PROTOCOL
Diagnostic accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected acute respiratory infection

Project team

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Plain English summary

What is the problem?

Respiratory infections are a common cause of illness in adults. They can be caused by viruses (such as a cold), or bacteria. Infections are often self-limiting and resolve without the need for treatment. However, people with more severe symptoms or those at risk of developing serious disease may require treatment. The treatment required depends on the nature of the infection. At present, healthcare professionals use their clinical expertise to identify those who are more severely unwell and/or at risk of deteriorating, and to determine whether they have a respiratory infection caused by a virus or bacteria. However, this is not always easy to establish. Consequently, many people are given antibiotics (to treat a possible bacterial infection), even if the actual cause of their illness is a virus.

Excessive use of antibiotics is a problem. It increases the chance of bacteria becoming resistant to current antibiotics - meaning that they will not be effective in the future. In addition, antibiotics often have unpleasant side effects. Ideally, antibiotics would only be given to people who genuinely need them.

Recently, tests have become available which may help to quickly indicate whether a respiratory infection is caused by a virus or bacteria. These tests are known as “rapid point of care” tests because the samples do not need to be sent to specialist laboratories and can be carried out in a GP surgery or in an emergency department.

1.1 What are we trying to find out?

We are trying to identify how effective rapid tests are at determining whether a respiratory infection is caused by a virus or bacteria.

If these tests are very effective, they may be a useful addition to current care. They may be able to identify people who require antibiotics and distinguish them from those people who do not require treatment (or require alternative treatment).

2 Background

Since the COVID-19 pandemic, rates of acute respiratory infection have increased. In response, NHS England has established new acute respiratory infection (ARI) hubs and ARI virtual wards. These are intended to reduce pressure on other parts of the health service, by providing appropriate care for people with respiratory infections.

NICE has been asked to produce a guideline which considers the initial assessment and management of acute respiratory infection in people aged over 16. This review comprises part of the guideline.

2.1 Epidemiology and burden of acute respiratory infections

Acute respiratory infections comprise any infection of the upper or lower respiratory tract, including the nose, sinuses, middle ear, larynx, and pharynx, as well as bronchitis and pneumonia. They represent a major cause of illness across the UK and worldwide and have a high burden on the healthcare system and significant associated costs. One study has estimated direct medical costs associated with acute respiratory infections in the UK at £86 million per year[1]. The causes of ARI are varied, but predominantly involve viruses (such as influenza, respiratory syncytial virus, parainfluenza, rhinovirus, adenovirus, coronavirus and human metapneumovirus[2]) or bacteria (including *Streptococcus pneumoniae, Haemophilus*, *Mycoplasma*, *Chlamydia*, *Staphylococcus aureus*, gram-negative rods and *Legionella*[3]). Identification of the causative pathogen can be challenging, as many of these species are carried as commensal organisms. Consequently, in many cases, no aetiologic pathogen is identified. In addition, standard microbiological diagnosis often takes too long to influence immediate management in primary care – as samples are transported to a central laboratory, and identification of an organism may require culture for several days. Decisions regarding initial treatment are therefore frequently taken without the benefit of a definitive microbiological result.

2.2 Presentation of acute respiratory infections

The symptoms of respiratory infections can vary from relatively mild, self-limiting problems to more severe symptoms requiring urgent assessment and potentially hospital admission. They often include a combination of symptoms including sore throat, rhinitis, cough, fever and shortness of breath, amongst others. Many people with acute respiratory infections will manage their symptoms without seeking advice from a healthcare professional. However, distinguishing between those individuals in whom symptoms are likely to resolve without treatment and those in whom symptoms may deteriorate and require intervention is a key issue.

2.3 Diagnosis of acute respiratory infections

Diagnosis of an acute respiratory infection is clinical, based on typical symptoms (as described above) and signs of disease. Identification of a specific causative pathogen is frequently not required, especially if symptoms are mild and considered likely to resolve spontaneously.

However, it is important to identify people whose symptoms may not resolve without intervention. This includes those with severe symptoms, who may require admission to hospital for escalation of

care. It may also include those with a bacterial infection, where symptoms are less likely to be self-limiting and may require antibiotics.

In some instances, a clinical diagnosis may be supplemented with laboratory confirmation of a bacterial or viral infection. However, there are challenges with this approach. As described above, many organisms that can cause acute respiratory infections are also carried as commensals in the respiratory tract. Consequently, identification of an organism does not definitively mean that this is the cause of the individual's symptoms, and there is a risk of false positives. Conversely, there may be low rates of shedding for particular pathogens, or the sampling technique may be inadequate. This can lead to false negative results.

2.4 Treatment pathway for suspected acute respiratory infections

The initial treatment of acute respiratory infections is determined by two key features. Firstly, it depends on the severity of the symptoms at presentation – including an assessment of whether the individual is acutely unwell and requires hospital admission, or management in an intermediate care facility (such as a virtual ward or ARI hub). Secondly, it depends on the anticipated prognosis for the illness – with consideration of whether the infection is likely to resolve or deteriorate without intervention. The likely prognosis will depend on features specific to the individual (such as their age and the presence of co-morbidities) as well as features of the infection itself (including whether a bacterial or viral cause is suspected).

Despite most acute respiratory infections being caused by viruses, antibiotics are frequently prescribed for these conditions. The reasons for this are multifactorial but may include patient expectations, time pressures and diagnostic uncertainty[4,5].

2.5 Relevant health inequalities

Antibiotic prescribing is higher in deprived areas and for people on low incomes[6,7]. There is some evidence that White people are prescribed more antibiotics than other ethnic groups in high income countries[8]. In the England, GP practices with a higher proportion of White patients and greater morbidity prescribe more antibiotics, characteristics which are associated with deprived areas[9].

People of lower socio-economic status and from ethnic minorities are more at risk from infectious disease and from antimicrobial resistance[10]. In the UK, pneumonia in over 65s is 70% higher in those living in the lowest quintile compared with the highest quintile[11]. People living in deprived areas are also at increased risk of carrying resistant bacteria[12].

Improved identification of which respiratory tract infections are bacterial could help to reduce over prescription while ensuring that those with more serious infections receive the treatment they need.

3 Review question

3.1 Population

People aged 16 years or over with suspected acute respiratory infection in a community or ambulatory care setting.

- Including the following symptoms/conditions:
    - Cough
    - Shortness of breath
    - Sore throat

  - Laryngitis
  - Pharyngitis
  - Bronchitis
  - Pneumonia
  - Upper and lower respiratory tract infections

Some specific populations will be excluded:

- Individuals known to have COVID-19;
- Inpatients in hospital (or cared for in a virtual ward), including those who acquire acute respiratory infections whilst admitted to hospital;
- Individuals who have a respiratory infection during end-of-life care;
- Individuals with aspiration pneumonia, bronchiectasis, cystic fibrosis, or known immunosuppression.
- Individuals with symptoms of otitis media or sinusitis.

3.2 Index tests

Near patient, rapid tests (also known as rapid, point of care tests [POCT]) aiming to distinguish between viral and bacterial infection. We will include tests which are currently licensed and available for use in the UK. This will include:

- Symptoms and signs of acute respiratory infection; either individual symptoms/signs, or in combination (as part of a clinical decision tool)
- "Host-response" (or "biomarker") POCTs including
  - CRP
  - Procalcitonin
  - CRP and MxA (FebriDx)
  - TRAIL, IP-10 and CRP (ImmunoXpert/MeMed BV)
  - White cell differential count
  - If we identify additional rapid, point of care tests for host response biomarkers that have been assessed as part of a systematic review then we will also include these data in the overview. However, if we need to conduct additional searches for primary data, these will only be performed for the index tests specified in the list above.

- Multiplex or single POCTs (with a turnaround time of <45 minutes) for (or including) the following specific organisms, selected on the basis of prevalence and burden of healthcare:
  - Influenza (A and B)
  - Respiratory syncytial virus (RSV)

POCTs for SARS-CoV-2 and group A streptococcus will be excluded, due to existing NICE guidance for the use of these tests.

3.3 Target condition

Bacterial infection or viral infection, or the presence of specific organisms targeted by the test.

3.4 Reference standards

Ideally, confirmation of bacterial or viral infection would be with a laboratory diagnosis (culture or other diagnosis of a bacterial or viral pathogen). However, this may not be available, and may also not actually be a gold standard. Firstly, inadequate sampling or poor viral shedding may result in false negative laboratory reports – where the pathogen remains unidentified. Furthermore, the presence of many bacteria as commensal organisms may result in false positives – where an organism is identified but is not actually the cause of the symptoms. Consequently, expert consensus, or clinical algorithms may also be used as an appropriate reference standard.

4 Aim and Objectives

The overall aim of this review is to determine the accuracy of rapid, point-of-care tests for bacterial and viral respiratory infections.

A systematic review will be conducted to summarize the evidence on the accuracy of diagnostic tests for bacterial and viral causes of respiratory infection. The systematic review will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[13], the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[14] and the NICE guideline development manual[15].

Health economic evidence will be included in the related systematic reviews for this guideline (RQ 1.1, 1.2 and 1.3). Therefore, we will not assess health economic data as part of this review.

4.1 Inclusion and exclusion criteria

Studies that meet the criteria summarized in Table 1 are eligible for inclusion:

Table 1: Inclusion criteria

	Diagnostic Accuracy
Participants	*Inclusion criteria:* • People aged 16 years or over with suspected acute respiratory infection, including (but not limited to) the following symptoms: o Cough or shortness of breath o Sore throat o Rhinitis *Exclusion criteria*: • Reviews that are exclusively in the following populations, or studies in which more than a quarter of the participants meet the following criteria: o People aged 16 years or over ▪ with known COVID-19. ▪ who are inpatients in hospital. ▪ who have a respiratory infection during end-of-life care. ▪ with aspiration pneumonia, bronchiectasis, cystic fibrosis (CF), or known immunosuppression. ▪ with symptoms of otitis media or sinusitis. o Children and young people under 16 years.
Index tests	*Inclusion criteria:*

<table>
<tr><td></td><td colspan="2">Diagnostic Accuracy</td></tr>
<tr><td></td><td colspan="2">POCTs or symptoms and signs aiming to distinguish between viral and bacterial infection. We will include tests that:
• Diagnose generic bacterial infection (i.e., any bacteria)
• Diagnose generic viral infection (i.e., any virus)
• Distinguish between a generic bacterial infection, a generic viral infection, and no infection

We will also include tests that aim to identify the presence of the following specific pathogens:
• Influenza (A+B)
• RSV

Exclusion criteria:
• POCTs for SARS-CoV-2 and group A streptococcus</td></tr>
<tr><td>Target</td><td colspan="2">Reference standard:
Any reference standard. We anticipate that this may include confirmation of bacterial infection or viral infection through laboratory testing, or defined via expert consensus, or a clinical algorithm.</td></tr>
<tr><td>Setting</td><td colspan="2">Inclusion criteria:
• Remote settings (via telephone, video call, online app, e-mail, or text message, e.g., NHS 111, 999 call centres or calls from GP practices)
• Face-to-face settings (e.g., the person’s home, a care home, primary care [including community pharmacy or acute respiratory infection hubs], NHS walk-in centres, emergency departments).

Exclusion criteria:
• Hospital inpatient settings</td></tr>
<tr><td>Studies</td><td>Systematic reviews of diagnostic accuracy studies. Systematic reviews will be identified by the use of all of the following:

○ clear and unambiguous eligibility criteria
○ comprehensive search (either stated as their aim or implied by use of 2 or more bibliographic databases)
○ details of included studies separately identifiable (for example with a table of characteristics, and references for all included studies)
○ the use of tools to assess the validity of primary studies (for example QUADAS-2).

We will seek to identify the most robust and up-to-date evidence for each test. Starting with the most recent published reviews, identified systematic reviews will be assessed for their applicability, and those eligible will be quality assessed using published tools. Systematic reviews of good</td><td>If no good quality, applicable systematic reviews are identified, or where there are evidence gaps (for example missing index tests) in the systematic reviews, we will conduct searches for diagnostic test accuracy studies.
○ We will include one-gate designs (also known as diagnostic cross-sectional or diagnostic cohort studies).
○ Two gate designs (also known as diagnostic case-control studies) will be excluded.

Quantitative data on diagnostic test accuracy will be collected (see section 4.3 for details).</td></tr>
</table>

	Diagnostic Accuracy	
	quality that closely match the review protocol will be extracted rather than extracting from the primary studies. Where multiple overlapping reviews are identified, we will include the most relevant review, considering the comprehensiveness of the search, date of publication and relevance to the current review question. Where a good quality review is found, earlier reviews with largely overlapping scope will not be assessed or extracted. Quantitative data on diagnostic test accuracy will be collected (see section 4.3 for details).	
Other considerations	No date limitation will be applied. *Exclusions*: • studies not published in English • pre-prints • dissertations and theses • registry entries for ongoing clinical trials • editorials, letters, news items and commentaries • animal studies • conference abstracts and posters • derivation studies	

4.2 Study identification

We will identify studies using bibliographic and non-bibliographic search methods following guidance in the NICE guideline development manual[15].

We will initially conduct searches to identify relevant published systematic reviews which address this review question. If a review is available which is sufficiently similar in scope to the current review then we will collect summary data and present the results. This may involve a single existing review, or multiple systematic reviews which consider different index tests.

We will also conduct a review of primary diagnostic test accuracy studies in the following circumstances:

- If a suitable systematic review is not identified for the specific index tests named in the protocol, or;
- If a systematic review is identified, but we consider that substantial additional data may be available through an updated literature search.

4.2.1 Bibliographic searching

The principal search strategy will be developed in MEDLINE (Ovid interface) and adapted, as appropriate for use in the other databases, taking into account their size, functionality and subject coverage. The following databases will be searched:

- MEDLINE (Ovid) 1946 onwards (Appendix-1);
- Embase (Ovid) (1974 onwards);
- Cochrane Database of Systematic Reviews (all available years);
- Epistemonikos (all available years);
- NIHR Journals Library (all available years).

We will use an iterative approach to searching, structuring the initial search around broad, top-level terms for the index tests (rapid point-of-care tests or clinical prediction rules) combined with terms for the target condition/causative agents of respiratory tract infections. We will limit the initial search to systematic reviews of diagnostic test accuracy studies using appropriate search filters.

Once we have screened the initial search results, we will extract the names of the individual index tests analysed in the reviews and feed these back into the search, to ensure we have not missed any key systematic reviews.

If it is necessary to search beyond reviews, for primary DTA studies, we will re-structure the search to include terms for named index test(s) and target condition. However, depending on the number of search results we may need to factor in the reference standard or include a parallel search strand including (but not limited to) a DTA filter. We will search MEDLINE and Embase and include an additional search of the International trial registers to identify completed trials with results:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (trialsearch.who.int).

We will not apply any date restrictions to the search but will limit to reports published in English. We will exclude pre-prints, conference abstracts, dissertations and theses and ongoing trial protocols.

4.2.2 Non-bibliographic search methods

Where insufficient systematic reviews are identified, or where update searches are also needed we will identify studies through searches of the following trial registries:

- ClinicalTrials.gov via https://www.clinicaltrials.gov/
- WHO International Clinical Trials Registry Platform (ICTRP) via https://www.who.int/clinical-trials-registry-platform

4.2.3 Managing the searches

Search results will be exported to EndNote for deduplication using the default deduplication settings and manual review of records. Search results will be exported to Rayyan for screening.

4.3 Review strategy

Two reviewers will independently screen titles and abstracts identified by the searches. We will obtain full copies of all reports considered potentially relevant and two reviewers will independently assess these for inclusion. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Data will be extracted using standardized data extraction forms developed in Microsoft Excel or Microsoft Access depending on the quantity of data available. Data extraction forms will be piloted on a small sample of papers and adapted as necessary. Data will be extracted by one reviewer and checked in detail by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

We will collect the following data: study design (systematic review, DTA or other), funding sources (public, industry, mixed), study location and setting, presentation (symptoms), sex, age, inclusion criteria, rapid test details (manufacturer, target condition/organism), reference standard test(s).

Accuracy data will be extracted as 2×2 tables comparing the index test with the reference standard where available. If measures of accuracy (e.g. sensitivity, specificity, ROC plot, AUC) are reported without providing the information needed to calculated 2×2 tables, then these data will be extracted.

4.4 Quality assessment strategy

The risk of bias in results of systematic reviews will be assessed using the ROBIS tool[16]. If DTA studies are included, then the risk of bias will be assessed using QUADAS-2[17]. We will assess applicability as part of the GRADE assessment, and through subgroup analyses. Quality assessment will be undertaken by one reviewer and checked by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Synthesis methods

We will present a narrative summary of all the included studies. This will include a summary of the study characteristics (e.g. study designs, sample size, year, baseline population characteristics, rapid test evaluated) and study quality. The synthesis will be stratified by technology evaluated.

If we identify suitable systematic reviews for inclusion then we will present an overview of reviews, according to methods reported in the Cochrane Handbook for Systematic Reviews of Interventions[18]. We will summarise data reported within the included systematic reviews, using the analysis presented by the original review authors. If necessary (for example, if only a subset of included studies are of relevance), we will conduct a re-analysis of included data to present summary estimates of sensitivity, specificity, positive and negative likelihood ratios.

If multiple diagnostic test accuracy studies are identified for the same rapid test, bivariate random effects meta-analysis of sensitivity and specificity will be performed, if they have not been performed to a suitable standard within existing systematic reviews. These will be based on binomial likelihoods[19,20]. Analyses will be stratified according to the type of test. Summary estimates of sensitivity and specificity together with 95% confidence intervals (CIs) will also be calculated. We will use coupled forest plots of sensitivity and specificity to display results from individual studies, to allow visual assessment of heterogeneity. Heterogeneity and inconsistency across studies will be quantified statistically using the tau and I^2 statistics, respectively[21]. Study-level and summary results will also be plotted in receiver operating characteristic (ROC) space, with 95% confidence ellipses around summary estimates representing the joint uncertainty in sensitivity and specificity.

4.5.1 Subgroup analyses

Where disaggregation is possible, we will repeat analyses according to the following subgroups:

- setting of study (primary care, secondary care)
- age of patient (65 years and under, 66 – 80 years, over 80 years)
- presence of chronic co-morbidity (for example, COPD)

- pregnancy and post-partum (up to 6 weeks)
- different reference standards

4.5.2 Certainty in the evidence

The five GRADE domains (risk of bias, indirectness, inconsistency, imprecision and publication bias) will be used to assess the certainty of the evidence for all outcomes.

If systematic reviews are included then – where possible – we will report the GRADE assessments presented in the included systematic reviews. If necessary, we may assess the GRADE domains based on the information reported in the systematic reviews[22].

4.5.3 Research gaps

We will provide a detailed description of any gaps in the evidence, together with any methodological limitations of the existing studies. This will help inform recommendations for future research and requirements for a full diagnostic assessment.

5 Competing interests of authors

None of the authors have any competing interests.

6 Timetable/milestones

Milestone	**Date to be completed**
Draft protocol	24 April 2023
Final protocol	16 May 2023
Draft report	
Final report	30 June 2023

7 References

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8 Appendices

8.1 Literature searches

Ovid MEDLINE(R) ALL <1946 to April 21, 2023>

1	[**Respiratory Tract Infection (RTI)**]	
2	exp Respiratory Tract Infections/	602447
3	exp Otorhinolaryngologic Diseases/	406785
4	((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (infect* or coinfect* or inflamm*)).tw,kf.	122968
5	((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf.	44615
6	(bronchit* or bronchiolit* or allergic bronchopulmon* or bronchopneumon* or common cold* or coryza or croup or empyem* or epipharyngit* or epiglottit* or epiglotit* or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or legionnair* disease or legionellos* or middle east respiratory syndrome or MERS or nasopharyngit* or otitis media or parainfluenza or pharyngit* or pleurisy or pneumoni* or pleuropneumoni* or rhinit* or rhinopharyngit* or rhinosinusit* or severe acute respiratory syndrome or SARS or sinusit* or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or	1087942

	tonsilit* or tracheit* or tuberculosis or whooping cough or pertussis or pertusis).mp.	
7	((acute* or exacerbat* or flare*) adj3 (asthma* or copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp.	24126
8	(RTI or AURI? or ALRI?).tw,kf.	4929
9	or/2-8	1578624
10	[**RTI Viral Infection**]	
11	exp Respiratory System/ and (exp Viruses/ or exp Virus Diseases/)	34925
12	exp pneumonia, viral/ or *orthomyxoviridae infections/ or influenza, human/	287761
13	((airway* or respiratory or pulmonary or broncho-pulmonar* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf.	35714
14	(rhinovir* or rhino* vir* or coryzavir* or coryza* vir* or influenzavir* or influenza* vir* or (H1N1 or H3N2) or parainfluenzavir* or parainfluenza* vir* or pneumovir* or pneumo* vir* or human metapneumovir* or human meta-pneumovir* or HMPV or respiratory syncytial vir*).mp. or RSV.tw,kf.	138696
15	(corona vir* or coronavir* or neocorona vir* or neocoronavir* or betacoronavir* or beta-coronavir* or COVID19 or COVID-19 or COVID2019 or COVID-2019 or nCov* or COVID or COVID-19).mp.	365980
16	or/11-15	514343
17	[**RTI Bacterial Infection**]	
18	exp Respiratory System/ and (exp Bacteria/ or exp Bacterial Infections/)	48030
19	pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/	22806
20	((airway* or respiratory or pulmonary or broncho-pulmonar* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf.	22331
21	(strep* pneumon* or diplococ* pneumon* or pneumococ* or staph* pneumon* or chlamyd* pneumon* or myco* pneumon* or influenza bacil* or bacteri* influenza* or h?emophil* influenza*).mp.	80651
22	((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory* or (ear adj3 nose adj3 throat) or ENT or Otorhinolaryng*))).mp.	22592
23	(GABHS or ("group a" adj3 strep*)).tw,kf.	10711
24	strep* pyogen*.mp.	18513
25	or/18-24	177103
26	[**Rapid Tests**]	
27	Point-of-Care Systems/	16311
28	(POCT or POCTs or (((point adj2 care) or poc) adj3 (analys* or antigen? or assay* or device? or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test* or (cassette? or dipstick? or film* or stick or strip)))).tw,kf.	21411
29	(point adj2 care).ti,kf.	14926
30	(((near adj2 patient) or nearpatient or rapid* or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 (analys* or antigen? or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or	203965

	identif* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test*)).tw,kf.	
31	(((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*).tw,kf.	636
32	Rapid Diagnostic Tests/	34
33	(rapid* adj3 (detect* or diagnos*)).tw,kf.	59055
34	(time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf.	24917
35	(antigen? adj3 (analys* or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf.	90641
36	(RADT or RADTs or RDT or RDTs).tw,kf.	3303
37	(biomarker or bio* marker* or ((biologic* or bacteri* or viral or virus or immuno* or inflammat* or molecular or protein or serum) adj marker*)).tw,kf.	315850
38	(rapid molecular or multiplex*).mp.	72653
39	lab-on-a-chip.tw,kf.	3496
40	((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf.	9947
41	(immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym* immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf.	60314
42	((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or assay*)).mp.	4679
43	*Symptom Assessment/	1884
44	(clinic* predicti* or (clinic* adj5 (decision* or predicti*) adj5 (aid? or algorithm? or characteristic? or criteri* or evaluation? or index or indices or marker? or method* or model* or panel? or parameter? or rule or rules or score? or scoring or screen* or signs or symptoms or system? or technique? or test* or tool? or value? or variable*))).mp.	47913
45	or/27-44	815708
46	(9 or 16 or 25) and 45	64783
47	[**Systematic Review Filter**]	
48	(systematic or structured or evidence or diagnostic or predicti* or trials or studies).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)	355294
49	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X or 2046-4053).is.	20963
50	meta-analysis.pt. or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).ti,ab,kf,hw.	299840
51	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).ti,ab,kf,sh. or (quantitativ$ adj5 synthesis$).ti,ab,kf,hw.	415550
52	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or ((diagnostic or evidence) adj3 review*).ti,ab,kf.	245577
53	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or	212045

	bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)	
54	or/48-53	804290
55	[**DTA Filter**]	
56	Diagnosis/	17526
57	"Diagnostic Techniques and Procedures"/	3694
58	Diagnostic Test Approval/	112
59	Diagnostic Tests, Routine/	15095
60	Molecular Diagnostic Techniques/	13705
61	exp Reagent Kits, Diagnostic/	20985
62	(diagnos* adj3 (analys* or assay* or immunoassay* or classif* or differenti* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test*)).ab.	407958
63	diagnos*.ti,kf,hw.	1367717
64	"sensitivity and specificity"/ or "predictive value of tests"/ or roc curve/ or signal-to-noise ratio/ or "limit of detection"/	645879
65	false negative reactions/ or false positive reactions/	39954
66	(sensitivity or specificity).tw,kf.	1237444
67	likelihood ratio.tw,kf.	14676
68	(predictive adj4 value*).tw,kf.	138077
69	((accura* or reliab* or valid*) and (point-of-care or POC or (rapid adj2 (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*)))).tw,kf.	29708
70	((accura* or reliab* or valid*) and (bacteri* and (viral or virus*) and (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*))).tw,kf.	3462
71	area under curve/	45535
72	(observer adj variation*).tw,kf.	1682
73	(roc adj curve*).tw,kf.	54336
74	likelihood functions/	23651
75	(false adj (positiv* or negativ*)).tw,kf.	89775
76	QUADAS*.mp.	2725
77	Diagnosis, Differential/	467518
78	(codetect* or co-detect* or codiagnos* or co-diagnos*).tw,kf.	1300
79	((discriminat* or differenti* or dual*) adj (detect* or diagnos*)).mp.	157585
80	(bacteri* adj5 (viral or virus*) adj5 (analys* or assay* or immunoassay* or classif* or detect* or codetect* or determin* or diagnos* or codiagnos* or differenti* or discriminat* or distinguish* or identif* or method* or misdiagnos* or predict* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf,hw.	5449
81	or/56-80	3230961
82	46 and 54 and 81	1278
83	[**Other**]	

84	(bacteri* adj5 (viral or virus*) adj5 (detect* or diagnos* or differenti* or predict* or screen* or test*)).tw,kf.	2889
85	(bacteri* and (viral or virus*) and (codetect* or co-detect* or codiagnos* or co-diagnos*)).tw,kf.	86
86	(9 or 16 or 25) and 54 and (84 or 85)	53
87	(((prescribing or prescription?) adj guideline?) or ((antibiotic? or antimicrobial) adj stewardship?)).mp.	11416
88	((guide or guiding or predict* or ration* or reduc* or steward*) adj3 (antibiotic* or antivir* or anti-vir* or antimicrob* or anti-microb*)).tw,kf.	25835
89	46 and 54 and (87 or 88)	109
90	82 or 86 or 89	1336
91	remove duplicates from 90	1322

1. <Castro-Guardiola 2000.pdf>.