TITLE: Point-of-Care Tests for Infectious Diseases: A Review of Clinical and Cost-Effectiveness, and Guidelines

DATE: 07 March 2016

CONTEXT AND POLICY ISSUES

Point-of-care (POC) diagnostics or "near-patient" devices are an emerging healthcare approach that can be used at the patient's bedside, in an emergency department, or in the field. POC diagnostics have been used to in the detection and monitoring of major conditions such as cardiovascular diseases, prostate cancer, and infectious diseases.[1-3] With nearly 50,000 new human immunodeficiency virus (HIV) infections and 12 million clinical center visits for acute pharyngitis in the US each year,[4,5] One percent of the total Canadian population is antibody positive for hepatitis C[6] and over 7700 hospitalizations with 591 deaths in Canada were due to influenza in the 2014-2015 season.[7] Community pharmacies, with their relative accessibility and affordability, can be practical and appealing venues for screening for global infectious diseases. In studies aiming to evaluate the acceptability and feasibility of pharmacist-provided rapid testing for HIV infection in community pharmacies, the testing was found feasible, nearly all participants felt comfortable with the testing, participants favorably reported willingness to pay for the test, both pharmacists and participants reported favorable perceptions of the HIV testing experience.[8-13] In Canada, an action plan has been developed with the objective to increase awareness and uptake of HIV POC testing by 2020.[14]

To identify antibodies (Ab) for HIV and hepatitis C infections, a rapid antibody test (e.g. OraQuick) is available for POC testing.[15] For influenza A and B infection, and streptococcal infection, a rapid antigen diagnostic test (RADT) (e.g. QuickVue) can be used as a POC diagnostic test.[16,17] There are different strategies to identify infections, and these strategies differ according to whether the test is done by a laboratory-conducted assay or POC assay; whether blood is sampled by venipuncture or fingerstick; and whether quantitative or qualitative nucleic acid tests (NAT) are used to confirm a positive Ab result.

This Rapid Response report aims to review the clinical- and cost-effectiveness of over-the-counter POC testing of patient self-test or pharmacist testing for HIV, hepatitis C, influenza, and Streptococcal infections. Guidelines associated with the use of POC testing for infectious diseases will also be examined.

RESEARCH QUESTIONS

1. What is the diagnostic accuracy of point of care tests (POCT) for HIV, hepatitis C, influenza, and Streptococcal infections compared with conventional testing in a laboratory?

2. What is the clinical effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory?

3. What is the cost-effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory?

4. What are the evidence-based guidelines regarding patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections?

KEY FINDINGS

Meta-analyses found that POC tests provide a reliable diagnostic strategy for hepatitis C virus or group A streptococcal pharyngitis infections, but performance may vary among different POC tests. Findings from one trial showed that POC testing can be a useful tool for diagnosis or triage (high specificity) for influenza A and B infection, but its low sensitivity suggests a negative POC tests needs confirmation using PCR assay. The costs for POC tests for hepatitis C infection or laboratory-based tests are similar.

There was no evidence found on the clinical effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory. No evidence-based guidelines for their use were identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, and meta-analyses, economic evaluations, randomized controlled studies, and guidelines. Where possible, retrieval was limited to the human population. The search was limited to English language documents published between January 1, 2011 and February 2, 2016.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria	
Population	General population
Intervention	POCT for HIV, hepatitis C, influenza, or Streptococcal infections; purchased at a pharmacy by the patient for self-testing or pharmacist testing
Comparator	Conventional testing for HIV, hepatitis C, influenza, or Streptococcal infections in a laboratory
Outcomes	Q1: Diagnostic accuracy Q2: Clinical effectiveness, harms Q3: Cost-effectiveness Q4: Evidence-based guidelines
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), RCTs, non-RCTs, economic evaluations, and guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2011, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews, diagnostic accuracy studies and cost evaluations was assessed using the AMSTAR,[18] QUADAS,[19] and Drummond,[20] checklists, respectively. Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 452 citations. After screening of abstracts from the literature search and from other sources, 22 potentially relevant studies were selected for full-text review. Four studies were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included SRs and primary studies is provided in Appendix 2 and 3, respectively.

Study design

Two systematic reviews/meta-analysis,[17,21] one diagnostic accuracy study,[16] and one cost study[15] were included. The systematic review on hepatitis C infection was published in 2015 and included 30 diagnostic accuracy studies.[21] The systematic review on streptococcal pharyngitis was published in 2014 and included 48 diagnostic accuracy studies.[17] The diagnostic accuracy study[16] and the cost study[15] were both published in 2015.

Population

The systematic review/meta-analysis on the diagnostic accuracy of POC tests for hepatitis C virus infection included studies of adults (> 18 years old) tested for hepatitis C virus infection.[21] The systematic review/meta-analysis on the diagnostic accuracy of POC tests for group A streptococcal infection included studies of patients of any age with pharyngitis.[17] The diagnostic accuracy study on the performance of POC test for influenza A and B included 600 patients with influenza-like illness (ILI) or with severe acute respiratory illness (SARI).[16] The costing study was based on a population tested for current hepatitis C infection.[15] Costs included the costs of the tests and the costs for the phlebotomists doing the blood draw.

Interventions and comparators

The systematic review on POC tests for hepatitis C virus infection compared different POC tests such as OraQuick to various laboratory-based reference tests such as enzyme-linked immunosorbent assay (ELISA), and recombinant immunoblot assay (RIBA).[21] The systematic review on the diagnostic accuracy of POC tests for group A streptococcal infection compared different RADTs such as QuickVue to throat microbial culture as the standard test.[17] The diagnostic accuracy study on the performance of POC test for influenza A and B compared QuickVue to a laboratory-based polymerase chain reaction (PCR) assay.[16] The cost study compared different strategies for hepatitis C virus infection testing, according to whether the test was done by a laboratory-conducted assay or POC assay; whether blood was sampled by venipuncture or fingerprick; and whether quantitative or qualitative NATs were used to confirm a positive Ab result.[15]

Outcomes

Outcomes of the systematic review on POC tests for hepatitis C virus infection were sensitivity, specificity, and positive and negative likelihood ratios of the POC tests.[21] Outcomes of the systematic review on the diagnostic accuracy of POC tests for group A streptococcal infection were sensitivity and specificity of the POC tests,[17] and those of the diagnostic accuracy study on the performance of POC test for influenza A and B were sensitivity, specificity, and positive and negative predictive values of the POC tests[16] The cost study reported costs per person tested, and the viremia sensitivity of the strategies.[15]

Summary of Critical Appraisal

The included systematic reviews provided a priori design, had a duplicate study selection and data extraction procedure in place, performed a comprehensive literature search, provided a list of included studies and study characteristics, and conducted a quality assessment of the included studies which was used in formulating conclusions.[17,21] For both systematic reviews, a

list of excluded studies was not provided, there was no assessment of publication bias, and there was considerable heterogeneity in the interventions tested.

The included diagnostic accuracy study has good validity and generalizability of results, except it is unclear whether the index test results were interpreted without knowledge of the results of the reference standard. Withdrawals from the study were not mentioned.[16]

The included cost study is likely to be usable, outcomes and costs were assessed and compared appropriately, presentation and discussion of results included all issues of concern to users. Incremental analysis of the outcomes and costs, and sensitivity analysis were not performed.[15]

Details of the strengths and limitations of the included studies are summarized in Appendix 4.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 5.

1. <u>What is the diagnostic accuracy of point of care tests (POCT) for HIV, hepatitis C, influenza, and Streptococcal infections compared with conventional testing in a laboratory?</u>

Hepatitis C virus infection

Meta-analyses of 30 POC tests gave a pooled estimate for sensitivity of 97.4% (95% confidence interval [CI] 95.9 to 98.4), specificity of 99.5% (95% CI 99.2 to 99.7), positive likelihood ratio of 80.7 (95% CI 55.35 to 116.14), and negative likelihood ratio of 0.03 (95% CI 0.02 to 0.04), compared to a variety of laboratory-based tests. Among the POC tests with three or more data points evaluated by the meta-analyses, Oraquick had the highest sensitivity (99.5%; 95% CI 98.9 to 99.8) and specificity (99.8%; 95% CI 99.6 to 99.9), while Spot had the lowest sensitivity (75.4%; 95% CI 14.1 to 98.3), and Chembio β had the lowest specificity (94.0%; 95% CI 74.2 to 98.8). The authors concluded that POC tests provide a plausible diagnostic strategy for hepatitis C virus infection, and physicians should consider the fact that performances varied widely among different POC tests.[21]

Streptococcus A infection

Meta-analyses of data from 48 studies (number of POC tests not reported) gave a pooled estimate for sensitivity of 0.86 (95% CI 0.83 to 0.88) and for specificity of 0.96 (95% CI 0.94 to 0.97), compared to the standard throat culture. The authors concluded that RADTs can be used for the diagnosis of group A streptococcal pharyngitis infection.[17]

Influenza A and B infection

The diagnostic accuracy study of the rapid influenza diagnostic test QuickVue found a sensitivity of 23% (95% CI 17.3 to 29.8), specificity of 100% (95% CI 99.1 to 100), PPV of 100% (95% CI 91.8 to 100), and NPV of 74.3% (95% CI 70.5 to 77.9), compared to the laboratory-based PCR assay. The authors concluded that the POC test QuickVue can be an useful tool for diagnosis or

triage (high specificity) but its low sensitivity suggests a negative POC tests needs confirmation using PCR assay.[16]

2. <u>What is the clinical effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory?</u>

There was no evidence found on the clinical effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory for improving health outcomes.

3. <u>What is the cost-effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory?</u>

The cost study on different strategies for testing hepatitis C virus infection found that the costs per test per person were similar between POC tests or laboratory-based assays.

The cost per test per person for the lab-based assay (VITROS) followed by quantitative NAT was US$30.08 (venipuncture); OraQuick followed by quantitative NAT was US$29.50 (venipuncture); and OraQuick followed by quantitative NAT was US$29.97 (fingerstick). Strategies with qualitative NAT follow-up were slightly cheaper than quantitative NAT follow-up. The strategies using venipuncture for testing (whether laboratory-conducted or POC test) achieve the highest viremia sensitivities (range 0.9950 to 0.9954). POC testing for hepatitis C virus with fingerstick followed by NAT using venipuncture yields relatively lower viremia sensitivity (0.9301). The authors concluded that the POC tests or laboratory-based assays tests were comparable economically.[15]

4. <u>What are the evidence-based guidelines regarding patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections?</u>

There were no evidence-based guidelines found regarding patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections

Limitations

One limitation in the included diagnostic accuracy systematic reviews is the heterogeneity of the methodologies (e.g., different throat swab techniques; diagnostic accuracy was assessed among patients both before and after receiving antibiotic treatment) and reference standard tests used in the included trials. Included systematic reviews found inadequate reporting by many trials (e.g., blinding of reference test results) which precluded classification of risks of bias. The cost study did not consider the variability of costs between different health care providers or laboratories. There was no Canadian cost study identified, thus the generalizability of the findings to the Canadian context is limited.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence seem to show that POC tests provide a reliable diagnostic strategy for hepatitis C virus, group A streptococcal pharyngitis infections, and influenza A and B, but performances may vary among different POC tests. The low sensitivity of the POC test for Influenza A and B of suggests a negative POC tests needs confirmation using PCR assay. There was no evidence found on the clinical effectiveness, or evidence-based guidelines regarding patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory.

Despite the efficacy, feasibility, and acceptability of patients and staff of HIV testing by pharmacists in community pharmacies,[22-25] private sale of rapid POC tests for HIV self-testing raises potential ethical, legal and human rights concerns such as disclosure to partners, coerced testing, or privacy. In addition to the concern that patients may perform the test incorrectly and get erroneous results, a positive diagnosis may have psychological impact which could include depression or suicide. One examination of such concerns concluded that HIV testing should not happen without counseling or supervision.[26]

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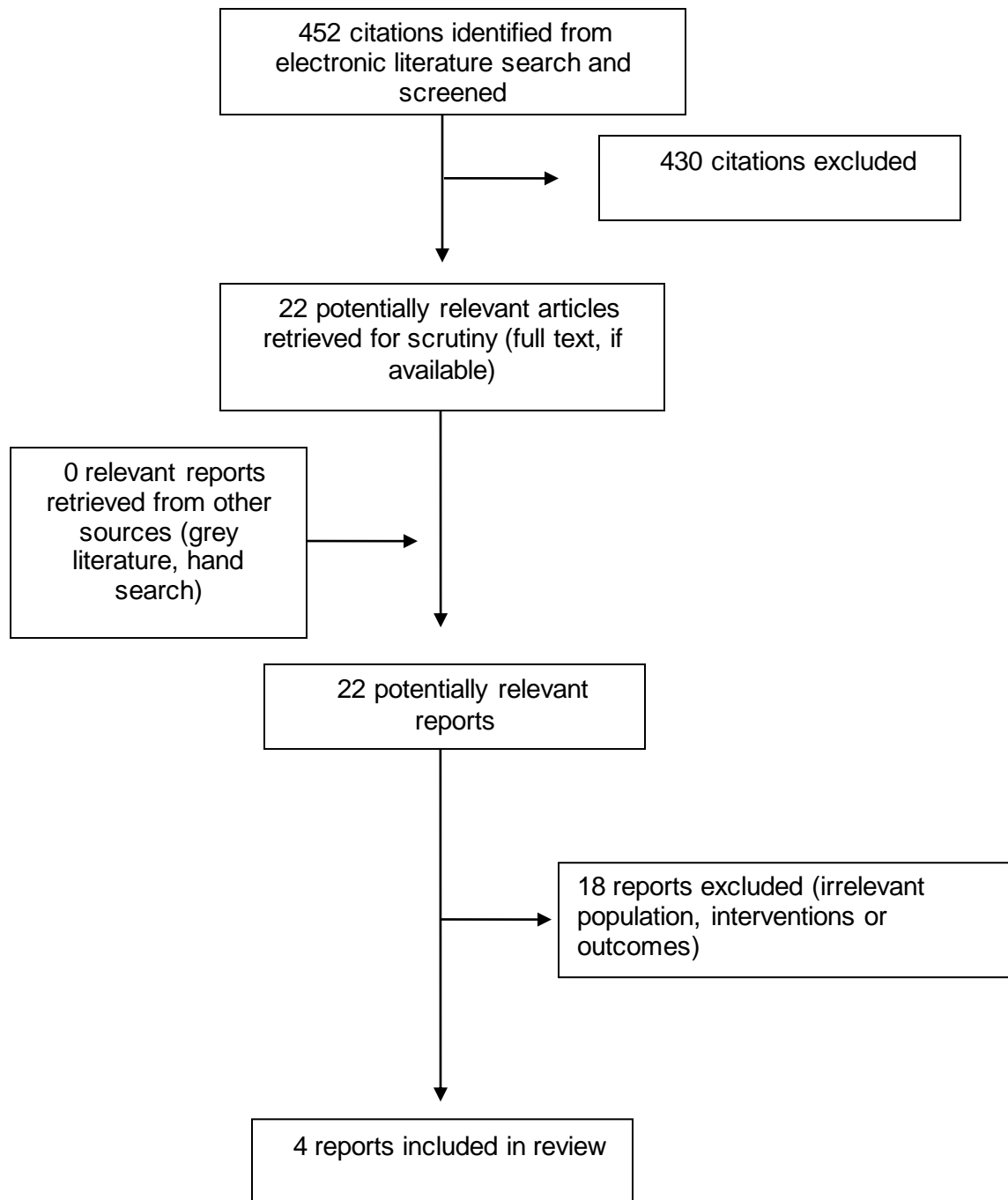Tel: 1-866-898-8439
www.cadth.ca

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Appendix 1: Selection of Included Studies

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Appendix 2: Characteristics of Included Systematic Reviews

Table A1: Characteristics of Included Systematic Reviews				
First Author, Year, Country	**Literature Search Strategy**	**Inclusion Criteria**	**Exclusion Criteria**	**Studies included Main outcomes**
Khuroo,[21] 2015, India	*"we conducted a literature search using the metasearch engine "Mettā" (accessible at http://mengs1.cs.binghamton.edu/metta/search.action) [16]. Mettā is a query interface that helps systematic reviewers to retrieve, filter, and assess articles from five leading medical databases: PubMed, EMBASE, CINAHL, PsycINFO, and the Cochrane Central Register of Controlled Trials. Medical Subject Headings (MeSH) terms used for key and text word searches included "Hepatitis C" OR "Hepatitis C Antibodies" OR "Hepatitis C Virus" AND "Point-of-Care Tests" OR "Rapid Test" OR "Rapid Assay"* (p 3)	*"The test had to have a quick turnaround time (less than 30 min), allow for easy sampling, execution and reading of results, and have no requirement, or a minimal requirement, for cold chain and specialized equipment…* *…We included studies of adults (>18 years old) published as abstracts or as full-text articles using any study design and conducted in any study settings (i.e., laboratory or field-based)"* (p 3)	*"we excluded studies that dealt with the accuracy of laboratory-based tests, those with data that were unsuitable for recreating the 2×2 diagnostic table, reports from manufacturers and package inserts that could be subject to overt conflict-of-interest, and duplicate reports"* (p 3)	Sensitivity, specificity, positive and negative likelihood ratios
Lean,[17] 2014, Australia	*"We systematically searched Medline and Embase via OvidSP for articles published between 1996 and 2013. We used the following search terms: Streptococcus pyogenes, streptococcal infections, group A streptococcal infection, pharyngitis, rapid test, diagnostic reagent kits, immunoassay, immunoenzyme technique, enzyme immunoassay, latex fixation test, latex agglutination test, diagnostic test, molecular biology."* (p 772)	*"We included articles in our review if they contained data on the accuracy of GAS RADTs…* *…Only studies that used throat swabs, not mouth swabs, were included"* (p 772)	*"All the analyzed studies used culture on a blood agar plate as a minimum reference standard; data within individual studies that were not compared with blood agar culture were excluded from analysis. Studies that used only throat culture as a backup for negative RADTs were excluded from the meta analysis"* (p 773)	Sensitivity, specificity

GAS: group A streptococcal; RADT: rapid antigen diagnostic test

Appendix 3: Characteristics of Included Studies

First Author, Year, Country	Study Objectives	Interventions/Comparators	Patients	Main outcomes
Koul,[16] 2015, India	*"To test the performance of a rapid influenza diagnostic test, QuickVue (Quidel) as a POC test against a real-time polymerase chain reaction (RT-PCR) assay for detection of influenza A and B in a developing country setting"* (p S26)	QuickVue (Quidel) POC test for Influenza A and B Real-time polymerase chain reaction (RT-PCR) assay	*"600 patients with influenza-like illness (ILL) or with severe acute respiratory illness (SARI) who were referred to the Influenza Clinic of a tertiary care hospital in Srinagar, India from September 2012 to April 2013"* (p S26)	Sensitivity, specificity, positive and negative predictive values
Chapko,[15] 2015, US	Cost-effectiveness of strategies for testing current hepatitis C infection *"Six strategies for identifying hepatitis C virus (HCV) viremia, involving testing for HCV antibody (HCVAb) followed by a nucleic acid test (NAT) for HCV RNA when the antibody test is positive, are compared"* (p 1396)	POC HCVAb testing Laboratory-conducted HCVAb testing	Blood specimens from patients tested for hepatitis C infection	Viremia sensitivity Cost per person tested

HCV: hepatitis C virus

Appendix 4: Summary of Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Table A3: Summary of Critical Appraisal of Included Study		
Critical appraisal of included systematic reviews (AMSTAR[18])		
Khoroo,[21] 2015	• a priori design provided • duplicate study selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, study characteristics provided • quality assessment of included studies provided and used in formulating conclusions • conflict of interest stated	• list of excluded studies not provided, • no assessment of publication bias performed • considerable heterogeneity in the design, reporting and reference standard test used among the included trials
Lean,[17] 2014	• a priori design provided • duplicate study selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, study characteristics provided • quality assessment of included studies provided and used in formulating conclusions • conflict of interest stated	• list of excluded studies not provided, • no assessment of publication bias performed • considerable heterogeneity in the methodology (eg, types of throat swab used) and intervention test used among the included trials
Critical appraisal of included diagnostic accuracy studies (Quadas[19])		
Kool,[16] 2015	Validity: the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the reference standard results interpreted without knowledge of the results of the index test. Generalizability of results: spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described	Validity: Unclear whether the index test results were interpreted without knowledge of the results of the reference standard Reporting: withdrawals from the study not mentioned
Critical appraisal of included cost studies (Drummond[20])		
Chapko,[15] 2015	• the economic evaluation is likely to be usable (a well-defined question posed in an answerable form; a comprehensive description of the competing alternatives given; evidence for the programme's effectiveness established)	• incremental analysis of the outcomes and costs of alternatives not performed • sensitivity analysis not performed

Table A3: Summary of Critical Appraisal of Included Study		
First Author, Publication Year	Strengths	Limitations
	• outcomes and costs assessed and compared appropriately (all the important and relevant outcomes and costs for each alternative identified; outcomes and costs measured accurately in appropriate units prior to evaluation; outcomes and costs valued credibly; outcomes and costs adjusted for different times at which they occurred) • the presentation and discussion of study results include all issues of concern to users	

Appendix 5: Main Study Findings and Authors' Conclusions

Table A4: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
Research question 1 (diagnostic accuracy of point of care tests (POCT) for HIV, hepatitis C, influenza, and Streptococcal infections compared with conventional testing in a laboratory)		
Hepatitis C virus infection		
Khuroo,[21] 2015	Pooled estimates from 30 POC tests: Sensitivity 97.4% (95% CI 95.9 to 98.4) Specificity 99.5% (95% CI 99.2 to 99.7) Positive likelihood ratio 80.7 (95% CI 55.35 to 116.14) Negative likelihood ratio 0.03 (95% CI 0.02 to 0.04) Among the POC tests, Oraquick had the highest sensitivity (99.5%; 95% CI 98.9 to 99.8) and specificity (99.8%; 95% CI 99.6 to 99.9)	*"Performances varied widely among individual point-of-care tests for diagnosis of hepatitis C virus infection. Physicians should consider this while using specific tests in clinical practice"* (p 1)
Streptococcus A infection		
Lean,[17] 2014	Pooled estimates from 48 studies (number of POC tests not reported): Sensitivity 0.86 (95% CI 0.83 to 0.88) Specificity 0.96 (95% CI 0.94 to 0.97)	*"RADTs can be used for accurate diagnosis of GAS pharyngitis to streamline management of sore throat in primary care"* (p 771)
Influenza A and B infection		
Koul,[16] 2015	QuickVue Sensitivity 23% (95% CI 17.3 to 29.8) Specificity 100% (95% CI 99.1 to 100) PPV 100% (95% CI 91.8 to 100) NPV 74.3% (95% CI 70.5 to 77.9)	*"The high specificity of QuickVue suggest that this POC test can be a useful tool for patient management or triaging during a public health crisis but a low sensitivity suggests that a negative test result need to be further tested using RT-PCR"* (p S26)
Research question 2 (clinical effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory)		
There was no evidence found on the clinical effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory		
Research question 3 (cost effectiveness of patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections compared with conventional testing in a laboratory)		
Hepatitis C infection		
Chapko,[15] 2015	HCVAb detection test – cost per test Lab-based assay (VITROS) followed by quantitative NAT: US$30.08 (venipuncture) OraQuick followed by quantitative NAT: US$29.50 (venipuncture) OraQuick followed by quantitative NAT: US29.97 (fingerstick)	*"Strategies involving HCVAb testing in venipuncture blood, whether laboratory conducted or using a point-of-care assay, when followed by quantitative NAT done reflexively or in separately drawn blood, are comparably economical and suitably viremia sensitive."* (p 1396)
Research question 4 (evidence-based guidelines regarding patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections)		
There were no evidence-based guidelines identified regarding patient self-testing or pharmacist testing with POCT for HIV, hepatitis C, influenza, or Streptococcal infections		

NAT: nucleic acid test; NPV: negative predictive value; PPV: positive predictive value; RADT: rapid antigen diagnostic test