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REPLY

The authors' reply: Population mixing and childhood leukaemia

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We thank Leo Kinlen for his interest in our recent study which provided little evidence for an association between childhood leukaemia and population mixing (PM) [1]. Kinlen argues that the degree of PM observed in our study did not qualify as *large rural PM* and that therefore his hypothesis could not be tested. The population increases in our highest exposure category (fifth quintile of relative change in population over a 5-year period) do not match the marked increases investigated in some previous studies. However, it is not evident what distinguishes our study from other studies Kinlen considered to be relevant to his hypothesis. For example, we used a similar measure of PM as two studies [2, 3] that Kinlen included in his recent meta-analysis of the association between PM and childhood leukaemia [4]. Neither of these studies investigated marked PM: the highest categories were population increases of >20 % over 5 [2] or 10 years [3]. In our study, the highest quintile of population growth ranged from 8.2 to 124 % (median 12.3 %) over a 5-year period. We regret not having reported the actual percentages corresponding to the quintiles in our study, and now include them in this reply (see Supplementary Table S1). We acknowledge that the study by Kinlen and Balkwil [5] was a cohort study and that our statement that all previous studies were either of the case–control or ecological type was indeed inaccurate.

Kinlen's comments highlight the inherent difficulty of "testing" the PM hypothesis. The hypothesis not only holds that PM is a cause of childhood leukaemia, but also that the effect is mediated through an infection that remains to be identified. While associations between measures of PM and childhood leukaemia can be examined, the putative immediate cause, the infection, is not observable. If no evidence for an association between PM and childhood leukaemia is found in a study, it can always be argued that the infectious agent did not circulate at the time, or the epidemic was not captured by the measure of PM. In contrast, the hypothesis will always be supported by positive findings. While it is true that positive associations with childhood leukaemia have mainly been found with marked rural PM, this may not necessarily be the case. Increases in population, even if large and occurring in isolated areas, need not always be followed by an epidemic of the infection, depending on unknown proportions of susceptible and transmitting individuals and the intensity of contact between them. Conditions favouring transmission of the infectious agent might also exist at lower levels of PM, as suggested by the positive findings of the two studies mentioned above [2, 3]. Surely, using different measures of PM is recommended in this situation because they could capture circumstances associated with higher rates of infection other than the extreme degrees of PM that gave rise to the hypothesis. We believe that the use of three different measures, population increase, level of in-migration and diversity of place origin of in-migrants was a strength of our study.

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