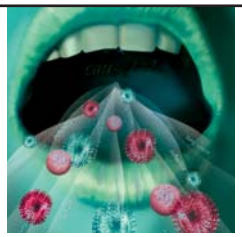

The causes and diagnosis of influenza-like illness

BACKGROUND Influenza and other respiratory viruses circulate between spring and autumn in temperate climates and all year in tropical climates. These viruses cause symptoms often referred to as influenza-like illness (ILI), but are not generally distinguishable on clinical grounds alone.

OBJECTIVE This article provides a brief review of the surveillance, viral causes and current diagnostic methods used to identify viruses causing ILI.

DISCUSSION Influenza-like illness surveillance with laboratory support, conducted in most Australian states and territories, aims to define the impact of influenza seasons in the community and provide virus strains that may be used in future vaccine formulations. Surveillance may also be useful in the early stages of an influenza pandemic. In addition to influenza, viruses known to cause ILI include respiratory syncytial virus, rhinovirus, adenovirus, parainfluenza viruses, human coronaviruses (including the virus that causes severe acute respiratory syndrome) and the recently recognised human metapneumovirus. Polymerase chain reaction assays are the most common diagnostic tests now used for the differential diagnosis of ILI.

Heath Kelly,
BSc, MBBS, MPH, FAFPHM, is Head, Epidemiology Unit, Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria.

Chris Birch,
BSc, MSc, PhD, is Head, Virus Identification Laboratory, Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria.

In temperate climates, influenza viruses (*Figure 1*) circulate from late autumn to early spring in both the southern and northern hemispheres. In tropical climates, there is less seasonality associated with virus circulation. In the Northern Territory, for instance, cases are diagnosed throughout the year with peaks around February-March and August-September.[1] However, it is not only influenza viruses that circulate in what is often referred to as the influenza season. Other viruses cause a similar clinical picture. This has led to the use of the term 'influenza-like' illness (ILI) to describe the clinical syndrome that may be attributed to influenza and other respiratory viruses.

Surveillance of ILI

In many Australian states, general practitioners contribute to annual influenza surveillance.[1] General practitioners report on patients with ILI, rather than influenza, as it is often difficult to distinguish the cause of the illness based on the symptom complex alone. Over five consecutive influenza seasons in Victoria, about 40% of all patients with an ILI had laboratory proven influenza.[2,3] This proportion has been reported to be higher in clinical trials of antiviral medication,[4] but clinical conditions in trials are not typical of day-to-day practice.

A definitive set of symptoms for a clinical diagnosis of influenza has been difficult to achieve. All surveillance definitions of influenza include cough and fever.[5] The Australian Sentinel Practice Research Network (ASPREN) definition of influenza is more complicated and relies on the recognition of influenza circulating in the community combined with a number of respiratory

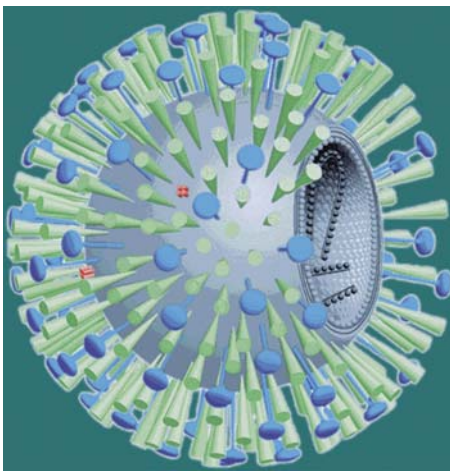

Figure 1. A model of the influenza virus

Table 1. The ASPREN case definition for influenza

An influenza epidemic and four of the criteria below, or six of the criteria below in the absence of an epidemic:

- Onset within 12 hours
- Cough
- Rigours or chills
- Fever
- Prostration or weakness
- Myalgia – widespread aches and pains
- No significant respiratory signs other than redness of the throat and nasal mucous membranes
- Influenza in close contacts (modified for this study to 'history of influenza like illness' to allow inclusion of illness in nonlaboratory confirmed close contacts)

Table 2. The positive predictive value of a clinical diagnosis of influenza based on laboratory confirmation, by GP certainty of diagnosis, Victoria 2001–2002

Respiratory virus detected	GP certainty of diagnosis			
	Almost certain	Probable	Less likely	Not stated
	Number confirmed (PPV %)			
2001	**n=66**	**n=91**	**n=22**	**n=32**
Influenza	30 (45.5%)	24 (26.4%)	2 (9.1%)	9 (28.1%)
Other virus	5 (7.6%)	8 (8.8%)	2 (9.1%)	2 (6.3%)
Not detected	31 (47.0%)	59 (64.8%)	18 (81.8%)	21 (65.6%)
2002	**n=151**	**n=241**	**n=83**	**n=50**
Influenza	81 (53.6%)	96 (39.8%)	23 (27.7%)	25 (50%)
Other virus	19 (12.6%)	39 (16.2%)	24 (28.9%)	6 (12.0%)
Not detected	51 (33.8%)	106 (44.0%)	36 (43.4%)	19 (38.0%)

PPV = positive predictive value

and systemic symptoms (*Table 1*). Using data from influenza seasons in Western Australia and Victoria we have shown that the ASPREN case definition was no more likely to identify cases of influenza than a more simple case definition of fever, cough and fatigue.[5]

Using the case definition of fever, cough and fatigue, GPs were asked to indicate their level of certainty that a patient with ILI had influenza. In the Victorian influenza seasons of 2001 and 2002, the proportion of cases confirmed to have influenza, ie. the positive predictive value of a clinical diagnosis of influenza, increased with increasing GP certainty of the diagnosis (*Table 2*). Although this was not the case for the entire 2003 season, it was true for metropolitan GPs in the weeks when influenza was circulating.[3] In general, the positive predictive value of a test increases with increasing disease prevalence.

Programs for sentinel ILI surveillance with laboratory support exist in a number of Australian states. Some of these programs attract continuing medical education points from The Royal Australian College of General Practitioners. In a survey conducted of 82 GPs who had participated in sentinel surveillance in Victoria in 2002, about 85% thought participation in the surveillance program assisted in the clinical diagnosis of influenza. Many of these GPs reported they were more aware of influenza as a possible diagnosis and had greater confidence in differentiating influenza from other respiratory tract infections as a result of knowing when influenza was circulating and having laboratory confirmation of the diagnosis. Some reported they were able to reassure patients they did not need antibiotics and others reported using antiviral medication when they were confident the patient had influenza. Thirty-six (44%) GPs reported having made changes in their clinical practice following participation in the sentinel surveillance program.

Thresholds for ILI surveillance

Experience from clinical practice indicates that influenza seasons have a varying impact from year to year. Based on a comparison of ILI activity in general practice with hospital admissions coded as influenza, we have tentatively described four levels of seasonal influenza activity:

- baseline
- normal seasonal activity
- higher than expected seasonal activity, and
- epidemic activity.[2]

The last year associated with epidemic activity and a very high hospital admission rate for influenza was 1997. In 2003 the ILI season in Victoria peaked late at the threshold described as 'higher than expected seasonal activity' (*Figure 2*).

Predicting circulation of influenza viruses from year to year is notoriously difficult. In 2003, for instance, many commentators attributed the low level of activity in the early weeks of the influenza season to interventions that had been implemented in response to anxiety about the spread of severe acute respiratory syndrome (SARS). However, there was a later and relatively high peak to the influenza season, despite the continuing SARS epidemic in some countries, the reduction in international travel, the early uptake of influenza vaccine and the considerable public understanding of the means by which SARS and other respiratory viruses can be transmitted.

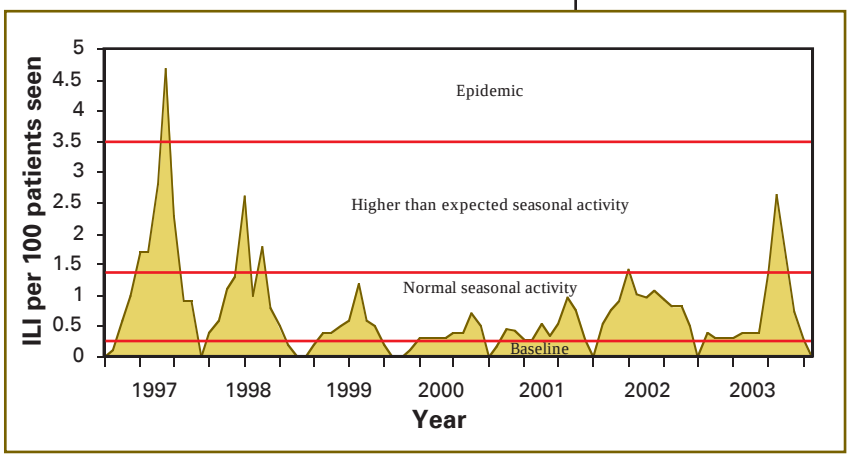

Figure 2. Thresholds for ILI (Victoria 1997–2003)

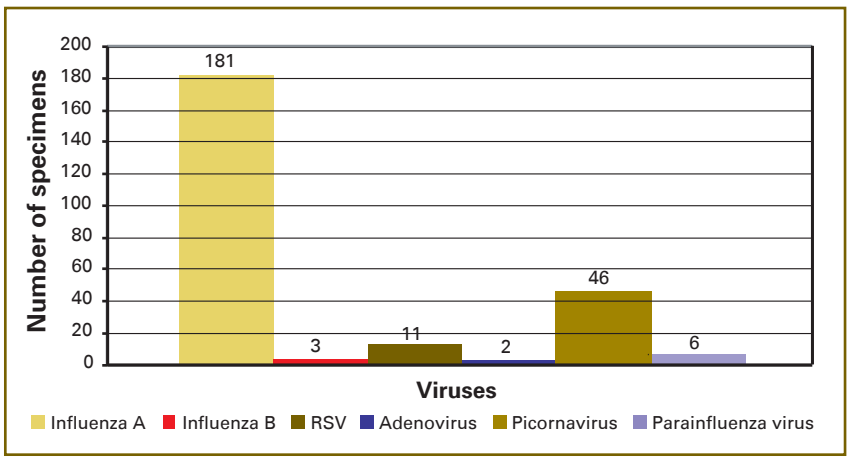

Figure 3. Viruses causing ILI in sentinel patients (Victoria 2003)

Causes of ILI

Many viruses are known to cause clinical illness that is difficult to distinguish from influenza. While a clinician may be confident of the diagnosis in a previously well person with a 12–36 hour onset of painful retro-sternal cough, fever, and fatigue or malaise during a time when influenza viruses are known to be circulating, the same symptoms may be due to other viruses at other times. Among the most common of these are respiratory syncytial virus (RSV) and picornaviruses (small RNA viruses that include enteroviruses and rhinoviruses). Rhinoviruses are the most common of the picornaviruses to cause an ILI. Less common causes of ILI include parainfluenza and adenovirus.

In a community based study in the United Kingdom over three successive winters (1995–1996 to 1997–1998), RSV was identified in 480 swabs submitted from general practice patients in all age groups and influenza virus from 709.[6] In Victoria in 2002, influenza was confirmed as the diagnosis in 43% of 524 patients with ILI. A further 17% had other respiratory viral infections.[2] In 2003, 37% of 504 patients with ILI had influenza and a further 13% were diagnosed with other respiratory viruses, of which picornavirus was the most common (*Figure 3*). Respiratory syncytial virus was not identified as frequently in Victorian patients as it was in the UK.

Other causes of ILI include the recently recognised human metapneumovirus (hMPV) and several coronaviruses. Human metapneumovirus was first reported in 2001 as a cause of bronchiolitis-like illness among Dutch children[7] and soon after identified in Australian children.[8] In a subsequent 2 year study at the Rochester General Hospital, New York, 44 of 984 (4.5%) hospitalised patients had evidence of hMPV infection. Although infections occurred in all age groups they were more common in young adults.[9]

Coronaviruses have received considerable publicity in recent time because of the association of a novel human coronavirus with SARS.[10] Previously only two human coronaviruses had been identified. These viruses, known as OC43 and 229E, are usually identified in patients suffering symptoms of the common cold. However, they have caused lower respiratory illness in institutionalised individuals, in particular the elderly and those with underlying chronic conditions.[11,12]

Although pneumonia, particularly streptococcal pneumonia, is a common complication of influenza

Table 3. Sentinel general practice networks for influenza surveillance in Australia

State/territory	Contact	Phone	Email
ASPREN	Nigel Stocks	(08) 8303 3460	nigel.stocks@adelaide.edu.au
Northern Territory	Lesley Scott	(08) 8922 8265	lesley.scott@nt.gov.au
Queensland	GP Influenza (ILI) Sentinel Surveillance Project	(07) 3234 1155	
South Australia	Rod Givney	(08) 8226 7177	rod.givney@dhs.sa.gov.au
Victoria	Joy Turner	(03) 9342 2636	joy.turner@mh.org.au
	Heath Kelly	(03) 9342 2608	heath.kelly@mh.org.au
Western Australia	David Smith	(08) 9346 2164	david.smith@health.wa.gov.au
	Annette Broom	(08) 9346 2213	abroom@cyllene.uwa.edu.au
Tasmania	David Coleman	(03) 6222 7727	david.coleman@dhhs.tas.gov.au
Australian Capital Territory	Rona Hiam	(02) 6205 8631	rona.hiam@act.gov.au

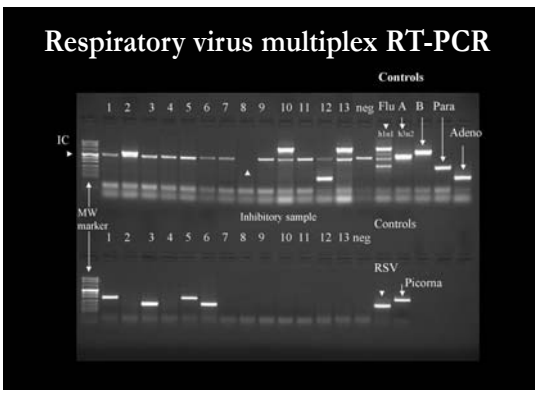

Figure 4. Detection on an agarose gel of respiratory virus products amplified using the multiplex respiratory virus RT-PCR. Molecular weight markers are shown on the left hand side of both rows of the gel, positive control samples on the right. This assay differentiates influenza A (H3N2) from H1N1 strains. The internal control is indicated. Specimens in lanes 8 (top gel), 2 and 4 (bottom gel) are inhibitory. Lane 2 on the top gel is positive for H3N2, lanes 10 and 13 are positive for H1N1, and lane 12 is adenovirus positive. Lanes 1 and 5 on the lower gel are positive for picornaviruses, lanes 3 and 6 are positive for RSV. (Lanes 7–12 do not contain samples)

infection, it is unusual for influenza to present with a pneumonic picture. On the other hand, common causes of atypical pneumonia in the community, including mycoplasma, chlamydia and legionella species, can present initially with influenza-like symptoms and these agents should be considered if laboratory testing is negative for respiratory viruses.

The laboratory diagnosis of ILI

A diagnosis of ILI involves laboratory testing for the presence of markers of influenza virus or other respiratory pathogens. These markers can be specific antibodies, antigens or nucleic acid. Virus isolation in susceptible cell lines can also be attempted, but this practice is increasingly being replaced by molecular testing. Tests to detect respiratory virus antigens such as immunofluorescence, require the collection of nasopharyngeal aspirates – a process often not practical in the general practice setting.

PCR assays for viral RNA

Most laboratories now use polymerase chain reaction (PCR) assays to detect viral RNA in clinical material. These assays involve the amplification of specific viral genomic sequences. The advantages over other test procedures are increased sensitivity, rapid turn around time, an expanded range of specimen types suitable for testing, and the ability to detect viruses that are difficult to grow in cell culture.

Polymerase chain reaction assays can be designed to detect nucleic acid from a specific pathogen or simultaneously detect several potential causative agents (so-called 'multiplexing'). A combined nose and throat swab, stored and transported at 4°C in viral transport medium, is the specimen generally used in the PCR assay to detect respiratory viral RNA. With good specimen collection and timely transport to the laboratory, a PCR result can be available within 24 hours.

The PCR assay used at the Victorian Infectious Diseases Reference Laboratory simultaneously detects influenza A and B viruses, RSV, all adenovirus types, parainfluenza types 1, 2 and 3, and picornaviruses (enteroviruses and rhinoviruses) (*Figure 4*). Influenza A viruses can be sub-typed according to their haemagglutinin content using specific PCR assays. It is therefore

possible to identify influenza strains as H1, H3 or even H5, an influenza sub-type associated with transmission from birds to humans.[13] There is a limit, however, to the number of assays that can be multiplexed.

Conclusion

Influenza-like illness surveillance aims to identify the duration and impact of annual influenza seasons and characterise circulating influenza strains. The ability to compare circulating strains with those present in the current vaccine provides the potential for a newly recognised strain to be considered for inclusion in future vaccine formulations. Surveillance may also have an important role in the early recognition of new viruses such as the human coronavirus causing SARS and may also be important in detecting the onset of an influenza pandemic.

Many reference laboratories throughout Australia have, or are developing, the diagnostic capabilities for SARS (PCR and serological assays) and pandemic influenza. The WHO laboratories can detect and characterise influenza viruses, including pandemic strains, if they arise, and are working on identification assays for avian influenza and human strains derived from it.

Influenza-like illness surveillance has an acknowledged community benefit and appears also to be a useful activity for those GPs who provide sentinel data. General practitioners interested in participating in sentinel surveillance should contact the influenza coordinator in their state or territory (*Table 3*).

Summary of important points

- ILI is generally characterised by cough, fever and fatigue.
- ILI are caused by influenza viruses, respiratory syncytial virus, rhinovirus, adenoviruses, parainfluenza viruses, human coronaviruses, and human metapneumovirus. Cases of atypical pneumonia including mycoplasma, chlamydia and legionella species may present with ILI symptoms.
- PCR assays are now generally used to diagnose ILI. With good sample collection (combined nose and throat swab) and appropriate transport to the laboratory, results may be available within 24 hours.
- Laboratory support for ILI surveillance is provided in some states and attracts CME points. Many GPs report that participation in ILI surveillance leads to an improvement in their recognition and management of patients with influenza.

Acknowledgment

We thank Joy Turner for providing *Table 1*, *Figure 2* and *3*, and Julian Druce for providing *Figure 4*.

Conflict of interest: none declared.

References

1. Roche P, Spencer J, Hampson A. Annual report of the national influenza surveillance scheme, 2001. Commun Dis Intell 2002;26:204–213.
2. Watts C, Andrews R, Druce J, Kelly H. Establishing thresholds for influenza surveillance in Victoria. Aust NZ J Public Health 2003;27:409–412.
3. Turner J, Tran T, Birch C, Kelly H. Higher than normal seasonal influenza activity in Victoria, 2003. Commun Dis Intell 2004; in press.
4. Hayden FG, Osterhaus ADME, Treanor J, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. New Engl J Med 1997;337:874–880.
5. Thursky K, Cordova S, Smith D, Kelly H. Working towards a simple case definition for influenza surveillance. J Clin Virol 2003;27:170–179.
6. Zambon MC, Stockton J, Clewley J, Fleming DF. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. Lancet 2001;358:1410–1416.
7. Van den Hoogen B, de Jong JC, Groen J, et al. A newly discovered pneumovirus isolated from young children with respiratory disease. Nat Med 2001;7:719–724.
8. Nissen MD, MacKay IM, Withers SJ, Siebert DJ, Sloots TP. Evidence of human metapneumovirus in Australian children. Med J Aust 2002;176:188–189.
9. Falsey AR, Erdman D, Anderson LJ, Walsh EE. Human metapneumovirus infections in young and elderly adults. J Infect Dis 2003;187:785–790.
10. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. New Engl J Med 2003;348:1967–1978.
11. Falsey AR, Walsh EE, Hayden FG. Rhinovirus and coronavirus infection associated hospitalisations among older adults. J Infect Dis 2002;185:1338–1341.
12. Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infection in patients with chronic chest disease. JAMA 2000;283:499–505.
13. Hien TT, Nguyen TL, Nguyen TD, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med 2004;350:1179–1188.

Email: heath.kelly@mh.org.au