of all forms of cancer, including leukaemia, during the first 20 years of life in those vaccinated neonatally with BCG.\textsuperscript{2} Similar observations of protective efficacy, particularly against childhood leukaemia, were made in Canada, several Scandinavian countries and Israel,\textsuperscript{3} but studies in Alabama and Puerto Rico failed to support these claims.\textsuperscript{4}

There is, however, substantial evidence that the protective efficacy of BCG against tuberculosis varies greatly from region to region and is generally much more protective when given early in life. A likely explanation of this variation is that exposure to a range of environmental micro-organisms induces patterns of immune regulation that antagonise protective immunity in tuberculosis and which BCG cannot reverse.\textsuperscript{5} The same principle may well apply to leukaemia as, in the studies in which protection was demonstrated, BCG was administered early in life and also afforded protection against tuberculosis. By contrast, in the studies in Alabama and Puerto Rico, the vaccine was given to those of all ages up to 18 years and only afforded 6\% and 29\% protection, respectively, against tuberculosis.\textsuperscript{4}

Protection by BCG vaccination early in life is not limited to leukaemia and other childhood cancers. A study in several European countries and Israel showed that such vaccination afforded \~60\% protection against melanoma in adult life,\textsuperscript{6} and significantly improved survival time in those with inoperable disease.\textsuperscript{7}

Two explanations, which are not mutually exclusive and may indeed by synergistic, may be advanced for these reported protective effects of BCG. Thus, vaccination could generate cross-reactive T-cells that recognize epitopes presented on cancer cells and it could also substitute for microorganisms that lead to the development of immune regulatory pathways; namely, microorganisms that are not readily encountered in ‘hygienic’ environments.

In this context, in 1986, Härō observed that BCG vaccination protected against leukaemia in Finland and suggested that this vaccine is not just a specific immunizing agent but has ‘long standing positive effects on the immunological mechanism as a whole’.\textsuperscript{8} This immunomodulating effect of BCG has been postulated as the explanation of health benefits conferred by the vaccine beyond a prevention of tuberculosis in Africa,\textsuperscript{9} and it fits in well with present-day concepts on the key role of immune dysregulation and chronic inflammation on the development and progression of a wide range of cancers.\textsuperscript{10}

As the incidences of both leukaemia and melanoma are increasing in the ‘hygienic’ developed nations, as both affect young people and as there is a global increase in the risk of multidrug and extreme drug-resistant tuberculosis, the introduction or re-introduction of routine neonatal BCG vaccination should be given serious consideration.

References


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Chronic diseases and call to action

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Further to the answer of Professors Guy de Backer and Marcel Kornitzer,\textsuperscript{7} concerning Dr Ebrahim’s comment on the WHO-Multifactorial Prevention Trial,\textsuperscript{2} I would like to add the following comments.
The Catalan Centre joined this study in 1974, 3 years after the beginning of the trial in the UK, and contributed with an additional 4 to the study 40 pairs of factories, with a total sample of 2851 men aged 40–59 years.

Due to its small size, the low coronary heart disease (CHD) mortality and the late joining, it was anticipated that the contribution weight of the Catalan data to the whole trial intervention effect on CHD would be small and unlikely to contribute in a decisive way to the final trial results. For these reasons, the participation of our data in the analysis of the Collaborative Project was limited to the assessment of the feasibility of the intervention and of the risk factor prevalence and changes, although the full protocol including the 5-year incidence and mortality follow-up was applied.

In addition, we also followed-up mortality up to 10 years. The decision not to include the Catalan Centre in the final trial analysis was made 'a priori' by the Project Chairman.

Initial concerns, which disappeared rather quickly, over the capability of the local team to perform to the quality standards required, also played a role in this decision. Although incidence and mortality results were not included in the final analysis of the Collaborative trial, our results were presented at the European Society of Cardiology Congress. Results showed a net 5-year decrease in total serum cholesterol of −4%, of −2% in weight, but net increases of 4% in systolic blood pressure and of +4.8% in the prevalence of smokers. This was reflected in a statistically significant reduction of 10-year all-cause mortality of 31%, a non-significant reduction of 22% for CHD mortality and a significant reduction of 33% for non-cardiovascular mortality, mainly due to cancer.

Stratified analysis by pairs of factories showed a significant net percent decline of CHD risk, assessed by a multiple logistic function, in three of the four pairs (Table 1). Like the Belgian arm of the Collaborative trial, our study showed a significant reduction in total mortality. It is important to point out that the intervention of the trial consisted in lifestyle advice only. No pharmacological treatment was used, other than what was freely prescribed by the local community general practitioners according to the knowledge of the times (pre-statin era).

Dr Ebrahim’s otherwise mostly achieved calling for renewed action towards chronic diseases, seems to put in the same basket, the 1980s’ WHO initiatives and programmes on community prevention programmes on chronic diseases, with cardiovascular primary prevention trials. The WHO Factories trial in Europe was contemporary to the Multiple Risk Factor Intervention Trial (MRFIT) study in the USA and to the Oslo primary prevention trial. The WHO Factories trial was fully ‘randomized’ by group study and not a quasi-experimental design study, unlike the community programmes. Some of the latter were very well designed as quasi experiments; i.e., the Five City Stanford Project and the Minnesota Heart Health Project, to name just two examples, and published quite extensively on the behavioural changes in regular scientific journals. The Catalan part of the WHO-Multifactorial Trial is not to be confused with the Community Prevention Program on Chronic Diseases (CRONICAT), which started in 1981 in Catalonia, partly encouraged by the results achieved in the Factory trial, although some of the investigators were the same. In 1984 CRONICAT incorporated the WHO-Multinational MONitoring of trends and determinants in Cardiovascular diseases (WHO-MONICA) study as the monitoring part of the programme. Nor is the CRONICAT program to be confused with other distinct data collection and preventive actions from the WHO countrywide integrated noncommunicable diseases (CINDI) program, which was initiated several years later and by another different team in the same region.

With these comments, I hope to have contributed and somehow refuted the claims of publication bias made by Dr Ebrahim.

### Table 1

<table>
<thead>
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<th>Factory pair</th>
<th>% change in multiple logistic function score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factory pair 1</td>
<td>−158</td>
</tr>
<tr>
<td>Factory pair 2</td>
<td>−19.8</td>
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<td>Factory pair 3</td>
<td>+11.2</td>
</tr>
<tr>
<td>Factory pair 4</td>
<td>−26.3</td>
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</table>

### References


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