Study Protocol: Supporting Antibiotic Stewardship in Primary Care via Point-of-care testing (POCT) for acute respiratory tract infections.

Short Title: Supporting Antibiotic Stewardship in Primary Care via POCT. The ASPIRE study.

A collaboration between the NHS and the University of South Wales supported by a KESS2 Scholarship.

Knowledge Economy Skills Scholarships (KESS) is a pan-Wales higher-level skills initiative led by Bangor University on behalf of the HE sector in Wales. It is part funded by the Welsh Government's European Social Fund (ESF) programme for East Wales.

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Confidentiality Statement:

1.1 Study Setting

The ASPIRE study is an uncontrolled observational feasibility study, and a collaboration between the University of South Wales and Cwm Taf Morgannwg University Health Board (CTMUHB). The study is based at Ysbyty Cwm Rhondda (YCR) and Keir Hardie

Primary Care (KHPC) centres, where participant recruitment will take place. Study participants will be invited to provide capillary blood samples (via finger prick sampling) for testing. The principal investigators are Dr Aled Davies at YCR and Dr Shyama Velupillai at KHPC. Upon clinical assessment, and after provision of consent, participants will undergo an ARI (acute respiratory infection) POC assay. This is a dual marker immunoassay designed to detect raised levels of C-reactive protein and MxA in capillary blood. The assay uses the sensitivity of CRP and specify of MxA to aid in the differentiation of ARI's in Primary Care.

The POC assay results will be compared to the participants' clinical outcomes and the physician directed treatment pathway via reviewing medical records and by contacting the patient from 14 days after their visit.

The study is funded by a KESS award.

2. Introduction

2.1 Lay Summary

Antibiotic stewardship is fast becoming an essential measure to improve antibiotic prescribing by clinicians. Antibiotic stewardship not only presents a cost-effective strategy for the NHS but addressed the issue of antimicrobial resistance (AMR) and protects patients from harm caused by unnecessary antibiotic use.

The economic costs of antibiotic resistance are largely unknown, but it is anticipated that with an increased number of cases, effects to the economy could be severe. Infections and infectious diseases cost England & Wales an estimated £30 billion a year, with many cases of acute respiratory infections (Chaplin, 2017). POC diagnostic tests in a clinical setting could give clinicians the ability to distinguish between microbial and viral infections, providing a more informed decision to antibiotic prescribing.

The purpose of this study is to safely distinguish between bacterial or viral respiratory infections in a primary care setting using "point of care" (POC) testing to provide a retrospective insight as to whether clinical assessment of an acute respiratory infection (ARI) is justified. Upon clinical assessment, the current clinical practice prescribes antibiotics based on symptoms reported by the patient and a subjective review by the GP. This results in antibiotics being prescribed from an informed decision made by the clinician, based only from patient symptoms. The use of a dual marker immunoassay could guide informed decisions based on qualitative data and degree of infection using POC testing in Primary Care.

The POC assay uses a dual marker immunoassay to differentiate between a viral and bacterial infection. C-reactive protein (CRP) is raised in the blood stream in response to inflammation. CRP can be elevated in viral infections, but generally the rise is to higher levels in bacterial infections, especially severe bacterial infections. Another blood protein, the MxA protein, is selectively increased in people with viral infections and therefore has the potential to greatly enhance the rapid distinction between viral and bacterial respiratory infections.

NICE guidance from 2014 recommends the use of CRP POC test in the diagnosis and appropriate management of lower respiratory tract infections in adults aged 18 and over (excluding people with COPD) after clinical assessment whether antibiotics should be prescribed. The study POC assay data could be used as an effective tool alongside NICE guidelines to prescribe antibiotics based on CRP concentration where an infection may be viral. Recent clinical studies suggest the POC test is highly effective, yielding over 80% sensitivity and over 90% specificity when identifying bacterial and viral infections in adults (NICE, 2020).

2.2 Background

Respiratory tract infections (RTI) are a frequent health problem in developed countries, and the third most common cause of medical referral worldwide. Acute respiratory infections (ARI's) account for most antibiotic prescriptions written and around 20% of all medical referrals in developed countries (Reed, 2015). Data from 88 countries in five continents, with a total population of nearly 1200 million, showed that deaths due to bacterial and viral ARI's in 1972 amounted to 666 000 (A. Bulla, 2021).

ARI's pose a problem for clinicians due to their overlapping profiles of signs and symptoms. Clinical uncertainty regarding a suspected ARI patient's infection aetiology along with patient expectation can frequently result in the prescription of antibiotics even when it is probable that an infection is viral (Davies, 2016). The unnecessary use of antibiotics can have negative consequences, including the spread of antibiotic resistance, which poses a global health threat.

The rise of antibiotic resistance (AR) in the NHS has resulted in the number of infections due to antibiotic-resistant bacteria rising dramatically. The uptake of antibiotics as a population along with how they are used by a patient, has shown to be proportional to the prevalence of AR (Goossens, Ferech, Vander Stichele and Elseviers, 2005). The effects of wrongly prescribing antibiotics unnecessarily expose patients to the risk of adverse events caused by AR, such as Stevens-Johnson syndrome and *Clostridium difficile* infection (Tandan et al., 2017). The magnitude of these adverse outcomes are more pronounced as disease severity, strain virulence, or host vulnerability increase. The cost of treatment delays and failure to patients in healthcare systems incur the greatest negative impact of antibiotic resistance (Ahmad and Khan, 2019).

The introduction of rapid, POC tests to Primary Care hold the potential to positively improve patient treatment and reduce the economic cost the healthcare systems. The study POC assay is a rapid, point-of-care diagnostic test that is designed to aid in the differentiation of bacterial and viral ARIs, with the objective to help reduce inappropriate prescriptions of antibiotics in Primary Care practices. The POC assay is designed to be used by clinicians and makes use of MxA and CRP biomarkers in capillary blood to provide qualitative data to distinguish between viral and bacterial infections. CRP however is not considered an effective biomarker to distinguish between infections solely, due to being largely nonspecific. CRP levels can be raised due to lifestyle habits such as diet, smoking and limited physical activity, that are not suggestive of infection (Young, Gleeson and Cripps, 1991). MxA is an intracellular GTPase protein that is induced by type I and type III interferons and which serves as a sensitive and specific marker for viral infection (Haller and Kochs, 2011). The rationale of the POC assay is therefore to use a combination of both biomarkers to combine the sensitivity of CRP and specify of MxA to aid in the differentiation of ARI's in Primary Care.

Early clinical studies using the POC assay at Primary Care level in the United Sates has proven effective as a decision-making tool. A two centre study produced a high degree of diagnostic accuracy with bacterial vs viral at 92% and viral vs non-viral at 84-87% agreement (Self et al., 2017). Complimentary to data regarding the performance of the POC assay at Primary Care, initial data suggests that the POC assay can be a vital decision-making tool, where it is uncertain if antibiotics should be prescribed (NICE, 2021). An additional feature of the POC assay would be in improving the clinical management of patients with ARI's as clinical uncertainty can lead to the inappropriate prescription of antibiotics for ARI's. The reduction in consultations and treatment of antibiotic-related adverse events could result in significant cost savings as an antibiotic stewardship method (Beck et al., 2017). However, further evaluation of the POC assay would be of great clinical significance to a Primary Care outpatient setting, including for use with patients that would benefit from antibiotics (Shirley, 2019).

3.0 Study Aims and Objectives

A Primary care administered POC dual marker immunoassay utilising new technologies allowing on-site "in-house" diagnosis of ARI's may reduce unnecessary antibiotic prescribing by defining the bacterial or viral source of the infection. The POC assay could be used to guide GP's patient treatment and management decisions.

The primary objective of the study is to determine whether the POC assay is useful in aiding clinicians in the decision to prescribe antibiotics (Table 1).

Primary aims	**Secondary aims**
• Use a POC assay to distinguish between bacterial and viral infection in the Primary Care setting. • To assess the feasibility of using POCT to support clinician decision making in prescribing antibiotics.	• Produce data to evaluate usefulness of the POC assay. • Compare POC assay use to other POC assays used in Primary Care.

Table 1: *Primary & Secondary Study aims.*

4.0 Study Participants

The study population will be recruited from self-referred patients attending YCR and KHPC centres with a self-suspected acute respiratory infection (ARI). The study aims to collect a minimum of 140 participants using a pragmatic sampling regime. The feasibility study will

provide the data required to design and conduct a more detailed and statistically powered trial.

The ASPIRE study will not replace clinical judgement or expertise. Patient management actions will be based on clinical judgement independent of the POC assay results. The physician will only have access to this data after the patient has finished their consultation.

4.1 Inclusion exclusion criteria

Inclusion criteria	**Exclusion criteria**
• Subject >18 years of age. • Having new onset symptoms suggestive of acute respiratory infection (ARI within 7 days of seeking care: runny nose, nasal congestion, sore throat, cough, hoarse voice, softness of breath) with or without fever.	• Unable to provide informed consent. • Undergoing end of life care. • Immunocompromised or taking chemotherapy, oral steroids, or interferon. • Receiving a live vaccine in the last 14 days. • Taking antibiotics or antivirals in the last 14 days. • Patients that have symptoms lasting more than 7 days.

Table 2: *Inclusion and Exclusion criteria for the Aspire study.*

Clinical assessment including the POC assay can also be offered to patients with any of the following conditions following NICE guidelines (see Appendix 1a for NICE guideline pathways, figures 3, 4, 5, 6):

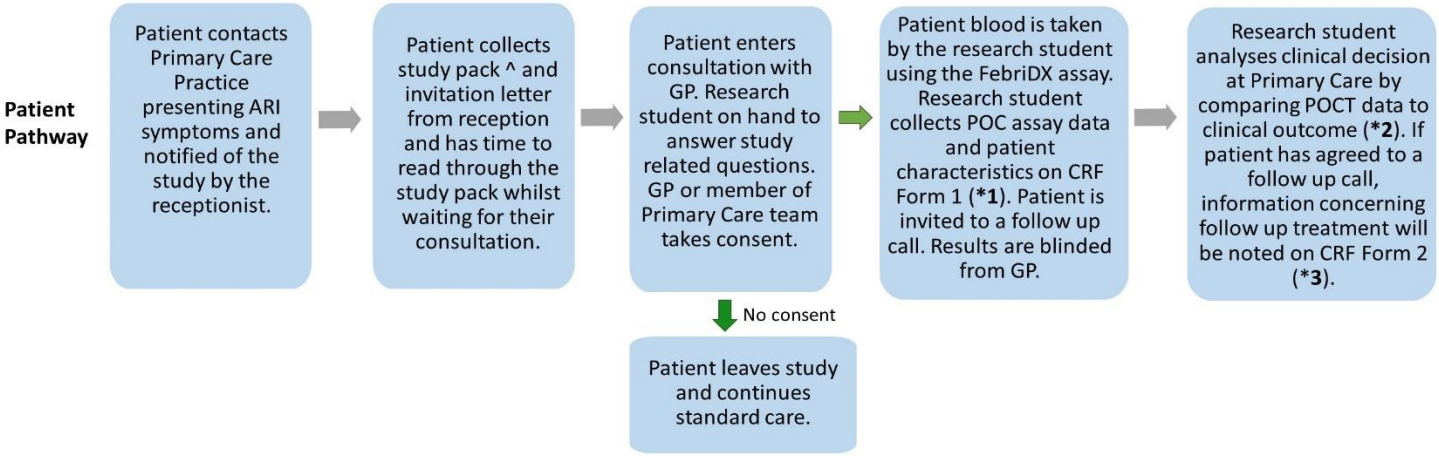
- Acute otitis media
- Pharyngitis
- Common cold
- Acute rhinosinusitis
- Acute cough/bronchitis

Patients testing positive for bacterial infections can be prescribed appropriate antibiotics following NICE prescribing pathway for common infections (see Appendix 1a fig 7).

5. Recruitment

Patients who have contacted their local Primary Care centre will be triaged for study inclusion by the receptionist when presenting with ARI symptoms and given an invitation letter and study pack (containing the Participant Information Sheet and Consent form).

Patients will be able to read through the study pack whilst waiting for their consultation and if required, additional time will be provided during the appointment.



ASPIRE Study Patient Pathway
***Data Collection : 1**= Quantitative & qualitative data from POC test systems, **2=** Patient clinical records, **3=** Telephone follow up.
^ Study Pack : Participant Information Sheet and Consent form.

Figure 1: *ASPIRE Study patient pathway.*

Once the GP has completed the routine consultation, the patient will be invited by their GP to partake in the study. Once consent has been obtained by the GP, the participant will be invited to take the POC test. A finger prick blood sample of 5 microliters will then be obtained by LAH and used for the POC test. The GP and nursing staff will be available in the event the patient feels anxious or stressed at any point in the sampling.

6. Data collection

The POC test result will be performed in a separate room after the consultation is over and the patient's treatment decided upon. The GP will be blinded to the study and presented an information sheet and consent form prior to the patient's consultation to agree upon these terms.

The POC assay outcome and the participant characteristics at presentation will be recorded on CRF 1. All patient identifiable data will remain at Keir Hardie and Ysbyty Cwm Rhondda Primary Care Centres. The following information will be collected:

Demographics: Age, Sex, Weight, Height

Clinical Findings, Arterial 0_2 Saturation, resting heart Rate, CRB, resting Respiratory Rate and (office) Blood Pressure (where available).

The CRF 1 will also record any additional tests the GP may have requested as per the standard treatment procedure such as sputum or PCT tests. CRF1 will record the final diagnosis.

CRF1 will include a tick-box to state whether the participant has agreed to participate in a follow-up call after 14 days of their initial appointment. Each participant will be asked if they would be able to conduct a short telephone call with the research student to discuss the

outcomes of the treatment. If consented, the participant will confirm this on a tick box on CRF 1 and will asked to provide a suitable contact mode and time to call back on the follow up form. Follow up data will be recorded on CRF 2.

Participant's medical records will be reviewed at the Primary care Practice to collect data concerning follow up treatment after 14 days to determine whether patients returned for medical treatment post appointment. Patient medical records will also be used to determine the clinical judgment of the initial assessment i.e. where they prescribed antibiotics or not. The clinical judgement and course of treatment followed will then be compared to the course of treatment that would have been suggested by the POC dual marker immunoassay result.

7. Data analysis

Anonymised study data will be stored on a password protected university computer. No personal data will be stored as participants will only be identifiable by their own unique PIN. If a participant decides to withdraw from the study for any given reason all the participant's data will be deleted.

Participant data will be compiled onto a computer spreadsheet for statistical analysis. Simple descriptive statistics will be used to characterise the study population. Diagnostic test results from primary care will be compared by statistical analysis and evaluated at a significance level at $p < 0.05$. Quantitative data from the POC assay will be analysed alongside medical records and clinical outcome at primary care.

8. Data management and quality control

All personal identifiable data will be treated as confidential. Each participant will be given a PIN upon providing consent which will be used across all their records and linked to their consent form. The study will comply with the requirements of the NHS Trust Data Protection and Confidentiality policy, which is based on the Data Protection Act 2018, the Caldicott Principles and Welsh Government guidance (GDPR). Identifiable personal data will be stored securely on an NHS computer with access controlled by the study PI's. Patient consent forms will be stored in a secured, locked cabinet at Ysbyty Cwm Rhondda and Keir Hardie Practices and will be destroyed within 6 months of the study closing. Anonymous research data will be stored on a spreadsheet, which can be accessed by other members of the research team within NHS and University of South Wales. Only the coded and anonymised data will be kept at the University of South Wales, according to USW policy (GDPR and Data Protection act 2018) for 5 years after completion of the study and then destroyed.

The Study research team will meet at the beginning and end of data collection of the study. Weekly review meetings between the research student and CI/DOS will be used to ensure the study follows the protocol.

9. Ethical considerations and Clinical governance

The study is hosted by CTMUHB and sponsored by the University of South Wales. The study will have received ethical approval from the Faculty of Life Sciences and Education Ethics committee, University of South Wales and a local NHS Research Ethics committee (LREC). Governance issues will be approved by Health Care Research Wales and managed by Cwm Taf Morgannwg Health Board via their Research and Development Department. Sensitive issues surrounding contacting patients with underlying health conditions will be met by appropriate caution under guidance of the clinical advisor. Any issues of distress arising from the study will be met by the appropriate services provided by the Medical practice.

10. Reporting and Dissemination

All data generated from the study will positively contribute to improving antibiotic stewardship in the NHS. The study will be presented by LAH as partial fulfilment of his PhD thesis. The processed anonymised data will be published in clinical journals and reported at appropriate professional meetings. KESS may advertise the study as a case study. Further reports for internal use and to the manufacturers of the assay will be made if requested.

11. Risks and Safety Reporting

11.1 Possible disadvantages and Risks to Patients by Taking Part

No adverse risks or disadvantages to patients taking part in this study is expected. There is a small risk of sharps injury from the lancet used for the finger prick test. There may be some minor discomfort and a small risk of infection.

If the patient or their healthcare professional believes that their participation in the study is negatively affecting the management of their condition in any way, they will be withdrawn from the study.

To monitor any potential risks or adverse effects, patient data will be reviewed at monthly study meetings.

11.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

11.3 Reporting Procedures for Serious Adverse Events

The investigators will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

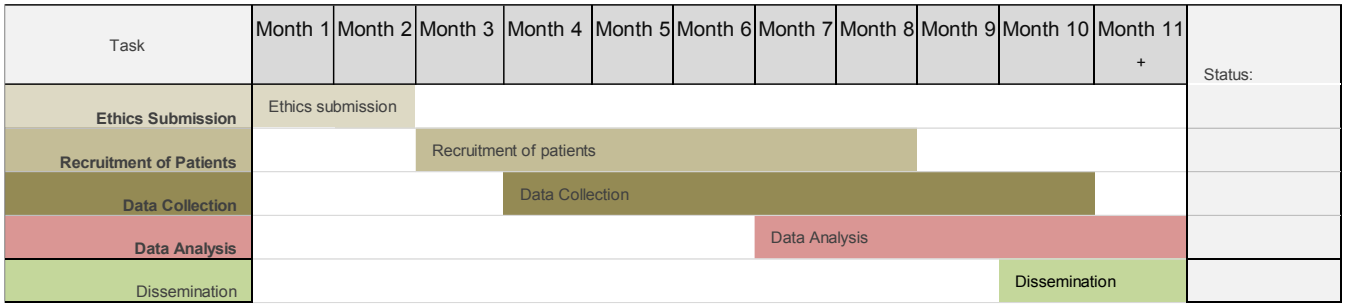
All SAE's (serious adverse event) will be reported to the research study team. The study does not anticipate reporting any SAE's, if the chief investigator believes that a SAE occurring is

related to the study it will be deemed a related unexpected serious adverse event (RUSAE). All SAE's identified by the local Investigator (PI) likely to be related to the protocol and be unexpected will be reviewed by the study team. The CI, local PI or other qualified NHS staff member may declare an SAE a RUSAE. This may be downgraded in discussion with the research team but if no agreement can be made the event should be reported as a RUSAE. A RUSAE once reported can be downgraded later upon the receipt of new information. The CI will then inform the local Research Ethics Committee (LREC) assigned to the study. RUSAEs must be reported to the REC within 15 calendar days of the CI (or their research team) being informed of the event.

12.0 Study timeline

The study is intended to progress over a period of 10 months. A timeline below describes an outline of the intended work plan.

10 Month Project Timeline



13. Reference List

A. Bulla, K., 2021. *Acute respiratory infections: a review*. [online] PubMed Central (PMC). Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2395579/> [Accessed 14 September 2021].

Ahmad, M. and Khan, A., 2019. Global economic impact of antibiotic resistance: A review. *Journal of Global Antimicrobial Resistance*, 19, pp.313-316.

Beck, J., Suppes, S., Smith, C., Lee, B., Leeder, J., VanDoren, M., Newland, J. and Goldman, J., 2017. Cost and Potential Avoidability of Antibiotic-Associated Adverse Drug Reactions in Children. *Journal of the Pediatric Infectious Diseases Society*, 8(1), pp.66-68.

Chaplin, S., 2017. Antimicrobial stewardship: changing the public's behaviour. *Prescriber*, 28(5), pp.52-53.

Chaplin, S., 2017. Antimicrobial stewardship: changing the public's behaviour. *Prescriber*, 28(5), pp.52-53.

Davies, S., 2016. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *Primary Health Care*, 26(1), pp.16-16.

Goossens, H., Ferech, M., Vander Stichele, R. and Elseviers, M., 2005. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet*, 365(9459), pp.579-587.

Haller, O. and Kochs, G., 2011. Human MxA Protein: An Interferon-Induced Dynamin-Like GTPase with Broad Antiviral Activity. *Journal of Interferon & Cytokine Research*, 31(1), pp.79-87.

Kurt.D, R., 2015. Respiratory Tract Infections A Clinical Approach. *Molecular Medicinal Microbiology*, 10, pp.1499-1506.

Nice.org.uk. 2020. [online] Available at: <https://www.nice.org.uk/advice/mib224/resources/febridx-for-creactive-protein-and-myxovirus-resistance-protein-a-testing-pdf-2285965512014533> [Accessed 17 January 2022].

Nice.org.uk. 2021. *Self-limiting respiratory tract and ear infections – antibiotic prescribing - NICE Pathways*. [online] Available at: <http://pathways.nice.org.uk/pathways/self-limiting-respiratory-tract-and-ear-infections-antibiotic-prescribing> [Accessed 21 September 2021].

Nice.org.uk. 2021. *Pneumonia in adults: diagnosis and management | Guidance | NICE*. [online] Available at: <http://www.nice.org.uk/guidance/cg191> [Accessed 15 September 2021].

Self, W., Rosen, J., Sharp, S., Filbin, M., Hou, P., Parekh, A., Kurz, M. and Shapiro, N., 2017. Diagnostic Accuracy of FebriDx: A Rapid Test to Detect Immune Responses to Viral and Bacterial Upper Respiratory Infections. *Journal of Clinical Medicine*, 6(10), p.94.

Shapiro, N., Self, W., Rosen, J., Sharp, S., Filbin, M., Hou, P., Parekh, A., Kurz, M. and Sambursky, R., 2018. A prospective, multi-centre US clinical trial to determine accuracy of FebriDx point-of-care testing for acute upper respiratory infections with and without a confirmed fever. *Annals of Medicine*, 50(5), pp.420-429.

Tandan, M., Vellinga, A., Bruyndonckx, R., Little, P., Verheij, T., Butler, C., Goossens, H. and Coenen, S., 2017. Adverse Effects of Amoxicillin for Acute Lower Respiratory Tract Infection in Primary Care: Secondary and Subgroup Analysis of a Randomised Clinical Trial. *Antibiotics*, 6(4), p.36.

Young, B., Gleeson, M. and Cripps, A., 1991. C-reactive protein: A critical review. *Pathology*, 23(2), pp.118-124.

14. Appendix 1

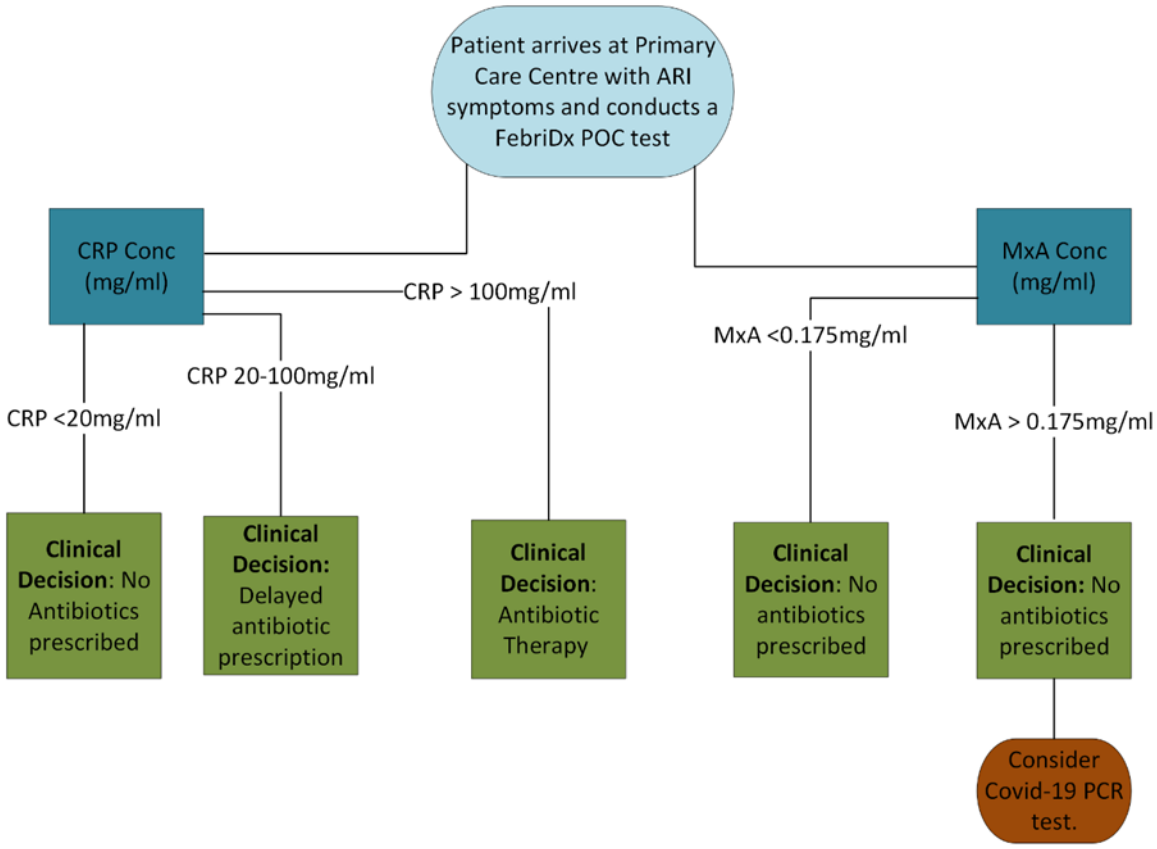


Figure 2. Possible future interventional implications of the FebriDx dual marker immunoassay at Primary Care level.

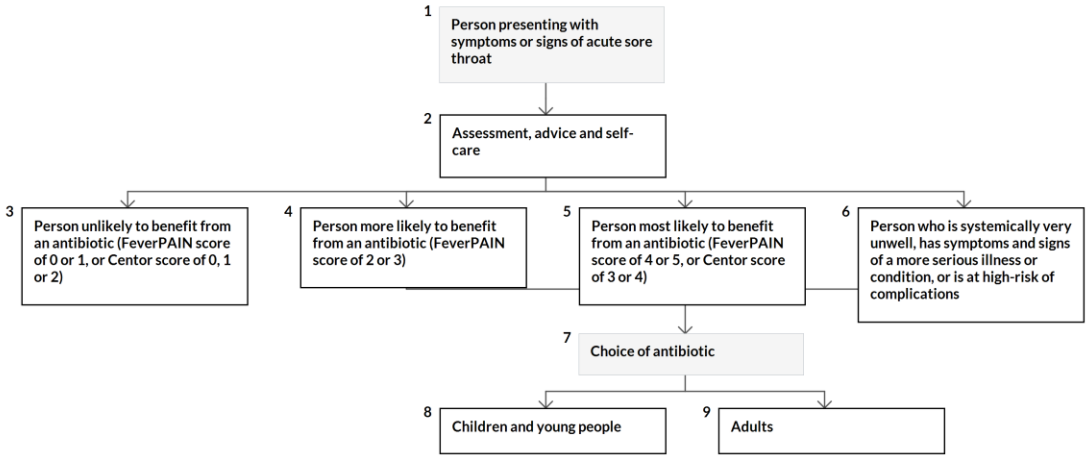


Figure 3. NICE Guidelines Pathway for Pharyngitis symptoms

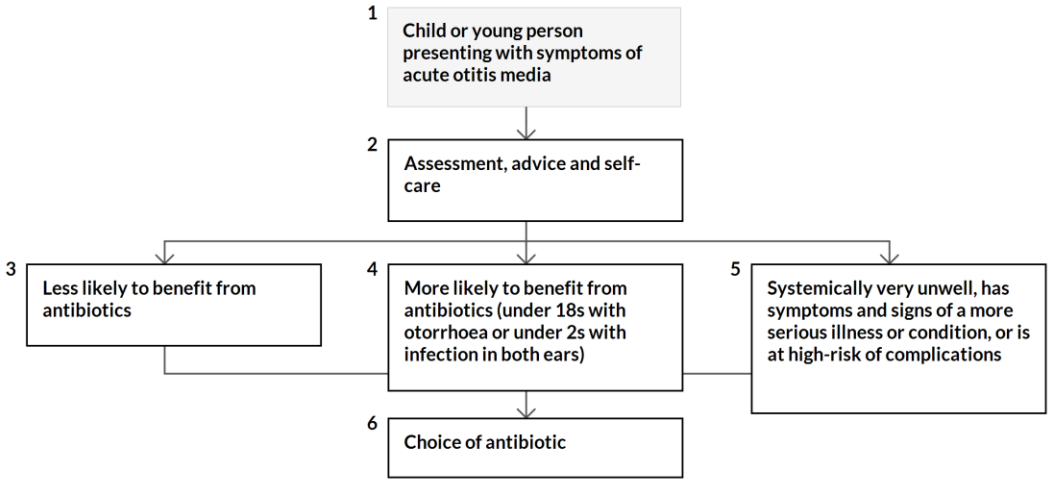


Figure 4. NICE Guidelines Pathway for Acute otitis media

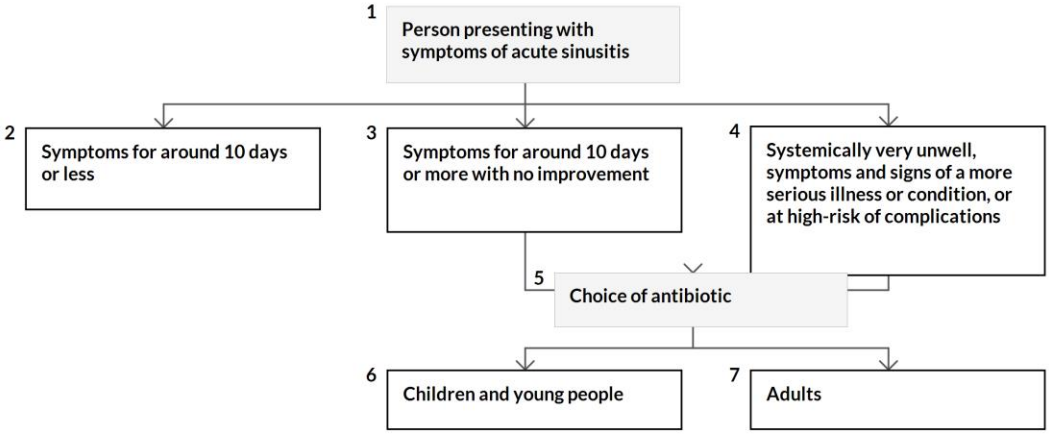


Figure 5. Nice Guidelines Pathway for acute rhinosinusitis

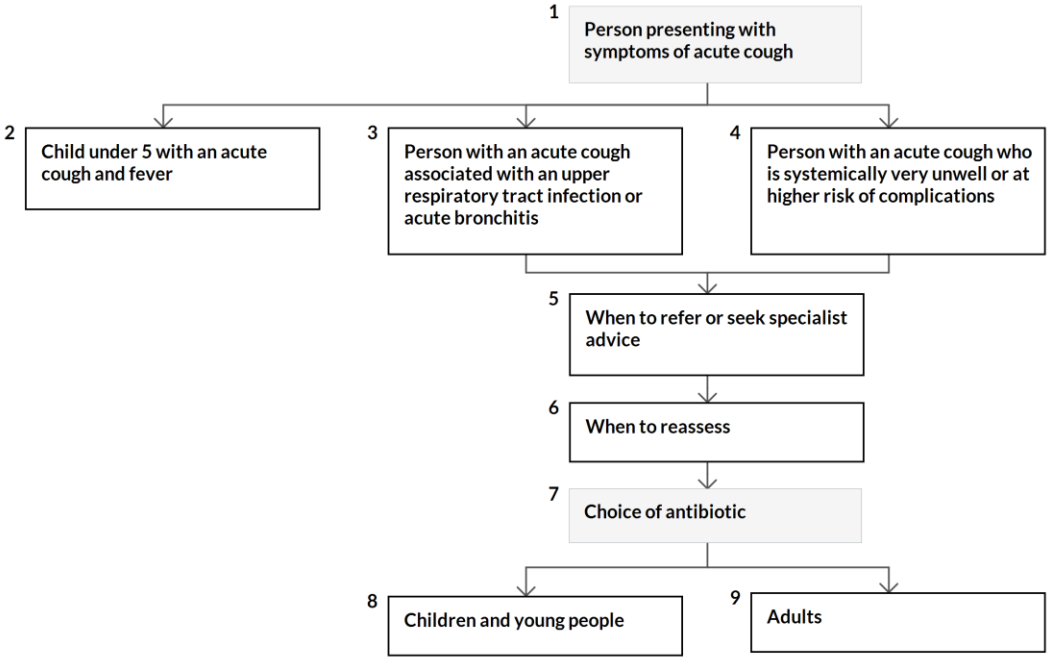


Figure 6. NICE Guidelines pathway for patients presenting acute cough/bronchitis

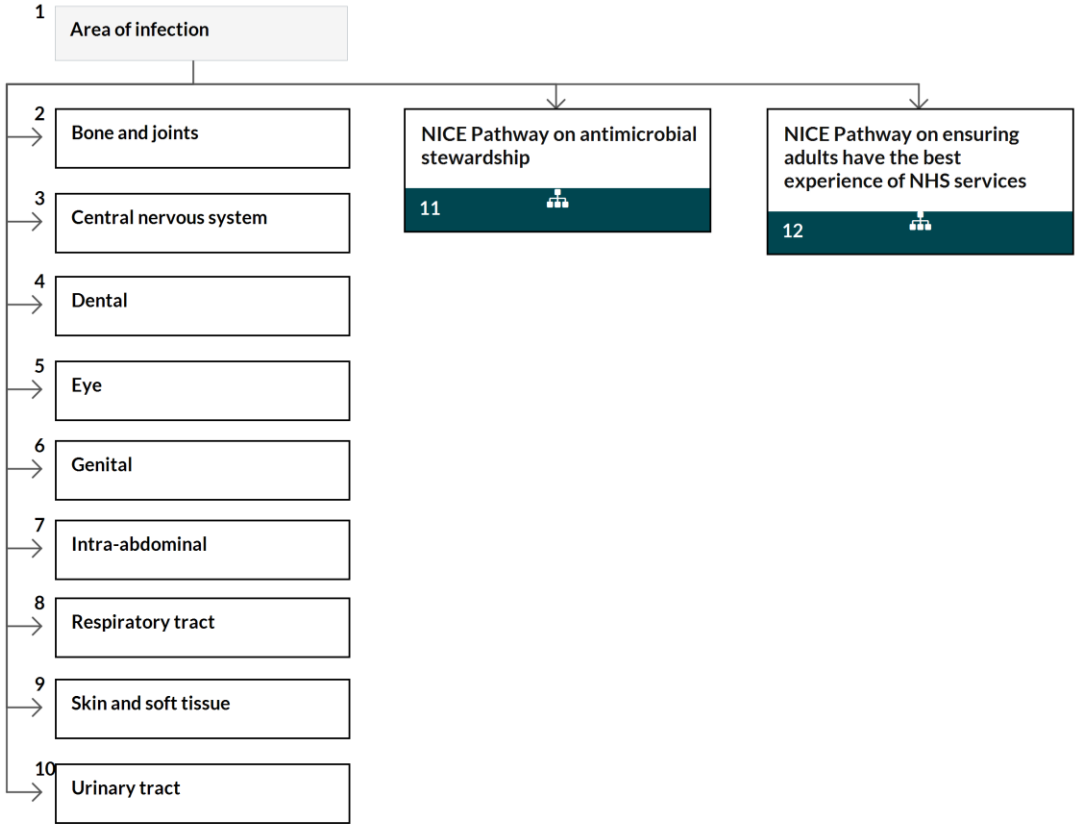


Figure 7. NICE Antimicrobial Prescription guideline overview for common infection.

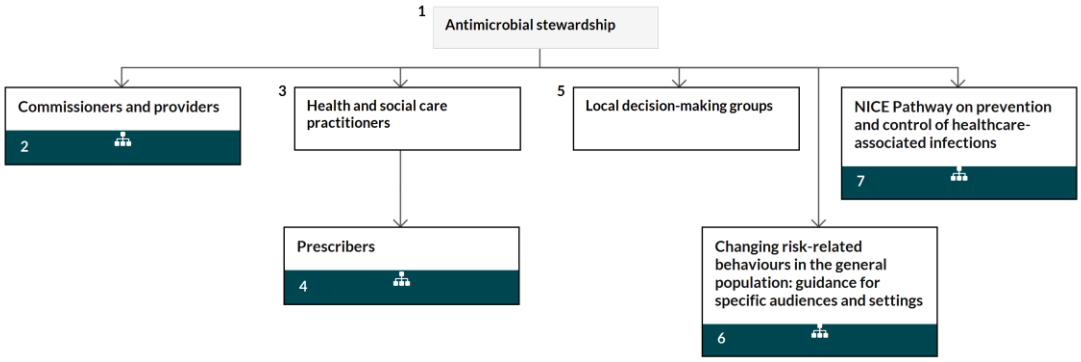


Figure 8. NICE Antimicrobial Stewardship pathway overview.