The National Neisseria Network 1979 – 200?

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Introduction

The federal nature of the Australian health system means that the different jurisdictions administer and deliver services appropriate to the diverse needs of populations of varied composition and density distributed over a continent. The different approaches that have developed as a consequence of this approach pose some problems in relation to defining and dealing with issues of public health microbiology. A number of laboratory-based programmes have emerged that examine specific issues of surveillance of infectious disease across the 'jurisdictional divide'. For example, significant data have been gathered by mycobacterial and enteric pathogen programmes over many years, to name but two. This article briefly describes the origins and aims, organisation and structure, and past, present and future functions of another of these programmes, the National Neisseria Network (NNN).

The NNN undertakes laboratory-based surveillance of isolates of the two pathogenic Neisseria, *Neisseria gonorrhoeae* and *Neisseria meningitidis*. It may seem incongruous to some that surveillance of these two pathogens would be dealt with in a single network given the quite different public health responses required for gonorrhoea and invasive meningococcal disease (IMD). however, there is considerable overlap in the laboratory procedures and approaches to the two organisms - *N. gonorrhoeae* is essentially a highly evolved meningococcus. The commonality of laboratory approaches is finite however, so that two separate systems exist within the NNN, namely, the Australian Gonococcal Surveillance Programme (AGSP) and its meningococcal equivalent the Australian Meningococcal Surveillance Programme (AMSP). The two systems will be described separately.

The Australian Gonococcal Surveillance Programme (AGSP)

Background

The AGSP is a programme of long-term continuous surveillance of the susceptibility of gonococci to antibiotics used in the treatment of gonorrhoea. It is a collaborative network of reference laboratories in each State and Territory which use an agreed methodology to determine the quantitative susceptibility (minimal inhibitory concentration – MIC) of gonococci to a core group of antibiotics.

Why gonococcal susceptibility surveillance?

The necessity for such a programme is now firmly established. Effective antibiotic treatment of gonorrhoea is one pillar by which control of gonococcal disease may be achieved. Appropriate treatment quickly renders patients non-infectious decreasing both the transmissibility of the disease and the duration of infectiousness of the individual. In terms of disease control there are thus direct benefits from use of proper treatment. Additionally the well-recognised complications of gonorrhoea – infertility, pelvic inflammatory disease, ophthalmia, foetal loss, disseminated infection – are significantly reduced by early and appropriate treatment. It is important also to remember that HIV transmission is significantly amplified in the presence of gonorrhoea. Males with HIV and gonorrhoea have greatly increased HIV loads in seminal fluids compared to controls with HIV but not gonorrhoea, but this load returns to the level found in controls once proper treatment is effected. Those with gonorrhoea without HIV are also more susceptible to HIV infection because the target cells for HIV are recruited to the inflammatory process initiated by gonococcal infection. Again this susceptibility is removed by effective treatment resolving the inflammatory infiltrate. There are thus very cogent reasons why gonorrhoea should now be actively diagnosed and effectively treated. Treatment of gonorrhoea is by single dose antibiotic treatment at first diagnosis – well before any susceptibility testing of individual isolates can be performed. Empiric treatment is thus used, but is directed not by testing of individual isolates on an emerging basis, but rather by determining the pattern of susceptibility of prevalent gonococcal isolates. This is ascertained by obtaining a suitable sample of isolates, measuring the in vitro susceptibility of the gonococci so obtained and, on this basis, establishing a suitable antibiotic treatment regimen. There is a strong correlation between in vitro susceptibility determinations (MICs) and likely outcome of treatment in gonorrhoea. It is usually necessary to discontinue a treatment regimen once 5% of isolates are resistant to that agent.

Gonococcal resistance to antibiotics can be quite volatile. Australians travel frequently in our region (where antibiotic resistant gonococci are highly prevalent) and introduce resistant isolates into local transmission chains. Surveillance of antibiotic resistance in gonococci should thus be designed not only to monitor patterns of resistance but also be able to detect emergence of new forms of resistance and the spread of these resistant strains. The spread of antibiotic resistant gonococci is by no means inevitable as antibiotic resistance is but one of many factors which determine the 'success' of a subset of gonococci in establishing themselves within a community. Determining the pattern of introduction of antimicrobial resistant gonococci (AMRGC) can assist in planning and control of the spread of such organisms.

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Origins and outcomes of the AGSP

This programme arose form a perceived need to have available in Australia reliable and comparable data on patterns of AMRGC. Data were being generated differently in a number of centres and could not be integrated or compared. In 1979 staff from a group of laboratories agreed to explore a common approach to gonococcal susceptibility testing with a view to describing a standard method for determining MICs. Over an 18-month period, systems were assessed and the AGSP method of MIC determination was agreed and introduced.[1] No one laboratory was able to examine all isolates available for testing in Australia. A networked approach was thus developed whereby the standard test method was used in each centre and an extensive and comprehensive quality assurance programme established.[2] Data on gonococcal susceptibility were first reported in *Communicable Diseases Intelligence (CDI)* in 1981[3] and quarterly reports have been published continuously since then. Initially, susceptibility to the penicillins was examined, but other antibiotics were introduced as their use warranted. Intermittent reviews of AGSP susceptibility data were reported[1,4] but in recent years *CDI* has provided a vehicle for regular publication of annual reports of the AGSP.[5-7,10]

In addition to the information on AMRGC, it became apparent that the AGSP could contribute meaningful data on trends in gonococcal disease in Australia. Although the AGSP did not obtain all gonococci from notified cases, it established a broadly based and stable sample from which site specific and trend data on gonococcal disease could also be derived. This 'secondary' benefit saw data published on this topic,[8] incorporated in other data sets[9] and included in AGSP annual reports[5-7,10] to complement more extensive information from clinical notification systems.

Current status

The 1999 report of the AGSP has recently appeared in *CDI*[10] and reinforced the need for continuing surveillance of AMRGC. This latest report described changing patterns of AMRGC in major urban centres and worrying levels of decreased susceptibility to agents used for treating gonorrhoea in rural and northern Australia where rates of disease are excessive. In the major centres of Sydney and Melbourne for practical purposes there is no suitable oral therapy for the treatment of gonorrhoea. Isolates with altered susceptibility to injectable third generation cephalosporins have now been detected. In northern Australia the proportion of isolates resistant to the penicillins, which is the mainstay of treatment, is reaching critical levels. Under these circumstances susceptibility surveillance should not just be maintained but enhanced.

Future

Newer diagnostic systems using non-culture based tests have been adopted widely in Australia. Those in use are nucleic acid amplification assays (NAA), with polymerase chain reaction (PCR) methodology the most widely employed. These tests have allowed the possibility of an aetiological diagnosis in STD syndromes in patients in remote regions where circumstances prevented culture-based assessment. This improved diagnostic capability has materially assisted in enhanced disease control,[11] but presupposes that treatment modalities will remain effective. In urban practice, use of NAA tests has increased following inclusion of a rebate for NAA testing in STDs in the pathology services table.

This change in diagnostic practice will mean that fewer isolates are available for susceptibility testing. Ironically this is occurring at a time when antibiotic resistance patterns are changing in both urban and rural areas and there is a need for enhanced susceptibility surveillance. At present the sample of isolates available to the AGSP is sufficient for its primary purpose of susceptibility surveillance. The AGSP has discussed strategies whereby this sample base can be maintained despite the use of PCR for diagnosis; for example, culture of urine samples positive on PCR testing. This of course imposes an extra cost on the health system. It should perhaps be remembered the NAA testing offers no real increase in sensitivity when proper culturing can be performed. Thus while NAA testing has significant advantages in outreach situations, culture-based examination should be maintained if not actively pursued in clinic-based practice.

Data on trends in disease patterns from AGSP sources will be progressively devalued if and when the isolate sample base is altered through introduction of NAA testing. Again this comes at a time when rates of gonococcal disease are increasing and precise definition of the subpopulations where this phenomenon is occurring is required.

The AGSP has been a successful model of laboratory-based surveillance with considerable public health relevance. It links antimicrobial resistance directly to disease control and health outcomes in a condition that is of major public health importance and which is highly transmissible. For over a decade, the AGSP methodology has been successfully adapted for use in World Health Organization programmes in about 30 countries in our region. This too is a benefit to Australia as gonococci do not recognise territorial boundaries and this knowledge of regional susceptibility patterns helps determine our treatment strategies.

The Australian Meningococcal Surveillance Programme (AMSP)

Background

Despite the high public profile of invasive meningococcal disease, laboratory data on invasive meningococcal isolates found in Australia was at best piecemeal until 1994 when the AMSP was formed. The AMSP laboratories used an approach similar to that adopted for the AGSP, namely, jurisdiction-based, collaborative and consensus-based methodologies, programme specific Quality Assurance and pooling of systematically generated and comparable data. Again the laboratory data were seen as complementary to the existing formal notification schemes.

The emphasis placed on laboratory-based meningococcal surveillance is tailored to the needs of disease control and concentrates on meningococcal strain characterisation and differentiation. Although the AMSP is laboratory-based it does obtain clinical data which have enabled it to provide other information of relevance e.g. the NNN reports provide data on serogroup linked to age group. Antibiotic resistance is not as well developed in meningococci as in gonococci, but the same principles of susceptibility surveillance developed for gonococci were readily applicable to meningococci.

Approach of the AMSP to strain characterisation and differentiation in relation to public health

Characterisation and differentiation of meningococci (typing) from cases of IMD undertaken for public health reasons is to confirm or to exclude a suspected outbreak or cluster of cases and to define the meningococcal population circulating at any one time. Various phenotypic and genotypic techniques are available and are employed for different purposes at different times.

Currently all isolates are phenotyped by NNN laboratories by determining the serogroup as soon as practicable after receipt and then the serotype and serosubtype using standard monoclonal reagents. Serotyping and serosubtyping is performed by batching of isolates and testing at regular intervals – less frequently in low incidence periods and more frequently in the winter/spring. Serotyping and subserotyping is NOT *routinely* performed on an emerging basis, as it is wasteful of reagents that are no longer produced. These techniques can however, be rapidly employed if an epidemiological link between cases is established or suspected clinically and can quickly exclude the presence of clustering of cases.

Many meningococcal strains cannot be typed by serological methods and reagent stocks are finite. Genotyping (molecular) procedures are thus now supplanting phenotyping (serotyping) methods. Those available include pulsed field gel electrophoresis (PFGE), *porA/porB* sequencing and MLST. These techniques are used for different purposes eg PFGE and *porA* sequencing are used for short-term studies of strain relatedness and MLST for longer-term 'population' studies of meningococci. PFGE methods are not uniform – there are significant variations in choice of cutting enzymes, and pulse and ramp times, but PFGE patterns are usually considered of short-term significance in differentiating suspected clusters under local conditions. The non-clonal nature of serogroup B meningococci, for example, means that comparisons of PFGE patterns are not suitable for distinguishing invasive meningococci separated temporally and/or geographically across Australia.

Similarly *porA/porB* typing is increasingly available and can also be applied for short-term examination of possible clusters but is not suited to longitudinal genotyping studies. A global standard nomenclature for *porA* sequencing is being developed meaning that greater comparability of strains may be achieved by this means.

As it examines more stable parts of the genome, MLST is at the moment a technique more appropriately used for studies of meningococcal populations.

The application and development of these techniques in Australia is under constant review by the NNN.

It should also be remembered that the presence of isolates with an indistinguishable phenotype (serogroup, serotype and serosubtype) and/or genotype *does not* of itself establish a true epidemiological link; the latter should properly be established by clinical public health procedures. That is the possibility of outbreaks or clusters of cases is raised on clinical epidemiological grounds and confirmed or excluded by application of the typing techniques described here. Using phenotyping data without *prior* clinical epidemiological analysis to define case clustering is to place the cart before the horse.

Diagnostic advances

The laboratory diagnosis of IMD depends on the demonstration of *N. meningitidis*, or detection of its polysaccharide antigen or DNA in samples from normally sterile sites, or positive serology. As with gonorrhoea, non-culture based diagnosis is making an increasingly important contribution to confirmation of IMD. In meningococcal disease, non-culture based diagnosis becomes increasingly important as 'treat first, diagnose later' management options are followed. Also relevant is an evident reluctance to undertake lumbar puncture in cases of suspected meningitis. This produces a bias in data from culture-based cases. The AMSP attempts to capture PCR and serologically based diagnoses, and includes these in its analyses. however, this becomes more difficult as technological innovations become more widely used.

Some outcomes of AMSP surveillance

Prior to 1994 there was not even a comprehensive knowledge of serogroup distribution of IMD isolates in Australia. Currently, national serogroup data on IMD are available to public health bodies in each jurisdiction on a fortnightly basis. Since its inception the AMSP has provided data on the epidemiology of IMD in Australia previously or still otherwise unavailable. It has determined that most IMD in Australia, like that in most industrialised nations, is sporadic and due principally to serogroup B and C meningococci. Importantly it has revealed significant regional variation in the proportion of these two serogroups and monitored the changing patterns in serogroup distributions in the past several years. Age related distribution of disease by serogroup is specifically included in reports. Some clusters of serogroup C disease have occurred in recent years, but no instances of serogroup A infections have been seen for some time. Particular subtypes of serogroups B and C have been responsible for outbreaks and clusters of disease and for hyperendemic disease. Changes in the antibiotic susceptibility of IMD isolates to penicillin have been recorded and the frequency of isolation of isolates resistant to agents used for prophylaxis of IMD in Australia monitored. Data are reported annually in *CDI*.[12-16]

Concluding remarks

In both surveillance systems that monitor isolates of the pathogenic *Neisseria*, a comprehensive amount of relevant data has been obtained, analysed and reported over many years. Benefits other than these published data, often intangible, also accrue to the participants e.g. commonality of methodology, method development and shared experience. The total output of the NNN is seemingly greater than the sum of its parts. NNN labs are often consulted formally and informally in relation to *Neisseria* infections in their jurisdiction.

Some essential features of networks of this kind are that publication and recognition accrues to the network itself and decisions are based on consensus and agreement. This collaborative system is the antithesis of the competition-based approach currently fashionable but at least, in this instance, it has the benefit of a proven track record as justification for its continuation.

The NNN and its members have always been delighted to work with other interested parties. Individual jurisdictions

have forged strong links between clinical and laboratory systems using models best suited to their needs. The NNN has anticipated a universal approach by maintaining jurisdictional independence of its participants while at the same time combining and analysing national laboratory data. We would hope that any attempts to provide additional insights into clinical and public health aspects of IMD in Australia would see fit to include the NNN as full partner and use the experience already gained to enhance this process.

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References

1. Australian gonococcal surveillance programme. Penicillin sensitivity of gonococci in Australia: development of Australian gonococcal surveillance programme. *Br J Vener Dis* 1984;60:226-230.
2. Tapsall JW. Use of a quality assurance scheme in a long-term multicentric study of antibiotic susceptibility of *Neisseria gonorrhoeae. Genitourin Med* 1990;66:8-13
3. Australian Gonococcal Surveillance Programme. Gonococcal surveillance - Australia (July-September 1981). *Commun Dis Intell* 1981;25:2-3.
4. Australian Gonococcal Surveillance Programme. Penicillin sensitivity of gonococci isolated in Australia 1981-6. *Genitourin Med* 1988;64:147-151.
5. Australian Gonococcal Surveillance Programme. Annual report of the Australian Gonococcal Surveillance Programme, 1997. *Commun Dis Intell* 1998;22:212-216.
6. Australian Gonococcal Surveillance Programme. Annual report of the Australian Gonococcal Surveillance Programme, 1996. *Commun Dis Intell* 1997;21:189-192.
7. Australian Gonococcal Surveillance Programme. Annual report of the Australian Gonococcal Surveillance Programme, 1998. *Commun Dis Intell* 1999;23:193-197.
8. Australian Gonococcal Surveillance Programme. Changing patterns in gonococcal infections in Australia 1981-1987. *Med J Aust* 1988;149:609-612.
9. National Centre in HIV Epidemiology and Clinical Research. HIV/AIDS and related diseases in Australia: annual surveillance report. Darlinghurst: National Centre in HIV Epidemiology and Clinical Research,1998.
10. Australian Gonococcal Surveillance Programme. Annual report of the Australian Gonococcal Surveillance Programme, 1999. *Commun Dis Intell* 2000;24:113-117.
11. Miller PJ, Torzillo PJ, Hateley W. Impact of improved diagnosis and treatment on prevalence of gonorrhoea and chlamydial infection in remote Aboriginal communities on Anangu Pitjantjatjara Lands. *Med J Aust* 1999;170:429-432.
12. National Neisseria Network. Meningococcal isolate surveillance Australia 1994. *Commun Dis Intell* 1995; 19:286-289.
13. National Neisseria Network. Meningococcal isolate surveillance Australia 1995. *Commun Dis Intell* 1996; 20:422-424.
14. Australian Meningococcal Surveillance Programme. Annual report of the Australian Meningococcal Surveillance Programme, 1996. *Commun Dis Intell* 1997;21:217-221.
15. Australian Meningococcal Surveillance Programme. Annual report of the Australian Meningococcal Surveillance Programme, 1997. *Commun Dis Intell* 1998;22:205-211.
16. Australian Meningococcal Surveillance Programme. Annual report of the Australian Meningococcal Surveillance Programme, 1998. *Commun Dis Intell* 1999;23;317-323.