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Neisseria meningitidis vaccines

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Introduction

The epidemiology of acute meningitis in the UK is changing fast and will continue to do so. The introduction of mumps vaccine (as a component of MMR) has almost eliminated the commonest cause of viral meningitis. In the 1980s, capsulated strains of *Haemophilus influenzae* type b and *Neisseria meningitidis* caused about equal numbers of cases of bacterial meningitis, predominating over pneumococci and other bacteria. There were more than 1,000 cases of invasive Hib disease (of which more than half manifested as meningitis) in each year from 1989 to 1993, but following the introduction of conjugated Hib vaccines for infants and young children in the UK in 1992, numbers then fell by more than two thirds in 1994, with a continuing downward trend that was sustained until very recently.

Meningococcal disease epidemiology

Man is the only known host of *Neisseria meningitidis*, the meningococcus, a Gram-negative diplococcus that colonises the nasopharynx of 10% of healthy humans, and up to 25-30% of teenagers and young adults at any one time[1]. Cigarette smoking is a potent risk factor for carriage[2]. Occasionally, soon after infection, the organism may invade to cause meningitis (85%) or septicaemia (10-15%). The latter has a much higher mortality[3]. Complex genetic switching occurs as meningococci migrate from the posterior pharynx through the pharyngeal epithelium and thence into the bloodstream and meninges. The characteristic vasculitic rash of meningococcal infection (**Figure 1**) is due to the abundant production of blebs rich in endotoxin (**Figure 2**).

Meningococci may be serogrouped (variations in the capsular polysaccharide), serotyped (variations in the class 2/3 outer membrane protein) and subtyped (variations in the class 1 outer membrane protein). More sophisticated typing methods are also available; multilocus enzyme electrophoresis (MLE or MLEE) is the gold standard typing method, allowing identification of clones of organisms which all share a common ancestor eg. the ET-5 clone which caused the Gloucestershire UK serogroup B outbreak of the 1980s. Genotyping by methods such as multi-locus sequence typing (MLST) is now starting to supplant all previous phenotyping systems other than serogrouping[4]. Meningococcal populations are highly diverse due to high rates of genetic transformation.

Though most carried strains are poorly virulent or even avirulent, probably helping to generate protective immunity, a few strains have the capacity to behave in a highly virulent manner, in contrast to transmissibility, which is generally low. Though there are exceptions, prolonged close contact is normally required to facilitate transmission of meningococci from person to person.

Distribution of serogroups causing disease

The meningococcal capsule is a major virulence factor and almost all cases of invasive meningococcal disease in immunocompetent individuals are caused by a limited range of serogroups. In Africa, serogroup A predominates, but in temperate countries serogroups B and C are most commonly

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Dr John Snow (1813–1858)

Epidemiology began as a science with Snow's classic investigation and control of an outbreak of cholera in London in 1854.

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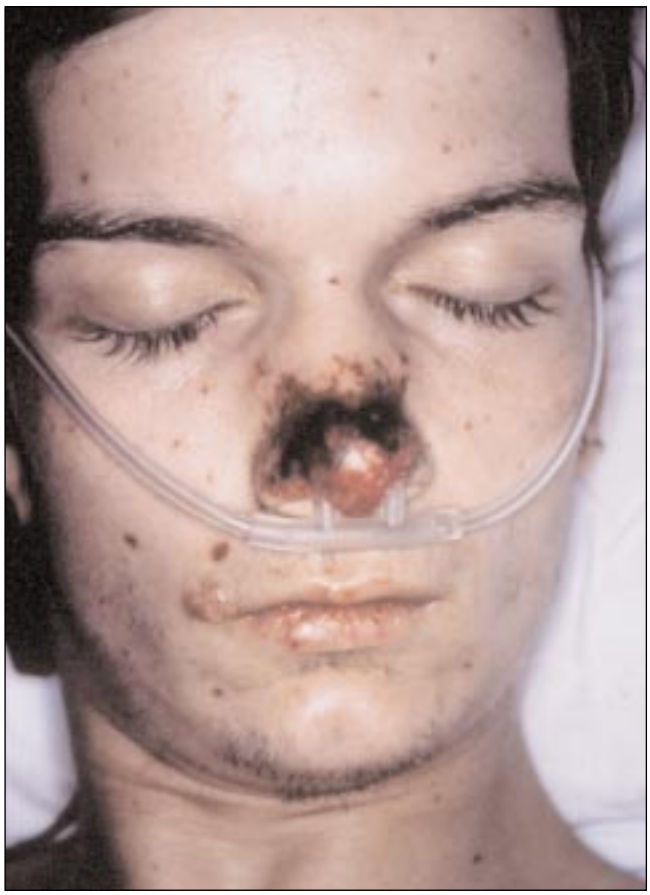

Figure 1. Vasculitic rash of meningococcal infection.

isolated[5]. However, individual virulent clones may express more than one serogroup. Thus the hypervirulent ET15-37 clone that normally expresses the serogroup C capsule can also express W-135, or B capsular polysaccharides with no apparent diminution of virulence. This phenomenon has obvious implications for the development of vaccines based solely on capsular polysaccharides. Bactericidal antibodies protective against serogroup B meningococcal disease recognise a variety of subcapsular antigens rather than the capsular polysaccharide itself[6].

Meningococcal disease is relatively common worldwide; substantial epidemics occur in sub-Saharan Africa (the "meningitis belt", **Figure 3**) every 5-10 years. In the UK there have been more than 1,000 notified cases annually for each of the last 10 years and until the year 2000, a rising trend showed increases in numbers of cases of both serogroup B and C. In 1999 there were almost 3,000 cases of meningococcal disease in the UK ascertained through laboratory diagnoses and clinical notifications - a fifty year high. Since then, the impact of the new *men C* vaccines has become apparent, and there has been a welcome levelling off in the incidence of *men B* disease[5] (**Figure 4**). Overall mortality in developed countries is between 5% and 10%, reducing recently, probably due in part to changes in notification patterns, but also to improved clinical management[7].

The Stroud outbreak of meningococcal disease

Local epidemics are a perplexing but well recognised feature of meningococcal disease. In the 1980s a protracted outbreak of meningococcal disease occurred in west

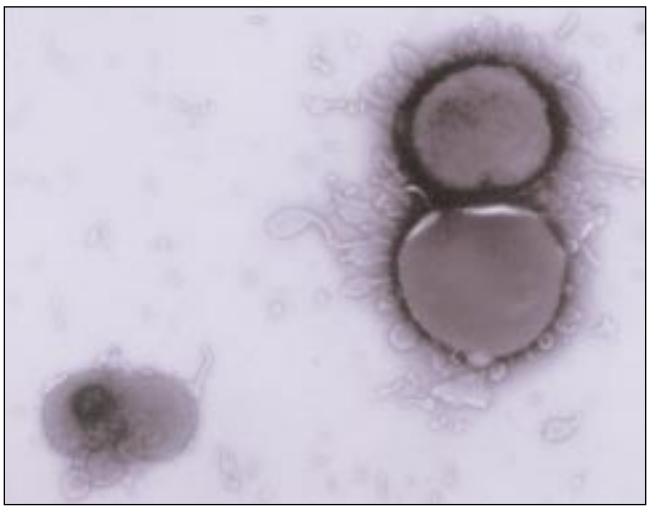

Figure 2. Blebs of vasculitic rash of meningococcal infection.

Gloucestershire, centred on the town of Stroud[8]. The strains causing the outbreak were almost all of one particular clone – the ET-5 clone expressing the serogroup B capsule. As is common in such local, clonal outbreaks, the mean age of cases rose, with the highest attack rates initially seen in teenagers and young adults, presumably reflecting increased circulation of a new, virulent strain within a relatively susceptible population. Over a 15 year period in west Gloucestershire there were more than 250 confirmed cases of meningococcal disease in a population of just over 300,000. As the outbreak waned, the epidemiology began to converge more closely with the national picture. The outbreak petered out in the early 1990s. At that time there were no group B vaccines available that would have protected against the outbreak strain, so population-wide vaccine interventions were not possible and the only public health tools available were good quality information and increased disease awareness.

Immunity to meningococcal infection

The major protective factor against invasive disease is the presence of serum bactericidal antibodies (SBAs). With the notable exception of serogroup B meningococci, most bactericidal antibody is directed against the capsular polysaccharide. Immunity increases with age, is provoked by exposure not only to meningococci but also to other bacteria sharing common surface antigens (e.g. *Neisseria lactamica*, a nasopharyngeal commensal) and is occasionally subverted by extrinsic factors such as intercurrent viral infection.

Risk factors for invasive disease

Both carriage and disease are rare in the elderly. Identified risk factors for disease include age less than 3 years (with highest risk in the first year of life), male sex, complement deficiency, poverty/low social class, exposure to a case, exposure to smokers, winter season, severe overcrowding and recent influenza A infection.

Diagnosis and treatment

Meningococci in the UK have become slightly less sensitive

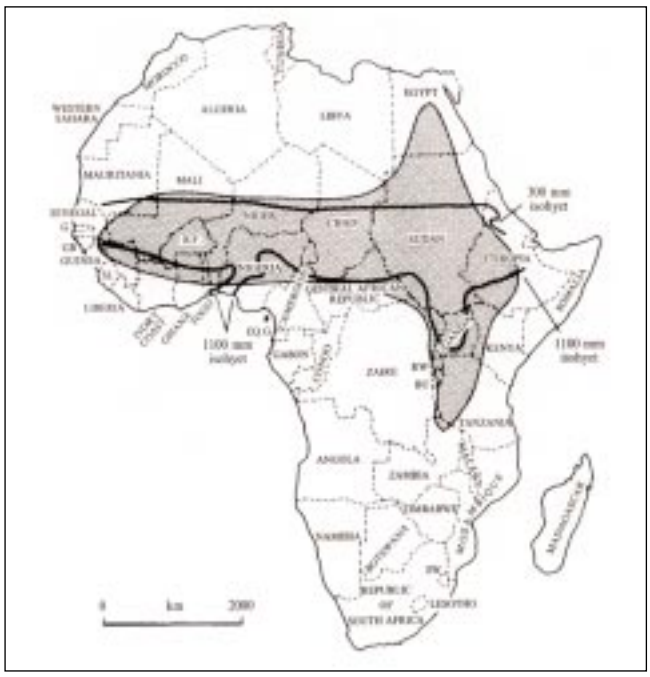

Figure 3. The meningitis belt.

to penicillin in recent years; this development is not yet therapeutically important but the prevalence is rising and the trend needs careful monitoring. Very rare strains that produce β-lactamase (and are therefore penicillin resistant) have been reported, but to date there have been no cases of treatment failure, or patient deaths, as a consequence of infection with a β-lactamase producing strain.

Treatment with parenteral penicillin by the GP reduces mortality by about 50%, though it makes the organism harder to isolate. Non-culture methods of diagnosis (such as PCR – polymerase chain reaction) are now of great importance in monitoring disease incidence. There were 20,000 requests for meningococcal PCR submitted to the England & Wales Reference Unit in 2000.

Vaccines

Early attempts to prevent meningococcal disease utilised crude, killed, whole cell preparations of meningococci[9]. These would have been highly reactogenic, since they included much endotoxin. The discovery and characterisation of the meningococcal polysaccharide capsule in the 1930s laid the foundation for the development of polysaccharide vaccines.

Non-conjugated polysaccharide vaccines

Purified polysaccharide vaccines for prevention of disease due to serogroups C (and later A, Y and W-135) were first developed for use in the US military at the end of the 1960s to control outbreaks in recruit camps[10]. These vaccines are safe but give only short-term protection, are poorly immunogenic in infants and therefore are unsuitable for large-scale population use. They have been used to protect travellers and contacts of cases caused by the homologous serogroup.

Conjugated serogroup C vaccines

Meningococcal polysaccharides have now been conjugated to protein carrier molecules (diphtheria and tetanus toxoids) to produce vaccines that are highly immunogenic in infants and should generate long-term immunity. Conjugated *men C* vaccines were introduced into the UK childhood immunisation schedule in November 1999, the first country in the world to deploy the new vaccines. By the end of the year 2000, all children up to the age of 17 years had been offered *men C* vaccine. All the new *men C* vaccines are extremely safe, effective and well tolerated. Data indicate short-term efficacy of around 90% following a single dose in both teenagers and younger children, and in infants receiving a three dose schedule[11]. By the end of 2001, the incidence of *men C* disease was reduced by more than 80% in those aged up to 18 years. The continuing burden of *men C* disease in young adults has led to the recent (January 2002) extension of the campaign to include those aged 20-24 years.

Impact of conjugated serogroup C vaccines on carriage

An added benefit of the new vaccines is their impact on meningococcal carriage. Conjugated *men C* vaccines produce high avidity, high titre antibodies that reduce nasopharyngeal carriage of *men C* bacteria[12]. Thus even non-immunised individuals gain some protection against disease through reduced risk of exposure – the so-called herd immunity effect. This is now beginning to impact materially on the *men C* disease incidence in unimmunised individuals in the UK, because the age groups most likely to be carrying meningococci have now all been offered *men C* vaccine. Despite intensive surveillance, there is no evidence to date of "serogroup shift" within the ET15/37 clone i.e. an expansion of strains within the clone that express capsular polysaccharides other than serogroup C. A major concern would be the replacement of serogroup C strains by

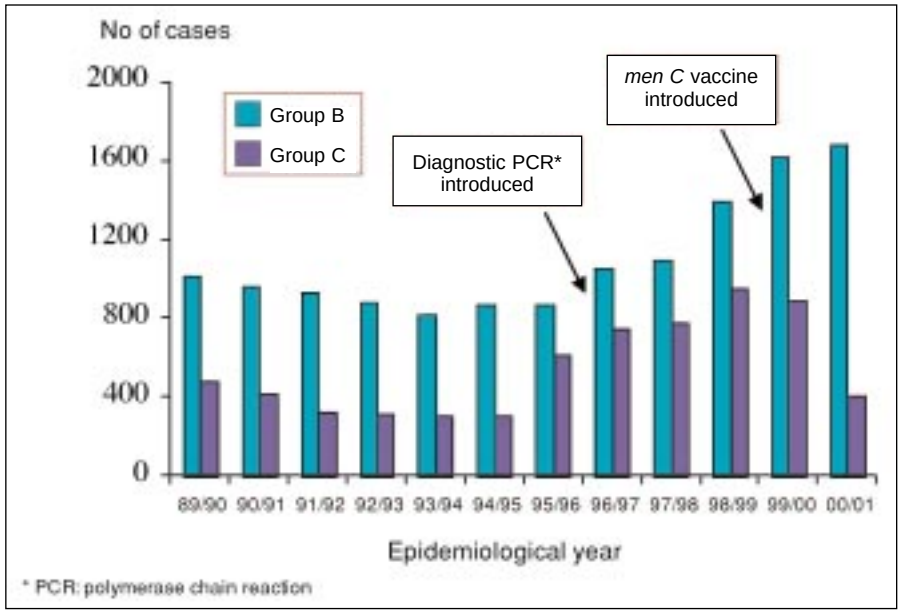

Figure 4. Laboratory-confirmed cases of meningococcal disease by epidemiological year (July–June), England & Wales, 1989/90 to 2000/01

serogroup B, currently not a vaccine-preventable infection[13], but this is not happening.

Other meningococcal conjugated vaccines

Conjugated polysaccharide vaccines for serogroups A, Y and W-135 have also been developed. Clinical trials are in progress and there is every expectation that these new conjugates will be as successful as the *men C* conjugates. A major international programme to control serogroup A meningococcal disease in the African meningitis belt through deployment of conjugated vaccines is now underway, benefiting from generous funding from the Bill and Melinda Gates Foundation.

Vaccines for prevention of serogroup B meningococcal disease

Considerable research is currently directed towards the goal of a vaccine protective against serogroup B meningococcal disease[14]. High levels of natural immunity are the norm within most human populations, indicating that development of vaccines should be feasible, but there are considerable hurdles to be overcome (**Table**). Since the group B polysaccharide itself does not evoke bactericidal antibodies, most attention has focused on a range of subcapsular antigens including class 1 and 2 outer membrane proteins (por A and por B), lipopolysaccharide, NspA (neisserial surface protein A) and iron-binding proteins. A problem with most such antigens identified to date has been their variability. Meningococci are highly adapted to life in their human hosts and it is likely that any meningococcal antigen recognised by the host's immune system will be intrinsically variable. Recently, the entire genome of the serogroup B meningococcus has been published and is now being screened to identify genes encoding well-conserved, surface-expressed antigens that evoke high levels of protective antibodies[15].

Other approaches to the development of group B vaccines include an attempt to mimic natural immunity through the development of a vaccine based on the closely related commensal, *Neisseria lactamica*[16], and the development of a live attenuated meningococcal vaccine. Clearly, the latter approach would need to ensure that such vaccine strains were incapable of acquisition of extrinsic DNA that might cause a reversion to virulence. A final approach currently under investigation is the conjugation of modified serogroup B polysaccharide[17]. Since the group B polysaccharide is chemically identical to a glycoside expressed in brain tissue[18] and elsewhere, there are safety aspects in this approach that would need to be addressed.

It is not yet clear which of these many different lines of research is most likely to meet with success, but it is apparent that though development of safe and effective *men B* vaccines should be technically feasible, vaccines suitable for large-scale use in human populations are still some years away.

Table. Problems in developing serogroup B vaccines

- B polysaccharide poorly immunogenic
- Cross-reactions with host tissues
- Correlates of protection unclear
- Intrinsic variability of subcapsular antigens
- Lack of good animal models
- Reactions with host tissues

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Advances in Epidemiological Investigation

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We all encounter disease in our place of work and we take much of it for granted as something which happens but is largely out of our control. Many infectious diseases are preventable or curable. We rely on vaccines for some diseases, antimicrobials for others and good hygiene and common sense to prevent us catching the rest. Within the UK over the last 200 years there have also been health benefits resulting from improvements in housing, work environments, drinking water quality, food safety, nutrition and overall economic well-being. There is a temptation to look at these improvements and to both undervalue the impact of improved public health measures and underestimate the potential improvements still to be made.

This article examines some of the advances in epidemiological investigation over recent years, concentrating particularly on waterborne disease. Waterborne disease still represents a significant cause of preventable morbidity and mortality worldwide, with the estimated disease burden due to water, sanitation, and hygiene being 4.0% of all deaths and 5.7% of the total disease burden (in Disability Adjusted Life Years (DALYs)) occurring worldwide (including diarrhoeal diseases, trachoma, helminths, etc.).

While much of the new knowledge about waterborne disease has resulted from research in developed countries, many of the emerging waterborne diseases have their biggest impact in developing countries where drinking water and sewage infrastructures are often poor. It is instructive to look back to the nineteenth century when Britain's infrastructure was fairly primitive, and to look at the advances there have been in more recent times.

John Snow and cholera

The purpose of epidemiological investigation is to identify the causes of disease and devise approaches to its prevention. Epidemiology began as a science with John Snow's classic investigation and control of an outbreak of cholera in 1854. Snow began his report by reviewing what was known about the disease called cholera, examining the pathology, incubation period, potential modes of transmission, and impact on the poor, the mentally impaired, coalminers and the young. He collected information on previous waterborne cholera outbreaks.

Snow recognised that there must be a replicating agent causing the disease although there was no agent identified at the time. Key to this investigation was the development of a hypothesis for the routes by which the disease was transmitted. Descriptive information on the affected people was predominantly obtained from registrations of deaths. Information on water purity was collected. Cases were analysed by geographic distribution and water supply zones, resulting in an effective intervention that stopped the outbreak. A report was produced that explained the outbreak and made suggestions for ways of reducing the risks of catching cholera. This landmark investigation also had an impact on government legislation. All this was done before *Vibrio cholerae* was isolated and shown to be the aetiological agent.

Microbiology and epidemiology

There have been dramatic changes in our ability to investigate the epidemiology of infectious diseases since John Snow. We know a lot more about the microbiology and epidemiology of organisms that cause human disease, and we have a considerably improved public health infrastructure that allows us to investigate a wider range of conditions. Despite this, the investigation of outbreaks is in many ways similar to what it was in the 19th century. However, diseases that do not appear to occur as outbreaks can represent intractable epidemiological puzzles that have failed to be solved using conventional public health tools.

Campylobacter is the most common of the bacterial diarrhoeal diseases and yet, despite knowing that *Campylobacter* occurs commonly on chicken, it remains unclear how most human infections are acquired. The genetic diversity that the organism shows and the occurrence of small outbreaks where more than one organism is responsible make the use of conventional epidemiological approaches more difficult.

There are also a variety of diseases where infection, or immunological responses to infection, is implicated in disease but where other factors such as genetic susceptibility and environmental exposure may be important. These include Crohn's disease, ulcerative colitis, Kawasaki disease and sarcoidosis. Elucidating the causes of these diseases requires both microbiological and epidemiological advances that look at techniques for detecting organisms and epidemiological studies that show a significant association.

Changing disease patterns

There has been a succession of emerging infectious diseases over the last twenty years that have exercised epidemiologists' and microbiologist skills. In addition, the epidemiology of apparently well-understood diseases is constantly challenged by new presentations and improved modes of control. The changing population of the UK, with an influx of people from Asia, Africa and Eastern Europe, has brought different disease problems and the free movement of food within Europe has altered the potential for large foodborne outbreaks. Travel to faraway destinations for holidays has been matched by an increase in travel-related infections. In addition to all these factors there are greater numbers of people with compromised immune systems, be it from HIV infection or immuno-suppressive drugs. The rapid movement of livestock and the potential for zoonotic agents to emerge within human populations is highlighted by the problems of BSE and Foot and Mouth disease, although similar problems remain with more conventional zoonotic pathogens such as *Salmonella* where multiple drug-resistant strains have been linked to veterinary antibiotic usage.

Methods for culture and detection

One of the principal drivers for improved epidemiological investigation is the development of appropriate methods for screening patients for the causative agents. This was as true for the development of selective and enrichment culture for *Salmonella* and *Listeria* as it was for staining methods for *Cryptosporidium* and *Microsporidia* and electron microscopy for enteric viruses. Of similar importance is the enthusiastic adoption and improvement of new laboratory techniques in diagnostic laboratories. Considerable credit is also due to the research and development conducted by the suppliers of culture media and detection kits, who often work in close collaboration with experts, reference laboratories and diagnostic laboratories to develop new approaches to the diagnosis of infectious diseases. With the rise in gene and genome sequencing, the ability to develop PCR based approaches to the detection of non-cultivable organisms such as *Mycobacterium leprae, Treponema pallidum, Enterocytozoon bieneusi* and *Tropheryma whippelii* allows better laboratory diagnosis and makes possible the detection of these organisms in environmental samples.

Many currently named species are poorly characterised and may well be separate species. What used to be called *Cryptosporidium parvum* in human cryptosporidiosis has now been split into *C. parvum, C. hominis, C. meleagridis, C. felis* and *C. canis* and it is likely that more species affecting humans will be described and further subdivided or typed. This type of nomenclatural change can be important in the elucidation of differences in the distribution, pathogenicity and epidemiological complexity of infectious disease.

Surveillance

Today the investigation of diseases still relies on broadly the same principles that Snow pioneered. Chief amongst these is surveillance. Although actively involved in investigating the outbreak as it was happening, Snow relied heavily on information from the Registrar General on deaths from cholera for his later analysis of the outbreak. This systematic collection of mortality data began in the sixteenth century through parishes, which published weekly Bills of Mortality. Medical certification and civil registration of deaths began in 1836 and is still collected today. Because the reliable data was on deaths, the true extent of an outbreak could not be determined. The notification of a range of infectious diseases was added to mortality data as an indicator of disease prevalence in 1899, allowing a more sensitive method of disease surveillance. In addition to the surveillance of deaths, laboratory surveillance began in the 1940s through PHLS (Public Health Laboratory Service) laboratories, and subsequently by all laboratories, and for many diseases this is a more reliable dataset for detecting disease prevalence than notifications.

There has been a blossoming of new surveillance systems within the last 20 years, partly because information technology has expanded the range of data that can be used for surveillance purposes. (**Table 1**). It is possible to access hospital admission records, clinic records, general practice attendance rates, and to look at surrogates of disease such as pharmacy prescribing, changes in food consumption and the microbiological quality of food and water. Surveillance of vaccine uptake has become an important tool in implementing infectious disease prevention, through modelling the population dynamics of vaccine-preventable diseases. On-going surveillance of HIV infection in affected people and in selected population groups allows new campaigns to target the groups that are most at risk.

Molecular epidemiology

Molecular typing has allowed information on organism types to be exquisitely detailed so that very small genetic changes, down to a single nucleotide, can be found between strains. The developing technology for dealing with this information, bioinformatics, has made it easier to use such information for useful epidemiological purposes. With organisms that have a very high mutation rate such as HIV, differences can be found between organisms from individual people. Other type differences in organisms from chronic diseases such as tuberculosis and *Helicobacter pylori* gastritis can also have a place in elucidating disease epidemiology.

One of the constant challenges is the utilisation of new molecular methods into effective disease surveillance programs that are able to significantly change our understanding and control of infectious disease. A particular example of this has been the utilisation of PCR protocols to detect, speciate and type human parasitic protozoa such as *Cryptosporidium* and *Giardia*, using the information to clarify differences in epidemiology between different species.

One of the keys to the effective linking of typing to epidemiological investigation is the archiving of isolates or genetic material from organisms. For most organisms the more strains that are tested in a typing scheme the greater number of types or species will be found. This is not the case for emerging organisms that have derived from a single clone, such as the *Salmonella enterica* Enteritidis Phage type 4 that caused the epidemic of infections in chickens and humans in the 1990s, where typing proved of limited value. However where new *S.* Enteritidis PT 4 strains are now isolated they can be compared to archived strains and may be sufficiently different to differentiate them from the previous strain. This was used in 2002 to investigate a number of *Salmonella* outbreaks in England and Wales that were linked to imported eggs. Typing clearly linked *S.* Enteritidis strains isolated from eggs with those isolated from patients in the outbreaks.

Networks

One of the important features of epidemiology since its inception is the development of epidemiological networks. With John Snow this amounted to a circle of acquaintances from which he gained knowledge of previous outbreaks of cholera and their likely modes of transmission. In modern times there are more formalised networks in addition to these informal ones. Outbreaks can range from two linked cases to a worldwide pandemic that affects much of the human population (as is the case with influenza). Because of these differences of scale, surveillance and public health, action needs to operate at local, regional, national, international and global levels.

Many outbreaks of food poisoning are local and linked to poor hygiene in catering premises. These are usually best investigated at a local level, although the number of cases seen by a single GP is likely to be small, and Consultants in Community Disease Control (CsCDC) and Environmental Health Officers will usually be involved in investigating the source of infection. Where there is a sudden increase in disease caused by a particular strain of *Salmonella* across the country, few cases may be present in a locality. In these instances national investigation is appropriate. European networks for disease surveillance have been established for a range of pathogens including *Legionella* (EWGLI), *Salmonella*, *E. coli* O157 (Enternet), *Norovirus*, *Listeria*,

Table 1. Types of human surveillance for infectious diseases

Type of surveillance	Details	Examples
Routine microbiological surveillance	Reporting the results of routine microbiological tests on clinical samples	Salmonella
Routine clinical surveillance	Reporting the results of routine clinical diagnoses	Tetanus, diphtheria
Histopathological surveillance	Reporting the results of routine histopathological tests on clinical samples	Crohn's disease
Notification of infectious diseases	Information collected on specific diseases as a statutory requirement by proper officers	Typhoid
Targeted clinical surveillance	Selective collection of information on specific clinical syndromes by medical and veterinary experts	Haemolytic-uraemic syndrome
At risk population surveillance	Information on people who are at an increased risk of infection but who are not necessarily infected	Needlestick injuries and HIV
Direct syndromic surveillance	Information on disease symptoms reported directly through telephone reporting by the population (NHS Net)	Fever
Enhanced routine surveillance	Active collection of additional data on patient demographics and risk factors	*Escherichia coli* O157
Enhanced laboratory surveillance	Improved standardization and completeness of testing by a group of laboratories	*Escherichia coli* O157
Sentinel site surveillance	The establishment of a key group of laboratories/centres that will participate in a particular enhanced or non-standard surveillance, often to look at a specific disease	Cryptosporidium
Survey	A fixed term study of the incidence of the disease in a defined population. This can represent the start of a surveillance system	Microsporidiosis
Surveillance of drug resistance	Systematic collection of information on antibiotic/antiviral resistance of pathogens	Salmonella, HIV
Sub-typing in surveillance	Subgrouping of organisms reveals differences in the transmission and epidemiology of pathogens	Cryptosporidium
Sero-surveillance	Determining the percentage of human and animal populations that are infected by different ages through antibody studies	Farm workers study
Vaccine cover surveillance data	Information on the percentage of humans or animals that have been vaccinated in different populations that feeds back directly into vaccination programs	Measles, mumps and rubella
Comparative surveillance	Comparison of surveillance information from different sources (e.g. laboratory reporting versus notifications)	Hepatitis A
Environmental surrogate surveillance	Collection of data on surrogate environmental sources that may reflect human infection	Enteroviruses in sewage
Environmental surveillance	Systematic collection of information on water, food or the environment that informs about the risks of human/animal disease	Cryptosporidium in water
Environmental coupling	Linking surveillance information from human or animal disease with information on environmental surveillance or weather data	Waterborne disease
Retrospective surveillance	Look back at contacts of infected humans following an infection incident	HIV, FMD
Rare disease register	A list of all known cases of a particular infectious disease	Leprosy
Outbreak surveillance	Systematic collection of information on disease outbreaks	Foodborne disease
Cluster detection	Development of algorithms for the demonstration of special and temporal clusters of infections that may represent small outbreaks	Cryptosporidium
Hospital infection rates	Information on post-operative infection rates with comparisons between hospitals and operations	MRSA
Hospital administration data	Collection of information on hospital admissions/discharges by diagnostic code	Rotavirus
Primary care metrics	Information from GP spotter practices giving information on disease within the community	Flu
Global burden	Collection of relevant data that can contribute to the establishment of information on the global burden of disease	Waterborne disease
International network surveillance	The development of standards for diagnosis and reporting of a disease with a common database across many countries	EnterNet
International reporting	WHO worldwide surveillance of infectious diseases based on national reporting	Cholera
International monitoring for strain variation	Worldwide surveillance of isolates of key organisms to determine new genetic variants	Influenza A
Imported animal surveillance	Serosurveillance of key animal pathogens	Equine viral arteritis
Imported food surveillance	Data on the microbiological quality of imported foods	*Vibrio cholerae*
Pharmacy sales	Information on pharmacy sales used as a surrogate of trends in disease	Diarrhoea
Media surveillance	Scanning key internet sites for information on outbreaks or new pathogens	ProMed, WHO

influenza, tuberculosis, etc. that cover all of Europe and some non-EC countries also.

The power of these approaches is that people infected with the same organism can be linked both by microbiological typing and epidemiological risk. Case-control studies can be conducted that indicate the common risk activities of people living thousands of miles apart. This approach can link people with legionella infections who have stayed in the same holiday hotel or people who have become infected with Salmonella through eating a widely distributed food product.

Changes to public health

Key to the maintenance of these approaches have been strong links between epidemiologists (both regional and national), diagnostic laboratories, food and water laboratories, reference laboratories, Environmental Health Officers and CsCDC. The strong Public Health Laboratory Service (PHLS) network, in England and Wales, established over the years has proved extremely effective in tackling infectious diseases. From April 2003 the PHLS will be replaced by the Health Protection Agency, which will also take

on the current activities of the Centre for Applied Microbiology and Research, the National Focus for Chemical Incidents, and in 2004 the National Radiological Protection Board. All CsCDC will be within the new Agency and a majority of PHLS laboratories will move into the NHS (National Health Service). Along with these changes will come new responsibilities that will be placed on laboratories to report infectious diseases and new public health laws. In these times the systems for ensuring patient confidentiality need to be tightly interwoven with the requirements for surveillance data to ensure that people remain confident in our systems of public health.

Burden of disease

In the time of cholera when John Snow was pacing the streets of Soho counting the bodies and mapping the location of water pumps, the total burden of illness related to cholera was difficult to judge. The burden of illness related to contaminated drinking water was completely unknown. In the 20th century a variety of outbreaks of waterborne disease were identified, with typhoid and paratyphoid being prominent in the first fifty years and waterborne cryptosporidiosis in the last ten years. Dramatic improvements in water quality have resulted from better water treatment by water utilities, using coagulation, filtration and disinfection, although the detection of waterborne outbreaks has remained in many ways very similar to the approach taken by John Snow. However, this still does not allow us to estimate the burden of illness related to drinking water.

A variety of different approaches have been tried within the last 15 years to look more systematically at the burden of illness that results from contaminated drinking water. Intervention studies in Canada, the US and Australia have compared populations served by the same water supply where half were fitted with in-line water filters that remove all microbial contaminants. This approach has been refined over the years to remove as far as possible the biases associated with the self-reporting of illness, although it still gives mixed results that have limited general applicability.

Alternative approaches looking at relationships between water quality and hospital admissions have also run into methodological difficulties. An approach within the UK has concentrated less on the global burden of disease and more on the known risks and prevention of disease rather than its measurement. In the year 2000 the Drinking Water Inspectorate introduced regulation of drinking water supplies using a combination of risk assessment and continuous monitoring to reduce *Cryptosporidium* contamination of treated water. This appears to have been effective in ensuring that water utilities optimise their water treatment, remove contaminated supplies and install new treatment where necessary. It is perhaps ironic that the instigation of this regulation resulted from the failure of a court to recognise epidemiological evidence as being of sufficient quality for use in a criminal prosecution of a water utility for causing the largest waterborne outbreak in the UK in the 20th century.

The future

Within the Public Health community there will be continuing advances in epidemiological investigation. Some of these will be technical but many will be implementing traditional epidemiological approaches in new and more imaginative ways. The foundation of epidemiological investigation is good surveillance. Although the UK surveillance of infectious diseases is admired worldwide and draws on the strength of the network of laboratories, there needs to be substantial improvements in the quality, timeliness and scope of surveillance data. The establishment of the new Health Protection Agency provides opportunities for developing closer working relationships between all laboratories, local public health professionals and regional, national and international experts in microbiology, epidemiology and public health. It should also strengthen the ability to respond to concerns about radiological, chemical and toxicological issues in a more integrated way.

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