

Management of upper respiratory tract infections in children

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To cite this article: MF Cotton, S Innes, H Jaspan, A Madide & H Rabie (2008) Management of upper respiratory tract infections in children, *South African Family Practice*, 50:2, 6-12, DOI: [10.1080/20786204.2008.10873685](https://doi.org/10.1080/20786204.2008.10873685)

To link to this article: <https://doi.org/10.1080/20786204.2008.10873685>



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Published online: 15 Aug 2014.



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Abstract

Upper respiratory tract infection (URTI) occurs commonly in both children and adults and is a major cause of mild morbidity. It has a high cost to society, being responsible for absenteeism from school and work and unnecessary medical care, and is occasionally associated with serious sequelae. URTIs are usually caused by several families of virus; these are the rhinovirus, coronavirus, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, influenza, enterovirus and the recently discovered bocavirus. This review will mainly focus on the rhinovirus, where significant advances have been made in understanding the epidemiology, natural history and relationship with other pathogens.

(P) This article has been peer reviewed. Full text available at www.safpj.co.za

SA Fam Pract 2008;50(2):6-12

Introduction

Upper respiratory tract infection (URTI) or "the common cold" is a symptom complex usually caused by several families of virus; these are the rhinovirus, coronavirus, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus and influenza. Occasionally the enterovirus is implicated in summer. Recently, the newly discovered bocavirus (related to the parvovirus) has also been linked to URTI.¹ The term "URTI" is probably a misnomer as it incorrectly implies an absence of lower respiratory tract symptoms. URTI occurs commonly in both children and adults and is a major cause of mild morbidity. URTIs have a high cost to society, being responsible for missed work and unnecessary medical care. Occasionally they have serious sequelae. Often regarded as trivial, URTIs do not receive serious attention in medical school curricula.

Bacterial complications such as otitis media and acute sinusitis and inflammatory sequelae such as asthma, however, are well described. Readers are referred to a recent review of symptomatic management of URTI in children in this journal.² This review will mainly focus on the rhinovirus, where significant advances have been made in understanding the epidemiology, natural history and relationship with other pathogens. Where relevant, features specific to other causes of URTI will be mentioned. By understanding the natural history, spectrum of complications and awareness of "warning signs", the family practitioner may be better equipped to manage the most common human viral infection. Management issues include the correct use of antibiotics, new information warning against over the counter

medication for URTI in children under two years of age, emerging data on complementary and alternate medications (CAM) and other low-cost evidence-based interventions.

Epidemiology of URTI

In industrial United States of America (USA), adults have two to four, and children have between six and eight URTIs a year.^{3,4} There is little data from developing countries. In a cross-sectional study from rural Uganda where data was collected from 300 women with children under two years of age, 37% of children had a current URTI.⁵

Recent studies from Kenya in the rural Kilifi district on RSV epidemiology in a birth cohort demonstrated that almost 70% of RSV infections were of the upper respiratory tract only with no seasonality.⁶

The majority of infections are spread through contact with infected secretions and can be interrupted through hand hygiene. Rhinoviral infections occur throughout the year, most commonly in spring and autumn. Influenza peaks in winter have been noted universally.⁷⁻⁹

Rhinovirus

Virology

The rhinovirus, a single-stranded RNA virus, has more than 100 antigenic types and is the most common cause of URTIs in adults and children. As the rhinovirus grows best in tissue culture at 33 °C, it was believed earlier that it would not infect the lower airways. However, it was recently found to replicate in the lower respiratory tract.¹⁰

Symptoms and signs

The symptoms and signs of the common cold have been well delineated in adult natural history studies since the 1960s.¹¹ Onset is heralded by nasal stuffiness and throat irritation, usually accompanied by low-grade fever, anorexia and myalgia. Sneezing is accompanied by a watery nasal discharge, which after one to three days becomes mucopurulent and can persist for up to ten days in over a third of patients. Coughing occurs commonly probably due to inflammation of the lower respiratory tract (Figure 1). Rhinovirus infection causes concomitant inflammation of the paranasal sinuses.¹²

Figure 1: Natural history and symptoms of rhinovirus infection

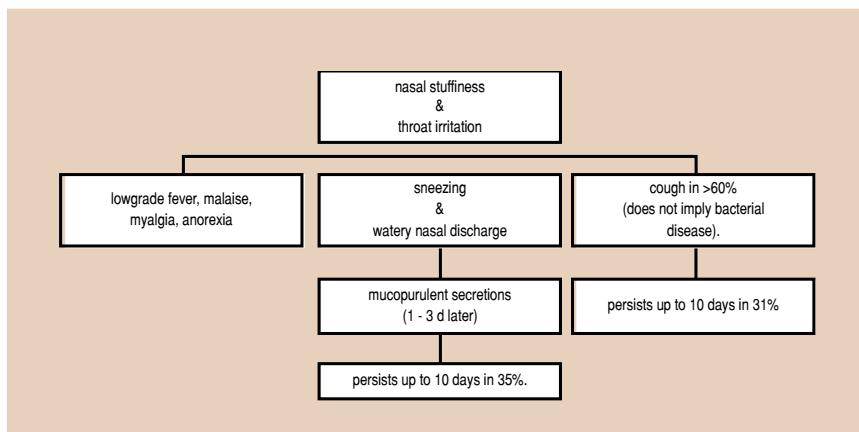


Table I: Comparison of signs and symptoms in adults and children^{11,13}

| | Adults | Children |
|------------------------------------|----------------------|----------------------------|
| Still reporting symptoms by day 10 | 20% | 73% |
| Cough Peak incidence Duration | 40% 20% by day 10 | 70% > 40% through day 9 |

The natural history of URTI in children has been less well defined because of reliance on parent recall or physician referral. As the rhinovirus is difficult to culture, only with the advent of sensitive and specific reverse transcriptase polymerase chain reaction techniques has the natural history been better documented. The first major community-based natural history study in children was published in 2008. Pappas and colleagues conducted a survey in Virginia, USA.¹³ Children between five and ten years of age were enrolled and data was collected on 81 cases from the onset of symptoms through day ten. Rhinoviruses were responsible for 37 (almost 50%) of cases.

The most common signs were coughing and sneezing and the most common symptoms were congestion and a runny nose. These signs and symptoms persisted for the first week. Coughing was present in 46% at onset, peaking at 69% on day one and still present in ≥ 50% at day seven. Rhinorrhoea occurred in 71% on day one and was still present in ≥ 50% by day five. Sneezing occurred in 36% at onset, peaking at 55% on day one and still noted in 35% by day five. Fever was uncommon, reported in only 15% on day one and declining even further. Headache was reported in 15% on day one and declined thereafter. Vomiting and diarrhoea were extremely uncommon. None of the children received antibiotics. A comparison between the course of URTI in children and adults is shown in Table I.^{11,13}

Important management points from natural history data are that coughing is extremely common in children and adults and can persist with high frequency until day nine. In contrast, fever is uncommon

especially after the first day, and its presence suggests either another cause such as influenza and/or a bacterial complication such as otitis media or sinusitis.

Lower respiratory disease associated with the rhinovirus

Two studies of hospitalised children have recently documented considerable lower respiratory disease caused by the rhinovirus. In the USA, the rhinovirus was implicated in 26% of children younger than five years of age hospitalised for acute respiratory disease.¹⁴ The rhinovirus was detected more frequently than RSV, the virus traditionally linked to most lower airway morbidity and was highly associated with a history of asthma. In infants under six months of age, apnoea was common (7 out of 62). In a similar study from Spain in children under two years of age, the rhinovirus was associated with 25% of admissions for respiratory disease.¹⁵ Diagnoses included recurrent wheezing, bronchiolitis and pneumonia. Sixty per cent of children were febrile. Multiple viruses were isolated in almost 40% of children, suggesting a role for co-infection in the pathogenesis of respiratory disease.

Treatment of URTIs

Symptomatic treatment

The main emphasis of management is symptom relief of fever, nasal congestion and coughing. A variety of adrenergic agonist, anticholinergic, antihistamine preparations, antitussives and expectorants are marketed for these purposes. Common constituents of such medication include first generation antihistamines, antipyretics (paracetamol) or anti-inflammatory agents (ibuprofen), cough suppressants such as dextromethorphan, expectorants (guaiifenesin) and decongestants such as pseudoephedrine and phenylpropanolamine.¹⁶

Although they provide symptom relief, there is no conclusive evidence that they shorten the duration of symptoms.^{17,18} Recently, the Food and Drug Administration issued an advisory statement warning against using over the counter medications for URTIs in children under two years of age.¹⁹ This arose from a report of three infants under six months of age who died after receiving these medications, possibly linked to the pseudoephedrine component. Since there is no proven benefit over placebo of these medications in children of any age, and the risks of side effects in children are great, practitioners should be cautious in recommending or prescribing such therapies.

Antibiotics

Antibiotic use in childhood URTIs remains contentious since more than 90% of the infections are of viral aetiology. The reasons cited for prescribing antibiotics include diagnostic uncertainty, socio-cultural and economic pressures, concern over malpractice litigation and parental expectations of an antibiotic.²⁰ Antibiotics are overprescribed for URTIs and promote antibiotic resistance.²¹ However, there is a role for defined indications, such as severe acute rhinosinusitis lasting more than ten days and severe acute otitis media.²²

Fahey et al's quantitative systematic review of randomised controlled trials comparing antibiotics to placebo for paediatric URTIs concluded that antibiotic treatment did not alter clinical outcome or reduce

complication rates.²³ The authors do, however, make the point that the efficacy of antibiotic treatment may be greater in a subgroup with a higher baseline risk of developing complications.

Complementary and alternative medicine (CAM) for URTI

There is growing interest in the use of complementary and alternative medicines for URTIs. Herbal remedies have been studied and conflicting results found. Two of the most commonly used and studied herbs are *Echinacea* and *Andrographis paniculata*, both of which are believed to be immunostimulants. Propolis (bee resin) has also been studied and stimulates antibody production.²⁴ A major problem with the investigation and use of herbal products is the lack of standardisation.²⁵

A recent meta-analysis by Shah et al found that *Echinacea* decreased the odds of developing the common cold by 58% and the duration of a cold by 1.4 days.²⁶ At least two of the fourteen studies reviewed included children. The authors call for large randomised trials using standardised preparations and measuring well-defined endpoints. There is still insufficient data on safety, especially with prolonged use. The effects on blood pressure and rate-corrected QT interval are not known. As *Echinacea* inhibits cytochrome P450 3A4 enzymes, there is considerable potential for drug interaction. Rash, including anaphylaxis, has also been reported.^{27,28}

A review of safety and efficacy of six CAM studies for prevention and treatment of URTIs in children found that *Echinacea* did not reduce the duration and severity of URTIs, but that both *Echinacea* and *Andrographis paniculata* decreased nasal secretions. *Echinacea* was associated with a higher frequency of rash compared with placebo ($p = 0.008$). This review also found that a combination of these herbs with propolis and ascorbic acid reduced the number of URTI episodes, duration of symptoms and the number of days of illness. The review concludes, however, that data are inadequate to support CAM use for the prevention or treatment of URTIs in children.²⁹ The impact of herbal immunostimulants on the immature immune system is unknown.

Other practical interventions

Saline nasal spray may be beneficial. For example, in a study of Swedish military recruits, daily spraying with physiological saline significantly reduced the incidence of the common cold and nasal symptoms.³⁰ In a recent study of children with URTIs, daily nasal wash with a sea water-based preparation significantly reduced symptoms in comparison to standard medications.³¹ Regrettably, the study agent was not compared to physiological saline.

Although zinc supplementation is ineffective for treatment of URTIs,³² iron supplementation is remarkably effective in areas where iron deficiency is endemic and easy to implement.³³

Honey is superior to both dextromethorphan and no treatment for night-time coughing associated with URTIs.³⁴ Although the authors hypothesise that the effect could be due to its anti-oxidant or antimicrobial effects, another hypothesis is that a sweet taste might induce endogenous opioids.³⁵ Honey should not be given to infants under 12 months of age, however, because of a real danger of infant botulism.³⁶

The promotion of hand washing in households significantly reduces the incidence of both respiratory and gastrointestinal infections in children from both impoverished and well-resourced communities.^{8,37}

Parental smoking exacerbates respiratory infections in children and

predisposes to asthma.³⁸ Tobacco is a highly addictive substance and is a major health problem requiring concerted efforts to assist addicts to wean themselves.³⁹

Influenza virus⁴⁰

Virology

The influenza A, B and C are double-stranded RNA orthomyxoviruses; A and B are usually responsible for influenza outbreaks in humans. The influenza viruses are classified according to haemagglutinin (HA) protein and neuraminidase (NA) proteins.

Symptoms

Fever is the most common sign and is higher and of longer duration than in rhinovirus infection.⁴¹ Rhinorrhoea occurs commonly. The classic symptoms are sudden onset of fever, with or without chills, headache, malaise, and cough. Older children may complain of myalgia. The upper respiratory symptoms usually have a later onset and include conjunctivitis, otitis media, and gastrointestinal symptoms. Influenza can lead to serious sequelae such as pneumonia, encephalopathy or encephalitis, myocarditis, and secondary bacterial infections.

Epidemiology

Patients are infectious for 24 hours prior to symptoms, and continue to be for about one week, or longer in young children or immunocompromised hosts. Children under four years of age and those older with bronchopulmonary dysplasia, asthma, cardiac abnormalities, cystic fibrosis, malignancy, diabetes, chronic renal failure and HIV are at risk for complications.

Both influenza A and B viruses cause epidemics almost annually in many parts of the world. Community outbreaks usually affect school children first. These epidemics are due to antigenic drift.

Diagnosis

Rapid diagnostic tests are becoming more available and can be very useful in determining whether influenza is circulating in the community and also in individual patients.⁴² Rapid tests are helpful in decision making with regard to antibiotics.^{43,44}

Treatment and prevention

The adamantanes (amantadine and rimantadine) M2 ion channel blockers are only effective against influenza A, and therefore of no use unless influenza A has been identified. Two neuraminidase inhibitors (oseltamivir [oral] and zanamivir [inhaled]) are active against influenza A and B.⁴⁵ If taken within 48 hours of onset, the duration of the disease and complications are reduced. They are also useful for post-exposure prophylaxis during outbreaks. Both drugs are licensed in South Africa for children older than one year of age. A presumptive diagnosis can be made in adults during epidemics or after close contact with a known case. Adults with an influenza-like illness with cough and fever in the first 48 hours are likely to have influenza.⁴⁶ Children at risk for serious disease exposed to adults with the typical symptom complex may benefit from prophylaxis during winter outbreaks.

As bacterial infections can complicate influenza, practitioners should have a low threshold for use of antibiotics if complications are suspected.

Influenza is vaccine-preventable. Licensed vaccines include the live, attenuated influenza vaccine (LAIV), and the trivalent inactivated vaccine (TIV). Only the TIV is available in South Africa. Both are

adapted every year for the recommended strains. The vaccines contain one influenza A (H3N2) and one (H1N1) virus, and also one influenza B virus.

Individuals at high risk for influenza complications should be vaccinated.⁴⁰ Additionally, people of any age with chronic underlying medical conditions, including HIV, should be immunised. The Centers for Disease Control and Prevention recommends that all children six months to eight years of age receive two doses of TIV separated by ≥ 4 weeks if they have not been vaccinated previously. Children who receive two doses in their first vaccination year can get a single annual dose in subsequent years. If they only received one dose in their first year of vaccination, they need two doses the following year, with single annual doses in subsequent years. Vaccination should be encouraged, particularly if there are high-risk people in the home.

Management of pharyngitis – syndromic or targeted

The two most important causes of pharyngitis requiring antibiotics are diphtheria and *Streptococcus pyogenes*. Fortunately diphtheria is extremely rare but can occur where public immunisation programmes have waned.

Pharyngitis due to *S pyogenes* may be easy to recognise, as it manifests as a febrile, purulent pharyngitis *without* rhinitis or cough. However, milder cases can be confused with viral URTI. The most important consequence of not treating pharyngitis is rheumatic fever, which can occur in all settings, but is far more common in resource-poor communities.^{47–49}

There are two approaches to managing pharyngitis. In the USA the emphasis is on limiting antibiotics to those with bacteriological confirmation. A streptococcal antigen test, which gives a rapid answer and is highly specific, is followed by a culture, in the event of a negative antigen test.⁵⁰

In the resource-limited primary healthcare settings where both laboratory tests and follow-up are unreliable, it is more appropriate to use a syndromic approach. In Costa Rica a single-dose of intramuscular benzathine penicillin for all infants and children with pharyngitis has been used very effectively since the 1970s to reduce the incidence of acute rheumatic fever from 90 to 1 per 100 000.⁵¹ Any patient presenting with fever or a sore throat who had halitosis, red throat, and tonsillar hypertrophy with a white exudate was treated. Over a 20-year period, *Streptococcus pneumoniae* remained fully susceptible to penicillin. This represents a major success in reducing the lifetime disease burden of rheumatic heart disease.

Pertussis

In infants and young children, the catarrhal stage of pertussis typically presents as a “common cold”. Complications are most severe in infants under six months of age, especially if preterm or unimmunised. Therefore, a “common cold” presenting in this age group should raise suspicion of pertussis. Infants are especially at risk until all three primary doses of vaccine have been given at 6, 10 and 14 weeks. Adolescents and adults are susceptible to pertussis due to waning immunity. A useful clinical case definition for adults is an acute cough illness lasting at least seven days, especially if associated with posttussive vomiting or gagging beyond two weeks.⁵² Any infant with URTI symptoms and in contact with an adult or adolescent fulfilling the

case definition of pertussis should receive a macrolide antibiotic. As pertussis remains a formidable disease with high morbidity and significant mortality in young infants, current recommendations still urge practitioners to consider pertussis in young infants and to give antibiotic prophylaxis to household contacts.⁵³

Azithromycin is now recommended for infants below a month of age at a dosage of 10 mg/kg/day for five days because of the risk of hypertrophic pyloric stenosis with erythromycin in neonates. However, erythromycin at a dosage of 50 mg/kg/day for 14 days can still be used. For older infants and adults, clarithromycin can also be used.⁵⁴

Conclusions

Knowledge of the natural history of rhinovirus infection and awareness of influenza, pertussis and *S. pyogenes* will help the clinician to make clinically relevant decisions. There is already a large body of evidence-based practical information that can easily be applied to diagnosis, management and prevention. 

References

- Allander T. Human bocavirus. *J Clin Virol* 2008;41(1):29–33.
- Green RJ. Symptomatic treatment of upper respiratory tract infections in children. *SA Fam Pract* 2006;48(4):38–42.
- Dingle JH, Badger GF, Jordan WS. Illness in the home: Study of 25,000 illnesses in a group of Cleveland families. Cleveland: Western Reserve University; 1964.
- Gwaltney JM, Jr., Hendley JO, Simon G, Jordan WS, Jr. Rhinovirus infections in an industrial population I. The occurrence of illness. *N Engl J Med* 1966;275(23):1261–8.
- Mbonye AK. Risk factors for diarrhoea and upper respiratory tract infections among children in a rural area of Uganda. *J Health Popul Nutr* 2004;22(1):52–8.
- Noles DJ, Okiro EA, Ngama M, et al. Respiratory Syncytial Virus epidemiology and disease in infants and young children observed from birth in Kilifi district, Kenya. *Clin Infect Dis* 2008;48:50–7.
- Ijpm FF, Beekhuis D, Cotton MF, et al. Human metapneumovirus infection in hospital referred South African children. *J Med Virol* 2004;73(3):486–93.
- Menegeotti A. Upper respiratory tract infection. In: 2007.
- Mizuta K, Oshitani H, Saito M, et al. Epidemiology of influenza virus infections in children with acute respiratory infections in Zambia. *Ann Trop Paediatr* 1997;17(2):115–9.
- Turner RB. Rhinovirus: More than just a common cold. *J Infect Dis* 2007;197:765–6.
- Gwaltney JM, Jr., Hendley JO, Simon G, Jordan WS, Jr. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. *Jama* 1967;202(6):494–500.
- Gwaltney JM, Jr., Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Engl J Med* 1994;330(1):25–30.
- Pappas DE, Hendley JO, Hayden FG, Winther B. Symptom profile of common colds in school-aged children. *Pediatr Infect Dis J* 2008;27:8–11.
- Miller EK, Lu X, Erdman DD, et al. Rhinovirus-associated hospitalizations in young children. *J Infect Dis* 2007;195(6):773–81.
- Calvo C, Garcia-Garcia ML, Blanco C, Pozo F, Flecha IC, Perez-Brena P. Role of rhinovirus in hospitalized infants with respiratory tract infections in Spain. *Pediatr Infect Dis J* 2007;26(10):904–8.
- MMWR. Infant deaths associated with cough and cold medications – two states, 2005; 2007 January 12, 2007.
- Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev* 2004(4):CD001831.
- Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004;114(1):e85–90.
- Nonprescription cough and cold medicine use in children: Food and drug administration; 2007 August 15, 2007.
- Pichichero ME. Understanding antibiotic overuse for respiratory tract infections in children. *Pediatrics* 1999;104(6):1384–8.
- Dowell SF, Schwartz B, Phillips WR. Appropriate use of antibiotics for URIs in children: Part I. Otitis media and acute sinusitis. The Pediatric URI Consensus Team. *Am Fam Physician* 1998;58(5):1113–8, 23.
- Dowell SF, Schwartz B, Phillips WR. Appropriate use of antibiotics for URIs in children: Part II. Cough, pharyngitis and the common cold. The Pediatric URI Consensus Team. *Am Fam Physician* 1998;58(6):1335–42, 45.
- Fahey T, Stocks N. Antibiotics for children with upper respiratory tract infections. *Jama* 1998;280(16):1399–400; author reply 401–2.
- Sforci JM, Orsi RO, Bankova V. Effect of propolis, some isolated compounds and its source plant on antibody production. *J Ethnopharmacol* 2005;98(3):301–5.

25. Goel V, Lovlin R, Barton R, et al. Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther* 2004;29(1):75–83.
26. Shah SA, Sander S, White CM, Rinaldi M, Coleman CI. Evaluation of echinacea for the prevention and treatment of the common cold: A meta-analysis. *Lancet Infect Dis* 2007;7(7):473–80.
27. Myers SP, Wohlmuth H. Echinacea-associated anaphylaxis. *Med J Aust* 1998;168(11):583–4.
28. Mullins RJ. Echinacea-associated anaphylaxis. *Med J Aust* 1998;168(4):170–1.
29. Carr RR, Nahata MC. Complementary and alternative medicine for upper-respiratory-tract infection in children. *Am J Health Syst Pharm* 2006;63(1):33–9.
30. Tano L, Tano K. A daily nasal spray with saline prevents symptoms of rhinitis. *Acta Otolaryngol* 2004;124(9):1059–62.
31. Slapak I, Skoupá J, Strnad P, Horník P. Efficacy of isotonic nasal wash (seawater) in the treatment and prevention of rhinitis in children. *Arch Otolaryngol Head Neck Surg* 2008;134:67–74.
32. Caruso TJ, Prober CG, Gwaltney JM, Jr. Treatment of naturally acquired common colds with zinc: a structured review. *Clin Infect Dis* 2007;45(5):569–74.
33. De Silva A, Atukorala S, Weerasinghe I, Ahluwalia N. Iron supplementation improves iron status and reduces morbidity in children with or without upper respiratory tract infections: A randomized controlled study in Colombo, Sri Lanka. *Am J Clin Nutr* 2003;77(1):234–41.
34. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM, Jr. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. *Arch Pediatr Adolesc Med* 2007;161(12):1140–6.
35. Eccles R. Efficacy and safety of over-the-counter analgesics in the treatment of common cold and flu. *J Clin Pharm Ther* 2006;31(4):309–19.
36. Tanzi MG, Gabay MP. Association between honey consumption and infant botulism. *Pharmacotherapy* 2002;22(11):1479–83.
37. Luby SP, Agboatwalla M, Feikin DR, et al. Effect of handwashing on child health: A randomised controlled trial. *Lancet* 2005;366(9481):225–33.
38. Peat JK, Keena V, Harakeh Z, Marks G. Parental smoking and respiratory tract infections in children. *Paediatr Respir Rev* 2001;2(3):207–13.
39. Sharma S. Nicotine addiction. In: *EMedicine*; 2006. More info needed.
40. Fiore AE, Shay DK, Haber P, et al. Prevention and control of influenza: Recommendations of the advisory committee on immunization practices MMWR 2007;56 (RR06):1–54.
41. Matsuzaki Y, Katsumiwa N, Nagai Y, et al. Clinical features of influenza C virus infection in children. *J Infect Dis* 2006;193(9):1229–35.
42. Prevention CfDCa. Rapid diagnostic testing for influenza. In; 2006.
43. Falsey AR, Murata Y, Walsh EE. Impact of rapid diagnosis on management of adults hospitalized with influenza. *Arch Intern Med* 2007;167(4):354–60.
44. Benito-Fernandez J, Vazquez-Ronco MA, Morteruel-Aizkuren E, Mintegui-Raso S, Sanchez-Etxaniz J, Fernandez-Landaluce A. Impact of rapid viral testing for influenza A and B viruses on management of febrile infants without signs of focal infection. *Pediatr Infect Dis J* 2006;25(12):1153–7.
45. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005;353(13):1363–73.
46. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000;160(21):3243–7.
47. Carapetis JR. Rheumatic heart disease in developing countries. *N Engl J Med* 2007;357(5):439–41.
48. Carceller A, Tapiero B, Rubin E, Miro J. Acute rheumatic fever: 27 year experience from the Montreal's pediatric tertiary care centers. *An Pediatr (Barc)* 2007;67(1):5–10.
49. Erdem G, Mizumoto C, Esaki D, et al. Group A streptococcal isolates temporally associated with acute rheumatic fever in Hawaii: differences from the continental United States. *Clin Infect Dis* 2007;45(3):e20–4.
50. Matthys J, De Meyere M, Van Driel ML, De Suter A. Differences among international pharyngitis guidelines: not just academic. *Ann Fam Med* 2007;5:436–43.
51. Arguedas A, Mohs E. Prevention of rheumatic fever in Costa Rica. *J Pediatr* 1992;121(4):569–72.
52. Strebel P, Nordin J, Edwards K, et al. Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995–1996. *J Infect Dis* 2001;183(9):1353–9.
53. Pediatrics AAo. Red Book. Report of the committee on infectious diseases. Elk Grove Village: American Academy of Pediatrics; 2006.
54. Tiwari T, Murphy TV, Moran J. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. 2005 CDC guidelines; 2005 (Accessed 25 January 2008). URL?