The burden of childhood influenza in a tertiary paediatric setting

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Abstract

Influenza is usually considered a mild winter-time illness but can be associated with a range of serious complications. We undertook a retrospective medical record review to study the impact of admissions of children with laboratory-confirmed influenza to The Children's Hospital at Westmead, Sydney, during 2007. One hundred and twenty-two children were identified, representing 530 hospital admission days. There was no clearly documented evidence of influenza vaccination for any patient eligible for vaccination. Fever (97.5%) and cough (69.7%) were the most frequent manifestations. Admissions occurred almost entirely between June and September with a peak in July (n=61, 50%). Two-thirds of the children were aged less than 2 years (median 1.5 years). Most (61.5%) had an underlying chronic medical disorder. Lumbar puncture was performed in 28 (23%) children, mostly infants aged less than 3 months (n=18). Antibiotics were commonly prescribed (67.2%), but use of available influenza-specific antiviral agents was uncommon (13.1%). The nosocomial infection rate was 9.8% and the clinical staff vaccination rate was low (less than 30%). Pneumonia was the most common complication (12.3%). No influenza-related deaths occurred. Influenza in young children poses a significant burden to health care services, tertiary admissions representing the tip-of-the-iceberg. Vaccination rates are inappropriately low in both eligible patients and hospital clinical staff. Early 'point of care' testing, use of influenza-specific antiviral agents, and extension of current vaccination schedules to include all children aged six to 23 months could considerably reduce over-investigation, unnecessary use of antibiotics and the health care impact of influenza. *Commun Dis Intell* 2009;33:209–215.

Keywords: influenza, child, hospitalisation, immunisation

Introduction

Influenza is a common illness of childhood and the burden of disease is highest among pre-school children[1,2] with attack rates up to 20%–30% each year in child care settings.[3] There is a wide range of symptom severity from minor respiratory illness to life-threatening multi-system complications and death.[4–13] Children act as a major viral reservoir during epidemics, transmitting infection to both their families and the community. Increasingly, the health care and wider socioeconomic costs of influenza are being recognised.[14,15] Economic modelling in the United States of America (USA) estimates the annual health care bill at $87.1 billion (CI $47.2–$149.5).[16] Australian data show that 82 cases per 100,000 hospitalisations and 0.2 per 100,000 deaths can be attributed to influenza in children aged less than 5 years.[17]

The current Australian Immunisation Schedule recommends influenza vaccination only for children at high risk for influenza and its complications; not routinely for all children.[18] This is in contrast to the USA where the American Advisory Committee on Immunization Practices (ACIP) recommends that all children aged 6 months to 18 years are immunised annually.[19] A recent systematic review by Matheson et al[20] confirmed the beneficial role of the neuraminidase inhibitors (Zanamivir and Oseltamivir) for treatment and probable prevention of influenza complications in children.

What is already known on this subject?

Influenza is a common infectious disease of childhood, widely regarded as a mild illness.

In Australia influenza vaccination is recommended only for children at high-risk of complications.

Point of care testing and influenza-specific antiviral agents are available and may reduce the annual impact of influenza on health care services and the wider community.

What this study adds

Influenza is a frequent cause of both hospital and intensive care admission: over 100 children admitted to one tertiary hospital in a single season, 10% required intensive care and over 500 hospital bed-days were occupied.

A large proportion of children did not have a risk factor and therefore were not eligible for influenza vaccination, so consideration of universal vaccination is required for more effective prevention.

Point of care testing and influenza-specific antiviral agents are rarely used and thus many children are managed with unnecessary antibiotics and invasive procedures such as lumbar puncture.

The 2007 influenza season was unusually severe with a number of paediatric deaths reported and higher than expected rates of hospitalisation, both in the USA[21] and Australia (www9.health.gov.au/cda/Source/Rpt_4.cfm). The Children's Hospital at Westmead is a large, tertiary paediatric teaching hospital in Sydney, Australia, with a bed capacity of 339 and serving a population of 549,760 children aged less than 16 years.[22] Our objective was to determine the burden of influenza admissions on this hospital during the 2007 influenza season.

Method

A retrospective medical record review was undertaken of all children admitted to the hospital with laboratory confirmed influenza A or B between 1 January and 31 December 2007, inclusive. Patients were identified by reviewing virology records. Data extracted from the records included patient characteristics, clinical presentation, underlying medical conditions, investigations, management and outcome.

A laboratory-confirmed case was defined as any child with influenza virus identified by direct immunofluorescence (DFA) from a nasopharyngeal aspirate (NPA). Samples negative on the initial DFA screen are subsequently cultured but culture-positive patients were not included in our study. NPA specimen testing is available on a daily basis and results available the same day, including weekends, during peak months, June to September.

Hospital infection control policy requires either isolation or co-location of children testing positive for influenza; however, it is possible that some DFA negative cases, which were not isolated, had influenza not yet confirmed by culture, which takes several days.

Nosocomial infection was conservatively defined as the onset of signs and symptoms at greater than 72 hours after admission to hospital. Fever was defined as an auxiliary temperature greater than 37.5°C, dyspnoea as increased respiratory effort or oxygen saturation less than 95%, and encephalopathy as an altered state of consciousness. Pneumonia was recorded if it was confirmed by chest radiograph. Secondary bacterial infections were defined by a positive culture from an appropriate clinical specimen. The remaining clinical manifestations were recorded as they appeared in the medical record.

Daily bed costs were estimated at $420 for a general paediatric bed and $1,250 for a paediatric intensive care unit bed. These figures do not include any additional costs e.g. medications, pathology, imaging and allied health costs.

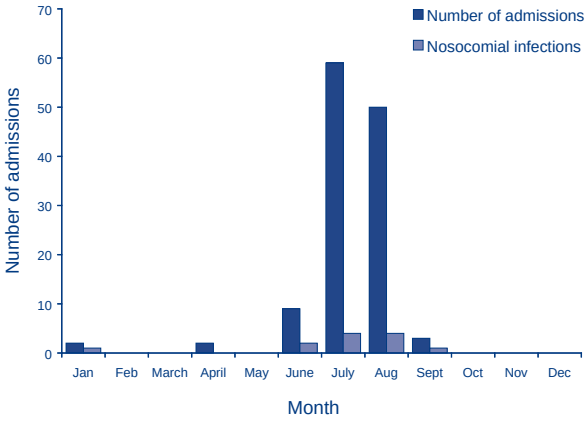
Ethical approval for this study was obtained from the Children's Hospital at Westmead Research Ethics committee (MR 2007-10-08). Data were analysed using descriptive statistics (SPSS v15).

Results

Of 155 influenza cases identified from virology records, 122 were admitted to hospital or were in hospital for another reason when they acquired influenza. Most children (119) had influenza A (H3N2) of the Brisbane/10/2007-like type and only three had influenza B: 1 Florida/4/2006-like type and 2 Malaysia/2506/2004-like types.

The majority (95.6%) of admissions occurred during the winter months, June to September (Figure 1), with a striking peak of admissions in July (n=61, 50%).

Figure 1: Seasonal variation in admissions for influenza and nosocomial infections



Patient characteristics

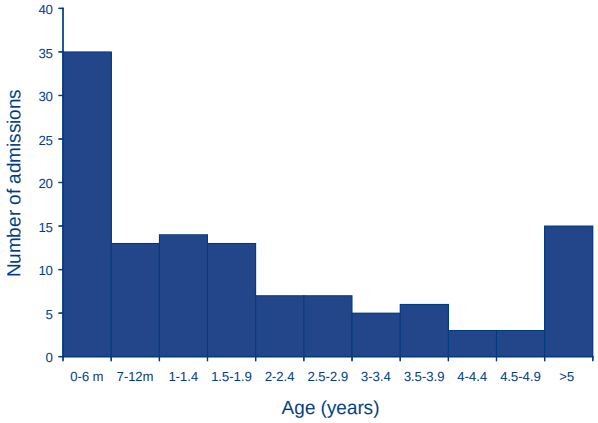
Of the 122 children admitted to hospital, 75 (61.5%) were aged less than 2 years and almost 35 (30%) were aged less than 6 months (Figure 2). The median age was 1.4 years (range: 1 week to 19.4 years) and 69 (56.6%) were male. Two patients identified as Aboriginal or Torres Strait Islander.

Influenza vaccination status was clearly recorded for only 1 unvaccinated child. There were no readily retrievable and clearly documented instances of prior influenza vaccination recorded in the other 121 cases.

Pre-existing chronic medical conditions were common (61.5%). Overall, 17% of children had primary or secondary immunodeficiencies, mostly associated with chemotherapy. Other chronic conditions included respiratory (n=12; 9.8%), neurological (n=8; 6.6%), neuromuscular (n=6;

4.9%), cardiac (n=5; 4.1%), endocrine/metabolic (n=4; 3.3%), gastrointestinal (n=3; 2.5%), renal (n=3; 2.5%); and haematological disorders (n=1; 0.8%). Seven babies were born preterm but none had been diagnosed with chronic lung disease or any other ongoing condition. Six other cases had other chronic complex medical disorders not categorised above. The proportion of children with chronic conditions increased from 20% in babies aged less than 6 months, to 55% in children aged between 6 months and 5 years and to 80% in children aged 5 years or older.

Figure 2: Age distribution of children admitted with influenza, 2007, by age group



Clinical presentation

Three-quarters of children first presented to medical services within 48 hours of the onset of symptoms, to either a primary health care setting or a hospital emergency department. Twelve patients required intensive care and nine of these needed ventilatory support for pneumonia, shock or apnoea. Three patients required emergency retrieval from another New South Wales hospital to our intensive care unit.

The main clinical manifestations at presentation were fever (mean temperature 38.8°C) and evidence of either an upper or lower respiratory tract infection indicated by cough, coryza or dyspnoea (Table 1). Only one half of cases (49.2%) had the triad of fever, cough and coryza and 14 (11.5%) presented with fever alone. One patient had dyspnoea alone whilst two were asymptomatic and diagnosed from a routine NPA following an inter-hospital transfer. Other presenting symptoms included malaise, vomiting, petechial rash and seizures (Table 1). Two of the patients with seizures were subsequently diagnosed with encephalopathy.

Nosocomial infection occurred in 12 (9.8%) patients (Figure 1). Five of these infections occurred

Table 1: Patient characteristics and clinical presentation

Patient characteristics (n=122)	n	%
Male	69	56.6
Median age (range)	1.4 (0.02 to 19.4)	
ATSI*	2	1.6
Influenza A	119	97.5
Immunocompromised	21	17.2
Other chronic disorder	54	44.3
Nosocomial infection	12	9.8
Documented influenza vaccination	1	0.08
Clinical presentation		
Fever	119	97.5
Cough	85	69.7
Coryza	79	64.8
Dyspnoea	29	23.8
Fever, cough and coryza	60	49.2
Fever alone	14	11.5
Other symptoms		
Malaise	31	25.4
Vomiting	16	13.1
Petechial rash	13	10.7
Mottled	8	6.6
Diarrhoea	8	6.6
Seizure	7	5.7
Headache	6	4.9
Sore throat	5	4.1
Apnoea	4	3.3
Myalgia	3	2.5

* Aboriginal or Torres Strait Islander.

in children admitted to 1 ward but there was no temporal association among these cases (Figure 1). The influenza vaccination rate for clinical staff at the Children's Hospital at Westmead for 2007 was estimated at 32%.

Investigations and management

Full blood count was performed at presentation in 113 (92.6%) admissions. The median total white cell count and neutrophil count were within the normal range (8.6 and 4.4 $*10^9$/L respectively). C-reactive protein was measured in 21 (17.2%) cases and the median C-reactive protein was mildly elevated at 21.7 mg/L (normal range 0–10 mg/L). Creatine kinase (measured in 2 patients with myalgia) was 223 in one and over 200,000 u/L (24–215u/L) in the other, and was associated with rhabdomyolysis and acute renal failure in the latter case.

Lumbar puncture was performed as an initial investigation in 28 (23%) children: none had a positive culture from the cerebrospinal fluid. The majority (18 of 28; 64%) of patients undergoing lumbar puncture were aged 3 months or less. Cerebral imaging was uncommon (5 occasions) and in only 1 child did the scan show new changes, consistent with a diagnosis of acute necrotising encephalopathy of childhood.

Antibiotics were the most common class of medication prescribed and two-thirds of patients received either oral or intravenous antibiotics. Third generation cephalosporins were the most commonly prescribed antibiotics (Table 2). Children most likely to receive antibiotics were infants aged under 3 months and presenting with fever (n=16). The documented reasons for commencing antibiotics are outlined in Table 2. In 5 cases there was no clearly documented rationale for starting antibiotics.

Supplemental oxygen was required by 23% of children: all presented with dyspnoea, were desaturated in room air and diagnosed with either pneumonia or bronchiolitis.

Overall, the prescription of specific anti-influenza viral agents was uncommon (n=16; 13.1%), except in the oncology and bone marrow transplant (BMT) setting where Oseltamivir was prescribed in 11 patients. Only 5 non-oncology/BMT patients received antiviral medication.

Complications and outcome

A wide range of complications occurred, most commonly pneumonia (n=15; 12.3%), requiring ventilatory support in 6 patients (Table 3). Other complications included encephalopathy (2) and rhabdomyolysis with associated acute renal failure (1).

Four children had co-infection with pertussis (confirmed by polymerase chain reaction) and two had co-infection with respiratory syncytial virus (RSV) on NPA. One patient had a positive blood culture (enterococcus) from an infected central venous access port, unrelated to the influenza illness.

The overall length of hospital stay ranged from 1 day to 50 days (median stay 2 days). The median length of stay for ICU patients was 2 days (range 1–25 days).

No deaths were attributed to influenza in our hospital during 2007. Only 1 child had residual physical problems following influenza due to the requirement for multiple fasciotomies for compartment syndrome, secondary to severe rhabdomyolysis, but was making good progress at follow-up.

Table 2: Investigations and management

Investigations	n	Median (range)
WCC (*10^9/L)	113	8.6 (0.5–57.9)
Neutrophils (*10^9/L)	113	4.4 (0.2–47.5)
CRP (mg/L)	21	21.7 (0–500)
		%
Lumbar puncture	28	22.9
Positive culture	Nil	N/A
Age <3 months	18	64.0
Age 3–6 months	3	10.7
Age 6–24 months	5	17.9
Age >24 months	2	7.1
CT head	5	4.1
New CT findings	1	0.8
Management		
Oxygen	28	23.0
Antibiotics	82	67.2
Oral	8	6.6
Intravenous	74	60.6
Antibiotic indication		
Fever < 3 months	16	13.1
Immunocompromised	15	12.3
Pneumonia	14	11.5
Petechial rash	10	8.2
Shock (fluid bolus)	8	6.6
General practitioner initiated	5	4.1
No clear indication	5	4.1
Raised WCC	3	2.5
Other indication	14	11.5
Antibiotic usage	82	67.2
Cefotaxime/ceftriaxone	25	20.5
Gentamicin	23	18.9
Ampicillin	20	16.4
Benzylpenicillin	16	13.1
Oncology 1st line*	13	10.7
Other	17	13.9
Antiviral agent (Oseltamivir)	16	13.1
Oncology	11	9.0
Other indications†	5	4.1

WCC=white cell count, CRP=C-reactive protein, CT=computerised tomography, N/A=not applicable

* Timentin, gentamicin, cephalothin.

† Other indications = post liver transplantation (1 case), steroid use for glomerulonephritis (1 case), metabolic disorder (2 cases) and general patient (1 case).

Table 3: Complications, co-infection and outcome

Complications*	n	%
Pneumonia	15	12.3
Shock (requiring fluid bolus)	13	10.7
Ventilated (IPPV+CPAP)	9	7.4
Bronchiolitis	8	6.6
Rapid deterioration	4	3.3
Inotrope use	3	2.5
Seizures	3	2.5
Clotting abnormality	3	2.5
Encephalopathy	2	1.6
Myositis	2	1.6
Co-infection		
Pertussis (PCR)	4	3.3
RSV	2	1.6
Coliform UTI	2	1.6
Strep pyogenes T/S	1	0.8
Pseudomonas sputum	1	0.8
Enterobacter CVL	1	0.8
Outcome		
Discharged alive	122	100
Associated disability	1	0.8
Length of stay	**Median (range)**	
Hospital	2 (1–50)	
PICU (12 patients)	2 (1–25)	

IPPV=intermittent positive pressure ventilation, CPAP=continuous positive airway pressure, RSV=Respiratory syncytial virus, T/S= throat swab, CVL=central venous line, UTI=urinary tract infection, PICU=paediatric intensive care unit, PCR=polymerase chain reaction.

* Some patients had more than 1 complication; complications occurring in only 1 patient included rhabdomyolysis, acute renal failure, compartment syndrome, thrombocytopenia, hypoglycaemia and pansinusitis.

Discussion

We have demonstrated the considerable impact of laboratory-confirmed influenza in children admitted to a tertiary children's hospital in Sydney, Australia. This is the largest reported case series we know of from a single tertiary paediatric centre during 1 influenza season, and equates to a total of 530 hospital admission days (including 52 intensive care admission days). This imposes a significant burden on hospital resources, equivalent to an estimated $264,000 AUD in direct bed costs alone. Our data are likely to underestimate the true burden of hospitalisation as in some children the disease will go unrecognised and we have no estimates of indirect costs such as lost productivity due to parental work absences.

The main burden of influenza in our cohort was among children under 2 years of age. Clinical manifestations were mainly respiratory, but only one half presented with the triad of fever, cough and coryza. A diagnosis of influenza should also be considered in the context of fever alone or fever plus 1 respiratory symptom. Influenza-related complications occurred in almost one-third of patients, with pneumonia being the most common. Influenza-associated encephalopathy was diagnosed in 2 patients and is a rare but well described serious complication.[11,23,24] Severe rhabdomyolysis[4,25] leading to acute renal failure and compartment syndrome (necessitating fasciotomies) is also a rare but well recognised serious complication, and occurred in 1 patient. No deaths were attributed to influenza in 2007, in contrast to 2003 when 3 deaths occurred in our hospital.[12]

Despite evidence that the early use of anti-influenza medication reduces the duration of illness and influenza complications, particularly otitis media,[20] only 13.1% of eligible children in our series received anti-influenza drugs. This suggests we are presently omitting a proven therapy. Children most likely to receive anti-influenza drugs were immunocompromised, mainly in the oncology and BMT clinical setting. Currently in Australia, Oseltamivir (Tamiflu™) is licensed for use in children aged 1 year or over by the Therapeutic Goods Administration of Australia, leaving 48 (39.3%) children in our series ineligible for treatment. There is a need for clinical trials to evaluate the role of anti-influenza medications in infants. No resistance to Oseltamivir of influenza A isolates was reported in Australia during winter 2007. This is in contrast to the growing resistance to Oseltamivir in 2009 isolates in the Northern Hemisphere, further emphasising the importance of vaccination.

'Point of care testing' (POCT) or 'near-patient' testing allows for the rapid diagnosis and treatment of influenza in the primary health care setting or at the inpatient's bedside.[26] Its use remains uncommon: only 1 patient in our series was thus diagnosed. This allowed treatment with an antiviral agent and potentially interrupted transmission of the disease. The majority of children in our series (77%) had first presented to medical services (usually their GP) within 48 hours of onset of symptoms and early diagnosis would have allowed initiation of antiviral treatment and potentially prevented admission in age-eligible patients.

Although influenza is known to predispose to secondary bacterial infection[27–30] there were no documented significant bacterial infections in this series. Despite this, over two-thirds of children received antibiotics, mainly third generation cephalosporins. In the absence of rapid POCT for influenza, there was a clear rationale for the instigation of antibiotics in all but five of the cases.

Free universal influenza vaccination of young children is not included on the National Immunisation Program[18] in Australia, although children with chronic medical problems are eligible. Documentation of the influenza vaccination status of eligible children in our study was poor; it was clearly documented for only 1 child. The Australian Childhood Immunisation Register does not collect information about influenza vaccinations in children because this vaccine is not on the Australian Immunisation Schedule. Nevertheless, it is noteworthy that amongst children requiring intensive care in our series, only three of 12 were eligible for vaccination due to a pre-existing chronic condition. The remainder were either previously healthy or aged less than 6 months and thus ineligible.[18] Overall, 28.7% of children were aged less than 6 months and not eligible for vaccination, due to the limited immunogenicity of the vaccine documented in this age group.[31]

A relatively high nosocomial influenza infection rate (9.8%) was found[32–34] and five of these cases occurred in 1 ward. During 2007 the hospital clinical staff influenza vaccination rate was estimated at only 32%. This is likely to be an overestimate as there were 431 recorded instances of hospital-based influenza vaccination out of a total of 1,346 full-time-equivalent medical, nursing and allied health staff and this does not account for the high proportion of part-time workers. This is despite a high-visibility staff vaccination campaign and a mobile staff vaccination clinic. Increased staff immunisation uptake along with stricter adherence to hand-hygiene may reduce this nosocomial infection rate. The possible impact of co-locating NPA negative, but true influenza, cases with other children on nosocomial infection rates is uncertain but potentially significant.

Current practice in the USA is for all children aged 6 months to 18 years to be offered vaccination annually against influenza.[19] Milne et al[12] and Isaacs[35] called for a similarly inclusive schedule to be adopted in Australia and our study adds further evidence to support this. Extending the immunisation schedule to include all children aged 6–23 months[35] would reduce the burden of influenza in the community and on health care services. Meanwhile, in view of the high proportion of children with medical co-morbidities admitted to hospital due to influenza it is important that health professionals involved in the care of such children ensure that this vulnerable group are immunised annually.

The heavy burden of influenza admissions to a tertiary paediatric centre is well demonstrated by this retrospective study, representing the tip-of-the-iceberg of the total number of community cases. Indeed, the number of admissions is most likely an underestimate as some cases will go unrecognised. A high nosocomial infection rate stresses the importance of annual staff influenza vaccination and hand hygiene. The development of treatment protocols and education of health professionals is needed to optimise the diagnosis and treatment of influenza, to reduce the use of antibiotics, over-investigation and to increase vaccination and the use of influenza-specific antiviral agents in eligible children. Economic evaluation of an extended immunisation schedule, point-of-care testing for influenza and routine use of anti-influenza medication in eligible patients is now necessary to help inform health policy.

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References

1. Ploin D, Gillet Y, Morfin F, Fouilhoux A, Billaud G, Liberas S, et al. Influenza burden in febrile infants and young children in a pediatric emergency department. *Pediatr Infect Dis J* 2007;26(2):142–147.
2. Smitherman HF, Caviness AC, Macias CG. Retrospective review of serious bacterial infections in infants who are 0 to 36 months of age and have influenza A infection. *Pediatrics* 2005;115(3):710–718.

3. Iskander M, Booy R, Lambert S. The burden of influenza in children. *Current Opinion Infect Dis* 2007;20(3):259–263.
4. Agyeman P, Duppenthaler A, Heininger U, Aebi C. Influenza-associated myositis in children. *Infection* 2004;32(4):199–203.
5. Aymard M, Valette M, Luciani J, Sentinel Physicians from the Grippe et Infections Respiratoires Aigües Pédiatriques Network. Burden of influenza in children: preliminary data from a pilot survey network on community diseases. *Pediatr Infect Dis J* 2003;22(10:Suppl):S211–214.
6. Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ, et al. Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med* 2005;353(24):2559–2567.
7. Centers for Disease Control and Prevention. Update: influenza-associated deaths reported among children aged <18 years--United States, 2003–04 influenza season. *MMWR Morb Mortal Wkly Rep* 2004;52(51–52):1254–1255.
8. Grose C. The puzzling picture of acute necrotizing encephalopathy after influenza A and B virus infection in young children. *Pediatr Infect Dis J* 2004;23(3):253–254.
9. Heikkinen T, Silvennoinen H, Peltola V, Ziegler T, Vainionpaa R, Vuorinen T, et al. Burden of influenza in children in the community. *J Infect Dis* 2004;190(8):1369–1373.
10. Kappagoda C, Isaacs D, Mellis C, Peat J, De Silva L, O'Connell A. Critical influenza virus infection. *J Paediatr Child Health* 2000;36(4):318–321.
11. Maricich SM, Neul JL, Lotze TE, Cazacu AC, Uyeki TM, Demmler GJ, et al. Neurologic complications associated with influenza A in children during the 2003–2004 influenza season in Houston, Texas. *Pediatr* 2004;114(5):e626–e633.
12. Milne BG, Williams S, May ML, Kesson AM, Gillis J, Burgess MA. Influenza A associated morbidity and mortality in a paediatric intensive care unit. *Commun Dis Intell* 2004;28(4):504–509.
13. Poehling KA, Edwards KM, Weinberg GA, Szilagyi P, Staat MA, Iwane MK, et al. The underrecognized burden of influenza in young children. *N Engl J Med* 2006;355(1):31–40.
14. Keren R, Zaoutis TE, Saddlemire S, Luan XQ, Coffin SE. Direct medical cost of influenza-related hospitalizations in children. *Pediatr* 2006;118(5):e1321–e1327.
15. Tsolia MN, Logotheti I. Papadopoulos NG, Mavrikou M, Spyridis NP, Drossatou P, et al. Impact of influenza infection in healthy children examined as outpatients and their families. *Vaccine* 2006;24(33–34):5970–5976.
16. Molinari NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007;25(27):5086–5096.
17. Brotherton J, Wang H, Schaffer A, Quinn H, Menzies R, Hull B, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. *Commun Dis Intell* 2007;31:Suppl-152.
18. National Health and Medical Research Council. 3.9 Influenza. *The Australian Immunisation Handbook*. 2007. National Health and Medical Research Council; Canberra: pp160–169.
19. Fiore AE, Shay DK, Haber P, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. *MMWR Morb Mortal Wkly Rep* 2007;56(RR–6):1–54.
20. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev* 2007;(1):CD002744.
21. Centers for Disease Control and Prevention. Update: influenza activity--United States and worldwide, May 20–September 15, 2007. *MMWR Morb Mortal Wkly Rep* 2007;56(38):1001–1004.
22. Childrens Hospital at Westmead. Demographic and child health profile. The Children's Hospital at Westmead Healthcare Services Plan 2007–2011. 2008: pp16–18.
23. Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. *Acta Neurol Scand* 2007;186:45–56.
24. Newland JG, Laurich VM, Rosenquist AW, Heydon K, Licht DJ, Keren R, et al. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr* 2007;150(3):306–310.
25. Augustin SL, Horton S, Thuys C, Bennett M, Claessen C, Brizard C. The use of extracorporeal life support in the treatment of influenza-associated myositis/rhabdomyolysis. *Perfusion* 2006;21(2):121–125.
26. Poehling KA. Zhu Y. Tang YW. Edwards K. Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses. *Archives Pediatr Adolescent Med* 160(7):713–718, 2006.
27. Hageman JC, Uyeki TM, Francis JS, Jernigan DB, Wheeler JG, Bridges CB, et al. Severe community-acquired pneumonia due to *Staphylococcus aureus,* 2003–04 influenza season. *Emerg Infect Dis* 2006;12(6):894–899.
28. Jensen ES, Lundbye-Christensen S, Samuelsson S, Sorensen HT, Schonheyder HC. A 20-year ecological study of the temporal association between influenza and meningococcal disease. *Eur J Epidemiol* 2004;19(2):181–187.
29. O'Brien KL, Walters MI, Sellman J, Quinlisk P, Regnery H, Schwartz B, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. *Clin Infect Dis* 2000;30(5):784–789.
30. Podewils LJ, Liedtke LA, McDonald LC, Hageman JC, Strausbaugh LJ, Fischer TK, et al. A national survey of severe influenza-associated complications among children and adults, 2003–2004. *Clin Infect Dis* 2005;40(11):1693–1696.
31. Neuzil KM, Edwards KM. Influenza vaccines in children. [Review] [52 refs]. *Seminars Pediatr Infect Dis* 2002;13(3):174–181.
32. Maltezou HC, Drancourt M. Nosocomial influenza in children. [Review] [71 refs]. *J Hosp Infect* 2003;55(2):83–91.
33. Slinger R, Dennis P. Nosocomial influenza at a Canadian pediatric hospital from 1995 to 1999: opportunities for prevention. *Infect Control Hosp Epidemiol* 2002;23(10):627–629.
34. Evans ME, Hall KL, Berry SE. Influenza control in acute care hospitals. *Am J Infect Control* 1997;25(4):357–362.
35. Isaacs D. Should all Australian children be vaccinated against influenza? Questions of cost-effectiveness, vaccine efficacy and feasibility are yet to be answered. *Med J Aust* 2005;182(11):553–554.