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Horizon Scanning Technology Prioritising Summary

Point-of-care influenza tests

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UPDATE PRIORITISING SUMMARY

REGISTER ID: **000130**

NAME OF TECHNOLOGY: **ZSTATFLU®**

PURPOSE AND TARGET GROUP: **POINT OF CARE INFLUENZA TEST**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☒	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
United States	✓		
Japan	✓		

IMPACT SUMMARY:

ZymeTx Inc manufacture the ZstatFlu®, a rapid point-of-care test for diagnosing influenza A and B. The ZstatFlu® test was given 510 (K) approval from the United States Food and Drug Administration in 2000 but is currently unavailable in Australia.

BACKGROUND

The influenza virus causes acute respiratory tract disease. The onset of illness is usually abrupt with symptoms that include headache, chills, dry cough, high fever, myalgia, malaise and anorexia. Virus progeny can be detected 24 hours prior to the onset of illness, with virus titres peaking 24-48 hours after the onset of symptoms. Influenza may have serious health consequences and may cause death in the very young and very old (Shimasaki et al 2001). Influenza may exacerbate underlying medical conditions (eg pulmonary or cardiac disease) or lead to secondary bacterial, or primary viral, pneumonia. Patients deemed at high risk from the disease complications of influenza should be treated with neuraminidase inhibitors, which act by limiting the release of viral progeny, reducing viral load and therefore reducing the severity of symptoms and duration of disease (Centers for Disease Control and Prevention 1999). To be effective neuraminidase inhibitors need to be administered within 36-48 hours of infection, therefore a rapid and accurate diagnosis of infection is required. Administration of anti-neuraminidase therapy when the infection is actually bacterial may result in severe complications and even death (Shimasaki et al 2001).

The ZstatFlu® Test is an endogenous viral-encoded enzyme assay. It is intended for use in the qualitative determination of influenza types A and B from throat swab specimens and is intended for use as an aid in the diagnosis of influenza A and B viral infections. The ZstatFlu® Test does not differentiate between types A and B and is not intended for the detection of influenza C. A negative result should be confirmed by culture. The ZstatFlu® test is based upon the reaction between viral influenza neuraminidase and a chromogenic (coloured dye) substrate which precipitates upon reaction. Throat swab specimens from patients infected with influenza types A or B virus are added to the reconstituted reagents and incubated at 41ºC for 20 minutes. The resulting reaction mixture is then transferred into a collection device and the colored precipitate is collected on a filter. Positive specimens are blue, and negative specimens are white (ZymeTx Inc 2003).

The Binax NowFlu test is a simple immunochromatographic membrane assay that detects the presence of influenza A or B nucleoprotein antigen in nasal wash or nasopharyngeal swab specimens. Sample is added to the test device and incubated at room temperature, the result can be read after 15minutes. A single pink-purple line in the lower half of the window is necessary to confirm that the test was valid, another pink-purple line above the control line indicates a positive test result.

CLINICAL NEED AND BURDEN OF DISEASE

The number of laboratory confirmed cases of influenza A and B in Australia for the year 2003 was 3,577, with peaks of 1583 and 1327 occurring in August and September, respectively. Of these confirmed cases, 1,723 were in the age bracket 0-4 years and 392 were aged 65^{+} years (Communicable Diseases Australia 2004). The number of public hospital separations for influenza during 2002-03 was 1,000 (AR-DRG numbers J10.0, 10.1 and 10.8) where the influenza virus had been confirmed, and 1,206 (AR-DRG numbers J11.0, 11.1, 11.8) where the influenza virus had not been confirmed. Of the hospitalisations with confirmed virus identification, 278 (28%) were under the age of one year and 426 (43%) were aged between 1 to 4 years of age. The number of cases for those hospitalisations with unconfirmed virus was spread evenly across all age groups (AIHW 2004).

DIFFUSION

ZstatFlu® has been trialled in an Australian hospital study (see below), however it is currently commercially unavailable in this country. Several other rapid influenza diagnostic kits are being trialled in Australia.

COMPARATORS

Infection with the influenza virus may be confirmed from a respiratory tract specimen by any of the following laboratory methods: isolation by culture of the virus, detection of viral nucleic acid using reverse transcriptase polymerase chain reaction (RT-PCR), detection of antigen or by detecting IgG seroconversion. Viral culture may take 2 to 21 days (Communicable Diseases Australia 2004).

EFFECTIVENESS AND SAFETY ISSUES

A recent cross-classification study conducted in Australia by Rawlinson et al (2004) compared the effectiveness of the ZstatFlu® test to conventional diagnostic procedures, including viral culture and RT-PCR (diagnostic levels of evidence II). A total of 1,249 specimens (469 nasopharyngeal aspirates (NPA), 520 throat (TS) and 260 nasal swabs (NS)) were collected from 726 patients who had presented with symptoms suggestive of influenza. Of these 726 patients, there were three patient populations: 219 adult patients (mean age 40 ± 18.7 years) from general practices around Sydney, 41 adults presenting to a hospital Emergency Department and 466 children (mean age 1.1 ± 1.4 years) presenting to the

children's hospital Emergency Department. Incubation of specimens with the ZstatFlu® test was varied (20, 60 and 90 minutes).

Results of this study are presented in Table 1. The sensitivity of the ZstatFlu® test increased with the increased incubation time, however the specificity and positive predictive values decreased with increased incubation time. The negative predictive values were relatively unaffected by incubation time and were reassuringly high indicating that patients were correctly identified as negative 85 to 96 per cent of the time. The test was specific for all specimen types (77-98%) for all incubation times. Sensitivity was poor for throat swabs (18-47%) and nasal swabs (29-65%) for all incubation times. Sensitivity for nasopharyngeal aspirates ranged from 65-77% and was greatest when specimens were incubated for 90 minutes (Rawlinson et al 2004).

Table 1 Sensitivity, specificity, PPV and NPV values of the ZstatFlu® test compared to viral culture

Incubation time (min)	Specimen type	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
20	NPA	65	97	72	96
20	TS	18	98	60	88
20	NS	29	97	63	89
60	NPA	74	87	50	95
60	TS	33	86	27	89
60	NS	44	79	25	90
90	NPA	77	77	40	94
90	TS	47	82	42	85
90	NS	65	82	50	89

PPV = positive predictive value, NPV = negative predictive value, NPA = nasopharyngeal aspirates, TS = throat swabs, NS = nasal swabs

In a similar cross-classification study on 300 nasopharyngeal aspirates collected from children, Hamilton et al (2002) reported a sensitivity of 88%, specificity of 92%, and positive and negative predictive values of 75% and 96%, respectively, when compared to viral culture or RT-PCR (diagnostic level of evidence II).

The cross-classification study by Mitamura et al (2000) (diagnostic level of evidence II) reported a sensitivity and specificity of 67% and 63%, respectively, for throat swabs taken from 172 paediatric patients and a sensitivity and specificity of 48% and 90% for nasopharyngeal aspirates, when compared to viral culture.

COST IMPACT

The current fee for laboratory testing of the influenza virus is $15.75 per test (Medicare Benefits Schedule item number 69384).

ZstatFlu® is currently commercially unavailable in Australia. If the kit was purchased in the United States, the end user would first purchase the starter kit, which contains a reusable heat block and includes enough reagent to perform 20 specimen collections in addition to a positive and negative control. The suggested retail price for both the starter kit and subsequent kits is US$290 (AUD$404), which would equate to approximately AUD$20 per test (ZymeTx Inc 2003).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

Several of the authors of articles cited in this summary are employees of ZymeTx Inc.

The Australian authors, Rawlinson et al 2004, from the Virology Division, University of New South Wales are currently trialling other flu diagnostic kits such as Binax, which are cheaper and available in Australia from Laboratory Diagnostics (personal communication Dr Fennell, Division of Virology).

RECOMMENDATION:

The good quality, level II diagnostic evidence regarding ZstatFlu® test indicates considerable variability in test sensitivity. Although, as a screening test the high test specificity and negative predictive value are more important indicators of accuracy. There would be a clear clinical benefit to identifying patients at high risk from influenza infection and its associated sequelae, therefore it was recommended that this technology be monitored.

SOURCES OF FURTHER INFORMATION:

Achyuthan, K. E., Pence, L. M. et al (2003). 'ZstatFlu-II test: a chemiluminescent neuraminidase assay for influenza viral diagnostics', *Luminescence,* 18 (3), 131-139.

AIHW (2004). *AIHW National Hospital Morbidity Database* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au [Accessed 28th September 2004].

Centers for Disease Control and Prevention (1999). 'Neuraminidase Inhibitors for Treatment of Influenza A and B Infections', *Morbidity and Mortality Weekly,* 48 (RR14), 1-9.

Hamilton, M. S., Abel, D. M. et al (2002). 'Clinical evaluation of the ZstatFlu-II test: a chemiluminescent rapid diagnostic test for influenza virus', *J Clin Microbiol,* 40 (7), 2331-2334.

Rawlinson, W. D., Waliuzzaman, Z. M. et al (2004). 'New point of care test is highly specific but less sensitive for influenza virus A and B in children and adults', *J Med Virol,* 74 (1), 127-131.

Shimasaki, C. D., Achyuthan, K. E. et al (2001). 'Rapid diagnostics: the detection of neuraminidase activity as a technology for high-specificity targets', *Philos Trans R Soc Lond B Biol Sci,* 356 (1416), 1925-1931.

SEARCH CRITERIA TO BE USED:

Chemiluminescence
Heterocyclic Compounds/chemistry
Influenza/*diagnosis/virology
Influenza A virus/*enzymology/isolation & purification
Influenza B virus/*enzymology/isolation & purification
Neuraminidase/*analysis
Sensitivity and Specificity
Virology/instrumentation/methods
Microbiological Techniques

HEALTH PACT DECISION:

- ☐ Horizon Scanning Report
- ☐ Full Health Technology Assessment
- ☐ Monitor
- ☐ Archive
- ☐ Refer

PRIORITY RATING

- ☐ **High**
- ☐ **Medium**
- ☐ **Low**

JUNE 2006 - AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐ Yes ARTG number

☐ No

☒ Not applicable

Diagnostic kits such as the Binax NowFlu A and B do not currently require TGA approval, however in July 2006 a new registration system will be in place at the TGA that will require diagnostic kits such as these to be registered.

JUNE 2006 UPDATE - EFFECTIVENESS AND SAFETY ISSUES

At the time of writing the original Prioritising Summary on ZStatFlu point-of-care diagnostic test for influenza A and B in October 2003, Australian researchers indicated that they were investigating alternative point-of-care tests such as NowFlu, produced by Binax Inc. There have been four studies published comparing this product to viral culture, the reference standard and to other point-of-care tests including the Immuno*Card* STAT! Flu A and B Plus, produced by Meridan Biosciences Inc. Both of these tests have United States Food and Drug Administration approval and the Binax NowFlu tests have been approved for use in Europe (CE marked). There is no further published evidence on the use of ZStat point-of-care diagnostic test for influenza A and B.

The cross-classification study by Booth et al (2006) compared the effectiveness of Immuno*Card* STAT! Flu A and B Plus and the Binax NowFlu A and NowFlu B to the conventional diagnostic tests for influenza, viral culture, immunofluorescence staining (IFA) and PCR (level II Diagnostic evidence). During May and November 2004, throat and nose swabs were collected from 59 adults and 165 nasopharyngeal aspirates were collected from children presenting to hospital with symptoms suggestive of influenza infection. A total of 224 specimens were tested by both culture and IFA.

Results indicated that the performance of both rapid tests were similar. Of the 87 specimens which tested positive for influenza A by IFA and/or culture, 85 and 94 specimens tested positive by Binax NowFlu and Immuno*Card* respectively. The positive predictive values (PPV) for influenza A for Binax NowFlu and Immuno*Card* assays were 97 per cent and 88 per cent respectively, and the negative predictive value (NPV) was 96 per cent for both assays. The specificity was 99 per cent for Binax NowFlu and 98 per cent for Immuno*Card*; the sensitivity for both assays was 80 per cent (Booth et al 2006).

In testing for influenza B, IFA and/or culture detected 39 positive samples among the 87 specimens. The Binax NowFlu assay detected 24 of these and the Immuno*Card*, 21. The PPV for Binax NowFlu and Immuno*Card* in detecting influenza B was 88 per cent and 100 per cent respectively. The NPV was the same for both assays at 96 per cent, as was the specificity at 100 per cent. However, both assays performed poorly with respect to sensitivity at 47 per cent which according to the authors, is characteristic of point of care tests which often range in sensitivity between 39 per cent and 96 per cent depending on the reference method used (Booth et al 2006).

A study conducted by Weinberg and Walker (2005) (level III-1 Diagnostic evidence), compared Binax NowFlu A and NowFlu B to two other rapid assays, Directigen EZ Flu A+B (EZ) and BD Directigen Flu A+B (Directigen). All specimens were tested by the reference standard, viral culture. This study collected 178 respiratory specimens (nasal wash fluids, sputa, bronchoalveolar lavage fluids, tracheal aspirates and nasopharyngeal swabs) and tested them using the three assays (note: due to gaps in reagent availability, not all specimens were tested by all three methods).

A true-positive specimen was defined as a positive result obtained by culture, by two or more antigen detection methods, or by a single antigen detection method confirmed by PCR. The results showed that there was little difference between the assays in terms of specificity, 98 per cent for Directigen and 94 per cent for both EZ and Binax NowFlu, however, Binax NowFlu had a higher sensitivity (76%) than Directigen and EZ with sensitivities of 56 per cent and 39 per cent respectively. The PPV for Directigen, EZ and Binax NowFlu assays were 93, 56 and 93 per cent respectively and the corresponding NPV were 85, 89 and 81 per cent (Weinberg and Walker 2005). The sensitivity of all three assays was markedly altered when the specimens were divided into age-related groups for analysis. The sensitivity of the assays for patients <9 years old was 71, 75 and 100 per cent for Directigen, EZ and Binax NowFlu respectively, compared to 53, 32 and 69 per cent for the age group >9 years old.

Fader (2005) also reported decreased sensitivity of the Binax NowFlu A assay as the age of the patient increased (level III-1 diagnostic evidence). Analysis of 455 respiratory specimens using both virus culture as the reference method and Binax NowFlu A rapid assay, showed sensitivity, specificity, positive and negative predictive values of 65, 98, 89 and 93 per cent respectively. Analysing the data according to age group showed that the sensitivity of the rapid assay decreased as age increased, from 85 per cent among 0-5yr old to 33 per cent >50yr (Fader 2005). It is important to note that this study was conducted during the 2003-2004 influenza season which was dominated by the influenza A strain (H3N2/Fujian) and therefore the influenza B test could not be evaluated.

Cruz et al (2006) investigated the performance of Binax NowFlu A compared to standard virus culture methods in paediatric specimens (level III-1 Diagnostic evidence). A total of 4383 respiratory specimens were collected at a paediatric hospital and analysed by rapid assay and virus culture. The sensitivity and specificity of the assay was demonstrated by Cruz et al to be 62 per cent (95% CI 60-63) and 96 per cent (95% CI 95-96) respectively (Cruz et al 2006). Thus, according to this data, the Binax NowFlu A test appears to be useful for confirmation of the virus, however a negative result cannot rule out influenza A.

JUNE 2006 UPDATE – COST IMPACT

The fee for laboratory testing of influenza virus remains unchanged at AUD$15.75 per test.

Binax NowFlu A and NowFlu B kits can be purchased in Australia for AUD$308. This kit enables testing of 22 nasal wash specimens only which equates to AUD$14 per test. Testing of nasopharyngeal swabs requires the separate purchase of a nasopharyngeal swab specimen accessory pack.

JUNE 2006 – CONCLUSION:

A high level of evidence suggests that point-of-care influenza assays are effective in detecting positive cases of influenza, ie a positive test indicates infection with the virus. However, all assays considered in this summary had poor sensitivities ranging from 39% to 62%, indicating a high number of false negatives. Sensitivities were highest in younger children (under the age of 5 years) and sensitivity decreased with age, which has been suggested is a result of reduced viral shedding in adult patients. Therefore it would appear that point-of-care influenza assays would be useful in confirming a suspected influenza infection, especially in very young children who may be at risk of the serious consequences of influenza infection, such as death. As a negative test cannot rule out influenza infection, all negative results with point-of-care assays would require further investigation through standard methods such as viral culture of PCR.

JUNE 2006 - HEALTHPACT ACTION:

Point-of-care tests are an area of current interest, particularly for monitoring influenza and other infectious diseases. For this reason it is recommended that the technology be monitored

JUNE 2006 - SOURCES OF FURTHER INFORMATION:

Booth, S., Baleriola, C. & Rawlinson, W. D. (2006). 'Comparison of two rapid influenza A/B test kits with reference methods showing high specificity and sensitivity for influenza A infection', *Journal of Medical Virology*, 78 (5), 619-622.

Cruz, A. T., Cazacu, A. C. et al (2006). 'Performance characteristics of a rapid immunochromatographic assay for detection of influenza virus in children during the 2003 to 2004 influenza season', *Ann Emerg Med*, 47 (3), 250-254.

Fader, R. C. (2005). 'Comparison of the Binax NOW Flu A enzyme immunochromatographic assay and R-Mix shell vial culture for the 2003-2004 influenza season', *J Clin Microbiol*, 43 (12), 6133-6135.

Weinberg, A. & Walker, M. L. (2005). 'Evaluation of three immunoassay kits for rapid detection of influenza virus A and B', *Clin Diagn Lab Immunol*, 12 (3), 367-370.

LIST OF STUDIES INCLUDED

Total number of studies	
Level II diagnostic evidence	1
Level III-1 diagnostic evidence	3

HEALTH PACT DECISION:

- ☐ Horizon Scanning Report
- ☐ Full Health Technology Assessment
- ☐ Monitor
- ☐ Archive
- ☐ Refer

PRIORITY RATING

- ☐ **High**
- ☐ **Medium**
- ☐ **Low**

AUGUST 2007 UPDATE

In the first update on this topic it was reported that no new information was published on the Z-stat kit reviewed in the initial prioritising summary. Again, for this second update, there was no new information published on the Z-stat kit. It was therefore decided to review the safety and effectiveness of the considerable amount of new research evaluating rapid influenza diagnostic tests. Thus this update will focus on new information available on these other tests.

AUGUST 2007 – SAFETY AND EFFECTIVENESS:

In an Australian study six rapid influenza diagnostic tests were compared to standard viral culture (Hurt et al 2007) (level III-2 diagnostic evidence). The tests analysed were Binax Now Influenza A&B, Directigen EZ Flu A + B, Denka Seiken Quick Ex-Flu, Fujirebio Espline Influenza A&B-N, and Quidel QuickVue Influenza A + B Test, Rockeby Influenza A Antigen Test. All of the tested kits detect Influenza A, and all except the Rockeby Influenza A Antigen Test, detect Influenza B. The 177 samples used to compare the kits were mostly of paediatric origin and were obtained during the June to October 2006 flu season.

Table 1 Test kit results compared to cell culture detection of Influenza A & B

	Influenza A				Influenza B			
Test Name	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Binax Now Influenza A&B	36/49 (73)	127/128 (99)	36/37 (97)	127/140 (91)	3/10 (30)	167/167 (100)	3/3 (100)	167/174 (96)
BD Directigen EZ Flu A + B	34/49 (69)	128/128 (100)	34/34 (100)	128/143 (90)	3/10 (30)	167/167 (100)	3/3 (100)	167/174 (96)
Denka Seiken Quick Ex-Flu	35/49 (71)	128/128 (100)	35/35 (100)	128/142 (90)	3/10 (30)	167/167 (100)	3/3 (100)	167/174 (96)
Fujirebio Espline Influenza A&B-N	33/49 (67)	128/128 (100)	33/33 (100)	128/144 (89)	3/10 (30)	167/167 (100)	3/3 (100)	167/174 (96)
Rockeby Influenza A Antigen Test	5/49 (10)	128/128 (100)	5/5 (100)	128/172 (74)	Test detects influenza A antigen only			
Quidel Quickvue Influenza A + B Test	33/49 (67)	128/128 (100)	33/33 (100)	128/144 (89)	3/10 (30)	167/167 (100)	3/3 (100)	167/174 (96)

adapted from (Hurt et al 2007)

For Influenza A, if only the samples from children under 5 were included in the analysis, all the test kits showed a sensitivity that was 17-19 percentage points higher than if all samples were included in the analysis. The authors attribute this to the fact that children younger than 5 have longer viral shedding periods and that higher viral levels are usually present in these individuals. The sensitivity reported in this study is higher than previous levels published in the literature. Hurt et al (2007) attributed this to the fact that the majority (85%) of the samples were of nasopharyngeal aspirate origin. This site of sampling is known to produce higher sensitivities compared to other sampling sites such as throat swabs. All of the tests, except the Rockeby Influenza A Antigen Test, were found to have similar levels of sensitivity and specificity. The number of samples that were Influenza B positive was not high enough draw statistically meaningful conclusions but the sensitivities reported in this study were low in themselves and also lower than sensitivity levels previously published for some of the test kits.

A New Zealand study compared the Binax NOW Influenza A & B, Binax NOW Flu A, Binax NOW Flu B, and the Becton–Dickinson Directigen Flu A+B rapid influenza test kits, to direct influenza antigen immunofluorescence and influenza culture from patient samples (Table 2) (Smit et al 2007)(level III-2 diagnostic evidence). The authors recommended the use of nasopharyngeal sampling over throat swabs to increase the sensitivity of the assays. Confirmatory test, such as immunofluorescence, to assess the sample quality, in this case the presence of epithelial cells, was also recommended.

Table 2 Test kit results and immunofluorescence vs cell culture detection of Influenza A & B

	Influenza A				Influenza B	
Test Name	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Binax NOW Influenza A & B	67/113 (59)	403/408 (99)	67/72 (93)	403/457 (88)	2/6 (33)	515/515 (100)
Binax NOW Flu A	66/113 (58)	404/408 (99)	66/70 (94)	404/452 (89)	Detects Influenza A only	
Binax NOW Flu B	Detects Influenza B only				2/6 (33)	515/515 (100)
Becton–Dickinson Directigen Flu A+B	38/72 (53)	336/337 (99.7)	38/39 (97)	408/490 (83)	2/6 (33)	403/403 (100)
Immunofluorescence	65/81 (80)	349/357 (98)	400/448 (89)	65/73 (89)	2/4 (50)	434/434 (100)

Adapted from (Smit et al 2007)

A study of 206 infants admitted to a hospital emergency department with febrile illness without focal infection found that the use of Directigen Flu A+B test kit led to reduced stay, less intensive hospital care, less diagnostic testing, and lower drug administration to those infants found to be positive for influenza (84 of 206; 40.7 percent) compared to those infants found to be negative for influenza (Table 3).

This is because Influenza is often less serious than other diseases that manifest with the same symptoms, and with the high-specificity "rule in" nature of these kits the patients testing positive do not need to be tested further and can be given specific care for Influenza. In this study no other confirmatory test was used to verify the rapid test kit results (Benito-Fernandez et al 2006)(level IV diagnostic evidence).

Table 2 Influence of Directigen Flu A+B test kit use in infants presenting with febrile symptoms

	Influenza positive infants n= 84 infants	Influenza negative infants n= 122 infants	Significantly different (P < 0.01)
Age in months (SD)	6.86 (6.3)	6.55 (6.8)	NS
Mean temperature in C° (SD)	39.38 (0.6)	39.3 (0.8)	NS
Blood tests	33.3%	100%	Yes
urinalysis	80.9%	100%	Yes
chest roentgenogram	14.2%	32%	Yes
cerebrospinal fluid analysis	1.33%	21.3%	Yes
mean length of stay in the ED in minutes(SD)	116.2 (75.5)	192.9 (76.3)	Yes
admission to the ED observation ward	8.3%	21.3%	Yes
inpatient care	2.3%	16.4%	Yes
antibiotic treatment	0%	38.5%	Yes

Adapted from (Benito-Fernandez et al 2006), NS = not significant

A comparison of the QuickVue® Influenza Test (Quidel Corporation) to viral culture in tissue culture and also to reverse transcriptase-polymerase chain reaction (RT-PCR) found that the QuickVue® test had a sensitivity and specificity of 77 and 96 percent, respectively, compared to viral culture and a sensitivity and specificity of 71 and 98 percent, respectively, compared to RT-PCR. The viral culture and RT-PCR were performed on nasopharyngeal samples and the QuickVue® test was performed using the kit nasal swab. Trained nurses performed the sample collection and testing using the QuickVue® Influenza Test kit. During a twelve month period (September 1st 2003 to August 31 2004) 1,092 patients (age range 1 month–86 years; median 35 years) were enrolled in the study. 192 (18%) and 205 (19%) patients were found to be influenza positive by QuickVue® test and viral culture, respectively (Simmerman et al 2007)(level III-2 diagnostic evidence).

The QuickVue® Influenza Test was compared to viral culture and RT-PCR in children younger than 5 presenting to a university based outpatient clinic or paediatric emergency department. Of an eligible 525 children, 468 were enrolled into the study which was randomised by day of admission to the medical facilities. Patients presenting on one half of the randomised days were tested with the QuickVue® Influenza Test and the patients presenting on the other days were not tested with the QuickVue® Influenza Test. Both groups were tested with virus culture and RT-PCR.

The number of patients in the QuickVue® Influenza Test performance group was 205. QuickVue® Influenza Test nasal swab and normal nasal and throat swabs were taken from eligible patients by trained nurses and the QuickVue® Influenza Test was performed at the point of care by the same nurses. On days when both QuickVue® Influenza Test and standard procedures were used for testing, 51 (25%) were influenza positive by standard procedures and 43 (21%) were influenza positive by QuickVue® Influenza Test, indicating 8 missed influenza infections by the QuickVue® Influenza Test. Compared to the standard diagnostic protocol the QuickVue® Influenza Test had a sensitivity of 82 percent (95% CI [69, 92]), a specificity of 99 percent (95% CI [96, 99.9]), a positive predictive value of 98 percent (95% CI [88,99.9]), and a negative predictive value of 94 per cent (95% CI [90, 97]). For the emergency centre patients, the patients in the QuickVue® Influenza Test tested group fewer received diagnostic tests versus patients in the standard test only group (39% vs. 52%, $p = 0.03$). Tests such as chest radiographs, blood cultures, and/or complete blood counts were reduced in the QuickVue® Influenza Test tested group. For the clinic patients there was no difference in the rate of diagnostic tests ordered, or prescription of antivirals and antibiotics between the QuickVue® Influenza Test and standard diagnostic methods groups (Poehling et al 2006)(level III-2 diagnostic evidence).

A study compared the effect of the specimen sampling method on the results of the QuickVue® Influenza Test, viral culture, and RT-PCR. Of the 122 subjects enrolled in the study, 59 had influenza infections. The mean age of the subjects was 5-years (range 2 weeks to 18 years). This study did not perform the QuickVue® Influenza Test immediately at the site of sampling, but rather within 15 minutes of the sample's receipt at the laboratory of the hospital to which the subjects presented. The different sampling methods used in this study were nasopharygeal swabs, nasopharygeal washes, and anterior nasal swabs. Measured against the viral culture gold standard, the highest sensitivity of 85 per cent (46/54) was achieved with the QuickVue® Influenza Test using the nasopharygeal swab sampling method followed by 78 per cent (42/54) with anterior nasal swabs and 78 per cent (37/54) nasopharygeal washes. The specificities ranged between 91-93 per cent. Compared to RT-PCR the QuickVue® Influenza Test the sensitivity achieved using the nasopharygeal swab sampling method was 85 per cent (50/59) followed by anterior nasal swabs 78 per cent (46/59) and nasopharygeal washes 69 percent (41/59). The specificities ranged between 97-98 percent. The QuickVue® Influenza Test PPV ranged from 96-98% and the NPV ranged from 78-87% for all sampling methods. The study was conducted in a period of high influenza incidence (48%) and the authors note the results achieved in their study might not be reproducible in times of lower incidence.

In a study testing a diagnostic microarray Mchip, the QuickVue Influenza A+B test was used as a comparator and both were compared to viral culture in cell culture and RT-PCR. Compared to viral culture the QuickVue Influenza A+B test had a sensitivity and specificity of 93 and 100 percent, respectively. 102 specimens were tested with 57 (56%) being positive for influenza A (Mehlmann et al 2007)(level III-2 diagnostic evidence).

Overall the Influenza rapid, point of care tests have very high specificities. This makes them ideal to rule in patients that present to various clinical settings. The patients that test positive are very likely to be truly positive and hence can be directed to appropriate levels of care, which in the case of Influenza infection often means less intensive care than given to patients presenting with comparable symptoms. The group of patients testing negative for Influenza will contain many Influenza positive patients due to the generally poor sensitivity of these kits. Because they are presenting with serious symptoms it is likely they will be clinically monitored despite testing negative for influenza. The fact that some of these patients will be unnecessarily given more intense hospital care is offset by the fact that probably all the patients would need more intensive hospital care if the kits were not used at all.

AUGUST 2007 - COST IMPACT:

No information was found regarding cost impact of the influenza test kits reviewed in this summary.

AUGUST 2007 SUMMARY OF FINDINGS:

Several medium level evidence studies show the utility of rapid point-of-care tests for quickly diagnosing patients presenting with influenza like symptoms. The impact of the faster diagnosis can be seen in several ways such as the reduction of ineffective therapeutic measures administered to patents identified as positive for influenza (due to the very high specificity all positives are likely to be true influenza cases). Despite the apparent reduction in inappropriate treatment there was no cost effectiveness data published. All of the kits in studies reviewed were of similar performance with only one kit performing poorly in one study. The kits perform best if used on younger patients (<5 yrs of age) and the sampling method is either nasopharyngeal aspirates or swabs. There is also a lack of cost effectiveness data.

AUGUST 2007: HEALTHPACT ACTION

The importance of point-of-care influenza tests is to confirm positive cases of influenza for epidemiological reasons, to be able to provide protection for health care workers and to isolate positive patients, rather than using them as an aid to the clinical management of confirmed cases. In addition, point-of-care influenza tests may be cost-effective in certain subgroups of patients, therefore HealthPACT have recommended that a Horizon Scanning Report be written on this technology.

AUGUST 2007: NUMBER OF STUDIES INCLUDED

Total number of studies	
Level III-2 diagnostic evidence	5
Level IV diagnostic evidence	1

AUGUST 2007 REFERENCES

Benito-Fernandez, J., Vazquez-Ronco, M. A. et al (2006). '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,* 25 (12), 1153-1157.

Hurt, A. C., Alexander, R. et al (2007). 'Performance of six influenza rapid tests in detecting human influenza in clinical specimens', *J Clin Virol,* 39 (2), 132-135.

Mehlmann, M., Bonner, A. B. et al (2007). 'Comparison of the MChip to viral culture, reverse transcription-PCR, and the QuickVue influenza A+B test for rapid diagnosis of influenza', *J Clin Microbiol,* 45 (4), 1234-1237.

Poehling, K. A., Zhu, Y. et al (2006). 'Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses', *Arch Pediatr Adolesc Med,* 160 (7), 713-718.

Simmerman, J. M., Chittaganpitch, M. et al (2007). 'Field performance and new uses of rapid influenza testing in Thailand', *Int J Infect Dis,* 11 (2), 166-171.

Smit, M., Beynon, K. A. et al (2007). 'Comparison of the NOW Influenza A & B, NOW Flu A, NOW Flu B, and Directigen Flu A+B assays, and immunofluorescence with viral culture for the detection of influenza A and B viruses', *Diagn Microbiol Infect Dis,* 57 (1), 67-70.

SOURCES OF FURTHER INFORMATION:

No other sources were identified.