likelihood of patient benefiting from an antibiotic (1 most to 10 least), antibiotic prescribing, C-

reactive protein result, secondary care referral and reason for recruitment. Standardised questions were used on the case report form to minimise measurement bias. Clinicians took two swabs, one each from the throat and lower nostril/s (anterior nares), noting the time.

Testing

Both swab tips were placed into viral transport medium (Sigma Virocult® Duo, Medical Wire and Equipment, UK) before processing according to stability parameters: ≤4 hours at room temperature (18-30°C) or <3 days if refrigerated (2-8°C). Staff received training on set-up procedures according to manufacturer instructions (Supplementary Material 1) and were provided with a stopwatch to measure processing time. The Biofire® Filmarray® Respiratory Panel v1.7 uses real-time nested polymerase chain reaction (PCR) techniques to detect the presence/ absence of 17 respiratory viruses and three atypical bacteria (Supplementary Material 2), processes one sample at a time, taking around 65 minutes, with final test results printed (Supplementary Material 3) and scanned into medical records.

Post-test measures

Test results were returned to the treating clinician who reported their revised working diagnosis, perceived benefit of antibiotics, antibiotic prescribing decision and whether they contacted the patient with the result. At the end of the study, they completed a 30-day follow-up record of National Health Service (NHS) contacts, antibiotic prescribing, requests for further testing, and serious adverse events.

Data analyses

Analyses were undertaken using Stata version 15.0 software (StataCorp. 2017. Stata Statistical Software: Release 15). We used summary statistics to describe participants' baseline characteristics; 'hands-on' time taken to set-up each test; time between sample collection and processing; and

antibiotic prescribing pre- and post-test. Pearson's chi-square test was used to compare diagnostic certainty pre- and post-test, and the Wilcoxon rank test to compare clinician predicted antibiotic benefit. Missing data was excluded to carry out a complete case analysis.

Qualitative interviews

LD and GL are experienced qualitative, non-medical researchers (PhD) and neither have worked in POCT manufacturing or sales. Both have experience working on studies relating to health services and AMR. Purposive sampling was used to ensure views and experiences of the POCT were obtained from clinicians, test processors, and administrators, until no new perspectives were observed. LD interviewed staff in person or via telephone after completion of POCT use. Written consent was obtained and a flexible topic guide used to aid questioning while allowing participants to discuss new issues. Interviews were transcribed, anonymised and thematically analysed[17] using NVivo (version 12) (LD). They were not returned to interviewees for comment. A subset of transcripts were coded inductively to establish an initial analysis framework (LD and GL); differences were discussed to ensure coding consensus[18] and all further analysis was undertaken by LD. Transcripts were coded using the following themes: (i) recruitment; (ii) test processing; (iii) results and analysis; (iv) study management; (v) positives, negatives and improvements; (vi) practice and surgery characteristics; (vii) patient characteristics; and (viii) interviewee characteristics.

RESULTS

Practices, clinicians and patients

Fifteen GP practices expressed interest of whom four were selected with varying list sizes (9,300 to 44,739), rurality (three urban, one rural), and deprivation (scores two to nine[19]). Forty-four staff (22 doctors, 12 nurses, 8 HCAs, 2 administrators) were trained in study methods (Supplementary Material 4).

Twenty clinicians (15 GPs and 5 nurses) recruited 93 patients to the study, estimated to be 1 in 3 eligible patients. Patient median age was 29 (0.5-83) years with 31% under 5 (Table 1, Supplementary Material 5), 57% female, the majority of white ethnicity and 44% with co-morbidities, including 18% with chronic respiratory diagnoses (Table 1). Median pre-consultation illness duration was 7 (range 1-28) days. Clinicians reported lower illness severity scores (median 4, interquartile range (IQR) 2-5) than patients (median 7, IQR 5-8). Pre-test diagnoses were upper RTI (47%), lower RTI (32%), viral/ influenza (18%, upper and lower RTIs) and 2% 'other' (one dust allergy and one unknown). Twenty-six (28%) patients were prescribed an antibiotic pre-test, more commonly in those with (51%) than without (15%) co-morbidities (Table 2). Clinicians reported they would have considered sending a swab to their local laboratory in 16%, for influenza or *Bordetella pertussis*.

Test processing, results, and antibiotic prescribing

75% of sample processing was conducted by nurses, 22% by HCAs and 3% by one GP. 72% of samples were processed <4 and 90% <24 hours (Supplementary Material 6). Median time to set up each test was 2.72 minutes.

Of the 93 samples tested, three were inconclusive (two equivocal and one invalid), 37% had no pathogen, 58% had at least one virus (one also with an atypical bacterium), and 2% had atypical

bacteria (Table 2). 41% tested positive for a single pathogen, 17% two pathogens, and 2% had three pathogens (Supplementary Material 7). Viral pathogens were Human Rhinoviruses/Enteroviruses (25%), Influenza A (20%), Adenovirus (14%), Human Metapneumovirus (HMPV) (11%), Parainfluenza Viruses (PIV) (5%) and Coronaviruses (3%). *Mycoplasma pneumoniae* was positive in two and *Bordetella pertussis* in one swab (Table 2). Antibiotics were prescribed (pre-test) to 35% with no pathogen and 25% testing positive for a virus. None with atypical bacteria were prescribed an antibiotic pre-test (Table 2).

Pre- and post-test comparison

The proportions of patients in whom clinicians' diagnoses were certain or very certain increased after test use (p=0.02), particularly when a pathogen was detected (p<0.001, Figure 1). Clinicians were less likely post-test to predict benefit from antibiotics (median score 9/10, IQR 8 to 10) than pre-test (9, IQR 5 to 10, p=0.02). Nineteen (20%) diagnoses changed post-test, including non-influenza to influenza (n=9), influenza to non-influenza (n=2), bacterial to viral (n=6), viral to bacterial (n=2), viral to non-infected COPD exacerbation (n=2) and non-infected COPD exacerbation to upper RTI (n=1, Table 3).

Seventy-one patients were contacted post-test to be advised of no change in management. Eight were advised of a change: three to collect a new antibiotic prescription; three that antibiotics prescribed were no longer required; one that the delayed prescription should be started immediately; and one that the immediate prescription should be delayed.

As this was a feasibility study we did not measure or assess the impact of confounders. There was no missing data in the 30-day follow-up notes review. Twenty-nine patients (31%) re-consulted or sought further NHS treatment (GP, A&E, out of hours or NHS 111) within 30 days, of whom 11 (38%) were subsequently prescribed antibiotics. No patient requested a repeat test. Three patients were admitted to hospital, none attributed to the study (Supplementary Material 8).

Qualitative interviews

Twenty-two interviews were conducted: thirteen clinicians (who recruited 88% of all patients), eight test processors (who ran 98% of all tests) and all four administrators (who included two of the clinicians; Table 4). TK identified study leads and administrators at surgeries and LD contacted these for interviews. 7 GPs responsible for recruiting 1-2 patients each (11 patients – 12% - in total) and 2 HCAs who tested 1 sample each (2% in total of samples), were not interviewed either because saturation had been reached at the practice (n=5) or because their role was not known to LD (n=4) until receipt of practice data at the end of the study. All those invited agreed to be interviewed. LD requested and arranged interviews using a brief phone call or email identifying herself as a University of Bristol health services researcher, the interviewee and interviewer were otherwise unknown to each other. Interviews were either face-to-face or via phone call, according to interviewee preference. Both methods were used at 3 sites, while all interviews at site 4 took place by phone. LD visited site 4 independently to familiarise herself with the setting. Face-to-face interviews were in private rooms, except for one interview with an administrator, which took place in an open plan space with another administrator who was working and did not participate in the interview. Interview duration was between 13-41 (mean 25) minutes. Interviews at sites I and 2 took place concurrently due to practical issues concerning the Easter break. After these were completed, interviews began at site 3, and were completed before those at site 4 began (Table 4). Understanding or novel issues arising were checked in subsequent interviews within and between practices. Three main themes emerged. Participants could not provide feedback on findings due to changing demands resulting from the COVID-19 pandemic.

Implementation

All staff commented on the enthusiasm for, and simplicity of operating, the test: *"The test was easy to run and the results were fairly quick. The clinicians seemed to like it, so we had lots of referrals…. It was quite rewarding actually to discover what was [clinically] wrong"* [Nurse, Site 3].

In terms of limitations, the test had a 65-minute single-sample runtime, required physical space, and was considered noisy during the initial minutes of operation. One GP working in a room adjacent explained: *"If you've got a patient who's hard of hearing…Or a patient who you know, needs some extra support for learning disabilities, for hearing… it could actually impact … I don't think it was so bad that they were like: 'we can't have this running', but…there was planning around it."* [GP, Site 4].

Clinical impact

For some clinical staff there were clear benefits, especially where there was diagnostic uncertainty: *"I think coughs and colds are quite easy generally. I think it's more the tonsillitis …it's sort of those things that you think, well actually is this viral, is this bacterial? I think they're useful …it's just for grey patients rather than you know, runny nose and a sore throat and you look like you've got a cold."* [GP, Site 4].

Another potential benefit of the POCT result was to persuade certain patients against unnecessary antibiotics: *"If the patient or parent was particularly after antibiotics, for example and you felt that this was very clearly a viral infection. It might add extra weight if you then did a swab and showed that it was a viral infection"* [GP, Site 3].

In contrast, some clinicians reported that the POCT results did not impact on their initial treatment plan: *"I loved having the test – guilty pleasure, but it didn't change what I did to any of those patients. So, all of those patients were managed on clinical grounds so what I thought was appropriate clinically."* [GP, Site 1].

Some clinicians raised concerns about developing an over-reliance on the POCT and undermining clinical skills: *"If you want a test that's costly, you need to know …'what's it adding to your patient's care?' And anything to my mind that undermines the value that we put on a clinician's ability is a problem. I don't think a scenario …where we use the test in every patient would be a good thing*." [GP, Site 1].

Clinicians also discussed the potential for medicalisation of minor illness. *"I think having a test that does that would make that more … particularly people with colds and coughs, we're trying to, it's normal for people to get colds and coughs. It doesn't mean you need treatment."* [GP, Site 4]

Improving the test

Key improvements identified included a reduced run time, and the inclusion of clinically relevant bacteria, with GPs naming *Streptococcus pneumoniae*, *Haemophilus influenza* and *Moraxella catarrhalis*: *"It only tests for certain bacteria and it's whether we could test for more. There is a question mark about whether we're picking up just commensals and there's no clinical background, whether we would start over-treating, because sometimes you can have lots of bacteria at the back of your throat and it's not causing any harm and would we then feel pressurised into prescribing based on those results?"* [GP, Site 1].

Overall, clinicians indicated they would reserve judgement until the POCT's ability to support clinical management, improve outcomes, and decrease antibiotic use could be demonstrated. Were these shown to be the case, they would support its routine use in primary care.

DISCUSSION

Summary of principal findings

We believe this is the first evaluation of a multiplex respiratory microbiological POCT in UK primary care. The test was acceptable and easy-to-use, led to increased diagnostic certainty, and reduced expectation of antibiotic effectiveness. However, clinicians wanted shorter time-to-results and a more detailed bacterial panel. Comparison of pre- and post-test diagnoses suggests there was over-diagnosis of suspected bacterial infections and under-diagnosis of influenza in the absence of POCT results. 71 patients were contacted after the test to be advised of no change in management but only 8 were advised of a change. We noted that the majority of patients prescribed an antibiotic pre-test were those with co-morbidities, and a negative result (a 'no pathogen detected' result) does not exclude the presence of a typical bacterial infection. We think this may be the reason for the 'no change in management' decisions. POCT results should be combined with clinical observations, patient history and epidemiological information when making patient management decisions.

Strengths and weaknesses of the study

The strengths of this study include originality, recruitment from practices with diverse characteristics, and non-restrictive inclusion criteria. Ethnicity classification differed between practices preventing harmonisation of data, but the sample was similar to UK national data.[20]

With regard to limitations, the observational design prevents us from concluding if the POCT led to changes in diagnostic reasoning/management. Second, clinicians estimated they recruited 1:3 potential participants, but did not have time to record their characteristics. It is possible those recruited differed in terms of infection severity. Third, the accuracy of Biofire® Filmarray® depends on both the adequacy of the respiratory sample and performance of the multiplex PCR system. Sensitivity and specificity values for the Biofire® Filmarray® respiratory panel vary by microbe with

performance generally comparable to laboratory testing. Fourth, our recruitment season spanned February to June, thereby missing some seasonal microbes such as Respiratory Syncytial Virus (RSV), which was not detected in any sample. Fifth, we did not assess the clinical or scientific validity of views expressed by clinicians, or the feasibility of implementing the improvements recommended. Finally, this study was not resourced to seek patient perspectives.

Results in the context of other studies

To date there have been no studies published on the use of multiplex microbiological POCTs for RTIs in UK primary care. One recent study assessed POCT use to detect influenza in UK primary care.[21] A systematic review of POCTs in international primary care identified ten non-UK studies evaluating six different devices for the detection of Influenza and RSV.[22] Only one study in the Netherlands, has evaluated the use of a multiplex PCR POCT (the mariPOC® Respi test that measured up to 9 respiratory viruses) in a primary health care setting.[23]

In UK secondary care, we are aware of one randomised controlled trial (RCT) investigating the impact of Biofire® Filmarray® testing in adults presenting to the Emergency Department with RTIs. This showed no overall reduction in the proportion of patients treated with antibiotics but more patients in the POCT group received single doses or brief courses of antibiotics than those in the control group.[12] A prospective, randomised, non-blinded study conducted in an Argentinian emergency department over two respiratory seasons reported a significant reduction in antibiotic prescriptions for both adults and children tested with the Biofire® Filmarray® compared to those tested by standard care (immunofluorescence assay) and more appropriate use of oseltamivir in adult patients.[24] Two observational studies of patients hospitalised with RTIs demonstrated decreased duration of antibiotic use in patients tested with the Biofire® Filmarray® respiratory panel.[25 26]

Implications for clinical practice and future research

This study shows microbiological POCTs can be used in primary care and are acceptable to clinicians. Future research should focus on the potential for POCTs to reduce antimicrobial prescribing, using mixed methods RCTs to investigate the safety and efficacy of POCTs with qualitative methods to further understand clinician and patient perspectives. We identified only one cost analysis study. This Canadian study demonstrated a $291 per in-patient cost saving from POCT use.[27]

It is worth noting that significant improvements have been made to the BioFire® FilmArray® Respiratory panel (now called RP 2.1 *plus*). The latest panel includes detection of Mers-CoV, SARS-CoV-2, and *Bordetella parapertussis,* provides a faster time to result (45 minutes), and allows for simultaneous multiple sample processing with the addition of more modules. Other drawbacks of the POCT include the limited range of microbes detected (typical bacteria are not detected), the lack of (semi-) quantitative data and high costs (equipment costs in the region of £30-35K and price per test approx. £90). We expect the technology to keep evolving especially given the huge investment in development arising from the COVID-19 pandemic.

Conclusion

The POCT was acceptable and appeared to influence clinical reasoning. Clinicians wanted faster time-to-results and an expanded bacterial panel. RCTs are urgently needed to first investigate safety and efficacy, and then understand the clinical and cost effectiveness of POCT use to improve patient outcomes and antibiotic prescribing.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

Declarations

Ethical approval: This study was approved by the South West – Central Bristol Research Ethics Committee (reference 18/SW/0203).

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The authors have no conflicts of interest to declare.

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FIGURE LEGEND

Figure 1. Clinician's diagnostic certainty before and after the Biofire® Filmarray® test for 93 patients with suspected respiratory tract infections presenting to UK primary care (2019).

TABLES

Table 1. Baseline characteristics of 93 study participants presenting to UK primary care with a suspected respiratory tract infection (2019).

Participants (n=93)	Number (%) unless otherwise stated
Gender	
Female	53 (57)
Male	40 (43)
Age, years (median, IQR)	29 (2 to 58)
Ethnicity	
Asian	4 (4)
Black	2 (2)
Mixed	2 (2)
British or mixed British	25 (27)
White (British or other)	32 (34)
Missing	28 (30)
Illness duration at recruitment, days (median, IQR)	7 (3 to 14)
Severity of illness score (median, IQR)	
Patient/ parent of young patient (92/93) Missing (1/93)	7 (5 to 8)
Clinician (92/93) Missing (1/93)	4 (2 to 5)
Pre-test diagnoses	
Upper respiratory tract infection (URTI) / cold	32 (34)
Influenza / influenza type illness / flu	14 (15)
Viral chest infection/acute bronchitis/ acute lower respiratory tract infection/ bronchiolitis	11 (12)
Bacterial chest infection/acute bronchitis/ acute lower respiratory tract infection	10 (11)
Tonsillitis / pharyngitis / quinsy / throat abscess /peritonsillar cellulitis	8 (9)
Viral exacerbation of asthma / COPD / bronchiectasis	5 (5)
Viral illness	3 (3)
Viral sore throat	3 (3)
Otitis media / ear infection	1 (1)
Croup	1 (1)
Whooping cough	1 (1)
Pneumonia	1 (1)
Non-infected exacerbation of asthma / COPD / bronchiectasis	1 (1)
Other Dust allergy Cough of unclear aetiology	2 (2) 1 (1) 1 (1)
Co-morbidities[a]	
Asthma	11 (12)
Chronic obstructive pulmonary disease/ bronchiectasis/ other chronic lung disease)	8 (9)
Atrial fibrillation	3 (3)
Cancer (under follow up/current treatment)	1 (1)
Coronary heart disease	5 (5)
Depression/anxiety/ other mental health condition	10 (11)
Diabetes mellitus (type 1 or 2)	5 (5)

Heart failure	2 (2)
Hypertension	8 (9)
Hypo/hyper-thyroidism	1 (1)
Rheumatoid arthritis	3 (3)
Stroke / transient ischaemic attack	1 (1)
Other	26 (28)
Inflammatory bowel disease	4
Glaucoma	3
Diverticulosis/ diverticular disease	2
Gastritis/ oesophagitis	2
Hypercholesterolemia	2
Anorexia nervosa	1
Ankylosing spondylitis	1
Coeliac disease	1
Hyperprolactinaemia	1
Insomnia	1
Irritable bowel syndrome	1
Migraine	1
Polycystic ovary syndrome	1
Polymyalgia rheumatic	1
Premature	1
Prostatism	1
Supraventricular tachycardia	1
None	52 (56)

[a] more than one co-morbidity per patient possible

Table 2. Biofire® Filmarray® result and pre-test antibiotic prescribing for 93 UK primary care patients with a suspected respiratory tract infection (2019)

Biofire Filmarray® results	Total	Antibiotics prescribed		Percentage prescribed antibiotic
		No	Yes	
No pathogen detected[a]	34	22	12	35.3
Atypical bacteria	3	3	0	0.0
Bordetella pertussis	1	1	0	0.0
Mycoplasma pneumoniae[b]	2	2	0	0.0
Viruses	53	40	13	24.5
Adenovirus[b]	13	10	3[c]	23.1
Coronaviruses	3	3	0	0.0
CoV 229E		1	0	
CoV HKU1		1	0	
CoV NL63		1	0	
Human Metapneumovirus	10	10	0	0.0
Human Rhinoviruses/Enteroviruses	23	17	6[c,d]	26.1
Influenza A	19	14	5	26.3
Untyped	1	1	0	
A/H1-2009	8	6	2	
A/H3	10	7	3[c,d]	
Parainfluenza Viruses	5	3	2	40.0
PIV 1	0	0	0	
PIV 2	1	0	1	
PIV 3	4	3	1	
PIV 4	0	0	0	
Inconclusive test results	3	2	1	33.3
Invalid	1	0	1	
Unequivocal	2	2	0	
Total	93	67	26	27.9

[a] Influenza B, Respiratory Syncytial Virus and *Chlamydia pneumoniae* were measured but not detected

[b] One patient was found to have a co-infection of *Mycoplasma pneumoniae* and adenovirus, this patient was not prescribed an antibiotic pre- or post-test.

[c] One patient was found to have a co-infection of adenovirus and influenza A/H3 and one patient was found to have a co-infection of adenovirus and human rhinovirus/enterovirus.

[d] One patient was found to have a co-infection of human rhinovirus/enterovirus and influenza A/H3.

Table 3. Changes in the clinical diagnosis of 19 primary care patients following Biofire® Filmarray® testing at their GP practice in the South West of England (2019)

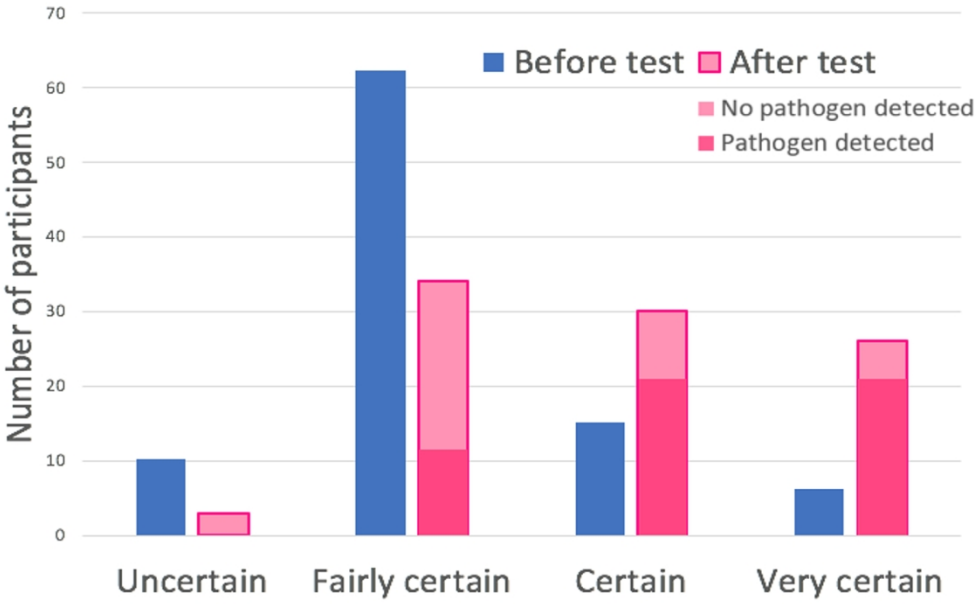
Category	Changes in the clinical diagnosis post test	N	Antibiotics prescribed pre-test (N)
1	Non-influenza to Influenza[a]	9	4
2	Influenza to non-influenza	2	0
3	Bacterial to viral[a]	6	6
4	Viral to bacterial[b]	2	1
5	Viral to non-infected COPD exacerbation	2	1
6	Non-infected COPD exacerbation to URTI	1	1
Total		19[b] (20% of total)	13

[a] Three patients contribute to both categories 1 and 3, therefore total number of patients in whom diagnoses changed = 19
[b] Only one patient in category 4 was prescribed an antibiotic post-test

Table 4: Staff interviewees - professional and study roles of 22 primary care staff from four GP practices in the south west of England (2019), interviewed for their perceptions of respiratory point-of-care test usage in primary care

Clinician	Number of patients recruited (%)	Test processor	Number of tests (%)	Administrator	Number of tests (%)
Site 1 (21 patients tested); Interviews took place between 18-04-19 and 16-05-19					
GP partner *(research lead)*	10 (48%)	HCA	13 (62%)	Administrator	21 (100%)
GP	3 (14%)	HCA	5 (24%)		
4 GPs (not interviewed)	*2 each (38%)*	Nurse manager	2 (9.5%)		
		1 HCA (not interviewed)	*1 (4.5%)*		
Site 2 (28 patients tested); Interviews took place between 10-04-19 and 14-05-19					
Nurse independent prescriber	18 (64%)	Research nurse	28 (100%)	Administrator	28 (100%)
GP *(research lead)*	6 (21%)				
Nurse independent prescriber	3 (11%)				
1 GP (not interviewed)	*1 (4%)*				
Site 3 (31 patients tested); Interviews took place between 20-05-19 and 05-06-19					
Nurse practitioner	12 (39%)	Research nurse[a]	23 (74%)	Research nurse[a]	31 (100%)
Urgent Care Practitioner	10 (32%)	Research nurse	7 (23%)		
GP partner	6 (19%)	*1 HCA (not interviewed)*	*1 (3%)*		
GP partner *(research lead)*	1 (3%)				
2 GPs (not interviewed)	*1 each (6%)*				
Site 4 (13 patients tested); Interviews took place between 14-06-19 and 11-07-19					
GP[b] *(research lead)*	6 (46%)	Practice nurse	10 (77%)	GP[b]	13 (100%)
Minor illness nurse	5 (38%)	GP[b]	3 (23%)		
GP partner	1 (8%)				
GP	1 (8%)				

[a] One research nurse at site 3 had roles as both test processor and administrator
[b] One GP at site 4 (the lead investigator) had all three roles



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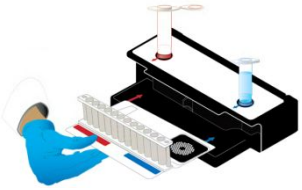
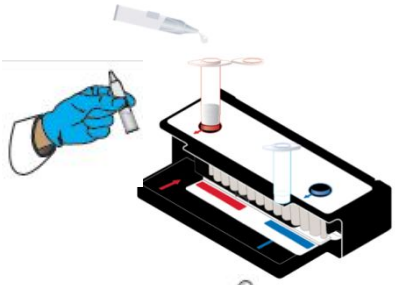
Supplementary Material 1. Instructions for Biofire® Filmarray® (running a sample)

1. Clean work surfaces with 10% bleach solution provided. Insert pouch into pouch loading station, place hydration vial into blue well and sample vial into red well

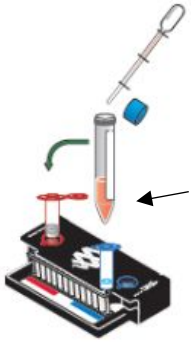


2. Unscrew hydration vial anticlockwise and inject into the pouch through the blue inlet port (forcefully push down to puncture seal)

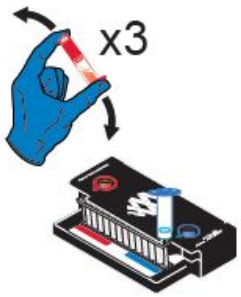
3. Invert sample buffer ampoule so tip is facing upwards and firmly pinch textured tap on side of ampoule until seal snaps, then add the sample buffer to sample vial



4. Using the transfer pipette draw up sample to third line and add to sample vial



5. Close the lid of the sample vial firmly and invert 3 times to mix the sample, then return sample vial to red well of pouch loading station



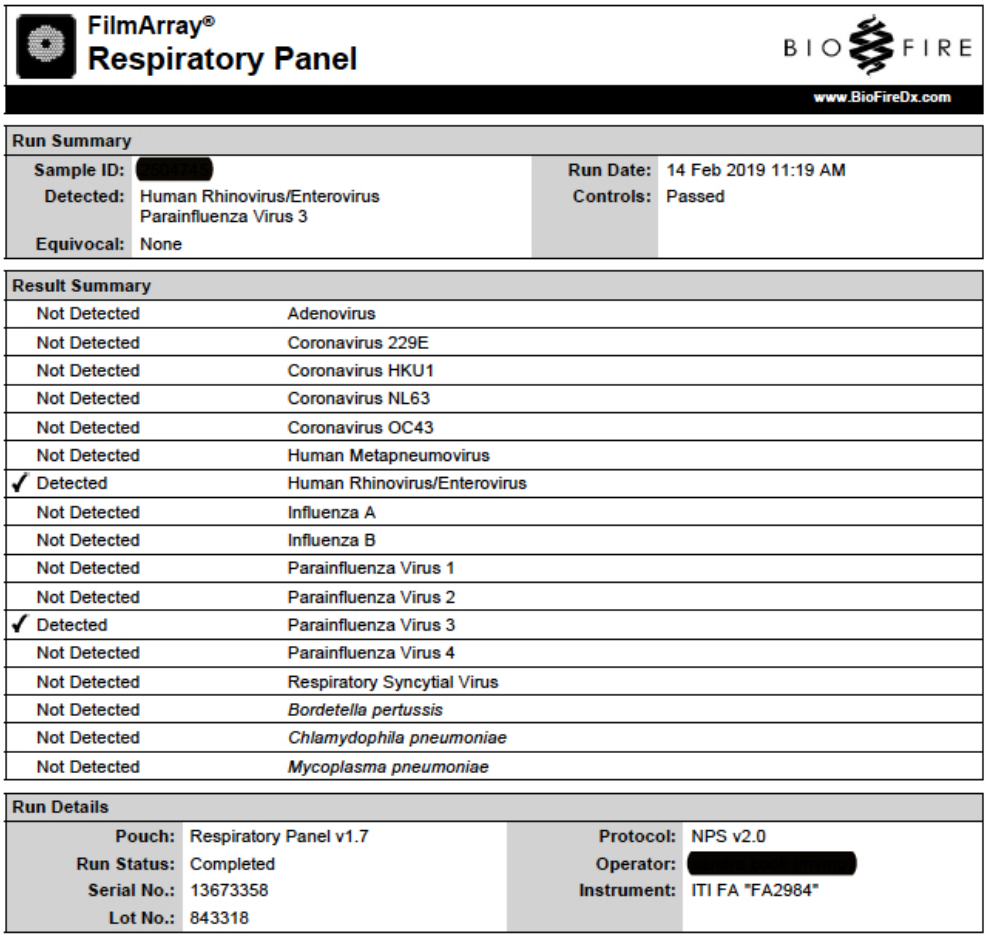
6. Unscrew sample vial anticlockwise, pause for 3-5 seconds, and inject into the pouch through the red inlet port

7. Change your gloves. Insert pouch into the instrument (it should click into place when properly seated) and follow on-screen instructions for initiating a test.
(Enter username and password)

Modified from the FilmArray® Respiratory Panel Quick Guide
BioFire Diagnostic, LLC, FilmArray® Respiratory Panel (RP) Instruction Booklet, 2015, by permission of BioFire Diagnostic, LLC.

Supplementary Material 2. Microbes tested

The pathogens measured by the Biofire® Filmarray® Respiratory Panel v1.7 consist of 17 viruses (Influenza A (untyped, A/H1, A/H1-2009, A/H3), Influenza B, Adenovirus, Coronaviruses (HKU1, NL63, 229E, OC43, not SARS-CoV-2), Human Metapneumovirus, Human Rhinovirus/ Enterovirus, Parainfluenza (types 1, 2, 3, 4) and Respiratory Syncytial Virus) and three atypical bacterial (*Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumonia*). Human Rhinovirus and Enterovirus cannot be distinguished due to genetic similarity. Results are presented as pathogen detected, not detected, equivocal or invalid. An equivocal result is returned where the run is successfully completed but there is discrepancy between the FluA-pan assay and a subtyping assay, which means results for Influenza A are inconclusive. An invalid result is returned when the run did not successfully complete including the control assays and this is typically associated with instrumental, software or communication errors. Retesting the original sample is advised for equivocal or invalid results.



FilmArray®
Respiratory Panel

BIOFIRE
www.BioFireDx.com

Run Summary

Sample ID:	[redacted]	**Run Date:**	14 Feb 2019 11:19 AM
Detected:	Human Rhinovirus/Enterovirus Parainfluenza Virus 3	**Controls:**	Passed
Equivocal:	None		

Result Summary

Not Detected	Adenovirus
Not Detected	Coronavirus 229E
Not Detected	Coronavirus HKU1
Not Detected	Coronavirus NL63
Not Detected	Coronavirus OC43
Not Detected	Human Metapneumovirus
✓ Detected	Human Rhinovirus/Enterovirus
Not Detected	Influenza A
Not Detected	Influenza B
Not Detected	Parainfluenza Virus 1
Not Detected	Parainfluenza Virus 2
✓ Detected	Parainfluenza Virus 3
Not Detected	Parainfluenza Virus 4
Not Detected	Respiratory Syncytial Virus
Not Detected	*Bordetella pertussis*
Not Detected	*Chlamydophila pneumoniae*
Not Detected	*Mycoplasma pneumoniae*

Run Details

Pouch:	Respiratory Panel v1.7	**Protocol:**	NPS v2.0
Run Status:	Completed	**Operator:**	[redacted]
Serial No.:	13673358	**Instrument:**	ITI FA "FA2984"
Lot No.:	843318		

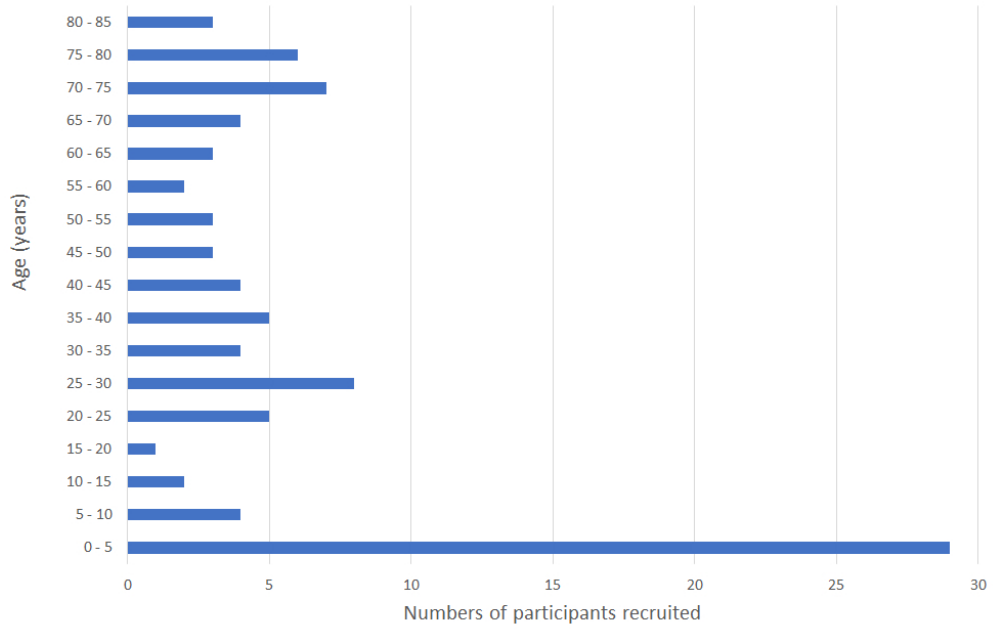
228x218mm (72 x 72 DPI)

Supplementary Material 4. Description of practices

GP site	Deprivation score[a]	Number of				
		Registered patients	Clinicians	Clinicians trained	Patients recruited	Patients in whom CRP[b] test used
1	9	16,500	17	14	21	3
2	9	44,739	24	7	28	2
3	9	13,500	21	16	31	0
4	2	9,300	11	7	13	0
Totals		84,039	73	44	93	5

[a] Deprivation scores are taken from the National General Practice Profiles as recorded by Public Health England

[b] C-reactive protein



258x168mm (96 x 96 DPI)

Supplementary Material 6. Time between swab collection and start of testing

Time (hours)	N	%
< 4	67	72
≥ 4 < 8	3	3
≥ 8 < 24	14	15
≥ 24 < 48	2	2
≥ 48 < 72[a]	7	8
Total	93	100

[a]6 of these samples were collected on a Friday afternoon

Supplementary Material 7. Number of samples reporting co-detection of two pathogens

	AdV	CoV 229E	hMPV	HRV/EV	Flu A/H1-2009	Flu A/H3	PIV 3	*M. pneumoniae*	Total
AdV			1	4	2	1		1	9
CoV 229E				1					1
hMPV	1			2					3
HRV/EV	4	1	2		1	2	1		11
Flu A/H1-2009	2			1					3
Flu A/H3	1			2					3
PIV 3				1					1
M. pneumoniae	1								1
Total	9	1	3	11	3	3	1	1	32[b]

a. Abbreviated pathogen names: Adv =Adenovirus, CoV = Coronavirus, hMPV = Human Metapneumovirus, HRV/EV= Human Rhinoviruses/Enteroviruses, Flu A= Influenza A, PIV = Parainfluenza Virus, *M. pneumoniae= Mycoplasma pneumoniae.*

b. 32 pathogens co-isolated from 16 patients

c. Co-infections not included in the table above include two samples reporting the presence of 3 viral pathopgens: one sample tested positive for CoV HKU1, HRV/EV, and Flu A/H1-2009, and another tested positive for Adv, hMPV and HRV/EV.

Supplementary Material 3. An anonymised Biofire® Filmarray® test report

Supplementary Material 5. Age distribution of 93 primary care patients tested by the Biofire® FilmArray® Respiratory Panel (2019)

Supplementary Material 8: Serious adverse events

Hospital admissions	Age	Sex	Duration (days)	Maximum intensity	Main diagnosis or symptom as on initial report	Discharged diagnosis (including hospital microbiological test results)	Biofire Filmarray® results[a]	Relatedness[b] /causality	Summary of relatedness reason
Subject A, event 1	9m	M	5	Moderate	Viral chest infection/acute bronchitis/acute lower respiratory tract infection/bronchiolitis	Clinical diagnosis: wheezy LRTI positive for Influenza A	Coronavirus HKU1, Human Rhinovirus/ Enterovirus, and Influenza A H1-2009	Unlikely to be study related	Evidence suggests the cause of the child's illness was viral
Subject A, event 2	9m	M	5	Severe	Viral URTI and diarrhoea	Bronchiolitis, right upper lobe consolidation, positive for Rhinovirus on PCR	Coronavirus HKU1, Human Rhinovirus/ Enterovirus, and Influenza A H1-2009	Not related	Evidence suggests the cause of the child's illness was viral
Subject A, event 3	10m	M	1	Moderate	Diarrhoea, not eating following E.coli UTI detected 4 days ago	Suspected UTI diagnosis	Coronavirus HKU1, Human Rhinovirus/ Enterovirus, and Influenza A H1-2009	Not related	Evidence suggests the cause of the child's illness was a UTI
Subject B	2.6y	F	5	Severe	Suspected sepsis, pyrexia, low saturations, unwell, lower respiratory tract infection	NPA[c]: Positive for Human Metapneumovirus, throat swabs negative, partial collapse of right lower lobe and L basal atelectasis. In-hospital investigations did not detect a bacterial infection however an underlying infective consolidation cannot be excluded.	Human Metapneumovirus	Not related	Difficult to assess if the Biofire Filmarray test result resulted in delayed referral to hospital. Clinicians opinion was that the cause of the child's illness was entirely viral.

Hospital admissions	Age	Sex	Duration (days)	Maximum intensity	Main diagnosis or symptom as on initial report	Discharged diagnosis (including hospital microbiological test results)	Biofire Filmarray® results[a]	Relatedness[b] /causality	Summary of relatedness reason
Subject C, event 1	70y	M	4	Moderate	Exacerbation of COPD	No significant in-hospital investigations	Negative for all microbes tested	Not related	Hospitalised due to COPD.
Subject C, event 2	70y	M	5	Moderate	Infective exacerbation of COPD	PCR throat swab negative for RSV, and negative for Influenza A and B.	Negative for all microbes tested	Not related	Hospitalised due to COPD.

[a] Due to the genetic similarity between Human Rhinovirus and Enterovirus, the Biofire Filmarray® test cannot reliably differentiate them and so they are grouped together.

[b] Relatedness is defined as follows (from the 009 SOP research safety reporting United Hospitals Bristol):

Not related: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

Unlikely: Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause, which can by itself explain the occurrence of the event.

[c] NPA= Naso-pharyngeal aspirate

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study Design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6&7
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7
Study Size	10	Explain how the study size was arrived at	6
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	N/A
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11 & Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1 p20-21
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10, Tbls 2&3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	9, Suppl. M5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, Suppl. M7
Discussion			
Key Results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	8
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	8
Occupation	3	What was their occupation at the time of the study?	8
Gender	4	Was the researcher male or female?	1
Experience and training	5	What experience or training did the researcher have?	8
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	11
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	11
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	8 & 11
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	8
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	8
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	11
Sample size	12	How many participants were in the study?	11
Non-participation	13	How many people refused to participate or dropped out? Reasons?	11
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	11
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	11
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	11, Table 4
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	8
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	8
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	8
Field notes	20	Were field notes made during and/or after the inter view or focus group?	8
Duration	21	What was the duration of the inter views or focus group?	11
Data saturation	22	Was data saturation discussed?	8 & 11
Transcripts returned	23	Were transcripts returned to participants for comment and/or	8

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	8
Description of the coding tree	25	Did authors provide a description of the coding tree?	8
Derivation of themes	26	Were themes identified in advance or derived from the data?	11
Software	27	What software, if applicable, was used to manage the data?	8
Participant checking	28	Did participants provide feedback on the findings?	11
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	11-13
Data and findings consistent	30	Was there consistency between the data presented and the findings?	11-13
Clarity of major themes	31	Were major themes clearly presented in the findings?	11-13
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	12-13

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.