

STDs on the rise

WITH RATES OF SEXUALLY TRANSMITTED DISEASES INCREASING, PETER LAVELLE LOOKS AT THE LAB TECHNIQUES USED TO TRACK THEM DOWN.

One of the great Australian success stories in public health was the safe sex campaign initiated in the 1980s when HIV first appeared. It was intended to prevent the spread of the virus, but it also promised to lower the incidence of other sexually transmitted diseases (STDs).

Alas, the fall-off in the incidence of STDs has not been sustained. There was a drop in the late 1990s, but since 2000 there has been a general increase in STDs, particularly in the case of male-to-male sex, says Dr David Leslie, a medical microbiologist at the Victorian Infectious Diseases Reference Laboratory.

Reported rates of HIV, syphilis, gonorrhoea and chlamydia in particular are rising, Dr Leslie says.

Part of the reason is the success of anti-retroviral therapy for HIV giving some people a false sense of security that HIV is no longer a terminal illness, leading in turn to unsafe sex practices.

Last year, there were almost 40,000 cases of chlamydia reported to Australia's National Notifiable Diseases Surveillance System, 8 per cent more than in 2004 and 30 per cent up on 2003 cases. In the past five years, HIV diagnoses have risen 41 per cent, according to the National Centre in HIV Epidemiology and Clinical Research.

Dr Robert Baird, an infectious diseases physician and microbiologist at Melbourne Pathology, says one of the most dramatic developments is the worldwide increase in syphilis cases, which in the past year or two has reached Australia.

"Some of it's coming in from East Timor, some from mainland Asia, but it's basically a worldwide phenomenon and not just in gay men, but the general heterosexual population," Dr Baird says.

A disease that had become almost non-existent has come back with a vengeance, he says.



"Our lab has seen 10 times more cases of primary syphilis in the last year than we've seen in the previous 10 years."

GPs are not used to seeing a lot of primary syphilis cases and can mistake them for other types of genital ulcer.

Often the disease occurs vaginally, anally or even inside the mouth or urethra and isn't recognised. A month or two later it is followed by secondary syphilis, a whole body rash that classically involves the palms and the feet as well.

Time was when every third-year medical student could pick the rash of secondary syphilis. But it came to be so infrequently seen that doctors don't think of syphilis and miss it, Dr Baird says.

Often the doctor will take a biopsy of the rash and send it to a pathologist and the pathologist too is so unused to seeing secondary syphilis that he or she mistakes it for something else.

There needs to be an education campaign aimed at GPs and pathologists about the resurgence of syphilis, Dr Baird argues.

Genital herpes, the most common sexually transmitted disease, has changed its epidemiology over the past 20 years, he says.

"Most genital herpes used to be caused by (the herpes simplex virus 2) and mouth herpes was caused by HSV 1.

There was always a little bit of crossover but only a few per cent. But now, depending on the age you are when infected, there are huge differences. For example, in a 50-year-old with genital herpes it's still nearly always HSV 2, but if you get it in your 20s, it's far more likely to be HSV 1."

The good news is that the incidence of HSV 2 is diminishing.

"There's less and less HSV 2 in the young, to the point where it could potentially disappear in a generation or two," Dr Baird says. "This phenomenon isn't confined to Australia; it's been noted in other Western countries too. We don't exactly know why it's happening – it could be one area where safe sex campaigns are having an effect."

But gonorrhoea remains a major public health problem. New strains from Thailand and other sex tourism destinations in Asia are appearing in Australia and are highly resistant to many of the usual antibiotics.

Says Dr Leslie: "Most strains show some resistance to penicillin. We're seeing increasing resistance to second line drugs like ciprofloxacin, though fortunately they appear to have remained sensitive to ceftriaxone, so there is still effective treatment available."

As for chlamydia, its prevalence is increasing in gay men and the general heterosexual population, he says. This is worrying because chlamydia often doesn't produce symptoms and can lead to silent pelvic inflammatory disease and infertility in women.

Lab diagnostic techniques are critical in the management of STDs. Many of the conditions present a similar picture. There are many other causes of genital ulcers besides primary syphilis, for example – it might be candida, herpes or a local trauma lesion that gets infected.

Chlamydia and gonorrhoea may produce a urethral discharge and pain on



urinating, but they are caused by different organisms and require different antibiotic treatments. The good news in all this is that the diagnostics have improved considerably in the past five years.

Nucleic acid amplification technologies, including polymerase chain reaction techniques, have revolutionised STD diagnosis. Rather than culturing the micro-organisms or viruses causing disease or detecting antibodies that the body has made to them, these tests look for the DNA (or RNA) they contain. They work in the same way as forensic DNA testing.

"You look for the specific DNA of the particular pathogen you suspect from the clinical picture, using primers that fix only to those particular sequences of DNA bases that are found in that pathogen, to identify it," Dr Baird says.

PCR technology has advantages over traditional technologies in that it is more sensitive and can be more specific. One of the problems of traditional diagnostic tests is sensitivity – whether they pick up the organism or not and avoid false negatives. Another is specificity – whether they pick up the right organism and not another one, so that they avoid the problem of false positives.

With immunoassay tests, for example, there are often false positives and false negatives. The immunoassay is looking for proteins – antibodies made against the bacteria or viruses – in a blood sample. But people's immunological responses vary. There may not even be antibodies to

the infecting agent, even though the person has been exposed and has the clinical picture.

Then there are timing issues – the assay may not be done when antibody levels in the blood are high enough.

Both these situations will produce false negatives. The immunoassay may also cross-react with other proteins that are not linked to the pathogen, giving false positives.

Nucleic acid techniques are highly sensitive and highly specific, because they are looking directly at the DNA or RNA of the organism, not the antibodies produced by the patient's immune response.

Part of the reason they are very sensitive is they can pick up the DNA even if the virus or bacteria is degraded.

"The organisms you're looking for don't have to be viable or alive; you can actually detect DNA in dead chlamydia or dead viruses, so viruses that have been shed and are not viable still may have nucleic acid that can be detected," Dr Baird says.

He says most of the laboratories that have changed to nucleic acid techniques have noticed their positivity rate go up by 50 to 70 per cent and this may be the reason behind what appears to be a marked increase in the incidence of chlamydia. Yes, there's more chlamydia being detected, but it could be due to more sensitive diagnostic techniques than was the case 10 years ago.

Dr Leslie says chlamydia is a difficult organism to culture and fluorescent microscopy tended to miss it, especially from anorectal and oral sites.

"With PCR we can pick up chlamydia from any site with ease," he says.

PCR testing can be manual or automated and faster than other methods. Being highly sensitive and specific means it can be used to make the initial diagnosis, not just to confirm an initial less specific test. Another plus is that PCR has less stringent specimen transport requirements than the traditional technologies.

"In the old days, to do dark ground microscopy for syphilis for example, we had to bring the patients into the lab where the microscope was, because we needed to look at the specimens within 30 minutes of taking them. But with PCR, timing is less of an issue because the DNA can be detected even in dead bacteria," he says.

PCR testing is widely available for chlamydia, and generally for gonorrhoea and herpes, though for syphilis it is only available at a handful of labs in Australia and is more of a research and development tool at this stage. There are some specificity problems with gonorrhoea, but the situation is gradually improving.

For trichomonas, a parasite that causes vaginal inflammation or infects the urethra, and human papilloma viruses (which can lead to genital warts and in some cases cervical cancer) PCR is less



widely available, but that will change. In a few years it will be widely available for all STDs, Dr Leslie predicts.

Has PCR made traditional pathology techniques such as light microscopy and immunoassay redundant? In some cases it does replace the traditional techniques. In herpes and chlamydia, the nucleic acid technologies are far better than the old culture methods.

But there is still an important role for the traditional methods. With gonorrhoea, light microscopy and culturing can determine bacterial susceptibilities. Also, as new strains appear, they may not be recognised by the PCR kits, which can only pick up DNA in existing strains.

"Some of the commercial gonorrhoea nucleic acid assays have recently been missing some of the gonorrhoea strains that are now coming into the Northern Territory," Dr Leslie says.

There is also a role for traditional testing methods in monitoring the effects of treatment. With treatment, antibody concentrations may fall, and this can be confirmed by immunoassay. Immunoassays are also useful for antenatal screening, screening of partners and contacts, and of blood and tissue donors. 📌

GPs NOTE: This article is available for patients at <http://pathway.rcpa.edu.au>

BEATING cervical cancer

One job pathologists are likely to be doing less of in years to come is looking at cervical cancer smears, thanks to the new human papillomavirus vaccine, Gardasil, which came on to the Australian market in September.

The vaccine is based on virus-like particle (VLP) technology developed at the University of Queensland, which produces virus-shaped particles that mimic the real virus to create an immune response.

The vaccine has four VLP components covering the HPV types 16, 18, 6 and 11, which are the most common strains affecting women and responsible for 70 per cent of cervical cancer and 90 per cent of genital wart cases.

It is administered as three injections over a six-month period and available from GPs on a private prescription at a cost of about \$150 a dose.

CSL, which markets the vaccine in Australia, has applied for it to be listed on the Pharmaceutical Benefits Scheme, and the Federal Government is also considering whether to have it administered to girls throughout Australian schools in a similar way to the existing rubella vaccination program – possibly by 2008.

PAP smears will still be needed to detect cancers caused by other HPV strains – but the welcome news is there will be fewer invasive cervical cancer slides turning up in pathology labs. There could be an additional role for pathologists though in the screening of those who are already sexually active. If they are found not to have been exposed to HPV types 16, 18, 6 and 11, then they could still be suitable for the vaccine.