Influenza (*Influenza virus*)

Laboratory case definition

The Public Health Laboratory Network (PHLN) has developed standard case definitions for the diagnosis of key diseases in Australia. This document contains the laboratory case definition for *influenza virus*.

Authorisation: PHLN
Consensus date: 26 November 2020

---

1 PHLN Summary laboratory definition

1.1 Condition:

Influenza

1.1.1 Definitive Criteria

- Detection of *influenza virus* by nucleic acid testing (NAT) from appropriate respiratory tract specimens; or
- Isolation of *influenza virus* by culture from appropriate respiratory tract specimens; or
- Detection of *influenza* antigen using detection by a properly validated *influenza virus* antigen assay from appropriate respiratory tract specimens; or
- Clear seroconversion or a fourfold or greater rise in antibody titre to *influenza virus*

1.1.2 Suggestive Criteria

- a single high *influenza virus*-specific antibody titre
- detection of *influenza virus*-specific IgM by immunofluorescence

1.1.3 Special Considerations / Guide for Use

- Results of 'Point of care' (POC) tests for *influenza* antigens based on immunoassay technology should be treated with caution due to their relatively low sensitivity. POC testing (also referred to as near patient testing (NPT)) usually refers to testing where healthcare is provided close to or near the patient, however, in practice these type of tests can be performed in a variety of locations including; self-testing at home, pharmacies, nursing homes, ED/ICU and in Australia also commonly in laboratories. Further laboratory-based testing

should be sought if *influenza* is suspected in the presence of a negative POC test result, especially if the test used was based on an immunoassay format.

- All samples to be tested for *influenza* should be typed (*influenza* A or B or both A and B) and where possible subtyped for the two *influenza* A epidemic subtypes (A(H3) and A(H1pdm09)). Most commercial tests detect *influenza* A or B but do not subtype the influenza A positive samples, If *influenza* A subtyping is performed and no result is obtained (**and** there is a sufficient viral load in the sample – such as a Ct<30 with a pan-*influenza* A Real Time PCR assay) then this sample should be re-tested (for A(H3) and A(H1)pdm09 subtypes). If it fails to subtype then it should also be and tested for other *influenza* A subtypes (if this testing is available) or referred to the WHO Collaborating Centre for Reference and Research (WHO CC) in Melbourne as soon as possible, as this may represent a human infection with a novel *influenza virus*.

1.1.4 Links to related documents and websites

Pandemic influenza

- Australian Health Management Plan for Pandemic *Influenza* (AHMPPI)

Seasonal influenza

- NCIRS Fact Sheet on *influenza*
- Australian Government Department of Health *influenza* page
- WHO Collaborating Centre for Reference and Research on *Influenza*, VIDRL, Melbourne

Avian influenza

- Avian *Influenza* landing page

2 Introduction

Influenza in humans is an acute, usually self-limited, febrile respiratory illness caused by infection with *influenza virus* type A or B, which in temperate climates occurs in outbreaks of varying severity almost every winter. Influenza infection may occur year round in tropical climates, although they typically have one or two main peaks often during the wet season. In pandemics, outbreaks may be seen outside the usual influenza season.

Influenza viruses are enveloped viruses of the family Orthomyxoviridae and contain segmented negative sense single-stranded RNA genomes. The i*nfluenza viruses* A, B, C and D can be distinguished on the basis of antigenic differences between their nucleocapsid and matrix proteins; *influenza* A viruses can be further subtyped based on the genetic sequence of the haemagglutinin (HA) and their neurarminidase (NA) glycoproteins which can also be differentiated antigenically with the appropriate antisera. They replicate in the columnar epithelial cells of the respiratory tract, and the primary mode of transmission is via respiratory droplets.

Influenza C causes very mild illness occurring mainly in children and has little clinical or public health implications compared to *influenza* A & B. *Influenza* D is a new classification that was included with *influenza* C and to date has only been detected in cattle, *Influenza* C and D do not undergo antigenic

shift or drift and they are NOT vaccine preventable. Standard laboratory tests do not detect *influenza* C or D. As only a few reference laboratories carry out *influenza* C testing (and very few *influenza* D), these *influenza* types are not covered further in this document.

In Australia, seasonal influenza (as well as all other *influenza viruses*) is a notifiable disease only with laboratory confirmation. *Pandemic influenza* is notifiable in Australia and New Zealand. Human cases of highly pathogenic *avian influenza* (HPAI) are subject to quarantine regulations Australia-wide. *Influenza* laboratory data are currently gathered from Lab-VISE, a number of GP surveillance systems, some jurisdictional Departments of Health and laboratory reporting to the WHO Collaborating Centre (WHOCC) for Reference and Research on Influenza in Melbourne. Surveillance programs for influenza are based upon laboratory, clinical or a combination of laboratory and clinical reporting schemes. Clinically based surveillance programs e.g. Australian Sentinel Practice Research Network (ASPREN), WHO, the NZ national surveillance program use various definitions of influenza-like illness (ILI). An example of a case definition of ILI would be the sudden onset (<24 hours) of three of fever, rigors or chills, myalgia, cough, and prostration and weakness[1,2].

Many large laboratories that perform *influenza virus* testing, send a selection of *influenza* positive clinical samples and isolates to the WHOCC in Melbourne either directly, or via one of the three Australian WHO National Influenza Centres (NIC). Only the NIC laboratories and a few other laboratories still isolate *influenza viruses* in cell lines. Clinical samples and isolates are used to help monitor the circulating viruses and also to select strains to be incorporated into the following season's *influenza* vaccine based on the monitoring of their antigenic and genetic changes and antiviral resistance at the WHOCC. Clinical samples (only) are used to isolate viruses in suitable embryonated hens eggs or qualified cell lines as potential human vaccine seed viruses. These latter procedures can only be performed at the WHOCC in Melbourne or at one of the other four WHOCC's.

This document outlines methods for the laboratory diagnosis of *influenza* to confirm the diagnosis of clinical ILI. Accurate laboratory and clinical diagnosis (or surveillance) of *influenza* is required for the annual winter epidemics (influenza activity is concentrated between May 1 and September 30 in southern Australia and New Zealand, and throughout the year in northern Australia with peaks around March and August). Occasionally imported or other cases of novel influenza infections that may have pandemic potential may be detected. The role of laboratory surveillance in influenza pandemic planning is discussed in the Australian Health Management Plan for Pandemic Influenza (AHMPPI).

3 Laboratory Diagnosis

3.1 Clinical specimens

3.1.1 Antigen detection

Nasopharyngeal swabs (NPS) or aspirates (NPA) are the best sample because they contain the highest number of potentially influenza infected respiratory epithelial cells. NPA's are usually only available from children because of the difficulty in collecting NPA from adults. NPS are the routine sample taken for most adults and are also acceptable samples from children. Combined swabs collected from the throat and from the anterior ends of the nasal turbinates can also be combined into a single specimen. This is better than separate swabs from either of these sites. Isolated throat swabs

or throat gargles are less useful as the majority of cells captured are squamous epithelial cells. Nasal washes can also be used although these are less popular in Australia than other countries such as the USA. Sputum is a poor sample for antigen detection or virus isolation due to bacterial contamination and the presence of mucous. In practice, lower respiratory tract specimens (e.g. Broncho alveolar lavage fluid) are indicated where possible if lower respiratory involvement is clinically apparent. Appropriate personal protective equipment should be worn during sample collection. Ideally, all samples should be collected within 96 hours of disease onset.

Swabs should be cotton, rayon or Dacron-tipped, plastic-coated or aluminium shafted. They either contain their own viral transport media (VTM), Universal Transport Medium (UTM) or can be placed into a vial of VTM/UTM immediately after collection. Other specimens should be placed in a sterile container. Specimens should be stored and transported at 4°C (according to the appropriate IATA standards) or, if they cannot be processed within 72 hours, they should be frozen at –70°C. Samples should never be frozen at –20°C. If samples are not to be used for virus isolation, then dry flocked swabs are the best choice of swab to use, preferably with a nasopharyngeal swab. Note that some molecular transport media are specifically designed to INACTIVATE viral and bacterial pathogens (eg PrimeStore MTM, EKF Diagnostics) and so should be avoided if virus isolation is going to be performed.

If antigen detection tests are positive, then the original clinical sample, if suitable, should be sent for virus culture (for at least in a representative proportion of cases) if facilities are available, or consider sending the sample(s) to the WHOCC in Melbourne. Contact the WHOCC (whoflu@influenzacentre.org) for further details on numbers and timing of samples to be sent for further testing and for vaccine seed preparation.

3.1.2 Virus culture

Virus culture is now only performed in selected laboratories and is not the preferred test for the rapid diagnosis of influenza. Virus culture may be performed on the same samples as those used for antigen or NAT detection. Samples that have dried out or leaked or have used an inactivating transport media are not suitable for viral culture. Other respiratory specimens suitable for culture include endotracheal aspirates, Broncho alveolar lavage fluid and lung biopsy tissue.

Laboratories undertaking inf*luenza virus* isolations should keep an aliquot of the original clinical sample at –70°C or below to allow re-inoculation should novel strains of *influenza* be isolated, or if strains are needed for vaccine development. They should send any *influenza* isolates to their local WHOCC or WHO NIC laboratory or public health laboratory.

3.1.3 Nucleic acid detection tests (NAT)

NAT is the preferred test for the rapid diagnosis of acute influenza for clinical purposes. This may be performed on the same samples as those used for antigen detection and virus isolation. Ideally samples for NAT should also be collected within 96 hours of onset of illness, but later samples may still contain detectable *influenza* viral nucleic acid. Samples should be stored and transported in the same way as those for isolation as culture from samples may also be required. However, if samples have not been properly transported and stored, they may still be suitable for NAT. Samples which are positive by NAT should be cultured if possible (for at least in a proportion of cases and for special

cases such as deaths or cases where there has been recent animal (e.g. pigs or poultry) contact). If no culture is required or is possible then dry flocked swabs can be used to collect nasopharyngeal-nasal samples.

3.1.4 Serum samples

Serological diagnosis of *influenza* may be useful for surveillance and epidemiological purposes, and in cases specific cases of suspected post-influenza complications, such as pericarditis but NAT is the preferred method of rapid diagnosis of acute *influenza* for clinical purposes.

For serological investigations, serum samples should be taken during the Acute phase (within 1-7days of ILI onset) and during the convalescent phase serum (14–28 days after ILI onset). The sensitivity of laboratory diagnosis of *influenza* is increased by using a combination of virus detection by NAT early in the illness and serology on acute and convalescent blood samples.

3.2 Detection of influenza virus antigen or viral genome

Virus antigen (protein) detection assays are typically directed towards circulating epidemic viruses. They are usually less sensitive in the detection of novel strains, e.g. New pandemic strains or those with a different HA subtypes such as A(H5N1) (HPAI) or A(H7N9) (HPAI or LPAI) or A(H9N2) (LPAI) or swine derived viruses.

3.2.1 Antigen detection

This is currently most often done using monoclonal antibody (Mab)-based assays, with detection of the product by direct fluorescence (DFA) or enzyme immunoassay (EIA), using fluorescein/enzyme/gold-labelled secondary antibodies. These can be done on the same clinical specimens as those used for culture. These assays have a sensitivity of 50–90% against seasonal *influenza viruses* compared to isolation (Table 2.3, 2,4), take from 15 mins to 2 hours to perform, and may be combined with other monoclonal antibodies to the other common viral respiratory pathogens, such as *parainfluenza* types 1–3, adenovirus, RSV and human metapneumovirus.

3.2.2 Nucleic acid detection tests (NAT)

Influenza RNA in samples can be detected by NAT such as reverse transcriptase PCR (RT-PCR) which requires thermal cycling, or other related assays such as Loop-mediated isothermal amplification that are isothermal-based. They are the most sensitive test for *influenza* detection and also have extremely high specificity and a much more rapid turnaround time than virus culture (3,4). NAT increases detection rates of *influenza* in clinical specimens compared with virus culture or other non-molecular tests. NAT tests are more tolerant of samples that have been improperly stored, transported, or excessively delayed, as NAT can detect non-viable virus. The sensitivity (depending on the primers/probes used) is ~80-100% compared with other direct detection tests, and the specificity approaches 100%. Primers/probes can be combined in a nested PCR to increase sensitivity or in a multiplex PCR to detect other respiratory pathogens. NAT primers should be reviewed annually (or as required) to ensure that *influenza virus* genetic drift has not affected assay sensitivity (especially if the target gene is the HA).

There are two major classes of *influenza* NAT

- Those directed at targets that are common to a specific *influenza* type, i.e. targets (usually matrix or nucleoprotein or NS genes) common to all *influenza* A strains or to all *influenza* B strains.
- Those that are specific to an *influenza* A subtypes, i.e. primers/probes are directed at targets in the HA gene that are specific for seasonal A(H3N2) or A(H1N1)pdm09 or other potentially zoonotic *influenza* viruses for example A(H5N6) or possibly the NA gene of seasonal A(HN1)pdm09 N1 or A(H3N2) N2 or *influenza* B NA.

Nucleic acid testing is the test of choice for definitive identification of human infection with *influenza* A viruses A(H5N1) or A(H5Nx) or A(H7N9), either of HPAI and LPAI-types and other zoonotic viruses that have infected humans overseas in the past.

Virus isolation for antigenic characterisation should be also be performed, where possible, on suitable NAT positive samples if there is sufficient virus present in the sample (e.g. if the cycle threshold – Ct – is ≤30 for the matrix gene).

Laboratories performing NAT detection of *influenza* are encouraged to participate in recognised testing quality assurance (QA) Programs (e.g. those run by the Australian RCPAQAP or alternative programs such as the Quality Control for Molecular Diagnostics (QCMD) or run by WHO HQ for seasonal in*fluenza viruses* (A(H1N1)pdm09, A(H3N2), B viruses) as well as other zoonotic and potentially zoonotic i*nfluenza viruses* (e.g. A(H5N6), A(H7N9), A(H9N2)).

3.3 Detection of the organism - virus isolation

Isolation of i*nfluenza A* or *B virus* in cell lines such as Madin-Darby canine kidney (MDCK) or other cell lines provides a definitive diagnosis of influenza infection, though it is less sensitive than NAT and requires the virus to remain viable during storage and transport. However, cell culture does provide virus stocks for the more detailed antigenic analysis needed for strain identification and to assist vaccine selection, as well as the potential capacity to detect new *influenza* types that may be missed by other methods. It is important that appropriate biosafety guidelines are followed when culturing and processing *influenza* positive samples.

3.3.1 Conventional culture and typing

Influenza viruses are usually isolated using trypsinised MDCK cells, SIAT-1 MDCK or other epithelial cell lines. Primary monkey kidney cells are difficult to obtain and problematic to work with, so they are now rarely used. I*nfluenza virus* growth is suggested by haemadsorption or observation of typical cytopathic effect at 4–5 days post -inoculation. Confirmation is usually achieved by IFA using *influenza* type or subtype-specific monoclonal antibodies or by NAT. Further strain typing can be carried out using the more time-consuming technique of haemagglutination inhibition (HAI).

All isolates should have preliminary typing and subtyping as *influenza* A(H1)pdm09 or A(H3) (or other subtype), or *influenza* B, as quickly as possible, either in the laboratory carrying out the culture or in a reference laboratory. All *influenza* isolates (including those that fail to type) should also be referred to the WHOCC in Melbourne directly, via a local WHO NIC or local reference laboratory. Where a new or significantly different strain is suspected, then isolates should be referred urgently directly to the WHOCC.

For egg-based *influenza* vaccines I *influenza* isolation is undertaken by inoculating cells lining the amniotic or allantoic cavity of embryonated chicken eggs, and this technique is still widely used for vaccine generation. This procedure is routinely performed using original clinical samples at the WHOCC in Melbourne as well as the isolation of inf*luenza viruses* into qualified cell lines for cell-based *influenza* vaccines.

Drug susceptibility testing using genotypic or phenotypic techniques is available at the WHOCC and in some reference laboratories, but is not currently part of routine testing. Antiviral susceptibility is monitored internationally via the WHO network[6].

3.3.2 Rapid culture assays

The time required for cell culture identification of in*fluenza virus* can be reduced to 1–3 days using shell-vial or multiwell plates (typically using MDCK cells) that can be stained after 48 hours culture using commercially available monoclonal antibodies. Sensitivity varies from 56–100% compared with conventional culture[3,4], and is ~85% compared to PCR. Specificity of culture is 100%. Rapid culture positive samples should be subsequently re-cultured in the testing or a reference laboratory to provide an isolate for antigenic analyses as part of surveillance and vaccine development.

There is currently no quality assurance program (QAP) specifically for virus isolation however the WHO does offer a QAP for *influenza* isolation for NIC's (performed by the Melbourne WHO CC) every 2 years.

3.4 POC tests

As noted above POC tests have traditionally been based on immunoassay technology using antibodies directed to conserved *influenza* proteins however some of these tests are now being replaced by more sophisticated second generation tests or by molecular-based tests. The original tests have been available for a number of years and may assist in the early management of suspected influenza cases. These may have a role in laboratories unable to perform NAT in outbreak situations, for doctors without reasonable laboratory access, or to guide the rapid use of *influenza* antiviral agents[4]. They are intended for use near the patient or at the bedside and the specificity has been shown to be generally high (90-95%). The original POC's are consistently less sensitive (60-85%) compared to NAT, or culture or IFA antigen detection tests. If a reliable negative result is required, or if the accuracy of a positive result is critical, then these samples should also be tested by NAT or a molecularly-based POC test.

Improvements in the sensitivity of POC tests have been made recently over the original visible immunoassay tests with the use of fluorescent labels (eg Sofia Influenza A+B Fluorescent Immunoassay (FIA) (Quidel)) and the use of a reader rather than relying on the naked eye to unequivocally determine positive or negative test results (eg. BD Veritor™ System for Rapid Detection of Flu A+B (BD), Sofia and Sofia 2 (Quidel)). In addition next generation POC tests are now available based on NAT technologies (eg. Cobas Liat [Roche Diagnostics], Solana [Quidel], GeneXpert (Cephid), BioFire FilmArray EZ (BioFire Diagnostics) and others) that are now approaching or have reached the performance of laboratory-based NAT testing and results generated using these platforms should therefore be considered more reliable than the traditional immunoassay based POC tests.

Multiplex POC tests are also becoming available that will detect multiple respiratory pathogens e.g. the Sofia 2 Flu + SARS Antigen FIA (Quidel) for the detection of i*nfluenza A, influenza B, SARS-CoV-2* and the GeneXpert Xpert® Xpress SARS-CoV-2/Flu/RSV (Cepheid) for the detection of *influenza A*, *influenza B*, SARS-CoV-2, RSV.

3.5 Serology

Detection of *influenza*-specific antibodies allows a retrospective diagnosis of influenza infection and is also a useful surveillance tool. As *influenza* is often a reinfection with pre-existing partial immunity present, recent infection can only be reliably diagnosed by demonstrating a significant (four-fold or greater) rise in *influenza*-specific antibody titres. Single samples with a high titre are less reliable as they may reflect past infection or vaccination. However, a single high titre is suggestive of probable recent infection when the patient has had a consistent ILI occurring during the influenza season[3,4]. This is because neither vaccination nor infection in the previous season produces high antibody titres. Serological methods include complement fixation (CF), haemagglutination inhibition (HAI), single radial haemolysis (SRH), virus neutralisation (VNT) and enzyme immunoassays (EIA). Sensitivity varies from 80–50% (EIA>HAI>CF). Enzyme immunoassay-based IgM (and IgA) assays have not proved useful in routine laboratory diagnosis as most influenza infections are reinfections.

CF tests detect antibodies directed at the *influenza* nucleoprotein and can distinguish between *influenza A* (but not between subtypes) and i*nfluenza B*. A fourfold rise is definitive evidence of acute infection. HAI and VNT are the gold standard assays that allow subtype determination. There are generally accepted criteria that correlate with post-vaccine "immunity". The technical difficulties associated with these tests mean that they are not in widespread diagnostic use. Also, they may not detect new *influenza A* subtypes due to antibody cross-reactivity with existing circulating i*nfluenza A* subtypes. For CF, a four-fold rise in *influenza*-specific antibodies is the most reliable indicator of recent infection. Single high titres are suggestive of recent infection in the appropriate clinical situation. Due to differences in how these tests are performed in different laboratories, the definition of "positive titre" and a “high positive titre” will vary between laboratories.

SRH is rarely used as theoretically being technically easier than HAI, it requires high antigen concentrations, and the correlation between zone sizes and antibody titres measured by other methods is not well established. EIA tests have not been widely used and the criteria for immunity and for significant or protective antibody levels are not established.

Laboratories performing serology testing for *influenza* should participate in the RCPA Serology QA Program: for further information please refer to RCPA, or a similar program or participate in an inter-laboratory exchange with a sister laboratory that performs the same assay(s).

3.6 Quality Assurance

Test-specific QA considerations are described under the various testing procedures.

3.7 Diagnosis of Human Cases with novel *influenza virus* infections (eg viruses of avian or swine origin)

Where there is a suspected case of human infection with novel *influenza virus* such as a highly pathogenic avian *influenza* (A(H5N1), A(H5N6), A(H7N9) or another novel strain such as swine-origin variant virus A(H1N2)v or A(H3N2)v, or in the event of a new pandemic *influenza* emerging, the laboratory case definition will be similar to that for seasonal *influenza*, but may include exposure history, travel history etc. as outlined in the AHMPPI with updates as appropriate from the WHO, US CDC and other websites.

Specimen collection for suspected novel influenza infections will be similar to that for seasonal *influenza* (combined NPS/nose and throat swabs are the recommended sample) except that additional non-respiratory specimens (e.g. serum, faeces, cerebrospinal fluid) can be useful in diagnosing some cases where the spread of *influenza* maybe more systemic (eg A(H5N1). Lower respiratory tract samples may also be useful for some severe in*fluenza virus* infections (eg A(H5N1), A(H5N6), A(H7N9).

The diagnostic test of choice is NAT with both *influenza A*-specific and novel strain-specific primers/probes. All NAT positive novel *influenza viruses* should be sequenced (minimum HA and NA genes and preferably Whole Genome Sequencing). If this cannot be performed in a timely manner at the testing laboratory, an aliquot of the positive sample should be shipped as soon as possible to the WHO CC in Melbourne for confirmation of the subtype (HA and NA) and a risk assessment performed.

At a minimum, laboratories must meet basic PC2 standards and use PC3 work practices to handle specimens that are suspected to contain novel or potentially pandemic inf*luenza viruses* and use a PC3 facility where ever possible. Appropriately equipped and accredited laboratories may also perform virus isolation under PC3 conditions.

The reliability of POC tests for detection of novel or potential pandemic influ*enza viruses* (of avian or swine or other origin) are not well established and should not be used for diagnostic purposes.

4 Agreed Typing & Subtyping Methods

4.1 Laboratory Nomenclature for National Database Dictionary

4.1.1 Organism Name(s) List

Orthomyxoviridae, Influenza A, Influenza B, Influenza C

4.1.2 Typing/Subtyping Nomenclature List(s)

Types: inf*luenza A, or influenza B* (i*nfluenza C* is rarely tested diagnostically).

I*nfluenza A* Subtypes: Currently there are two inf*luenza A viruses* that are currently circulating in humans, A(H3N2) and A(H1N1)pdm09. The H refers to the haemagglutinin type of which there are 18, and the N refers to the neuraminidase type of which there are 11 subtypes. Most of these subtypes can be found in avian species but only a few of these HA and NA subtypes have been detected in

man (eg H1N1, H3N2 and in the past H2N2). There are two other subgroups of distantly related i*nfluenza A viruses* included in this list that have recently been detected in certain bat species (H17N10 and H18N11).

4.1.3 *Influenza B*-lineage determination.

Lineage: B/Victoria/2/87-like or B/Yamagata/16/89-like

Two lineages of in*fluenza B viruses* infect human that differ in their antigenic and molecular characteristics are currently circulating in the human population, These two lineages diverged in the 1990's and B-viruses are referred to as being either of B/Victoria/2/87-lineage (B/Victoria-lineage) or B/Yamagata/16/88-lineage (B/Yamagata-lineage).

4.2 SNOMED CT concepts

SNOMED CT concept	Code
Influenza (disorder)	6142004
Influenza-like illness (clinical finding)	95891005
Influenza A virus (organism)	442438000
Influenza B virus (organism)	24662006
Influenza C virus (organism)	81524006

5 References

1. Joseph C. (1995) Virological surveillance of influenza in England and Wales: results of a two year pilot study 1993/4 and 1994/5. Communicable Disease Review 5(10): R141-R145.
2. Thursky K et al. (1993) Working towards a simple case definition for influenza surveillance. Journal of Clinical Virology
3. 27 (2): 170-179.
4. Zambon M. (1998) Laboratory Diagnosis of Influenza. In: Textbook of Influenza. Eds. Nicholson K.G, Webster R.G, Hay A.J. Ch.22: 291-313.

5. Playford EG and Dwyer DE. (2002) Laboratory diagnosis of influenza virus infection. Pathology 34:115-125.
6. Kok, J. et al. (2010) Comparison of a rapid antigen test with nucleic acid testing during cocirculation of pandemic influenza A/H1N1 09 and seasonal influenza A/H3N2. Journal of Clinical Microbiology 48:290-291.
7. Hayden F.G. (2006) Antiviral resistance in influenza viruses – implications for management and pandemic response. New England Journal of Medicine 2006; 354 :785-788.
8. Australian Health Management Plan for Pandemic Influenza.