American Journal of Epidemiology

Letter to the Editor

RE: "A PROSPECTIVE STUDY OF THE EFFECTIVENESS OF THE NEW ZEALAND MENINGOCOCCAL B VACCINE"

Although Kelly et al. (1) demonstrate the effectiveness of the outer-membrane-vesicle, strain-specific, meningococcal vaccine known as ''MeNZB'' in the overall New Zealand population with reported vaccine effectiveness of 73 percent (95 percent confidence interval: 52, 85), this may not reflect the true picture.

First, there is an indication of the poor fit of the model (1, figure 1), where the model's rates of disease determined by modes in children less than 1 year of age are considerably less than those in children 1–4 years of age. Data published elsewhere show the highest rates to be in children less than 1 year of age (2).

Further, there appear to have been difficulties with the model that may influence the vaccine effectiveness estimate. The model assumes that vaccine uptake within an analysis stratum was random for an individual's risk of disease. Despite great effort to achieve high coverage, this assumption may not be true. Ethnicity and household crowding (3) are known to be major risk factors for disease. Coverage is known to have varied by ethnicity (www.moh.govt.nz). Indigenous Maori who sustained a higher rate of disease prior to vaccine introduction had 67 percent vaccine coverage among those aged from 6 weeks to 4 years compared with the remaining population with 74 percent coverage. Ethnicity was included in the model, but household crowding and other factors were not. An indication that coverage may have been reduced in subgroups with risk factors not included in the model may be seen in the crude estimates of vaccine effectiveness (the risk ratios of the rates of disease in the unvaccinated vs. the vaccinated cases). These crude 2005 risk ratios (1) do not reflect decreasing geometric mean antibody titers (GMTs) with decreasing age (4, 5). Antibody levels by age are likely to be reflected in vaccine efficacy levels (6–8). Kelly et al. (1) observed a crude risk ratio four times higher in the children aged 1–4 years compared with those aged 5–19 years, contrary to that expected. Older children were vaccinated in school with high coverage nationwide. Vaccination of preschool children was general practice based with more variable coverage. The unexpected crude risk ratios by age could be a result of disproportionately low coverage in children 1–4 years of age with an inflated estimate of vaccine effectiveness in this age group.

The authors also speculate as to whether the risk ratio in young babies (0–11 months of age) at 0.9 is spurious. Infants were offered their fourth vaccination of the priming series at 10 months of age (5). Thus, it seems likely that the quoted risk ratio is correct with little vaccine effectiveness before 12 months of age.

The authors fail to discuss the change, region by region, in the increasing disease confirmation rate (50–100 percent) over the 6 years of the study and the corresponding change in the proportion of cases included in the analysis (2).

Kelly et al. (1) raise the question of long-term vaccine effectiveness. The group C meningococcal vaccine used in the United Kingdom was a conjugate vaccine producing very high GMTs (e.g., 629 after a three-dose priming series in one trial in infants) (9). In contrast, in New Zealand infants aged 6–8 months after three doses of MeNZB vaccine, an outer-membrane-vesicle vaccine, lower GMTs of 27 were observed (4). Higher titers are likely to remain longer. In persistence studies, antibody decay occurred very rapidly (GMT of 2 at 7 months after the third dose) (5).

Although it seems likely that the mass vaccine program has indeed had some effect, the concerns raised above shed some doubt on the reliability of the estimates as quoted.

ACKNOWLEDGMENTS

Conflict of interest: D. L. and J. S. were part of the MeNZB trials team sponsored by the New Zealand Ministry of Health; S. C. with J. S. and D. L. provided expert advice to the New Zealand Ministry of Health for the strategy to control New Zealand's meningococcal epidemic.

REFERENCES

1. Kelly C, Arnold R, Galloway Y, et al. A prospective study of the effectiveness of the New Zealand meningococcal B vaccine. Am J Epidemiol 2007;166:817–23.
2. Dyet K, Devoy A, McDowell R, et al. New Zealand's epidemic of meningococcal disease described using molecular analysis: implications for vaccine delivery. Vaccine 2005;23:2228–30.
3. Baker M, McNicholas A, Garrett N, et al. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. Pediatr Infect Dis J 2000;19:983–90.
4. Oster P, Lennon D, O'Hallahan J, et al. MeNZB: a safe and highly immunogenic tailor-made vaccine against the New Zealand *Neisseria meningitidis* serogroup B disease epidemic strain. Vaccine 2005;23:2191–6.
5. Oster P, O'Hallahan J, Aaberge I, et al. Immunogenicity and safety of a strain-specific MenB OMV vaccine delivered to under 5-year olds in New Zealand. Vaccine 2007;25:3075–9.
6. Boslego J, Garcia J, Cruz C, et al. Efficacy, safety, and immunogenicity of a meningococcal group B (15:P1.3) outer membrane protein vaccine in Iquique, Chile. Chilean National Committee for Meningococcal Disease. Vaccine 1995;13:821–9.
7. Milagres LG, Ramos SR, Sacchi CT, et al. Immune response of Brazilian children to a *Neisseria meningitidis* serogroup B outer membrane protein vaccine: comparison with efficacy. Infect Immun 1994;62:4419–24.

8. Holst J, Feiring B, Fuglesang JE, et al. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. Vaccine 2003;21:734–7.
9. MacLennan JM, Shackley F, Heath PT, et al. Safety, immunogenicity, and induction of immunologic memory by a serogroup C meningococcal conjugate vaccine in infants: a randomized controlled trial. JAMA 2000;283:2795–801.

Diana Lennon[1], Joanna Stewart[2], and Sue Crengle[3]
(e-mail: d.lennon@auckland.ac.nz)

[1] *Department of Community Paediatrics, Faculty of Medical and Health Sciences, The University of Auckland, Auckland 1142, New Zealand*
[2] *Department of Biomedical Statistics, Faculty of Medical and Health Sciences, The University of Auckland, Auckland 1142, New Zealand*
[3] *Department of Maori and Pacific Health, School of Medical Sciences, The University of Auckland, Auckland 1142, New Zealand*

DOI: 10.1093/aje/kwn051; Advance Access publication