Review Paper

Tropical diseases - implications for the year 2000: bacterial diseases

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Introduction

We are approaching the end of the twentieth millennium and can hardly be blamed for assuming that by now bacrerial diseases should be a thing of the past. The tremendous strides made in socioeconomic development, public health measures such as water supplies and sanitation, immunization procedures, vector control, and the discovery and easy availability of a wide array of antibiotics would have been expected to herald the global eradication of these infections .

There are many countries though, for whom these developmental changes have just passed them by and the so called diseases of poverty continue to rage, an unfinished agenda so to speak, of which the infective bacterial diseases constitute a significant part. In these countries diarrrhoeal diseases and acute respiratory infections are the major killers especially in children under five years of age. It has been said that the number of children who die from these diseases would equare to those dying should a jumbo jet crash every thirty minutes.

In the advanced developing countries, there is a concomitant change in the pattern of diseases from the diseases of poverty to the so called diseases of affluence. Chronic and degenerative diseases, neoplasms and others related to life style changes have replaced infectious diseases as the major causes of death. However, here and even in the most developed of countries, bacterial diseases continue to be a public health problem either because of the emergence of new diseases or of reemergence of old ones.

The region in which we live is a highly heterogeneous one and its member countries stretch across a wide spectrum ranging from the very poor to the most affluent. The health status of these various countries quite accurately portrays their level of development.

Reemergence of bacterial diseases in developed countries

What has occurred in the United States of America can be taken as a case study and as a warning to us in this region. At various fora concern had been expressed about the apparent complacency of the scientific and medical communities, the public and the political leadership of the United States towards the danger of emerging infections and the potential for devastating epidemics. Recognising these concerns, the Board of Health Sciences Policy of the Institute of Medicine (IOM) determined that the IOM could play a unique role by reviewing the relevant science, developing a research agenda, considering the implications for policy, and making specific recommendations for minimizing the public health impact of future emerging microbial threats (Institute of Medicine, 1992). The study identified the following as major factors in the emergence of such threats - human demographics and behavior; technology and industry; economic development and land use; international travel and commerce; microbial adaptation and change; and breakdown of public health measures.

Factors for reemergence

As countries develop and the incidence of infectious diseases decreases there is a tendency to become complacent. There are immediate calls for shifting priorities, budget cuts for public health, loss of interest in the subject among the scientific and medical communities (this being considered a sunset industry), research almost stops, expertise grows thin and all of these set the stage for the reemergence of infectious disease.

Bacteria once again coming to the fore can do so by a number of mechanisms. One is where previous scourges return because of a breakdown in public health measures either due to complacency as described above or to unwillingness or inability to pay because of poverty or changing modes of financing health in general and public health in particular. The second is through the acquisition of enhanced pathogenic properties by the bacteria themselves. By genetic mutation bacteria can gain new properties that enhance their invasiveness, their infectivity or their virulence and their resistance to antibacterial agents and some of these properties may even be transferable through plasmids. Thirdly, the agent may be discovered and described for the first time, some because they have only been recognized now as we tend to find only what we look for whilst others have probably genuinely recently emerged. Lastly host factors may predispose patients to opportunistic infections.

It would be interesting to give some examples of these different mechanisms in operation. In this respect, chlamydia can typify the group of newly discovered pathogens, Lyme's disease that due to environmental changes, the sexually transmitted diseases due to behavioral changes, pneumonias due to ageing,

salmonellosis due to current food production practices, tuberculosis due to poverty and finally the emergence of resistant strains among the commonly encountered bacteria due to changes in the bacteria themselves.

Antibiotic resistance

Even with the vast array of antibiotics that are currently available in the market, serious bacterial infections remain difficult to trear due to continuous emergence and subsequent rapid spread of antibiotic resistant strains. The following reasons have been frequently cited: importation through increased travel and movement of people for business, political, tourism and religious reasons; selection pressure through the widespread and indiscriminate use of certain antibiotics leads to the selective proliferation of strains resistant to that antibiotic; non compliance on the part of patients, leading to incomplete treatment; and finally the extensive use of antibiotics which helps propagate and maintain drug resistant strains. The question of antibiotic resistance is complicated by the fact that ir is increasingly time consuming and expensive to discover and put on the market new drugs including antibiotics . It is said that one such drug can cost up to $300 to $400 million US$ in development costs.

Opportunistic pathogens

The melieu is being created to provide an increasing role to the so called 'opportunistic pathogens'. These were organisms that generally caused no trouble but have become a nuisance in the face of increasing cohorts of immunocompromised individuals either due to AIDS and other diseases or to medical manipulations. Predisposing factors with increased susceptibility to such pathogens include granulocytopenia, cellular immune dysfunction, humoral immune dysfunction, blood product transfusion, vascular access devices, endogenous sources and finally exogenous sources.

Examples of emerging infections

Group A *Streptococcus* has been receiving notoriery recently because of strains that have the ability to cause necrotising fasciitis. In the US and rhe UK a few outbreaks resulting in some deaths have been reported, and the lay press have given this strain the sobriquet of "flesh eating bacteria" (Henrich *et al.*,1995).

Atypical mycobacteria, earlier thought to be strictly saprophytes, are now increasingly being implicated as causative agents of human disease. These organisms are resistant to conventional antituberculous drugs and infections caused by them are generally difficult to treat. They can cause various types of infections, and it has been noted that they are now the commonest cause of granulomatous lymphadenopathy (Sigalet *et al.*, 1992)

While cholera remains an important cause of morbidity and mortality worldwide, its epidemiology has changed in the 1990's wirh the emergence of a new *Vibrio cholerae* serogroup 0139. This was first isolated in Bengal in October 1992 and then spread rapidly through the Indian subcontinent and has now been reported in many parts of Asia including Malaysia and even in travelers to North America and the Middle East (Morris, 1995)

Helicobacter pylori, an important cause of chronic active gastritis, is strongly associated with peptic ulcer disease and gastric cancer, The evidence linking *H. pylori* and non cardiac gastric carcinoma is accumulating. In populations with high gastric carcinoma risk, *H. pylori* infection is associated with multifocal atrophic gastritis, which frequently advances to intestinal metaplasia, occasionally to dysplasia and rarely to carcinoma (Hannson *et al.*,1995; Eidt & Stolte,1995; Lambert *et al.*, 1995).

The possibility of *Mycoplasma genitalium* being the causative agent of non specific urethritis has been raised (Horner & Taylor-Robinson, 1994).

The worldwide clinical incidence of *Salmonella enteritidis* has increased markedly and is associated with the enhanced ability of the organism to systemically colonise layer chickens. Subsequently contamination and consumption of intact shell eggs from colonised layer hens, either directly or in foods containing raw or lighrly cooked eggs, can cause human disease (Cox, 1995).

Eschericia coli, amongst the best known and the commonest aerobic bacteria of the human and animal gut, was and is still used as an indicator organism for faecal pollution. However it was soon recognized that some strains of *E. coli* could cause gastrointestinal infections. Such strains have incrementally been implicated in the literature and we now recognize as pathogenic enteropathogenic *E.coli* (EPEC), enteroroxigenic *E.coli* (ETEC), enteroinvasive *E.coli* (EIEC), enteroadherent *E.coli* (EAEC), and enterohemorrhagic *E.coli* (EHEC) strains.

The Salmonella paradox

The rype of *Salmonella* infections in a particular area appears to bear a curious relationship ro the state of development of the place. In places where sanitary conditions are poor, reflective of a lack of socioeconomic development, ryphoid persists and outbreaks are not uncommon. By comparison, the level of non-typhoidal salmonellosis is not that high. By conrrast as a place develops socio-economically with increasing affluence and improving sanitary conditions, typhoid tends to disappear bur paradoxically the level and types of non-typhoidal salmonellas increases. This is consequent on changing lifesryles with its concomitant change in food production and consumption habits.

The raging comeback of tuberculosis

In many parts of the world, including most affluent places like New York, tuberculosis is staging a raging

comeback with a double pronged attack. It is riding on the crest of the AIDS epidemic where it has evolved into a major opportunistic infection in the immunocompromised, while at the same time enjoying enhanced pathogenicity through the emergence and proliferation of multiple drug resistance strains. WHO statistics show that every year nearly 8 million new cases occur with a million deaths. Of the 14 million people globally who were HIV positive in 1994, some 5.6 million were believed to be infected with TB as well (Crawford, 1994).

Recent advances in antibacterial measures

In the face of the above multipronged assault by microbes, it is indeed fortunate that advances are also being made in our efforts to combat them. Recent advances in molecular biology and biotechnology and their application to practical methods have allowed quantum leaps to be made in the development of diagnostic and therapeutic tools. This and other related developments have allowed microbiology to move away from its 'horse and buggy days' and join the ranks of its more technologically advanced partners in laboratory medicine. Clinicians have hardly been enamored of the slow response of microbiology laboratories necessitated by the need to culture the causative organism before it can be characterized and identified, a tardy process at best. Modern microbiology methods incorporating rapid tests, on-site-testing kits, automation and computerisation has brought more clinical relevance to the art and science of diagnostic microbiology, not only facilitating more timely responses but allowing better ability to ascribe causative roles to microbes that are encountered in clinical specimens, once the bane of routine clinical microbiology workups.

Rapid tests

Rapid diagnostic tests in microbiology focus on the detection of bacterial antigens in body fluids and tissues which can be made visible through techniques such as agglutination, enzyme linked immunoassay, and immunofluorescence. For instance, in the processing of cerebrospinal fluids, antigen detection tests and particulate agglutination tests for *Hemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pnuemoniae* are now available for routine use. Other examples are the EIA for *N. gonorrhoeae* from genital specimens the direct immmunofluorescence test for *Legionella pneumophila* in lower respiratory tract specimens. Newer generation tesrs based on molecular biology techniques include DNA probes for chlamydia, mycobacteria, *Legionella*, etc. as well as Polymerase Chain Reaction (PCR) (Daly, 1994). Other approaches include biosensor technology, conductance methods for food microbiology and HPCL for mycobacteria. Biosensor technology is one of the newer methods introduced which combines the unique specificity accorded by biological sensing elements in association with a suitable physico-chemical transducer enabling the conversion of analyte concentrations into digital electronic signals. The biosensor exploits the unique specificity of biological recognition events by coupling an enzyme, antibody and even nucleic acids to a transducing device. Interaction of the biocomponent with substrate or antigen is thus converted into a suitable quantitative output. This was brought about by exploiting the semiconductor and optical technologies. It could meet the needs of clinical specimens screening, food product quality control, industrial hygiene monitoring and environmental microbial screening. (Ann, 1992).

While extolling the value of rapid tests which can certainly provide life saving laboratory results, it must be pointed out that they will have some disadvantages and constraints which must be objectively reviewed before all these innovations are put into routine service. These include the high cost, the disincentive for empirical therapy, the sometimes low cost effectiveness and the possibility of false positives and negatives due to sensitivity and specificity issues.

Molecular biology techniques

The molecular biology techniques which have formed the basis of the newer methodologies include hybridomas, peptide synthesis and recombinant proteins, DNA probes and hybridisation and amplification techniques such as PCR. Laboratory managers will encounter many broad and complex DNA technologies in the coming years. Proper evaluation will have to be done as to which of these one will adopt. The confidence of clinicians though has increased and they have seen that molecular biology is technically and intellectually approachable (Hillyard, 1994)

The principle of nucleic acid hybridisation has been used in a wide array of techniques such as the dot blot, southern blot, northern blot, in situ hybridisation, plaque hybridization, and colony hybridisation. Molecular biology techniques have even been used for detecting antimicrobial resistance genes. This follows the concept of detecting resistant genotypes rather than the phenotypes as is done in conventional antibiotic susceptibility testing (Tenover *et al.*, 1993).

Molecular biology techniques are also coming to the fore as epidemiological marking tools. They are beginning to supplant the traditional tools such as phage typing which have had their own limitations. Methods that have been used include ribotyping, plasmid fingerprinting, PCR based methods, pulse-field gel electrophoresis (PFGE), and analysis of restriction fragment length polymorphism (RFLP).

Automation

Automation was introduced into clinical microbiology laboratories in the 1960's but this initially met with little success. Today, instruments are an integral part of

many laboratories and are used for microbial detection and identification, susceptibility testing, detection of positive blood cultures, screening urine samples for potential pathogens and assaying levels of antimicrobial agents in body fluids. Automation has allowed more rapid diagnosis and elimination of the subjective interpretation of many manual tests. In addition, some automated tests are more sensitive and specific, but are more expensive and require large capital costs. They are also associated with possible systems failure with inconvenient down times. Automation will however continue to be of increasing importance and will incorporate more molecular biology techniques such as the PCR (Woods, 1992).

Vaccine development

Molecular biology is also making its impact on vaccine development and allows some novel approaches towards improving vaccines as well as producing potential ones for those diseases which do not have a vaccine as yet. Synthetic peptide technology has simplified the production of antigenic epitopes of infectious agents for use in the development of vaccines. Several approaches have been employed to achieve the ultimare goal of single immunization against major childhood infectious diseases, namely poliomyelitis, measles, tuberculosis, diphtheria, pertussis and tetanus. The approaches are: i) to control the release of antigen molecules following injection, eg. tetanus toxoid is incorporated into microcapsules of varying chemical composition with different rates of biodegradation thus mimicking a booster injection; ii) to use the live vaccine carrier whereby unrelated viral or bacterial components will be used as a carrier to deliver the required vaccine more efficiently; and iii) to use microencapsulation and live vaccine carrier for oral administration thereby obviating the complex logistic of repeated injections.

The improvement of vaccine efficiency and the simplification of vaccine delivery systems constitute a new specialty called 'trans disease vaccinology'. Important areas of this new science are: i) the use of highly attenuated harmless viruses or bacteria to carry vaccine molecules or antigen derived from disease causing organisms, into the body, and this line of research depends mainly on genetic engineering, eg. the use of vaccine virus to carry a gene or piece of DNA from malaria parasite that codes for a protein that truly induces protective immune response in the host; ii) to widen the search for even safer vectors, and iii) to combine several key genes and create a cocktail vaccine against a wily parasite such as malaria so that the parasite would be attacked on several fronts. It is possible that a single harmless virus or bacterium could be the vector for genes from several pathogens and thus for a combined vaccine against several diseases (Nossal, 1993).

Other strategies include the use of subunits of vaccines such as that for cholera where the subunit of the B toxin is combined with the killed whole cell. Other initiatives for cholera include the live oral vaccine CVD-103 HgR. Possibilities along the same lines exist for shigella and enterotoxigenic *E.coli* strains (Levine & Noriega, 1993).

Production of glyco-conjugate vaccines which consist of a relatively small saccharide covalently linked to immunogenic carrier proteins has considerably improved prophylactic immunisation. Today we have an efficacious vaccine for the capsulated *Hemophilus influenzae* type b. Similar approaches have potential for pneumococcal and menigococcal vaccines.

Antibiotics

While it is true that it is costing more and more and taking longer to put an antibiotic on to the market, due to increasingly stringent studies needed by regulatory agencies, the first step of screening potential new products has been facilitated by the science of combinatorial chemistry. Using computerised techiques, it is now possible to screen hundreds of products in the time taken previously to go through a few.

The implications of health care reform

The whole world is in the throes of health care reform as it grapples with the issue of rising health care costs. The region is now at a cross road where major decisions have to be made as the factors that led to the massive expenditures on health in the West catches up with us. Governments find that they can no longer afford to pay for the health services as they have done in the past and the current paradigm is to attempt to share the cost with people who can afford it. Various models are being looked at and there is a growing tendency to lean towards corporatisation and or / privatisation of the health services, in particular the curative services. Public goods, such as public health services, immunisation and the like are thought best left in government hands as the private marketplace would see no advantage in dabbling in this area. The government also needs to address the issues of equity in the face of health reforms and has to ensure that no one is disenfranchised because of either geography or economics. One mode that is being touted as an answer to the galloping costs spawned by a fee for service system is managed care and this would have serious implications on how laboratories are run and tests are paid for. Public Health laboratories, of which microbiology is a major component , ate likely to be subjected to trends towards downsizing, centralisation and systems of payment on the lines of managed care through the capitation method (Dowdle, 1993).There is also likely to be more on site testing as methodologies change and new information technolo-

gies make their presence felt. There is a possibility of failure of public goods as in the transition periods these become 'no man's lands'.

Changing scenario in laboratory medicine

Weilert (1994) also summarises the factors which are likely to force changes in the laboratory systems. These are the influence of managed care models, integrated health care systems, cost control pressures, capitation reimbursement, point of care testing, utilisation control and lean production.

Preventive measures

It is clear that ifleft unchecked and not seriously thought about, infectious diseases including many caused by bactetia can become serious public health problems. What is needed is a proactive plan to minimize the potential for risk. A strategy for surveillance should be put in place that will allow an early warning system to be activated. This would require good laboratory support in addition to a good epidemiological surveillance system. All this should be strung together by an efficient information network perhaps even on a global scale as national and regional boundaries blur and the world rushes headlong into a path of globalisation. Research must continue directed at basic or strategic areas which will engender knowledge that can lead to better diagnostic and therapeutic tools and improved vector control measures. Investment should also be encouraged towards rhe development of vaccines and drugs directed at these diseases.

Conclusion

The risk of continuing problems from bacterial infections is a real one but with increasing awareness as well the determination to continue investing in measures needed to overcome or contain them one need not take too pessimistic a view. A state of preparedness will place us in a strong position to face the challenges ahead as we rush expectantly towards the dawn of a new millennium.

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