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Contents

Pneumococcal conjugate vaccine in children

Y. W. Kwan, Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital

Pneumococcal disease is a leading cause of serious illness in children throughout the world. The infectious agent, *Streptococcus pneumoniae*, is a Gram-positive α-haemolytic encapsulated diplococcus. The polysaccharide capsule defines the serotype and at present, 91 distinct serotypes were identified (a new serotype 6C was reported in April 2007) [1]. The prevalence of each serotype varies with the age of the population and the geographical region.

Infection by *S. pneumoniae* may cause non-invasive diseases e.g. otitis media, sinusitis, bronchitis and community acquired pneumonia. However, *S. pneumoniae* may also cause invasive diseases e.g. empyema, septicaemia and meningitis. The definition of invasive disease is the isolation of *S. pneumoniae* in a normally sterile site or the demonstration of *S. pneumoniae* antigen in the cerebrospinal fluid.

The major virulence factor of *S. pneumoniae* is the polysaccharide capsule, which prevents phagocytosis of the bacteria by macrophages. Invasive diseases were caused by only a limited number of serotypes.

Epidemiology

Pneumococcus infection is very common in the very young and the very old. The bacteria colonise the upper respiratory tract of healthy people and it was transmitted through respiratory droplets. The incubation period ranged from 1-3 days.

The rate of nasopharyngeal carriage of *S. pneumoniae* varies with age, geographical location, socio-economic status and in households with children [2,3]. In London, 51% of children attending child care centre aged between 6 months and 5 years carry *S. pneumoniae* in their nasopharynx [4]. Study in Hong Kong found that 19.4% of all children carry the bacteria in their nasopharynx (28.8% in children age between 2-3 year-old and 15.2% in children 6 year-old) [5].

Disease burden

In 2005, WHO estimated that 1.6 million people die of pneumococcal disease every year, this estimate includes the death of 0.7-1 million children aged <5 years, most of them live in developing countries [6]. Otitis media due to *S. pneumoniae* in children is the most frequent reason for paediatric office visits in the United States [7]. There were studies showing that language development of children is affected by the duration of otitis media [8,9]. In adults, pneumococcal pneumonia causes significant morbidity and mortality, predominantly in the elderly and immunocompromised.

Another global emerging problem concerning *S. pneumoniae* disease is that pneumococcus has become increasingly resistant to antibiotics during the last decade.

Prevalence of invasive pneumococcal disease (IPD)

The prevalence of pneumococcal disease varies with geographical region, age, underlying disease and ethnic group. The rate was higher in children <2 years old, with underlying disease or had attended daycare centre in the previous 3 months [10,11].

The incidence of IPD per 100,000 population in children in the United States during the pre-vaccine era was 165.3 in <1 year old and 203.3 in <2 years old. It was 37.1-48.1 and 96.4 in children <1 year old in the United Kingdom and Australia respectively [12]. The

incidence in children <2 years old is 45.3 in Finland and 458 in Kenya [13].

In Hong Kong, in a study performed during 1995-2004, the annual incidence of culture confirmed IPD was 18.8 and 15.6 per 100,000 population in <1 and <5 years old respectively [14]. The overall estimate of the pneumococcal burden in Hong Kong for children <5 years old would be 20 per 100,000 for bacteraemia, 1 per 100,000 for meningitis and 1 per 1,000 for pneumonia [12].

Polysaccharide vaccine

Antibodies targeting the capsular polysaccharide provide serotype specific protection against pneumococcal infections. An unconjugated polysaccharide vaccine covering 23 serotypes primarily designed for older children and adult is available [15]. The indications for this polysaccharide vaccine include: healthy elderly people (>65 years of age), particularly those living in institutions; patients with chronic cardiopulmonary disease, diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid leak; patients with immunodeficiency; and children with high risk of IPD, such as sickle cell anaemia or post-splenectomy.

However, the polysaccharide vaccine does not work well in children <2 years old because these children respond poorly to T-cell independent antigens. Vaccination with polysaccharide T-cell vaccine cannot mount an adequate immune response.

Conjugate vaccine

A new generation of vaccine was developed in which the pneumococcal polysaccharide was conjugated with a protein carrier. The conjugated product produces a good T-cell dependent immune response with protective effect against IPD even in children <2 years old.

The conjugate vaccine available in Hong Kong contains 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, 23F). These 7 serotypes are responsible for causing 85% of pneumococcal diseases in the United States and 65-85% of IPD among young children in western countries [4]. In Hong Kong, this heptavalent conjugate vaccine respectively covers 89.7% of invasive isolates causing IPD [16].

Immunogenicity

In a study done in the United States, 212 2 months old infants were given the heptavalent pneumococcal vaccine, a stepwise increase in the geometric mean concentration of serotype specific antibodies to all the 7 vaccine serotypes were detected. A four dose regimen with the last dose given at 18 months of age demonstrated a brisk anamnestic response [17].

IPD in children

In the randomised double blind controlled trial done in the Kaiser Permanente population in North California, 37,868 healthy infants were enrolled and randomised to receive the heptavalent pneumococcal conjugate vaccine (PCV7) or the meningococcus type C conjugate vaccine as control. PCV7 contains serotypes responsible for 85% of pneumococcal disease in infants and children in the studied population. The vaccines were administered at 2, 4, 6 and 12 to 15 months of age, along with the standard immunisation schedule. The efficacy in reducing IPD was 97.4% in fully immunised children, 93.9% in intention to treat analysis and 89.1% effective in reducing overall IPD regardless of serotype. There was no increase in non-vaccine serotype IPD [18].

In a post-licensure study performed in the same Kaiser population between the period from April 1996 to March 2003, the incidence of IPD was dramatically reduced in children 1 year old from 51.5 – 98.2 per 100,000 to 0. The author concluded that PCV7 is highly effective in

reducing the burden of invasive pneumococcal disease in children <5 year of age [19].

In a recently published matched case-control study performed to evaluate the effectiveness of PCV7, the overall effectiveness of one or more doses of vaccine against disease caused by one of the seven vaccine serotypes was 72%. When controlled for underlying medical disorders, the effectiveness was 96% in healthy children and 81% in children with underlying medical disorders [20].

Effect on otitis media in children

The vaccine was shown to be effective in reduction of otitis media in children. In an efficacy study of PCV7 against acute otitis media (AOM) done in Finland on 1,662 infants, the efficacy of the vaccine against acute otitis media from any cause was 6%. The reduction of AOM caused by vaccine serotypes was 57% [21].

Similar efficacy was observed in the Kaiser Permanente population study on 37,868 healthy infants. PCV7 reduced the otitis media episodes by 7.0%, otitis media visits by 8.9%, and ventilatory tube placement by 20.1% compared with the control [18].

Nasopharyngeal carriage of pneumococcus

A study using two tetravalent pneumococcal conjugate vaccines, conjugated to either tetanus toxoid or diphtheria toxoid, showed a significant reduction in the carriage of vaccine-related serotypes after vaccination compared with the control [22].

A double-blinded, randomised study involving 264 toddlers attending day care centres showed that a 9-valent pneumococcal conjugate vaccine significantly reduced the carriage rate of vaccine and vaccine-related serotypes but there was evidence that the rate of carriage of non-vaccine type pneumococci was higher in the vaccine group than in the control [23].

Herd immunity effect

Herd immunity was defined as “when vaccinated persons in a population indirectly protect unvaccinated members by impeding the transmission of the infectious agents in the population”. Poehling observed a 42% drop in IPD rates among infants (<2 months) and children (5-17 years old) outside vaccinated age group who are not the target of vaccine prevention. These observations showed that unvaccinated population are benefiting from the herd immunity [24].

In the United States, the indirect effects of PCV7 (i.e., cases prevented in vaccine non-targeted persons) exceeded direct protective benefits among immunised children, with more than twice as many cases of IPD prevented indirectly as directly in 2003. These indirect effects of PCV7 are believed to be caused by decreased nasopharyngeal carriage of vaccine serotypes among immunised children, which results in decreased transmission to non-immunised children and adults [25].

In the post-licensure study performed in the North California Kaiser Permanente population, there was statistically significant decrease in the risk of IPD among all individuals older than 5 years as well as those 20-39 years of age and among those elderly people ≥60 years of age [19]. This indirect effect was also observed in other studies [26, 27].

Effect on antibiotics resistance

Changes in the level of pneumococcal resistance to antibiotics were also observed in the Kaiser population post-licensure study. Comparing 2001-2002 with the period 1998-1999, the proportion of isolates resistant to penicillin decreased from 28.9% to 19.5%; the

proportion of isolates resistant to erythromycin decreased from 29.5% to 15.0%; the proportion of isolates resistant to tetracycline decreased from 39.3% to 13.9%, with each comparison P value <0.001 [19].

Safety information

The safety of the vaccine was assessed in different controlled clinical studies in which 18,000 healthy infants (6-18 months) were included [28]. The most frequently reported adverse events included injection site reactions, fever (38ºC), irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhoea and rash. The rate of these adverse events was similar to other vaccines. Contraindications for vaccination include hypersensitivity reaction to any vaccine component, including diphtheria toxoid.

Advisory Committee on Immunization Practices (ACIP) and WHO position paper

The US ACIP recommends universal vaccination of all infants ≤23 months of age and vaccination of all children 24-59 months of age, with the following conditions: sickle cell anaemia, splenic dysfunction, HIV / AIDS, chronic disease and immunocompromising condition [29].

In the WHO Position Paper on Pneumococcal Conjugate Vaccine for Childhood Immunization, WHO considers that pneumococcal conjugate vaccine should be a priority for inclusion in national childhood immunisation programmes [4].

Conclusion

From research evidence, conjugate pneumococcal vaccine seems to have a significant impact on pneumococcus epidemiology. The conjugate vaccine was shown to cause a large decline in invasive disease rates in young children. It also reduces the nasal carriage of vaccine serotypes. The resulting herd effect benefits other unvaccinated children and adults. There is also reduced antibiotics resistance in the pneumococcal isolates in the vaccinated communities. The effectiveness and health benefit in the use of this vaccine in the local community need detailed analysis of the local IPD data and calculation of the health economic benefit if universal vaccination is to be instituted.

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A patient with invasive listeriosis

Ken H. L. Ng, Department of Microbiology, Tuen Mun Hospital

Case summary

A 55 year old male patient with underlying systemic lupus erythematosis, steroid induced diabetes mellitus, lupus nephritis and end stage renal failure was admitted in February 2007 for one day history of dyspnoea. He was treated as fluid overload and his condition improved with fluid restriction, diuretic therapy and temporary haemodialysis. Four days after admission, he developed high swinging fever and chills, hypotension and acute confusion with Glasgow coma scale (GCS) of E3V4M6 (13/15). On physical examination, the haemodialysis catheter site was normal and there was no neck rigidity. Examination of the cardiovascular, respiratory and abdominal systems was unremarkable. Blood results showed a mild leucocytosis (WBC 10.35 x 10^9/L, neutrophil 90%, lymphocyte 3.4%), thrombocytopenia (platelet count 108 x 10^9/L) and markedly elevated alanine amino-transferase to 753 U/L (normal liver function tests on admission). Ceftazidime was started empirically after sepsis workup. Blood culture grew Gram-positive bacilli and antibiotic regimen was switched to high dose ampicillin and gentamicin to cover for possible invasive listeriosis. Urgent computed tomography scan of abdomen revealed multiple small liver abscesses. Lumbar puncture was not performed because of persistent low platelet count. Four sets of blood culture were collected and all of them detected growth of *Listeria monocytogenes*. MRI of brain done around one month after his presentation showed multiple tiny supratentorial enhancing nodules at the grey-white matter junction, basal ganglia, thalami and periventricular white matter. One of the lesions at the left thalamus appeared ring-enhancing but the brainstem was relatively spared. The patient was given more than three weeks of intravenous ampicillin and gentamicin and then switched to a three month course of oral co-trimoxazole. He responded well to the antibiotic treatment and was discharged in April 2007. Latest out-patient follow-up in August 2007 did not find any evidence of relapse of disease.

Discussion

Listeria is a catalase producing, non-sporulating facultative anaerobic Gram-positive bacillus. In clinical specimens, the organism may be Gram-variable and look like diphtheroids, cocci, or diplococci. Laboratory misidentification as diphtheroids, streptococci, or enterococci is not uncommon. It grows readily on blood agar with a narrow zone of beta-haemolysis. When being cultured at 25℃, it shows a characteristic tumbling motion produced by polar flagellae. Of the six species of *Listeria*, only *L. monocytogenes* is pathogenic for humans. There are at least 13 serotypes of *L. monocytogenes*, with serotype 4b most frequently associated with invasive listeriosis, while serotype 1/2a and 1/2b being the dominant isolates for gastroenteritis outbreaks. The bacterium is ubiquitous in soil and water. Being found in soil and vegetations, it can be easily contracted and transmitted by herd animals. As the bacterium can survive in temperatures from below freezing (-7℃) to body temperature, it can be found in a wide variety of foods even when they are properly refrigerated, including dairy products, processed meats, fresh meats and fish from delicatessen counters or supermarkets and raw vegetables. Human exposure is common and asymptomatic stool carriage can be detected in 1 to 5% of healthy adults. Despite the common exposure, listeriosis is relatively uncommon with an estimated annual rate of 0.7 cases per 100,000 people in Western countries [1]. Listerial infection is generally thought of as a foodborne disease and transmission is mainly from the gastrointestinal tract. Large-scale outbreaks of listerial infections have been reported worldwide, with contaminated food as the culprit of such outbreaks. It is among the most important foodborne diseases as the mortality rate may be up to 30% in at-risk people [2].

The clinical manifestations of listerial infection may be divided into neonatal and

post-neonatal infections. Neonates may acquire the infection through maternal infection and during birth. The infants may present as early onset neonatal sepsis with multi-organ involvement, or late onset disease with meningitis. Post-neonatal infection can present in different ways. Firstly, listerial infection usually manifests as acute, self-limited, febrile gastroenteritis in healthy persons. Symptoms typically occur within 24 hours (ranged from 6 hours to 10 days) and the usual duration of symptoms is 1 to 3 days. The most frequently reported symptoms are fever (60-100%), diarrhoea (33-88%), arthromyalgia (20-100%) and headache (15-88%) [3]. Up to 2-20% of patients may require hospitalisation. Secondly, pregnant women are more prone to develop listerial infection compared with the general population. Maternal listeriosis usually manifests as a nonspecific febrile illness that is rarely diagnosed prepartum. In one review, 65% of patients had fever, 32% had “flu-like” syndrome, 21.5% had back pain, 10.5% had headache but 29% were asymptomatic [4]. Serious illness is uncommon for the pregnant women. However, the bacterium appears to have a predilection for the placenta and the foetus. Maternal infection may result in spontaneous abortion, stillbirth, death within hours after birth, or neonatal sepsis. Thirdly, *Listeria monocytogenes* may cause invasive infection that is associated with a high mortality. Several groups of individuals are at higher risks of suffering from invasive listeriosis, including the elderly, patients with diabetes mellitus, immunocompromised patients like transplant recipients and AIDS patients. Primary bacteraemia without obvious focus of infection is the commonest form and the patients may present with non-specific features like fever and myalgia. Central nervous system infection is not uncommon. Meningitis, cerebritis, brain abscess and meningoencephalitis have been reported and the patients may develop altered consciousness, seizures, movement disorders, or clinical features of meningoencephalitis. Brainstem encephalitis (rhombencephalitis) is an uncommon entity that occurs in healthy adults. It may present with cranial nerve deficits, cerebellar signs, and hemiparesis or hemisensory deficits after a prodrome of fever, headache, nausea, and vomiting. The presentation may be non-specific and misdiagnosed as other non-infectious clinical conditions, since fever may be absent in certain proportion of patients. Other focal infections, like endocarditis, pneumonia, spontaneous bacterial peritonitis, osteomyelitis and septic arthritis, have also been reported [2].

In-vitro studies showed that *Listeria monocytogenes* is susceptible to a large range of antibiotics including ampicillin, aminoglycosides, glycopeptides and co-trimoxazole, but it is resistant to cephalosporin antibiotics. Gentamicin has synergistic killing effect with ampicillin in in-vitro and animal studies [5]. There have been no controlled trials to look for the best antibiotic regimens for listerial infection. In general, ampicillin is the suggested treatment of choice for invasive infections. Many authorities also suggest that gentamicin should be added in treating cases of listerial bacteraemia in at-risk groups and all cases of meningitis and endocarditis. Co-trimoxazole appears to be the best alternative to ampicillin and gentamicin. In one series of 22 adult patients with severe meningoencephalitis, the combination of trimethoprim-sulfamethoxazole plus ampicillin was associated with a much lower failure rate and fewer neurologic sequelae than ampicillin combined with an aminoglycoside [6]. Prevention of listeriosis can be achieved by control of the organism at different levels. In the food processing environment, programmes like Hazard Analysis at Critical Control Points help to improve control of *Listeria* and other foodborne pathogens. At the household level, dietary recommendations, with emphasis on thorough cooking and pasteurisation of food, together with avoidance of high risk food items for persons at increased risk were effective measures in preventing foodborne listeriosis. Finally, there is circumstantial evidence that antimicrobial prophylaxis, like co-trimoxazole used in protecting against *Pneumocystis jirovecii* pneumonia for HIV patients, might have a role in preventing listeriosis in such high risk patients [2].

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Chronic malaria infection revealed after a decade

Jacky M. C. Chan, Department of Medicine and Geriatrics, Princess Margaret Hospital

Case presentation

A 75-year old lady presented with syncope and was admitted to a local hospital. She lived in Hong Kong with her son. She had history of old cerebral vascular accident and hypertension with regular visits to general outpatient clinics.

She presented with an episode of syncope while having dinner in a restaurant. It lasted for a few seconds and she spontaneously recovered. There was no preceding palpitation or dizziness. On further questioning, she complained of on and off fever and chills for one month. There was no chest or urinary symptom.

Physical examination revealed the presence of moderate splenomegaly without hepatomegaly. She had low grade fever and examination of other symptoms was unremarkable. A complete blood picture revealed pancytopenia (haemoglobin 8.1 x 10^9/L, WCC 3.7 x 10^9/L, platelet count 50 x 10^9/L). Serum biochemistry showed normal transaminase and creatinine levels. Blood for malaria smear revealed the presence of *Plasmodium malariae*. Urine for multistix revealed no abnormality. Blood for IgM level was normal. Ultrasound of the abdomen confirmed the presence of splenomegaly, measuring 15 cm in length.

Travel history was reviewed. She lived with her son in Panama in Central America from 1989 to 2000, while her son was staying there for work. She did not have other travel history.

The patient was started on chloroquine. Fever subsided and blood smear for malaria parasite was negative six days after a course of treatment. She was discharged home and her progress was monitored in our outpatient clinic. Repeated blood smears for malaria parasite were negative in follow-up and complete blood picture also normalised.

Discussion

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The four *Plasmodium* species that infect humans are *P. falciparum, P. vivax, P. ovale* and *P. malariae*. Malaria most commonly presents as an acute systemic, febrile illness but may manifest more indolently as chronic anaemia, glomerulonephritis, or tropical splenomegaly syndrome. Although all the major malaria parasites of humans cause acute illness that may be accompanied by splenomegaly, *P. malariae* is the only one recognised to cause asymptomatic infections that can last for decades [1].

P. malariae often establishes parasitaemia that is below levels of detection by microscopy. A recrudescence is sometimes induced by splenectomy performed for reasons unrelated to malaria [1]. Recrudescence of malaria may present as recurrent febrile episodes after splenectomy or quartan malarial nephropathy [2]. In our case, the patient presented with moderate splenomegaly and pancytopenia.

Hyper-reactive malarial splenomegaly (HMS) is the commonest cause of huge splenic enlargement in many malaria-endemic areas. It was formerly known as tropical splenomegaly syndrome. The underlying abnormality appears to be an aberrant immune response to repeated malaria infections, leading to overproduction of IgM and hyperplasia of lymphoreticular system [3,4,5]. Massive splenomegaly poses deleterious effects like hypersplenism and risk of splenic trauma [4].

Criteria for the diagnosis of HMS were first published in 1979 and modified shortly after to comprise both major and minor criteria [3]. Among these criteria gross splenomegaly >10 cm, IgM titre more than 2x standard deviation of the local mean and clinical and immunological response to long term therapy are the cornerstone of diagnosis [3,6].

P. malariae should be treated with the standard regimen of chloroquine. It does not require radical cure with primaquine, as its life cycle does not involve the hypnozoite stage. Resistance of *P. malariae* is not well characterised and infection caused by this species is considered to be generally sensitive to chloroquine. For patients living in endemic areas with diagnosis of HMS, antimalarial therapy (chloroquine / proguanil / sulphadoxine + pyrimethamine) is the recommended treatment. However, the duration of treatment is not standardised [4,7]. Splenectomy is not recommended for the treatment of HMS unless in critically ill patients, such as patients with splenic trauma [4].

In summary, we described a case of chronic *P. malariae* infection presented with splenomegaly and pancytopenia, with past history of residence in a malaria-endemic area. Chronic malaria infection should be included in the differential diagnosis for patients with splenomegaly and pancytopenia. The lack of significant rise in IgM made the diagnosis of HMS less likely. Early diagnosis and heightened awareness of malaria help saving patients from invasive investigations, as well as achieving an early recovery from complications.

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Journal review

Alan K. L. Wu, Department of Pathology, Pamela Youde Nethersole Eastern Hospital

Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007; 45:302-7.

Nowadays in acute hospital settings Clostridium difficile is undoubtedly the single most important cause of nosocomial diarrhoea. It is of note that the efficacies of two available therapies for *C. difficile*–associated diarrhoea (CDAD), namely metronidazole and vancomycin, had not been formally compared in large randomised placebo-controlled trials before. Recently a group of US researchers have conducted a single-centre, double-blind study in which patients with diarrhoea and either *C. difficile* toxin A in the stool or documented pseudo-membranous colitis were randomised to receive oral vancomycin 125 mg or metronidazole 250 mg, each plus placebo, four times daily. Patients were stratified by CDAD severity according to a scoring system which took into account clinical, laboratory and endoscopic findings. Cure was defined as resolution of diarrhoea by day 6 and a negative stool toxin assay taken around the same time.

A total of 150 participants were enrolled, with 69 of them classified as having severe CDAD. For patients with severe disease, the cure rate was significantly higher with vancomycin than with metronidazole (97% vs. 76%; P=0.02). However, for patients with mild CDAD, the difference was much smaller and did not reach statistical significance (98% vs. 90%; P=0.36). There were no significant differences in relapse rates or adverse events between the two therapies. Having a serum albumin level <2.5 mg/dL, presence of pseudo-membranous colitis, as well as ICU admission were factors significantly associated with metronidazole failure.

Points to note: These findings are in line with several other observations that metronidazole has become increasingly less effective in the treatment of CDAD. However, metronidazole is still currently recommended in most guidelines as first-line therapy for CDAD, primarily because it is less expensive and because of the concern with increasing prevalence of vancomycin-resistant organisms in the intestinal lumen. In light of the recent findings, however, such recommendations may have to be re-evaluated and possibly modified in the near future.

Madruga JV, Cahn P, Grinsztejn B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet. 2007; 370: 29-38.
Lazzarin A, Campbell T, Clotet B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet. 2007; 370: 39-48.

Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) (such as efavirenz and nevirapine) are commonly prescribed to treat HIV infection and their uses have been recommended in various guidelines. However, a single mutation in the virus may confer cross-resistance to NNRTIs that are currently in use. Etravirine, a second-generation NNRTI, has been demonstrated to have in-vitro activity against HIV that is resistant to older NNRTIs. Investigators recently reported results from two ongoing, multinational studies of etravirine in treatment-experienced HIV-infected adults with genotypic evidence of NNRTI resistance and

three or more protease inhibitor (PI) mutations.

All patients received a standard PI (darunavir boosted with low-dose ritonavir) and an optimised regimen selected by the investigators. In both studies (DUET 1 and 2), more than 500 patients were randomised and treated. It was found that the proportion of participants with undetectable viral loads (<50 copies/mL) at week 24 was significantly higher in the etravirine group than in the placebo group for both trials (56% vs. 39% in DUET-1; 62% vs. 44% in DUET-2). Etravirine conferred no added benefit for patients with darunavir-sensitive virus who were receiving enfuvirtide for the first time as part of the optimised regimen. Adverse events were similar between groups. Of note, etravirine was not associated with an excess risk for the neuropsychiatric side effects, and some patients developed mild skin rash which did not lead to discontinuation of their drugs.

Points to note: A number of new experimental drugs for HIV have emerged this year, including raltegravir (integrase inhibitor), maraviroc (CCR5 antagonist), and etravirine, a new NNRTI with activity against drug-resistant virus. Now that etravirine may be available in the future, there is a theoretical reason to avoid continuing the NNRTI portion of a failing HIV regimen, because continuation of such a regimen may lead to selection for multiple mutations that could eventually compromise the activity of etravirine. Etravirine, like raltegravir and maraviroc, is currently only available in the US through expanded access programmes. Further studies on its efficacy and safety are eagerly awaited.

Corneli HM, Zorc JJ, Majahan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. N Engl J Med. 2007; 357: 331-9.

Bronchiolitis is a common cause of hospital admission for infants worldwide. Although bronchodilators and steroids have been used to ameliorate this condition, results have been mixed and no definite conclusions could be drawn from previous small studies. A group of US investigators has recently evaluated the use of dexamethasone in a large, randomised, placebo-controlled trial and published their findings in the *New England Journal of Medicine*.

A total of 600 infants, aged 2 to 12 months, who presented with moderate-to-severe bronchiolitis to 20 emergency departments (EDs) in the US were enrolled into the trial. Half of the infants received a single dose of dexamethasone (1 mg/kg orally) in the ED, and half received placebo. No significant difference was seen in the proportion of infants who were eventually admitted to the hospital after 4 hours of observation in the EDs (dexamethasone group 39.7% vs. placebo group 41%). While in the ED, the two groups experienced similar improvements in symptoms, and those admitted to hospitals had similar lengths of stay and similar rates of subsequent readmissions. No apparent benefit in any parameters was detected even in the subsequent subgroup analyses.

Points to note: These results suggested that dexamethasone may not be useful in patients with bronchiolitis, despite what was suggested on the contrary by previous smaller, possibly under-powered studies. This study demonstrated the superiority of evidence from well-conducted studies over that of intuition of clinicians. Further studies are needed to clarify the situation. Until such results are available, the practice of giving steroids routinely for patients who presented with bronchiolitis to EDs may no longer be warranted.