Lastly, Helleringer and Reniers point out that reduction in the number of unprotected acts (the outcome in our analyses) does not always translate to a reduced number of HIV transmissions. We agree, and they provide plausible scenarios where behavioural risk at the level of the population declines, but HIV transmission continues because of particularly risky sexual mixing patterns or behavioural disinhibition. (Our manuscript also described possible but unmeasured consequences of learning one’s HIV status, including relationship dissolution.) However, we disagree that the logical conclusion of these alternative scenarios is that reductions in the number of unprotected acts is a meaningless behavioural goal to measure or pursue. Reduction in the number of unprotected acts will lead to reductions in HIV transmission at least within serodiscordant partnerships. As we describe in our manuscript, 9–10% of HIV-positive women reported no sex at all after their diagnosis (one reason for the overall drop in number of unprotected acts), and 44% reported no unprotected acts. For these women (assuming truthful self-report about condom use), the probability of onward transmission during the observation period was zero.

In sum, we agree with Helleringer and Reniers that population-level analyses often mask important sub-group heterogeneity, and that sexual network studies will contribute substantially to the overall understanding of sexually transmitted disease transmission. However, we disagree that population-level analyses ‘hardly shed light on the actual social process of behavioral change’. Taken to the extreme, this statement implies that the heterogeneity within the response would invalidate all population-level research, including randomized intervention trials. Interventions nearly always have an effect on many, but not all, participants, and yet we consider the (population-average) results of randomized trials the research gold standard. We firmly believe that epidemiological studies using population-average models and sexual network studies are complementary. Both are necessary to enhance our understanding of the HIV epidemic.

References


Prophylactic intervention for childhood leukaemia

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The meta-analysis, by Urayama et al.,1 of studies on the association between day-care attendance and the risk of childhood acute lymphoblastic leukaemia is both timely and important in the light of emerging interest in the ‘hygiene hypothesis’ as an explanation for the increasing incidence of several diseases in the industrialized nations. The authors end their discussion with the statement ‘An important implication of these ‘hygiene’-related hypotheses and supportive data is that some form of prophylactic intervention in infancy may ultimately be possible’.

We would claim that prophylactic intervention in infancy is already possible. For example, there have been several reports that vaccination with Bacille Calmette–Guerin (BCG) early in life provides a significant degree of protection against leukaemia and, possibly, other cancers in childhood and early adult life. Rosenthal reported a 74% reduction in the incidence
of all forms of cancer, including leukaemia, during the first 20 years of life in those vaccinated neonatally with BCG. Similar observations of protective efficacy, particularly against childhood leukaemia, were made in Canada, several Scandinavian countries and Israel, but studies in Alabama and Puerto Rico failed to support these claims. 

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. 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. 

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, and significantly improved survival time in those with inoperable disease. 

Two explanations, which are not mutually exclusive and may indeed be 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, Härö 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’. 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, 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. 

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, concerning Dr Ebrahim’s comment on the WHO-Multifactorial Prevention Trial, I would like to add the following comments.