MedicineToday 2012; 13(2): 14-21

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

Recurrent infection in childhood: how much is too much?

PAUL E.A. GRAY BA(Hons I)Cantab, MB ChB Edin, FRACP, FRCPA
JOHN B. ZIEGLER AM, MB BS(Hons), FRACP, MD, FAAAAI

Even the healthiest children can suffer frequent infections, leading to considerable parental concern. This article discusses the normal frequencies of infection in different contexts, and the features that should raise suspicion of immunodeficiency.

Key points

- **Young infants can be expected to have at least six infections per year, with an average of 10 infections for those in institutional childcare.**
- **Recurrent infection of a single site or organ is commonly due to an anatomical abnormality at that site.**
- **Features that should raise the question of immunodeficiency include undue severity of infection, recurrent deep-seated infections, lack of response to antibiotics, failure to thrive and the involvement of less virulent causative organisms.**
- **When there is no causative organism, consider a non-infective reason for recurrent symptoms, such as a periodic fever syndrome.**

Improved nutrition, housing and vaccination have diminished the impact of childhood infectious diseases in developed countries. However, the incidence of infection in children remains high, particularly in early childhood. Otherwise healthy children may suffer frequent infections, causing considerable parental concern, and the investigating clinician must be aware of what is normal in terms of frequency and severity of infection and also how the environment and underlying health of the child can impact on susceptibility to infection. This article considers the normal frequency of infection in different contexts and discusses the features that should raise the suspicion of primary immunodeficiency (PID).

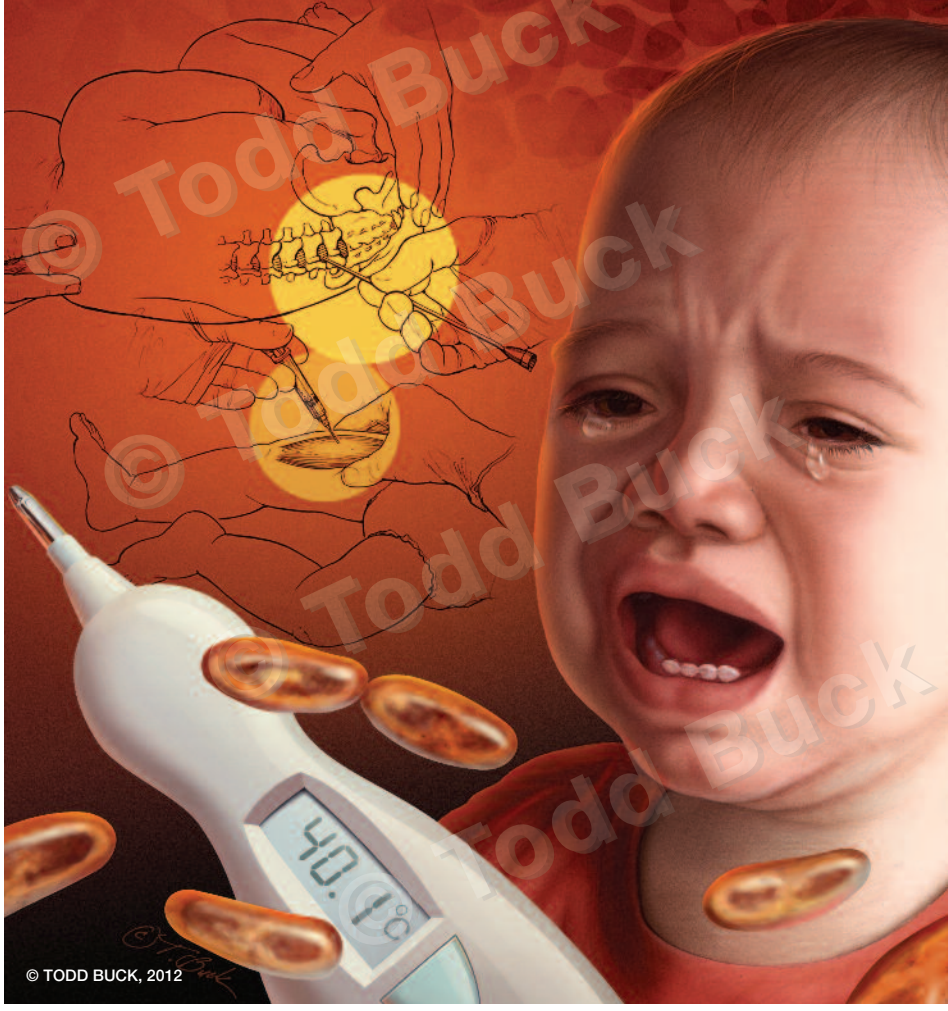
INFECTION FREQUENCY: AGE AND ENVIRONMENTAL FACTORS

The most recent Australian data on infection frequency come from the early 1980s, and suggest that the average toddler might have six or more infections per year.[1] The frequency of infection increases with increased exposure to micro-organisms, such as when there are a large number of siblings, and decreasing as the child approaches school age. It is likely, however, that the transition to more widespread use of large daycare settings – which increases the number of infectious contacts – will have raised infection rates among Australian children. American data suggest that the average infant cared for in institutional daycare services will have nine to 10 respiratory infections

Dr Gray is a Paediatric Immunologist and Immunopathologist at Sydney Children's Hospital and the School of Women's and Children's Health, University of NSW, Sydney. Associate Professor Ziegler is a Paediatric Immunologist, Head of the Department of Immunology and Infectious Diseases at Sydney Children's Hospital and Associate Professor of Paediatrics in the School of Women's and Children's Health at the University of NSW, Sydney, NSW.

per year, almost half of which are complicated by acute otitis media and a lower respiratory tract infection.[2]

Environmental factors that impact on the frequency of infection include poor nutrition and cigarette smoke (e.g. respiratory and middle ear infections). Overcrowded living conditions lead to an increased risk of pyogenic infection (e.g. *Streptococcus pneumonia* and *Staphylococcus aureus* infections), and may underlie the increased rate of such infections among indigenous children, a group that has a high incidence of secondary end organ damage such as conductive hearing loss and bronchiectasis.[3] Finally, the presence in the environment of virulent strains of common micro-organisms can lead to recurrent infections. The most topical of these currently is the *S. aureus* strain possessing the Panton valentine leukocidin (PVL) virulence factor – a predisposing factor for recurrent skin abscesses that tend to affect multiple family members.[4]



CASE 1

Robert, a 2-year-old boy, attended his GP following discharge from hospital. He had presented initially with low-grade fever and increasing respiratory distress, with changes to his right upper and left lower lobes on chest x-ray (Figure 1). He had been treated with intravenous (IV) cefotaxime, oxygen and bronchodilators, but deteriorated and required mechanical ventilation for one week. There was no microbiological diagnosis. Robert's medical history included a previous episode of chest infection requiring one week of ventilation at 1 year of age, as well as two episodes of gastroenteritis, two urinary tract infections, three lower respiratory tract infections, two episodes of otitis media, and treatment with up to eight courses of antibiotics. Robert was being investigated by a paediatric neurologist for gross motor delay with hypotonia, and had gastro-oesophageal reflux disease manifest as vomiting. He attended a childcare centre on four days each week.

Commentary

Although this child has had frequent infections and two severe episodes of possible chest infection, several factors point away from immunodeficiency. Firstly, the infection frequency is not out of keeping with the range expected for a healthy child attending a large group childcare facility; secondly, the events have not been unduly refractory to antibiotic therapy; and, thirdly, no unusual organisms had been identified. This left only the two severe episodes of possible chest infection to explain, and in fact these turned out to be secondary to aspiration of food related to hypotonia of his pharyngeal muscles. Robert had a normal immunodeficiency screen.

RECURRENT INFECTION: ANATOMICAL DEFECTS AND SECONDARY IMMUNODEFICIENCY

Anatomical defects and secondary immuno - deficiency may cause recurrent infection in children. Case 1 illustrates the importance of structural defences in protecting against a build-up of micro-organisms within organs, in this case the upper oesophageal sphincter and gag reflex that normally block fluid aspiration. Other mechanical defences against infection include epithelial barriers (e.g. skin, gut wall) and mechanisms for removing micro-organisms (e.g mucus, cilia). Children

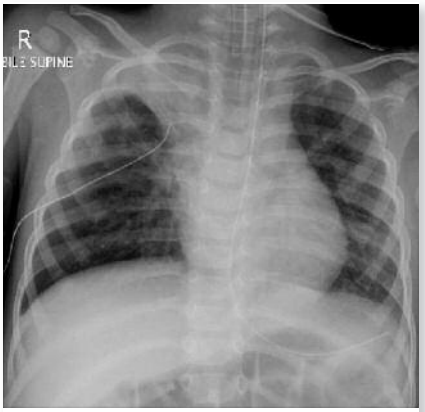


Figure 1. Case 1: post-intubation chest x-ray demonstrating right upper and left lower lobe changes in a 2-year-old boy.

can sometimes have structural abnormalities that undermine these defensive processes, therefore enabling infection to become established – for example, a urinary system that allows retrograde flow and the movement of organisms to a sterile site (e.g. vesicoureteric reflux), or a nonfunctioning mucociliary escalator e.g. cystic fibrosis). Anatomical abnormalities that predispose to infection are summarised in the first box on this page.

There are also many reasons why a child with no anatomical abnormalities and who does not have a PID can nonetheless become susceptible to serious infections. These secondary immuno - deficiencies are also summarised in the second box on this page.

The most common secondary immunodeficiency in the contemporary setting is iatrogenic immunodeficiency, resulting from treatment of the child with medications that impair immune function. The medications with the greatest immunosuppressive effects include chemotherapeutic agents used in the treatment of cancer and immune suppressants used to treat inflammatory diseases and to stop transplant rejection. Patients most profoundly affected by these medications, such as those who have had bone marrow transplant, may lack both myeloid and lymphoid lineage cells and are at risk of infection from an array of pyogenic bacteria, fungi and viruses, including low virulence opportunistic pathogens. At the other end of the spectrum are medications such as corticosteroids, low-dose antiproliferative agents (e.g. methotrexate), T-cell blockers (e.g. cyclosporin) and the new biological agents, including monoclonal antibodies used in connective tissue and inflammatory bowel diseases. Although the infectious predisposition is lower with these medications than with chemotherapeutic agents or immune suppressants, there are still specific risks to the patient. For example, there is a predisposition to severe varicella in patients treated with T-cell blockers (warranting postexposure prophylaxis with hyperimmune globulin), whereas an increased risk of mycobacterial infections is present in patients receiving antitumour necrosis factor alpha blockers.[5]

NON-PRIMARY IMMUNO - DEFICIENCY FACTORS PREDISPOSING TO INFECTION: ANATOMICAL ANOMALIES

Damaged epithelial surfaces

Skin
- Eczema
- Bullous skin diseases

Gut
- Inflammatory bowel disease
- Myopathic bowel

Vessels
- Indwelling cannulae

Central nervous system
- Sacral sinus

Compromised drainage

Respiratory tract
- Cystic fibrosis
- Ciliary dyskinesia
- Foreign body obstruction
- Eustachian tube dysfunction

Valve dysfunction

Oesophageal sphincter
- Cerebral palsy
- Pneumonia

Vesicoureteric junction
- UTI

Heart valves
- Endocarditis

NON-PRIMARY IMMUNO - DEFICIENCY FACTORS PREDISPOSING TO INFECTION: SECONDARY IMMUNODEFICIENCIES

Drugs
- Immunosuppressives
- Anticonvulsants

Microbial infection
- HIV
- Measles

Biochemical disorders
- Diabetes
- Renal failure, dialysis
- Hepatic failure, cirrhosis

Autoimmune disease
- Systemic lupus erythematosus, rheumatoid arthritis
- Anti-interferon-g antibodies

Malignancy
- Leukaemia
- Hodgkin's disease

Trauma
- Burns

Environmental exposure
- Ionising radiation
- Ultraviolet light
- Toxic chemicals

Age extremes
- Prematurity; neonate

Other
- Malnutrition
- Protein losing enteropathy
- Stress
- Asplenia, hyposplenism

One peculiarly paediatric condition that predisposes to infection and warrants specific mention is being young. Infants are generally more susceptible to severe infections than are older children or adults.[6] This susceptibility increases when the infant is born prematurely and has not therefore benefited fully from the passive transfer of maternal immunoglobulin G (IgG) during the last trimester of pregnancy.

FINDINGS SUGGESTIVE OF PRIMARY IMMUNODEFICIENCY*

Excessive frequency/severity of infection
- Mucopurulent discharge (particularly important)
- Chronic suppurative chest infection
- Rare or unusual complications, e.g. complicated varicella zoster virus infection

Large requirement for antibiotics
- Need for intravenous antibiotics to clear infection
- Rapid reinfection following conclusion of treatment

Infectious syndromes
- More than one organ involved
- Recurrent deep skin or organ abscesses
- Two or more deep-seated infections (e.g. sepsis, meningitis, pneumonia)

Micro-organisms
- Persistent oral or cutaneous candidiasis
- Less virulent or opportunistic causative agent

Constitutional symptoms
- Failure to thrive
- Chronic diarrhoea

Family history
- Primary immunodeficiency
- Consanguinity

Age and gender
- Infancy (profound immunodeficiency presents in first year of life)
- Male gender (severe immune deficiencies more commonly affect boys)

* Adapted from the Jeffrey Modell Foundation: 10 warning signs of primary immunodeficiency (available at www.info4pi.org).

PRIMARY IMMUNODEFICIENCY

PID involves a predisposition to infection that is associated with an inherited deficiency of immune function. More than 200 different PIDs have been reported.[7] It is not surprising then that although individual PID syndromes are rare, it is estimated that about one in 10,000 children have a PID.

Along with increased frequency of infection, there are several other valuable pointers to the presence of PID. Recurrent infections accompanied by copious amounts of pus (e.g. discharging otitis media, mucopurulent sinusitis) are suggestive of PID, and in particular antibody deficiency, as is the development of end organ damage such as conductive hearing loss or bronchiectasis. In these cases, a diagnosis of PID would be reinforced if clearance of infections required IV antibiotics or if there was slow resolution with rapid reinfection post-treatment. Deep-seated infections (e.g. osteomyelitis, lymph node or liver abscess) are more indicative of immune deficiency than are superficial skin infections, whereas infections caused by less virulent or opportunistic micro-organisms (e.g. *Pneumocystis jiroveci* [formerly *P. carinii*] pneumonia [PCP], oesophageal thrush) should always prompt consideration of PID.

The age and sex of the child can be a pointer to the presence and type of PID. Many patients with severe PIDs present in infancy, including those with severe combined immune deficiency (SCID) and severe antibody deficiency. Furthermore, many severe PIDs are also X-linked and therefore affect boys preferentially. A listing of relevant clues to PID is outlined in the box on this page.

When deciding whether to investigate for PID, it is important to remember that immune deficiency implies recurrent infection. If infection cannot be identified in any patient presenting with suspected recurrent infective symptoms then immune deficiency is unlikely to be present. In such cases, it may be necessary to look for other answers to explain the presentation – such as:
- airway hyper-responsiveness to explain episodes of cough and shortness of breath
- a rheumatological disorder or periodic fever syndrome, to explain recurrent episodes of fever[8]
- a noninfective cause of recurrent osteomyelitis, such as chronic recurrent multifocal osteomyelitis.[9]

Case 2

Jenny, a 3-year-old Caucasian girl, has had a history of recurrent fevers every four to six weeks over the past eight months, with each episode lasting seven to 10 days. The episodes were unresponsive to antibiotics and remitted spontaneously without specific treatment. They were associated with mouth ulcers, tonsillitis and cervical lymphadenopathy. Jenny's inflammatory markers during these episodes were markedly elevated (C-reactive protein, 175 mg/L; erythrocyte sedimentation rate, 101 mm/h), but she had a normal full blood count. There has never been a positive microbiological diagnosis: Jenny tested negative for Epstein-Barr virus, cytomegalovirus, *Streptococcus*, parvovirus, *Mycoplasma*, *Toxoplasma* and *Bartonella* serology, and negative for herpes simplex virus PCR on her mouth lesions.

Commentary

With recurrent fevers and no infecting organism, this child may have a periodic fever syndrome. She did, in fact, fit the diagnostic criteria for periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome (also known as Marshall's syndrome), which is a

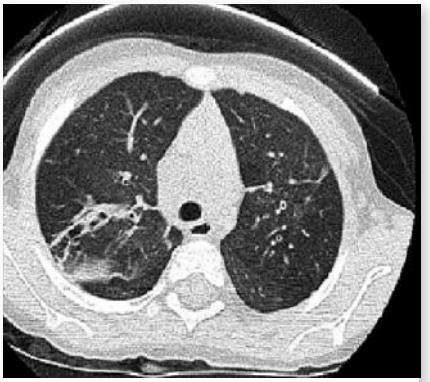


Figure 2. Case 3: high-resolution chest CT showing diffuse bronchiectasis in a child with immunodeficiency.

relatively common, benign condition of early childhood that usually remits by school age.[10] Episodes of PFAPA are usually responsive to a single dose of prednisolone given at time of onset.

There are several other monogenic periodic fever syndromes, the most common being familial Mediterranean fever, which should be considered in children of Mediterranean or Middle Eastern ethnicity.

Case 3

Yasmin, the 6.5-year-old daughter of non-consanguineous parents, presented to her GP with chronic cough. She had a normal birth and early childhood and between the ages of 4 and 6 years had several episodes of acute otitis media with discharge, one of which cultured *Pseudomonas*. At 6 years of age, Yasmin had bronchopneumonia, and although she recovered, she continued to have an ongoing cough and intermittent low-grade temperatures despite repeated courses of antibiotics. On examination, she was below the third percentile for height and weight, and had bilateral coarse inspiratory crackles and finger clubbing.

Commentary

Otitis media with discharge in association with bronchopneumonia with an apparent chronic suppurative chest is suggestive of a diffuse immune problem. Although Yasmin was investigated for cystic fibrosis (sweat test) and ciliary dyskinesia (ciliary motility studies), the most likely diagnosis was an antibody immune deficiency. This proved to be the case, and Yasmin was shown to have low levels of IgG (4.57 g/L [normal range, 6.0 to 15 g/L]), IgA (0.08 g/L [normal range, 0.14 to 2.36 g/L]) and IgM (0.26 g/L [normal range, 0.40 to 2.40 g/L]), as well as a poor response to both protein and polysaccharide vaccines. The presence of clubbing and diffuse crackles implied that her immunodeficiency has led to the development of bronchiectasis, which was confirmed on a subsequent CT scan (Figure 2).

CATEGORIES OF PID

PIDs can be divided into broad, although not entirely exclusive, groups based on the types of immune components involved and the presence of other features. The main categories include antibody (humoral) deficiency, combined T-cell and B-cell deficiency, innate immune defects and syndromic immune deficiency. A limited description of these categories, along with a guide to potential testing, is provided below (see also the box on page 20).

Antibody (humoral) deficiency

Antibody deficiency predisposes to recurrent sinopulmonary infections with polysaccharide encapsulated microorganisms, including *S. aureus, Streptococcus spp.* and *Haemophilus spp*. It is commonly associated with purulent discharges in the form of chronic perforated otitis media, mucopurulent sinusitis or chronic suppurative lung disease. Onset of antibody deficiency in the first year of life suggests a more severe deficiency usually due to a single gene defect, with the most common causes being:

- defects that affect B-cell development, leading to an absence of B-cells and

antibody (e.g. X-linked agammaglobulinaemia)
- defects blocking isotype switching from IgM to IgA, IgG and IgE, which are characterised by a hyper IgM pattern.

INVESTIGATION RESULTS IN VARIOUS PRIMARY IMMUNODEFICIENCIES

Full blood count
- Profound lymphopenia in severe combined immune deficiency
- Neutropenia in congenital neutropenia syndromes
- Neutrophilia occurs with certain types of neutrophil dysfunction
- Small platelets, thrombocytopenia and eosinophilia in Wiskott–Aldrich syndrome

IgG, IgA, IgM, IgE measurement
- IgG levels fall in the first year of life as maternally acquired antibody levels fall, with a nadir between three to six months.
- Infants born prematurely have less maternal antibody, and may reach a lower nadir
- IgA may be absent in the first year of life and is slow to reach adult levels

Lymphocyte subset analysis
- Specific patterns of deficiency can guide diagnosis in combined immune deficiencies
- CD4 count and CD4:CD8 ratio reduced in HIV infection
- B-cells (CD19- or CD20-positive lymphocytes) are absent in X-linked agammaglobulinaemia

Chest x-ray
- Absence of thymus may occur in T-cell deficiency but is also seen in infants who are immunocompetent

Note: If more specialised testing is considered necessary, refer the patient to a paediatric immunologist.

These defects generally present at between four and eight months of age as IgG acquired transplacentally from the mother begins to wane.[11] Antibody deficiency in older infants and young children may be transient, in which case it is referred to as transient hypogammaglobulinaemia of infancy.[12] The diagnosis is made in retrospect once the child's antibody levels have corrected. If the child's deficiency persists or is first noted at an older age, then the diagnosis is likely to be common variable immunodeficiency[13] – which was the actual diagnosis in Case 3.

When children present with symptoms suggestive of antibody deficiency but with normal immunoglobulin levels, the diagnosis may occasionally be specific antibody deficiency, which is defined by an inability to make antibodies against polysaccharide antigens. IgA deficiency is a common investigative finding but is less commonly of clinical importance, with many individuals remaining asymptomatic and others developing sinopulmonary infections in later childhood. Deficiency of IgG subclasses is rarely tested. Many patients with antibody deficiency will require lifelong antibody replacement.

Combined T-cell and B-cell immunodeficiency

The combined immunodeficiency disorder that is generally the most familiar to clinicians is acquired immunodeficiency syndrome (AIDS) caused by HIV infection. However, due to pregnancy screening and transmission reduction strategies,[14] perinatally-acquired HIV is extremely rare in Australia, and is most likely to occur when the mother has been inadequately screened, such as for recent migrants arriving in Australia from HIV-endemic areas.[15]

The most important type of primary combined immunodeficiency is SCID. Patients with SCID present in the first few months of life with failure to thrive, diarrhoea and infections caused by opportunistic micro-organisms (e.g. thrush or PCP). The patient is most commonly male (X-linked SCID accounts for half of all cases) and is usually significantly lymphopenic with low antibody levels. Treatment in most instances involves antibody replacement, PCP prophylaxis and antimicrobial agents to support the patient through to a bone marrow transplant, which is currently the only available definitive treatment.

Other specific defects of the T-cell response may lead to recurrent candida infection or autoimmunity.

Innate immune defects

Neutrophil deficiency in children may be persistent or cyclical.[16] Functional neutrophil defects are extremely rare monogenic disorders. The most common defect is chronic granulomatous disease (CGD), which is caused by a deficiency of the respiratory burst used in killing bacteria. CGD is characterised by deep-seated infections and lymph node and skin abscesses. Infections are caused by catalase producing organisms (e.g. *Staphylococci*, *Nocardia*, *Serratia*, *Aspergillus*, *Candida*).[17] Defects of neutrophil adhesion, chemotaxis and opsonophagocytosis may also cause specific

infectious predisposition.

Defects of the complement pathway can predispose either to autoimmune disease or to infection with encapsulated organisms. Terminal complement component deficiency predisposes to recurrent neisserial infection (e.g. meningococcal disease). Screening for these defects involves assessing classical and alternative complement pathway activity.[18]

Syndromic immune deficiency

A wide array of single gene defects or chromosomal microdeletion syndromes involve a component of immunodeficiency, in conjunction with specific syndromal associations. Important examples include:

- Di George syndrome or velocardiofacial syndrome – usually caused by a microdeletion on chromosome 22q and which may demonstrate cardiac and parathyroid involvement, cleft palate and dysmorphic facies, as well as immunodeficiency secondary to thymic hypoplasia[19]
- Wiskott Aldrich syndrome (WAS) – caused by mutation of the WAS protein gene (*WASp*) and in which affected boys suffer eczema, thrombocytopenia and a predominately antibody immunodeficiency.[20]

CONCLUSION

Infections occur frequently in childhood. The frequency is greater with younger age and greater exposure, as well as when the child has an underlying structural abnormality or systemic illness. PID is less common. When investigating a child with recurrent infections it is therefore important to be aware of the background incidence of infection and of the patterns of infection that make immunodeficiency more likely. These include undue severity, recurrent deep-seated infections, lack of response to antibiotics and the involvement of less virulent causative organisms. When there is no infection, there is no immunodeficiency and it is important to consider another cause for symptoms, such as a periodic fever syndrome. MT

REFERENCES

1. Hosking CS, Roberton DM. The diagnostic approach to infections in childhood. In: Webster ADB, ed. The assessment of immunocompetence. London: WB Saunders; 1982. p. 631-639.
2. Schwartz B, Giebink GS, Henderson FW, Reichler MR, Jereb J, Collet JP. Respiratory infections in day care. Pediatrics 1994; 94: 1018-1020.
3. Chang AB, Grimwood K, Mulholland EK, Torzillo PJ; Working Group on Indigenous Paediatric Respiratory Health. Bronchiectasis in indigenous children in remote Australian communities. Med J Aust 2002; 177: 200-204.
4. Costello ME, Huygens F. Diversity of community acquired MRSA carrying the PVL gene in Queensland and New South Wales, Australia. Eur J Clin Microbiol Infect Dis 2011; 30: 1163-1167.
5. Keane J, Gershon S, Pharm D, et al. Tuberculosis associated with infliximab, a tumor necrosis factor-neutralizing agent. N Eng J Med 2001; 345: 1098-1104.
6. Kemp AS, Campbell DE. The neonatal immune system. Semin Neonatol 1996; 1: 67-75.
7. Geha RS, Notorangelo LD, Casanova JL, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007; 120: 776-794.
8. Scholl PR. Periodic fever syndromes. Current Opin Pediatr 2000; 12: 563-566.
9. Galeazzi M, Gasbarrini G, Ghirardello A, et al. Autoinflammatory syndromes. Clin Exp Rheumatol 2006; (1 Suppl 40): S79-85.
10. Padeh S, Brezniak N, Zemer D, et al. Periodic fever, aphthous stomatitis, pharyngitis and adenopathy syndrome: clinical characteristics and outcome. J Pediatr 1999; 135: 98-101.
11. Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr 2002; 141: 566-571.
12. Walker AM, Kemp AS, Hill DJ, Shelton MJ. Features of transient hypogammaglobulinaemia in infants screened for immunological abnormalities. Arch Dis Child 1994; 70: 183-186.
13. Yong PF, Tarzi M, Chua I, Grimbacher B, Chee R. Common variable immunodeficiency: an update on etiology and management. Immunol Allergy Clin North Am 2008; 28: 367-386.
14. Giles ML, McDonald AM, Elliott EJ, et al. Variable uptake of recommended interventions to reduce mother-to-child transmission of HIV in Australia. 1982-2005. Med J Aust 2008; 189: 151-154.
15. Blyth CC, Palasanthiran P, Miller A, et al. Missed opportunities in prevention of paediatric HIV – has much changed? 18th Annual Conference of the Australasian Society for HIV Medicine; 2006; Melbourne, Australia.
16. Horwitz MS, Duan Z, Korkmaz B, et al. Neutrophil elastase in cyclic and severe congenital neutropenia. Blood 2007; 109: 1817-1824.
17. Seger RA. Modern management of chronic granulomatous disease. Br J Haematol 2008; 140: 255-266.
18. Wen L, Atkinson JP, Giclas PC. Clinical and laboratory evaluation of complement deficiency. J Allergy Clin Immunol 2004; 113: 585-593.
19. McLean-Tooke A, Spickett GP, Gennery AR. Immunodeficiency and autoimmunity in 22q11.2 deletion syndrome. Scand J Immunol 2007; 66: 1-7.
20. Notarangelo LD, Miao CH, Ochs HD. Wiskott-Aldrich syndrome. Current Opin Hematol 2008; 15: 30-36.

COMPETING INTERESTS: None.