beyond infancy, in contrast to infections experienced in infancy, which would tend to be protective (2). Unfortunately, the authors did not provide data on the most informative group with which to assess protection resulting from early infection: children aged 1–4 years during the study period (1991–1996, though mainly 1992–1994) who were exposed to the highest numbers of recent migrants. Instead, the only results presented for specific age groups, the groups 5–9 and 10–14 years, concerned children who were mainly well past infancy in 1991. From Greaves’ hypothesis (2), one would expect that for these children, a high level of exposure to migrants would have represented a source of “delayed” infections and therefore of increased ALL risk. However, Law et al. reported increased risks of ALL in these age groups of 1.92 and 2.06, respectively, among children who were least exposed to migrants (1). Contrary to their conclusions, the findings of Law et al. for children aged 5–14 years appear to contradict Greaves’ hypothesis.

Particularly since Greaves himself was associated with this study, it is also rather surprising that his hypothesis should now be claimed as predicting protection against ALL from population mixing; previously (2) he stated that it readily accommodates the opposing effects postulated and found by Kinlen (3)—that is, excesses of childhood leukemia associated with marked population mixing in rural or isolated areas.

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THE AUTHORS REPLY

We thank Professor Kinlen (1) and Dr. Tucker (2) for their observations on our recently published United Kingdom Childhood Cancer Study (UKCCS) report on childhood cancer and population mixing (3). The investigation was aimed at evaluating the relation between population mixing and childhood leukemia risk in small geographic areas across the United Kingdom. Subjects involved in the UKCCS were not selected on the basis of the leukemia incidence or population density of their region of residence. Furthermore, the census-based method used is reproducible and robust, and the analyses are not affected by participation or recall bias.

We are aware that Professor Kinlen’s hypothesis (4) is not applicable to the majority of leukemias diagnosed in children and that it is difficult to test in a national setting (5). In this context, we agree that it is important to focus on extremes of population mixing in sparsely populated areas (1), both within the United Kingdom and elsewhere in the world. With respect to the former, such an investigation will form the basis of an upcoming UKCCS analysis comparing small-area census data of cases with those of controls at birth as well as at diagnosis. The recent acquisition of the birth certificates of all subjects registered in the UKCCS means that we can investigate area characteristics at both of these time points, as well as examine mobility and other changes occurring in between.

Dr. Tucker (2) rightly notes that we did not provide data on the age and diagnostic group most relevant to the delayed infection hypothesis (4). When the analysis was restricted to common acute lymphoblastic leukemia (ALL) diagnosed between the ages of 2 and 5 years, the results were similar to those presented for total ALL (3). For example, for ALL in the lowest category of diversity of migrants, the odds ratio was 1.29 (95 percent confidence interval: 0.79, 2.12) as compared with 1.37 (95 percent confidence interval: 1.00, 1.86) for the totality. The results did not differ when adjustment was made for deprivation and rural status, and there was no evidence of increased risk for areas with a high volume of migrants.

The biologic diversity of childhood leukemias makes it unlikely that there is a solitary cause. It seems clear, however, that research on possible immunologic and infectious etiologies is worth pursuing.

REFERENCES

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Ki et al. (1) used a case-crossover design to evaluate the relative risk of aseptic meningitis after measles-mumps-rubella vaccination. Although their results are broadly in line with those of others on the same topic, the case-crossover...
design cannot generally be recommended for investigating associations between adverse events and childhood immunizations because it requires the probability of exposure (i.e., vaccination) to be constant over time (2). This requirement is certainly not met by childhood immunizations administered according to highly age-dependent schedules. Measles-mumps-rubella vaccines, for example, are typically given at 12–15 months of age.

Ki et al. (1) correctly state that, in the case-crossover method, each person serves as his or her own control, but they then assert that confounding due to vaccination age is thereby eliminated. This is not the case: If the underlying probability of vaccination varies with age, then exposure and control periods are not comparable, introducing what is in effect a control selection bias.

For example, suppose for simplicity that the hazard period includes the month preceding the event and that the control period includes the 6 months prior to the hazard period. Consider an aseptic meningitis case with onset at the end of month 14. The hazard period then includes month 14. The probability of measles-mumps-rubella vaccination in this period is high. The control period covers the period from age 7 months to age 13 months. The average monthly probability of measles-mumps-rubella vaccination during this period is likely to be lower. In contrast, an aseptic meningitis case occurring at the end of month 18 has a hazard period including month 18 and a control period including months 12–17. In this case, the chances are that the case will be vaccinated during the control period. These age effects can produce biases, which are apparent in table 2 of the paper by Ki et al. (1): The relative risks are highest for aseptic meningitis cases that occur at less than 18 months of age and much lower for cases that occur at later ages. Although it is quite possible that the biases roughly cancel out across cases in this particular study, this cannot be relied upon in general. For example, an adverse event unrelated to measles-mumps-rubella vaccination but occurring primarily before age 18 months would appear to be positively associated with measles-mumps-rubella vaccination. On the other hand, if the event occurred primarily after age 18 months, measles-mumps-rubella vaccination would appear protective.

The requirement of constant underlying exposure probability is fundamental to the case-crossover method. In fact, it has been shown that exposures in successive time periods must satisfy the even stronger requirement of exchangeability to avoid bias in logistic regression analyses of case-crossover designs (3). This mirrors the tacit assumption in matched case-control studies that the controls are exchangeable. The exchangeability requirement, a demanding one for case-control studies, stems from the method’s origins in the case-control paradigm, and it cannot be sidestepped by controlling for age at exposure. In contrast, the self-controlled case-series method (4) referred to by Ki et al. (1) does not suffer from this shortcoming. This design, superficially similar to the case-crossover design insofar as both are self-matched, derives from cohort (fixed exposure, random event) rather than case-control (fixed event, random exposure) logic and hence has quite different properties. Full adjustment for age and time effects is possible in self-controlled case-series designs, which have been applied to the study of adverse events after vaccination (5) and drug safety more generally (6).

REFERENCES

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TWO AUTHORS REPLY

We appreciate Dr. Farrington’s letter (1) and his interest in our paper (2). Dr. Farrington raised quite an important fundamental issue regarding the case-crossover design. The case-crossover design compares the probability of exposure between the control period and the hazard period (figure 1). If the probability of exposure is time dependent, the control period and the hazard period cannot be comparable, and the analysis by case-crossover design may have time-trend bias (3).

However, we do not agree that the case-crossover design should not be recommended for investigating the association between adverse events and childhood immunizations. The reasons are as follows.

In general, “time dependent” is totally different from “age dependent.” “Time” has the same meaning as “age” only for the specific instance when the observation ages of all cases are the same as the observation time period (figure 2).

It is true that, in the study by Ki et al. (2), the probability of vaccination is not constant over age. Rather, the probability of vaccination is constant over calendar time. The aseptic meningitis incidence rates based on symptom criteria were not significantly different among those under 3 years of age (<12 months, 21.6; 12–23 months, 26.0; and 24–35 months, 27.0 per 100,000, respectively; p > 0.05) (2). If the event (aseptic meningitis) occurs randomly between 6 and 36 months of age, then the observation ages of all cases are different. The exposure age (i.e., 12–15 months of age) was regarded as randomly located during the observation time periods (1 year before onset of aseptic meningitis). Eventually, the exposure is age dependent but not time dependent. Thus, the hazard period and the control period are compa-