Influenza epidemiology, vaccine coverage and vaccine effectiveness in sentinel Australian hospitals in 2012: the Influenza Complications Alert Network (FluCAN)

Allen C Cheng, Simon G Brown, Grant W Waterer, Mark Holmes, Sanjaya Senenayake, Nadia Deborah Friedman, Saliya Hewagama, Graham Simpson, Peter A Wark, John W Upham, Tony M Korman, Dominic E Dwyer, Richard Wood-Baker, Louis B Irving, Simon D Bowler, Tom Kotsimbos, Paul M Kelly

Abstract

Influenza is mostly a mild, self-limiting infection and severe infection requiring hospitalisation is uncommon. Immunisation aims to reduce serious morbidity and mortality. The Influenza Complications Alert Network (FluCAN) is a sentinel hospital-based surveillance program that operates at 15 sites across all states and territories in Australia. This study reports on the epidemiology of hospitalisation with confirmed influenza, estimate vaccine coverage and influenza vaccine protection against hospitalisation with influenza during the 2012 influenza season. In this observational study, cases were defined as patients admitted to one of the sentinel hospitals with influenza confirmed by nucleic acid detection. Controls were patients who had acute respiratory illnesses who were test-negative for influenza. Vaccine effectiveness was estimated as 1 minus the odds ratio of vaccination in case patients compared with control patients, after adjusting for known confounders. During the period 9 April to 31 October 2012, 1,231 patients were admitted with confirmed influenza at the 15 FluCAN sentinel hospitals. Of these, 47% were more than 65 years of age, 8% were Indigenous Australians, 3% were pregnant and 76% had chronic co-morbidities. Influenza A was detected in 83% of patients. Vaccination coverage was calculated from the vaccination status of 1,216 test negative controls and was estimated at 77% in patients 65 years or over and 61% in patients with chronic comorbidities. Vaccination effectiveness was estimated at 41% (95% CI: 28%, 51%, $P<0.001$). Vaccine coverage was incomplete in at-risk groups, particularly non-elderly patients with medical comorbidities. The study results suggest that the seasonal influenza vaccine was moderately protective against hospitalisation with influenza during the 2012 season. *Commun Dis Intell* 2013;37(3):E246–E252.

Keywords: influenza; vaccine effectiveness

Introduction

Hospitalisation due to influenza is an uncommon complication, and the case hospitalisation ratio has been estimated in the United States of America at around 0.45%.[1] However, because infection with influenza virus is relatively widespread and estimated to affect 5%–10% of the population, the incidence of hospitalisation is of significance to public health. Influenza vaccination is recommended in Australia for high risk groups, including the elderly, patients with chronic comorbidities, pregnant women and Indigenous Australians.[2] The National Immunisation Program, funded by the Australian Government and implemented by state and territory departments of health, provides public funding for influenza immunisation to reduce serious morbidity and mortality from influenza. Hospital-based surveillance is able to detect a dimension of severity not captured in a timely manner by other surveillance systems for influenza and influenza-like illnesses. This study aimed to describe the epidemiology of hospitalisation with confirmed influenza, estimate vaccine coverage in hospitalised patients with acute respiratory illnesses but without influenza, and estimate influenza vaccine protection against hospitalisation with influenza during the 2012 influenza season.

Methods

The Influenza Complications Alert Network (FluCAN) has operated since 2009.[3] In the 2012 season, the participating sites were The Alfred Hospital (Vic), Royal Melbourne Hospital (Vic), Canberra Hospital (ACT), Calvary Hospital (ACT), Monash Medical Centre (Vic), Geelong Hospital (Vic), Royal Perth Hospital (WA), Royal Adelaide Hospital (SA), Royal Hobart Hospital (Tas.), Mater Hospital (Qld), Princess Alexandra Hospital (Qld), Cairns Base Hospital (Qld), Alice Springs Hospital (NT), Westmead Hospital (NSW), and John Hunter Hospital (NSW). Ethics approval has been obtained at all participating sites and the Australian National University.

An influenza case was defined as a patient admitted to hospital with influenza confirmed by polymerase chain reaction (PCR). Surveillance was conducted from 9 April to 31 October 2012. Test negative controls (up to two for each case) were the next tested patients with acute respiratory

symptoms who were negative for influenza by PCR. Admission or transfer to the intensive care unit (ICU) included patients managed in a high dependency unit (HDU). The onset date was defined as the date of admission except for patients where date of test is more than 7 days after admission, where the onset date was the date of the test. Admissions that are listed as influenza A includes both untyped and seasonal strains, and may include infections involving the pandemic H1N1/09 strain if not specifically typed.

Vaccination coverage was estimated separately in two groups of patients. Prior to the onset of the influenza season (from study commencement on 9 April), vaccine status was collected in patients with radiologically-confirmed pneumonia. This was different by state/territory and was defined by National Notifiable Diseases Surveillance System data as follows: Australian Capital Territory (to 15 June), New South Wales (to 25 May), Northern Territory (not included, as influenza activity evident from 30 March), Queensland (22 June), South Australia (1 June), Tasmania (28 June), Victoria (8 June), and Western Australia (22 June). Subsequent to the commencement of the season, vaccine status was collected from patients admitted with influenza like illness but who were negative on influenza testing. Patients were defined as being vaccinated if they reported (as documented in the medical record or from self-report) receiving the 2012 trivalent seasonal vaccine more than 2 weeks prior to presentation. In Australia, only unadjuvanted vaccines are available under the National Immunisation Program although 1 adjuvanted vaccine is approved for use.

Vaccine effectiveness was estimated by comparing the odds of a confirmed case being vaccinated with the odds of a test negative control being vaccinated, assuming that vaccination would have no effect on admissions with non-influenza respiratory infections. This was calculated as 1 minus the odds ratio of vaccination using methods previously described.[4] A multivariate model was constructed from factors known to be associated with vaccination, and therefore potential confounders. Where the vaccine is assumed to only partially protect vaccinated individuals, the odds ratio of vaccination in cases compared with controls can be shown to be arithmetically equivalent to the relative rate of disease in vaccinated vs. unvaccinated individuals, as long as the time at risk is the same.[5–6] This has led to the development of the incidence density test design, where controls are selected from patients without influenza contemporaneous to a case.[7] A convenience sample of controls can be obtained from patients tested for influenza but who are negative for influenza using a sensitive and specific assay; this assumes that influenza vaccination has no effect on the prevention of non-influenza influenza-like illnesses (i.e. those due to other respiratory viral infections), and that these patients are generally representative of the population at risk.

Results

During the period 9 April to 31 October 2012, 1,231 patients were admitted with confirmed influenza at the 15 FluCAN sentinel hospitals. In most jurisdictions, the peak number of hospitalised cases occurred during July 2012 (Figure 1). The majority

Figure 1: Date of admission in patients hospitalised with confirmed influenza

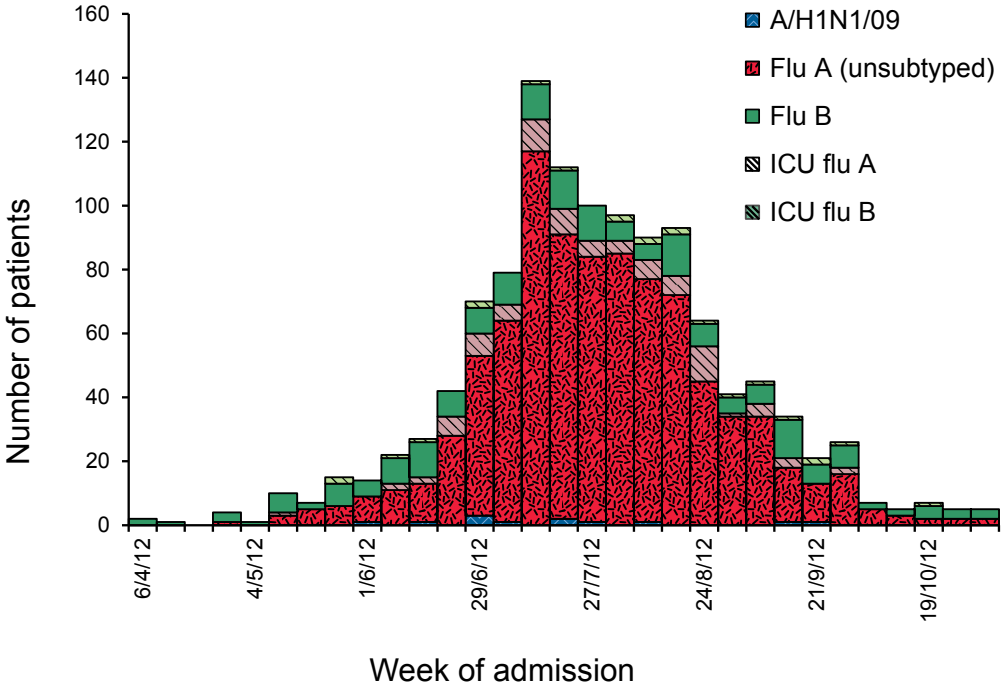

Table 1: Demographics, risk factors and outcomes in hospitalised patients with confirmed influenza

Variable	Confirmed influenza		Test negative controls	
	n	%	n	%
Total	1,231	100.0	1,694	100.0
Influenza strain				
H1N1/09	12	1.0	–	–
Flu A (unknown/ seasonal)	1,006	81.7	–	–
Flu B	213	17.3	–	–
Age group				
<18 years	148	12.0	25	1.5
18–39 years	229	18.6	185	10.9
40–64 years	281	22.8	340	20.1
65–79 years	307	24.9	398	23.5
>80 years	266	21.6	746	44.0
Male	614	49.9	869	51.3
Indigenous	99	8.0	168	9.9
State or territory				
ACT	105	8.5	30	1.8
NSW	84	6.8	137	8.1
NT	83	6.7	155	9.1
Qld	167	13.6	311	18.4
SA	200	16.2	275	16.2
Tas.	99	8.0	103	6.1
Vic.	390	31.7	546	32.2
WA	103	8.4	137	8.1
Risk factors				
Pregnancy	39	3.2	13	0.8
Nursing home resident	68	5.5	107	6.3
Medical co-morbidities*	944	76.7	1,410	83.2
Chronic respiratory disease	446	36.2	743	43.9
Diabetes	260	21.1	350	20.7
Chronic liver disease	38	3.1	71	4.2
Immunosuppressed	217	17.6	452	26.7
Chronic cardiac disease	353	28.7	495	29.2
Chronic neurological disease	175	14.2	260	15.3
Chronic renal disease	116	9.4	193	11.4
Other characteristics				
Received 2012 trivalent seasonal vaccine	437/963	45.4	689/1,216	56.7
Days from onset of illness (median, Interquartile range)	3 (2, 5) days (n=1097)		4 (2, 7) days (n=1519)	
Admitted to intensive care unit	123	10.0	272	16.1
Treated with oseltamivir	665/1,120	59.4	264/1,465	18.0
In-hospital mortality	40/1,157	3.5	49/1,413	3.4

* Multiple co-morbidities possible

of cases were due to influenza A, with 213 (17%) due to influenza B. Influenza B was more common in patients admitted to Alice Springs Hospital in the Northern Territory, accounting for 59 of 83 (71%) admitted cases.

Of these 1,231 patients, 573 (47%) were more than 65 years of age, 99 (8%) were Indigenous Australians, 39 (3%) were pregnant and 944 (77%) had chronic co-morbidities (Table 1). Of the 963 (78%) patients where influenza vaccination status was ascertained, 437 (45%) had been vaccinated. Of all cases, 108 (9%) were initially admitted to ICU and a further 15 patients were subsequently transferred to ICU after initial admission to a general ward. Of the 1,157 patients where discharge status was known, 40 (4%) patients died during the hospital admission, of which 15 (38%) patients died in intensive care.

During the surveillance period, 1,694 control patients were enrolled; of which vaccination status was ascertained for 1,216 (72%). Based on the vaccination status of patients admitted with pneumonia prior to the commencement of the season, vaccination coverage was estimated at 71% in patients aged more than 65 years and 64% in patients with chronic comorbidities. In test negative controls during the season, vaccination coverage was estimated at 78% and 61% in the elderly and those with medical comorbidities respectively (Table 2).

The effectiveness of the 2012 trivalent seasonal influenza vaccine in reducing the risk of hospitalisation with influenza was estimated at 41% (95% CI: 28%, 51%, $P<0.001$) in the 2012 influenza season (Table 3). Vaccine effectiveness was estimated to be lower for elderly patients and in those with medical comorbidities (Figure 2).

Discussion

In 2012, FluCAN recorded more than 1,200 admissions to the 15 hospitals that participate in this surveillance network, in a year where the A/H3N2 strain predominated but the vaccine match to circulating strains was good.[8] As the hospitals

Table 2: Estimated vaccine coverage in pre-season pneumonia and test-negative groups

	Test negative acute respiratory illness*		Pre-season pneumonia†	
	n/N	%	n/N	%
All patients	690/1,216	56.7	222/370	60.0
Age >65 years	420/541	77.6	171/241	71.0
Medical comorbidities	397/506	78.5	159/217	73.3
No medical comorbidities	23/35	65.7	12/24	50.0
Age <65 years	270/675	40.0	51/129	39.5
Medical comorbidities	238/532	44.7	42/95	44.2
No medical comorbidities	32/143	22.4	9/34	26.5

* The 9 April to 31 October 2012 cohort.

† Radiologically confirmed pneumonia prior to influenza season

Figure 2: Estimated vaccine effectiveness against hospitalisation in all patients, in specified subgroups and against infection with influenza subtypes

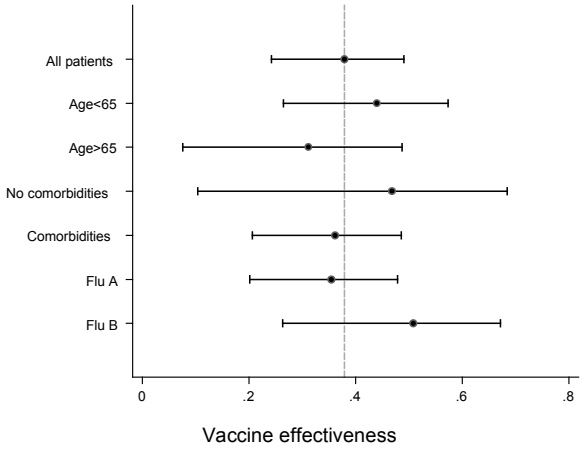

Table 3: Factors associated with hospitalisation with influenza compared with admission with non-influenza acute respiratory illnesses

Variable	Crude odds ratio	*P*	Adjusted odds ratio	*P*
Primary outcome				
Influenza vaccination	0.67 (0.56, 0.80)	<0.001	0.62 (0.51, 0.76)	<0.001
Potential confounders				
Age ≥ 65 years	1.13 (0.97, 1.32)	0.12	1.65 (1.34, 2.03)	<0.001
Medical comorbidities	0.70 (0.58, 0.85)	<0.001	0.65 (0.51, 0.83)	0.001
Pregnancy	4.99 (2.50, 9.95)	<0.001	6.05 (2.68, 13.66)	<0.001
Indigenous	1.04 (0.70, 1.54)	0.86	1.59 (0.89, 2.84)	0.12

represented in this network represent approximately 12% of the national hospital bed capacity, the cases detected here are likely to reflect approximately 10,000 admissions nationally. It is difficult to compare this with previous years as a different number of hospitals participated in 2010 and 2011, but it was noted that the age of patients was older than in the H1N1/09 dominant seasons in 2010 and 2011, and case numbers were higher.[9] It should be noted that the relative number of cases between jurisdictions does not reflect true influenza activity, due to differences in the number and size of sentinel hospitals in each jurisdiction.

The FluCAN surveillance system was established in 2009 to fill a gap between long-running, established surveillance systems based in the community and primary care, and mortality statistics.[8] We have previously demonstrated that sentinel surveillance broadly reflects population level data from notifications and ICU surveillance,[3] and had used these data to describe the clinical features of infection with the H1N1/09 strain,[10] and have previously estimated vaccine effectiveness against influenza in the 2010 and 2011 seasons.[4,11]

Influenza vaccine coverage has only been estimated infrequently in hospitalised patients in Australia.[12] An important issue is the degree to which these patients represent the population at risk of hospitalisation with respiratory illness. This study therefore estimated vaccine coverage in 2 distinct groups: patients with pneumonia prior to the influenza season, and in patients during the influenza season who had tested negative for influenza. Previous Australian studies that aggressively pursued a microbiological diagnosis have only found that influenza was implicated in only 7% of patients with pneumonia, and this is likely to be much lower outside the influenza season,[13] suggesting that influenza vaccine is not likely to be protective against pneumonia prior to the influenza season. The study found that the estimates of vaccine coverage were consistent in both groups. Self-reported vaccination status has been shown to slightly overestimate true influenza vaccination status.[12,14,15] Community-based estimates of influenza vaccine coverage, last reported in 2009, have shown that the proportion vaccinated has remained stable in periodic surveys since 2002.[16]

The effectiveness of influenza vaccines in preventing influenza has most commonly been considered in the primary care setting. A systematic review which included studies where PCR confirmation was the outcome measure has suggested that vaccine effectiveness against influenza presenting to primary care was 59%.[17] In that review, it was found that most randomised controlled trials enrolled healthy adults or children, but a smaller number of observational studies have specifically examined vaccine effectiveness in the elderly. Only 1 study was identified in this review that estimated vaccine effectiveness against hospitalisation,[18] and we are aware of a few other studies published since.[4,11,19,20] In general, results from these studies have been consistent and have shown that protection against hospitalisation ranges from 49%–61%.[4,18,19] We note that estimated vaccine effectiveness was lower in patients with comorbidities and in the elderly but this difference was not statistically significant.

There are several limitations to this study. Despite the diagnosis of influenza having both infection control and therapeutic implications in hospital, it is likely that not all patients with influenza are diagnosed. Additionally, some patients with acute respiratory infections due to influenza may test negative due to delayed presentation or secondary bacterial pneumonia after clearance of the primary infection with influenza. There also may be unmeasured confounding of the association between vaccination and admission with influenza, a bias that has plagued studies of influenza mortality.[21] In a sentinel surveillance system it is not possible to define the denominator population and therefore the true incidence of hospitalisation. Although previous studies have suggested that self-reported influenza vaccination status only slightly overestimates vaccination coverage, we have not validated this in our population.[12,14,15] In particular, differential recall bias between cases and control patients may bias estimates of vaccine effectiveness. Finally, it is difficult to reconcile studies based on diagnosed influenza with those that indirectly estimate the burden of disease from excess seasonal hospitalisations or mortality.[22]

In summary, this study detected a large number of hospital admissions with confirmed influenza in a national observational study in 2012. Vaccine coverage was low in at-risk groups, particularly non-elderly patients with medical comorbidities. The results suggest that the seasonal influenza vaccine was moderately protective against hospitalisation with influenza.

Acknowledgements

We thank study staff at all participating sites for their contributions, including at The Alfred Hospital (Jill Garlick, Janine Roney, Leah Christie), Princess Alexandra Hospital (Tina Collins), Monash Medical Centre (Lynn Houghton and Ainsley Swanson), The Canberra Hospital (Claire Chatwin), Royal Adelaide Hospital (Catriona Doran, Sarah Richards, Mary McAlister, Jenny McGrath, Louise Milazzo, Elizabeth Lyne, A/Prof Hubertus Jersmann, Dr Shanka Karunarathne, Dr Brendan Doherty, Dr Dien

Dang, Dr Hugh Greville), Cairns Base Hospital (Sue Richmond, Sue Dixon, Dr Stephen Vincent), Geelong Hospital (Julie Heath), John Hunter Hospital (Lorissa Hopkins, Douglas Dorahy), Royal Melbourne Hospital (Michelle Thompson, Lovisha Dousha), Royal Perth Hospital (Ellen MacDonald, Sophie Damianopoulos, Julie Honeyman), Royal Hobart Hospital (Susan Wagg, Carol Phillips), and Westmead Hospital (Delene Assam, June Kelly).

Author details

Allen C Cheng[1]
Simon Brown[2,3]
Grant Waterer[2,3]
Mark Holmes[4,5]
Sanjaya Senenayake[6,7]
N Deborah Friedman[8]
Saliya Hewagama[9]
Graham Simpson[10]
Peter Wark[11,12]
John Upham[13,14]
Tony Korman[15]
Dominic Dwyer[16,17]
Richard Wood-Baker[18]
Louis Irving[19,20]
Simon Bowler[21]
Tom Kotsimbos[1]
Paul Kelly[22]

1. Alfred Health; Monash University, Melbourne, Victoria
2. University of Western Australia, Perth, Western Australia
3. Royal Perth Hospital, Perth, Western Australia
4. Royal Adelaide Hospital, Adelaide, South Australia
5. University of Adelaide, Adelaide, South Australia
6. Australian National University, Acton, Australian Capital Territory
7. The Canberra Hospital, Garran, Australian Capital Territory
8. Barwon Health, Geelong, Victoria
9. Alice Springs Hospital, Alice Springs, Northern Territory
10. Cairns Base Hospital, Cairns, Queensland
11. University of Newcastle, Newcastle, New South Wales
12. John Hunter Hospital, Newcastle, New South Wales
13. Princess Alexandra Hospital, Brisbane, Queensland
14. University of Queensland, Brisbane, Queensland
15. Monash Medical Centre, Melbourne, Victoria
16. University of Sydney, Sydney, New South Wales
17. Westmead Hospital, Sydney, New South Wales
18. University of Tasmania, Hobart, Tasmania
19. Royal Melbourne Hospital, Melbourne, Victoria
20. University of Melbourne, Melbourne, Victoria
21. Mater Hospitals, Brisbane, Queensland
22. ACT Health Directorate, Canberra, Australian Capital Territory

Corresponding author: A/Prof Allen Cheng, Department of Epidemiology and Preventive Medicine, Monash University, Commercial Road, Melbourne VIC 3004. Email: allen.cheng@monash.edu

References

1. Reed C, Angulo FJ, Swerdlow DL, Lipsitch M, Meltzer MI, Jernigan D, et al. Estimates of the prevalence of pandemic (H1N1) 2009, United States, April–July 2009. *Emerg Infect Dis* 2009 15(12):2004–2007.
2. Australian Technical Advisory Group on Immunisation. *The Australian Immunisation Handbook*. Canberra: Commonwealth of Australia; 2013.
3. Kelly PM, Kotsimbos T, Reynolds A, Wood-Baker R, Hancox B, Brown SGA, et al. FluCAN 2009: initial results from sentinel surveillance for adult influenza and pneumonia in eight Australian hospitals. *Med J Aust* 2011;194(4):169–174.
4. Cheng AC, Kotsimbos AT, Kelly H, Irving L, Bowler S, Brown S, et al. Effectiveness of H1N1/09 monovalent and trivalent influenza vaccines against hospitalization with laboratory-confirmed H1N1/09 influenza in Australia: a test-negative case control study. *Vaccine* 2011;29(43):7320–325.
5. Smith PG, Rodrigues LC, Fine PE. Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies. *Int J Epidemiol* 1984;13(1):87–93.
6. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol* 1982;116(3):547–553.
7. Rodrigues L, Kirkwood BR. Case-control designs in the study of common diseases: updates on the demise of the rare disease assumption and the choice of sampling scheme for controls. *Int J Epidemiol* 1990;19(1):205–213.
8. Australian Government Department of Health and Ageing. Australian Influenza Surveillance Summary Report: 12 October, 2012. Accessed on 30 January 2013. Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/cda-surveil-ozflu-flucurr.htm#four
9. Cheng AC. Hospitalisation with confirmed influenza in a sentinel surveillance system in 2010 and 2011. *Med J Aust* 2012;197(4):217.
10. Cheng AC, Kotsimbos T, Reynolds A, Bowler S, Brown SG, Hancox RJ, et al. Clinical and epidemiological profile of patients with severe H1N1/09 pandemic influenza in Australia and New Zealand: an observational cohort study. *BMJ Open* 2011;1(1): e000100.
11. Cheng AC, Holmes M, Irving LB, Brown SG, Waterer GW, Korman TM, et al. Influenza vaccine effectiveness against hospitalisation with confirmed influenza in the 2010–11 seasons: A test-negative observational study. PLoS ONE. 2013;8(7):e68760.
12. Skull SA, Andrews RM, Byrnes GB, Kelly HA, Nolan TM, Brown GV, et al. Validity of self-reported influenza and pneumococcal vaccination status among a cohort of hospitalized elderly inpatients. *Vaccine* 200715;25(25):4775–4783.
13. Charles PG, Whitby M, Fuller AJ, Stirling R, Wright AA, Korman TM, et al. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. *Clin Infect Dis* 200815;46(10):1513–1521.

14. Hutchison BG. Measurement of influenza vaccination status of the elderly by mailed questionnaire: response rate, validity and cost. *Can J Public Health* 1989;80(4):271–275.

15. Mangtani P, Shah A, Roberts JA. Validation of influenza and pneumococcal vaccine status in adults based on self-report. *Epidemiol Infect* 2007;135(1):139–143.

16. Australian Institute of Health and Welfare. 2009 Adult Vaccination Survey: Summary Results. Canberra: Australian Institute for Health and Welfare, 2011 Contract No.: Cat. no. PHE 135.

17. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2011;12(1):36–44.

18. Talbot HK, Griffin MR, Chen Q, Zhu Y, Williams JV, Edwards KM. Effectiveness of seasonal vaccine in preventing confirmed influenza-associated hospitalizations in community dwelling older adults. *J Infect Dis* 2011;203(4):500–508.

19. Puig-Barbera J, Diez-Domingo J, Arnedo-Pena A, Ruiz-Garcia M, Perez-Vilar S, Mico-Esparza JL, et al. Effectiveness of the 2010–2011 seasonal influenza vaccine in preventing confirmed influenza hospitalizations in adults: a case–case comparison, case-control study. *Vaccine* 2012;30(39):5714–5720.

20. Puig-Barbera J, Arnedo-Pena A, Pardo-Serrano F, Tirado-Balaguer MD, Perez-Vilar S, Silvestre-Silvestre E, et al. Effectiveness of seasonal 2008–2009, 2009–2010 and pandemic vaccines, to prevent influenza hospitalizations during the autumn 2009 influenza pandemic wave in Castellon, Spain. A test-negative, hospital-based, case-control study. *Vaccine* 2010;28(47):7460–7467.

21. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet Infect Dis* 2007;7(10):658–666.

22. Newall AT, Wood JG, Macintyre CR. Influenza-related hospitalisation and death in Australians aged 50 years and older. *Vaccine* 2008;26(17):2135–2141.