

Horizon Scan Report 0022

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Diagnostic Technology: Point-of-care tests for influenza in children

Clinical Question:

1. In children with symptoms of acute infection or signs and symptoms of influenza what is the accuracy and utility of point-of-care influenza testing compared to standard care?
2. What are the main factors affecting accuracy of point-of-care tests for influenza in children?
3. What impact does point-of-care testing for influenza have on the child's management in primary care?

Advantages over Existing Technology:

A Point-of-Care Test (POCT) for influenza is intended to allow rapid, accurate diagnosis, with implications for patient management. Early diagnosis may avoid unnecessary further investigation, inappropriate administration of antibiotics and limit the spread of the virus. A diagnosis reached within 48 hours of onset of symptoms permits the use of influenza antiviral drugs, such as neuraminidase inhibitors, which may reduce the severity and duration of illness in children. Rapid diagnosis may also be used for public health purposes to investigate suspected influenza outbreaks.

Details of Technology:

There are a large number of commercially available POCTs for influenza. The majority are chromatographic immunoassays, using monoclonal antibodies against a highly conserved viral nucleoprotein, to ensure reliability even in the presence of antigenic drift. Most POCTs differentiate influenza A, responsible for the majority of seasonal flu, and B antigens and provide results within 15 minutes. The test should be performed as soon after onset of symptoms as possible as sensitivity peaks in the first 4 to 5 days.

1. BinaxNOW Influenza A&B (Alere, USA).
2. Clearview Exact Influenza A+B (Alere, USA).
3. Directigen EZ Flu A+B (Becton, Dickinson, & Co. Diagnostics, USA).
4. Directigen Flu A+B (Becton, Dickinson, & Co. Diagnostics, USA).
5. Remel Xpect Flu A&B (Thermo Fisher Scientific, USA).
6. QuickVue Influenza A+B (Quidel Corp, USA).
7. QuickVue Influenza (Quidel Corp, USA) detects but does not differentiate influenza A and B.
8. 3M Rapid Detection Flu A+B (3M, USA).
9. OSOM Influenza A&B (Sekisui Chemical Co. Ltd, Japan (previously Genzyme, USA)).
10. SAS FluAlert A&B (SA Scientific Ltd, USA).
11. TRU FLU A/B (Meridian Bioscience, USA).
12. Influzatop (All.Diag, France).
13. Actim Influenza A&B (Medix Biochemica, Finland).
14. Inlu-A&B Respi-Strip (Coris BioConcept, Belgium).
15. Quick Ex-Flu/ Quick S- Inlu A/B (Denka Seiken Co Ltd, Japan).
16. Espline Influenza A&B-N (Fujirebio, Japan).
17. Rockeby Influenza A Antigen (Rockeby, Singapore) detects only influenza A.

Patient Group and Use:

1. Children with signs and symptoms of influenza
2. Children with fever and exacerbation of underlying chronic lung disease
3. Children with fever and cough or sore throat without another focus for infection

Importance:

Influenza viruses cause significant morbidity and mortality in children and can be difficult to diagnose as symptoms and signs overlap with a number of respiratory pathologies. Epidemics occur mainly in the winter months, taking 4 weeks to peak and lasting for 8 to 10 weeks. Influenza activity is monitored through surveillance schemes, which record the number of new GP consultations for influenza-like illness (ILI) per week per 100,000 population. In England, normal seasonal activity is currently defined as 30 to 200 consultations, with greater than 200 defined as an epidemic (1). Infection rates are highest in children and complications include febrile convulsions, otitis media, and pneumonia. In the UK, the average number of deaths (all ages) attributed directly to influenza is approximately 600 in non-epidemic years and between 12,000 and 13,800 deaths in epidemic years (2).

Previous Research:*Accuracy compared to existing technology*

According to the UK Health Protection Agency, the most sensitive test for the differential diagnostic detection of Influenza A viruses in clinical samples is detection of influenza-specific RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) (3). The process takes 2 to 4 hours and requires laboratory equipment and trained staff. Alternative laboratory tests for influenza are viral isolation in cell culture, which is less sensitive than RT-PCR and may take 3 to 10 days to provide results, or direct fluorescent assay (DFA), which provides timely results but requires significant technical expertise and equipment.

In practice, the most commonly used approach to influenza diagnosis may be clinical prediction rules such as those identified in a large European cross-sectional study involving 138 general practitioners (4). Samples from 4,584 adults and children presenting with ILI were analysed and the clinical diagnosis of influenza was confirmed by RT-PCR in only 53%, with accuracy increased during epidemics. The study reported that, during an epidemic, the symptoms of cough, early expectoration and fever and previous flu-like contacts increased the likelihood of influenza significantly and that the additional diagnostic value of POCTs for influenza still had to be established. However, the study was not designed to evaluate the use of POCTs in primary care.

A US study assessed the value of cough and fever as clinical predictors of influenza infection during influenza season in two antiviral drug trials in children (5). For the 268 children aged 5 to 12 years in the zanamivir trial, cough and fever were the best predictors of influenza virus infection - the positive predictive value (PPV) was 83% (95% CI, 79%–88%) for temperature ≥ 38.2 degrees combined with cough. However in the oseltamivir trial, cough (PPV 70%), but not fever (combined cough and fever PPV only 71%; 95% CI, 68%–81%), was the best predictor of infection in the 255 children aged 5 to 12 years old. In the 221 children aged 1 to 4 years neither cough nor fever was a successful predictor and only myalgia independently predicted influenza infection (PPV 73%; 66%–81%).

This compared with a prospective study of 128 children (mean age 6.2 years), suspected of having influenza, which identified cough, headache and pharyngitis as most predictive of influenza infection, confirmed by viral culture (6). This triad of symptoms had a sensitivity of 80%, specificity of 78%, likelihood ratio for positive viral culture of 3.7 and post-test probability of 77%. However, the study did not stratify its participants into different age groups so it was not possible to determine whether the prediction model was as useful in younger children.

A Canadian study compared the efficacy of a clinical prediction rule, based on fever and cough, to two different POCTs for influenza, Directigen Flu A+B and QuickVue Influenza (7). Nasopharyngeal (NP) aspirates from 192 patients, including 70 children, were tested against viral culture and RT-PCR. The overall sensitivity of the clinical definition was 86% and the specificity was 42% (PPV 48%, negative predictive value (NPV) 83%) when compared with viral culture, however in children up to 5 years of age, the sensitivity fell to 63% and specificity to 54% (PPV 48%, NPV 68%). When compared with RT-PCR, the overall sensitivity was lower (80%) but the sensitivity in children up to 5 years old was higher (65%). Specificity was largely unchanged.

Both POCTs had equal or greater sensitivity than the clinical case definition overall when compared with viral culture (Directigen Flu A+B 86%, QuickVue Influenza 91%) and significantly higher sensitivity in children up to 5 years (Directigen Flu A+B 95%, QuickVue Influenza 95%). The specificity was also higher overall (Directigen Flu A+B specificity 94% (PPV 89%, NPV 92%), QuickVue Influenza 86% (PPV 78%, NPV 95%) and in children up to 5 years. When compared with RT-PCR, the POCTs still had equal or greater sensitivity than the clinical case definition overall (Directigen Flu A+B 80%, QuickVue Influenza 86%) and significantly higher sensitivity in children up to 5 years (Directigen Flu A+B 95%, QuickVue Influenza 96%). Specificity was increased for both POCTs overall and in children up to 5 years. The authors concluded that the clinical case definition of influenza based on fever and cough was inaccurate for the prediction of influenza virus, but that the high rate of indeterminate results and false negatives, particularly in adults, limited the efficacy of the POCTs.

Accuracy range of POCTs for influenza

POCTs for influenza provide results within 15 minutes, assisting clinical decision-making, however the manufacturers' reported sensitivity and specificity (see Table 1) for influenza A differ by test, specimen, and patient age, and sensitivity is lower than cell culture and RT-PCR.

Table 1. Manufacturers' reported sensitivities and specificities for influenza A (where available).

POCT for influenza:	Sensitivity	Specificity
BinaxNOW Influenza A&B	81%	97%
Clearview Exact Influenza A+B	82%	99%
Directigen EZ Flu A+B	77% -91%	86%-99%
Directigen Flu A+B	86%	91%
Remel Xpect Flu A&B	92%	100%
QuickVue Influenza A+B	77%-94%	89%-99%
3M Rapid Detection Flu A+B	80%	94%-97%
OSOM Influenza A&B	74%	96%
SAS FluAlert A&B	76%	98%
TRU FLU A/B	85%-87%	89%-93%
Influenzatop	94%-100%	99%-100%
Influ-A&B Respi-Strip	97%	100%
Quick S- Infl A/B	90%-93%	98%-99%

Note. A range is given when a single overall figure could not be found.

The 2005 WHO report on rapid testing for influenza diagnosis includes a list of the commercially available tests and the range of their sensitivities, specificities, PPVs and NPVs as reported by 2005 (8).

Focussing primarily on children, a 2003 review reported on 28 studies, dating from 1991 to 2002, of five different POCTs for influenza, of which only Directigen Flu A+B and QuickVue Influenza are still available (9). Three studies of Directigen Flu A+B reported sensitivities for influenza A between 87% and 100% and specificities between 96% and 100%. A fourth study reported an overall sensitivity for influenza A and B of 75%, which reflects lower sensitivity for influenza B than A (80.8% versus 86.2% according to the manufacturer), and specificity of 93%. The PPV for Directigen Flu A+B ranged from 74% (from the fourth study) to 100% and the NPV from 89% to 100%.

QuickVue Influenza detects but does not differentiate between influenza A and B, therefore the five studies of QuickVue Influenza reported lower sensitivities (74% to 95%) and specificities (76% to 98%) than Directigen Flu A+B for influenza A alone. The PPV ranged from 49% to 94% and the NPV from 77% to 98%.

This compares with a more recent US study testing 3M Rapid Detection Flu A+B and BinaxNOW Influenza A&B against cell culture and DFA in 500 patients, of whom 40% were under 18 years old (10). The sensitivity of 3M Rapid Detection Flu A+B was 70% overall but increased to 72% in the paediatric samples alone. The specificity was 100% (PPV 99%, NPV 93%). In comparison, the sensitivity of BinaxNOW Influenza A&B was 46% and specificity 100% (PPV 100%, NPV 89%). The low sensitivity of BinaxNOW Influenza A&B was ascribed to a change in the circulating influenza strains.

Effect of specimen type on accuracy

Nasopharyngeal or nasal washes, aspirates, swabs or throat swabs may all be used as specimens. The highest sensitivities and specificities are reported using NP swabs or aspirates according to manufacturers' data (see Table 2). However, obtaining an aspirate is unpleasant, not well-tolerated by children and requires a suction device, making it unfeasible for widespread use in clinical practice, whereas the collection of a nasal swab is easy, painless and requires no additional devices.

Looking at the quality of the specimen, an Australian study compared 303 paired nose-throat swabs and NP aspirates collected from children aged 5 days to 17.5 years with respiratory illnesses confirmed by RT-PCR (11). In the 37 cases of influenza A, the NP aspirate had a sensitivity of 100%, compared with 92% sensitivity for the nose-throat swab.

Table 2. Manufacturers' reported sensitivities and specificities for influenza A by specimen type (where available).

POCT for influenza:	NP swab		NP aspirate		Nasal swab		Nasal wash/aspirate		Throat swab	
	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
BinaxNOW Influenza A&B	77%	99%			83%	96%				
Clearview Exact Influenza A+B					82%	99%				
Directigen EZ Flu A+B ₁	91%	93%	86%	99%					77%	86%
Directigen Flu A+B ₂	89%	90%	96%	91%					77%	91%
Remel Xpect Flu A&B					89%	100%	93%	100%	100%	100%
QuickVue Influenza A+B	83%	89%			94%	90%	77%	99%		
3M Rapid Detection Flu A+B ₃	80%	97%					80%	94%		
OSOM Influenza A&B					74%	96%				
SAS FluAlert A&B							76%	98%		
Influzatop for influenza A&B	100%	100%					94%	99%		
Quick S- Infl A/B					90%	99%	93%	98%		

Note 1. NP aspirate and wash results reported together.

Note. 2 - NP swab and wash results reported together. Throat swab and lower nasal swab results reported together.

Note. 3 - Nasal wash/ aspirate and NP aspirate results reported together.

Accuracy of tests for influenza virus type B

The majority of POCTs for influenza report equal specificity but lower sensitivity for influenza virus type B than A, however the lower prevalence of influenza B means that less data is available.

A Finnish study of Actim Influenza A&B on 158 children, aged 1 to 3 years, reported a sensitivity of 90% for influenza A (PPV 97%, NPV 98%), compared with 25% for influenza B (PPV 100%, NPV 96%), and specificity of 99% for both (12). A US study of Remel Xpect Flu A&B and BinaxNOW Influenza A&B in 9186 patients, of whom the majority were under 18 years (median age: 14.9 months), found the sensitivities of both tests were higher for influenza A than B, whilst the specificity was not significantly different (13).

A 2007 study compared the accuracy of five POCTs (BinaxNOW Influenza A&B, Directigen EZ Flu A+B, Denka Seiken Quick Ex-Flu, Fujirebio Espline Influenza A&B-N, QuickVue Influenza A+B) for influenza A and B in 177 patients aged 4 days to 64 years (14). Whilst they reported sensitivities of 67% to 73% for influenza A (PPV 97-100%, NPV 89-91%), the sensitivity for influenza B was 30% for each POCT (PPV 100%, NPV 96%). Specificity was 99-100% for both influenza A and B for all POCTs.

Effect of patient age on accuracy

A number of studies indicate that the sensitivity of POCTs is higher the younger the child due to increased viral shedding.

A Greek study of 217 children, aged 6 months to 14 years, using QuickVue Influenza A+B reported an overall sensitivity for influenza A of 68% and specificity of 96% (PPV 79%, NPV 93%) but, when stratified by age, the sensitivity rose to 80% for children aged 6 to 12 months (PPV 67%, NPV 97%), compared with 66% for children over 12 months (PPV 82%, NPV 92%) (15). Specificity did not change significantly.

A US study of 3,561 participants, aged 1 day to 41 years, using BinaxNOW Influenza A&B, stratified sensitivity for influenza A by age and found that overall sensitivity was 62% and specificity was 96% but, for patients aged up to 90 days, the sensitivity was 70% and specificity was 97% (16).

The 2007 study described above (14) also assessed the sensitivity of different POCTs (the five listed above plus the Rocheby Influenza A Antigen) for influenza A in different age groups. The sensitivities of all the tests (excluding Rocheby) were higher in those aged up to 2 years and up to 5 years than those up to 15 years, although the up to 15 years group sensitivities were still higher than the overall sensitivities, which included patients up to 64 years. In five out of the six POCTs, the sensitivities in the up to 2 years group were higher than in the up to 5 years group.

However, a Swiss study of 301 children aged up to 18 years (mean: 6.8years) using Influzatop for the detection of influenza A reported an overall sensitivity of 64% and specificity of 99% (PPV 98%, NPV 70%) but, when stratified by age, the sensitivity dropped to 62% in those aged up to 1 year (PPV 100%, NPV 88%), fell to 45% in the 1 to 5 years group (PPV 100%, NPV 78%) and rose to 68% in the over 5s (PPV 97%, NPV 56%) (17). Specificity was largely unaffected.

Two US studies by the same author published conflicting results. One used Directigen Flu A+B in 118 patients of whom 41 were under 2 years (18). This study reported an overall sensitivity for influenza A of 41%, falling to 27% in the under 2s, rising to 38% in the 2-64 years and rising again to 56% in the over 65s. However a subsequent study using BinaxNOW Influenza A&B in 73 patients, of whom 27 were under 18 years, reported the opposite trend, with an overall sensitivity of 61% (PPV 100%, NPV 89%), rising to 83% in the under 18s (PPV 100%, NPV 95%) and falling to 50% in the over 18s (PPV 100%, NPV 85%) (19).

The fact that each study stratified its results by different age groups makes direct comparison of sensitivities more complicated.

Effect of influenza prevalence on accuracy

The Greek study mentioned above (15), reported that the sensitivity of QuickVue Influenza A+B was higher (76%) during the 4 week peak period of the influenza epidemic, than during the first and third phases of the epidemic, 57% and 50% respectively, whilst the specificity remained almost unchanged. However the US study (16) reported no significant difference in the sensitivity of BinaxNOW Influenza A&B for influenza A during periods of high and low influenza prevalence (62% vs. 59%, respectively).

The PPV and NPV of the POCTs is affected by the population prevalence of influenza, with false positive results more likely to occur when disease prevalence in the community is low, and false negatives more likely when disease prevalence is high. A US study, which used one of four different tests (Directigen Flu A+B/ Directigen A (no longer manufactured)/ QuickVue Influenza A+B/ BinaxNOW Influenza A&B) on 270 children under 5 years old found that the overall PPV reached 97% when community prevalence was 60% but fell to 50% when prevalence was 5% (20). At 60% community prevalence, the NPV was 63%, compared with 98% at 5% community prevalence. This study highlighted the importance of estimating community prevalence when interpreting results as POCTs, as predictive values are highly dependent on prevalence.

Effect of setting on accuracy

The majority of accuracy studies of POCTs for influenza have taken place in hospitals. Those studies that have been conducted in the community have tested QuickVue Influenza A+B and several have reported significantly lower results than the manufacturer's data. A recent US study (21) of QuickVue Influenza A+B on nasal swabs from schoolchildren, tested in the home, found a low sensitivity of 27%, while a Canadian study recorded a sensitivity of only 18% for influenza A using NP swabs in 491 patients, of whom 126 were under 19 years old (22).

In 2009, a multi-site study compared QuickVue Influenza A+B test on nasal swabs to RT-PCR and culture in a population primarily of children (age range: 3 months to 71 years) presenting with ILI at outpatients, paediatric clinics, day care centres and school visits (23). The sensitivity of QuickVue Influenza A+B for influenza A ranged from 20% to 56% across the sites. The specificity ranged from 92% to 100%, PPV from 50% to 100% and NPV from 80% to 94%.

These results contrast with other community studies that used nasal swabs and reported higher sensitivities for influenza A of 64% to 89% in 230 children under 16 years in Hong Kong (24), 65% in a study of 1,157 children under 13 years in Nicaragua (25) and 81% in 587 children under 6 years in Thailand (influenza A and B sensitivity combined) (26). However these studies have limited applicability to the UK.

The only community study in children in the UK that we have identified was conducted in Oxfordshire by general practitioners in 2003 and compared QuickVue Influenza, which detects but does not differentiate influenza A and B, to RT-PCR on samples from 157 children aged 6 months to 12 years (27). The sensitivity, using nasal swabs, was 44%, the specificity was 97% and the likelihood ratio for a positive test result was 14.2 and for a negative result 0.58.

Impact on management compared to existing technology

A number of studies have reported that the use of POCTs for influenza has had a significant impact on patient management in terms of reducing the number of tests ordered (Chest X-ray (CXR), full blood count (FBC), urinalysis (UA)), the time spent in the emergency department (ED), the administration of antibiotics and the prescription of antiviral drugs.

In a randomised controlled trial (RCT) of 1,007 children, aged 3 to 36 months, presenting to the ED during flu season, 288 children were tested with Directigen Flu A+B and managed in accordance with the results, whilst the remainder received standard care (28). When comparing the standard care group to the POCT group, significantly more tests for RSV (RR 2.5) and CXRs (RR 1.3) were ordered. When comparing only those patients who were found to have influenza

in both groups, there were significant increases in the number of investigations ordered for the standard care patients, including tests for RSV (RR=9.2), FBC (RR=12), blood culture (BC) (RR=12), CXR (RR= 2.2) and UA (RR=5.7) and they spent longer in the ED (195 minutes versus 156 minutes).

Two studies, one in Istanbul, one the US, randomised patients presenting with ILI to POCT for influenza or standard care and assessed the impact on patient management. The Turkish study of 97 children, aged 3 to 14 years, found that, although the prevalence of influenza was similar between the two groups, the POCT group (Roche Influenza A/B Rapid Test, not currently marketed) was less likely to be prescribed antibiotics when compared to the standard care group (32% versus 100%, $p < 0.0001$) (29). The US study of 486 patients under 5 years old found that the use of QuickVue Influenza A+B significantly reduced further diagnostic testing ($P=0.03$) among children with respiratory symptoms in the flu season (30).

A prospective study tested 206 patients of up to 3 years of age, with Directigen Flu A+B, and found 84 of them to have influenza (31). Comparison of their management with the influenza negative patients also revealed significant differences ($P < 0.01$) in the percentage of patients undergoing blood tests (33% vs. 100%), UA (81% vs. 100%), CXR (14% vs. 32%), LP (1% vs. 21%), mean length of stay in the ED (116 minutes vs. 193 minutes), admission to the ED observation ward (8% vs. 21%), inpatient care (2% vs. 16%) and antibiotic treatment (0% vs. 39%).

A systematic review and meta-analysis of the sensitivity and specificity of QuickVue compared to clinical diagnosis of ILI showed that for children under 15, sensitivity and specificity for QuickVue was 63% and 94%, respectively compared to sensitivity and specificity of 70% and 61% for clinical diagnosis (42). However studies showed high heterogeneity.

One study that randomised 700 patients, aged 2 to 24 months, to testing with QuickVue Influenza A+B or standard care found significant differences in the adjusted odds ratios for only BC ($p = 0.088$) and urine culture (UC) ($p = 0.005$) when comparing the influenza positive to negative patients in the POCT and standard care groups (32).

Caution needs to be exercised in practice as complications may occur if febrile children are under-investigated and subsequently found to have serious bacterial infections (“SBIs”). Although a US study of 705 children aged 3 to 36 months found the odds of an SBI were 72% less in children who tested positive for influenza A than in those who tested negative (OR 0.28), SBI, especially urinary tract infection, and influenza can co-exist (33). Therefore it is suggested that, for febrile infants and children diagnosed with influenza, blood tests may not be needed but urine cultures should still be considered (34).

Guidelines and Recommendations

The WHO recommends that “Patients with lower respiratory tract illness, especially children ..., should be considered for rapid influenza virus diagnostic testing during their outpatient triage” (8).

We have not identified any guidelines from NICE on POCTs for influenza specifically, however a 2007 clinical guideline entitled ‘Feverish illness in children: assessment and initial management in children younger than 5 years’(35) assessed the data on the risk of co-existing SBIs and influenza and concluded: “Given that rapid detection of viral illness (such as influenza or RSV infection) does not exclude a co-existing SBI, the Guideline Development Group recognised that the use of these tests is not an efficient use of scarce healthcare resources.”

Cost-effectiveness and economic impact:

Only one study has investigated the cost-effectiveness of POCT for influenza in children in the USA (36) no evidence exists for the UK.

Iyer and colleagues investigated the impact of POCT v standard testing for influenza in febrile children who are at risk of SBI on the basis of age and temperature (age 2-3 months $\geq 38^{\circ}\text{C}$, age 3-24 months $\geq 39^{\circ}\text{C}$). The method of testing did not appear to significantly alter physician management, cost, or length of stay in the paediatric ED. However, if the interaction of the method of testing and the test result (positive or negative) were considered, a positive POCT for influenza was associated with a significant reduction in orders for urinalyses and urine cultures (32).

Rothberg et al. reported the results from a model they developed to determine the cost-effectiveness of rapid influenza testing and antiviral treatment in children compared with no testing and antiviral treatment and no antiviral treatment (36). They found no role for rapid diagnostic testing during local outbreaks, because clinical diagnosis was found to be highly predictive, whereas rapid testing led to frequent false negative results, thus adding cost without improving outcome. Similar conclusions were drawn from analyses in adults (37, 38). Rapid testing is useful when the probability of influenza is less than 50%, especially during influenza B outbreaks, because oseltamivir is expensive relative to the cost of testing, and sensitivity is less important when the pre-test probability is low.

Similar conclusions were drawn by two separate decision analytic cost-effectiveness models of rapid testing compared with treatment in adults. Smith and Roberts found rapid testing to be more costly and less effective than treatment without testing, but did suggest that it became more cost-effective when the influenza probability was below 30%, such as early in the influenza season or when influenza is uncommon (39). Sintchenko et al. concluded that pre-treatment POC testing was the cost-effective strategy in the non-epidemic stages of influenza outbreaks, while treatment was the cost-effective option in times of epidemic (40).

Lee and colleagues concluded that for healthy young adults (aged 20-64) the cost of antivirals outweigh any potential benefits of rapid testing plus antiviral use, hence doing nothing is favourable until influenza constitutes 20% or more ILI cases, for older adults (>65 years) testing is the cost-effective option (41).

Research Questions:

1. Which currently available POCT for influenza is the most accurate in children, particular in community settings?
2. What is the utility of POCTs for influenza in children in the UK when compared with clinical prediction rules for influenza?
3. Does the use of POCTs for influenza positively impact patient management in children in the UK?

Suggested next step:

1. A systematic review of the sensitivity and specificity of the different POCTs for influenza in children given the wide range of reported data.
2. Studies to compare the accuracy of POCTs for influenza in UK children, in particular in community settings, where accuracy tends to be lower, and in both epidemic and non-epidemic seasons.
3. Comparison of efficacy of POCTs with clinical prediction rules for diagnosis of influenza in children.
4. Feasibility studies of the use of POCTs for influenza in UK primary care settings.

Expected outcomes:

POCTs for influenza may result in quicker diagnosis, avoiding unnecessary further investigation or referral to hospital, and reducing inappropriate administration of antibiotics, which leads to antibiotic resistance in the community and can cause adverse drug reactions. Rapid diagnosis permits early administration of antiviral drugs if appropriate, which may reduce the severity and duration of illness in children and limit the spread of the virus.

References:

1. National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 158: Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza. 2008.
2. National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 168: Amantadine, oseltamivir and zanamivir for the treatment of influenza. 2009.
3. Health Protection Agency. RT-PCR for the Detection of Influenza A Viruses. 2009.
4. Michiels B, Thomas I, Van Royen P, Coenen S. Clinical prediction rules combining signs, symptoms and epidemiological context to distinguish influenza from influenza-like illnesses in primary care: a cross sectional study. *BMC Fam Pract* 2011 Feb 9;12:4.
5. Ohmit SE, Monto AS. Symptomatic predictors of influenza virus positivity in children during the influenza season. *Clin Infect Dis* 2006 Sep 1;43(5):564-568.
6. Friedman MJ, Attia MW. Clinical predictors of influenza in children. *Arch Pediatr Adolesc Med* 2004 Apr;158(4):391-394.

7. Ruest A, Michaud S, Deslandes S, Frost EH. Comparison of the Directigen flu A+B test, the QuickVue influenza test, and clinical case definition to viral culture and reverse transcription-PCR for rapid diagnosis of influenza virus infection. *J Clin Microbiol* 2003 Aug;41(8):3487-3493.
8. World Health Organisation. WHO recommendations on the use of rapid testing for influenza diagnosis. 2005.
9. Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. *Pediatr Infect Dis J* 2003 Feb;22(2):164-177.
10. Ginocchio CC, Lotlikar M, Falk L, Arora S, Kowerska M, Bornfreund M, et al. Clinical performance of the 3M Rapid Detection Flu A+B Test compared to R-Mix culture, DFA and BinaxNOW Influenza A&B Test. *J Clin Virol* 2009 Jun;45(2):146-149.
11. Lambert SB, Whiley DM, O'Neill NT, Andrews EC, Canavan FM, Bletchly C, et al. Comparing nose-throat swabs and nasopharyngeal aspirates collected from children with symptoms for respiratory virus identification using real-time polymerase chain reaction. *Pediatrics* 2008 Sep;122(3):e615-20.
12. Heinonen S, Silvennoinen H, Lehtinen P, Vainionpaa R, Heikkinen T. Feasibility of diagnosing influenza within 24 hours of symptom onset in children 1-3 years of age. *Eur J Clin Microbiol Infect Dis* 2011 Mar;30(3):387-392.
13. Cruz AT, Cazacu AC, Greer JM, Demmler GJ. Rapid assays for the diagnosis of influenza A and B viruses in patients evaluated at a large tertiary care children's hospital during two consecutive winter seasons. *J Clin Virol* 2008 Feb;41(2):143-147.
14. Hurt AC, Alexander R, Hibbert J, Deed N, Barr IG. Performance of six influenza rapid tests in detecting human influenza in clinical specimens. *J Clin Virol* 2007 Jun;39(2):132-135.
15. Stripeli F, Sakkou Z, Papadopoulos N, Georgiou V, Gratsia P, Christodoulou I, et al. Performance of rapid influenza testing in hospitalized children. *Eur J Clin Microbiol Infect Dis* 2010 Jun;29(6):683-688.
16. Cruz AT, Cazacu AC, McBride LJ, Greer JM, Demmler GJ. Performance characteristics of a rapid immunochromatographic assay for detection of influenza virus in children during the 2003 to 2004 influenza season. *Ann Emerg Med* 2006 Mar;47(3):250-254.
17. Keitel K, Wagner N, Lacroix L, Manzano S, Gervaix A. Performance characteristics of a rapid immunochromatographic assay for detection of pandemic influenza A (H1N1) virus in children. *Eur J Pediatr* 2010 Oct 12.
18. Rahman M, Kieke BA, Vandermause MF, Mitchell PD, Greenlee RT, Belongia EA. Performance of Directigen flu A+B enzyme immunoassay and direct fluorescent assay for detection of influenza infection during the 2004-2005 season. *Diagn Microbiol Infect Dis* 2007 Aug;58(4):413-418.
19. Rahman M, Vandermause MF, Kieke BA, Belongia EA. Performance of Binax NOW Flu A and B and direct fluorescent assay in comparison with a composite of viral culture or reverse transcription polymerase chain reaction for detection of influenza infection during the 2006 to 2007 season. *Diagn Microbiol Infect Dis* 2008 Oct;62(2):162-166.
20. Grijalva CG, Poehling KA, Edwards KM, Weinberg GA, Staat MA, Iwane MK, et al. Accuracy and interpretation of rapid influenza tests in children. *Pediatrics* 2007 Jan;119(1):e6-11.
21. Stebbins S, Stark JH, Prasad R, Thompson WW, Mitruka K, Rinaldo C, et al. Sensitivity and specificity of rapid influenza testing of children in a community setting. *Influenza Other Respi Viruses* 2011 Mar;5(2):104-109.
22. Rouleau I, Charest H, Douville-Fradet M, Skowronski DM, De Serres G. Field performance of a rapid diagnostic test for influenza in an ambulatory setting. *J Clin Microbiol* 2009 Sep;47(9):2699-2703.
23. Uyeki TM, Prasad R, Vukotich C, Stebbins S, Rinaldo CR, Ferng YH, et al. Low sensitivity of rapid diagnostic test for influenza. *Clin Infect Dis* 2009 May 1;48(9):e89-92.
24. Cheng CK, Cowling BJ, Chan KH, Fang VJ, Seto WH, Yung R, et al. Factors affecting QuickVue Influenza A + B rapid test performance in the community setting. *Diagn Microbiol Infect Dis* 2009 Sep;65(1):35-41.
25. Gordon A, Videa E, Saborio S, Lopez R, Kuan G, Reingold A, et al. Performance of an influenza rapid test in children in a primary healthcare setting in Nicaragua. *PLoS One* 2009 Nov 19;4(11):e7907.
26. Simmerman JM, Chittaganpitch M, Erdman D, Sawatwong P, Uyeki TM, Dowell SF. Field performance and new uses of rapid influenza testing in Thailand. *Int J Infect Dis* 2007 Mar;11(2):166-171.
27. Harnden A, Brueggemann A, Shepperd S, White J, Hayward AC, Zambon M, et al. Near patient testing for influenza in children in primary care: comparison with laboratory test. *BMJ* 2003 Mar 1;326(7387):480.
28. Abanses JC, Dowd MD, Simon SD, Sharma V. Impact of rapid influenza testing at triage on management of febrile infants and young children. *Pediatr Emerg Care* 2006 Mar;22(3):145-149.
29. Ozkaya E, Cambaz N, Coskun Y, Mete F, Geyik M, Samanci N. The effect of rapid diagnostic testing for influenza on the reduction of antibiotic use in paediatric emergency department. *Acta Paediatr* 2009 Oct;98(10):1589-1592.
30. Poehling KA, Zhu Y, Tang YW, Edwards K. Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses. *Arch Pediatr Adolesc Med* 2006 Jul;160(7):713-718.

31. Benito-Fernandez J, Vazquez-Ronco MA, Morteruel-Aizkuren E, Mintegui-Raso S, Sanchez-Etxaniz J, Fernandez-Landaluce A. Impact of rapid viral testing for influenza A and B viruses on management of febrile infants without signs of focal infection. *Pediatr Infect Dis J* 2006 Dec;25(12):1153-1157.
32. Iyer SB, Gerber MA, Pomerantz WJ, Mortensen JE, Ruddy RM. Effect of point-of-care influenza testing on management of febrile children. *Acad Emerg Med* 2006 Dec;13(12):1259-1268.
33. Smitherman HF, Caviness AC, Macias CG. Retrospective review of serious bacterial infections in infants who are 0 to 36 months of age and have influenza A infection. *Pediatrics* 2005 Mar;115(3):710-718.
34. Curran J, Shah NB, Platt SL. Impact of the Rapid Influenza Test on Evaluation of the Febrile Child in the Emergency Setting. *Clinical Pediatric Emergency Medicine* 2008 12;9(4):228-232.
35. National Collaborating Centre for Women's and Children's Health. NICE Clinical Guideline: Feverish illness in children: assessment and initial management in children younger than 5 years. 2007.
36. Rothberg MB, Fisher D, Kelly B, Rose DN. Management of influenza symptoms in healthy children: cost-effectiveness of rapid testing and antiviral therapy. *Arch Pediatr Adolesc Med* 2005; 159(11):1055-1062.
37. Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. *Ann Intern Med* 2003; 139(5 Pt 1):321-329.
38. Rothberg MB, He S, Rose DN. Management of influenza symptoms in healthy adults. *J Gen Intern Med* 2003; 18(10):808-815.
39. Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. *Am J Med* 2002; 113(4):300-307.
40. Sintchenko V, Gilbert GL, Coiera E, Dwyer D. Treat or test first? Decision analysis of empirical antiviral treatment of influenza virus infection versus treatment based on rapid test results. *J Clin Virol* 2002; 25(1):15-21.
41. Lee BY, McGlone SM, Bailey RR, Wiringa AE, Zimmer SM, Smith KJ et al. To test or to treat? An analysis of influenza testing and antiviral treatment strategies using economic computer modeling. *PLoS One* 2010; 5(6):e11284.
42. Petrozzino JJ, Smith C, Atkinson MJ. Rapid diagnostic testing for seasonal influenza: an evidence-based review and comparison with unaided clinical diagnosis. *J Emerg Med*. 2010 Oct;39(4):476-490.e1.

Comments:

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