

REVIEW

Systematic review of the impact of point-of-care testing for influenza on the outcomes of patients with acute respiratory tract infection

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Summary

Acute respiratory tract infections are a major cause of morbidity and mortality and represent a significant burden on the health care system. Laboratory testing is required to definitively distinguish infecting influenza virus from other pathogens, resulting in prolonged emergency department (ED) visits and unnecessary antibiotic use. Recently available rapid point-of-care tests (POCT) may allow for appropriate use of antiviral and antibiotic treatments and decrease patient lengths of stay.

We undertook a systematic review to assess the effect of POCT for influenza on three outcomes: (1) antiviral prescription, (2) antibiotic prescription, and (3) patient length of stay in the ED.

The databases Medline and Embase were searched using MeSH terms and keywords for influenza, POCT, antivirals, antibiotics, and length of stay.

Amongst 245 studies screened, 30 were included. The majority of papers reporting on antiviral prescription found that a positive POCT result significantly increased use of antivirals for influenza compared with negative POCT results and standard supportive care. A positive POCT result also led to decreased antibiotic use. The results of studies assessing the effect of POCT on ED length of stay were not definitive.

The studies assessed in this systematic review support the use of POCT for diagnosis of influenza in patients suffering an acute respiratory infection. Diagnosis using POCT may lead to more appropriate prescription of treatments for infectious agents. Further studies are needed to assess the effect of POCT on the length of stay in ED.

KEYWORDS

influenza, point of care, systematic review

Abbreviations used: ED, emergency department; ILI, influenza-like illness; LOS, length of stay; POCT, point-of-care test; RCT, randomised controlled trial; RIDT, rapid influenza diagnostic test

Ece Egilmezer and Gregory J. Walker contributed equally. William Rawlinson and Sacha Stelzer-Braid contributed equally

1 | INTRODUCTION

Respiratory infections are the third most common cause of death globally.¹ Many of these are precipitated by viral infections either directly through damage to the host (influenzavirus, severe acute respiratory syndrome, and Middle East respiratory syndrome coronaviruses²⁻⁴) or indirectly through adverse effects on patients with other conditions such as asthma, chronic obstructive pulmonary disease, or cystic fibrosis.⁵ The

World Health Organisation have reported that annual influenza epidemics result in an estimated 3 to 5 million cases of severe illness, and approximately 250 000 to 500 000 deaths annually.⁶

The current reference standard laboratory test for influenza diagnosis is quantitative reverse transcription PCR. Viral culture^{7,8} is now uncommon, as it is time consuming and expensive and requires specifically trained operators.⁹⁻¹¹ New rapid diagnostic tests for influenza are available that show sensitivity and specificity comparable to real-time PCR assays^{12,13} (Figure 1).

We aimed to systematically review the literature to determine the effects of point-of-care testing for influenza on outcomes for patients, including (1) use of antivirals for influenza virus, (2) administration of antibiotics, and (3) length of stay (LOS) in the emergency department (ED) for patients presenting with symptoms of acute respiratory infection.

2 | METHODS

2.1 | Search strategy

The electronic databases Medline and Embase were independently searched from inception to December 31, 2017. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹⁴ The references of the included studies and recent scientific review articles on influenza point-of-care test (POCT) diagnostics were manually searched for any additional relevant studies, and these were included. The database search strategy was created with a focus on terms for influenza AND point of care testing, and these were combined with terms for any of the targeted outcomes—antibiotic use OR antiviral use OR length of stay.

The specific search terms for influenza used for Embase included “exp influenza” [MeSh] OR “exp influenza virus” [MeSh]. By exploding these terms, we included all types of influenza as well as the different influenza subtypes. The search terms for point-of-care testing included “exp point of care testing” [MeSh] OR “exp rapid test” [MeSh]

OR “influenza a rapid test” [MeSh] OR “ridt.” These terms contained subheadings that included brand names for the most commonly used commercial POCT for influenza.

For the antibiotic and antiviral component of the systematic review, the search terms used were “exp antivirus agent” [MeSh] OR “exp antiviral therapy” [MeSh] OR “exp antibiotic agent” [MeSh] OR “exp antibiotic therapy” [MeSh]. The search terms used for length of stay were “exp length of stay” [MeSh] or “los.”

The search terms for Medline for influenza were “exp Influenza, Human” [MeSh] OR “exp Orthomyxoviridae” [MeSh]. The search terms for point-of-care testing included “exp Point of Care Testing” [MeSh] OR “exp Point of Care Systems” [MeSh] OR “rapid test” OR “ridt” OR “radt” OR “influenza A rapid test.” The search terms for antivirals were “exp Antiviral Agents” [MeSh] OR “Oseltamivir” [MeSh] OR “antiviral ther*.” For antibiotics, we used the search terms “exp Anti-Bacterial Agents” [MeSh] OR “antibiotic*” OR “antibacterial*.” The search terms used for length of stay were “exp Length of Stay” [MeSh] OR “LOS.”

Two reviewers (G.W. and S.S.B.) independently screened the title and abstracts of articles that were eligible using the above criteria. These were supplemented with additional papers that were searched manually using the references of the suitable articles. In cases where there was uncertainty about the eligibility and relevance of a particular article, a resolution was achieved through consensus between reviewers. We excluded scientific review articles, commentaries, Cochrane reviews, case studies, case series studies, analytical model studies, conference abstracts, and studies involving surveys. Studies published only in English were considered.

2.2 | Study selection criteria

Studies were eligible for inclusion if they assessed the effect of POCT on the clinical management of the patient presenting to a physician in a hospital, acute medical centre, or house visit with influenza-like illness (ILI). For this review, a POCT was defined as a commercially available diagnostic assay that detects influenza in respiratory

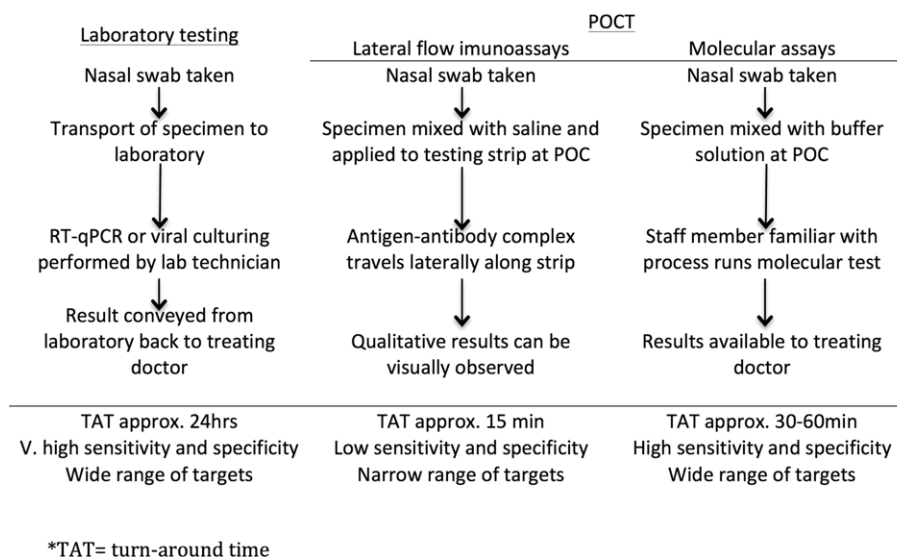


FIGURE 1 Generalised steps in different methods of diagnostic testing for influenza. POC, point of care; POCT, point of care tests; RT-qPCR, quantitative reverse transcription PCR

samples. For a test to be considered as a POCT, it needed to be conducted immediately after specimen acquisition. Studies that did not specify when the test was performed were excluded, as they were presumed to not have been done at point of care. Tests that were not commercially available and that were used in routine influenza diagnosis such as enzyme-linked immunosorbent assay serology were not included in this definition. Studies that used as reference standards viral cell culture, nucleic acid test, immunofluorescence, or diagnosis based on patient symptoms and signs were eligible.

For this systematic review, papers were excluded if the results of the POCT were withheld from the health care professional and not used for diagnosis. Attempts were made to contact authors if information or data were lacking in order to construct the tables.

2.3 | Quality appraisal

The searches were performed by two investigators separately (G.W. and S.S.B.), with quality of the data assessed by two investigators according to Oxford Centre for Evidence-based Medicine (OCEBM) guidelines.¹⁵ Papers included in this systematic review were eligible to be graded from levels 2 to 4 of the OCEBM Levels of Evidence. We considered a level 2-graded study as "excellent" quality, level 3 as "good," and level 4 as "fair."

3 | RESULTS

3.1 | Results of search

The database search yielded 245 publications after removal of duplicates (Figure 2). Titles and abstracts were screened, and 90 papers were assessed for further eligibility. Additional 10 studies were found

through citation of relevant publications in the assessed papers. After full text assessment of study methods and outcomes, a total of 30 met the selection criteria and were included in this systematic review.

Using the OCEBM Levels of Evidence Table,¹⁵ nine studies were graded level 2 or excellent quality, 12 were graded level 3 or good quality, and nine were graded level 4 or fair quality (Table S1, found in the Supporting Information). Results between studies of differing levels of evidence were examined qualitatively, and similar trends were observed between studies.

3.2 | Description of studies

The included studies consisted of retrospective; prospective; and randomised, controlled trials. The POCT used is composed of both antigen-based and molecular-based techniques. Study methods included randomisation of patients to POCT or standard care, comparisons of preimplementation and postimplementation of POCTs, and analysis of positive and negative POCT results. The patient populations in this review included children (<18 years) and adults (≥18 years) from a wide range of study locations including Asia, Australia, Europe, and North America.

3.3 | Antiviral prescription

There were 14 publications that measured the effect of POCT on antiviral prescription (Table 1). Of these, 12/14 (86%) reported increased antiviral use associated with a positive diagnosis by POCT.

A recent randomised controlled trial by Brendish et al¹⁶ found significantly higher prescription rates (91% vs 65%, $P = 0.0026$) amongst study groups diagnosed by POCT. Another recent study by Nitsch-Osuch et al¹⁷ of preimplementation and postimplementation of POCTs showed increased antiviral use in post-POCT patients

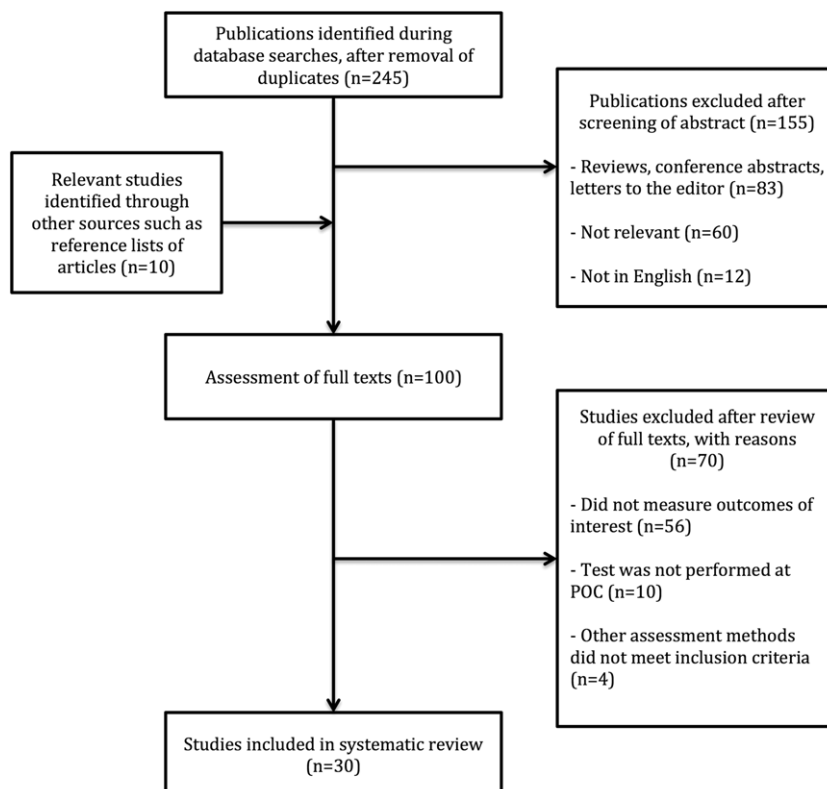


FIGURE 2 Literature search and selection process

TABLE 1 Included studies assessing antiviral prescription^a

Authors, Year, Location	Population, Study Period, Patient Groups	POCT	Results
Brendish et al, 2017, ¹⁶ UK ^{16b}	A RCT enrolling 720 adults (>18 years) with acute respiratory illness at a large UK hospital during Jan-July 2015, and Oct 2015-April 2016. Patients randomly assigned either POCT (n = 362) or routine care (n = 358).	FilmArray Respiratory Panel	Significant, POCT+ vs standard+: 52/57 (91%) vs 24/37 (65%), P = 0.0026
Nitsch-Osusch et al, 2017, ¹⁷ Poland ^b	A study comparing treatment of hospitalised children in a paediatric ward during two consecutive influenza seasons: Jan-Mar 2015, when no RIDT were in use (n = 52), and Jan-march 2016, when RIDT were implemented into routine practice (n = 63).	bioNexia Influenza A+B	Significant, POCT+ vs standard+: 7/11 (64%) vs 0/15 (0%), P < 0.05
Trabattoni et al, 2017, ²⁴ France ^{b,c}	A single centre prospective observational study comparing two diagnostic strategies over 2 months. During Feb 2016 standard laboratory testing was used for diagnosis of influenza (n = 169), and in Mar 2016, a POCT was performed (n = 132).	Alere i Influenza A&B	Not significant, POCT vs standard: 7/132 (5.3%) vs 4/169 (2.4%), P = 0.22
Li-Kim-Moy et al, 2016, ¹⁸ Australia ^{b,c}	A retrospective review of 364 lab-confirmed influenza cases presenting at a paediatric ED during Jan-Dec 2009. Children (<18 y) were diagnosed with influenza by either POCT (n = 236) or standard testing (n = 65).	QuikVue Influenza A+B	Significant, POCT+ vs standard+: 109/236 (46.2%) vs 14/65 (21.5%), P = 0.001
Chu et al, 2015, ³⁰ USA ^b	A retrospective study of 350 adult (>18 y) patients at a teaching hospital and medical centre in USA over two influenza seasons, Feb-Mar 2012 and January 2013. The first season was prior to implementation of POCT (n = 175) and in the second season POCT was used systematically (n = 175).	Simplexa Flu A/B & RSV Kit	Significant, pre-POCT vs post-POCT: 79/175 (45%) vs 97/175 (55%), P = 0.05
González-Del Vecchio et al, 2015, ³⁹ Spain ^b	Cohort of 217 children and adults influenza positive from a general teaching hospital in Spain over one influenza season, Jan-Mar 2014. Patients were divided into: A-POCT negative, reference positive (n = 132) or B-POCT positive (n = 85)	Xpect Flu A&B	Significant, A vs B: 89/132 (67.4%) vs 70/85 (82.3%), P = 0.02
Blaschke et al, 2014, ¹⁹ USA ^{b,d}	A retrospective study using data from the National Hospital Ambulatory Medical Care Survey over three influenza periods: Jan-Apr 2007, Oct-Dec 2008, and Jan-Apr 2009. 1166 of an estimated 4.9 M eligible ED visits were sampled and examined in three groups: POCT+, POCT-, and Influenza (+) by standard test.	Not specified	Significant, POCT+ vs standard+: 56% vs 19%, P = 0.002Significant, POCT+ vs POCT-: 56% vs 2%, P < 0.0001
Lim et al, 2014, ²³ Korea ^b	A retrospective review of medical records of 770 children (<15 y) hospitalised with laboratory confirmed influenza between Feb 2004 and June 2007. Different treatment groups were analysed and included patients receiving; oseltamivir only (n = 27), antibiotics-only (n = 620), antibiotics/oseltamivir combination (n = 67), or standard supportive care (n = 56).	Directigen EZ Flu A+B Test Kit	Significant, oseltamivir only vs antibiotics only, antibiotics/oseltamivir combination, standard supportive care: likelihood of diagnosis by POCT- 22/27 (81.5%) vs 21/620 (3.4%) P < 0.001, 37/67 (55.2%) P = 0.017, 9/56 (16.1%) P < 0.001
Suryaprasad et al, 2014, ²¹ USA	A retrospective analysis of patients with ILI who presented to four US healthcare facilities during the May-Dec 2009 period. A POCT was performed on 290 subjects within 48 h of symptom onset.	BinaxNOW® influenza A & B	Significant, POCT+ vs POCT-: 48/84 (57%) vs 37/206 (18%) (rate ratio 3.3, 95% CI 2.4, 4.6)
Theocharis et al, 2010, ²² Greece ^b	An observational study of patients with ILI who received house call visits from a network of doctors in Greece during Jan-May 2009. 3412 visits were due to ILI, 184 of which had data available from a POCT.	Coris BioConcept Influenza A&B Uni-Strip	Significant, POCT+ vs POCT-: 74/97 (76.2%) vs 1/87 (1.1%), P < 0.01
Jennings et al, 2009, ²⁰ Germany ^b	A study analysing data from a standardised questionnaire that was used by paediatricians in Germany assessing children 1-12 y with ILI. During the study period Jan-April 2007, 16 907 patients were evaluated, 15 871 of which received a POCT.	Clearview Exact Influenza A+B	Significant, POCT+ vs standard+: 4618/7658 (60.1%) vs 178/725 (24.6%)
Falsey et al, 2007, ³⁷ USA ^b	Retrospective analysis of 166 adult (>18 y) hospitalised patients at a hospital in USA over four influenza seasons, Nov-Apr 1999-2003. Comparison of POCT positive (n = 86) and POCT negative/no POCT (n = 80)	Directigen Test Kit	Significant, POCT+ vs POCT-/no test: 63/86 (73%) vs 6/80 (8%), P < 0.001
Poehling et al, 2006, ²⁵ USA ^b	A RCT enrolling children <5 y presenting with ILI in a Tennessee county over two consecutive influenza seasons (2003-2004). All subjects (n = 468) had a nasal and throat swab obtained for PCR, and surveillance days were randomised to perform POCT (n = 205).	Quikvue influenza test	Not significant, POCT vs standard: 1/205 (0.5%) vs 0/263 (0%)

(Continues)

TABLE 1 (Continued)

Authors, Year, Location	Population, Study Period, Patient Groups	POCT	Results
Bonner et al, 2003, ³¹ USA ^b	An RCT of patients aged 2 mo to 21 y at a children's teaching hospital ED in USA over one influenza season, Jan-Mar 2002. All patients (n = 391) received a POCT. Of 202 influenza positive patients, the physician was either made aware of the result (n = 96) or unaware (n = 106).	Flu OIA®	Significant, aware vs unaware: 18/96 (18.8%) vs 7/106 (6.6%), $P < 0.02$

Abbreviations: ED, emergency department; ILI, influenza-like illness; POCT, point of care tests; RCT, randomised controlled trial; RIDT, rapid influenza diagnostic test.

^aListed by year of publication, alphabetical.

^bAlso assessed antibiotic prescription (Table 2).

^cAlso assessed ED length of stay (Table 3).

^dReported as weighted percentages, exact numbers not available.

(64% vs 0%, $P < 0.05$). Likewise, Li-Kim-Moy et al¹⁸ (46.2% vs 21.5%, $P = 0.001$); Blaschke et al¹⁹ (56% vs 19%, $P = 0.002$); and Jennings et al²⁰ (60.1% vs 24.6%, 4618/7658 vs 178/725) all reported that influenza positive patients had significantly increased antiviral use amongst those diagnosed by a POCT compared with standard testing. Blaschke et al¹⁹ also demonstrated antiviral prescription was significantly higher in patients who received a positive POCT result in comparison with a negative POCT result (56% vs 2%, $P < 0.0001$), as did Suryaprasad et al²¹ (57% vs 18%, 48/84 vs 37/206) and Theocharis et al²² (76.2% vs 1.1%, $P < 0.01$). One study²³ of treatment outcomes showed that patients who were prescribed oseltamivir only were significantly more likely to have been diagnosed by POCT compared with patients receiving antibiotics only, antibiotic/antiviral combination, or supportive care. Two studies found no significant effect of POCT on antiviral use.^{24,25}

3.4 | Antibiotic prescription

Twenty-six studies assessed the effect of POCT on antibiotic prescription rates (Table 2). Eleven (42.3%) of these papers^{17-20,26-32} compared POCT with standard testing and reported significant decreases in antibiotic use in patients receiving an influenza positive POCT diagnosis. In addition to comparing POCT and standard testing, three of the studies^{19,27,32} also assessed differences between positive and negative POCT results, demonstrating that patients positive for influenza by POCT were significantly less likely to receive antibiotics. Eight other studies (30.8%)^{22,33-39} reported similar findings. There were six (23.1%) studies that found no significant changes in antibiotic prescription with POCT use.^{16,24,25,40-42}

3.5 | Length of stay (LOS)

Nine studies assessed the effect of POCT on ED length of stay (Table 3). Five (55.6%) of these reported significant reductions in time spent in ED in association with POCT use.

Trabattoni et al²⁴ (4.2 vs 6.1 hours, $P = 0.03$) and Abanses et al⁴³ (2.6 vs 3.3 hours, 95% CI, 0.32-1.00) demonstrated decreased mean ED LOS in prospective studies comparing POCT vs standard testing over a single influenza season. Similarly, in two retrospective studies comparing post- and pre-POCT implementation, Soto et al⁴⁴ reported

a reduced mean ED LOS (20.7 vs 28.1 hours, $P = 0.003$) as did Rogers et al⁴⁵ (4.3 vs 4.7 hours, $P < 0.002$). Fernandez et al³⁵ also demonstrated a significant decrease in ED LOS, in this case between POCT(+) and POCT(-) patients (3.6 vs 7.84 hours, $P < 0.01$).

Two studies found no significant differences in the ED LOS of POCT and standard testing groups,^{18,41} whilst two studies reported that POCT increased ED LOS. Jeong et al²⁷ showed in a retrospective study the median length of ED stay was significantly longer after systematic implementation of POCT (4.3 vs 3.6 hours, $P < 0.01$), whilst Jun et al³³ also reported paediatric mean LOS to be significantly longer when POCT were used (4.8 vs 3.04 hours, $P = 0.001$).

4 | DISCUSSION

This is the first systematic review to examine the effects of using current, commercially available influenza POCT for diagnosis on the prescription of antibiotics and antivirals, and patient LOS in the ED.

Diagnosis of influenza positive patients by POCT resulted in significantly higher rates of antiviral prescription. A number of the studies comparing POC with standard testing^{16,18,40} attributed the increased antiviral use to faster turnaround time to diagnosis by POCT. Given that antivirals are of most clinical benefit if taken within 48 hours of symptom onset,^{10,46,47} this is a key point. In the studies comparing positive and negative POCT results, the increased antiviral use in influenza positive patients is likely due to the removal of diagnostic uncertainty, which also commonly causes patients to be overprescribed antibiotics.⁴⁸ A positive result may eliminate unnecessary antibiotic prescription, whilst a negative POCT result may allow a bacterial infection to be treated promptly. This was evident in the 11 studies included in this review, which demonstrated that a positive POCT diagnosis led to decreased antibiotic use compared with a negative POCT result.^{19,22,27,32-39} Shortening or eliminating avoidable antibiotic use can be of benefit by reducing risk from antibiotic resistance on both a patient and large-scale level.

Length of stay is an important variable to consider when evaluating the effectiveness and quality of patient care. Our systematic review highlights the potential of POCTs for influenza in reducing ED LOS; however, results were mixed, and two studies actually reported that POCT led to an increased LOS in ED. Jeong et al²⁷

TABLE 2 Included studies assessing antibiotic prescription^a

Authors, Year, Location	Population, Study Period, Patient Groups	POCT	Results
Andrews et al, 2017, ⁴⁰ UK	Quasi-randomised study assessing 606 adults (>16 y) at a single NHS centre over one influenza season, Jan-July 2015. Standard testing used on odd days (n = 211), POCT used on even days (n = 334).	FilmArray Respiratory Panel	Not significant, POCT+ vs standard+ on decision to stop, remain off or reduce AB: 35.8% vs 32%, <i>P</i> < 0.05
Brendish et al, 2017, ¹⁶ UK ^b	An RCT enrolling 720 adults (>18 y) with acute respiratory illness at a large UK hospital during Jan-July 2015, and Oct 2015 to April 2016. Patients randomly assigned either POCT (n = 362) or routine care (n = 358).	FilmArray Respiratory Panel	Not significant, POCT+ vs standard+: 301/360 (84%) vs 294/354 (83%), <i>P</i> = 0.96
Nitsch-Osusch et al, 2017, ¹⁷ Poland ^b	A study comparing treatment of hospitalised children in a paediatric ward during two consecutive influenza seasons: Jan-Mar 2015, when no RIDT were in use (n = 52), and Jan-Mar 2016, when RIDT were implemented into routine practice (n = 63).	bioNexia Influenza A+B	Significant, POCT+ vs standard+: 7/11 (64%) vs 14/15 (93%), <i>P</i> < 0.05
Trabattoni et al, 2017, ²⁴ France ^{b,c}	A single centre prospective observational study comparing two diagnostic strategies over 2 months. During Feb 2016 standard laboratory testing was used for diagnosis of influenza (n = 169), and in Mar 2016, a POCT was performed (n = 132).	Alere i Influenza A&B	Not significant, POCT vs standard: 39/132 (29.5%) vs 60/169 (35.5%), <i>P</i> = 0.32
Jun et al, 2016, ³³ Korea ^c	A retrospective study conducted in the ED of a Korean university hospital over two influenza periods: Dec 2008 to Jan 2009, and Feb-Mar 2013. Consisted of 342 paediatric patients (146 in period 1 and 196 in period 2), and 132 adult patients (61, period 1; 71, period 2).	Not specified	Significant, POCT+ vs POCT-: 3/17 (17.6%) vs 31/54 (57.4%), <i>P</i> < 0.05
Li-Kim-Moy et al, 2016, ¹⁸ Australia ^{b,c}	A retrospective review of 364 lab-confirmed influenza cases presenting at a paediatric ED during Jan-Dec 2009. Children (<18 y) were diagnosed with influenza by either POCT (n = 236) or standard testing (n = 65).	QuikVue Influenza A+B	Significant, POCT+ vs standard+: 78/236 (33.1%) vs 35/65 (53.8%), <i>P</i> = 0.003
Berthod et al, 2015, ⁴² Switzerland	An RCT of adult patients presenting with ILI to two Swiss hospitals within 14 d of returning from a trip abroad. The study ran over a 4-y period (Dec 2008 to Nov 2012), and patients randomly received either a POCT (n = 60) or standard care (n = 33) following a nasopharyngeal swap that was taken for laboratory confirmation.	Directigen Flu A +B rapid test	Not significant, POCT vs standard: 14/60 (23%) vs 13/33 (39%), <i>P</i> = 0.15
Chu et al, 2015, ³⁰ USA ^b	A retrospective study of 350 adult (>18 y) patients at a teaching hospital and medical centre in the US over two influenza seasons, Feb-Mar 2012 and January 2013. The first season was prior to implementation of POCT (n = 175), and in the second season, POCT was used systematically (n = 175).	Simplexa Flu A/B & RSV Kit	Significant, pre-POCT vs post-POCT: 133/175 (76%) vs 110/175 (63%), <i>P</i> = 0.008
González-Del Vecchio 2015, ³⁹ Spain ^b	Cohort of 217 child and adult influenza positive from a general teaching hospital in Spain over one influenza season, Jan-Mar 2014. Patients were divided into A-POCT negative, reference positive (n = 132) or B-POCT positive (n = 85)	Xpect Flu A&B	Significant, A vs B: 118/132 (89.3%) vs 57/85 (67.0%), <i>P</i> < 0.01
Lacroix et al, 2015, ³⁴ France	A prospective study of febrile children (<5 y) presenting to a paediatric ED in France during a single influenza season. 170 subjects were included in the Jan-Mar 2013 period, all of whom received diagnosis by POCT.	Quikvue influenza A+B	Significant, POCT+ vs POCT-: 4/80 (5%) vs 33/90 (36.6%), <i>P</i> < 0.05
Tillekeratne et al, 2015, ²⁹ Sri Lanka	A prospective two phase study in the outpatient department of a Sri Lankan hospital. During the first phase (Mar-Dec 2013), patients were attended by physicians who were not aware of their POCT results (n = 316). During the second phase (Jan-Oct 2014), patients were attended by physicians who were made aware of POCT results (n = 241).	Veritor Flu A+B	Significant, IF positive patients phase 1 vs phase 2: 123/147 (83.7%) vs 43/69 (62.3%), <i>P</i> = 0.001
Blaschke et al, 2014, ¹⁷ USA ^{b,d}	A retrospective study using data from the National Hospital Ambulatory Medical Care Survey over three influenza periods: Jan-Apr 2007, Oct-Dec 2008, and Jan-Apr 2009. 1166 of an estimated 4.9 M eligible ED visits were sampled and examined in three groups: POCT+, POCT-, and Influenza (+) by standard test.	Not specified	Significant, POCT+ vs standard+: 11% vs 23%, <i>P</i> = 0.05 significant, POCT+ vs POCT-: 11% vs 47%, <i>P</i> < 0.0001

(Continues)

TABLE 2 (Continued)

Authors, Year, Location	Population, Study Period, Patient Groups	POCT	Results
Jeong et al, 2014, ²⁷ Korea ^c	A retrospective review of data from 437 patients who were suffering from ILI and were discharged from the ED of a Korean hospital over two influenza seasons. In 2010-2011 patients received standard care (n = 221), and in 2011-2012, patients were diagnosed by POCT (n = 216).	Alere SD Bioline Influenza	Significant, POCT vs standard: 54/216 (25.0%) vs 97/221 (43.9%), P < 0.01; significant, POCT+ vs POCT-: 7/73 (9.6%) vs 42/123 (34.1%), P < 0.01
Lim et al, 2014, ²³ Korea ^b	A retrospective review of medical records of 770 children (<15 y) hospitalised with laboratory confirmed influenza between Feb 2004 and June 2007. Different treatment groups were analysed and included patients receiving: oseltamivir only (n = 27), antibiotics only (n = 620), antibiotics/oseltamivir combination (n = 67), or standard supportive care (n = 56).	Directigen EZ Flu A + B	Significant, oseltamivir only vs antibiotics only, antibiotics/oseltamivir combination, standard supportive care: likelihood of diagnosis by POCT- 22/27 (81.5%) vs 21/620 (3.4%) P < 0.001, 37/67 (55.2%) P = 0.017, 9/56 (16.1%) P < 0.001
Nitsch-Osusch et al, 2013, ²⁶ Poland	A prospective cohort study conducted in three Warsaw primary care clinics over two influenza seasons of 2009/2010 and 2010/2011. 256 children with ILI aged 0-5 y were given either a POCT (n = 115), or standard care (n = 141).	Directigen EZ Flu A+B	Significant, POCT vs standard: 7% vs 16%, P = 0.032
Theocharis et al, 2010, ²² Greece ^b	An observational study of patients with ILI who received house call visits from a network of doctors in Greece during Jan-May 2009. 3412 visits were due to ILI, 184 of which had data available from a POCT.	Influ A&B Uni-Strip Dry Swabs (C-1512)	Significant, POCT+ vs POCT-: 4/97 (4.1%) vs 32/87 (36.8%), P < 0.01
Jennings et al, 2009, ²⁰ Germany ^b	A study analysing data from a standardised questionnaire that was used by paediatricians in Germany assessing children 1-12 y with ILI. During the study period Jan-April 2007, 1.6 907 patients were evaluated, 15 871 of which received a POCT.	Clearview Exact Influenza A+B	Significant, POCT+ vs standard+: 271/7658 (3.5%) vs 125/725 (17.2%)
Ozkaya et al, 2009, ²⁸ Turkey	A cross-sectional, single blinded trial of children aged 3-14 who presented to the ED of a Turkish paediatric hospital between November 2006 and Mar 2007. Patients were allocated into two groups that received either a POCT or a standard physical examination.	Influenza A/B Rapid Test	Significant, POCT vs standard: 32% vs 100%, P < 0.0001
D'Heilly et al, June 2008, ³⁸ USA	Retrospective study of 311 adults patients at a medical centre in USA over two influenza seasons; Nov 2003 to May 2004 and Oct 2004 to May 2005. Compared positive (n = 78) and negative (n = 233) POCT results.	FLU OIA A/B	Significant, POCT+ vs POCT-: AB odds ratio = 0.20 (95% CI, 0.10-0.42)
Falsey et al, 2007, ³⁷ USA ^b	Retrospective analysis of 166 adult (>18 y) hospitalised patients at a hospital in USA over four influenza seasons, Nov-Apr 1999-2003. Comparison of POCT positive (n = 86) and POCT negative/no POCT (n = 80)	Directigen	Significant, POCT+ vs POCT- /no test: 74/86 (86%) vs 79/80 (98.8%), P = 0.002
Bhavmani et al, 2006, ³⁶ Thailand	A retrospective analysis of medical records from 300 patients of all ages selected from 5 outpatient departments in Thailand. Records were selected at a 1:2 ratio of ILI cases that were diagnosed as influenza positive (n = 106) or negative (n = 194) by POCT.	Quikvue influenza test	Significant, POCT+ vs POCT-: 77/106 (73%) vs 168/194 (87%), P = 0.003
Benito-Fernandez et al, 2006, ³⁵ Spain ^c	A prospective study of febrile infants (<36 months) presenting to a single paediatric ED in Spain. 206 patients received diagnosis by POCT, with no conformational laboratory testing performed.	Directigen Flu A +B Test Kit	Significant, POCT+ vs POCT-: 0/84 (0%) vs 47/122 (38.5%), P < 0.01
Poehling et al, 2006, ²⁵ USA ^b	An RCT enrolling children <5 y presenting with ILI in a Tennessee county over two consecutive influenza seasons (2003-2004). All subjects (n = 468) had a nasal and throat swab obtained for PCR, and surveillance days were randomised to perform POCT (n = 205).	Quikvue influenza® test	Not significant, POCT vs standard: 61/205 (29.8%) vs 75/263 (28.5%)
Iyer et al, ⁴¹ 2006, USA ^c	A prospective, quasi-randomised controlled trial of febrile children aged 2-24 months during two influenza periods. Diagnosis was determined by either POCT (n = 345) or standard test (n = 355), which was determined by alternating testing days.	Quikvue influenza test	Not significant, POCT vs standard: 54/345 (15.7%) vs 59/355 (16.6%)

(Continues)

TABLE 2 (Continued)

Authors, Year, Location	Population, Study Period, Patient Groups	POCT	Results
Bonner et al, 2003, ³¹ USA ^b	An RCT of patients aged 2 mo to 21 y at a children's teaching hospital ED in USA over one influenza season, Jan-Mar 2002. All patients (n = 391) received a POCT. Of 202 influenza positive patients the physician was either made aware of the result (n = 96), or was unaware (n = 106).	Flu OIA	Significant, aware vs unaware: 7/96 (7.3%) vs 26/106 (24.5%), P < 0.001
Esposito et al, 2003, ³² Italy	An RCT of 957 paediatric (<15 y) patients at the ED of a teaching hospital in Italy over one influenza season, Jan-Feb 2002. Patients were randomly allocated POCT/no POCT, and outcomes for POCT positive (n = 43), POCT negative (n = 435), and standard care (n = 479) were compared.	Quickvue Influenza Test	Significant, POCT+ vs POCT-, standard care: AB (%) 32.6 vs 64.8 (P < 0.0001), vs 61.8 (P = 0.0003)

Abbreviations: ED, emergency department; POCT, point of care tests; RCT, randomised controlled trial.

^aListed by year of publication, alphabetical.

^bAlso assessed antiviral prescription (Table 1).

^cAlso assessed ED length of stay (Table 3).

^dReported as weighted percentages, exact numbers unavailable.

attributed longer ED stay to the significantly older age of their POCT cohort that may have had more comorbidities, whilst reasons for the other study are unclear.³³ Emergency department LOS can be influenced by many factors including availability of beds, overcrowding, admission and discharge procedures, and the efficiency of ED staff. Thus, it may be that the benefits of POCT in terms of ED LOS are somewhat diminished and that this is reflected in the mixed findings of publications in this systematic review. Nonetheless, studies finding reduced ED stay associated with POCT are encouraging, as this can lead to improved clinical outcomes through prevention of nosocomial spread, and easing burden on the healthcare system. More significant reductions in ED LOS can likely be established by further monitoring as health care centres become more familiar with POC technologies.

Early antigen-based POC tests are poor in terms of sensitivity, such as the Quikvue influenza test, which has a sensitivity of 74.0%, and a negative predictive value of 75.0%.³⁴ Physicians are in many cases aware of such limitations and used confirmatory tests to avoid false-negative results.¹⁸ Nonetheless, the findings of studies in this systematic review suggest that antigen-based POCTs can still significantly affect clinical decision-making and patient outcomes. Newer molecular-based POCTs boast high sensitivity and specificity, meaning that results can be trusted by physicians.

Some of the studies using newer molecular POCT saw a limited effect on antibiotic prescription rates, with one group suggesting¹⁶ that in many cases, antibiotics were administered very early in patient assessment, even before POCT results were available. An outcome measuring the proportion of patients treated with brief courses of antibiotics may be more clinically relevant in these cases. At times, molecular POCTs were performed by research investigators rather than clinical staff,^{16,40} suggesting that the study protocol was not initiated immediately upon ED admission. Adoption of new diagnostic technologies will require changes to management protocol and ED collaboration in order to maximise the benefits of improved clinical decision-making and patient workflow.

This paper expands upon a 2014 systematic review,⁴⁹ which assessed the effect of rapid viral diagnosis for children with acute febrile respiratory illness on a range of clinical outcomes including antibiotic use and length of hospital stay. The previous publication was a quantitative analysis of four randomised controlled trials, whereas this systematic review was a qualitative analysis of 30 studies, and thus, we were able to make vastly different conclusions. Our findings were similar to those of another publication⁵⁰; however, these reviews differed in a number of key ways. The study of Ko and Drews⁵⁰ is an expert opinion of studies published between January 2000 and June 2016. Their literature search was performed on PubMed only and did not specify criteria for selection of studies. The search for our systematic review was performed on two databases up to December 2017, yielding different results including six recent studies using molecular-based POCTs. Our search was also supplemented by screening citations of included publications and relevant review papers for additional studies meeting our selection criteria.

Biases due to corporate interests are an important consideration when reviewing literature on the potential benefits of POCT. Because of this, the conflict of interest statements of all publications included

TABLE 3 Included studies assessing ED length of stay^a

Authors, Year, Location	Population, Study Period, Patient Groups	POCT	Results
Trabattoni et al, 2017, ²⁴ France ^{b,c}	A single centre prospective observational study comparing two diagnostic strategies over 2 months. During Feb 2016 standard laboratory testing was used for diagnosis of influenza (n = 169), and in Mar 2016, a POCT was performed (n = 132).	Alere i Influenza A&B	Significant, POCT vs standard (mean): 4.2 vs 6.1 h, P = 0.03
Jun et al, 2016, ³³ Korea ^c	A retrospective study conducted in the ED of a Korean university hospital over two influenza periods: Dec 2008 to Jan 2009, and Feb-Mar 2013. Consisted of 342 paediatric patients (146 in period 1 and 196 in period 2), and 132 adult patients (61, period 1; 71, period 2).	Not specified	Significant, POCT vs standard (mean): 4.8 vs 3.0 h (P = 0.001, period 1), 2.2 vs 1.7 h (P = 0.048, period 2)
Li-Kim-Moy et al, 2016, ¹⁸ Australia ^{b,c}	A retrospective review of 364 lab-confirmed influenza cases presenting at a paediatric ED during Jan-Dec 2009. Children (<18 y) were diagnosed with influenza by either POCT (n = 236) or standard testing (n = 65).	QuikVue Influenza A+B	Not significant, POCT+ vs standard+ (median): 2.7 vs 2.4 h, P = 0.53
Soto et al, 2016, ⁴⁴ Spain	A retrospective study of 1057 adult patients attending the ED of a Barcelona hospital over two influenza seasons. Patients enrolled between Jan and Mar 2013 had samples analysed by standard PCR (n = 366), and between Jan and Mar 2014, patients were diagnosed by a POCT (n = 691).	Xpert Flu Assay	Significant, POCT vs standard (mean): 20.7 vs 28.1 h, P = 0.003
Rogers et al, 2015, ⁴⁵ USA	Retrospective analysis of 1136 patients (3 mo to 21 y) at a tertiary care centre in the US over two influenza seasons, comparing pre- and post-POCT implementation. In Nov 2011 to Jan 2012, patients received standard care (n = 365), and during Nov 2012 to Jan 2013, patients underwent POCT (n = 771).	FilmArray Rapid Respiratory Panel	Significant, pre- vs post-POCT (mean): 4.3 vs 4.7 h, P < 0.002
Jeong et al, 2014, ²⁷ Korea ^c	A retrospective review of data from 437 patients who were suffering from ILI and were discharged from the ED of a Korean hospital over two influenza seasons. In 2010-2011, patients received standard care (n = 221), and in 2011-2012, patients were diagnosed by POCT (n = 216).	SD Bioline Influenza Antigen Test	Significant, POCT vs standard (mean): 4.3 vs 3.6 h, P < 0.01
Abanses et al, 2006, ⁴³ USA	Prospective analysis of 1007 febrile infants (3-36 mo old) at a children's hospital ED in the US over one influenza season (Dec 2002 to Mar 2003). Compared patients receiving a POCT (n = 288) to standard care (n = 719).	Directigen Flu A + B	Significant, POCT vs standard care (mean): 2.6 vs 3.3 h (95% CI, 0.32-1.00)
Benito-Fernandez et al, 2006, ³⁵ Spain ^c	A prospective study of febrile infants (<36 mo) presenting to a single paediatric ED in Spain. 206 patients received diagnosis by POCT, with no conformational laboratory testing performed.	Directigen Flu A+B Test Kit	Significant, POCT+ vs POCT- (mean): 3.6 vs 7.8 h, P < 0.01
Iyer et al, 2006, ⁴¹ USA ^c	A prospective, quasi-randomised controlled trial of febrile children aged 2-24 months during two influenza periods. Diagnosis was determined by either POCT (n = 345) or standard test (n = 355), which was determined by alternating testing days.	Quikvue influenza test	Not significant, POCT vs standard (mean, 95% CI): 3.4 h (3.2-3.5) vs 3.4 h (3.2-3.6)

^aListed by year of publication, alphabetical.

^bAlso assessed antiviral prescription (Table 1).

^cAlso assessed antibiotic prescription (Table 2).

in this systematic review were thoroughly checked. Two studies^{40,41} declared potential conflicts of interest, as they were financially supported by commercial manufacturers of POCT, and three others^{19,20,45} disclosed professional relationships between contributing authors and such companies.

A limitation of this systematic review is that its focus is restricted to (1) influenza diagnosis only and (2) antiviral, antibiotic, and LOS outcomes. Whilst these outcomes are highly applicable for influenza management, new molecular POCTs such as the FilmArray Respiratory Panel can test for a range of viruses and bacteria simultaneously. Hence, these technologies have the potential to affect variables not covered in this review, and this is an area that may be targeted by future research.

In the past decade, numerous studies reporting the diverse use of nanoparticles in POCT have received great interest because of their unique chemical and physical properties.⁵¹ Several research groups have proposed simple colorimetric approaches based on controlled assembly of gold nanoparticles on the surface of viruses,

including influenza.^{52,53} The limit of detection of these proposed methods is up to 385 times lower than that of conventional enzyme-linked immunosorbent assay.⁵⁴ Such reports represent a step forward in the development of tools for the facile detection and surveillance of influenza viruses. Future integration of nanoparticles with specific biological markers will facilitate low-cost, next generation diagnostic methods for on-site detection of respiratory viruses.

The findings of this systematic review support the use of influenza POCT for patients with acute respiratory infection. The majority of studies reported that POCT is associated with more appropriate use of antivirals and antibiotics, which can lead to improved health outcomes for patients. Point-of-care tests may also reduce LOS in ED; however, further clinical trials are needed to properly assess the effect of rapid diagnostic technologies on this variable.

CONFLICT OF INTEREST

The authors have no competing interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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