Australian Government

Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

National Horizon Scanning Unit
Horizon scanning prioritising summary

Update Number 7

ZstatFlu® point-of-care influenza test

June 2006

AHTA

Adelaide Health Technology Assessment

© Commonwealth of Australia 2006

[add ISSN]
[add Publications Approval Number]

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at http://www.ag.gov.au/cca

Electronic copies can be obtained from http://www.horizonscanning.gov.au

Enquiries about the content of this summary should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

DISCLAIMER: This summary is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements to health technologies. This summary is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

The Commonwealth does not guarantee the accuracy, currency or completeness of the information in this summary. This summary is not intended to be used as medical advice and it is not intended to be used to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. The Commonwealth does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information.

The production of this *Horizon scanning prioritising summary* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This *Horizon scanning prioritising summary* was prepared by Elizabeth Buckley, Linda Mundy and Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, Mail Drop 511, University of Adelaide, South Australia, 5005.

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).

OCTOBER 2004 - CONCLUSION:

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.

OCTOBER 2004 - 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

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