Tuberculosis prevention: BCG versus INH, the price of uncertainty

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INTRODUCTION

The ultimate goal of tuberculosis (TB) control programs is the elimination of tuberculosis from society by stopping the transmission of TB infection, resulting in the disappearance of the disease. It can be best achieved through the identification and effective treatment of all contagious active cases, without creating at the same time resistance to the antibiotics used [1]. This has been shown in a number of communities which have developed such national TB programs. However, a recent review by WHO of the establishment of national programs around the world showed that only a minority of nations followed the international recommendations, leading to only a slight decline in TB notifications [2]. Thus, even if treatment of active cases of TB remains the foundation for national policies to control its spread, it is still unknown whether this strategy will be sufficient to attain national goals for the elimination of TB. This strategy implies, first, a strong commitment by health authorities to give priority to TB within health planning, and, second, the recognition that this disease is a truly major health problem among persons in the economically productive years of life. Perceiving the full impact of TB is of major importance in establishing the strategy to fight it. Moreover, regular analyses of TB control measures have not usually examined the potential gains from limiting the secondary spread of TB over consecutive years. Such long-term secondary spread could be reduced by preventive measures (chemoprophylaxis and vaccination). Nevertheless, the best preventive measures for TB in developing and industrialized nations are equally debatable. The major controversial features of the prevention methods are the use of isoniazid (INH) chemoprophylaxis in some industrialized and rich nations, particularly the USA, and the use of BCG vaccine in most of the developing nations. However, this dichotomy does not only arise from the feasibility of establishing and carrying out such preventive measures, but is also associated with more profound pseudoscientific or dogmatic assertions opposing these control interventions.

SHORT-TERM PROPHYLAXIS WITH ANTITUBERCULOUS CHEMOTHERAPY

When the INH regimen (300 mg daily for 12 months) is taken, the drug has been shown to be effective in preventing infection from progressing to active disease and in inhibiting recurrence of past disease [3]. In the cited review, it was shown that INH was associated with an 88% reduction in cases of evolving TB infection after 1 year, but such reduction was only 54% when evaluation was done 10 years later. However, the efficacy of chemoprophylaxis was directly related to the length of the course and to the compliance of the patients; the efficacy was 93% for patients with good compliance taking the drug for 12 months, but was reduced to 69% for patients with good compliance and taking the drug for 6 months. Such results and others [4,5] were used for recommendations for chemoprophylaxis 25 years ago among tuberculin skin test converters in the USA [6]. The benefit–risk ratio has been clearly established for subgroups of high-risk tuberculin reactors: contacts of active TB cases, recent tuberculin converters, diabetics, silicotics, postgastrectomy patients, and patients under immunosuppressive therapy. All the published data from the literature
indicate the effectiveness of INH in treating early TB infection in immunocompetent and immunodepressed hosts and that progression to active TB should be preventable. Chemoprophylaxis, using a single agent such as INH at a relatively low dosing, has never been associated with any increased selection of INH resistance of TB bacilli. This might be due to the relatively small numbers of INH-susceptible bacilli present during TB infection and also to the normal capacity of the host to strengthen its acquired immune protection.

Nevertheless, if one considers that more than 50% of newly diagnosed cases of TB are due to reactivation, this can be viewed as a failure of the prevention program. Also, prevention of TB by the use of INH is a multistep process and is a more complicated undertaking than simply prescribing a medication when it is indicated. Several steps are involved, and each of them presents problems. Individuals at risk for developing TB must be identified, must be offered INH, and must accept it and take it in adequate amounts for an adequate length of time, and the drug must be effective in each specific case. One of the main difficulties of chemoprophylaxis may lie in the absence of an effective public-health system covering the whole population. Another may be the absence of screening for TB infection or, if screening is done, a failure to offer INH or poor compliance. A third deficiency may lie in the low sensitivity of the tuberculin skin test.

If one considers the need for a well-functioning TB control program for the delivery of INH chemoprophylaxis, it is clear that INH prevention will not be feasible in most of the low-income countries. Thus, in 1991 the World Health Assembly recommended that a national TB program should achieve two main targets, in order to obtain a favorable impact on TB control: (1) to detect 70% of new sputum smear-positive cases, and (2) to treat successfully 85% of them [7]. There was no suggestion of contact tracing, or chemoprophylaxis [7]. Contact tracing has traditionally been recommended as a useful preventive measure, and a series of studies has indicated a high degree of adherence to established preventive guidelines at public-health clinics in the USA [8]. However, analysis of the potential failure of such preventive measures, made by Glassroth et al. [9], showed that one third of the 279 TB cases studied had had no contact with healthcare professionals for at least 5 years before the development of TB. In one group of 64 individuals who had been recognized as contacts of potentially infectious persons, only half indicated having receiving a tuberculin test, and only eight were offered chemoprophylaxis. It is also reported that among another group of patients at risk of TB, a few received a skin test. In this group of 98 patients who indicated either prior TB contact (64 patients) or another risk factor (34 patients), only 11 (11.2%) were offered chemoprophylaxis and 10 (90.9%) accepted it. From this particular study, one can observe that about 90% of individuals at risk were either not screened or not given chemoprophylaxis. Such failures need to be re-examined, since they indicate that healthcare workers (HCWs) may not be well acquainted with current prevention guidelines. One of the limits of chemoprophylaxis is the perception of its benefit for the asymptomatic tuberculin converters. Chemoprophylaxis of TB by giving INH to individuals whose only abnormality is a positive PPD skin test reaction suffers severely from imbalance between the low risk of TB, being diluted by its spread over a life-span, and the risk of treatment (hepatotoxicity) which may occur during the short period when medication is taken. It is, then, not surprising that some persons prefer to avoid immediate risk rather than distant threat of disease [10]. It would appear desirable to concentrate on and publicize those aspects of TB prevention where a general agreement exists, and also to improve TB education in high-risk populations.

The perception of the risk to HCWs themselves should be more acute and prevention more efficient. As indicated by several studies and in particular by the investigation of Sepkowitz [11], the current view of TB care as an occupational hazard emerged only in the late 1950s after a fierce and extensive debate. The resurgence of TB and above all the increased prevalence of multidrug-resistant (MDR) TB over the past decade has increased the perception of the risk of nosocomial transmission from patients to HCWs and several effective infection control systems have been published [12]. However, there will always be some degree of occupational risk, and a mandatory comprehensive skin-testing program has been recommended by the CDC for all healthcare facilities as a part of TB infection control efforts [13]. A recent report from Emory University School of Medicine (Atlanta, USA) showed that when such a mandatory, comprehensive tuberculin skin-testing program was associated with physician referrals, the acceptance and completion of chemoprophylaxis was very high [14] for all those with a positive tuberculin skin test. This contrasts with previous studies in which very poor physician compliance was reported with absence of a formal or mandatory tuberculin skin-testing program or established protocols for referrals at many institutions for those with TB [15,16].

The tuberculin testing program cost was estimated at less than 10 US dollars per person, but it increased to 4500 dollars for a person eligible for chemoprophylaxis with INH and to 350 000 dollars per case.
of TB prevented, given the additional costs associated with investigation, treatment and follow-up [17]. Nevertheless, the CDC has proposed a policy of regular surveillance and tuberculin testing, depending on the level of risk. It seems that such recommendations will be more interesting in evaluating the short-term efficacy of the administrative measures needed to control the transmission of TB to HCWs than satisfactory in the long term for the individual HCW. In fact, adoption of such tuberculin skin–testing recommendations is still lacking for those in many institutions (such as long-term care), and in some hospitals [18]. It should be noted that the risk of tuberculin conversion among employees in an urban hospital may in some cases be unrelated to working conditions and associated instead with social and demographic factors [19]. In any case, the reaction to tuberculin is not just a simple correlate of infection by a member of the Mycobacterium tuberculosis complex, and epidemiologic information obtained with such testing will be reliable only if potential methodological problems are solved, including selection bias, the booster effect, differences in the antigen used for testing, the techniques of administration, and the interpretation of the results [20,21].

Chemoprophylaxis has been proposed as a strategy to control TB in the HIV-infected population [22]. HIV-positive patients with induration of 5 mm or more in reaction to five tuberculin units of PPD should be considered as having tuberculous infection and be offered chemoprophylaxis, if shown to be free of active TB. Treatment for 12 months is recommended. Moreover, HIV-positive persons exposed to active cases of TB should be given chemoprophylaxis, regardless of the results of tuberculin testing. BCG should not be given to patients with AIDS, because of the possibility of their developing disseminated BCG infection. The benefit of chemoprophylaxis has been suggested by several observational studies in injecting drug users [23] and in the HIV populations of low-income countries [24,25]. However, a recent study of INH chemoprophylaxis in HIV-positive anergic patients at high risk for TB did not show any benefit in comparison with the placebo group [26]. A more accurate method of detecting latent tuberculosis than the old PPD skin test needs to be developed in order to identify people likely to benefit from prophylaxis. As jointly stated by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) in 1993, the incorporation of chemoprophylaxis should only be considered in areas where national TB programs are achieving the targets established by WHO and where voluntary testing and counseling for HIV infection are available [27]. These statements emphasize that recommendations will depend on the setting and the target population. In countries where the annual risk of TB infection and the incidence of TB are low, chemoprophylaxis can be a standard medical practice in TB control. In low-income countries, where dual infection is common, and there is continuous exposure to active TB, while chemoprophylaxis might provide benefit to the individual patient, at least for a short period of time, there are no data on the effect on TB control. Both operational and efficacy trials are needed to further clarify the role of chemoprophylaxis in HIV-positive patients [28]. Although the frequency of INH-resistant and MDR TB has increased dramatically, especially among HIV-infected individuals, injecting drug users, homeless people and contacts of MDR TB (including HCWs), there have been no controlled trials of alternative chemoprophylaxis regimens for the management of such individuals. In this situation, there is no consensus to give them chemoprophylaxis with more toxic and unproven new drugs [29].

LONG-TERM PROPHYLAXIS WITH VACCINATION

Given the high costs and poor compliance associated with tuberculin testing and chemoprophylaxis with INH, combinations of alternative preventive measures have been devised by the use of mathematical models [30]. In this work it has been shown that improvements in the coverage or effectiveness of treatment of diagnosed cases of TB are unlikely alone to achieve established national goals for elimination of TB. However, these goals can be achieved through a combination of improvements in current programs with targeted chemoprophylaxis and BCG vaccination.

Although it has generally been accepted that BCG has no direct impact on the epidemiology of TB in low-prevalence countries [31], the debate still continues about its potential value in selected risk groups [32] and in HCWs [33]. Three decision analyses have been performed comparing BCG vaccination with tuberculin screening strategies [34-36]. The first study [34] demonstrated that BCG vaccination would lead to fewer cases of TB among tuberculin-negative medical students and house officers over a 10-year period. BCG vaccine would require an efficacy rate of only 13.1% to prevent more cases of TB than tuberculin screening and INH chemoprophylaxis. The second study [35] showed that BCG vaccination would result in net cost-savings, in comparison with INH chemoprophylaxis, in persons attending shelters for the homeless, over a wide range of assumptions, but this conclusion was strongly dependent on the efficacy of the vaccine. The threshold for cost-savings was a
vaccine having an efficacy equal to or higher than 40%. In a high-risk transient population in which serial annual tuberculin testing and INH chemoprophylaxis would be fraught with difficulty, BCG vaccination policy needs to be reconsidered, in view of the alarming increase in MDR TB and increased reports of TB in shelters in urban areas. The third report [36], which also concerned HCWs, favored the use of BCG for all assumed vaccine protective efficacies greater than 26% and the preference for BCG increased directly with increased efficacy, as reported in the two studies already discussed. This indicates that BCG should be considered for HCWs in an environment where a substantial risk of exposure to MDR TB exists. BCG would increase its advantage with a decrease in the efficiency of detection of TB infection by tuberculin skin testing, with an increase in multiresistance rates and with a decrease in compliance with chemoprophylaxis. The loss of the potential to use tuberculin prophylaxis. The loss of the potential to use tuberculin skin testing in the diagnosis of TB infection after BCG vaccination has been claimed as a disadvantage by several epidemiologists, and the numerical analysis in this paper [35] included this potentially negative aspect of the use of BCG.

The clear message from these studies is that BCG vaccination in persons exposed to TB or at risk of progressing from TB infection to disease should be reconsidered. However, BCG vaccination has not been recommended in the USA [37,38], because the overall efficacy of the vaccine in various trials has been variable, ranging from 0% to 80% [39] (see below) and because when given to adults the vaccine makes subsequent reactions to tuberculin uninterpretable, as discussed in two letters, by Miller and Castro [40] and by Reichman and Mangura [41].

Approximately 100 million newborns and children received the BCG vaccine in 1992, thanks to the organizational, financial and technical involvement of Expanded Programme for Immunization (EPI) [42]. Moreover, the BCG vaccine presents several advantages as compared with other vaccines: it can be given at birth or any time thereafter; a single inoculation can produce a long-lasting immune response; it is safe; it is relatively stable as a freeze-dried vaccine; it produces a scar, which is useful for epidemiologic surveillance; and it is inexpensive (from 0.02 to 0.5 US dollars). However, while its worldwide global immunization coverage in newborns was reported to be 85%, its efficacy remains a source of contention. Results from several controlled trials showing very high and very low vaccine efficacy have meant that there is little international agreement on the BCG vaccine [43]. A recent meta-analysis of selected trials concluded that BCG vaccination in infants and newborns is about 50% effective in preventing cases of pulmonary TB, but the data accepted for the review included those from trials recording much higher and lower protective efficacies [44]. It is still indicated in countries where the annual risk of infection during childhood is high. WHO [45], outlining problems and recommendations, noticed that the four major vaccine strains (Pasteur, Glaxo, Copenhagen, Tokyo) show great antigenic heterogeneity and that numerous other strains are also in use which are not well characterized. At present there is no laboratory test available to demonstrate the protective efficacy of any particular antigenic mixture. Since it has not been possible to determine a threshold dose for any BCG vaccine, the rational procedure is to give the highest dose that is acceptable, acceptability being determined by the local vaccination reaction (ulcer, scar), and, in young children, by the incidence of suppurative axillary lymphadenitis. Thus, as suggested recently [46], variations in the BCG strain potency may have resulted from subtle pressures to minimize adverse reactions while maintaining tuberculin reactivity, during vaccine development and testing. In fact, during the last prospective study carried out in Hong Kong (1978–86), it was shown that the Pasteur strain, known to be highly reactogenic, was better able to protect newborns than a less reactogenic Glaxo strain. Thus, quantitative differences between vaccines can be of practical importance [47]. WHO also states that vaccine efficacy appears highest among the youngest recipients and that BCG immunization does not prevent infection but limits initial spread of bacilli, as evidenced by animal experiments [48] and autopsy studies [49]. BCG vaccine appears much less effective in preventing primary complexes in the lungs (20% efficacy), primary complexes with local extension (32%) and lymphadenitis (32%) than in preventing TB meningitis (52%) and disseminated TB (80%). The WHO recommendations are to give one dose at birth, or at the first contact with the health service, and that there is no known advantage in giving a booster dose. Even if some studies indicated that BCG vaccine may be in fact more effective when given in the third month after birth, such studies did not evaluate protection, but only tuberculin conversion or scar production, which are by no means correlates for prevention [50]. The several cost–benefit analyses of BCG vaccination given in children concluded that the cost and benefit of BCG were almost equal where the average annual risk of TB infection did not exceed 0.1% [47]. Such analyses included only the direct individual protective effect, since it is believed that BCG has little impact on the overall transmission of the TB bacillus in the general population [31].

Most western European countries either have no
BCG policy or have a policy of vaccinating only high-risk children, revaccination being uncommon. Most eastern European countries vaccinate all infants at birth and revaccinate tuberculin-negative children at least once. However, there have been only a few evaluations of the efficacy of repeated BCG vaccination against TB. As stated by WHO recently, repeat vaccination is not supported by scientific evidence and is not recommended. Multiple revaccinations are not indicated in any person [51].

Another shortcoming of BCG vaccine is the absence of controlled trials to evaluate its ability to prevent TB in adults at risk, such as HCWs. Nevertheless, a recent review of several published reports suggested that BCG vaccination is effective in reducing the incidence of TB in HCWs [33]. Despite the methodological flaws, the cohort studies indicate that rates of TB have been substantially lower (from 54% to 85%) among HCWs receiving BCG vaccine than among unvaccinated HCWs with negative tuberculin skin tests. The data seem also to indicate that the vaccine efficacy increases with the risk of exposure to TB: the protection was greater in nurses in sanatoria than in all sanatoria employees or hospital-based student nurses. These observed results have not been generally accepted for two reasons: first, because of some inconsistencies in these old studies, and second, because BCG vaccination produces the same response to PPD as TB infection, thereby confusing and obscuring the diagnosis of recent infection [52].

Although, as already discussed, the efficacy of chemotherapy for tuberculin test converters in practice may be low [16], this remains a useful measure for protection of HCWs. The operational problems concerning such intervention are well characterized and could be easily solved [53]. This contrasts with the inconsistencies in BCG results that have long been the subject of debate without any consensus about the causes of variation. Bloom and Fine [54] believe that interference by environmental mycobacteria provides the best explanation for the observed results of BCG immunization, both in experimental studies and in the patterns of protection observed in different parts of the world. They suggest that other interfering factors (methodological flaws, heterogeneity between BCG vaccines, or M. tuberculosis strains, genetic difference within and between populations, various capacity of BCG vaccines to protect against exogenous or endogenous infection) could play a role, but the evidence for these is not so convincing.

One of the most important causes of the controversy about BCG vaccination may comprise the narrow viewpoints of some epidemiologists and health planning authorities, who concentrate on the immediate (e.g. the annual reduction rate of TB infection, through the reduction of bacilli transmission) rather than on the long-term future (e.g. the long-term acquisition of a protective individual immunity). In this way, the varying reported results of the controlled trials, case-control studies and cohort studies have been utilized inappropriately as the exact intrinsic variability of the BCG vaccine potency in inducing acquired immunity against TB in a defined population (e.g. newborns, children, adults, HCWs). Yet, as for experimental models, the validity of any trial will depend upon the adequacy and accuracy of the endpoint measures of the model used. Since there is no simple in vitro or ex vivo measurable parameter of human acquired immunity to TB, the only measurable variable has been always the diagnosis of a TB case. The less accurate diagnosis will be then associated with the less accurate evaluation of differences between controls and vaccines. Such important methodological bias was emphasized several years ago by Clemens et al [55], who stated that 'because the trials with the best methodological quality and greatest statistical precision reported high efficacy, the evidence suggests that BCG can confer a high degree of protection against TB, and that bias or inadequate statistical power may have contributed to the conflicting data'. Such bias and inadequate statistical power did not seem to have been taken into consideration, since several epidemiologists and health planning authorities continue to propagate the idea that variability in results is solely due to the variability of the BCG vaccine efficacy, instead of describing the relative factors involved among the reported trial results. As such, the observed variations mean that results of one trial cannot simply be extrapolated to other populations and conditions. Recently, the incursion of MDR TB has led the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices to recommend that BCG vaccination should be considered for HCWs, on an individual basis, when the local epidemiology of TB indicates that such workers have a high likelihood of exposure to MDR TB and are not served by an effective infection control program [56].

Considering the chronic nature of TB, it may have been naive to expect BCG vaccination to protect against every form of TB [57]. By analogy, we have recently demonstrated that while BCG appeared able to protect with medium efficacy against leprosy in general, in fact its efficacy was only evident in unstable subpolar forms of leprosy, and not in the polar forms (lepromatous and tuberculoid) [58].

One of the big challenges for TB immunologists is to understand the physiopathologic mechanisms of the progression from infection to disease, and to detect the
underlying causative immunologic regulatory pathways that are associated with progression. The second task will be to analyze the possible interfering effect of BCG vaccination on such regulatory pathways, since BCG has been shown not to interfere with infection, but with disease progression [48,49]. Such fundamental approaches will give opportunities to select surrogate immunologic markers of induced protection and the factors that are able to downregulate it. In this way, the confounding effect of BCG vaccination on the tuberculin test may be eliminated. Until that time, the use of BCG vaccination will make questionable the usefulness of PPD testing for contact tracing. However, this situation also exists in individuals previously infected with atypical mycobacteria [53]. In a recent study [59], the authors stated that the age and infectivity of the index case, but not the BCG status in the contact, should be considered as key variables in the decision-making process in the management of contacts. Moreover, available data suggest that disease-related hypersensitivity (PPD testing) and immunity (protection) are dissociable, giving us the prospect that it may be possible to induce immunity to infection without compromising the continued need for an ongoing system of immunodiagnosis. In conclusion, in populations at risk for TB, it is likely that a combination of immunodiagnosis, other modes of diagnosis, chemoprophylaxis and immunoprophylaxis will be required to eradicate the disease [60], as has been suggested by the computer simulations of TB control policies [30].

References