While these comments may well apply to the inpatient therapy of pneumonia with intravenous penicillin, consideration also needs to be given to outpatient treatment, which is commonly undertaken with oral agents. Unfortunately, in this area there are as yet no published studies or data on the possible efficacy of oral agents (such as penicillin or amoxycillin) on which one could base firm recommendations. Treatment failure with the emergence of resistant strains has been described with several different antibiotics.[29] It remains important to be aware of susceptibility patterns in one's area, and to use appropriate therapy based on those results.[24,29]

These recommendations are based on current knowledge. It is essential for microbiology laboratories to test the susceptibility of isolated pneumococci not only to penicillin but to other antibiotics such as the cephalosporins. Physicians treating patients with pneumonia need to be aware of these results, not only to treat individual cases, but to be familiar with trends in the community as a whole. Changes in antibiotic susceptibility patterns in the future may be a reason to modify the current recommendations.

Lastly, it may well be timeous to re-examine the use of the pneumococcal vaccine for the prevention of pneumococcal infections.[3] There is ongoing debate as to the efficacy of this vaccine, especially in patients with co-morbid illness and/or concomitant HIV infection that may predispose them to infections with resistant pneumococci.[38] Currently available vaccine preparations contain antigen that should provide cover for most serotypes commonly associated with penicillin resistance, and we would encourage more widespread use of the vaccine, as has been suggested by others.[3] These developments are also encouraging investigators to develop pneumococcal conjugate vaccines to improve the protective effect of the pneumococcal vaccine, particularly in highly vulnerable paediatric populations and elderly patients with co-morbid illness.

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Tuberculosis research — the way forward

Tuberculosis is back on the world stage with a vengeance, perhaps at least partly as a consequence of complacency about the threat it posed in the recent past. A number of historical sources have documented that much of the currently developed world was, in the past, subject to an epidemic of tuberculosis that ran its course over a period of several centuries.[1,2] It seems likely that one of the main causes of this epidemic was the process of urbanisation and industrialisation, the accompanying stresses and strains imposed by overcrowding, unemployment and the associated social disruption. Long before the availability of chemotherapy it was apparent that the mortality associated with the tuberculosis epidemic was declining. In the opinion of some researchers this decline also antedated any improvement in the precipitating poor socio-economic factors, suggesting that the elimination of susceptible individuals had created a population with increased resistance to tuberculosis. On its introduction into a susceptible population, tuberculosis spreads rapidly and

affects predominantly younger individuals and characteristically more females than males. The course of the disease is acute in individuals from a susceptible population and, left untreated, it has a high mortality rate. The destructive effects of tuberculosis among black and coloured African troops in both world wars are well known.[3,4] Other features of an epidemic are the absence of clearly identifiable high-risk groups[5] and a high annual risk of infection, with the majority of the population becoming tuberculin-positive at a relatively young age.[6] Such features were well documented in several populations during the last century.[7] As the epidemic wanes, the clinical features of disease become less florid and it tends to affect mainly older, predominantly male, individuals.

In an embarrassing reversal of the previous long-term decline in the incidence of tuberculosis, a number of relatively affluent developed nations have recently experienced an increased incidence of tuberculosis. This is at least partly due to HIV. Unfortunately, many parts of the developing world still experience tuberculosis in epidemic proportions, and the disease is a major cause of morbidity and mortality — to such an extent that the WHO recently took the unprecedented step of declaring tuberculosis a global emergency. Approximately one-third of the world population has been infected with the bacillus and the combination of a high incidence of tuberculosis and HIV infection is already wreaking havoc in some developing countries.

At present, vaccination often appears to be of questionable benefit and cannot prevent infection. The key to the control of tuberculosis remains the efficient detection and treatment of smear-positive cases, even within a well-managed national control programme. However, because the chemotherapeutic regimen is protracted, compliance may be problematic and health workers will require the long-term enthusiastic support of the community. There is also the disconcerting emergence of multidrug-resistant organisms. These considerations necessitate the search for novel drugs and vaccines, and a better knowledge of the pathogenesis of the disease is a prerequisite for this. These goals are being actively pursued in South Africa, the UK and Canada by the Glaxo-Wellcome Action TB initiative. The prime motivation for this effort is to discover an entirely new antituberculosis agent. Recognising that there tends to be an inverse relationship between feasibility and novelty, the research initiative has elements that range from community and systems research to basic molecular biology. Some of the recent work, particularly in the latter category, is highlighted below.

In many developing countries, including South Africa, little information is available on the burden and spread of this disease. One of the advances that will aid the epidemiological study of tuberculosis is the discovery that an insertion element found in the genome of *Mycobacterium tuberculosis* may be present in different locations and at variable copy numbers.[8] This has made it possible to genotype (DNA fingerprint) any culture of the organism accurately, and has introduced the new study of molecular epidemiology. Fingerprinting studies show that essentially one strain of bacteria resides within a given patient at one time. This apparent strain dominance is not understood, but even in high-incidence communities it may potentially be used to trace the routes of transmission in a community. Even under the apparent blanket of an epidemic, it may prove possible to identify high-risk groups precisely for better targeting of the approach to tuberculosis control. Given the high incidence of tuberculosis in some South African communities, which may exceed 1 000/100 000 per annum, one might expect little strain diversity; this is evidence of a high degree of contact and recent transmission. Surprisingly, in communities as diverse as an urban, low HIV incidence community (Cape Town) and a high HIV incidence rural community in KwaZulu-Natal, strain diversity is high. This result is unexpected, given similar surveys done elsewhere. Such studies will help to address questions about the role of exogenous reinfection and endogenous reactivation and will allow assessment of efficacy of treatment in a community. It will also aid the formulation of strategies to combat the disease by identifying sources and routes taken as disease spreads, as has been done in other urban centres.[9] In this regard, the establishment of a uniform, national strain database could be an extremely valuable and desirable future objective.

A tuberculosis strain database may be of considerable importance in view of the association between tuberculosis and HIV with regard to spread (e.g. via long-distance transport routes) and chemoprophylaxis. Recent results, for example, show that over half of the drug-resistant cases of tuberculosis detected in a high-incidence community in Cape Town are probably the result of recent transmission of drug-resistant strains, and not due to the development of drug resistance in an existing strain. Further studies on the genome are likely to identify other markers[10] which may be useful in these studies.

The key to unravelling the pathogenesis of tuberculosis lies in understanding the balance between the virulence determinants of *M. tuberculosis* and the host immune response. These are two sides of the same coin, and the one cannot be understood without the other. The pathogen displays prodigious capacities for invasion and long-term persistence in host cells and tissues. On the other hand, the human host is well equipped to suppress, in the great majority of cases, an *M. tuberculosis* infection and to prevent progression to active disease. This interplay between organism and host depends on the genetics, cell wall components, metabolism and secreted factors of the bacterium, its adhesion to and uptake by host cells, killing mechanisms or intracellular survival and dormancy, antigen presentation and specific T-cell responses. Given this background, more research effort is needed to unravel these processes.

Molecular genetic approaches are being used to study genes encoding specific mycobacterial proteins that may be involved in the virulence, immunopathology or drug resistance of *M. tuberculosis*. The evaluation of potential drug targets is dependent on the availability of efficient methods for specifically creating mutations in candidate genes and analysing their effects on the organism *in vivo*. Therefore, several targeted mutagenesis approaches have been investigated. Gene replacement has been successfully achieved in some of the mycobacteria and the methodology is currently being developed further for application in *M. tuberculosis*. In the light of these and other significant advances around the world in the development of alternative specific 'gene knockouts' and random mutagenesis methodologies,[11,12] the possibility of readily generating mutants of pathogenic mycobacteria for virulence screening may soon become a reality. The pathogenic mycobacteria

have obviously evolved mechanisms for ensuring their survival in the intracellular phagocytic host cell environment. Since a major component of the killing mechanism employed by macrophages involves the production of DNA-damaging agents during the oxidative burst of these cells, it is likely that the existence of efficient DNA repair mechanisms is central to the survival strategy adopted by the pathogenic mycobacteria *in vivo*.[13] Several mycobacterial enzymes involved in DNA repair are being analysed via a combination of genetic, biochemical and physiological approaches. The genes encoding the repair enzyme DNA polymerase I (PolI) from *M. tuberculosis* and *M. smegmatis* have been cloned, and the *M. tuberculosis* enzyme has been enzymatically analysed.[14] In addition, significant progress has been made in probing the role of mycobacterial PolI *in vivo* by analysis of the phenotype of a polymerase-deficient mutant of *M. smegmatis* that was constructed by targeted gene replacement. Another enzyme implicated in the mechanism of recovery from DNA damage, ribonuclease (RNase) HI, has been analysed with a similar integrated approach.[15] The mechanisms underlying the regulation of RNase HI levels in mycobacteria that have sustained DNA damage are currently under investigation. The response of mycobacteria to damage induced by alkylating agents is also under investigation within the initiative. The presence of alkylation repair (Ada) activity has been demonstrated in mycobacteria. The Ada gene from *M. tuberculosis* has been cloned and partially sequenced, and was found to be significantly homologous to the corresponding gene from *Escherichia coli*. In addition to this repair enzyme, other enzymes may protect the mycobacterial genome from DNA-damaging agents. One candidate enzyme is the dual-function catalase/peroxidase, KatG. This enzyme inactivates reactive oxygen radicals. Studies indicate that the enzyme may have additional activities — for example, mutations in the gene can lead to isoniazid resistance.

Related studies have focused on the ability of mycobacteria to cope with changes in environmental conditions, such as temperature and nutrient deprivation, since it is likely that the ability of *M. tuberculosis* to counter such challenges successfully is inextricably linked to its ability to persist in macrophages and granulomatous caseous lesions. Significant emphasis is therefore being placed on the understanding of the regulatory networks governing gene expression under a variety of growth conditions of this organism.

The emergence of drug-resistant organisms is cause for concern and has led to research linked to understanding this process. For example, attempts are being made to elucidate the mode of action of pyrazinamide and the molecular basis of pyrazinamide resistance in *M. tuberculosis*. It is thought that the pyrazinamide is converted by a pyrazinamidase enzyme to pyrazinoic acid, which is lethal to *M. tuberculosis*. A pyrazinamidase from *E. coli* has been purified and characterised and studies aimed at identifying a mycobacterial homologue are currently under way. It has been shown that the products of the *katG*, *inhA*, *rpoB* and *rpsL* and *16srRNA* genes are involved in resistance to isoniazid, rifampicin and streptomycin, respectively. However, aberrations in these genes do not account for all cases of resistance[16] and other mechanisms are being sought. Work is under way to investigate the feasibility of a rapid test for rifampicin resistance, since it has been shown that this is indicated by mutations in *rpoB* in nearly all cases. This could be a useful test, since the work also shows that approximately 95% of rifampicin-resistant samples are also isoniazid-resistant.

A key virulence determinant of *M. tuberculosis* is its invasiveness. The bacillus rapidly invades host monocytes and macrophages and freely grows and replicates in these cells, despite the fact that macrophages are a central component of the host immune system. We now know that the organism binds to specific macrophage receptors[17] and that this binding is both opsonic (i.e. it depends on serum proteins such as complement) and non-opsonic. Work within Action TB has established conditions under which non-opsonic binding can occur, and this probably depends on specific molecules (ligands) on the surface of the bacteria.[18] This offers the prospect of designing antagonists that can block the critical first step of attachment to the host cell.

After attachment, the organism invades the macrophage and takes up long-term residence in the face of formidable defences. It accomplishes this by blocking the normal processing of ingested particles.[19] In addition to disabling these innate macrophage defences, *M. tuberculosis* also interrupts the ability of the macrophage to signal to patrolling lymphocytes that it is infected, thereby reducing the effectiveness of specific, acquired immunity.[20] Lymphocytes, which confer acquired immunity, inspect cells in tissues, including macrophages, for the presence of pathogen-derived molecules (i.e. antigens) on their surfaces. As well as interfering with antigen processing and presentation by the macrophage, *M. tuberculosis* may also reduce the ability of infected macrophages to respond appropriately to T lymphocytes that have detected the infection, as indicated by preliminary work within the initiative.

Notwithstanding the impressive virulence strategies of *M. tuberculosis*, the human host is, as stated earlier, quite capable of successfully suppressing an infection in most instances. This depends on both innate (pre-immune) defences and specific, acquired immunity. The former involves the macrophage defences already alluded to, as well as the activation of natural killer (NK) cells by macrophages and vice versa. The extent to which macrophages can control intracellular pathogens depends on the state of readiness or 'priming' of the macrophage. In the mouse there is clear evidence that this priming is genetically determined.[21] In humans this is controversial, but Action TB is actively addressing this question through the use of a molecular genetics approach in accurately defined, high-incidence communities. Work has been initiated on some candidate genes for disease susceptibility, such as Nramp,[21] TNF and HLA; a whole-genome search may become a reality in the future.

Acquired immunity, on the other hand, depends on T lymphocytes directed against specific antigens of *M. tuberculosis*. There is increasing evidence that not only CD4+, but also CD8+, cells contribute to the specific immune response to *M. tuberculosis*.[22,23] These lymphocytes can produce large amounts of cytokines which activate macrophages, NK cells and also the lymphocytes themselves.[23] Certain cytokines (specifically IL-4, IL-10 and TFG-β), however, suppress the cell-mediated immune response and it is of great interest to determine the exact mechanisms determining the choice of cytokine secretion.[24] Another function of T cells is to kill cells infected with *M.*

tuberculosis. The jury is still out on whether the killing of infected macrophages by cytotoxic cells contributes to the actual killing of tubercle bacilli.

It is hoped that the elucidation of *M. tuberculosis* virulence factors and the components of the host defence that are critical for protection will provide novel targets for the rational design of unconventional drugs, the development of an effective vaccine and the application of hitherto untried immunological interventions.

The authors would like to thank the Glaxo-Wellcome Action TB initiative for generously funding their work.

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OPINION

Tuberculosis control in South Africa — time for a new paradigm?

Globally, the World Health Organisation (WHO) estimates that about 8 million new cases of tuberculosis occur, and that there are about 3 million deaths from tuberculosis, each year.[1] The situation is so grave that the WHO has declared tuberculosis to be a global public health emergency.[2] With the current HIV pandemic, the tuberculosis situation (in Africa in particular) is very serious; case rates have doubled in some African countries.[3] In central Africa more than 70% of adults with tuberculosis may be HIV-positive.[4]

South Africa's tuberculosis problem reflects that of the global community. More cases of tuberculosis than of any other disease are reported annually in South Africa. There were about 82 500 cases in 1992, with an overall incidence rate of about 250/100 000 population.[5] The basic epidemiology of tuberculosis in South Africa is well described; for example, incidence rates are highest in the coloured population in the Western Cape (700/100 000).[6] South Africa is suffering an explosive HIV epidemic, with KwaZulu-Natal hardest hit.[7] At Hlabisa Hospital, a typical rural district hospital in the northern part of the province, 35% of adults diagnosed with tuberculosis in mid-1993 were HIV-positive.[8] (The HIV seroprevalence in women attending antenatal clinics in Hlabisa district was 7.9% at that time[9]). The tuberculosis case load at Hlabisa has increased dramatically in recent years (Fig. 1). While some of this increase reflects a higher general workload from improved staffing, referral in from neighbouring districts and the impact of a more 'user-friendly' service, the impact of HIV infection and the worsening poverty in the area probably account for the rest. It is clearly very difficult for any service to cope with a 300% increase in workload at a time of major political and health service transition and no increase in resources.

Tuberculosis control is, in theory, simple and highly cost-effective. Passive case-finding and the provision of short-course (6-month) chemotherapy will cure the vast majority of cases and, if coverage is high enough, will lead to a sustained reduction in case rates. This is the basic strategy advocated by the WHO and the International Union against Tuberculosis and Lung Disease (IUATLD).[10] Why then has this strategy failed on a global level? Why is tuberculosis a global public health emergency? The reasons are many and well documented.[11] That it can be effective, as seen in Tanzania for example, is encouraging.[12] The failure to control tuberculosis in this country in large part reflects the apartheid legacy of poverty, discrimination and fragmentation of health services. But what now? Should South Africa follow the conventional WHO/IUATLD path, or could an alternative approach yield better results?

We would advocate a change in the way that tuberculosis control is both viewed and implemented (Table I).

What justifications for these proposals exist in the world literature? Intermittent therapy for tuberculosis has long been known to be at least as effective as daily treatment.[13] It was first used in the very early days of chemotherapy for tuberculosis when large numbers of patients had to be