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Editorial Board

New methods in the diagnosis of tuberculosis

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Introduction

Tuberculosis (TB) remains one of the major causes of death from a single infectious agent worldwide. In Hong Kong, the notification rate was 91.46 per 100,000 population while the death rate was 3.44 per 100,000 population in the year 2004. Although the notification rate was on the downward trend, it is still of hundred folds of that of developed countries. Even greater concern is the emergence of drug resistance since there is no drug for some multidrug resistant strain of *Mycobacterium tuberculosis* (MTB) and there is concern that they may spread worldwide. Directly observed treatment short course (DOTS) is effective in preventing the emergence of drug resistance. In practice, only 27% of tuberculosis patients actually receive DOTS. Additional control measures, such as new diagnostic tools, more effective drugs, or even a more effective vaccine need to be developed. The gold standard for tuberculosis diagnosis is still the cultivation of MTB. Recent advances in the field of molecular biology and progress in the understanding of the molecular basis of drug resistance of MTB have provided new tools for the rapid diagnosis by molecular methods.

Detection of tuberculosis infection

At present tuberculin skin test is used to detect latently infected patient with the aim to treat before active tuberculosis is developed. New methods such as interferon assays based on the fact that T cells sensitised with tuberculous antigens will produce IFN-γ when they are re-exposed to mycobacterial antigen [1-2]. It has the advantage of higher specificity and better correlation with previous exposure to MTB and low cross reaction due to BCG vaccination or previous exposure to nontuberculous mycobacteria. However, it is only available in some research centres in Hong Kong.

Microscopy

Auramine O is a fluorescent stain which allows a faster rate of detection is used in our daily practice. This fluorescent method is associated with a higher rate of detection, since slides can be examined at lower magnification. The traditional method of Ziehl-Neelsen is then used to confirm the presence of acid fast bacilli (AFB) [3].

Culture

Cultivation of MTB with Lowenstein-Jensen (LJ) medium and Middlebrook agar from clinical samples is still the gold standard for the diagnosis of active TB. It can detect 100 bacilli/mL of sputum in comparison with 5000-10000 bacilli/mL needed for microscopy.

Recent advance in this aspect is the use of automatic system for culturing mycobacteria initially with the introduction of radiometric system such as BACTEC 460 (14 C-labelled palmitic acid as substrate with detection of 14 CO_2 gas in headspace). This was followed by non-radiometric systems e.g. BACTEC 9000MB (which was available in Hong Kong and was used in the presence of high clinical suspicion), BACTEC MGIT (mycobacteria growth indicator tube) [4]. The underlying principle of both systems is that oxygen in the medium quenches the fluorescence of the ruthenium complex sensor. Growth of mycobacteria or other organism in the broth depletes oxygen and the indicator fluoresces brightly when the tube is illuminated with UV. Other automatic system e.g. MB/BacT system employs a colorimetric carbon dioxide sensor to detect mycobacteria growth. Moreover, MGIT and MB/BacT can be used for sensitivity tests as well.

These advances allow the detection of MTB in 1-2 weeks compared with at least 3-8 weeks in the conventional culture media. However they are available mainly in selected centres.

Identification

Identification by conventional biochemical test is slow. Rapid test include GLC of short chain fatty acids and HPLC of mycolic acid of mycobacterium species [5]. They are available in reference centres only. Therefore, molecular methods were introduced for identification of mycobacteria.

DNA probe complementary to species specific sequence of rRNA become commercially available in 1987 for identification of MTB complex, MAI complex, *M gordonae* and *M kansasii*. There are currently 2 approved commercial nucleic acid amplification techniques, the amplified mycobacterium tuberculosis direct test (AMTD) (Gen-Probe) and the Cobas Amplicor mycobacterium tuberculosis assay (Roche). Both methods have been approved for the direct detection of MTB in smear-positive respiratory specimens.

A non-amplification molecular assay, the AccuProbe (Gen-Probe) is also available for rapid identification. It is based on species-specific DNA probes that hybridise to rRNA [7]. Up to 6 probes are available for species identification. It has a very good sensitivity and specificity and can give result in 2 hours from culture-positive specimens. When compared with culture and the clinical status, these methods have a high sensitivity and specificity in smear-positive specimens, but lower values are obtained in smear-negative specimens precluding their use as a screen to rule out the disease. For this reason, it has been recommended that molecular methods should be interpreted in conjunction with the patient's clinical data.

Two other methods recently introduced for TB diagnosis involve real-time PCR and strand-displacement amplification methods. The real-time PCR technology is based on hybridisation of amplified nucleic acids with fluorescent-labelled probes spanning DNA regions of interest and monitored inside thermal cyclers [7]. The sensitivity ranges from 71-98%, with specificity close to 100%. The main advantage of real-time PCR is its speed in giving results 1.2-2 hours after DNA extraction, and the decrease in the risk of contamination since both reaction and detection occurs in a single tube. However, further studies are necessary to confirm the real value of this new method in the clinical setting.

The strand-displacement amplification technique is performed by the BDProbe Tec MTB test, a semi-automated system developed by Becton Dickinson for the rapid detection of MTB in respiratory samples. It is based on the enzymatic replication of target sequences of the insertion sequence IS6110 and the hypervariable regions of 16S rRNA gene of mycobacteria. The overall sensitivity is 97.6% and specificity of 95%. The drawback is the presence of false-positive results. This can provide rapid identification and phylogenetic information. However they are expensive.

Detection of antibiotic resistance against rifampicin and isoniazid by molecular method is another major advance in TB diagnostics [6]. Drug susceptibility testing by DNA sequencing of mutation in the rpoB gene in rifampicin-resistant strains is available in some laboratories in Hong Kong.

Molecular epidemiology techniques

DNA fingerprinting techniques include the restriction fragment length polymorphism (RFLP) typing as the most commonly used method in the study of the epidemiology and

pathogenesis of TB. It is based on the insertion sequence IS6110 present in MTB and is accepted as the standard typing method. More recent methods include genomic deletion analysis and mycobacterial interspersed repetitive units (MIRU) typing. Genomic deletion analysis uses DNA microarrays to detect genomic evolution, and population structure of MTB [7]. MIRU typing is based on the variability in the numbers of tandem repeats that are 40-100bp elements dispersed in intergenic regions of the MTB genome. This typing technique has been compared with RFLP typing and spoligotyping producing more distinct patterns. These techniques would probably provide insights into epidemiology, genomic evolution, and population structure of MTB.

Conclusion

New diagnostic approaches are becoming available. New diagnostic methods should be as good or even better than the currently existing tools and be adequate for low resource countries where the burden of TB is still high. Moreover, these tests should be evaluated in well designed and controlled clinical trials and tested in high-endemic, low-resource settings where the implementation and use of these methods are more needed to contribute to the improvement of tuberculosis control.

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Multidrug-resistant *Pseudomonas aeruginosa*

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Multidrug resistance in *Pseudomonas aeruginosa* is frequent, and clinical isolates resistant to virtually all anti-pseudomonal agents are increasingly being reported worldwide including Asia-Pacific region.

P. aeruginosa is a Gram-negative straight or slightly curved rod with a length ranging from 1 to 3 μ m and a width of 0.5 to 1.0 μ m. *P. aeruginosa* is able to grow on a wide variety of media, ranging from minimal to complex, and can metabolise a large array of carbon sources. This metabolic versatility contributes to a broad ecological adaptability and distribution. In the community, *P. aeruginosa* is commonly found in soil, water, and plants. It is occasionally pathogenic for plants as well as animals. The organism is tolerant to temperatures as high as 45℃ to 50℃ and can grow in distilled water using dissolved carbon dioxide and residual sulfur, phosphorus, iron, and divalent carbon cations as carbon and essential nutritional substrates. Within the hospital environment *P. aeruginosa* can colonise moist surfaces of patients on the axilla, ear, and perineum and is also isolated from other moist, inanimate environment including water in sinks and drains, toilets, and showers.

P. aeruginosa emerged as a major human pathogen in the 1960s because of its ability to cause infections in immunocompromised and burn victims as well as cystic fibrosis patients. Since then, it has become one of the most serious causes of nosocomial bacterial infections, notably in the lung, blood and urinary tract, particularly in patients undergoing mechanical ventilation, antibiotic treatment, chemotherapy, or surgery.

Antimicrobial susceptibility of Pseudomonas aeruginosa

The antimicrobial susceptibility rates of *P. aeruginosa* have been decreasing in recent years. Data from the global SENTRY antimicrobial programme showed that Latin America had the lowest susceptibility rate to all antimicrobial agents tested, followed by Asia-Pacific (to beta-lactams) and European strains (to fluoroquinolones) [1]. Amikacin was associated with the highest susceptibility, in all regions except Latin America. On the other hand, Europe was the only region in which there was a significant decline in the beta-lactam and aminoglycoside susceptibility rates over the years. The SENTRY study also showed that a total of 218 (3.3%) multidrug-resistant *P. aeruginosa* (MDRPA) isolates (resistant to piperacillin, ceftazidime, imipenem, and gentamicin) were noted from 6,631 *P. aeruginosa* isolates based on data collected from 1997-1999. In Europe, there was considerable inter-country variation in the proportion of *P. aeruginosa* that were MDR, ranging from 50% in Turkey to <3% in Spain, the UK, Germany, Bulgaria and Malta [2].

Mechanisms of antimicrobial resistance in *P. aeruginosa*

P. aeruginosa is inherently resistant to many antibiotics including most beta-lactams, the older quinolones, chloramphenicol, tetracycline, macrolides, trimethoprim-sulfamethoxazole and rifampin. Acquired resistance arises by mutation or acquisition of exogenous resistance determinants.

Understanding of the underlying mechanisms of drug resistance aids the selection of antibiotic therapy in clinical practice. For example, when resistance is mutational, tobramycin and meropenem are the drugs most likely to retain activity whereas imipenem should be considered in isolates with efflux-mediated resistance to meropenem, penicillins, and cephalosporins. The mechanisms of antimicrobial resistance were summarised in Table 1.

Table 1. Multiple mechanisms for antimicrobial resistance in *Pseudomonas aeruginosa* [3,4]

Resistance mechanisms	Affected antipseudomonal agents
Mutational resistance	
AmpC derepression	Penicillins, cephems, monobactams
Membrane changes	Polymyxins, aminoglycosides
OprD loss	Carbapenems
Reduced affinity of topoisomerase II/IV	Fluoroquinolones
Up-regulations of efflux pumps	
MexAB-OprM	All beta-lactams except imipenem Fluoroquinolones
MexCD-OprJ	Some beta-lactams (cefoperazone, cefpirome, cefepime, meropenem)
MexEF-OprN	Fluoroquinolones, carbapenems
MexXY-OprM	Some beta-lactams (cefoperazone, cefpirome, cefepime, meropenem) Fluoroquinolones, aminoglycosides
Acquired genes	
Beta-lactamases	
Narrow-spectrum molecular class A	Penicillins, cefoperazone
Extended-spectrum molecular class A	Penicillins, cephems, monobactams
Molecular class B metallo-enzymes	All beta-lactams except monobactams
Aminoglycoside-modifying enzymes	
AAC(3')-I	Gentamicin
AAC(3')-II	Gentamicin, tobramycin, netilmicin
AAC(6')-I	Tobramycin, netilmicin, amikacin
AAC(6')-II	Gentamicin, tobramycin, netilmicin
AAC(2')-I	Gentamicin, tobramycin

Control of MDRPA

Prevention and control of infections caused by *P. aeruginosa* requires attention to many aspects of patient care and the hospital environment. In addition, judicious use of antibiotics is of paramount importance to prevent development of multidrug-resistant strains.

The major vehicles by which *P. aeruginosa* is conveyed into hospitals are food and tap water. Vegetables are the most commonly contaminated foods in western countries; however, in Asia the vegetables are usually well cooked instead of in the form of salads and hence food probably carry less significance as a vehicle for contamination. Studies to ascertain whether environmental isolates of *P. aeruginosa* cause colonisation or infection of patients have implicated most of the potential sources listed in Table 2. *P. aeruginosa* can persist in biofilms within the hoses, pipes, and filters despite the use of disinfectant and *P. aeruginosa* can proliferate rapidly if disinfectant levels decrease below recommended concentrations. Apart from inanimate reservoirs, colonisation of patients constitutes an important animate reservoir, particularly in specialty care units where patients are exposed to broad-spectrum antibiotics, medical devices, and healthcare personnel.

Table 2. Hospital sources of Pseudomonas aeruginosa [5]

Sources		
Tap water supply	Water for humidification	Distilled water
Sterile water or saline	Nonsterile water	Injected medications
Ventilator	Faucet aerator	Whirlpool or hydrotherapy tank
Sink drain	Showerhead	Water fountain or ice machine
Urine collection device	Endoscope washer	Endoscope, cystoscope, or bronchoscope
Suction apparatus	Sink or wash basin	Haemodialyzer or dialysis machine
Blood products	Enteral formula	Linen, bedclothes, or mattresses
Mouth wash	Skin cream	Antiseptic or disinfectant

Nosocomial transmission of *P. aeruginosa* almost always results either from contact with environmental sources or from patient-to-patient spread via personnel. Patient-to-patient transmission of *P. aeruginosa* is documented by prospective studies in which periodic surveillance cultures of patients, personnel, and the environment were performed. Contaminated hands of personnel are the likely vehicles of cross-transmission. The frequency of patient-to-patient transmission by personnel probably reflects the inadequacy of staffing, availability of gloves and hand-washing sinks, and attention to hand washing and other aseptic techniques. There is evidence that when proper aseptic practices are observed, most of the apparent acquisitions of *P. aeruginosa* represent the emergence of strains carried in the gastrointestinal tract at concentrations below the threshold of detection [5].

Control measures against drug-resistant *Pseudomonas aeruginosa* should start with surveillance of antibiotic resistance via the laboratory database. Continuous surveillance enables earlier identification of outbreak with multidrug-resistant strains and monitoring of its subsequent control. Patient care practices should be reinforced aiming at general reduction of nosocomial spread. Disinfections and sterilisation of both medical equipment and the environment would serve to reduce microbial contamination and eliminate common source of infection. Appropriate isolation and barrier precaution should be applied in cases proven to be infected or colonised with multidrug-resistant organisms in order to minimise the risk of patient-to-patient transmission. Antibiotic stewardship programme should be instituted as a means to reduce the selective pressure on drug-resistant organisms. Finally, modification of host risk profile would be as important as the above mentioned control measures to reduce colonisation and halt progression to infection. For example, removal of unnecessary indwelling catheters may already suffice to stop the colonisation and even subsequent outbreak of multidrug-resistant organisms.

Currently, unlike Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus*, there is no specific recommendation on isolation policy on drug-resistant Gram-negative organisms. Besides *Pseudomonas aeruginosa*, other hospital acquired non-fermentative Gram-negative organisms like *Acinectobacter* and *Stenotrophomonas* are well equipped to resemble MDRPA in causing infection control and therapeutic headaches in any hospital with patients requiring antimicrobial therapies. Therefore, it would be prudent to set up recommendations for cohorting these patients, better before acquiring organisms 'pan-resistant' to all antibiotics, to avoid cross-transmission in view of the potential for large-scale outbreak and lack of effective treatment.

Treatment for MDRPA
When strains have multiple mutational or acquired resistance, the choice of therapy is often limited, especially when it is preferable to use a synergistic combination for serious *Pseudomonal* infections. Ciprofloxacin remains the most potent fluoroquinolone against *P. aeruginosa*, but none of others in the same class retains activity against ciprofloxacin-resistant isolates. Tobramycin and meropenem are the aminoglycoside and the beta-lactam with the best inherent activity against *P. aeruginosa*, and are the drugs most likely to retain activity in mutational resistance. For treatment of *P. aeruginosa* in which the susceptibilities of beta-lactams, aminoglycosides, and quinolones are lost, the polymyxins remain drugs of last resort despite their toxicity. Aerosolised colistin may be an effective route of administration for these patients. Multidrug efflux inhibitors are promising for use with fluoroquinolones or beta-lactams, and metallo-beta-lactamase inhibitors are the focus of laboratory investigation.

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An elderly lady springs a big surprise

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Malaria often presents with an acute illness, classically in a returning traveller. The following patient illustrates that common disease can present in an unusual manner.

The case

Our patient is a 77-year-old lady who presented in November 2004 for self-noticed left-sided abdominal mass and ankle swelling for several weeks. She had no fever, bowel symptoms or weight loss. Her medical history was only remarkable for type 2 diabetes mellitus, with good glycaemic control with oral hypoglycaemic agent. She had no family or past history of liver or haematological diseases. She moved to Hong Kong from Guangdong province in 1949 and had never travelled out of Hong Kong since then. She currently lives in a village house in Tai Po. Physical examination revealed gross hepatosplenomegaly, with the liver extending 4cm and the spleen 20cm below the costal margins, and bilateral lower limb pitting oedema. Initial investigations revealed marked pancytopenia and normal liver and renal function tests. Ultrasonography of the abdomen revealed a liver span of 17cm at mid-clavicular line and a splenic size of 27cm, as well as mildly enlarged para-aortic lymph nodes. Bone marrow examination was refused when offered at that time.

The patient was first noticed to have episodic fever, chills and rigors since February 2005. Quartan fever pattern was noticed. Routine blood, sputum and urine cultures were negative. Two blood films sent for malarial screen were negative in March 2005. Bone marrow examination was performed after obtaining the patient's consent, and showed hypercellular marrow with multiple foci of nodular interstitial infiltration by abnormal lymphoid cells positive for CD20 and BCL-2. A diagnosis of low-grade lymphoma of B cell lineage (small lymphocytic lymphoma) was made. The patient was given a course of dexamethasone 20mg daily for 4 days for palliation and discharged.

She was re-admitted again in April 2005 for recurrent episodes of fever. Repeated sepsis workup was negative and her symptoms showed no response to empirical broad-spectrum antibiotics. As she had persistent quartan fever pattern, a repeated malarial screen was performed and 3+ parasitaemia of *Plasmodium malariae* was revealed on the blood film. A standard 3-day therapy with chloroquine was given. Repeated blood films for malaria up to one month post-treatment were negative. A repeat bone marrow examination two months post-treatment showed persistent features of lymphoma. The patient remained afebrile and had improvement in her cell counts and partial resolution of splenomegaly during follow-up at 3 months post-treatment.

Discussion

This interesting case raised several issues regarding the clinical course of malaria and its relationship with haematological malignancy.

Plasmodium malariae is the only plasmodial infection that can be associated with low-grade or undetectable parasitaemia and symptomatic recrudescence decades after the last exposure to infection [1]. Local transmission of malaria was interrupted in 1969 and sporadic indigenous cases were reported up to the early 1980s in Hong Kong [2]. As our patient had no travel history outside Guangdong province and Hong Kong during her lifetime, she had most likely acquired the infection in Hong Kong or even in Guangdong province at least 20

years prior to the onset of her symptoms. Similar cases of recrudescence of symptoms of *P. malaria* infection 20 to 40 years after exposure in endemic areas were not uncommonly reported in the literature [3,4,5,6].

As no hypnozoites were present in the liver in *P. malariae* infection, the appearance of symptoms after long periods of latency is most likely a result of recrudescence of the primary attack from erythrocytic forms persisting in small numbers in internal organs [7]. In most of the cases reported in the literature, the onset of symptoms following latent periods were preceded by various events, including splenectomy [8,9,10], acute infection [4] and immunosuppressive treatment [3]. In our patient, the onset of quartan fever should have been preceded by the development of lymphoma and the detection of parasitaemia by light microscopy was only feasible after the initiation of corticosteroid therapy. Thus, from experience in these human cases and similar observation for *P. inui* infection in macaques [11], it has been postulated that cellular immunity plays an important role in the control of *P. malariae* infection and T-cell immunosuppression accounts partly for the recrudescence of symptoms [3].

While various micro-organisms, such as *Helicobacter pylori* and *Epstein-Barr* virus, have been associated with lymphoproliferative diseases, so are *Plasmodium* species. An example is hyper-reactive malarial splenomegaly (HMS), a syndrome characterised by massive splenomegaly, elevated IgM levels and response to anti-malarial in persons residing in malarious areas. Splenic lymphoma with villous lymphocytes, a subtype of lymphoma found in West Africa, shares marked epidemiological and clinical similarities with HMS. The dysregulated immune response in HMS, together with additional mutational events, is believed to result in clonal lymphocyte proliferation [12]. Although our patient did not satisfy the diagnostic criteria of HMS, there exists a possibility that her long-standing malarial infection played a role in the development of lymphoma. Whether the treatment of malaria will lead to resolution of lymphoma, only time could tell.

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Journal Review

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Lau SK, Woo PC, Li KS, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci U S A. 2005; 102:14040-5.
Li W, Shi Z, Yu M, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science. 2005; 310:676-9.

Studies done previously have implicated palms civets as a probable animal source responsible for transmission of SARS-associated coronavirus (SARS-CoV) to humans, which led to the global emergence of the severe acute respiratory syndrome (SARS). However, civets are not widely believed to be a natural reservoir of the virus; this has led to efforts to identify other potential animal species harbouring the virus. Two new studies have now independently provided evidence that bats may serve that function.

Lau et al from HKU obtained nasopharyngeal and anal swabs from 127 bats, 60 rodents, and 20 monkeys found in rural areas around Hong Kong, and examined these specimens for presence of SARS-CoV by means of PCR testing. Anal swabs from 29 lesser bent-winged and horseshoe bats were found to yield positive test results. Subsequently the authors performed complete genome sequencing on three separate samples and noted that they exhibited 88% nucleotide and 93% amino acid homology to SARS-CoV from humans and civets. Serological testing on 38 serum samples from patients with recent human SARS-CoV infections demonstrated that only 1 had antibodies that recognised the bat SARS-CoV.

In another study, Li and colleagues obtained blood, faecal, and throat specimens from a total of 408 bats from 4 locations in China, which represented 9 different bat species. Antibodies to SARS CoV were detected in 20 of the 59 horseshoe bats tested; in 5 of the 20 animals, faecal samples revealed SARS-like CoVs on PCR testing. Complete genome sequencing of the PCR products from one faecal sample revealed a 92% nucleotide sequence identity to SARS-CoV. Considerable genetic diversity was found between this complete genome sequence and partial sequences from the four other PCR-positive faecal samples.

Points to note: Two independent studies have now demonstrated asymptomatic infection of a relatively high percentage of horseshoe bats in China with SARS- CoV like viruses. These findings certainly raise the intriguing possibility that bats might have served as a primary reservoir from which SARS-CoV emerged. Further study and monitoring of bats in the region are warranted and should be undertaken on a regular basis.

Lexau CA, Lynfield R, Danila R, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of paediatric pneumococcal conjugate vaccine. JAMA. 2005; 294: 2043-51.

The pneumococcal conjugate vaccine, now given routinely to all infants born in the U.S., has been shown to reduce nasopharyngeal carriage of the included pneumococcal serotypes in immunised individuals. Post-licensure studies performed shortly after its introduction in the U.S. in 2000 provided evidence that it was also inducing a herd effect among the general population. To determine the extent of this herd effect, researchers have now analysed the Active Bacterial Core Surveillance data on invasive pneumococcal disease (IPD) taken from eight U.S. regions, spanning a period from 1998 to 2003, among individuals aged 50 years or above.

Lexau et al found that the incidence of IPD declined significantly from 1998-1999 to 2002-2003 in all age groups studied: by 17% in individuals aged 50-64, by 29% in those 65-74, by 35% in those 75-84, and by 28% in those aged 85 or above. The decrease in pneumococcal infections was restricted to the seven vaccine-related serotypes. The rates of disease due to the serotypes included only in the pneumococcal polysaccharide vaccine showed no significant change, whereas the rates of disease due to non-vaccine serotypes actually increased slightly. The proportion of IPD patients with HIV infection or any chronic condition that is an indication for pneumococcal polysaccharide vaccine also increased significantly during the study period.

Points to note: These data demonstrate the important role that young children play, by acting as carriers, in maintaining certain virulent pneumococcal serotypes within the community. The findings also emphasise the need to incorporate an assessment of herd immunity into cost-effectiveness analyses of the pneumococcal conjugate vaccine. The study will have implications for local health authorities when considering whether to introduce universal vaccination programs for infants and children.

Ward JI, Cherry JD, Chang SJ, et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. N Engl J Med. 2005; 353: 1555-63.
Halperin SA. Pertussis — a disease and vaccine for all ages. N Engl J Med. 2005; 353: 1615-7.

More and more reports now indicate that the incidence of pertussis is increasing among adolescents and adults in the U.S., likely due to waning vaccine- or infection-induced immunity. Although the actual disease process tends to be milder in these populations, infected adolescents and adults can transmit Bordetella pertussis to infants, who may then develop severe diseases. In this randomised, double-blind, multi-cantered Adult Pertussis Trial conducted in the U.S., researchers prospectively evaluated the efficacy of an acellular pertussis vaccine administered to healthy 15- to 65-year-olds from 1997 through 1999.

The 2781 participants were randomised to receive either an acellular pertussis vaccine (in a dose one third of that given to children) or a hepatitis A vaccine as the control. They were subsequently followed for up to 2.5 years (median, 22 months) for development of pertussis-like illnesses, namely cough illnesses lasting >5 days. Such illnesses were evaluated by culture and PCR of nasopharyngeal aspirates and by serologic tests.

Cases of illness with prolonged cough (n=2672) were evenly distributed between the study groups. Ten cases of laboratory-confirmed pertussis occurred (9 of them in controls), yielding an overall vaccine efficacy of 92%. Pertussis incidence in the control group was 370 to 450 cases per 100,000 person-years, which translates to about a million cases annually in the U.S. among individuals 15 years or older. Laboratory-confirmed pertussis accounted for 0.7% to 5.7% of clinically-defined pertussis-like illnesses with prolonged cough.

Points to note: Optimal control of pertussis will probably require immunisation of adolescents and adults as well as children, and this definitive study now shows that acellular pertussis vaccine is highly efficacious in individuals older than and equal to 15 years old. Two acellular pertussis vaccines formulated for adults (and combined with an adult formulation of diphtheria and tetanus toxoids) are now licensed in North America and Europe. As an editorialist pointed out in an accompanying commentary, these vaccines should be widely used in place of the traditional diphtheria and tetanus vaccines for adolescents and perhaps

also for adults. It is expected that ACIP recommendations on the use of such vaccines would be published in the near future.

Meetings	
20-22 Feb 2006 The Sydney Masonic Centre Sydney, Australia	5th Australasian Viral Hepatitis Conference Contact: Locked Mail Bag 5057, Darlinghurst, NSW 1300, Australia Tel: 61 2 8204 0770 Fax: 61 2 9212 4670 E-mail: conferenceinfo@hepatitis.org.au Web: http://www.hepatitis.org.au
7-10 Mar 2006 Waterfront Hotel Lahug, Cebu City Philippines	3rd Asian Congress of Pediatric Infectious Diseases and 13th Pediatric Infectious Diseases Society of the Philippines Annual Convention "Pediatric Infections in the 21st Century: Meet the Challenges" Contact: Pediatric Infectious Disease Society of the Philippines (PIDSP) Unit 4 Metro Square Townhomes #35 Scout Tuazon corner Scout de Guia Sts., Quezon City Tel (632) 526-9167; (632) 374-1855 Fax (632) 404-2397; (632) 412-6998 E-mail: aspid@uplink.com.ph Web: http://www.asianpids.org
19-22 Mar 2006 Atlanta Marriott Marquis Atlanta, Georgia	International Conference on Emerging Infectious Diseases Contact: American Society for Microbiology ExpoExchange, P.O. Box 3867, Frederick, MD 21705 Phone: 202-942-9330 Fax: 202-942-9340 E-mail: iceid@asmusa.org
1-4 Apr 2006 Wellington Convention Centre, Wellington, New Zealand	Annual Scientific Meeting 2006 Australasian Society for Infection Diseases Contact: Dart Associates, PO Box 781, Lane Cove, Australia 2066 Tel: 61 2 9418 9396 Fax: 61 2 9418 9398 E-mail: dartconv@mpx.coom.au Web: http://www.racp.edu/asid
8-10 May 2006 Baltimore Marriott Inner Harbor Hotel Baltimore, Maryland	Ninth Annual Conference on Vaccine Research National Foundation for Infectious Diseases Contact: Sharon Cooper-Kerr or Sheena Majette 4733 Bethesda Avenue, Suite 750 Bethesda, Maryland 20814-5278 Tel: 301 656 0003 ext19 Fax: 301 907 0878 E-mail: vaccine@nfid.org Web: http://www.nfid.org/conferences/vaccine06

15-18 Jun 2006 Lisbon, Portugal	12th International Congress on Infectious Diseases International Society for Infectious Diseases Contact: 181 Longwood Avenue, Boston MA 02115, USA Tel: 61 7 277 0551 Fax: 61 7 731 1541 Web: http://www.isid.org
26-28 Jun 2006 Hyatt Regency Bethesda, Maryland, USA	2006 Annual Conference on Antimicrobial Resistance Contact: National Foundation for Infectious Diseases 4733 Bethesda Avenue Suite 750 Bethesda, Maryland 20814 Web: http://www.nfid.org
2-6 Jul 2006 Gold Coast Convention Centre Queensland, Australia	Australian Society for Microbiology Annual Conference 2006 Contact: Janette Sofronidis Conference Manager Australian Society for Microbiology Inc Suite 23, 20 Commercial Road, Melbourne, Vic, 3004 Tel: 61 3 9867 8699 Fax: 61 7 731 1541 Web: http://www.asmconferecnes.org
27-30 Sept 2006 San Francisco, California, USA	ICAAC 2006 46th Interscience Conference on Antimicrobial Agents and Chemotherapy Contact: American Society for Microbiology, 1752 N Street, NW, Washington, DC, 20036-2904 USA Tel: 1.202.942.9248 Email: icaac@asmusa.org Web: http://www.icacc.org