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Horizon scanning prioritising summary

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ZstatFlu®: Point-of–care influenza test.

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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).

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, Division of Virology, University of New South Wales).

CONCLUSION:

The good quality, level II diagnostic evidence regarding ZstatFlu® test indicates considerable variability in test sensitivity. However, 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.

HEALTHPACT ACTION:

Therefore it is recommended that this technology be monitored.

SOURCES OF FURTHER INFORMATION:

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Mitamura, K., Yamazaki, M. et al (2000). '[Evaluation of the rapid detection test for influenza A and B viruses using neuraminidase activity]', *Kansenshogaku Zasshi,* 74 (1), 12-16.

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.

ZymeTx Inc (2003). *ZstatFlu Info* [Internet]. ZymeTx Inc. Available from: http://www.zymetx.com/physician/zstat.html [Accessed 29th September 2004].

SEARCH CRITERIA TO BE USED:

Chemiluminescence
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