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Horizon Scanning Report

Point-of-care influenza diagnostic tests

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Executive Summary

Nichols et al (2007) defined point-of-care testing (POCT) as "laboratory testing conducted close to the site of patient care by clinical personnel whose primary training is not in the clinical laboratory sciences." POCT is intended to be used by clinicians or nursing staff at the bedside to facilitate patient management and to enable treatment decisions to be made rapidly. POCT for influenza is intended to allow the rapid diagnosis of infection with the influenza virus in high-risk patients. This is to facilitate appropriate treatment of positive cases through the administration of neuraminidase inhibitors or antivirals in a timely fashion, with the aim of reducing morbidity and mortality.

Influenza is highly contagious, affecting people of all ages. Most seasonal epidemics are caused by influenza A with few reported cases of influenza B. Infection rates are usually highest in children, however serious complication rates such as the development of pneumonia are highest in the elderly. This is usually due to the presence of underlying conditions such as chronic pulmonary and cardiovascular disease, immunosuppression or diabetes. The gold standard for the diagnosis of influenza is viral isolation and culture, however results are not available for 2-3 days or longer (range 2-14 days).

The major antigenic determinants of the influenza virus are the glycoproteins haemagglutinin (H) and neuraminidase (N). The influenza A virus is subtyped on the basis of serological and genetic differences in these surface glycoproteins. Current circulating *human* influenza A strains are H1N1 and H3N1. Since 2003, the *avian* influenza A (H5N1) has caused a pandemic in domestic poultry and the wild bird population. This strain is *not* readily transmitted to humans but has infected at least 300 humans (laboratory confirmed) with a 60 per cent case-fatality rate.

There are several rapid influenza diagnostic tests available that are capable of detecting the presence of either influenza A, influenza B or influenza A and B. Influenza A POCT kits are capable of testing whether or not a patient has been infected with influenza A. This includes both the *human* influenza strains and *avian* influenza A. POCT is only capable of identifying the *strain* not the *subtype* of influenza. Further pathology testing is required to ascertain whether or not the influenza subtype is *human or avian.*

None of the studies included in this assessment reported any adverse events associated with the use of point-of-care-testing for influenza. In addition, none of the included studies reported on adverse events associated with the administration of antiviral medication once a positive influenza diagnosis had been obtained.

One small-scale study was identified which assessed the ability of rapid POCT to detect different subtypes of influenza A (Chan 2007). The avian influenza H5N1 subtype was detected with comparable sensitivity to that of the common human H3N2 and H1N1 influenza A subtypes by all the POCT kits assessed. Significantly, however, the limits of detection for *all* subtypes of influenza A using the POCT kits were reported to be more than a thousand fold *lower* than

that obtained with the gold standard of viral isolation. Although POCT can identify avian subtypes of influenza A, the WHO recommends that the gold standard for the diagnosis of H5N1 subtypes should remain viral culture or reverse transcriptase polymerase chain reaction (RT-PCR).

In general, all of the POCT kits, when compared to viral culture or RT-PCR, reported high test specificity (94.5-100% without stratification by age) and moderate-to-low sensitivity. Thus, a *negative* POCT result does not rule out the possibility of influenza as a diagnosis, and all negative patients should undergo conventional viral culture or other diagnostic tests to confirm the presence or absence of influenza infection.

Results for individual POCT kits were highly variable. Of the POCT kits currently available in Australia, the Directigen A+B kit reported test sensitivity for detecting influenza A ranging from 41-69 per cent (4 studies) and 33-50 per cent for influenza B (3 studies). Sensitivity values were reported by two studies using the Binax Now Flu A kit (58 and 79%) and the Binax Flu B kit (33 and 50%), and three studies using the Binax Flu A+B kit (59, 61 and 73%). Three studies used the QuickVue A+B POCT kit. Two reported sensitivity values (67 and 85%) for influenza A, one reported 47 per cent sensitivity for influenza A or B and one study reported 30 per cent sensitivity for influenza B. The variable sensitivity values obtained with POC tests may be a reflection of the population that was tested. POCT has been reported to be more sensitive when used to diagnose children, as a consequence of increased viral shedding in children for longer periods of time. In addition, the study by Agoritsas et al (2006) reported that the sensitivity of POCT kits is affected by sample collection methods, with superior test sensitivity obtained when using nasopharyngeal swabs (85%) compared to nasopharyngeal washes (69%) or nasal swabs (78%). POCT kits designed to diagnose both influenza A or B performed poorly in terms of sensitivity in the diagnosis of influenza B, however this may due to the low prevalence of that strain.

Several high level studies were included for assessment that reported on the effect of POCT on patient management. For patients who received POCT for influenza, studies reported a significant decrease in the number of additional pathology tests (chest x-rays, complete blood culture, urine analysis) ordered when compared to patients who received standard care. When only influenza positive patients from the two groups were compared, the majority of studies reported a significant decrease in the amount of time spent in the emergency department, a decrease in the administration of antibiotics and an increase in the administration of antivirals in patients who received POCT. Although all of the included studies reported on the immediate effect of POCT for influenza on patient management within the emergency department or hospital, none of the studies reported on whether POCT, followed by appropriate treatment, affected the duration or severity of the influenza infection.

Several economic studies on the use of POCT for influenza were assessed. A cost-benefit analysis examined three alternatives: no treatment, treat all patients (empiric treatment) or, test and treat only those patients who return a positive influenza infection result. Treatment options included the antivirals amantadine and rimantadine, or the neuraminidase inhibitors zanamivir and oseltamivir. Patients were only tested for influenza A. Empiric treatment with

the antivirals was favoured when the probability of influenza was low. It was not cost-effective to pursue rapid testing followed by treatment with antivirals for test positive patients. If using neuraminidase inhibitors, the preferred strategy was no treatment when the probability of influenza was 19-22 per cent. It was cost-beneficial to test and treat with zanamivir when the probability of influenza was between 19-28 per cent, and with oseltamivir when the probability was between 22-36 per cent. Empiric treatment with zanamivir and oseltamivir was favoured when the probability of influenza was greater than 28 and 36 per cent, respectively. The authors concluded that rapid testing has a limited role in the clinical management of influenza in high-risk patients (Hueston & Benich 2004).

A cost-effectiveness analysis reported similar results and determined that not giving antiviral therapy is the most expensive and the least effective strategy, costing US$471 per patient. Time lost from productive work accounts for the majority of this cost. The strategies of (1) testing followed by treatment for positive patients or (2) no antiviral therapy, were found to increase costs and to decrease health. The authors concluded that the only two cost-effective strategies were either *not* testing, or of treating *all* patients with either amantadine or zanamivir. The choice of whether to treat with the antiviral or neuraminidase inhibitor depends on the prevalence of influenza B infection. As the proportion of influenza B increases in comparison to influenza A, treatment with zanamivir is favoured (Rothberg et al 2003).

It remains to be determined whether or not POCT has a role in the rationing of either anti-retrovirals or neuraminidase inhibitors at times of pandemic infection when these drugs may be in short supply.

In summary, point-of-care diagnostic tests are highly specific compared to the gold standard of viral culture but have medium-to-low sensitivity. The sensitivity of these tests varies according to patient group and method of sampling and the positive predictive value varies according to the prevalence of influenza at the time of testing. Point-of-care testing for influenza may be of greatest value when used in times of high influenza prevalence and in children presenting with influenza-like symptoms. Improved test sensitivity may be obtained by ensuring a nasopharyngeal swab is used to collect viral samples. Although several studies reported the number of additional pathology tests in patients testing positive for influenza was reduced compared to those who underwent standard testing, economic analyses conducted in the United States indicate that it is more cost-effective to treat *all* patients with suspected influenza with either antivirals or neuraminidase inhibitors without the use of POCT.

Diagnostic tests for influenza administered at the point of care offer the promise of increased diagnostic accuracy and thus improved therapeutic decision-making. A review of the published evidence regarding the safety, effectiveness and cost-effectiveness of point-of-care influenza diagnostic tests has found that, although the currently available tests are highly specific, they are of low-to-moderate sensitivity (high rate of false negative results), with limits of detection of the influenza virus about a thousand times lower than for viral isolation and culture conducted in a laboratory setting. Furthermore, economic analyses have demonstrated that it is not cost-effective to use these tests to directly inform therapeutic decision-making.

However, in light of the rapid rate of development of this technology, an improvement in the sensitivity of point of care tests for influenza may well result in a change to the current recommendation against their widespread use in Australia.

Introduction

The National Horizon Scanning Unit, AHTA, Discipline of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of point-of-care testing for human influenza.

Several companies provide rapid point-of-care diagnostic tests for the detection of human influenza A and B viruses to be used among symptomatic patients presenting to a health care professional. These tests may be offered through general practitioners or emergency department personnel and are currently in limited use in Australia and New Zealand.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of point-of-care testing for human influenza A and B viruses, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with point-of-care testing for human influenza A and B viruses.

Background

Description of the technology

Influenza

Influenza viruses belong to the family of large RNA viruses, *Orthomyxoviridiae*, consisting of three immunologically distinct groups: influenza A, B and C. As influenza C usually causes only a mild cold-like illness it will not be considered further in this report.

Influenza A and B viruses contain eight single-stranded, negative sense RNA strands[1] (Figure 1). Segmentation of the RNA facilitates the exchange of genetic material or genetic reassortment between influenza viruses. The RNA strands encode 10 different influenza proteins, including the glycoproteins haemagglutinin (HA or H) and neuraminidase (NA or N). As demonstrated in Figure 1, NA and HA protrude from the viral lipid envelope bilayer and are the major antigenic determinants of the influenza virus. The influenza A virus is further subtyped on the basis of serological and genetic differences in the HA and NA surface glycoproteins. Fifteen subtypes of HA (H1-H15) and nine subtypes of NA (N1-N9) have been identified, however only three subtypes of

[1] See glossary for definition

HA (H1, H2 and H3) and two subtypes of NA (N1 and N2) are found on circulating human influenza viruses (Cox & Subbarao 1999; Harper et al 2002; Olshaker 2003).

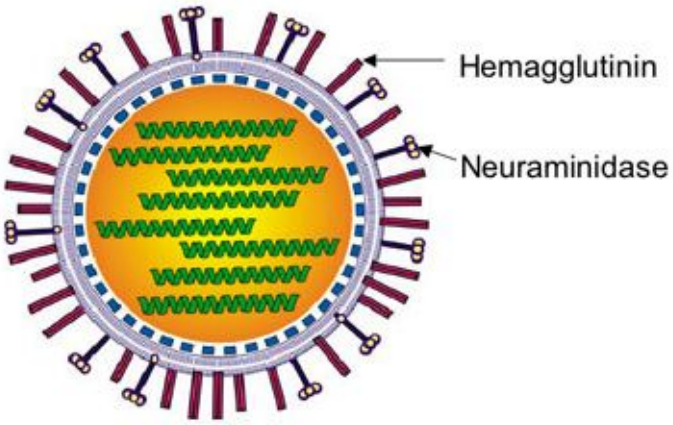

Figure 1 The structure of an influenza virus particle (Conger 2005)

The ability of the influenza virus to cause recurrent epidemics is due to two types of antigenic variation in the major surface proteins, HA and NA. Antigenic drift occurs in both influenza A and B and is caused by point mutations in the viral RNA, resulting in immunologically distinct viruses. Antigenic drift is a dynamic process and occurs more rapidly in influenza A than in influenza B. New antigenic variants render individuals susceptible to infection from new influenza strains despite previous infection by other strains of the virus. Hence the need for yearly immunisation with new vaccines based on the previous season's influenza strains. As infection with the new strain of virus increases, antibodies to old strains also increase, allowing the new strain to predominate by natural selection. An epidemic variant may predominate for several years before another variant emerges to replace it (Cox & Subbarao 1999; Harper et al 2002).

Antigenic shift results in a radical change in antigenicity and is defined as the emergence of a new, immunologically distinct influenza virus in the human population, bearing either a novel HA or a novel combination of HA and NA. Antigenic shifts may occur when novel subtypes of influenza emerge either as a result of direct transmission of an animal influenza strain (from birds or pigs) to humans, or from genetic reassortment between human and animal influenza viruses. Antigenic shifts may lead to pandemics if the new virus is transmissible person-to-person in a large susceptible population (Cox & Subbarao 1999; Harper et al 2002). Since 2003, the *avian* influenza A (H5N1) has caused a pandemic in domestic poultry and the wild bird population. Although this strain is *not* readily transmitted to humans it has infected at least 300 humans (laboratory confirmed) with a 60 per cent case-fatality rate (Davey 2007).

Influenza is a highly contagious illness, affecting people of all ages, and may cause seasonal epidemics (Harper et al 2002). Seasonal influenza is caused by viral strains that have previously circulated in the population, therefore some individuals may be immune and an effective vaccine against these strains is usually available (Davey 2007). An influenza pandemic may occur when a

new subtype of influenza A virus emerges and spreads worldwide. Pandemics are unpredictable and occur infrequently but are associated with a substantial increase in morbidity and mortality. Pandemics occurred in 1918 (H1N1 virus), 1957 (H2N2 virus) and 1968 (H3N2 virus) (Harper et al 2002). The World Health Organization believes that the world is now closer to experiencing an influenza pandemic that at any time since 1968 (AIHW 2006).

Uncomplicated influenza illness is characterised by the abrupt onset of symptoms including fever (38-40° lasting between 1-5 days), chills, sore throat, headache, myalgias, malaise, anorexia and fatigue. Photophobia, abdominal pain and diarrhoea are less common symptoms. Most cases of influenza are self limiting. Infection rates are usually highest in children and complications of infection in this patient group may include febrile seizures. However serious complication rates such as the development of pneumonia are highest in the elderly. This is usually due to the presence of underlying conditions such as chronic pulmonary and cardiovascular disease, immunosuppression or diabetes. Influenza combined with primary viral pneumonia is associated with a high mortality rate in the elderly (Cox & Subbarao 1999; Harper et al 2002; Olshaker 2003).

The influenza virus is spread via aerosols produced by the coughing or sneezing of infected individuals. The incubation period for influenza ranges from 1-4 days and virus can be isolated from the nasopharynx of adults for up to four days after symptom onset, with children shedding the virus for longer periods of time. Infection and viral replication takes place in the epithelial cells of the respiratory tract. Infection induces both a T and B lymphocyte response. Antibodies to HA may persist for long periods of time, however antibodies to NA are not capable of neutralising the influenza virus, but may restrict the release of progeny viral particles from infected cells, reducing the intensity of infection and aiding a more rapid recovery (Harper et al 2002).

There are currently four drugs available to treat influenza. These include the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Adamantanes are active against influenza A but not influenza B. Adamantanes are no longer recommended for use in the United States due to the recent emergence of resistance to these drugs, which has rendered them ineffective.

The neuraminidase inhibitors are effective in treating influenza A or B, and for prophylaxis in selected adults and children. Resistance to neuraminidase inhibitors is rare, but influenza strains resistant to oseltamivir have been detected (Lynch & Walsh 2007). Oseltamivir is administered orally (75-mg dose twice daily) and is recommended for the treatment of patients older than one year. Zanamivir is inhaled through the mouth at a high flow rate (two 10-mg inhalations twice daily) and is only recommended in patients older than seven years. The recommended course of treatment for both drugs is five days. To be effective neuraminidase inhibitors need to be administered within 36-48 hours of infection, therefore a rapid and accurate diagnosis of influenza infection is required. Neuraminidase inhibitors should only be used in patients with uncomplicated illness presenting within this time frame. Administration of neuraminidase inhibitors to patients infected with influenza has been demonstrated to reduce the duration of illness by 1-2 days, the severity of

symptoms and complications in high-risk individuals (Harper et al 2002; Hessen 2007; Olshaker 2003). Oseltamivir and zanamivir are registered in Australia by the Therapeutic Goods Administration as Tamiflu and Relenza respectively, but are not listed on the Pharmaceutical Benefits Schedule.

Vaccination still remains the most effective means of influenza control (Lynch & Walsh 2007).

The procedure

Point-of-care testing (POCT) is defined as "clinical laboratory testing conducted close to the site of patient care by clinical personnel whose primary training is not in the clinical laboratory sciences" (Nichols et al 2007). POCT refers to pathology tests that are performed outside of traditional pathology laboratories. POCT is intended to be used by clinicians at the bedside to facilitate patient management and to allow treatment decisions to be made rapidly (Nichols et al 2007).

There are several rapid influenza diagnostic tests available which are capable of detecting the presence of either influenza A alone, influenza A and B separately or both influenza A and B but not differentiating between the two viruses (Table 1). It is important to note that these kits are capable of testing whether or not a patient *has been infected with influenza A*, which would include *the human influenza subtypes* (H1N1 and H3N1) *and avian influenza A subtype* (H5N1). POCT is *only* capable of identifying the *strain* (ie A, A+B, A or B) *not* the subtype. Further pathology testing is required to ascertain whether or not the influenza subtype is *human or avian* (Davey 2007). No large scale study has been conducted to assess the accuracy of rapid POCT influenza to detect human infection with avian influenza (WHO 2005).

The majority of these influenza POCT kits are CLIA[2]-waived by the United States Food and Drug Administration. The tests require either a nasal wash, nasal swab, throat swab or a nasopharyngeal swab. The amount of virus will vary according to the type of sample collection, which may affect analytical sensitivity. Nasal samples contain a higher quantity of detectable virus when compared to throat swabs and are therefore the preferred method of sample collection (Sharma et al 2006). It is important that assays detect a highly conserved viral protein which will enable the assay to be reliable in the presence of antigenic drift (Demmler 2002). The majority of rapid influenza kits are capable of detecting viral infection within 10-30 minutes (Sharma et al 2006). Detection of influenza virus using rapid POCT is confounded in patients who have recently received immunisation with a live attenuated viral vaccine and should be avoided in these patients (Petric et al 2006).

[2] CLIA = Clinical Laboratory Improvement Amendments. Waived tests are defined as simple laboratory examinations and procedures that are cleared by the FDA for home or clinical use. The methodologies employed are simple and accurate with the likelihood of erroneous results negligible. In addition the tests pose no reasonable risk or harm to the patient if performed incorrectly Avitar (2007). *SAMS™ Glossary Substance Abuse Management Solution* [Internet]. Avitar on site diagnostics. Available from: http://www.avitarinc.com/Services/SAMS_glossary.cfm [Accessed 5th December 2007].

Table 1 Rapid tests for the diagnosis of influenza

Test	Type of influenza detected	Method of detection	Specimen	Time required to complete assay
Directigen Flu A (Becton Dickinson)	A	Chromatographic enzyme immunoassay detecting viral antigens	Nasopharyngeal wash, swab or aspirate, throat swab	15 min
Directigen Flu A + B (Becton Dickinson)	A + B	Chromatographic enzyme immunoassay detecting viral antigens	Nasopharyngeal wash, swab or aspirate, throat swab	15 min
FLU OIA (ThermosBiostar)	A and B (does not distinguish)	Optical immunoassay detecting nucleoprotein	Nasopharyngeal swab or aspirate, throat swab	15 min
NOW Influenza A (Binax)	A	Immunochromatographic using monoclonal antibodies against nucleoprotein	Nasal wash or aspirate; nasopharyngeal swab	15 min
NOW Influenza B (Binax)	B	Immunochromatographic using monoclonal antibodies against nucleoprotein	Nasal wash or aspirate; nasopharyngeal swab	15 min
NOW Influenza A + B (Binax)	A + B	Immunochromatographic using monoclonal antibodies against nucleoprotein	Nasal wash or aspirate; nasopharyngeal swab	15 min
QuickVue Influenza Test (Quidel)	A and B (does not distinguish)	Enzyme immunoassay using monoclonal antibodies against influenza A + B antigens	Nasal wash or aspirate; nasopharyngeal swab	10 min
QuickVue Influenza A + B Test (Quidel)	A and B	Enzyme immunoassay using monoclonal antibodies against influenza A + B antigens	Nasal wash or aspirate; nasopharyngeal swab	10 min
SAS Influenza A Test	A	Immunochromatographic using monoclonal antibodies against nucleoprotein	Nasopharyngeal wash or aspirate	30 min
SAS Influenza B Test	B	Immunochromatographic using monoclonal antibodies against nucleoprotein	Nasopharyngeal wash or aspirate	30 min
ZstatFlu (ZymeTx)	A and B (does not distinguish)	Chemiluminescent assay which detects enzyme activity of neuraminidase	Throat swab	20-30 min

(Charles & Grayson 2007; Harper et al 2002; Hessen 2007)

The tests vary in their method of detecting viral influenza with some tests utilising an immunoassay that detects viral nucleoprotein, and others an enzyme-based assay that detects neuraminidase (Demmler 2002; Sharma et al 2006). Most of the assays use simple methodologies such as that employed by the QuickVue Influenza test (Figure 2).

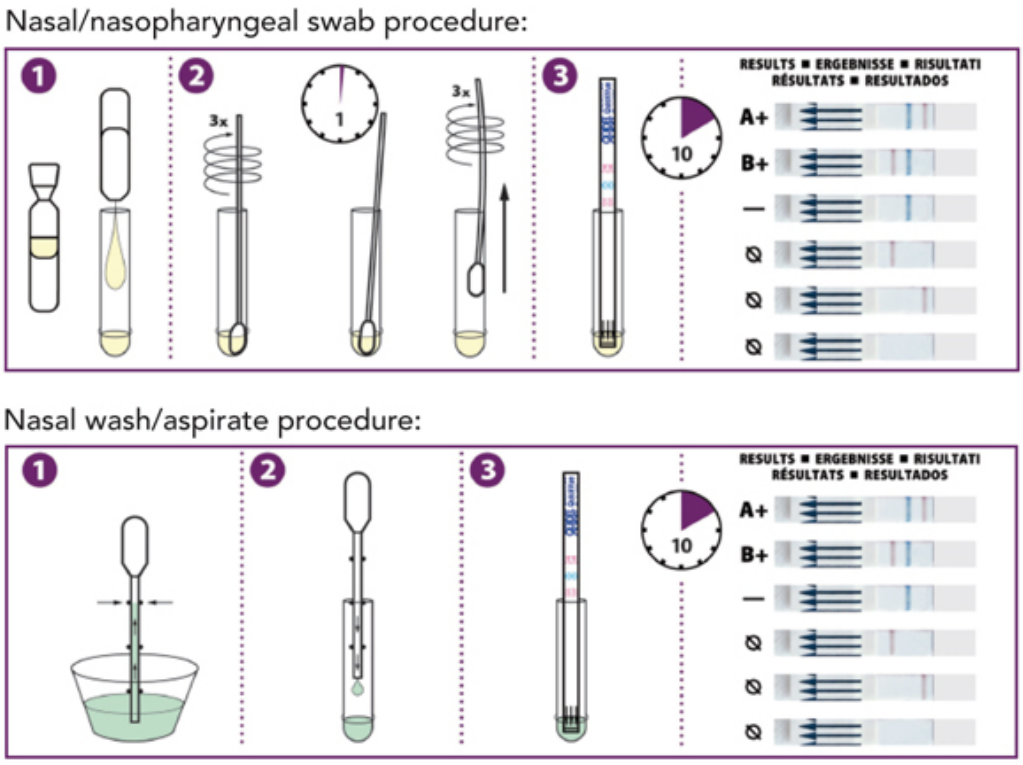

Figure 2 **The QuickVue influenza test A + B (Charles & Grayson 2007)**

The sample is applied to a test strip that has been impregnated with antibodies. A reagent solution is added to an extraction tube (step 1). The nasal swab is added to this solution and shaken (step 2), or in the case of a nasal wash, the sample is added to the solution via a provided pipette. The test strip is incubated in this solution for the prescribed amount of time (step 3). The influenza viral antigens, if present, react and bind with the antibodies embedded in the test strip forming a complex that is visualised by a colour change (Charles & Grayson 2007). Medical staff should not experience difficulty using the kits, however training may be required to ensure the correct, effective and reproducible method of sample collection (Turner et al 2006). The FLU OIA diagnostic kit, an optical immunoassay, is considered to be more complex than other available diagnostic kits and therefore unlikely to be used for POCT in a clinical setting (Charles & Grayson 2007).

Intended purpose

POCT is intended to rapidly diagnose the presence or absence of infection with the influenza virus in high-risk patients. This will allow appropriate treatment, which is the administration of neuraminidase inhibitors, to be delivered in a timely fashion. The aim is to reduce morbidity and mortality. Other viruses including respiratory syncytial virus, adenovirus, parainfluenza virus and rhinovirus as well as bacterial infections such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumoniae*, can produce symptoms similar to influenza, highlighting the importance of a correct influenza diagnosis and appropriate treatment (Harper et al 2002).

Clinical need and burden of disease

The number of influenza cases in any given year may be difficult to ascertain accurately as many patients suspected as being infected do not seek medical assistance. Of those who do seek medical assistance, most do not undergo laboratory tests to confirm the presence or absence of influenza infection and are treated according to standard clinical practice for viral infections (Cox & Subbarao 1999).

The seasonal aspect of influenza infection is demonstrated by data collected by the Australian Communicable Diseases Network. The number of influenza notifications (laboratory confirmed) in Australia for the years 2004-2006 were 2136, 4565 and 3257, respectively. However, an influenza epidemic occurred in Australia during 2007. For the year 2007 to date (November 22nd) there were 10,334 laboratory confirmed influenza cases Australia-wide. The number of 2007 cases peaked in July and August with 2,488 (24%) and 5,268 (51%), respectively. Interestingly the majority of these cases occurred in Queensland (42.7%). A large number of infants were infected by the influenza virus in 2007, with 2370 (22.9%) aged 0-4 years and 980 (9.5%) aged 5-9 years. The remaining cases were more evenly spread across all age groups (Communicable Diseases Australia 2007). Hospital admission data are not available for the 2007 period, however during the 2003-04 period the public hospital separation rate for influenza was 13.8 per 100,000 population, with a corresponding mortality rate of 0.2 per 100,000 (AIHW 2006).

Influenza-like illness[3] is monitored in New Zealand via a national sentinel network of 90 general practices. During the 2006 winter season it was estimated that influenza-like illness affected 38,239 persons, or one per cent of the total population of New Zealand. However this figure was markedly reduced from the 47,108 affected by influenza-like illness in the 2004 season. The highest rate of influenza infection, 181 per 100,000, occurred in children less than one year, followed by 43.5 per 100,000 in children ages 1-4 years and 32 per 100,000 in adults aged over 65 years. In New Zealand during 2006, there were a total of 652 hospital admissions for influenza, compared to 528 admissions in 2005 and 430 in 2004. The highest number of hospital admissions, 233 (36%), occurred in July of that year. Of those cases sent for laboratory confirmation, 768 isolates were positive for influenza, with the majority (99.2%) confirmed as influenza A and the remaining being influenza B. Of those samples subtyped, 384/762 (50%) of the influenza A samples were the H3N2 strain and 56/762 (7.3%) were H1N1 (Institute of Environmental Science and Research Limited 2007; Lopez & Huang 2007).

Stage of development

Several of the rapid POCT influenza diagnostic kits are available and in use in Australia including the Binax FluNow, the Directigen and the QuickVue kits (personal correspondence). Currently, these kits are not required to be listed on the Australian Register of Therapeutic Goods. POCT for influenza is likely to

[3] Influenza-like illness: acute upper respiratory tract infection characterised by abrupt onset and two of the following: fever, chills, headache and myalgia. Lopez, L. & Huang, Q. S. (2007). *Influenza in New Zealand 2006*, New Zealand Ministry of Health, Wellington, http://www.surv.esr.cri.nz/PDF_surveillance/Virology/FluAnnRpt/InfluenzaAnn2006.pdf.

be used in emergency departments, paediatric wards and enclosed community settings such as nursing homes where an influenza outbreak may affect a large number of people living in close proximity to each other.

Diagnostic Alternatives

Existing comparators

A definitive diagnosis of infection with influenza may be achieved either by the isolation of the virus or by directly testing the clinical sample with immunofluorescence or nucleic acid testing. Although these last two techniques will give a more rapid result than virus isolation by cell culture, they do not provide an isolate for subsequent characterisation and subtyping. This is information which may prove important epidemiologically and for the development of potential influenza vaccines (Dwyer et al 2006; Gavin & Thomson 2003).

Virus culture and isolation

The gold standard for the diagnosis of influenza is viral isolation and culture. To ensure a positive culture in adults, samples (nasal wash or aspirate, or a throat or nose swab) should be collected within the first three days of infection, when viral shedding is at its maximum. Children continue to actively shed virus for longer periods of time after symptom onset when compared to adults, and therefore samples may be obtained after three days in children. Viable virus may be obtained for up to four days from samples which have been correctly stored and refrigerated. Suspected viral samples are inoculated into cell lines[4] or embryonated hen eggs. Results are not available for 2-3 days or longer (range 2-14 days). Influenza virus replication is then detected by haemagglutination, haemadsorption or by cytopathic effect (Cox & Subbarao 1999; Demmler 2002; Gavin & Thomson 2003; Harper et al 2002; Petric et al 2006). Cell cultures can then be further categorised using immunofluorescence microscopy which uses monoclonal antibodies directed against either influenza A or B (Gavin & Thomson 2003).

Although results from culture are not rapid enough to impact on the clinical management of patients, cell culture may identify index cases and is therefore important for infection control. In addition, negative results obtained via rapid POCT should also undergo testing by cell culture to rule out false negatives as these will impact on the treatment of individual patients and their contacts (Gavin & Thomson 2003).

Rapid shell-vial culture is a technique developed to speed up virus isolation. Clinical samples are centrifuged on to a monolayer of PMK or MDCK[4] cells on a coverslip placed in a shell-vial or multi-well plate. After incubation for 24-48 hours, the cells are stained with fluorescent monoclonal antibodies directed against influenza A or B. Although this technique is more rapid than conventional culture, producing results within 1-3 days, sensitivity is reduced (60-84%). The shorter time frame for the shell vial assay is still not fast

[4] Primary rhesus monkey (PMK) or Madin-Darby canine kidney (MDCK) cells

enough for the optimal treatment of patients with antiviral medication (Gavin & Thomson 2003).

Virus typing

Further viral characterisation to ascertain the haemagglutinin and neuraminidase subtypes can only be carried out by specialised reference pathology laboratories. Once virus has been isolated, immunofluorescence using type-specific monoclonal antibodies may be used. In addition, the haemagglutination inhibition assay, using specific antisera directed against influenza A H1N1 and H3N2 and influenza B, may be used by reference laboratories to subtype viral cultures.

Subtyping on either viral isolates or directly on clinical specimens may also be achieved with reverse transcription polymerase chain reaction (RT-PCR) using PCR primers specific to the various human and avian influenza strains. The majority of RT-PCR assays for influenza A and B use primers complementary to gene 7 of the influenza virus, which is relatively stable and encodes a conserved matrix protein. RT-PCR is more successful than cell culture in identifying influenza viral infection in patients who are immuno-compromised or have chronic lung disease. The time taken to perform a RT-PCR assay is approximately 1-2 days, however of all the diagnostic techniques used to diagnose influenza, RT-PCR is the most expensive (Dwyer et al 2006; Gavin & Thomson 2003; Petric et al 2006).

More recently, multiplexed RT-PCR assays have been developed that are capable of detecting multiple respiratory viruses including influenza A, influenza B, parainfluenza and respiratory syncytial virus. These assays combine multiple sets of primers and can detect all of the included viruses in a single reaction. Turn around time for multiplexed RT-PCR reactions range from 4-7 hours. Early studies report encouraging results with these assays when compared to other methods for the differentiation of influenza from other respiratory viruses, however none of the studies report on the ability of these assays to further subtype the influenza strains (Letant et al 2007; Marshall et al 2007; Nolte et al 2007).

Safety

None of the studies included in this assessment report any adverse events associated with the use of point-of-care-testing for influenza. In addition, none of the included studies report on adverse events associated with the administration of antiviral medication once a positive influenza diagnosis has been obtained.

In general, all of the POC tests reported high specificities and moderate-to-low sensitivities. A low sensitivity indicates that the diagnostic test in question has a *poor* ability to *correctly* identify those individuals who have the disease, and will therefore result in a *high* number of *false negative* results. Whereas a *high* specificity indicates the ability to *correctly* identify those individuals who *do not* have the disease, resulting in a *low* number of *false positive* results. The variable sensitivity values obtained with POC tests may be a reflection of the population being tested. Test sensitivity has been reported to be higher in children, which may be a result of increased viral shedding for longer periods of time. In addition, the method of sampling may affect the sensitivity of POC tests, with nasopharyngeal aspirates or washings demonstrated to be superior to nasal or throat swabs. Although test sensitivity is not affected by the prevalence of the disease in question (unlike the positive predictive value of the test), sensitivities of POCT have been reported to be higher during periods when the prevalence of influenza infection is elevated. This may be due to a difference in disease spectrum (high risk versus low risk populations receiving the test) or the method of testing used (Weitzel et al 2007).

In addition, most of the studies included in this assessment emphasised that individuals who tested *negative* with POCT kits are not ruled out from the possibility of influenza as a diagnosis, and all negative, but symptomatic patients should undergo conventional viral culture or other diagnostic tests to confirm the presence or absence of influenza infection.

Effectiveness

Diagnostic accuracy

Ten studies were included that assessed the diagnostic accuracy of POCT kits (Table 2). All of these studies were cross classification studies which compared the ability of POCT kits to diagnose influenza compared to either the gold standard viral culture, and indirect immunofluorescence or RT-PCR. There is considerable heterogeneity in the results of these studies reflecting differences in the POCT kit used, the age of the population tested and the method of sampling.

A good quality, large study (n=3561) was conducted by Cruz et al (2006) on a mixed population of adults and children (21% were aged ≤ 90 days) who presented to hospital with influenza-like symptoms (level II diagnostic evidence). The sensitivity and specificity of the BinaxNow Flu A+B kit for all patients was 62 and 96 per cent, respectively. The sensitivity increased

markedly when a sub group analysis was conducted on all infants aged less than 90 days (70%) compared to all patients aged >90 days (60%). It has been postulated that the increased sensitivity of POCT in young patients is due to an increase in influenza viral shedding in this patient group. Although it has been reported that POCT for influenza is more effective during times of high prevalence, Cruz et al reported that there was no difference in sensitivity during periods of high and low influenza prevalence (62% vs 59%, respectively).

Of the remaining nine studies (level III-2 diagnostic evidence), seven were conducted on mixed populations of adults and children and two were conducted on adults only. Four of the mixed population studies stratified their results by age. The study by Hurt et al (2007) reported on the ability of six different POCT kits to diagnose influenza, five of which were capable of diagnosing influenza A and B. Sensitivities for the entire patient population ranged from 10-73 per cent for influenza A and a sensitivity of 30 per cent was reported for all kits capable of diagnosing influenza B. When results were stratified by age, sensitivities for all kits bar one (Rock A) were high for infants aged 0-2 years (89%). When the number of older patients included in analysis increased, the sensitivity of the test decreased. Test sensitivity ranged between 85-91 per cent for patients aged 0-5 years, and 78-85 per cent for those aged 0-15 years (excluding the Rock A kit). This result was confirmed by the study by Rahman et al (2007b) when the Binax Now A+B POCT kit was used with test sensitivity of 61, 83 and 50 per cent reported for all patients, those aged 0.5-17 years, and those aged ≥ 18 years, respectively. However a study conducted by the same group (Rahman et al 2007a) with the Directigen A+B POCT kit reported contradictory results with test sensitivity of 27, 38 and 56 per cent for patients aged 6-23 months, 2-64 years and ≥65 years, respectively. This disparity cannot be explained by differences in sample collection as both studies were conducted using nasopharyngeal swabs.

The study by Agoritsas et al (2006) reported on the differences in sensitivity obtained by alternative sample collection methods, with nasopharyngeal swabs performing better (85%) than nasopharyngeal washes (69%) or nasal swabs (78%).

Results for individual POCT kits were variable. Of the POCT kits currently available in Australia, the Directigen A+B kit was described in 4 studies. Test sensitivity for detecting influenza A ranged from 41-69 per cent and 33-50 per cent for influenza B (reported in 3 studies). Two studies discussed the Binax Now Flu A (sensitivity 58% and 79%) and the Binax Flu B (sensitivity 33% and 50%), and three studies used the Binax Flu A+B kit (sensitivity 59%, 61% and 73%). Three studies reported on the QuickVue A+B POCT kit. Two studies reported sensitivity values (67% and 85%) for influenza A, one study reported 47 per cent sensitivity for influenza A or B and one study reported 30 per cent sensitivity for influenza B.

From these disparate results it is difficult to ascertain which kit is the most accurate (sensitive) for use in mixed age populations. POCT kits designed to diagnose both influenza A or B performed poorly in terms of sensitivity for the diagnosis of influenza B, however this may due to the low prevalence of this strain.

Test specificity for all POCT kits was high when compared to viral culture (94.5-100%) without stratification by age. Slight variations in test specificity were noted when POCT kits were compared to either immunofluorescence or RT-PCR.

A further 20 papers which described similar diagnostic accuracy studies were identified. Comparable sensitivity and specificity values to those described in Table 2 were reported for the various point-of-care influenza kits considered. Due to the time limitations involved in writing a Horizon Scanning report, these studies were not assessed but are listed in Appendix C.

The clinical usefulness of POCT for the detection of influenza appears greatest during the peak of an outbreak or the influenza season, when false positive results are less likely and the positive predictive value is likely to be high. When influenza activity is low in the community, false positive results are more likely, resulting in a low positive predictive value and a high negative predictive value. Therefore it is recommended that POCT for influenza should only be conducted during periods of high influenza activity in the community. In addition, a negative POCT result should not be used to rule out influenza and further laboratory tests should be conducted to confirm a negative result. However, the clinical usefulness of a positive POCT result is that it *rules in* influenza and appropriate treatment may be administered quickly (Nichols et al 2007; Petric et al 2006).

Table 2 Diagnostic accuracy of POCT kits

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Cruz et al 2006	II	Cross classification of samples on viral culture and POCT using Binax NOW Flu A+B.	3,561 consecutive patients (4,383 samples) presenting to ED with influenza-like symptoms. Median age 1.4 years (range 1 day to 41 years). 911/3561 (20.7%) aged ≤90 days	**%, [95% CI]** **Sens** **Spec** Overall 61.6[60, 63] 95.7[95, 96] ED 66.2[64, 68] 95.2[94, 96] Non-ED 49.6[41, 58] 96.5[96, 97] ↑ prev 61.7[60, 64] 90.4[90, 92] ↓ prev 59.1[57, 61] 99.4[99, 100] Age (days) ≤ 90 70.3[68, 73] 96.6[95, 98] > 90 60.1[59, 62] 95.6[95, 97] PPV = 61.8% NPV = 95.7%
Agoritsas et al 2006	III-2	Cross classification of samples on viral culture, RT-PCR and POCT using QuickVue Influenza A+B.	122 patients mean age 5 years (range 2 weeks to 18 years) presenting to ED with influenza-like symptoms.	54/122 (44.3%) patients influenza +ve by viral culture **QuickVue Influenza A+B** **Sens** **Spec** **PPV** **NPV** NS 78 97 96 82 NPS 85 98 98 87 NPW 69 98 98 78 Difference in sensitivity NS vs NPS NS NS vs NPW NS NPS vs NPW OR = 2.64 [1.35, 5.2] p= 0.005

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Booth et al 2006	III-2	Cross classification of samples on viral culture, IFA and POCT using ImmunoCard STAT! Flu A+B, Binax NowFlu A and Binax NowFlu B.	224 patients (mixed population of adults and children) presenting to hospital with influenza-like symptoms. Only samples positive by viral culture (VC) or IFA were tested by POCT.	35/224 (15.6%) +ve influenza A by viral culture and IFA. 15/224 (6.7%) +ve influenza B by viral culture and IFA. 23/224 (10.3%) +ve influenza A by IFA. 10/224 (4.5%) +ve influenza B by IFA. 29/224 (12.9%) +ve influenza A by viral culture. 14/224 (6.3%) +ve influenza B by viral culture. 87/224 (38.8%) specimens +ve influenza A by IFA and/or culture 39/224 (17.4%) specimens +ve influenza B by IFA and/or culture **Binax NowFlu** **Influenza A, %** **Sens Spec PPV NPV** IFA+VC 80 99 97 96 IFA 83 95 66 98 VC 79 98 85 97 **Influenza B, %** IFA+VC 47 100 88 96 IFA 60 99 75 98 VC 50 100 88 97 **ImmunoCard STAT** **Influenza A, %** **Sens Spec PPV NPV** IFA+VC 80 98 88 96 IFA 83 94 61 98 VC 81 97 81 97 **Influenza B, %** IFA+VC 47 100 100 96 IFA 60 100 86 98 VC 50 100 100 97
Drinka 2006	III-2	Cross classification of samples on viral culture and POCT using Directigen A+B.	327 patients mean age 74 ± 10 years from a veteran's nursing home presenting with influenza-like symptoms.	**Sens Spec PPV NPV** **%** 64.0 99.2 94.4 93.5
Hurt et al 2007	III-2	Cross classification of samples on viral culture, RT-PCR and POCT using 6 different kits: Now Influenza A+B, Directigen EZ Flu A+B, Seiken Quick Ex-Flu, Espline Influenza A+B, Rockeby Influenza A, QuickVue Influenza A+B.	177 patients aged 4 days to 64 years presenting to hospital with influenza-like symptoms. 78% patients ≤ 5-years.	**Influenza A, %** **Sens Spec PPV NPV** Now A+B 73 99 97 91 Dir A+B 69 100 100 90 Quick-Ex 71 100 100 90 Esp A+B 67 100 100 89 Rock A 10 100 100 74 QuickVue 67 100 100 89 **Influenza B, %** **Sens Spec PPV NPV** Now A+B 30 100 100 96

Study	Diagnostic level of evidence	Study design	Population	Outcomes
				Dir A+B 30 100 100 96 Quick-Ex 30 100 100 96 Esp A+B 30 100 100 96 QuickVue 30 100 100 96 **Influenza A, % patient age (years)** **Sensitivity** **0-2 0-5 0-15 All** Now A+B 89 91 85 73 Dir A+B 89 88 80 69 Quick-Ex 89 88 83 71 Esp A+B 85 85 78 67 Rock A 15 12 13 10 QuickVue 89 85 78 67
Rahman et al 2007a	III-2	Cross classification of samples on viral culture and POCT using Directigen A+B.	818 patients presenting to clinical practice. Patients were eligible for an influenza vaccine trial and included children aged 6-23 months, adults ≥ 65 years, and individuals aged between 2-64 years with specific high-risk medical conditions.	**Directigen A+B, %** **Sens Spec PPV NPV** Flu A or B 42 96 86 74 Flu A 41 98 88 78 Flu B 50 99 75 97 **By age group** 6-23 mon 27 97 75 78 2-64 yrs 38 95 86 66 ≥ 65 yrs 56 77 56 96 **DFA, %** **Sens Spec PPV NPV** Flu A or B 68 96 93 82 Flu A 68 96 93 82 Flu B 100 100 100 100 **By age group** 6-23 mon 57 96 80 88 2-64 yrs 67 100 100 82 ≥ 65 yrs 74 93 93 72
Rahman et al 2007b	III-2	Cross classification of samples on viral culture and POCT using Directigen A+B.	Patients presenting to clinical practice. 932 patients were eligible for an influenza vaccine trial and included children aged 6-23 months, adults ≥ 65 years, and individuals aged between 2-64 years with specific high-risk medical conditions.	**Binax NOW A+B, %** **Combined viral culture + RT-PCR** **Sens Spec PPV NPV** All patients 61 100 100 89 0.5-17 yrs 83 100 100 95 ≥18 yrs 50 100 100 85 **Viral culture alone** 65 100 100 90 **RT-PCR alone** 61 100 100 89 **DFA** **Sens Spec PPV NPV** All patients 81 100 100 92 0.5-17 yrs 69 100 100 84 ≥18 yrs 100 100 100 100 **Viral culture alone** 85 100 100 94 **RT-PCR alone** 81 100 100 92

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Smit et al 2007	III-2	Cross classification of samples on viral culture and POCT using 4 different kits: Now Influenza A+B, Now Flu A, Now Flu B, Directigen Flu A+B	521 samples collected from adults and children presenting to hospital with influenza-like symptoms.	**Influenza A, %** **Sens Spec PPV NPV** Now A+B 59 99 93 88 Now A 58 99 94 89 Dir A+B 53 99.7 97 83 ImmunoF 80 98 89 89 **Influenza B, %** **Sens Spec PPV NPV** Now A+B 33 100 100 99 Now B 33 100 100 99 Dir A+B 33 100 100 99 ImmunoF 50 100 100 100 **Patients ≥ 16 years (n=67)** **Influenza A, %** **Nasopharyngeal samples** **Sens Spec PPV NPV** Now A+B 71 98 91 92 Now A 70 98 93 91 Dir A+B 67 100 100 93 ImmunoF 97 97 86 99 **Throat swabs** **Sens Spec PPV NPV** Now A+B 25 100 100 79 Now A 25 100 100 79 Dir A+B 20 100 100 79 ImmunoF 58 97 88 87
Weitzel et al 2007	III-2	Cross classification of samples on viral culture and POCT using ImmunoSTAT! Flu A+B.	203 travellers presenting to hospital with influenza-like symptoms.	**%** **Sens Spec PPV NPV** Flu A 64 99 93 96 Flu B 67 100 100 99 Flu A+B 67 99 95 95
Yoo et al 2007	III-2	Cross classification of samples on viral culture and POCT using QuickVue and SD Bioline.	295 patients presenting to hospital with influenza-like symptoms. 174 children mean age 4.8 years (range 0.3-15 years). 121 adults mean age 48 years (range 18.5-81.9 years).	**%** **Sens Spec PPV NPV** SD Bioline Flu A 61.9 96.8 76.5 93.1 Flu B 54.5 100 94.6 94.9 QuickVue 46.7 94.5 74.5 83.9

POCT = point-of-care testing, ImmunoF = immunofluorescence, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, mon = months, yrs = years, DFA = direct fluorescent assay, NS = nasal swab, NPS = nasopharyngeal swab, NPW = nasopharyngeal wash, IFA = indirect immunofluorescence assay, VC = viral culture, CI = confidence interval, ↑ prev = high prevalence months, ↓ prev = low prevalence months

Effect on patient management

Eight studies were included for assessment which reported on the effect of POCT on patient management (Table 3). Five of these studies were conducted on children aged 0-60 months (level III-1, III-2 and IV intervention evidence), one study was conducted on adults with cardio-pulmonary disease (level III-2 intervention evidence) and two studies were conducted on a mixed adult/infant population (level II and III-2 intervention evidence). Although all of these studies reported on the immediate effect of POCT for influenza on patient management within the emergency department or hospital, none of the studies reported on whether POCT followed by appropriate treatment affected the duration or severity of the influenza infection.

A good quality randomised controlled trial was conducted by Bonner et al (2003) on a mixed population of adults and children presenting to the ED with influenza-like symptoms (level II intervention evidence). All patients underwent POCT but were randomly allocated to two groups according to whether or not the treating clinician was made aware of the result of the rapid test and treated the patient accordingly. When only influenza positive patients in both groups were considered there was a significant increase in the number of additional pathology requests made in the group where the clinician was unaware of the POCT result. These included urine analysis (p=0.011), urine culture (p=0.011), complete blood count (p<0.001), chest x-ray (p=0.001), and blood culture (p<0.001). Importantly there was also a significant increase in the administration of antibiotics to patients in the 'clinician unaware' group (p<0.001) as well as a significant increase in the administration of antivirals in the 'clinician aware' group (p=0.02), indicating that patients were given appropriate treatment according to their diagnosis. Patients in the 'clinician aware group' were discharged faster from the ED than patients in the unaware group (49 vs 25 mins, p<0.001). There were no differences reported in any of these parameters when the influenza negative patients from both groups were compared.

Two good quality pseudo-randomised trials were assessed for inclusion in this report (level III-1 intervention evidence). Similar results to those reported previously by Bonner et al were reported by Iyer et al (2006) and Poehling et al (2006). The study by Iyer et al, conducted in children aged 3-24 months, reported a significant increase in the number of some additional pathology tests being requested for influenza positive children in the standard testing group compared to children in the POCT group. There was no significant difference in the administration of antibiotics to either group, or in the number of patients admitted to hospital. A subgroup analysis was conducted, comparing influenza positive patients within the POCT and standard care group to the influenza negative patients within the same group. The adjusted odds ratio was only statistically significant for the number of urine analyses and urine cultures ordered. The study by Poehling et al (2006) was conducted in children less than five years. In contrast to the results of other studies, significantly fewer children had additional pathology tests ordered in the POCT group compared to the standard care group, regardless of influenza status (p=0.03). There was no difference in the number of children who were administered antibiotics or antivirals between the two groups. Compared to

previous studies, there was also no statistical difference between the number of pathology tests ordered when only influenza positive patients were considered from each group.

Abanses et al (2006) conducted a non-randomised experimental trial on children aged 3-36 months presenting to the emergency department (ED) with influenza-like symptoms (intervention level III-2 evidence). Patients were randomly allocated into two groups: those who received standard care and conventional testing at the discretion of the ED clinician (n=494) and those who received triage POCT for influenza and were treated according to the result (n=513). However, after randomisation over half of the POCT group were re-allocated to the conventional testing group. Differences in treatment were compared between the two groups. When the number of additional pathology tests ordered by clinicians was compared for *all patients* between the two groups, additional testing for respiratory syncytial virus and chest x-rays in the standard care group was significantly higher (RR[5] 2.5 95%CI [1.6, 3.9] and 1.3 95%CI [1.01, 1.07], respectively). There was no difference in the length of stay within the ED. However, when only *influenza positive* patients were considered there were significant increases in the number of pathology tests requested in the standard care patients including tests for respiratory syncytial virus (RR=9.2), complete blood count (RR=12), blood culture (RR=12), chest x-ray (RR= 2.2) and urine analysis (RR=5.7). These results should be interpreted with caution, however, as several of these point estimates had wide confidence intervals which may indicate great variation within the sample (see Table 2). In addition there was an increase in the amount of time spent in the ED by influenza positive patients in the standard care group compared to the POCT group (195 ± 57 mins, vs 156 ± 67 mins, p value not stated).

Three cohort studies (prospective and retrospective) compared the management of influenza positive to influenza negative patients (level III-2 intervention evidence). The majority of these studies reported a significant *decrease* in the number of pathology tests ordered, the length of ED stay and the number of hospital admissions for patients who were diagnosed as influenza positive by POCT, compared to influenza negative patients. The administration of antibiotics was also reduced and the administration of antivirals was increased in POCT influenza positive patients. Lastly, a retrospective case series (level IV intervention evidence) determined that influenza POCT significantly reduced additional pathology testing for symptomatic infants presenting to the ED when test results were available before discharge from the ED, compared to after discharge from the ED.

[5] RR = relative risk

Table 3 Effect of POCT on patient management

Study	Intervention level of evidence	Study design	Population	Outcomes
Bonner et al 2003	II	Randomised controlled trial	391 patients aged between 2 months and 21 years presenting to hospital with a temperature ≥ 100.4°F and influenza-like symptoms for ≤ 72 hours. Patients randomised to physician aware (PA, n=193) and physician unaware (PU, n=198).	202/391 (51.7%) influenza +ve by POCT PA 96/202 (47.5%) influenza +ve PA 97/189 (51.3%) influenza -ve PU 106/202 (52.5%) influenza +ve PU 92/189 (48.7%) influenza -ve **+ve influenza PA vs +ve influenza PU** **Additional pathology, % patients** PA % n=96 / PU% n=106 / p value UA 2.1 / 11.3 / 0.011 UC 3.1 / 13.2 / 0.011 CBC 0 / 12.3 / <0.001 CXR 7.3 / 24.5 / 0.001 BC 0 / 10.4 / <0.001 LP 0 / 1.9 / 0.499 AB 7.3 / 24.5 / <0.001 AV 18.8 / 6.6 / 0.02 Mean time in minutes from examination to discharge PA 25 mins PU 49 mins p <0.001 There were no significant differences reported for the same parameters when influenza –ve patients in the PA group were compared to the influenza –ve PU group and the numbers in each of these groups were similar to the numbers in the PU influenza +ve group.
Iyer et al 2006	III-I	Pseudo-randomised controlled trial with alternate day allocation of POCT and standard influenza testing (ST).	700 patients aged 3-24 months presenting to ED over a 2-year period with a rectal, oral or axillary temperature ≥39ºC.	105/345 (30.4%) influenza +ve by POCT 100/355 (28.2%) influenza +ve by ST **+ve influenza POCT vs +ve influenza ST** **Additional pathology, % patients** ST % n=100 / POCT% n=105 / p value UA 21 / 7.6 / 0.006 UC 20 / 7.6 / 0.01 CBC 25 / 13.3 / 0.033 CXR 26 / 19.1 / 0.23 BC 24 / 13.3 / 0.049 LP 3 / 0 / 0.07 AB 9.0 / 6.7 / 0.53 Discharged with AB 16.0 / 14.3 / 0.73 Hospital admission 5.0 / 6.7 / 0.611 Return to ED 15.0 / 19.1 / 0.44 **-ve influenza POCT vs –ve influenza ST** **Additional pathology, % patients** ST % n=255 / POCT% n=240 / p value UA 21.2 / 30.8 / 0.151 UC 21.2 / 26.7 / 0.22

Study	Intervention level of evidence	Study design	Population	Outcomes
				CBC 31 30.8 0.974 CXR 29 27.5 0.71 BC 29.4 28.8 0.871 LP 0.8 2.9 0.076 AB in ED 19.6 19.6 1.0 Discharged with AB 36.8 30.4 0.129 Hospital admission 12.6 13.8 0.69 Return to ED 16.1 17.1 0.76 Adjusted odds ratio of test positive to test negative within POCT and ST groups ST n=345 POCT n=355 p value UA 0.67 0.45 0.002 UC 0.67 0.46 0.005 CBC 0.69 0.56 0.058 BC 0.71 0.59 0.088 AB in ED 0.57 0.53 0.703 Discharged with AB 0.59 0.64 0.522 Hospital admission 0.53 0.56 0.716
Poehling et al 2006	III-1	Pseudo-randomised controlled trial with alternate block allocation of POCT and standard influenza testing (ST).	468 eligible children aged ≤ 5-years presenting with influenza like symptoms. 205 patients underwent POCT and 263 patients underwent standard testing.	43/205 (21.0%) influenza +ve by POCT 42/43 (97.7%) true +ve by culture 1/43 (2.3%) false +ve by culture 162/205 (79.0%) influenza –ve by POCT 9/162 (5.6%) false-ve by culture 153/162 (94.4%) true –ve by culture 37/263 (14.1%) influenza +ve by ST 226/263 (85.9%) influenza –ve by ST **Impact of influenza testing on ED n (%) All patients** ST n=170 POCT n=135 p value Any test 88 (52) 53 (39) 0.03 UA/UC 27 (16) 18 (13) 0.53 CXR 56 (33) 31 (23) 0.06 CBC/BC 31 (18) 14 (10) 0.05 AB 49 (29) 43 (32) 0.57 AV 0 (0) 1 (1) 0.44 **Impact of influenza testing on ED n (%) Influenza positive patients only** ST n=29 POCT n=28 p value Any test 12 (41) 9 (32) 0.47 UA/UC 3 (10) 3 (11) 1.0 CXR 7 (24) 3 (11) 0.18 CBC/BC 3 (10) 1 (4) 0.61 AB 5 (17) 4 (14) 1.0 AV 0 (0) 1 (4) 0.49

Study	Intervention level of evidence	Study design	Population	Outcomes
Abanses et al 2006	III-2	Non-randomised experimental trial	Children aged 3-36 months, randomised into triage group (POCT) (n=513) or standard testing (ST) (n=494). 268 of POCT group did not receive intervention, reassigned to ST group. 20 of ST group did not receive intervention, reassigned to POCT group. After reallocation: ST n=719 POCT n=288. All patients in POCT group underwent POCT with Directigen Flu A+B kit.	81/288 (28.1%) influenza +ve by POCT 252/719 (35.0%) ST group tested after being seen by clinician. Of these 75/252 (29.8%) were influenza +ve **Comparison of all patients** **Additional pathology, % patients** ST % n=719 / POCT% n=288 / RR [95%CI] UA 18.4 / 13.5 / 1.4 [0.98, 1.9] CBC 21.7 / 17.0 / 1.3 [0.95, 1.7] CXR 26.4 / 20.1 / 1.3 [1.01, 1.7] BC 21.1 / 16.7 / 1.2 [0.95, 1.7] RSV 18.1 / 7.3 / 2.5 [1.6, 3.9] LP 0.3 / 0 / NA AB 29.9 / 35.4 / 0.84 [0.7, 1.02] **Mean length of stay in ED, mins** ST = 185 ± 80 POCT = 185 ± 86 **Comparison of influenza positive only patients in ST and POCT groups** **Additional pathology, % patients** ST % n=75 / POCT% n=81 / RR [95%CI] UA 28 / 4.9 / 5.7 [2.0, 16] CBC 29.0 / 2.5 / 12.0 [2.9, 49] CXR 24.0 / 11.1 / 2.2 [1.04, 4.5] BC 30.7 / 2.5 / 12.0 [3.0, 51] RSV 45.3 / 4.9 / 9.2 [3.4, 25] **Mean length of stay in ED, mins** ST +ve influenza = 195 ± 57 POCT +ve influenza = 156 ± 67
Benito-Fernandez et al 2006	III-2	Prospective cohort	206 infants aged 0-36 months presenting to ED with fever in the absence of focal infection.	84/206 (40.7%) influenza +ve 82/84 (97.6%) influenza A +ve 2/84 (2.4%) influenza B +ve **Additional pathology, % patients** Influenza +ve / -ve / p value UA 80.9 / 100 / < 0.01 CBC 33.3 / 100 / < 0.01 CXR 14.2 / 32 / < 0.01 LP 2.3 / 21.3 / < 0.01 AB 0 / 38.5 / < 0.01 Hospital admission 2.3 / 16.4 / < 0.01 Return for care 11.5 / 11.9 / NS **Mean length of stay in ED, mins** Influenza +ve = 213.5 ± 289.2 Influenza –ve = 470.4 ± 399.7 p< 0.01

Study	Intervention level of evidence	Study design	Population	Outcomes
Falsey et al 2007	III-2	Retrospective cohort	166 hospitalised adult patients with acute cardio-pulmonary disease tested for influenza over a 4-year period. Mean age 74 ± 13 years in POCT –ve group and 75 ± 16 years in the POCT +ve group.	86/166 (51.8%) influenza +ve by POCT I80/166 (48.2%) influenza -ve by POCT, diagnosis delayed: 30/80 (37.5%) culture +ve 30/80 (37.5%) culture -ve & RT-PCR +ve 20/80 (25%) sero-positive POCT +ve % -ve% p value AB 86.0 98.8 0.002 AV 73.3 7.5 < 0.01 **Length of antibiotic use, days** POCT +ve = 6.2 ± 5.0 POCT –ve = 6.9 ± 3.2, NS Multivariate analysis of patients in whom antibiotics were withheld or discontinued due to positive POCT compared to those in whom antibiotics were continued OR = 6.9, 95%CI [2.0, 32.7], p =0.005 **Length of hospital stay, days** POCT +ve = 9.6 ± 10.0 POCT –ve = 7.9 ± 4.2, NS
Noyola et al 2000	III-2	Retrospective cohort	1530 patients presenting to ED with respiratory symptoms who underwent POCT for influenza in children's hospital in a 2-year period. Group 1: patients +ve by POCT. Median age 1 year, range 1 month to 19 years. Group2: patients –ve by POCT. Median age 1 year, range 1 month to 15 years. Group 3: patients -ve by POCT but +ve by conventional virology. Median age 7 months, range 1 month to 22 years.	110/1530 (7.1%) influenza A +ve +ve POCT 56/110 (50.9%) of these evaluated in ED -ve POCT 56 negative patients evaluated in ED -ve POCT but +ve virology 56/1530 (3.66%) **Hospital admission** +ve POCT = 21/56 (37.5%) versus -ve POCT = 41/56 (73.2%) p< 0.001 +ve virology = 27/56 (48.2%) NS **Duration of hospital admission** +ve POCT = 4.3 days (range 2-11) versus -ve POCT = 7.4 days (range 2-43) p=0.02 +ve virology = 7.5 days (range 1-75) NS **AB administered** +ve POCT = 24/56 (42.9%) versus -ve POCT = 36/56 (64.3%) p=0.04 +ve virology = 28/56 (50.0%) NS **AB admin to discharged patients** +ve POCT = 7/35 (20.0%) versus -ve POCT = 8/15 (53.0%) p=0.04 +ve virology = 8/29 (27.6%) NS **AB administered to admitted patients** +ve POCT = 17/21 (80.9%) versus -ve POCT = 28/41 (68.3%) NS +ve virology = 20/27 (74.1%) NS

Study	Intervention level of evidence	Study design	Population	Outcomes
				AV administered +ve POCT = 14/56 (25.0%) versus -ve POCT = 0/56 (0%) p < 0.001 +ve virology = 1/56 (1.8%) p <0.001 **AV admin to discharged patients** +ve POCT = 2/35 (5.7%) versus -ve POCT = 0/15 (0%) NS +ve virology = 1/29 (3.4%) NS **AV administered to admitted patients** +ve POCT = 12/21 (57.1%) versus -ve POCT = 0/41 (0%) p <0.001 +ve virology = 0/27 (0%) p <0.001
Sharma et al 2006	IV	Retrospective case series	183 infants aged 2-24 months presenting to ED with temperature >39ºC who underwent POCT for influenza.	72/183 (39.3%) influenza A +ve 47/72 (65%) had results available before discharge (early group) 25/72 (35%) had results available after discharge (late group) **Additional pathology, % patients** Influenza Early Late p value UA 2.1 24.0 0.006 CBC 17.0 44.0 0.02 CXR 46.8 68.0 NS AB 2.1 24.0 0.006 Hospital admission 17.0 24.0 NS **Mean length of stay in ED, mins** Early = 187 Late = 204, NS

ED = emergency department, NS = not significant, POCT = point-of-care testing, ST = standard testing, RT-PCR = reverse transcriptase polymerase chain reaction, OR = odds ratio, CI = confidence interval, UA = urine analysis, UC = urine culture, LP= lumbar puncture, CXR = chest radiograph, CBC = complete blood count, BC = blood culture, RSV = respiratory syncytial virus rapid test, UC = urine culture, AB = antibiotics, AV = antivirals, PA = physician aware, PU= physician unaware.

POCT for the detection of influenza A subtypes

Only one small-scale study (level III-2 diagnostic evidence) was identified which assessed the ability of rapid POCT to detect different subtypes of influenza A (Table 4) (Chan 2007). Six commercially available POCT kits were utilised to detect influenza A in clinical isolates of known subtype. Of main interest was the ability of the commercial kits to identify both avian and human isolates of the H5N1 subtype. The limit of detection for each kit was the mean of the lowest $TCID_{50}$[6] (log 10) detectable.

[6] $TCID_{50}$= Tissue culture infectious dose. The quantity of a cytopathogenic agent, such as a virus, that will produce a cytopathic effect in 50% of the cultures inoculated.

The Rapid Testa and Poctem kits were able to detect influenza A with a greater sensitivity for all of the clinical isolates compared to the other four kits, however neither of these kits is currently available in Australia. Of the three kits available in Australia, the BinaxNow kit appeared to have the greatest sensitivity at detecting all subtypes of influenza A. All POCT kits were able to detect the avian influenza H5N1 subtype with comparable sensitivity to that of the common human H3N2 and H1N1 influenza A subtypes. This result was not unexpected as the POCT kits target a *highly conserved* internal viral protein of the influenza virus. Importantly, however, the limits of detection for *all* subtypes of influenza A using the POCT kits were reported to be more than a thousand fold lower than that obtained with the gold standard of viral isolation. Although POCT has the ability to identify both human and avian subtypes of influenza A, the poor sensitivity of these kits emphasises that the gold standard for the diagnosis of H5N1 subtypes should remain viral culture or RT-PCR.

Table 4 POCT for the detection of influenza A subtypes

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Chan et al 2007	III-2	Cross classification of samples on viral culture and POCT.	Four human clinical isolates of influenza A: two H1N1, two H3N2. Two human isolates of avian influenza H5N1 and one avian H5N1 sample.	Log 10 $TCID_{50}$ limit of detection Rapid POCT kits

	$TCID_{50}$	QuickVue	BinaxNow	Directigen	Directigen EZ	Poctem	Rapid Testa
Avian H5N1	5.5	2.5	3.0	3.0	2.7	3.3	4.0
Human H5N1							
Vietnam	6.7	3.3	4.0	3.3	4.0	4.9	5.2
Thailand	6.2	3.4	4.0	3.9	3.4	4.2	4.7
Human H1N1							
Hong Kong 1	7.3	4.0	4.8	4.5	4.3	4.8	5.3
Hong Kong 2	6.0	2.6	3.7	2.6	2.7	3.7	4.5
Human H3N2							
Hong Kong 3	7.3	4.1	4.8	4.8	4.5	4.8	5.8
Hong Kong 4	6.5	3.5	4.5	3.7	4.0	4.5	5.0

$TCID_{50}$= Tissue culture infectious dose. The quantity of a cytopathogenic agent, such as a virus, that will produce a cytopathic effect in 50% of the cultures inoculated.

Cost Analysis

Hueston and Benich (2004) conducted a cost-benefit analysis to examine the most effective and efficient influenza treatment strategy for patients in the United States, at high-risk of influenza complications. The main outcome assessed was the cost of care for an episode of influenza and the summary benefit measure was an increase in productivity based on the ability of the patient to return to work. Modelling was conducted on a simulated cohort of 1,000 unvaccinated individuals at high risk of complications from influenza, including those >65 years and those >50 years with an underlying condition such as chronic obstructive pulmonary disease. Three alternatives were considered: no treatment, empiric treatment[7], or test and treat only those patients with a positive test result. Rapid testing costs were based on those of an average of five commercially available kits. Medications included the antivirals amantadine and rimantadine, and the neuraminidase inhibitors zanamivir and oseltamivir. The sensitivity of the rapid tests was reported to be 72.5 per cent (range 50-95%) and the specificity was 90 per cent (range 80-100%). The probability of drug side effects and complications from influenza were three per cent (range 0-6%) and 0.5 per cent (range 0.3-5%), respectively.

Empiric treatment with the older anti-retroviral drugs, amantadine or rimantadine, was favoured over other scenarios when the probability of influenza was five or 11 per cent or higher, respectively. Rapid testing followed by treatment with amantadine and rimantadine for test positive patients only was *not* cost-beneficial. When using the neuraminidase inhibitors zanamivir and oseltamivir, the preferred (least costly) scenario was no treatment when the probability of influenza was 19 and 22 per cent, respectively. It was cost-beneficial to test and treat with zanamivir when the probability of influenza was between 19-28 per cent, and with oseltamivir when the probability was between 22-36 per cent. Empiric treatment with zanamivir and oseltamivir was favoured when the probability of influenza was greater than 28 and 36 per cent, respectively. In the sensitivity analysis, when drug side effects were set at 10 per cent and the cost of each episode was US$300, empiric treatment still saved money compared to no treatment when the probability of influenza was greater than 50 per cent. The authors concluded that rapid testing has a limited role in the clinical management of influenza in high-risk patients (Hueston & Benich 2004).

A cost-effectiveness analysis of the rapid testing and treatment of patients with antiviral medication, compared to no treatment, was conducted in the United States by Rothberg et al (2003). Modelling was conducted on a hypothetical healthy, unvaccinated population less than 65 years and presenting with a cough and fever during the influenza season. Rapid testing costs were based on an average of four commercially available kits. As in the previous study,

[7] Empiric treatment in this case refers to treatment of all symptomatic patients with the drug regardless of verification of disease status.

three alternatives were considered: no treatment, treat all patients or test and treat only those patients with a positive test result. The sensitivity analysis considered treatment with all four drugs: the antivirals (amantadine and rimantadine), and the neuraminidase inhibitors (zanamivir and oseltamivir). However the base case analysis only considered treatment with amantadine and zanamivir, the cheaper of the two alternatives in each case.

In the base case analysis, not giving antiviral therapy is the most expensive and the least effective strategy, costing US$471 per patient. Time lost from productive work accounts for the majority of this cost. Treating all patients empirically with amantadine was the least expensive option and increased life expectancy by 0.0014 QALYs[8], saving US$108 per patient when compared to no antiviral therapy. Relative to treatment with amantadine, treating all patients with zanamivir saves an additional 0.0002 QALYs at a marginal cost of US$31, equating to US$133,000 per QALY saved. The two strategies of testing followed by treatment for positive patients, or no antiviral therapy were found to increase costs and to decrease health. The model was sensitive to the probability of influenza infection, the proportion of influenza B in the population, the efficacy of the drugs considered and the value of a work day. However, antiviral therapy was favoured when the probability of influenza was greater than 20 per cent. In addition, as the proportion of influenza B increased, treatment with zanamivir was favoured over treatment with amantadine. The authors concluded that the only two cost-effective strategies were *not* testing, or treating *all* patients with either amantadine or zanamivir, the choice of which was dependent on the prevalence of influenza B infection (Rothberg et al 2003).

A Canadian study reported on the incremental benefits and costs of the use of rapid testing for influenza A in nursing homes. Twelve nursing homes with a total population of 1,705 residents were included in the study. Matched pairing of facilities was undertaken and the experimental group included patients who would have access to the Directigen Flu-A assay, while the control group included patients who would have access to normal laboratory testing. Rapid testing was conducted off site but results were known within a two hour time frame. Of the total number of residents, 159 were evaluated for suspected influenza. Eighty of these patients were in the experimental group and of these 79 (98.8%) were tested for influenza A. Although 79 patients were suspected of having influenza in the control nursing homes, only 22/79 (27.8%) were tested. In the experimental group, 15/80 (18.8%) had confirmed influenza, with two of these patients being hospitalised. Similar figures were reported in the control group with 13/79 (16.5%) of patients having confirmed influenza. Although there was a lack of laboratory confirmation in this group, the attack rates in the experimental and control groups were similar. No patients in the control nursing homes were hospitalised. Interestingly more patients in the control nursing homes received amantadine prophylaxis than the experimental group (77% vs 61%). Costs per patient for influenza testing were lower in the experimental group (Can$24.18) compared to the control group (Can$48.87). If hospital costs are not factored into the equation, rapid influenza testing results in a cost (including drugs, testing and facilities) per patient is

[8] QALY = quality adjusted life year

Can$29.03 less than current practice. This would have the overall effect of saving the Canadian health system Can$11,612 per year in resource costs in nursing homes. In this study, those savings would be offset by higher hospitalisation rates, however the authors were reluctant to generalise about the rate of hospitalisation and speculated that the observed difference in hospitalisation rates may have been an anomaly (Church et al 2002).

It remains to be determined whether or not POCT has a role in the rationing of either anti-retrovirals or neuraminidase inhibitors at times of pandemic infection when these drugs may be in short supply.

The BD Directigen Flu A+B and Flu A POCT kits are available in Australia at the cost of $413 and $302, respectively. Both kits can perform 20 tests at a cost of $20.65 and $15.10 per test, respectively. The Binax Now Flu A+B kit is distributed in Australia and New Zealand by Inverness Medical Professional Diagnostics. The kit currently costs $280 for 22 tests, which equates to $12.72 per test.

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

Ethical Considerations

In general, all of the POCT kits reported high specificity and moderate-to-low sensitivity. Particular care is needed, therefore, in explaining the results of POCT for influenza to patients, who may find it difficult to grasp that a negative test result means that they may or may not have influenza.

POCT for influenza may be useful in settings where there is limited access to pathology testing facilities, for example in rural and remote settings. It may also be useful where early diagnosis would facilitate the earlier implementation of infection control systems, for example in a nursing home setting. In the event of an influenza pandemic, in which pathology laboratories may be unable to cope with the number of tests requested, the use of POCT in fever clinics and general practices could decrease the strain on pathology services.

It is well recognized that an influenza pandemic would create a number of ethical problems (Coleman & Reis 2007). One of the most important questions concerns who should have access to therapeutic and prophylactic measures when there are inadequate resources to treat or protect everyone. The use of POCT in a pandemic could lead to questions about what role, if any, a positive test result should play in decisions about access to antiviral therapy. For example, would it be reasonable to treat a patient with a positive POCT result ahead of a patient with a negative POCT result?

There is a range of ethical principles that can be applied to questions such as these. The principle of utility says that we should allocate resources to give the greatest health benefits. Without studies of the cost effectiveness of POCT during an epidemic, it is difficult to judge whether preferentially treating patients with a positive POCT result with antivirals would enhance utility.

A second approach to resource allocation applies the principle of equity, suggesting that we should allocate resources in ways that do not discriminate unfairly against particular individuals or groups in society. The question here is whether discriminating on the basis of a positive POCT result would provide legitimate grounds to treat people differently. It might be reasonable to use the results of POCT testing to decide who to treat with antivirals, if the sensitivity of POCT kits was high. In this situation, we would be preferentially treating those who have the greatest capacity to benefit, which is often accepted as a legitimate reason for differential access to resources. If, however, the sensitivity of POCT remains low to moderate, one could argue that having a positive test result is rather more a matter of chance. In this situation, using the POCT result to make decisions about who to treat would seem unfair, particularly when other equity considerations (such as treating the most vulnerable, those with the most threatening conditions or those with the greatest capacity to benefit) can be used instead.

Whatever approach is taken to allocation of antivirals in a pandemic, there is a clear consensus internationally that decisions about priority setting and access to treatment work best in a climate of public debate which is open, transparent and inclusive.

Training and Accreditation

Training

The POCT diagnostic kits for influenza are designed for clinicians or nursing staff to easily use in a near patient setting, however a degree of training and education is required initially to ensure the correct and effective method of sample collection. Training would ensure that the testing protocol was reliable between users (Turner et al 2006).

Clinical Guidelines

The WHO guidelines recommend that rapid POCT for influenza should only occur when the result will influence a clinical decision. Patients with lower respiratory tract illness, particularly children and adults with underlying medical conditions which may lead to the development of complicated influenza, should be considered for rapid POCT for influenza. A positive diagnosis within 48 hours of symptom onset may alter patient management allowing the use of anti-viral medication. Other benefits of rapid testing include the avoidance of inappropriate use of antibiotics and the ability to isolate patients, and in so doing prevent nosocomial outbreaks. Rapid POCT for influenza should only be conducted when the prevalence of influenza infection is high. Confirmatory diagnosis using alternative diagnostic techniques (viral culture, PCR or immunofluorescence) should always be conducted. The clinical accuracy of rapid POCT for the detection of avian influenza has not been established therefore it is recommended that these kits are not used for this purpose (WHO 2005).

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of

early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of point-of-care influenza diagnostic tests, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Availability and Level of Evidence

Nineteen peer reviewed studies were included for assessment in this Horizon Scanning Report. See Appendix B for profiles of these studies.

Ten studies reported on the diagnostic accuracy of various POCT kits. All of the studies were comparative, reporting cross classification of patients diagnosed with POCT and conventional viral culture. There was one good quality study (consecutive patients and a blinded comparison) conducted by Cruz et al 2006 (level II diagnostic evidence). The remaining nine studies were of poorer quality as they did not state whether patients were consecutive or if researchers were blinded to results of POCT diagnosis (level III-2 diagnostic evidence) (Agoritsas et al 2006; Booth et al 2006; Drinka et al 2002; Hurt et al 2007; Rahman et al 2007a; Rahman et al 2007b; Smit et al 2007; Weitzel et al 2007; Yoo et al 2007). A further 20 papers which described similar studies on diagnostic accuracy were identified. These studies all reported comparable sensitivity and specificity values to those described in Table 2 for the various point-of-care influenza kits considered. Due to the time limitations involved in writing a Horizon Scanning report these studies were not assessed and, thus, are listed in Appendix C.

One study was included which reported on the ability of POCT to identify different subtypes of influenza A (level III-2 diagnostic evidence) (Chan et al 2007)

Eight studies reported on the effect of point-of-care testing for influenza on patient management. Of these, there was one randomised controlled trial (level II intervention evidence) (Bonner et al 2003), two pseudo-randomised controlled trials (level III-1 intervention evidence) (Iyer et al 2006; Poehling et al 2006), one non-randomised experimental trial (level III-2 intervention evidence) (Abanses et al 2006), one prospective cohort study (level III-2 intervention evidence) (Benito-Fernandez et al 2006), two retrospective cohorts (level III-2 intervention level of evidence) (Falsey et al 2007; Noyola et al 2000) and one retrospective case series (Sharma et al 2006). Six of the eight studies reported on patient management in children less than five years of age, one study was conducted on a mixed population ranging from one month to 19 years and one study was conducted on adult population (mean age 74 ± 13 years).

Search Strategy used for the Report

The medical literature (Table 6) was searched utilising the search terms outlined in Table 5 to identify relevant studies and reviews, until November

2007. In addition, major international health assessment databases were searched.

Table 5 Search terms utilised

Search terms
MeSH
Point-of-Care Systems; Reagent Kits, Diagnostic; Influenza, Human/diagnosis; Influenza A virus AND diagnosis; Influenza B virus AND diagnosis
Text words
Influenza, flu, point of care, POCT
Limits
English, Human

Table 6 Literature sources used in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Pubmed	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au/default.aspx
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html

Sources of Further Information

The Infectious Diseases Unit situated in the Leicester Royal Infirmary (United Kingdom) is currently conducting a randomised controlled trial to evaluate the impact of diagnostic testing for influenza, respiratory syncytial virus and *streptococcous pneumoniae* infection on the management of acute admissions in the elderly. Three rapid technologies will be evaluated for their diagnostic accuracy, cost-effectiveness and their clinical value in the management of acute hospital admissions in the elderly due to lower respiratory tract infections. Recruitment for this study began in November 2005 and the study is expected to be published in late 2009 (NCCHTA 2007).

In addition, Doan et al (2007) are conducting a systematic review to determine if the use of a rapid viral detection test for children with an acute respiratory infection in emergency departments changes patient management and resource use within the emergency department. Patients in the intervention group will undergo rapid testing while still in the emergency department, whilst those in the control group will have no rapid viral test conducted. The primary outcome measure of the review is the rate of antibiotic prescription. Other outcome measures include admission to hospital, rate of ancillary pathology tests, length of hospital stay, rate of adverse events and rate of death (Doan et al 2007).

Conclusions

Influenza viruses belong to a family of large RNA viruses, consisting of three immunologically distinct groups: influenza A, B and C. Influenza is highly contagious, affecting people of all ages, and most seasonal epidemics are caused by influenza A with sporadic cases of influenza B. Most cases of influenza are self limiting. Infection rates are usually highest in children and complications of infection in this patient group may include febrile seizures. However serious complication rates such as the development of pneumonia are highest in the elderly usually due to the presence of underlying conditions such as chronic pulmonary and cardiovascular disease, immunosuppression or diabetes.

The influenza virus encodes 10 different influenza proteins, including the glycoproteins haemagglutinin (H) and neuraminidase (N) which are the major antigenic determinants. The influenza A virus is subtyped on the basis of serological and genetic differences in the haemagglutinin and neuraminidase surface glycoproteins. Current circulating *human* influenza A strains are H1N1 and H3N1, and the *avian* influenza A strain is H5N1. Since 2003, the *avian* influenza A (H5N1) has caused a pandemic in domestic poultry and the wild bird population. Although this strain is *not* readily transmitted to humans it has infected at least 300 laboratory confirmed human cases with a 60 per cent case-fatality rate.

Point-of-care testing (POCT) is defined as "clinical laboratory testing conducted close to the site of patient care by clinical personnel whose primary training is not in the clinical laboratory sciences." POCT refers to pathology tests that are performed outside of traditional pathology laboratories and is intended to be used by clinicians or nursing staff at the bedside to facilitate patient management and for treatment decisions to be made rapidly. POCT for influenza may be especially useful in rural and remote areas where pathology laboratories are not available.

There are several rapid influenza diagnostic tests which are capable of detecting the presence of either influenza A alone, influenza A and B separately or both influenza A and B but not differentiating between the two viruses. It is important to note that these kits are capable of testing whether or not a patient has been infected with influenza A, which would include the *human* influenza subtypes *and* the *avian* influenza A. POCT is only capable of identifying the *strain not the subtype* of influenza. Further pathology testing is required to ascertain whether or not the influenza subtype is *human or avian.* POCT is intended to rapidly diagnose the presence or absence of infection with the influenza virus in high-risk patients to enable appropriate treatment to be delivered in a timely fashion, with the aim of reducing patient morbidity and mortality. POC tests require either a nasal wash, nasal swab, throat swab or a nasopharyngeal swab. The tests vary in their method of detecting viral influenza with some tests utilising an immunoassay which detects viral nucleoprotein, and others an enzyme-based assay which detects neuraminidase. Most of the studies included in this assessment emphasised that individuals who tested *negative* with POCT kits may still have a diagnosis

of influenza, and all negative patients should undergo conventional viral culture or other diagnostic tests to confirm the presence or absence of influenza infection.

The gold standard for the diagnosis of influenza is viral isolation and culture, however results are not available for 2-3 days or longer (range 2-14 days). A definitive diagnosis of infection may also be achieved by immunofluorescence or nucleic acid testing. Although these last two techniques will give a more rapid result than virus isolation by cell culture, they do not provide an isolate for subsequent characterisation and subtyping, information which may prove important epidemiologically and for the development of potential influenza vaccines. Subtyping on either viral isolates or directly on clinical specimens may also be achieved using reverse transcription polymerase chain reaction (RT-PCR).

None of the studies included in this assessment reported any adverse events associated with the use of point-of-care-testing for influenza. In addition, none of the included studies reported on adverse events associated with the administration of antiviral medication once a positive influenza diagnosis had been obtained.

In general, all of the POCT kits reported high test specificity and moderate-to-low sensitivity. Results for individual POCT kits were highly variable. Of the POCT kits currently available in Australia, the Directigen A+B kit was provided in 4 studies. Sensitivities for detecting influenza A ranged from 41-69 per cent and 33-50 per cent for influenza B (reported in 3 studies). Two studies used the Binax Now Flu A (sensitivity 58% and 79%) and the Binax Flu B (sensitivity 33% and 50%) kits, and three studies used the Binax Flu A+B kit (sensitivities 59%, 61% and 73%). Three studies applied the QuickVue A+B POCT kit. Two studies reported sensitivity values (67% and 85%) for influenza A, one study reported 47 per cent sensitivity for influenza A or B and one study reported 30 per cent sensitivity for influenza B.

The variable sensitivity values obtained with POC tests may be a reflection of the population upon which the tests are used. Test sensitivity has been reported to be higher in children, which may be a result of increased viral shedding for longer periods of time. Test sensitivity has also been reported to be higher during periods when the prevalence of influenza infection is elevated.Another consideration is that the method of sampling may affect the sensitivity of POC tests. The study by Agoritsas et al (2006) reported on the differences in sensitivity obtained by alternative sample collection methods, with nasopharyngeal swabs performing better (85%) than nasopharyngeal washes (69%) or nasal swabs (78%). From these disparate results it is difficult to ascertain which kit is the most accurate for use in mixed age populations. POCT kits designed to diagnose both influenza A or B performed poorly in terms of sensitivity in the diagnosis of influenza B, however this may due to the low prevalence of influenza B.

One small-scale study was identified which assessed the ability of rapid POCT to detect different subtypes of influenza A (Chan 2007). All POCT kits were able to detect the avian influenza H5N1 subtype with comparable sensitivity to that of the common human H3N2 and H1N1 influenza A subtypes. This result

was not unexpected as the POCT kits target a *highly conserved* internal viral protein of the influenza virus. Importantly, however, the limits of detection for *all* subtypes of influenza A using the POCT kits were reported to be more than a thousand fold *lower* than that obtained with the gold standard of viral isolation. Although POCT has the ability to identify both human and avian subtypes of influenza A, the WHO recommends that the gold standard for the diagnosis of H5N1 subtypes should remain viral culture or RT-PCR.

Several high level studies reported on the effect of POCT on patient management. For patients who received POCT for influenza, all studies reported a significant decrease in the number of additional pathology tests (e.g. chest x-rays, complete blood culture) ordered when compared to patients who received standard care. When only influenza positive patients from the two groups were compared, the majority of studies reported a significant decrease in the amount of time spent in the emergency department, a decrease in the administration of antibiotics and an increase in the administration of antivirals in patients who received POCT. Although all of the included studies reported on the immediate effect of POCT for influenza on patient management within the emergency department or hospital, none of the studies reported on whether POCT, followed by appropriate treatment, affected the duration or severity of influenza infection.

Several economic studies on the use of POCT for influenza were assessed. A cost-benefit analysis conducted in the United States examined the most effective and efficient influenza treatment strategy for patients at high-risk of influenza complications (Hueston & Benich, 2004). Three alternatives were considered: no treatment, treat all patients (empiric treatment) or test and treat only those patients with a positive test result. Empiric treatment with the older anti-influenza drugs, amantadine or rimantadine, was favoured when the probability of influenza was five or 11 per cent or higher, respectively. Rapid testing followed by treatment with amantadine and rimantadine for test positive patients only was not cost-beneficial. When using the neuraminidase inhibitors zanamivir and oseltamivir, the preferred strategy was no treatment when the probability of influenza was 19 and 22 per cent, respectively. It was cost-beneficial to test and treat with zanamivir when the probability of influenza was between 19 and 28 per cent, and with oseltamivir when the probability was between 22 and 36 per cent. Empiric treatment with zanamivir and oseltamivir was favoured when the probability of influenza was greater than 28 and 36 per cent, respectively. The authors concluded that rapid testing has a limited role in the clinical management of influenza in high-risk patients (Hueston & Benich 2004). A similar cost-effectiveness analysis reported that *not* giving antiviral therapy is the most expensive and the least effective strategy, costing US$471 per patient. Time lost from productive work accounts for the majority of this cost. The two strategies of testing followed by treatment for positive patients, or no antiviral therapy were found to increase costs and to decrease health. Empiric antiviral therapy was favoured when the probability of influenza was greater than 20 per cent. In addition, as the proportion of influenza B increased, treatment with zanamivir was favoured over treatment with amantadine. The authors concluded that the only two cost-effective strategies were *not* testing, or treating *all* patients with either amantadine or zanamivir, the choice of which was dependent on the

prevalence of influenza B infection (Rothberg et al 2003). It remains to be determined whether or not POCT has a role in the rationing of either anti-retrovirals or neuraminidase inhibitors at times of pandemic infection when these drugs may be in short supply.

In summary, point-of-care diagnostic tests are highly specific but have medium-to-low sensitivity. The sensitivity of these tests varies according to patient group and method of sampling and the positive predictive value varies according to the prevalence of influenza at time of testing. Point-of-care testing for influenza may be of greatest use when used in times of high influenza prevalence in children presenting with influenza-like symptoms. Improved test sensitivity may be obtained by ensuring a nasopharyngeal swab is used to collect viral samples. Several studies reported that the number of additional pathology tests in patients testing positive for influenza was decreased compared to those who underwent standard testing. However, economic analyses in the Unites States (that may or may not be applicable to the Australian health care system) indicate that it is cost-effective to *not* test patients with POCT but simply treat *all* patients with suspected influenza with either antivirals or neuraminidase inhibitors.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis [**]	Prognosis	Aetiology [†††]	Screening
I [*]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among consecutive patients with a defined clinical presentation [††]	A prospective cohort study [***]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among non-consecutive patients with a defined clinical presentation[††]	All or none [§§§]	All or none [§§§]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study [‡] Interrupted time series without a parallel control group	Diagnostic case-control study [††]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [‡‡]	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

‡ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: (Bandolier editorial 1999; Lijmer et al 1999; NHMRC 1999; Phillips et al 2001)

Appendix B: Profiles of studies

Study	Location	Study design	Study population	Study details	Outcomes assessed
Abanses, J.C. Dowd, M.D. Simon, S.D. Sharma, V. (2006)	Kansas City, USA	Intervention evidence level III-2	1007 patients aged 3-36 months presenting to ED with rectal temperature >39ºC.	Children aged 3-36 months randomised into triage group (TT) (n=513) or standard testing (ST) (n=494). 268 of TT group did not receive intervention, reassigned to ST group. 20 of ST group did not receive intervention, reassigned to TT group. After reallocation: ST n=719 TT n=288. All patients in TT group underwent POCT with Directigen Flu A+B kit.	Patient management: influenza infection, number of additional pathology tests, length of ED stay.
Agoritsas, K. Mack, K. Bonsu, B.K. Goodman, D. Salamon, D. Marcon, M.J. (2006)	Ohio, USA	Diagnostic evidence level III-2	122 patients mean age 5 years (range 2 weeks to 18 years) presenting to ED with influenza-like symptoms.	All samples tested with conventional viral culture, RT-PCR and POCT: QuickVue Influenza A+B. All patients underwent 3 types of sample collection: nasal swab, nasopharyngeal swab and nasopharyngeal wash.	Sensitivity, specificity, PPV and NPV.
Benito-Fernández, J. Vázquez-Ronco, M.A. Morteruel-Aizkuren, E. Mintegui-Raso, S. Sánchez-Etxaniz, J. Fernández-Landaluce, A. (2006)	Bizkaia, Spain	Intervention evidence level III-2	206 infants aged 0-36 months presenting to ED with fever in the absence of focal infection.	All infants underwent POCT with Directigen Flu A+B kit. Treatment based on outcome of test result.	Patient management: influenza infection, number of additional pathology tests, length of ED stay, hospital admission, antibiotic usage, return for medical care.

Study	Location	Study design	Study population	Study details	Outcomes assessed
Bonner, A.B. Monroe, K.W. Talley, L.I. Klasner, A. E. Kimberlin, D.W. (2003)	Alabama, USA	Intervention evidence level II	391 patients aged between 2 months and 21 years presenting to hospital with a temperature ≥ 100.4°F and influenza-like symptoms for ≤ 72 hours.	Patients randomised into 2 groups: Group 1 where the POCT result was known to treating physician. Group 2 where the POCT result was not known to treating physician. POCT kit used Biostar FluOIA.	Patient management: influenza infection, number of additional pathology tests, length of ED stay, antibiotic and antiviral use.
Booth, S. Baleriola, C. Rawlinson, W.D. (2006)	Sydney, Australia	Diagnostic evidence level III-2	224 patients (mixed population of adults and children) presenting to hospital with influenza-like symptoms.	All samples tested with conventional viral culture and indirect immuno-fluorescence. Only samples positive by viral culture or IFA were tested by POCT kit ImmunoCard STA! Flu A+B, Binax NowFlu A and Binax NowFlu B.	Sensitivity, specificity, PPV and NPV.
Chan, K.H. Lam, S.Y. Puthavathana, P. Nguyen, T.D. Long, H.T. Pang, C.M. Chan, K.M. Cheung, C.Y. Seto, W.H. Peiris, J.S.M. (2007)	Hong Kong	Diagnostic evidence level III-2	Four human clinical isolates influenza A: two H1N1, two H3N2. Two human isolates of avian influenza H5N1 and one avian H5N1 sample.	All samples tested with conventional viral culture and six POCT kits: QuickVue Influenza A+B, BinaxNow Influenza A+B, Directigen Flu A+B, Directigen EZ Flu A+B, Poctem Inflenza A/B and Rapid Testa Flu II.	Log 10 $TCID_{50}$ limit of detection.

Study	Location	Study design	Study population	Study details	Outcomes assessed
Cruz, A.T. Cazacu, A.C. McBride, L.J. Greer, J.M. Demmler, G.J. (2006)	Texas, USA	Diagnostic evidence level II	3,561 consecutive patients (4,383 samples) presenting to Ed with influenza-like symptoms. Median age 1.4 years (range 1 day to 41 years). 911/3561 (20.7%) aged ≤90 days	All samples tested with conventional viral culture and BinaxNow Influenza A+B. Technicians were blinded to the results of POCT.	Sensitivity, specificity, PPV and NPV.
Drinka, P.J. (2006)	Wisconsin, USA	Diagnostic evidence level III-2	327 patients mean age 74 ± 10 years from a veteran's nursing home presenting with influenza-like symptoms.	All samples tested with conventional viral culture and the Directigen AB POCT kit.	Sensitivity, specificity, PPV and NPV.
Falsey, A.R. Murata, Y. Walsh, E.E. (2007)	New York, USA	Intervention evidence level III-2	166 hospitalised adult patients with acute cardio-pulmonary disease tested for influenza over a 4-year period. Mean age 74 ± 13 years in POCT –ve group and 75 ± 16 years in the POCT +ve group.	All patients underwent POCT for influenza with Directigen Flu kit. Viral culture performed on all samples.	Patient management: influenza infection, length of antibiotic use, antiviral use, length of hospital stay, complications.
Hurt, A.C. Alexander, R. Hibbert, J. Deed, N. Barr, I.G. (2007)	Victoria, Australia	Diagnostic evidence level III-2	177 patients aged 4 days to 64 years presenting to hospital with influenza-like symptoms. 78% patients ≤ 5-years.	All patients underwent POCT testing, rapid viral culture and RT-PCR. Kits assessed: Now Influenza A+B, Directigen EZ Flu A+B, Seiken Quick Ex-Flu, Espline Influenza A+B, Rockeby Influenza A, QuickVue Influenza A+B.	Sensitivity, specificity, PPV and NPV.

Study	Location	Study design	Study population	Study details	Outcomes assessed
Iyer, S.B. Gerber, M.A. Pomerantz, W.J. Mortensen, J.E. Ruddy, R.M. (2006)	Ohio, USA	Intervention evidence level III-1	700 patients aged 3-24 months presenting to ED over a 2-year period with a rectal, oral or axillary temperature ≥39ºC.	Patients were randomised according to the day they presented to ED. POCT and standard influenza testing (ST) conducted on alternative days.	Patient management: influenza infection, number of additional pathology tests, hospital admission, antibiotic usage, return for medical care.
Noyola, D.E. Demmler, G.J. (2000)	Texas, USA	Intervention evidence level III-2	1530 patients who underwent POCT for influenza in children's hospital in a 2-year period. Group 1: patients +ve by POCT. Median age 1 year, range 1 month to 19 years. Group2: patients –ve by POCT. Median age 1 year, range 1 month to 15 years. Group 3: patients -ve by POCT but +ve by conventional virology. Median age 7 months, range 1 month to 22 years.	All infants underwent POCT with Directigen Flu A kit. Treatment based on outcome of test result.	Patient management: influenza infection, duration of hospital stay if admitted, antibiotic and antiviral usage.
Poehling, K.A. Zhu, Y. Tang, Y-W. Edwards, K. (2007)	Tennessee, USA	Intervention evidence level III-1	468 eligible children aged ≤ 5-years presenting with influenza like symptoms. 205 patients underwent POCT and 263 patients underwent standard testing.	Patients were randomised according to the day they presented to ED or acute care clinic. POCT and standard influenza testing (ST) conducted on alternating blocks of 4 and 6 days. All patients underwent viral culture and PCR for influenza.	Patient management: influenza infection, number of additional pathology tests, antibiotic and antiviral usage.

Study	Location	Study design	Study population	Study details	Outcomes assessed
Rahman, M. Kieke, B.A. Vandermause, M.F. Mitchell, P.D. Greenlee, R.T. Belongia, E.A. (2007)	Wisconsin, USA	Diagnostic evidence level III-2	Patients presenting to clinical practice. 932 patients were eligible for an influenza vaccine trial and included children aged 6-23 months, adults ≥ 65 years, and individuals aged between 2-64 years with specific high-risk medical conditions.	All patients underwent viral culture and RT-PCR. POCT performed in 73 patients. POCT kit used: Directigen A+B. Direct fluorescent assay performed in 70 patients.	Sensitivity, specificity, PPV and NPV.
Rahman, M. Vandermause, M.F. Kieke, B.A. Belongia, E.A. (2007)	Wisconsin, USA	Diagnostic evidence level III-2	818 patients presenting to clinical practice. Patients were eligible for an influenza vaccine trial and included children aged 6-59 months, adults ≥ 50 years, and individuals aged between 5-49 years with specific high-risk medical conditions.	All patients underwent POCT, direct fluorescent assay and viral culture. POCT kit used: Binax NOW influenza A+B.	Sensitivity, specificity, PPV and NPV.
Sharma, V. Dowd, D. Slaughter, A.J. Simon, S.D. (2002)	Kansas, USA	Intervention evidence level IV	183 infants aged 2-24 months presenting to ED with temperature >39ºC who underwent POCT for influenza	All patients underwent POCT with Directigen Flu A kit. Treatment based on outcome of test result.	Patient management: influenza infection, number of additional pathology tests, hospital admission and length of ED stay.

Study	Location	Study design	Study population	Study details	Outcomes assessed
Smit, M. Beynon, K.A. Murdoch, D.R. Jennings, L.C. (2007)	Christchurch, New Zealand	Diagnostic evidence level III-2	521 samples collected from adults and children presenting to hospital with influenza-like symptoms.	All patients underwent POCT and viral culture. Some samples were considered suitable for immuno-fluorescence (n=389). Now Influenza kits performed on all 521 samples, Directigen Flu A+B used on 354 samples.	Sensitivity, specificity, PPV and NPV.
Weitzel, T. Schnabel, E. Dieckmann, S. Börner, U. Schweiger, B. (2007)	Berlin, Germany	Diagnostic evidence level III-2	203 travellers presenting to hospital with influenza-like symptoms.	All patients underwent POCT with Immunocard STAT! Flu A+B, viral culture and PCR.	Sensitivity, specificity, PPV and NPV.
Yoo, Y. Sohn, J.W. Park, D.W. Kim, J.Y. Shin, H.K. Lee, Y. Choung, J.T. Lee, C.K. Kim, M.J. (2007)	Seoul, Korea	Diagnostic evidence level III-2	295 patients presenting to hopsital with influenza-like symptoms. 174 children mean age 4.8 years (range 0.3-15 years). 121 adults mean age 48 years (range 18.5-81.9 years).	All patients underwent POCT with QuickVue and SD Bioline and viral culture.	Sensitivity, specificity, PPV and NPV.

ED = emergency department, $TCID_{50}$ = tissue culture infectious dose (50%), PCR = polymerase chain reaction, PPV= positive predictive value, NPV = negative predictive value.

Appendix C: Diagnostic Accuracy Studies Not Included in Assessment

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.

Alexander, R., Hurt, A. C. et al (2005). 'A comparison of a rapid test for influenza with laboratory-based diagnosis in a paediatric population', Commun Dis Intell, 29 (3), 272-276.

Bellei, N., Benfica, D. et al (2003). 'Evaluation of a rapid test (QuickVue) compared with the shell vial assay for detection of influenza virus clearance after antiviral treatment', J Virol Methods, 109 (1), 85-88.

Cazacu, A. C., Demmler, G. J. et al (2004). 'Comparison of a new lateral-flow chromatographic membrane immunoassay to viral culture for rapid detection and differentiation of influenza A and B viruses in respiratory specimens', J Clin Microbiol, 42 (8), 3661-3664.

Effler, P. V., Ieong, M. C. et al (2002). 'Enhancing public health surveillance for influenza virus by incorporating newly available rapid diagnostic tests', Emerg Infect Dis, 8 (1), 23-28.

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.

Grondahl, B., Puppe, W. et al (2005). 'Comparison of the BD Directigen Flu A+B Kit and the Abbott TestPack RSV with a multiplex RT-PCR ELISA for rapid detection of influenza viruses and respiratory syncytial virus', Clin Microbiol Infect, 11 (10), 848-850.

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

Harnden, A., Brueggemann, A. et al (2003). 'Near patient testing for influenza in children in primary care: comparison with laboratory test', BMJ: British Medical Journal, 326 (7387), 480.

Hindiyeh, M., Goulding, C. et al (2000). 'Evaluation of BioStar FLU OIA assay for rapid detection of influenza A and B viruses in respiratory specimens', J Clin Virol, 17 (2), 119-126.

Landry, M. L. & Ferguson, D. (2003). 'Suboptimal detection of influenza virus in adults by the Directigen Flu A+B enzyme immunoassay and correlation of results with the number of antigen-positive cells detected by cytospin immunofluorescence', J Clin Microbiol, 41 (7), 3407-3409.

Noyola, D. E., Paredes, A. J. et al (2000). 'Evaluation of a neuraminidase detection assay for the rapid detection of influenza and B virus in children', Pediatric and Developmental Pathology, 3 (2), 162-167.

Pregliasco, F., Puzelli, S. et al (2004). 'Influenza virological surveillance in children: the use of the QuickVue rapid diagnostic test', J Med Virol, 73 (2), 269-273.

Quach, C., Newby, D. et al (2002). 'QuickVue influenza test for rapid detection of influenza A and B viruses in a pediatric population', Clin Diagn Lab Immunol, 9 (4), 925-926.

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', Journal Of Medical Virology, 74 (1), 127-131.

Rodriguez, W. J., Schwartz, R. H. & Thorne, M. M. (2002). 'Evaluation of diagnostic tests for influenza in a pediatric practice', Pediatr Infect Dis J, 21 (3), 193-196.

Ruest, A., Michaud, S. et al (2003). '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, 41 (8), 3487-3493.

Shimasaki, C. D., Achyuthan, K. E. et al (2001). 'Rapid diagnostics: the detection of neuraminidase activity as a technology for high-specificity targets', Philosophical Transactions Of The Royal Society Of London Series B-Biological Sciences, 356 (1416), 1925-1931.

Stein, J., Louie, J. et al (2005). 'Performance characteristics of clinical diagnosis, a clinical decision rule, and a rapid influenza test in the detection of influenza infection in a community sample of adults', Annals of Emergency Medicine, 46 (5), 412.

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.

Appendix D: Glossary

POCT	point-of-care testing
Epidemic	An epidemic is a classification of a disease that appears as new cases in a given human population, during a given period, at a rate that substantially exceeds what is "expected," based on recent experience.
Pandemic	A pandemic is an epidemic that spreads through human populations across a large region (eg a continent), or even worldwide.
Negative sense RNA	Negative-sense viral RNA must be converted to positive-sense RNA by an RNA polymerase prior to translation. This RNA cannot be translated into protein directly. Instead, it must first be transcribed into a positive-sense RNA which acts as an mRNA. Influenza has a negative-sense genome and therefore must carry an RNA polymerase within the virion.
Neuraminidase	Is an enzyme involved in the release of the progeny influenza virus from infected cells, by cleaving sugars that bind the mature viral particles.
Haemagglutinin	Is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell. The haemagglutinin and neuraminidase proteins are targets for antiviral drugs and are recognised by antibodies.
Sensitivity	The ability to correctly identify those who have the disease.
Specificity	The ability to identify those who do not have the disease.
Positive predictive value	The proportion of people with a *positive* test results who have been correctly identified as *having* the disease.
Negative predictive value	The proportion of people with a *negative* test who have been correctly identified as *not* having the disease.
Haemagglutination (inhibition) assay	The serial dilution of a virus suspension into an assay tray containing a standard amount of blood cells. A virus may attach to the surface of red blood cells (agglutinate) preventing them from settling out of solution. An estimation of the number of virus particles can then be made. This assay may be modified to include the addition of an antiserum. By using a standard amount of virus, a standard amount of blood cells and serially diluting the antiserum, one can identify the minimum inhibitory concentration of the

	antiserum ie the greatest dilution which inhibits haemagglutination.
Antisera	Blood serum containing antibodies.
$TCID_{50}$	Tissue culture infectious dose. the quantity of a cytopathogenic agent, such as a virus, that will produce a cytopathic effect in 50% of the cultures inoculated.

Definitions sourced from Wikipedia.[9]

[9] http://en.wikipedia.org/wiki/Main_Page

Appendix E: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.mihsr.monash.org/cce/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?accueil

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.cadth.ca/index.php/en/

- Canadian Health Services Research Foundation (CHERA/ACRES) – Cabot database http://www.chsrf.ca/home_e.php

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI)
  http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES)
  http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM) http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp

- Catalan Agency for Health Technology Assessment (CAHTA) http://www.gencat.net/salut/depsan/units/aatrm/html/en/Du8/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland http://www.nhshealthquality.org/nhsqis/qis_display_home.jsp?pContentID=43&p_applic=CCC&pElementID=140&pMenuID=140&p_service=Content.show&

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC) http://www.bcbs.com/tec/index.html

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