Reduced susceptibility of *Staphylococcus aureus* to vancomycin - a review of current knowledge

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Abstract

Antibiotic options for patients with methicillin resistant *Staphylococcus aureus* infections are severely limited. Unfortunately, infections with *S. aureus* with reduced susceptibility to vancomycin and teicoplanin have been recently reported for the first time. Commonly used laboratory methods for determining antibiotic susceptibility may be inadequate for detecting reduced susceptibility to vancomycin. Even though no confirmed cases have yet been detected in Australia, a high index of suspicion must be maintained for the occurrence of such organisms. Strategies for prevention of the spread of *S. aureus* with reduced susceptibility to vancomycin should be prepared by Australian hospitals prior to their first cases being identified. This article outlines the background to this developing issue and discusses laboratory methods and findings, with some current recommendations for diagnostic laboratories. *Comm Dis Intell* 1999;24:69-73

Introduction

For many years it has been recognised that *Staphylococcus haemolyticus* (a relatively rare coagulase negative *Staphylococcus*) may exhibit some degree of vancomycin resistance.[1] Vancomycin resistance in *Staphylococcus epidermidis* has also been demonstrated, although rarely.[2,3] However it is the possibility of vancomycin resistance in *Staphylococcus aureus (S. aureus)* which has become a much more significant concern. Unfortunately, hypothetical concern has now developed into practical reality.[4-12]

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History

Known cases of infection with 'vancomycin intermediate *Staphylococcus aureus*'

The first reported case of *S. aureus* infection with reduced susceptibility to vancomycin occurred in Japan in May 1996.[4] Since this report, three cases of *S. aureus* with reduced susceptibility have been reported in the United States of America and one in France. A further clinical specimen has been isolated in Slovakia, although confirmation that it truly has reduced susceptibility to vancomycin has not yet been established.[13]

The Japanese case was a 4 month old infant who underwent heart surgery for pulmonary atresia. Two weeks after surgery the patient developed a sternal wound infection with methicillin resistant *Staphylococcus aureus* (MRSA). The patient was treated with vancomycin (45 mg/kg/day) for 29 days, but fever and discharge of pus continued. The infection eventually resolved with debridement of the infected area and 23 days of therapy with ampicillin/sulbactam and arbekacin (an aminoglycoside available in Japan). The MRSA strain (designated Mu50) obtained both from the original sternal incision site and the debridement sample had a vancomycin minimal inhibitory concentration (MIC) of 8 mg/L by the broth microdilution method. The National Committee for Clinical Laboratory Standards (NCCLS) gives the following guidelines as to the susceptibilities of *S. aureus* to vancomycin; MIC less than or equal to 4 mg/L = susceptible, MIC 8-16 mg/L = intermediate, MIC greater than or equal to 32 mg/L = vancomycin resistant.[14]

The first case from the United States of America was isolated in July 1997 in Detroit from a 59 year old with metastatic lung cancer and end-stage renal disease (on peritoneal dialysis) who had a history of repeated episodes of peritonitis treated with both intravenous and intraperitoneal vancomycin for six months.[5] Peritoneal fluid cultures grew multiple organisms including vancomycin resistant *Enterococcus faecium* and multiple strains of *S. aureus*. All but one of the *S. aureus* strains were susceptible to vancomycin; the exception (designated *S. aureus* 14342) had a vancomycin MIC of 8 mg/L. The organism was methicillin resistant and resistant to teicoplanin (MIC 16 mg/L). The patient improved following treatment with trimethoprim-sulfamethoxazole plus rifampicin.

Another case of infection with MRSA exhibiting a vancomycin MIC of 8 mg/L was isolated in August 1997 from a patient from New Jersey.[10] The patient was known to be colonised with both MRSA and vancomycin resistant Enterococci. From March to August the patient had repeated MRSA bacteremias for which multiple courses of vancomycin had been given (he had received vancomycin for 18/23 weeks from March 1997).[6] In August, a blood culture from the patient grew an MRSA strain with intermediate resistance to vancomycin. The patient stabilised after treatment with a combination of vancomycin, gentamicin and rifampin but died in October 1997 from candidemia.

The most recent case from the United States of America was from New York.[12] A 79 year old man with a history of renal failure requiring haemodialysis presented in December 1997 with MRSA bacteremia. The source was thought to be an infected dialysis catheter. The catheter was removed and the patient treated with vancomycin for four weeks. In January 1998 the patient had recurrent MRSA bacteremia again treated with vancomycin. Finally, in March 1998 the patient presented with fever, confusion and respiratory distress and died within 12 hours of admission. MRSA was again grown from blood cultures. The vancomycin MIC for this final isolate was 8 mg/L.

Finally, a case has been reported from France of MRSA bacteremia of presumed central venous line origin from a 2 year old girl with leukaemia.[11] The organism was initially susceptible to vancomycin (MIC 2 mg/L), but after 10 days of vancomycin therapy a blood culture isolate with a vancomycin MIC of 8 mg/L and teicoplanin MIC of 16 mg/L was obtained. Her infection was eventually successfully treated with the drainage of pus and administration of quinupristin plus dalfopristin for ten days.

Methods

Laboratory detection of *S. aureus* with reduced susceptibility to vancomycin

In each of the confirmed cases above, the MIC of vancomycin was 8 mg/L. Hence these organisms have been referred to as vancomycin intermediate *S. aureus* (VISA), although the finding of associated teicoplanin resistance has prompted other authorities to refer to the isolates as glycopeptide intermediate *S. aureus* (GISA). (At least 15 patients have been previously reported who had infection with *S. aureus* with decreased susceptibility to teicoplanin (MIC 8-16 mg/L) but whose isolates were susceptible to vancomycin).[15-17]

Of major practical importance is that the use of disc diffusion methods in determining susceptibility of *S. aureus* to vancomycin may be inadequate for the detection of VISA. Using NCCLS recommended methods, inhibitory zone diameters of the VISA strains for vancomycin overlap those produced by susceptible isolates (that is, 17-19 mm). Use of 30 µg teicoplanin discs as a screen for VISA appears more useful. Each of the first three confirmed strains of VISA described above had a zone of 15mm or less around teicoplanin discs (F. Tenover, personal communication).

Contents, ***continued***

Two VISA strains have been tested by the CDS method. One strain was not recognised as VISA by the CDS method, while the other was recognised without difficulty (SM Bell, personal communication). The strain which was not recognised (Mu 50 from Japan) gave an annular radius on Sensitest agar of 2.5 mm (cut-off annular radius of 2mm for resistance to vancomycin). The other strain (HIP 5827 from Detroit) gave an annular radius of less than 2.0 mm. It should be noted that both VISA strains had a fuzzy growth at the edge of the zone of inhibition; this fuzzy edge is not seen in susceptible Staphylococci and corresponds to the light growth that was recorded with these strains on agar dilution plates containing 2.0 or 4.0 mg/L vancomycin (SM Bell, personal communication).

Automated systems are also somewhat unreliable in the detection of VISA. The 'Vitek' test has measured the first three known strains at 4 mg/L consistently (that is, they would have been recorded as susceptible). However, MICs of 4mg/L are extremely rare for vancomycin susceptible strains of *S. aureus* (occurring in only 0.4% of all MRSA strains), so such a finding should prompt testing of the isolate by reference dilution methods.[12] Microscan conventional panels recorded the MICs as 8-16 mg/L in the field, but 4 mg/L when repeated in a reference laboratory. Microscan rapid panels recorded MICs from less than 2 mg/L to 16 mg/L.[12]

Manual MIC methods are therefore necessary to reliably record the MIC as in the intermediate range.[18] When 'E test' was used, for each of the strains, the MIC was 6 mg/L, which would round up to 8 mg/L (since E test results should be reported to the next higher doubling dilution). Broth dilution or agar dilution methods are an alternative reference method.

Although the above results are preliminary and are only based on a small number of strains, it is clear that detection of vancomycin resistance may create problems for clinical microbiologists across Australia. Should manual MIC methods be used on all *S. aureus* isolates in our clinical microbiology laboratories? Since all isolates detected so far have been concurrently methicillin-resistant (MRSA) it would be practical to restrict manual methods to isolates known to be MRSA. Although by doing this detection of reduced susceptibility to vancomycin will be delayed by 24 hours, (given that detection of methicillin susceptibility will be determined first), this delay seems justifiable given the current rarity of VISA isolates. Individual laboratories will have to devise their own strategies, depending on resources and current prevalence of MRSA, but restricting MIC testing to MRSA isolates from patients who have had failure of vancomycin therapy may be preferable to blanket MIC testing of all MRSA isolates at the present time. There may also be a place for performing intermittent surveillance of all MRSA isolates in a specified time period or in regular surveillance of isolates from patients in high-risk units (for example, renal or intensive care units). In this circumstance, use of brain heart infusion plates containing 6 mg/L of vancomycin, may be a useful screening method.[12] Appropriate negative controls include *S. aureus* ATCC 29213 and *E. faecalis* ATCC 51299.

Some may argue against a targeted approach and suggest that, given the potential global seriousness of VRSA, all laboratories should screen all MRSA isolates for vancomycin resistance now.

Discussion

Mechanism of Resistance

The mechanism by which the VISA isolates have reduced susceptibility to glycopeptides has not yet been determined. What is known, however, is that the current isolates have not acquired the vancomycin resistance genes of enterococci (van A or van B).[4,5] It is known however, that acquisition of these genes by Staphylococci can occur in the test tube.[19]

VISA isolates have a markedly thick cell wall on electron microscopy.[12] The Japanese isolate of VISA (Mu50) has also been found to have a high level of production of the penicillin-binding protein, PBP-2.[20] Laboratory selected mutants of *S. aureus* with decreased susceptibility to glycopeptides (obtained by incubating previously susceptible clinical isolates in vancomycin or teicoplanin) have also been shown to have elevated PBP-2 production.[20] Although it is possible that the genes encoding PBP-2 may be coregulated along with genes encoding another protein which is responsible for vancomycin resistance, present data suggest hyperproduction of PBP-2 as a possible mechanism of resistance in the current clinical isolates. It has been suggested that increased production of PBP-2 by VISA might increase the concentration of glycopeptide that is needed to interfere with the interaction between the PBP and D-alanyl-D-alanine during peptidoglycan synthesis.[20]

The first clinical strain from Japan (Mu50) exhibited homogeneous insensitivity to vancomycin (all individual bacterial cells in the culture population expressed resistance). However, a strain from the sputum of a patient from the same hospital (strain Mu3) exhibited heterogenous resistance (dubbed 'hetero VISA'. Strain Mu3 had a vancomycin MIC of 3 mg/L but a small fraction (one in a million) of the cell population had subclones with MICs of 8 mg/L.[21,22] Heterogeneously resistant *S. aureus* has now been found in hospitals throughout Japan. A case has of heterogeneously resistant *S. aureus* also been reported from Bristol in the United Kingdom.[23] Heteroresistance to vancomycin in coagulase negative Staphylococci has now also been well-described in New York City.[24] It has been hypothesised that heteroresistant *S. aureus* may swiftly evolve into homogeneous VISA during exposure to glycopeptide antibiotics. Further investigation into the mechanisms of occurrence of heteroresistant VISA is currently in progress.

Antimicrobial Susceptibility of VISA

One of the major concerns regarding vancomycin resistance in *S. aureus* is that this common bacteria would therefore become resistant to all antibiotics which are currently available. Fortunately the clinical isolates of VISA so far obtained have retained susceptibility to other antibiotics. For example, the isolate from Detroit was susceptible to low concentrations of trimethoprim-sulfamethoxazole, rifampin, chloramphenicol, mupirocin and tetracycline.[5] It was also susceptible to investigational agents such as quinupristin-dalfopristin (MIC 0.5 mg/L), arbekacin (MIC < 0.12 mg/L), clinafloxacin (MIC 1 mg/L), LY 333328 (MIC 2 mg/L) and the oxazolidinones, eperezolid and linezolid (MIC for both 1 mg/L).[5] The isolate from the patient in New Jersey was susceptible to chloramphenicol, gentamicin, tetracycline and

Table 1. Suggestions for the microbiology laboratory in the identification and control of vancomycin-resistant *S. aureus* or Vancomycin intermediate *Staphylococcus aureus* (VISA)

1. Recognise that failure to correctly identify *S. aureus* strains as VISA has occurred with NCCLS disc diffusion methods, the CDS method and automated susceptibility tests, such as Vitek. Clues to the presence of VISA include a teicoplanin zone size of 15mm or less (NCCLS disc diffusion), a 'fuzzy edge' (CDS method) and MIC of 4 mg/L (Vitek).
2. Strains exhibiting any of these characteristics or strains of *S. aureus* from patients with persistent infection despite use of vancomycin, should be considered for testing by a manual MIC test.
3. Strains with an MIC of 8mg/L or more should have the MIC reconfirmed by a reference laboratory.
4. The Director of Microbiology and the Director of Infection Control should be contacted upon suspicion that an isolate is VISA or VRSA.
5. The organism should be stored for future studies at -70^{o}C in a freezer located in an area of the laboratory to which there is limited access. Consideration should be given to sending the isolate to the Nosocomial Pathogens Laboratory Branch, Centers for Disease Control and Prevention, Atlanta, United States of America, which has studied all of the known strains of VISA

trimethoprim-sulfamethoxazole, and was susceptible to quinupristin-dalfopristin (MIC 0.5 mg/L) and linezolid (MIC 1 mg/L).[6]

In the absence of extensive clinical experience, optimal treatment of VISA is unknown. Teicoplanin is unlikely to offer any advantage over vancomycin since those VISA isolates which have been assessed also have reduced susceptibility to teicoplanin. Synergy has been observed in vitro when vancomycin and anti-staphylococcal beta-lactams have been used in combination.[25]

Infection Control Issues

Since other resistant microbes are well known to spread from patient to patient (often via the hands of healthcare workers) concern existed that patients in addition to those reported may have become infected or colonised with VISA. In Juntendo University Hospital (Tokyo, Japan) where the first clinical isolate was discovered, 20% of MRSA isolates now have heteroresistant VISA.[22] By pulsed field gel electrophoresis these isolates were found to be identical to, or similar to, Mu50 (the originally described strain). Four other Japanese hospitals have isolated heteroresistant VISA. In contrast, no contacts of the first three VISA isolates in the United States of America have been found to be positive for VISA (although 16% of nares and 25% of hand cultures of healthcare providers and hospital roommates were positive for *S. aureus).*[6]

Guidelines on the control of spread of vancomycin resistant *S. aureus* have been published.[26-29] In general they are similar to guidelines already in place across Australia for control of MRSA infection. It should be noted that many of the recommendations have failed to control the spread of MRSA, so may not control spread of VISA. However the guidelines also draw attention to nasal colonisation with *S. aureus*, and possible ways to prevent nasal colonisation of healthcare workers.

In the absence of known cases of VISA or vancomycin-resistant *S. aureus* in Australia, present attention should be concentrated upon restriction of vancomycin usage in the hospital. Guidelines on the prevention of vancomycin resistant enterococci have recently been developed by the Australasian Society for Infectious Diseases and include guidance as to situations where vancomycin use is appropriate. For example, vancomycin use is inappropriate as first line treatment of *C. difficile* colitis, as prophylaxis in the absence of penicillin allergy or a significant risk of MRSA infection, and as treatment of methicillin susceptible gram-positive infections in the absence of penicillin allergy. Table 1 presents some suggested guidelines for laboratories.

Conclusion

There is no doubt that *S. aureus* with reduced susceptibility to vancomycin has arrived. Although there is no evidence the organism exists in Australia (yet), strenuous efforts to prevent dissemination of these organisms in Australian hospitals needs to be instigated now in order to avoid a public health disaster.

Note

Since this article was written, two major papers pertaining to VISA have been published.[25, 30]

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Salmonellosis outbreak, South Australia

In late February the Communicable Disease Control Branch, South Australia was notified of an unusual number of cases of gastroenteritis. This was later determined to be caused by *Salmonella* Typhimurium phage type 135a. A case control study conducted on 6 and 7 March implicated a brand of commercially packaged fresh unpasteurised orange juice. On 8 March a bacteria presumptively identified as a *Salmonella* was isolated from a sample of the suspect brand purchased unopened from a retailer. A product recall was issued that day. On 10 March the presumptive *Salmonella* isolated from the juice 2 days previous was definitively identified as *S.* Typhimirium PT135a. As at 23 March, 405 cases of infection with this *Salmonella* had been laboratory confirmed and investigations are continuing into the source of the contamination of the orange juice. Although this product may be distributed to States other than South Australia there are, as yet, no reports of this unusual phage type causing recent infections in humans elsewhere in Australia.

Staphylococcus aureus; will vancomycin resistant strains become common in the future?

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Staphylococcus aureus (*S. aureus*) is an aggressive pathogen that is a common cause of infections both in the community and in hospitals. Before the advent of antibiotics *S. aureus* bacteraemia was associated with an 80% mortality and the disease often occurred in young adults.[1] The advent of penicillin marked a major breakthrough in the treatment of serious *S. aureus* infections. However, many of these benefits were lost within 10 to 15 years of the introduction of penicillin because of the widespread resistance that developed along with widespread dissemination of these resistant bacteria.

In the late 1950's during an influenza outbreak there were many people who died of what was again untreatable *S. aureus* infections.[2] We were however fortunate in the late 50s and early 60s because new antibiotics were developed to overcome this problem. Vancomycin was developed and its release was closely followed by beta-lactamase stable penicillins (such as methicillin and later cloxacillin). Cephalosporins which have activity against *S. aureus* also subsequently became available.

In the 1960's and 70's methicillin resistant *S. aureus* (MRSA) developed and became widespread in hospitals around the world. These strains could no longer be efficiently killed by any beta-lactam antibiotic (methicillin, flucloaxacillin or cephalosporins). Vancomycin remained the only predictable active antibiotic against all strains of *S. aureus* and MRSA in particular. Until recently there have been no strains of *S. aureus* that would not respond to vancomycin, providing vancomycin could reach the site of infection. The recent discovery of a vancomycin resistant strain of *S. aureus* (initially abbreviated as VRSA) in Japan has been to many microbiologists a nightmare scenario. It is of concern that these resistant strains have already been found in other countries including the United States of America and France.[3]

These strains do not appear to have developed from just a single clone of *S. aureus*. They are generally in the intermediate level of resistance to vancomycin with moderately raised minimal inhibitory concentrations (MICs). They have previously been described as 'vancomycin intermediate resistant *S. aureus*' (VISA). However, they are frequently also resistant to the other glycopeptide used in clinical practice (teicoplanin) and are therefore more accurately described as GISA (with the G referring to glycopeptides).[4] They appear to have developed from strains of MRSA. Many of the clinical and laboratory difficulties in treating and recognising this new and emerging infection are discussed by Paterson in the accompanying article.[5] It is of interest that there were similar difficulties in the laboratory recognition of strains of MRSA when they were initially discovered.

The concern regarding the development of VRSA was particularly worrying because of the now widespread occurrence of vancomycin resistant strains of enterococci (VRE).[6] Enterococci are generally much less virulent than *S. aureus,* however VRE bacteraemia is associated with a higher mortality when compared to strains that remain antibiotic sensitive. In the laboratory, the complex genome coding for vancomycin resistance has been transferred to *S. aureus.*[7] VRE is more likely to occur in long term hospital patients and these patients are also frequently colonised with MRSA. Because vancomycin remains one of the few (and in many cases the only) antibiotic to treat MRSA, there is concern that the genetic material encoding for vancomycin resistance in enterococci could transfer to clinical isolates with MRSA. To date this does not appear to have occurred (or at least been described in the literature).[8,9]

What was surprising about the Japanese and the American isolates is that the mechanism of resistance appears to be different from the vancomycin resistance in VRE.[9] In some strains of *S. aureus* it involves a markedly altered and thicker cell wall as well as changes in penicillin binding proteins. This again however highlights one of the problems with bacteria and antibiotic resistance. We frequently do not have the ability to accurately predict what will happen in the future. Microbes have the ability to come up with unexpected and novel mechanisms of resistance.

Vancomycin may be needed more frequently to treat community-acquired infections. We are recently seeing a new variety of MRSA that are now circulating in the community (cMRSA), and not infrequently causing serious infections. They are particularly common in some areas in New Zealand, but also found in Australia and the United States of America.[10] Fortunately most strains of cMRSA are not multi-resistant and there remain some therapeutic options available besides vancomycin. However, if we look at what has occurred with MRSA in the past in hospitals, it is almost inevitable with time that these cMRSA strains will become resistant to currently available agents. Some new agents such as 'Synercid' are being developed but even in these new agents there has already been resistance encountered in enterococci (that may partially be related to the use of a similar agent, virginiamycin, in animals as growth promoters).[11]

The other concern, besides the development of having strains resistant to all available antibiotics (and those in the pipeline), is the ability of these strains to disseminate. Strains of MRSA that show heterogenous resistance to vancomycin have already spread within some Japanese hospitals. In the teaching hospital where the GISA strain was first isolated 20% of MRSA strains show heterogenous resistance to vancomycin. In seven other teaching hospitals the rate was 9.3% and in non university

hospitals it was 1.3%.[3] If the numbers have increased so rapidly in Japan, and are now being found elsewhere in the world, it would appear inevitable over the next five to ten years that they will approach levels, in particularly hospital situations, that we are seeing with MRSA (between 20-50% in many institutions). In addition to GISA strains, this resistance can also be seen in some MRSA strains which can be heteroresistant.

The question is what can Australia do about this. Unfortunately once these strains have developed there is no way of putting the 'genie' back into the bottle. We need to slow down the spread and amplification of these strains as much as possible (by good infection control, conservative measures, prudent use of antibiotics, and good hygiene). Hopefully then, in the next few years new antibiotics will be developed that will be active against GISA (or fully vancomycin resistant strains when they inevitably occur). We should not use antibiotics when they are not needed. When we do use antibiotics we should use as narrow a spectrum agent as possible. This means in particular, avoiding using agents such as vancomycin unless it is essential.

Antibiotic resistance is an inevitable consequence of antibiotic use, whether they are used appropriately or inappropriately. However, the rate of rise of antibiotic resistance, and amplification of these bacteria, can be modified by our behaviour through improved hygiene, infection control and the most appropriate use of antibiotics.

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Victorian measles outbreak

In the face of a continuing rise of reported measles cases among young adults in Victoria, the Communicable Diseases Network of Australia New Zealand (CDNANZ) have called on all Australians aged 18 to 30 to check their vaccination status.

The measles outbreak was first reported in the western suburbs of Victoria several weeks ago and has now spread to involve young adults in the northern and eastern suburbs and border areas.

Everyone should be protected against measles and other vaccine-preventable diseases by vaccination. The recent successful primary schools campaign appears to be protecting children in that age group.

Statistics at 23 March 1999

- 41 cases of measles have been reported to Victorian Health authorities.
- the index case was a young adult who had returned from Bali.
- 90% of cases are between 17 and 27 years of age.
- 2 cases are in the 30 to 34 age group.
- 1 case is a 10 months old child - below the recommended age for routine immunisation at 12 months of age.
- 1 case is an unimmunised 8 year old boy.
- 40% of cases have been admitted to hospital.

Polio Eradication

Rennie M D'Souza,[1,2] Elizabeth J Elliott[3,4]

The goal of polio eradication in the Western Pacific Region is within reach. The last case of polio seen in the region occurred in Cambodia in March 1997 and the region aims to be certified polio-free by the World Health Organization (WHO) in the year 2000. The Global Commission for Certification of Eradication of Poliomyelitis has specified three criteria to be fulfilled by countries in order that they may be certified polio-free:

- absence of wild poliovirus for 3 years in the presence of adequate Acute Flaccid Paralysis (AFP) surveillance in children under the age of 15 years;
- a National Certification Committee in each country to validate and submit the certification documentation; and
- the establishment of mechanisms to detect and respond to the importation of wild poliovirus.

Active surveillance of AFP in children under 15 years was established in Australia in March 1995 through the Australian Paediatric Surveillance Unit. However, as polio has not been seen in Australia for over 20 years it is generally not considered as a differential diagnosis in a child with AFP. Similarly, paediatricians may omit to report cases of AFP when an alternative diagnosis to poliomyelitis has been proven. This may have affected the number of AFP cases being reported and investigated by paediatricians. To comply with WHO's certification requirements all cases of AFP should be investigated as potential cases of polio. This maximises the chance that cases of polio imported into Australia would be detected, and detection of even one case of polio is considered an outbreak in a non-endemic country. It is also essential that population immunity be maintained at a high level to prevent spread of infection in the event of an imported case. AFP surveillance in the region must be continued in the post-certification period until the time global eradication is achieved. In the meantime, paediatricians are urged to report and investigate all cases of AFP. This includes stool testing, which is considered the gold standard for excluding polio in an AFP case even when the diagnosis of polio is unlikely.

The next major objective will be the containment of poliovirus. Materials that may be infected or potentially infected with wild poliovirus in laboratories and research institutions, will need to be rendered non-infectious or destroyed. Achievement of polio eradication will make polio the second infectious disease after smallpox, to be eradicated.

The current issue of *CDI* includes an article by Kennett et al regarding the last case of polio reported in Australia in 1986 and its reclassification as 'vaccine associated'.[1] In the 'Current Issues on Immunisation,' Burgess and McIntyre discuss issues related to vaccine associated paralytic poliomyelitis in Australia.[2] A forthcoming issue of *CDI* will include both a report on the Surveillance of Acute Flaccid Paralysis scheme over the past four years by D'Souza et al and a report from the Australian National Polio Reference Laboratory, which was established at the Victorian Infectious Disease Reference Laboratory in 1994.

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Australia's last reported case of wild poliovirus infection

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Abstract

In 1986 tests on faeces collected from a 22 year old Australian born man who had symptoms consistent with poliomyelitis yielded poliovirus type 3. In a neutralisation test using a panel of monoclonal antibodies the isolate was identified as wild poliovirus type 3 at that time. After further classification using microneutralisation, nucleic acid probe hybridisation, immunoassay and sequencing carried out in three laboratories between 1994 and 1997, the isolate has been reclassified as 'Sabin-like' with 'wild type' characteristics. This case has been quoted in the literature as Australia's last case of locally acquired wild poliovirus. Efforts are now being made to identify the true last case in Australia. This article describes the isolation, identification and further characterisation of this virus. ***Comm Dis Intell*** **1999;23:77-79**

Introduction

In May 1988, the 41st World Health Assembly committed the member states of the World Health Organization (WHO) to the global eradication of poliomyelitis by the year 2000. The strategy to achieve this aim involves high routine immunisation coverage, supplementary immunisation in the form of National Immunisation Days or mass campaigns, effective surveillance and, in the final stages, 'mopping up' in areas where wild polio virus is present.[1]

Committees have been established to certify that Australia is free of wild poliovirus by assessing national acute flaccid paralysis (AFP) surveillance and immunisation. In order for a country to be declared polio- free there must be no evidence of indigenous wild poliovirus transmission for a period of at least three consecutive years of quality surveillance.[2]

The last case of poliomyelitis caused by wild poliovirus acquired in Australia has been believed to have occurred in a 22 year old male.[3] A virus was isolated from the case's faeces and identified as poliovirus type 3 in the Entero-Respiratory Laboratory at Fairfield Hospital (renamed The Victorian Infectious Diseases Reference Laboratory, VIDRL in 1992) in September 1986. It was characterised, in a neutralisation test using monoclonal antibodies as 'wild type', at the National Institute for Biological Standardisation and Control (NIBSC) in the United Kingdom (UK) in early 1987. Subsequent testing from 1994 to 1997 at the Victorian Infectious Diseases Reference Laboratory (VIDRL), at NIBSC UK, and at the National Institute for Public Health and the Environment (RIVM), the Netherlands has led to the reclassification of this virus as a 'drifted Sabin-like' virus. This virus, for over 10 years, had been recognised as the last indigenous wild poliovirus in Australia.

Methods

Patient

A man aged 22 years was admitted to a teaching hospital in September 1986 suffering from lower back pain, slight weakness of his left leg and difficulty in initiating micturition. The physical and CSF findings at the time were consistent with a diagnosis of poliomyelitis (Dr L. Irving, former Medical Microbiologist, Fairfield Hospital, personal communication).

Isolation and Identification (1986)

Faeces were collected from the patient, placed in a sterile container and transported to the Fairfield Hospital virus laboratory for virus culture. The methods used for the collection and treatment of the faeces in cell culture for the identification of enteroviruses were as previously described.[4] Virus isolates which developed rapid cytopathic effects in primary monkey kidney epithelial cells (PMK), continuous monkey embryonic kidney epithelial cells (MEK), HeLa cells (Rhinovirus sensitive), Borrie epithelial cells and human embryonic lung fibroblast cells were provisionally considered to be polioviruses. These were identified in microneutralisation tests using reference horse antisera prepared against prototype polioviruses supplied by the National Institutes of Health, Maryland, USA.[5]

Intratypic differentiation (1986/7)

In the United Kingdom laboratory (NIBSC), microneutralisation tests were performed using pools of monoclonal antibodies prepared against the prototype poliovirus type 3 (Mab-N).[6]

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Intratypic differentiation (1994-1997)

Nucleic acid probe hybridisation (NAPH) tests, using DIG (digoxigenin) labelled probes that recognise the VP1/2A region (either of Sabin poliovirus type 3 or of all polioviruses from all three types), were performed using a dot blot technique[7] at VIDRL in 1994.

As in 1986/7, Mab-N tests were performed at NIBSC in 1995, but using different monoclonals.[8]

Enzyme immunoassay tests were performed in 1994 at VIDRL using cross absorbed polyclonal rabbit antisera prepared against Sabin and wild poliovirus type 3.[9]

RNA sequence analysis of the VP1/2A region using the method of Mulders et al[10] and neutralisation tests using cross absorbed polyclonal antisera prepared against Sabin polio 3 and wild polio 3[11] were carried out at RIVM in the Netherlands in 1997.

Results

Isolation and identification (1986)

Poliovirus type 3 was isolated from the faecal specimen and was identified using a microneutralisation test at Fairfield Hospital.

Intratypic differentiation (1986/7)

Microneutralisation tests using type-specific monoclonal antibodies (Mab-N) were performed in the UK laboratory (NIBSC). Initial tests on the isolate in 1986/7 using a panel of 7 monoclonal antibodies identified it as a 'normal type 3 wild' virus with no relationship to the 'Sabin type 3' virus.

Intratypic differentiation (1994-1997)

In a nucleic acid probe hybridisation test performed at VIDRL, the isolate was clearly identified as 'Sabin-virus polio type 3'.

In an enzyme immunoassay at VIDRL and a serum neutralisation test at RIVM, the isolate reacted equally to cross absorbed polyclonal antisera, to both Sabin and wild poliovirus type 3.

When testing was repeated in 1995 at NIBSC on the isolate by Mab-N using the current monoclonal antibody panel, it was found to contain a type 3 vaccine-like isolate. At high virus challenge doses the Sabin specific monoclonal was unable to completely neutralise a type 3 virus.

RNA sequence analysis of the VP1/2A region at RIVM showed 100% identity with the 'Leon type 3', the wild-type progenitor of the Sabin poliovirus type 3 used in oral polio vaccine.

Discussion

After OPV was introduced in Australia in 1966,[3] both wild and vaccine polioviruses were co-circulating for several years. In most situations, vaccine virus isolation was incidental to patients' illnesses (for example, from a throat swab from a child with acute respiratory infection) and could be linked to OPV immunisation several days earlier. Several methods for differentiation of wild and vaccine polioviruses which were employed in the 1960s and 1970s were found to be unreliable once more specific serological and molecular methods were developed.[12] As the newer methods were not established at that time, polioviruses isolated at the Fairfield Hospital Virus Laboratory from suspected paralytic poliomyelitis cases in 1977 and 1986 were referred to international laboratories for characterisation. In 1986, the type 3 isolate from the 22 year old man was characterised as 'wild' at the UK reference laboratory. The finding was reported to the State and Australian Health Departments. It was then believed to be the last confirmed wild poliovirus infection contracted within Australia in a person who had not travelled outside Australia and who had not been a contact of any person recently returned from a polio-endemic country.

Currently, intratypic differentiation (ITD) of polioviruses may be carried out by at least three serological methods. Enzyme immunoassay (EIA) using cross-absorbed polyclonal antisera, or neutralisation tests using either cross-absorbed polyclonal antibodies or monoclonal antibodies (Mab-N), are those most commonly used. Most poliovirus strains are clearly identified as either 'wild' or 'Sabin vaccine-like'. However, some may react with both anti-wild and anti-Sabin antisera or with other than expected monoclonal antibodies.

The well-established molecular methods for intratypic differentiation (ITD) in use are nucleic acid probe hybridisation (NAPH), polymerase chain reaction (PCR) or restriction fragment length polymorphism (RFLP). These methods use different primers and probes specifically reacting with coding sequences from the VP1/2A region. As all Sabin strains are similar, these can be readily differentiated from wild viruses whose sequences vary over this region.[13]

From the findings of a multi-centre study of five methods for intratypic differentiation of polioviruses initiated by WHO, two methods, NAPH and EIA, were selected for introduction into the Polio Laboratory Network. The combination of serological and molecular tests diminishes the number of possible discrepancies.[14]

In optimising NAPH and EIA testing at VIDRL in 1994, several stored polioviruses, including the poliovirus type 3 isolate, which had previously been characterised as 'wild' in international laboratories, were retested. However, when the NAPH test result interpretation was Sabin-like and that of the EIA test was 'double reactive' for this isolate, its characterisation as a 'wild poliovirus type 3' was in doubt.

The staff at the United Kingdom reference laboratory were briefed on these findings in 1995. Using their current panel of monoclonal antibodies for differentiating poliovirus type 3 isolates, they carried out further monoclonal work on the strain which had been stored in their laboratory. The panel of monoclonals used for the 1995 analysis was different from that used in 1987. Although the isolate contained a type 3 vaccine-like isolate, a minor population most likely to be a vaccine variant, with changes in the antigenic site recognised by the Sabin-specific monoclonal, was not neutralised by this monoclonal at high challenge doses.

The virus was also despatched to RIVM in 1996 for further analysis. This included microneutralisation using cross-absorbed polyclonal antisera prepared against wild and vaccine poliovirus type 3, and sequencing of the VP1/2A region of the virus. The double reactivity of the virus in the EIA test performed at VIDRL can be interpreted in two ways. Either the virus is a mixture of a wild and a vaccine strain of poliovirus type 3, or is a single

strain with antigenic properties of both parent strains as a result of antigenic drift or a recombination event. As the virus was neutralised equally by both the wild virus-specific and the vaccine-specific cross-absorbed antiserum, a mixture of two viruses could be excluded.

Sequence analysis over the VP1/2A region outside of major antigenic sites provides definitive proof that the virus was indeed a Sabin poliovirus type 3. The aberrant antigenic features indicated the drifted nature of the Sabin strain. The patient's diagnosis is now reclassified as vaccine-associated paralytic poliomyelitis.

When OPV is administered for the first time, mutations of the Sabin poliovirus types 1,2 and/or 3 may appear in the gut of the recipient. Some, particularly those of types 2 and 3, may revert to virulent viruses which may be excreted in the faeces. However, the recipient should have developed antibodies by this time and is unlikely to become symptomatic. A reverted virulent virus in the faeces of a vaccine recipient may infect an unimmunised individual who may develop symptoms of polio infection.[15]

In Victoria, the last confirmed wild poliovirus was a type 1 isolated from a baby girl who had been born in Australia in 1977 but taken to Turkey soon after birth. On return to Australia in October 1977 at age 3 months she was admitted to the Royal Children's Hospital, Melbourne and later to Fairfield Hospital with a diagnosis of paralytic poliomyelitis. Because it was likely that the child became infected in Turkey, her isolate has been considered to be an imported strain.

With the imminent global eradication of polio, laboratories will become the only remaining reservoirs of polioviruses. One year after the last wild poliovirus has been detected, it is planned that all institutes in which wild polioviruses or clinical material which may contain wild polioviruses are stored will be required to transfer them to WHO designated repositories or destroy them.

It would be of interest to identify Australia's last locally acquired wild poliovirus. Over the next few months, the Polio Reference Laboratory at VIDRL plans to characterise local poliovirus isolates stored since 1954 and offers intratypic differentiation testing of strains stored in other Australian laboratories.

Acknowledgments

We wish to thank the staff of the Entero-Respiratory Laboratory, Fairfield Hospital, 1986 for isolation and identification of the isolate.

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We also wish to thank Dr Louise Irving former Medical Microbiologist, Fairfield Hospital, for advice on the case history, subsequent public health information and critical review of the manuscript.

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Vaccine–associated paralytic poliomyelitis

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The World Health Organization's polio eradication program

In the wake of the World Health Organization's (WHO) program to eradicate poliomyelitis globally by the end of the year 2000 (in 1997 only 5,186 cases were reported world-wide), attention has focussed on the importance of good surveillance of acute flaccid paralysis, which is essential for a country to qualify for being declared polio-free, and on the occurrence of vaccine–associated paralytic poliomyelitis (VAPP).[1,2]

VAPP in New Zealand

In June 1998, a 4 month old boy in New Zealand was notified with acute flaccid paralysis which had commenced 2 weeks after he received his second dose of oral polio vaccine.[3] Sabin oral polio vaccine virus type 3 was isolated from his stool. His clinical course fitted the case definition for VAPP; 'acute flaccid paralysis in a vaccine recipient 7-30 days after receiving oral polio vaccine (OPV), with no sensory or cognitive loss and with paralysis still present 60 days after the onset of symptoms.'

VAPP in Australia

Local transmission of wild polio virus in Australia probably ceased in 1962. The last case of polio due to wild virus was reported in 1977 in a young child who acquired the infection abroad (M. Kennett, personal communication). A second case, attributed to wild virus infection in 1978, is currently being reviewed (M. Kennett, personal communication),[4] and one case previously suspected as being due to wild virus in 1986 has been reclassified as Sabin–like with wild type characteristics.[5] Another case of probable VAPP was reported in 1995 in the healthy unvaccinated mother of a recently vaccinated infant.[6,7]

It is likely that the incidence of VAPP in Australia is similar to the incidence in the United States of America (USA). We should therefore expect about 1 case in every 2.4 million doses distributed (1 case in every 6.2 million doses in recipients of the vaccine and 1 case in 7.6 million doses for contacts of recipients). The expected overall rate associated with a first dose of the vaccine is 1 in 750,000 doses distributed.[8]

Australia should therefore be detecting in about 1 case every 3 years, as each year 250,000 infants receive a first dose and over 1 million doses are administered. Why then are we not detecting cases at this rate? The most likely reason is that the cases are either not recognised or not reported. This demonstrates a deficit in our surveillance system as notification is mandatory in each State and Territory. In addition, active surveillance of acute flaccid paralysis in persons under the age of 16 years is in place through the Australian Paediatric Surveillance Unit (APSU) and no case of VAPP was reported in the 3 years 1995 to 1997.[2] However, as the only way to confirm VAPP is to examine appropriate stool specimens, and as only 24% of the cases of AFP notified to the APSU had these examinations, cases of VAPP may be being overlooked (R. D'Souza, personal communication).[2] An alternative, but unlikely, explanation for our lack of notified cases could be that the vaccine available in Australia has a lower incidence of VAPP.

Reintroduction of inactivated polio vaccine in the United States of America

Because of concern about the 8-10 cases of VAPP reported each year in the USA, in 1997 the Advisory Committee on Immunisation Practices (ACIP) recommended adoption of a sequential schedule of inactivated polio vaccine (IPV) and OPV, with either all IPV or all OPV as acceptable alternatives.[8] The preferred schedule for healthy children was for the first two doses to be IPV and the later two doses OPV. The advantages of the sequential schedule were considered to be a potential halving of the incidence of VAPP, and postponement of administration of OPV until an age when most immunodeficient children will have been diagnosed and excluded from this risk, but with retention of the benefits of mucosal immunity from OPV for the healthy children. The disadvantages of the sequential schedule are the complexity of the schedule, the increased number of injections required at each immunisation visit for young infants, and the very much greater cost of the IPV than OPV in countries such as Australia, compared with the USA.

Over the past two years the USA has embraced the use of IPV.[1] In 1997, 29% of all polio vaccine doses distributed were IPV. Now the American Academy of Pediatrics has revised its recommendation to strongly favour the sequential or all IPV options while continuing to recommend the use of OPV to control the spread of any wild type outbreak.[1] Denmark has successfully used a similar sequential schedule since 1968.

The World Health Organization's position on OPV

The WHO strongly supports the use of OPV to achieve global eradication of poliomyelitis, especially in countries with continued or recent circulation of wild type poliovirus.[9] This recommendation is endorsed by the authorities in the USA and Europe including those who routinely use IPV.[10-12]

Conclusions

Every case of VAPP represents a personal tragedy and a public health dilemma. Australia must continue to strengthen surveillance of AFP to obtain a reliable

estimate of the incidence of VAPP and to ensure that we reach the WHO minimum reporting rate of 1 case per 100,000 children under 16 years (our current rate is 0.7[2]) required for certification. In preparation for combination vaccines containing IPV becoming available the feasibility and costs of changing the Australian schedule are in the process of being reviewed, bearing in mind that once polio is eradicated within a few years (possibly as early as 2007), polio vaccination will no longer be necessary. A vaccine containing diphtheria, tetanus, pertussis, Hib and IPV is already available in Canada.[13]

Acknowledgement

We wish to thank Margery Kennett, Senior Scientist, National Polio Reference Laboratory, Epidemiology and Public Health Division, Victorian Infectious Diseases Reference Laboratory, Locked Bag 815, Carlton South, Victoria 3053 for her help with the preparation of this report.

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The NCIRS was established by the National Centre for Disease Control, Commonwealth Department of Health and Aged Care. The Centre analyses, interprets, and evaluates national surveillance data on immunisation coverage and vaccine preventable diseases. NCIRS also identifies research priorities, and initiates and coordinates research on immunisation issues and the epidemiology of vaccine preventable diseases in Australia.

Communicable Diseases Surveillance

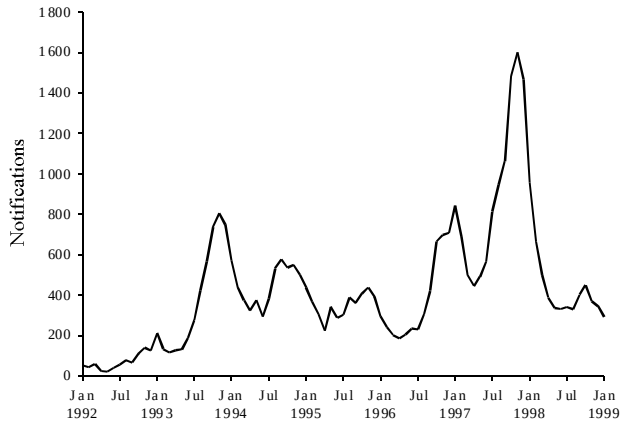
Highlights

Communicable Diseases Surveillance consists of data from various sources. The National Notifiable Diseases Surveillance System (NNDSS) is conducted under the auspices of the Communicable Diseases Network Australia New Zealand. The *CDI* Virology and Serology Laboratory Reporting Scheme (LabVISE) is a sentinel surveillance scheme. The Australian Sentinel Practice Research Network (ASPREN) is a general practitioner-based sentinel surveillance scheme. In this report, data from the NNDSS are referred to as 'notifications' or 'cases', whereas those from ASPREN are referred to as 'consultations' or 'encounters' while data from the LabVISE scheme are referred to as 'laboratory reports'.

Vaccine Preventable Diseases

Pertussis notifications remain low when compared with the peak in late 1997 and early 1998. The disease however has not disappeared and continues to be reported at a magnitude which is approximately that of the endemic years of 1995 and 1996 (Figure 1).

Figure 1. Notifications of pertussis, Australia, 1992 to 1999, by month of onset

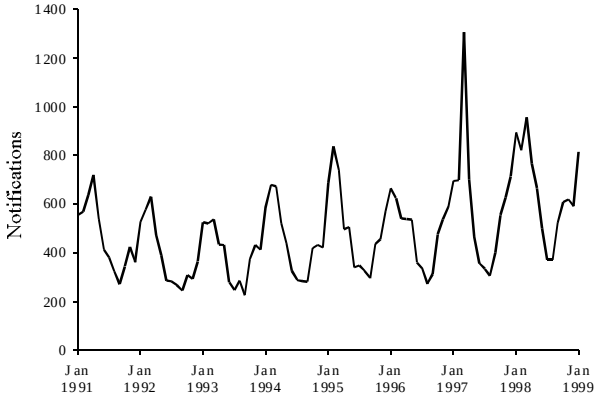


Although measles notifications for the country as a whole remain at a low level, an outbreak in Victoria in young adults is causing concern and is described elsewhere in this issue of *CDI*.

Arboviruses

A higher number of notifications has been received for Ross River Virus infection for this reporting period than for the same period of last year. The relative number of notifications appears lower than historical data (Figure 2) because of the very high numbers reported for this period of 1996 and 1997.

Figure 3. Notifications of salmonella, Australia, 1991 to 1999, by month of onset

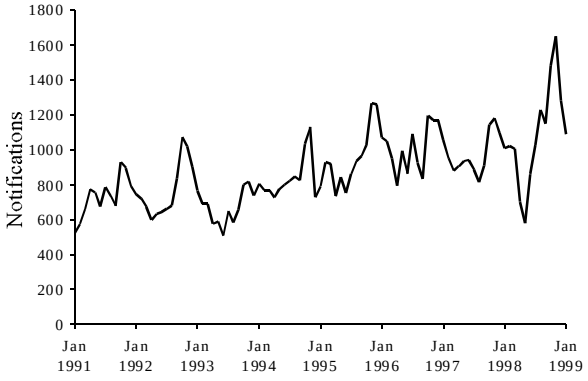


Gastrointestinal diseases

Numbers of infections from Salmonella and Campylobacter continue at a high level. Campylobacteriosis regularly has the highest number of incident cases reported across Australia for any communicable disease, and that is without any reports from the most populous state, New South Wales.

Salmonellosis notifications show a marked seasonal pattern, with a peak in the warmer months of each year (Figure 3). A similar seasonal pattern is present, although less marked, for campylobacteriosis (Figure 4). Even in the low season, a large number of notifications is received for each condition.

Figure 4. Notifications of campylobacter, Australia, 1991 to 1999, month of onset



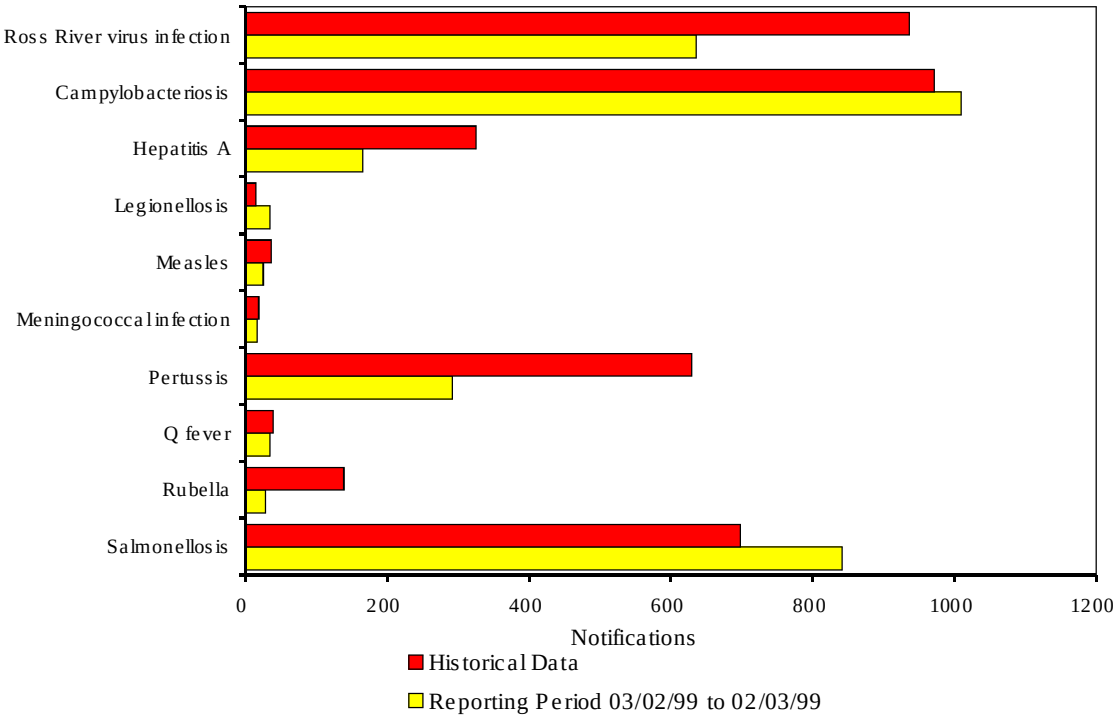
Tables

There were 6,924 notifications to the National Notifiable Diseases Surveillance System (NNDSS) in the four week period, 3 February to 2 March 1999 (Tables 1 and 2). The numbers of reports for selected diseases have been compared with historical data for corresponding periods in the previous three years (Figure 2).

There were 1,438 reports received by the *CDI* Virology and Serology Laboratory Reporting Scheme (LabVISE) in the four week period, 28 January to 24 February 1999 (Tables 3 and 4).

The Australian Sentinel Practice Research Network (ASPREN) data for weeks 1 to 8, ending 28 February 1999, are included in this issue of *CDI* (Tables 5 & 6).

Figure 2. Selected National Notifiable Diseases Surveillance System reports, and historical data[1]



1. The historical data are the averages of the number of notifications in the corresponding 4 week periods of the last 3 years and the 2 week periods immediately preceding and following those.

Table 1. Notifications of diseases preventable by vaccines recommended by the NHMRC for routine childhood immunisation, received by State and Territory health authorities in the period 3 February to 2 March 1999

Disease[1,2]	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	This period 1999	This period 1998	Year to date 1999	Year to date 1998
Diphtheria	0	0	0	0	0	0	0	0	0	0	0	0
H. influenzae type b infection	0	2	1	1	0	0	0	1	5	2	9	3
Measles	2	6	0	0	0	2	12	3	25	34	38	71
Mumps	0	3	0	1	1	0	4	3	12	18	17	30
Pertussis	9	89	0	93	17	1	79	4	292	918	681	2,161
Rubella[3]	6	2	1	11	0	0	7	1	28	59	59	126
Tetanus	0	0	0	0	0	0	0	0	0	1	0	2

NN. Not Notifiable

1. No notification of poliomyelitis has been received since 1978.
2. Totals comprise data from all States and Territories. Cumulative figures are subject to retrospective revision, so there may be discrepancies between the number of new notifications and the increment in the cumulative figure from the previous period.
3. Includes congenital rubella.

Table 2. Notifications of diseases received by State and Territory health authorities in the period 3 February to 2 March 1999

Disease[1,2,3,4]	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	This period 1999	This period 1998	Year to date 1999	Year to date 1998[5]
Arbovirus infection (NEC)	0	0	0	2	0	0	20	0	22	6	43	12
Barmah Forest virus infection	0	28	0	26	0	0	2	2	58	56	103	117
Botulism	0	0	0	0	0	0	0	0	0	0	0	0
Brucellosis	0	0	0	1	0	0	0	0	1	2	3	12
Campylobacteriosis[6]	24	-	22	356	165	28	322	93	1,010	1,099	2,307	2,182
Chancroid	0	0	0	0	0	0	0	0	0	0	0	0
Chlamydial infection (NEC)[7]	4	NN	65	391	72	18	229	124	903	826	2,095	1,604
Cholera	0	1	0	0	0	0	0	0	1	1	1	1
Dengue	1	0	2	44	0	0	0	0	47	60	109	79
Donovanosis	0	NN	0	2	NN	0	0	0	2	12	5	14
Gonococcal infection[8]	0	88	114	88	9	2	70	60	431	397	925	803
Haemolytic uraemic syndrome[9]	NN	4	NN	0	1	0	NN	0	5	0	6	1
Hepatitis A	1	57	3	65	14	0	12	13	165	304	331	576
Hepatitis B incident	1	5	1	11	0	0	4	5	27	20	58	44
Hepatitis B unspecified[10]	5	164	0	91	0	1	131	15	407	581	867	1,192
Hepatitis C incident	4	2	0	-	5	0	0	10	21	14	61	32
Hepatitis C unspecified[5,10]	13	411	21	290	82	25	508	78	1,428	1,830	3,122	3,633
Hepatitis (NEC)[11]	0	1	0	0	0	0	0	NN	1	0	1	4
Hydatid infection	0	0	0	0	0	0	2	0	2	1	5	8
Legionellosis	0	10	1	6	5	1	11	1	35	24	56	36
Leprosy	0	0	0	0	0	0	0	0	0	1	0	1
Leptospirosis	0	2	0	26	2	0	2	0	32	11	65	26
Listeriosis	0	1	0	1	0	0	2	0	4	3	10	13
Malaria	2	18	0	66	3	0	9	0	98	70	160	122
Meningococcal infection	0	7	0	2	1	0	1	5	16	16	63	37
Ornithosis	0	NN	0	0	0	0	4	1	5	2	13	5
Q Fever	0	14	0	18	1	0	2	0	35	41	80	88
Ross River virus infection	1	114	37	323	13	2	114	32	636	267	1,117	524
Salmonellosis (NEC)	10	138	33	317	107	19	168	50	842	835	1,747	1,791
Shigellosis[6]	0	-	13	20	5	0	7	6	51	50	107	119
SLTEC, VTEC[12]	NN	0	NN	NN	2	0	NN	NN	2	1	7	3
Syphilis[13]	2	30	35	79	0	0	0	4	150	98	298	205
TTP[14]	0	0	0	0	0	0	0	0	0	0	0	0
Tuberculosis	2	54	2	10	0	1	26	3	98	121	210	226
Typhoid[15]	0	2	0	0	2	0	1	2	7	13	12	26
Yersiniosis (NEC)[6]	0	-	0	12	2	0	0	3	17	30	42	72

1. Diseases preventable by routine childhood immunisation are presented in Table 1.
2. For HIV and AIDS, see Tables 7 and 8.
3. Totals comprise data from all States and Territories. Cumulative figures are subject to retrospective revision so there may be discrepancies between the number of new notifications and the increment in the cumulative figure from the previous period.
4. No notifications have been received during 1999 for the following rare diseases: lymphogranuloma venereum, plague, rabies, yellow fever, or other viral haemorrhagic fevers.
5. Data from Victoria for 1998 are incomplete.
6. Not reported for NSW because it is only notifiable as 'foodborne disease' or 'gastroenteritis in an institution'.
7. WA: genital only.
8. NT, Qld, SA and Vic: includes gonococcal neonatal ophthalmia.
9. Nationally reportable from August 1998.
10. Unspecified numbers should be interpreted with some cation as the magnitude may be a reflection of the numbers of testings being carried out.
11. Includes hepatitis D and E.
12. Infections with *Shiga*-like toxin (verotoxin) producing *E. Coli* (SLTEC/VTEC) became nationally reportable in August 1998.
13. Includes congenital syphilis.
14. Thrombotic thrombocytopaenic purpura became nationally reportable in August 1998.
15. NSW, Qld: includes paratyphoid.

NN Not Notifiable.

NEC Not Elsewhere Classified.

\- Elsewhere Classified.

Correction: South Australian data were included with Western Australian data in the last issue of *CDI*.

Table 3. Virology and serology laboratory reports by State or Territory[1] for the reporting period 28 January to 24 February 1999, and total reports for the year

	State or Territory[1]								Total this period	Total reported in *CDI* in 1999
	ACT	NSW	NT	Qld	SA	Tas	Vic	WA		
Measles, mumps, rubella										
Measles virus		1			1		1		3	10
Mumps virus							2	3	5	9
Rubella virus			1	4	1		1	1	8	16
Hepatitis viruses										
Hepatitis A virus		3	3	25	3			8	42	88
Hepatitis D virus				1					1	1
Arboviruses										
Ross River virus		6	25	127	11		12	10	191	314
Barmah Forest virus		1		7				2	10	22
Dengue type 3				2					2	22
Flavivirus (unspecified)				4			1		5	8
Adenoviruses										
Adenovirus type 2							2		2	5
Adenovirus type 3							2		2	9
Adenovirus type 37							2		2	2
Adenovirus type 40								1	1	13
Adenovirus not typed/pending		10		6	13		25	8	62	295
Herpes viruses										
Cytomegalovirus	1	14		31	34	1	25	3	109	249
Varicella-zoster virus		1	2	50	41		45	16	155	425
Epstein-Barr virus	2	22		79	88		22	18	231	621
Other DNA viruses										
Molluscum contagiosum								1	1	2
Contagious pustular dermatitis (Orf virus)		1						1	2	5
Parvovirus		1		10	3	1	7	7	29	81
Picorna VIRUS family										
Coxsackievirus A16							2		2	2
Echovirus type 9		2							2	16
Echovirus type 11		4							4	19
Echovirus type 30		1							1	14
Poliovirus type 1 (uncharacterised)		1				1			2	4
Poliovirus type 2 (uncharacterised)		1							1	9
Rhinovirus (all types)		4			1		1	2	8	82
Enterovirus not typed/pending	1	3	2	1			5	21	33	148
Ortho/paramyxoviruses										
Influenza A virus		1		2	21		8	1	33	169
Influenza A virus H3N2							1		1	1
Influenza B virus					2			3	5	20
Parainfluenza virus type 1				1					1	9
Parainfluenza virus type 2					2				2	7
Parainfluenza virus type 3				1	15		2	9	27	198
Respiratory syncytial virus		5		8	8		4	8	33	163

Table 3. Virology and serology laboratory reports by State or Territory[1] for the reporting period 28 January to 24 February 1999, and total reports for the year (continued)

	State or Territory[1]								Total this period	Total reported in *CDI* in 1999
	ACT	NSW	NT	Qld	SA	Tas	Vic	WA		
Other RNA viruses										
Rotavirus		3			14		7	1	25	223
Norwalk agent							11		11	20
Other										
Chlamydia trachomatis not typed		10	8	78	40		6	53	195	556
Chlamydia psittaci							8		8	17
Chlamydia species				1			1		2	2
Mycoplasma pneumoniae		11	1	25	26		37	5	105	312
Coxiella burnetii (Q fever)		2		16	1		1		20	31
Rickettsia spp - other								2	2	2
Bordetella pertussis		4		29			16		49	115
Legionella pneumophila					1				1	4
Legionella longbeachae					2				2	17
TOTAL	4	112	42	508	328	3	257	184	1,438	4,357

1. State or Territory of postcode, if reported, otherwise State or Territory of reporting laboratory.

Table 4. Virology and serology laboratory reports by contributing laboratories for the reporting period 28 January to 24 February 1999

State or Territory	Laboratory	Reports
New South Wales	Institute of Clinical Pathology & Medical Research, Westmead	26
	South West Area Pathology Service, Liverpool	69
Queensland	Queensland Medical Laboratory, West End	552
	Townsville General Hospital	15
South Australia	Institute of Medical and Veterinary Science, Adelaide	328
Victoria	Monash Medical Centre, Melbourne	30
	Royal Children's Hospital, Melbourne	86
	Victorian Infectious Diseases Reference Laboratory, Fairfield	144
Western Australia	PathCentre Virology, Perth	188
TOTAL		1,438

Table 5. Australian Sentinel Practice Research Network reports, weeks 1 to 4, 1999

Week number	1		2		3		4	
Week ending on	10 January 1999		17 January 1999		24 January 1999		31 January 1999	
Doctors reporting	49		48		47		50	
Total encounters	5,837		6,080		5,329		5,546	
Condition	Reports	Rate per 1,000 encounters	Reports	Rate per 1,000 encounters	Reports	Rate per 1,000 encounters	Reports	Rate per 1,000 encounters
Influenza	3	0.5	7	1.2	4	0.8	1	0.2
Rubella	2	0.3	0	0.0	0	0.0	1	0.2
Measles	0	0.0	0	0.0	0	0.0	0	0.0
Chickenpox	3	0.5	14	2.3	14	2.6	4	0.7
New diagnosis of asthma	10	1.7	9	1.5	7	1.3	4	0.7
Post operative wound sepsis	8	1.4	10	1.6	4	0.8	10	1.8
Gastroenteritis	55	9.4	60	9.9	45	8.4	49	8.8

Table 6. Australian Sentinel Practice Research Network reports, weeks 5 to 8, 1999

Week number	5		6		7		8	
Week ending on	7 February 1999		14 February 1999		21 February 1999		28 February 1999	
Doctors reporting	53		59		50		51	
Total encounters	6,865		7,418		6,275		6,363	
Condition	Reports	Rate per 1,000 encounters	Reports	Rate per 1,000 encounters	Reports	Rate per 1,000 encounters	Reports	Rate per 1,000 encounters
Influenza	8	1.2	3	0.4	13	2.1	20	3.1
Rubella	0	0.0	0	0.0	0	0.0	0	0.0
Measles	0	0.0	0	0.0	0	0.0	0	0.0
Chickenpox	8	1.2	5	0.7	9	1.4	9	1.4
New diagnosis of asthma	3	0.4	9	1.2	6	1.0	9	1.4
Post operative wound sepsis	6	0.9	17	2.3	12	1.9	8	1.3
Gastroenteritis	59	8.6	65	8.8	69	11.0	61	9.6

The NNDSS is conducted under the auspices of the Communicable Diseases Network Australia New Zealand. The system coordinates the national surveillance of more than 40 communicable diseases or disease groups endorsed by the National Health and Medical Research Council (NHMRC). Notifications of these diseases are made to State and Territory health authorities under the provisions of their respective public health legislations. De-identified core unit data are supplied fortnightly for collation, analysis and dissemination. For further information, see CDI 1999;23:55.

LabVISE is a sentinel reporting scheme. Twenty-one laboratories contribute data on the laboratory identification of viruses and other organisms. Data are collated and published in Communicable Diseases Intelligence every four weeks. These data should be interpreted with caution as the number and type of reports received is subject to a number of biases. For further information, see CDI 1999;23:58.

ASPREN currently comprises about 100 general practitioners from throughout the country. Up to 9,000 consultations are reported each week, with special attention to 12 conditions chosen for sentinel surveillance in 1999. CDI reports the consultation rates for seven of these. For further information, including case definitions, see CDI 1999;23:55-56.

Additional Reports

Gonococcal surveillance

John Tapsall, The Prince of Wales Hospital, Randwick, NSW, 2031 for the Australian Gonococcal Surveillance Programme

The Australian Gonococcal Surveillance Programme (AGSP) reference laboratories in the various States and Territories report data on sensitivity to an agreed 'core' group of antimicrobial agents on a quarterly basis. The antibiotics which are currently routinely surveyed are the penicillins, ceftriaxone, ciprofloxacin and spectinomycin, all of which are administered as single dose regimens. When in vitro resistance to a recommended agent is demonstrated in 5% or more of isolates, it is usual to reconsider the inclusion of that agent in current treatment schedules. Additional data are also provided on other antibiotics from time to time. At present all laboratories also test isolates for the presence of high level resistance to the tetracyclines. Tetracyclines are however not a recommended therapy for gonorrhoea. Comparability of data is achieved by means of a standardised system of testing and a programme-specific quality assurance process. Because of the substantial geographic differences in susceptibility patterns in Australia, regional as well as aggregated data are presented.

Reporting period 1 July to 30 September 1998

The AGSP laboratories examined 840 isolates of *Neisseria gonorrhoeae* for sensitivity to the penicillins, ceftriaxone, quinolones and spectinomycin and for high level resistance to the tetracyclines in the September quarter of 1998.

Penicillins

Resistance to this group of antibiotics (penicillin, ampicillin, amoxycillin) shows considerable regional variation. Penicillin resistance was present in a high proportion of isolates examined in Melbourne (31%) and Sydney (56%). In Adelaide, Brisbane and Perth the proportion of penicillin-resistant strains was 22%, 17% and 4% respectively. A lower proportion of strains was resistant in the Northern Territory (2.3%). Figure 1 shows the proportion of isolates fully sensitive, less sensitive or relatively resistant to the penicillins by chromosomal mechanisms (CMRNG) and the proportion of penicillinase-producing gonococci (PPNG) in different regions and as aggregated data for Australia. penicillinase-producing gonococci and relatively resistant isolates usually fail to respond to therapy with the penicillins. Those in the fully sensitive and less sensitive categories (minimal inhibitory concentration - MIC ≤0.5 mg/L) usually respond to a regimen of standard treatment with the above penicillins.

There were 44 PPNG identified in this reporting period (5.2% of all isolates). These were distributed widely with 9 PPNG reported from Melbourne, 20 from Sydney, 4 from Perth, 8 from Brisbane, 2 from the Northern Territory and 1 from Adelaide. Infections with PPNG were acquired locally, but more frequently in South East Asian countries often visited by Australians. The Philippines, Thailand, Singapore, China, Indonesia, Vietnam, and Mexico were among the counties where infections with PPNG were acquired.

Of relatively greater importance than PPNG were the 217 (26%) of all isolates resistant to the penicillins by separate chromosomal mechanisms. These so-called CMRNG were most often seen in Sydney (168 strains, 50%), Melbourne (35 strains, 25%), Brisbane (9 strains, 9%) and Adelaide (4 strains, 18%). One relatively resistant isolate was seen in the Northern Territory.

Ceftriaxone and spectinomycin

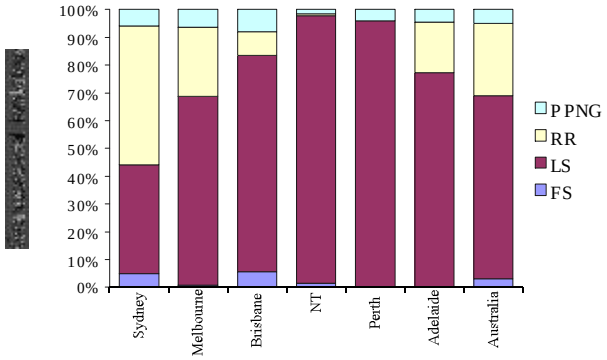
Although all isolates from all parts of Australia were sensitive to these injectable agents, a small number of isolates showed some decreased sensitivity to ceftriaxone.

Quinolone antibiotics (Ciprofloxacin, norfloxacin and enoxacin)

Thirty-seven isolates (4.4%) throughout Australia had altered resistance to this group of antibiotics (QRNG) with 23 of these showing high level resistance. Twenty-two QRNG (6.5%) were detected in Sydney, 9 (6.3%) in Melbourne and 5 (5%) in Brisbane. QRNG were also detected in Canberra and Perth.

An increase in rates of isolation of QRNG was noted in

Figure 5. Penicillin resistance of gonococcal isolates for Australia and by region, 1 July to 30 September 1998



FS Fully sensitive to penicillin, MIC≤ 0.03 mg/L
LS Less sensitive to penicillin, MIC 0.06 - 0.5 mg/L
RR Relatively resistant to penicillin, MIC ≥1 mg/L
PPNG Penicillinase producing *Neisseria gonorrhoeae*

AGSP reports in 1997. Additionally, the appearance of QRNG in locally acquired infections especially in Sydney but also in Melbourne was specifically mentioned. Local acquisition of high level resistance to quinolone antibiotics was seen again in Sydney and Melbourne in this quarter and additionally in this quarter in Perth and Brisbane. However, most of the infections with QRNG were acquired overseas. The countries identified as sources of acquisition included Singapore, Pakistan, Vietnam, New

Zealand, Thailand, the Philippines, Indonesia and China reflecting the wide dispersal of these strains.

In the corresponding period of 1997, 51 QRNG comprised 7.2% of all Australian isolates.

The quinolone agents are the oral agents most often used in centres where penicillins are ineffective. The appearance of quinolone resistance reduces options for successful treatment of gonorrhoea.

High level tetracycline resistance - 'TRNG'

Forty six TRNG were detected throughout Australia (5.5% of all strains) with isolates of this type again present in most centres. The highest number and proportion of TRNG was found in Sydney where the 27 TRNG represented 8% of all isolates. TRNG were also prominent in Perth (7 isolates, 7%) and Brisbane (7 isolates, 7%). Three TRNG were seen in Melbourne and single isolates of this type were present in Adelaide and the Northern Territory. There were 32 (4.5%) TRNG isolated in the corresponding period of 1997. Infections with TRNG were acquired in Indonesia, the Philippines, Thailand, Singapore and the USA. Local acquisition of TRNG was increasingly prominent in Sydney and also noted in other centres.

Sentinel Chicken Surveillance Programme

Sentinel chicken flocks are used to monitor flavivirus activity in Australia. The main viruses of concern are Murray Valley encephalitis (MVE) and Kunjin which cause the potentially fatal disease Australian encephalitis in humans. Currently 26 flocks are maintained in the north of Western Australia, seven in the Northern Territory, nine in New South Wales and ten in Victoria. The flocks in Western Australia and the Northern Territory are tested year round but those in New South Wales and Victoria are tested only from November to March, during the main risk season.

Results are coordinated by the Arbovirus Laboratory in Perth and reported bimonthly. For more information see CDI 1999;23:57-58

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January to February 1999

Sentinel chicken serology was carried out for 25 of the 27 flocks in Western Australia in January and February 1999. There were a large number of seroconversions to flaviviruses in both the Kimberley and Pilbara flocks during this period. The increased flavivirus activity was a result of early, heavy wet season rainfall in the Kimberley region of Western Australia. To date, only one mild case of Kunjin virus infection from Kununurra has been reported.

The number of chickens for flavivirus antibodies by ELISA and the virus (or viruses) they were infected with, is shown in Table 1.

Serum samples from all of the seven Northern Territory sentinel chicken flocks were tested in our laboratory in January and February 1999. Seroconversions to flaviviruses were detected in serum samples from

Table 1. Flavivirus seroconversions in Western Australian sentinel chicken flocks in January and February 1999

Location	January '99			February '99		
	MVE	KUN	MVE/KUN	MVE	KUN	MVE/KUN
Kimberley						
Kalumburu	1					
Wyndham				2		
Kununurra	1		1	5		2
Halls Creek				1		
Fitzroy Crossing				6		
Derby[1]				8		2
Broome[1]				3	2	
Pilbara						
Karratha				1		1
Pardoo			1			

1. 2 Flocks of 12 chickens at these sites.

MVE Antibodies to Murray Valley encephalitis virus detected by ELISA.

KUN Antibodies to Kunjin virus detected by ELISA.

MVE/KUN Antibodies to both MVE and Kunjin viruses detected by ELISA.

Katherine, Tennant Creek and Gove in February 1999. These results are shown in Table 2.

There were no seroconversions to flaviviruses recorded in Victoria or New South Wales in January or February 1999.

Table 2. Flavivirus seroconversions in Northern Territory sentinel chicken flocks in February 1999

Location	Antibodies detected			
	MVE	KUN	MVE/ KUN	FLAVI only
Katherine	2		1	
Tennant Creek	4		4	
Gove		4		2

Flavi only Antibodies in serum competed only with flavivirus monoclonal in ELISA.

HIV and AIDS Surveillance

National surveillance for HIV disease is coordinated by the National Centre in HIV Epidemiology and Clinical Research (NCHECR), in collaboration with State and Territory health authorities and the Commonwealth of Australia. Cases of HIV infection are notified to the National HIV Database on the first occasion of diagnosis in Australia, by either the diagnosing laboratory (ACT, New South Wales, Tasmania, Victoria) or by a combination of laboratory and doctor sources (Northern Territory, Queensland, South Australia, Western Australia). Cases of AIDS are notified through the State and Territory health authorities to the National AIDS Registry. Diagnoses of both HIV infection and AIDS are notified with the person's date of birth and name code, to minimise duplicate notifications while maintaining confidentiality.

Tabulations of diagnoses of HIV infection and AIDS are based on data available three months after the end of the reporting interval indicated, to allow for reporting delay and to incorporate newly available information. More detailed information on diagnoses of HIV infection and AIDS is published in the quarterly Australian HIV Surveillance Report, available from the National Centre in HIV Epidemiology and Clinical Research, 376 Victoria Street, Darlinghurst NSW 2010. Telephone: (02) 9332 4648 Facsimile: (02) 9332 1837.

HIV and AIDS diagnoses and deaths following AIDS reported for 1 to 31 October 1998, as reported to 31 January 1999, are included in this issue of CDI (Tables 7 and 8).

Table 7. New diagnoses of HIV infection, new diagnoses of AIDS and deaths following AIDS occurring in the period 1 to 31 October 1998, by sex and State or Territory of diagnosis

										Totals for Australia			
		ACT	NSW	NT	Qld	SA	Tas	Vic	WA	This period 1999	This period 1998	Year to date 1999	Year to date 1998
HIV diagnoses	Female	0	4	0	0	1	0	1	0	6	7	74	65
	Male	0	23	2	5	2	0	12	2	46	57	524	600
	Sex not reported	0	1	0	0	0	0	0	0	1	0	7	12
	Total[1]	0	28	2	5	3	0	13	2	53	64	605	678
AIDS diagnoses	Female	0	1	0	0	0	0	0	0	1	2	9	24
	Male	0	3	0	2	0	0	0	0	5	20	193	263
	Total[1]	0	4	0	2	0	0	0	0	6	22	202	287
AIDS deaths	Female	0	0	0	0	0	0	1	0	1	2	8	12
	Male	0	3	0	2	0	1	2	0	8	12	94	190
	Total[1]	0	3	0	2	0	1	3	0	9	14	102	203

1. Persons whose sex was reported as transgender are included in the totals.

Table 8. Cumulative diagnoses of HIV infection, AIDS and deaths following AIDS since the introduction of HIV antibody testing to 31 October 1998, by sex and State or Territory

		State or Territory								
		ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Australia
HIV diagnoses	Female	21	571	8	131	55	4	198	99	1,087
	Male	183	10,456	101	1,856	642	77	3,720	868	17,903
	Sex not reported	0	260	0	0	0	0	24	0	284
	Total[1]	204	11,306	109	1,994	697	81	3,955	970	19,316
AIDS diagnoses	Female	8	166	0	45	20	2	65	23	329
	Male	83	4,476	32	775	325	43	1,562	337	7,633
	Total[1]	91	4,653	32	822	345	45	1,634	362	7,984
AIDS deaths	Female	2	113	0	30	15	2	47	16	225
	Male	62	3,078	24	538	222	28	1,226	241	5,419
	Total[1]	64	3,198	24	570	237	30	1,279	258	5,660

1. Persons whose sex was reported as transgender are included in the totals.

Overseas briefs

Source: World Health Organization (WHO)
This material has been condensed from information on the WHO Internet site. A link to this site can be found under 'Related sites' on the CDI homepage.

Cholera, Somalia

Cholera has occurred seasonally in the country for a number of years and usually starts in late November/ early December ending around May. In the first week of December 1998 cholera was reported in Mogadishu (Banadir Region) and since then several regions have reported cases. The other regions currently affected are Bay, Gedo, Lower Juba and Lower Shabelle. A total of 4,457 cases with 166 deaths have been reported since December, up to 19 February.

The epidemic is occurring in communities already weakened by severe shortage of food and in areas where only polluted water is available as wells have dried up. Supplies for treatment have been made available by WHO to UNICEF. The UN agencies, NGOs and the local health authorities are all collaborating in dealing with the epidemic. As well as clinical case management, efforts have also been directed at preventive measures such as chlorination of public water sources and health education on personal hygiene. At present, tests for cholera can be conducted in four laboratories.

Meningococcal disease

Sudan - update

The outbreak that started in Northern Darfur State in December 1998 has now spread to 15 States, some of them reaching epidemic level. From the beginning of the epidemic up to 9 March, 2,293 cases and 262 deaths have been reported by the Federal Ministry of Health. An appeal has been launched by the Ministry of Health in Khartoum, with support from the executive members of the International Coordinating Group, WHO, UNICEF, IFRC and MSF, for the provision of meningococcal vaccine. There is an urgent need for more vaccines, drugs and technical support to strengthen the surveillance systems and laboratory capacity.

Guinea-Bissau

An outbreak of meningococcal meningitis has been reported in Guinea-Bissau. The outbreak started early January and has mainly affected the regions Oio, Bafata and Gabu. The causative organism has been identified as *Neisseria meningitidis* serogroup A.

Since the beginning of 1999 up to 21 February, 139 cases have been notified, of which 36 were fatal. During 1998 Guinea-Bissau reported 112 cases of meningococcal disease, of which 12 died.

The national health authorities and the local representatives of the Executive Group of the International Coordinating Group for the Provision of Meningococcal Meningitis (ICG) are implementing measures to control the outbreak.

Acute respiratory infection, Afghanistan

On 13 February, an outbreak of an unidentified disease was reported to have occurred in Darwaz, Badakhshan,

Afghanistan. On 26 February, a specialised WHO team arrived on site at one of the affected villages, Jamarche Bala, with the logistic support of the United Nations system. Other villages were visited by *Médecins sans frontières* and Focus (Aga Khan Foundation).

The outbreak began around mid-January after two young men returned from the village of Waram, both suffering from an acute respiratory infection. Over the next two days, approximately 40 persons living in the same household became ill. The disease then spread through the whole village, affecting 70 to 80 per cent of households. The village has a population of 5,400. Preliminary results available on 26 February indicated that in five of the 18 villages affected there had been 6,300 cases and 135 deaths. The deaths occurred among both males and females and involved primarily infants and the elderly. Cases were treated by the team with chloramphenicol, which resulted in a significant improvement, suggesting that severely ill patients were suffering from secondary bacterial infections. There were no deaths among those treated.

The disease is flu-like and is characterised by abrupt onset of fever, headaches and myalgia, followed by chest pain and cough. Living and sanitary conditions are crowded, and the water supply is unprotected. Nutrition is of poor quality. There are no health services in this very remote area, which has not been accessed by routine immunisation teams.

Preliminary conclusions of the WHO team in the field is that the outbreak now declining was an influenza-like illness which has affected a large proportion of the population. The rate of secondary complications (mainly pneumonia) was high. Mortality is 1%-2% of the total population primarily due to lack of antibiotic availability and overall poor living and nutritional conditions.

WHO and its local partners are now helping local authorities to organise follow-up treatment and arranging for additional medical supplies to the area. Clinical specimens collected by the field team will be analysed shortly.

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Contributions

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