Changing epidemiology of tuberculosis in Hong Kong

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Hong Kong is situated in the south part of Mainland China. It has a total population of near 7 million and a land area of 1098 square kilometers. The population density is high and it has an ageing population. There is also high mobility of the population with 129 million going in and out of Hong Kong in 1999. Such demographic and environmental characteristics have significant effect on the control of tuberculosis (TB) in Hong Kong.

In Hong Kong, there has been an overall decrease in the notification rate of TB in the past 4 to 5 decades, from the peak of 697.2 per 100,000 population in 1952. However, in the past decade, the rate has remained rather stagnant, being at around 110 per 100,000 in recent years. This rate is roughly about 10 times that of western developed countries like the United Kingdom and the United States. A similar phenomenon of stagnant trend of TB notification has also been observed in some neighbouring countries such as Singapore, Japan, and Malaysia. Hong Kong, together with these countries, were grouped as areas with intermediate TB burden and good health infrastructure in the Western Pacific Region by the World Health Organisation.

The contribution to the stagnant TB trend is probably multifactorial. Factors which affect the apparent change in notification rate include notification behaviour, diagnostic practice, and case finding activities. Factors which affect the real change in notification rate include those which affect the 3 components of the TB transmission model: source, vehicle, and host. Sources are infectious TB patients, while vehicles are infectious air droplets. Hosts are the population at risk.

One of the important contributing factors is probably the ageing population. In 1999, the elderly aged 65 and above among the general population is about 10.7%, while that among TB patients is about 36.9%. In fact, the age specific notification rate among the elderly group has been found to be remaining rather stagnant or showing a slight increase in the past decade, while that among the younger age group continued to decrease.

A survey of all notified TB cases in the month of August 1999 showed that among 594 TB cases, about one quarter of them have one or more medical conditions which can predispose to the development of TB disease. Prolonged survival of those with chronic medical illnesses thus give rise to a greater pool of individuals in the community who are at higher risk of developing TB.

Sources of TB notifications can be broadly classified into four: chest clinics, chest hospitals, general hospitals, and the private sector. Analysis of the sources of notification showed that the increase in the number of notified TB cases in recent years could nearly all be accounted for by the increase in

notifications from general hospitals and the private sector. Increased publicity and awareness, resulting in a change in notification behaviour with more complete notification of TB cases under care of those sources is probably the underlying reason.

The development of active TB disease can result from primary infection, exogenous re-infection, or endogenous reactivation. From the various epidemiological surveillance data, it is likely that endogenous reactivation is playing a bigger role among all the notified TB cases.

Measures employed in the control of TB should be directed against those 3 components of the transmission model: source, vehicle and host. Hence, measures targeted at the source include good personal hygiene, case finding and effective treatment. For the vehicle, adequate ventilation and isolation of infectious sources are the relevant measures. As regards host, measures include BCG vaccination, preventive treatment, and maintenance of good bodily health of the general population. Among the various measures for TB control, DOTS (directly observed treatment, short course) targeting at the source has the greatest impact.

Treatment of pulmonary tuberculosis in Hong Kong

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Short-course chemotherapy (SCC) comprising 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z) plus streptomycin (S) or ethambutol (E) followed by 4 months of H and R is the cornerstone regimen for treating new cases of smear-positive pulmonary tuberculosis or smear-negative pulmonary tuberculosis with substantial radiographic extent. [1,2] For retreatment in patients who have had previous therapy (say relapse or resumption of treatment after interruption), a 8-month regimen has been recommended by the World Health Organisation / International Union Against Tuberculosis & Lung Disease, namely 2SHRZE / 1HRZE / 5HRE or $5H_3R_3E_3$. [1] Recently, data from China (including Hong Kong) have also demonstrated the efficacy of thrice-a-week regimens, namely $2S_3H_3R_3Z_3$ / $4H_3R_3$ or $2E_3H_3R_3Z_3$ / $4H_3R_3$ [1] In th6 management of new cases of tuberculosis, provided that the initial bacterial load is not exceedingly high. The use of fixed dose drug combinations (FDC) comprising 2-3 (H+R, H+R+Z) and even 4 drugs (H+R+Z+E) enables ease of prescription for physicians and treatment adherence by patients.[2,3] The main concern in the use of FDC is the quality and bioavailability of its component drugs, particularly rifampicin.[3] Another important new drug development among the rifamycins is the discovery of rifapentine, a long-acting cyclopentyl rifamycin which is currently being evaluated for use concurrently with isoniazid on a once-weekly basis in the continuation phase of treatment of tuberculosis after the initial 2-month intensive phase.[4] The preliminary results are somewhat encouraging although delineation of the optimal dosage is still required. The distinct advantage of this once-weekly regimen is facilitation of Directly Observed Therapy (DOT), thus enhancing patient adherence.[4] DOT was in fact shown to be highly efficacious by the earlier experience gained in Madras and Hong Kong several decades *ago*.[5,6] In order to facilitate the delivery of DOT, other concomitant strategic interventions must be incorporated. SCC has been shown to be the most important component.[6] In 1993, the WHO officially announced the new global tuberculosis control strategy known as Directly Observed Therapy, Short-course (DOTS).[5] This strategy has 5 key components that include[5] (1) a network of trained healthcare or community workers to administer DOT, (2) properly equipped laboratories with personnels trained to perform sputum microscopy diagnosis for tuberculosis, (3) a reliable supply of high-quality drugs (preferably at no cost to patients), (4) an accurate record-keeping and cohort analysis system for monitoring case findings, treatment and outcome, and (5) sustained political commitment and funding. The DOTS strategy, currently in place in Hong Kong results in a high cure plus treatment completion rate (-90%) and low drug resistance rates (combined MDR-TB rate ≈*2%)*.[7]

For patients with streptomycin or isoniazid mono-resistant pulmonary tuberculosis, treatment only requires slight modification of the standard regimen. For example, for isoniazid-resistant tuberculosis, one may utilise all 4 drugs in the initial phase of SCC for a total of 6 months, or change the regimen after drug

susceptibilities are known, to R, E together with Z (at least initially) in combination for continuation up to 1 year.[2] There is even some suggestion that persistence with the standard SCC alluded can bring about cure in the majority of patients though the relapse rate is higher than that of drug-susceptible disease.[8] However for multidrug-resistant tuberculosis (MDR-TB), caused by bacillary strains resistant to at least H and R, specific alternative second-line regimens, preferably individualised, as guided by drug susceptibility testing is required.[9,10] One regimen recommended by the WHO includes ethambutol, ethionamide/prothionamide, ofloxacin/ciprofloxacin, pyrazinamide and aminoglycoside - for 3 months and then the first 3 drugs being administered for at least another 18 months.[9] There is also preliminary local data, indicating possibly optimal treatment of a subset of MDR-TB patients with 1 year of second-line regimens delivered in a somewhat different format.[10] Among the drugs utilised in the multidrug regimens, the fluoroquinolones are most likely the pivotal drugs that have the major contribution to therapeutic efficacy.[10] It is important to note that second-line regimens are generally more toxic and costly.[9,10] Furthermore, the cure rate is only about 60 - 80% with chemotherapy alone.[10] Adjunctive surgery may have a place in selected MDR-TB patients with localised disease and adequate cardio-pulmonary reserve.[11] Immunotherapy is a potentially attractive adjunct therapy, but much more clinical evaluation is required.[12]

Therapeutic drug monitoring, mainly through studying the serum drug concentrations may emerge as a new paradigm of care for some selected patients with tuberculosis.[13] The 3 major indications are (1) optimisation of therapy to ensure/improve success in specific clinical settings like HIV co-infection and MDR-TB, (2) management of pharmacokinetic drug interactions, particularly in at-risk populations like HIV-infected, geriatric and organ-transplanted patients, and (3) management of drug-disease interactions especially renal impairment.

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Tuberculosis in immunocompromised patients

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The last two decades saw a reversal in the declining incidence of tuberculosis (TB) over the century. Up to one third of such reversal was attributed to the AIDS pandemic. Worldwide more than 4 million people have dual HIV and TB infection. At the same time, more widespread use of various immunosuppressive therapeutic modalities also contributes to rising incidence of TB.

In Hong Kong, TB was the primary AIDS defining illness in about one-fifth of the AIDS patients.

HIV is the most powerful factor known to increase the risk of TB. The chance of active TB after infection increases from a lifetime risk of 5-10% in the HIV negative individual to 8% per year in the HIV infected.

As opposed to other opportunistic infections, which tend to affect advanced HIV patients, TB can occur at any stage of HIV infection. However, the clinical features of TB differ according to the degree of immunosuppression. Whereas early HIV cases (CD4 lymphocyte count more than 300 per cc) behave similarly to HIV seronegative cases and follow a reactivation pattern, TB in advanced HIV patients is characterised by more disseminated disease and more extrapulmonary involvement. In advanced AIDS, CXR often shows no cavity or may be normal. Sputum AFB smears are often negative. There is a greater frequency of tuberculin nonreactivity.

Response to first line anti-TB agents is generally excellent whether or not patient is HIV infected. Sputum culture time and cure rate is similar, but treatment is complicated by the use of highly active antiretroviral therapy (HAART) because of drug-drug interactions. Rifampicin is a strong enzyme inhibitor and it increases clearance of the anti-retrovirals, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifabutin may be substituted for rifampicin in certain cases in connection with adjustment to dosage of PIs or NNRTIs.

HIV-seropositive status is a risk factor for multidrug resistant (MDR) TB which is a public health emergency. When MDR-TB is strongly suspected, like when fever persists in a patient receiving standard 4-drug therapy, at least 2 new agents lacking cross resistance to previously used agents should be included until confirmatory susceptibility result is available.

Paradoxical transient worsening of TB symptomatology and lesions has been reported to develop in up to 40% of patients treated with concurrent anti-TB

medications and HAART. This occurs at about 2 weeks after initiation of ART. This phenomenon, termed immunorestitution disease, is a diagnosis by exclusion. Symptoms generally improve on continuation of anti-TB medication.

Treatment of latent TB infection based on tuberculin skin testing should be considered since it reduces the risk of active TB by 40 - 90%. Active disease has to be excluded. Regimens include isoniazid for 9 months or alternatively rifampicin plus pyrazinamide for 2 months. The cut off value in HIV infected persons is taken as 5 mm induration (2 TU of PPD-RT23 as testing agent, equivalent to 5 TU of PPD). There are insufficient local data on the treatment of latent TB infection in HIV infected.

HIV testing should be offered to all TB patients and their close contacts. This is a good opportunity for starting HAART for those who need it and for considering treatment for latent TB infection respectively.

Similar to HIV infected persons but to a lesser extent, solid organ transplant recipients and patients on chronic high dose steroid are more prone to TB. Disseminated and extrapulmonary disease occurs in more than half of cases. There are more atypical clinical pictures and delay in diagnosis is common because of lack of suspicion. Overall mortality is high (15%). More aggressive diagnostic workup is advocated.

Rapid laboratory diagnosis of tuberculosis

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Early diagnosis, isolation and treatment of infected patients is the key to the control of tuberculosis Identifying tuberculosis of respiratory tract is particularly important for infection control purpose because of generation of infectious aerosol in coughing, sneezing and speaking. Despite much advance in technology, no perfect test for TB diagnosis exists at present.

1. AFB smear examination

The time honoured test is rapid and inexpensive. It is not sensitive nor specific for Mtb and is positive only in about 50% of cases of active TB. The need for 10^4 to 10^5 organism/ml of specimens accounts for low sensitivity. The smear report should be available within 24 hours of specimen receipt.

2. Culture

This is the most sensitive method and the gold standard for evaluating other new diagnostic technique. However, due to inherent slow growing property of Mtb, positive report need prolonged time averaging 4-6 weeks for solid media and 1 to 3 weeks for liquid medium. It is recommended to use both solid and liquid medium for optimal detection. Commercial automatic systems are now available for detecting growth saving some manpower in the laboratory.

Identification of Mtb can be made within hours with the probe hybridisation technology e.g. Accuprobe from Gen-Probe. This is a big improvement over conventional biochemical tests and NAP inhibition test which take 1 to 4 weeks. Other rapid technique include HPLC analysis of mycolic acids which are available only in reference laboratories.

Susceptibility tests are technically demanding and should be done only in established laboratory with competent staff, adequate workload and strict quality assurance programs. Inaccurate result will do more harm than good to the patients e.g. less effective and more toxic second line drugs might be used in case of false resistance of first line anti-TB drugs. The most rapid method using BACTEC still requires an additional 1 to 2 weeks after the culture is positive.

3. Nucleic acid amplification test (NAA)

This new molecular biology technique holds the promise for detecting one bacillus by amplifying the target nucleic acid and within matter of hours identifying the presence of TB. In practice however, it is accurate and reliable only in smear positive respiratory tract specimens with > 90% sensitivity and 99% specificity. The low and uneven distribution of TB in other specimens, efficacy of extracting nucleic acid and presence of undefined inhibitors are among the factors decreasing the sensitivity. Contamination is always a threat to the accuracy of the test. Strict control in the segregation of reagent preparation, preamplification and postamplification areas and direction of

workflow are required for control of contamination problems. Because of this and the cost it cannot replace the conventional culture method at this point of time. As with any test, clinical correlation is essential in assessing the NAA test result.

4. Surrogate marker

It is worth mentioning that surrogate marker can be helpful for diagnosing TB. Adenosine deaminase in pleural fluid is elevated in TB pleural effusion. It has sensitivity and specificity of 94% and 93% respectively providing a rapid and inexpensive alternative diagnostic method for this disease entity. Empyema, rheumatoidpleurisy and lymphoma have to be excluded.

5. Future development

Progress has been made in delineating the mutation of the genes that are associated with the resistance to rifampicin, isoniazid, streptomycin, ethambutol, ofloxacin and pyrazinamide. In case of rifampicin, researcher has identified mutations in RNA polymerase B gene that are associated with > 90% rifampicin resistant strains. As a marker for multi-drug resistant TB and its critical role in efficacy of anti-TB drug regimen, rapid detection of TB and rifampicin resistance by genotypic resistance testing are being developed. Now that the entire genome of Mtb has been sequenced and there is rapid advance in nucleic acid amplification and microarray chip technology, its is foreseeable that one day we can identify TB and its resistance pattern all in one step in a rapid and cost effective way.

Report on Global Resistance Day, ICAAC, Toronto

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During the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), American Society for Microbiology and 7 other co-sponsoring international societies has organised a one day program to address the world-wide problem of antimicrobial resistance (AR). In that day, 4 questions concerning AR had been addressed: What are the dimension of problem? What are the driving forces? What needs to be done? How should it be done?

(1) Dimensions of Problem:

Antimicrobial resistance is a global problem, it affects developed countries as well as developing countries. Due to economic and other reasons, antibiotics are used less in developing countries and thus the average collective magnitude of resistance problem lags some 5-10 years behind that of the developed world. However, a dramatic increase in prevalence of resistance is also seen recently in developing countries as well. Resistance costs money as expensive drugs have to be used for resistant organisms. Moreover, prolong hospitalisation and expensive infection control measures are usually required for these organisms. Dr R. J. Williams from WHO said that resistance is beginning to be considered as a societal issue and in economic terms, as a negative externality in the health care context. Furthermore, this can be a threat to global stability and national security.

(2) Driving Forces:

Antibiotics use is the key driver of resistance and selection pressure comes from a combination of overuse, misuse and under-use of antibiotics. Overuse is common in many parts of world, in particular for 'minor' infection. Misuse is due to choosing of inappropriate drug or giving antibiotics for inappropriate duration. Under-use includes taking subdose, substandard drug, counterfeit drug and expired drug. Moreover, non-compliance is also an important cause of under-use of antibiotics. Use of antibiotics in animals is also known to have great impact on antibiotic resistance. Antibiotics are used in livestock for treatment, prevention of disease, and promotion of growth. Evidence indicates that antimicrobial growth promoter (AGP) are associated with development of bacterial resistance in food-animal and resistant bacteria can spread easily from animals to human by direct contact & via food. Moreover, most AGPs are not absorbed from gut by animals and thus the AGPs, along with resistant enteric bacteria, are released into the environment in relatively large amounts which play a significant role in AR.

(3) What needs to be done:

Global problem needs global action. WHO is coordinating a global strategy for containment of anti-microbial resistant, **(www.who.int/emc/amr.html).** It aims to provide a framework of interventions to slow the emergence and reduce the spread of antimicrobial resistant micro-organisms, through improving use of antibiotics, improving access to appropriate antibiotics, reducing the disease burden and the spread of infection; strengthening health systems and encouraging the development of appropriate new drugs and vaccines.

(4) How it should be done:

We have to commit that resistance is created by man, therefore only man can solve the problem.

(a) Prevention and Control:

As antibiotic is a multi-factorial issue, multi-sectoral approach is needed to solve the problem.

i) Prescribers & Dispensers

Educate all groups the importance of appropriate antimicrobial use and containment of AR. Provide them knowledge on accurate diagnosis and treatment of infections. Encourage development and use of guidelines to foster appropriate use of antibiotics. Educate them that their prescribing habits may be influenced by economic incentive and pharmaceutical industry.

ii) Patients & General Community

Correct patients' misperception and educate them about appropriate use of antimicrobials. Encourage appropriate health seeking behaviour.

iii) Hospital

Infection control programs and therapeutic committees should be established. Antimicrobial usage (pattern and quality) should be monitored and results feed back to the prescribers. 2 approaches can be used in hospital setting for controlling AR: (1) Persuasive. This includes education, setting guideline, advocating immediate concurrent feedback and peer review. (2) Restrictive. Examples are using drug formulary, use of order form, selected reporting of sensitivity, autostop system and antibiotics cycling.

iv) Agriculture

Use of AGP belonging to classes of antimicrobials used in human should be stopped immediately. All AGP should be phased out within next five years.

v) Pharmaceutical Industry

- ❖ Introduce regulation of promotion for pharmaceutical company.
- ❖ Industry should take effort to insure the efficiency of antibiotic classes as long as possible rather than to encourage doctors to broadly use antibiotics.
- ❖ Role of industry includes (1) Research and development for innovative antibiotics (2) Research in the mechanisms, epidemiology & driving factors of resistance (3) Provide guidance how to maintain the continuous value of antibiotics.

vi) Governments, Health Systems & Professional Societies

Encourage collaboration and cooperation between governments and professional societies in implementation of strategies to improve the appropriate use of antimicrobials and contain AR.

vii) Media

May be able to educate the public and inform opinion through the media.

(b) Surveillance

- ❖ Design & implement national AR surveillance plan.
- ❖ Monitor antibiotics use in human, agriculture & consumer products.

(c) Research & Product Development

- ❖ Develop and evaluate new antibiotics & novel therapeutics.
- ❖ By studying the pharmacokinetics and pharmacodynamics, revise duration of therapy and dosage of antibiotics so as to prevent the development and emergence of resistant organisms.
- ❖ Development of new rapid diagnostic methods for resistant organisms (e.g. tests for resistant gene and diagnostics for drug resistance in microbial pathogens).
- ❖ Research in the mechanisms, epidemiology & driving factors of resistance.