infected with human immunodeficiency virus type I. Multicenter AIDS Cohort study Group. *N Engl J Med* 1990; **322:** 161–65.
3 Grant AD, Djomand G, De Cock KM. Natural history and spectrum of disease in adults with HIV/AIDS in Africa. *AIDS* 1997; **11** (suppl B): S43–54.
4 Lucas SB, Hounnou A, Peacock C, et al. The mortality and pathology of HIV infection in a West African city. *AIDS* 1993; **7:** 1569–79.
5 Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet* 1999; **353:** 1469–75.

Authors' reply

Sir—In our trial, the total number of days in hospital was 18% lower in patients from the co-trimoxazole group than in those from the placebo group (758 *vs* 924). This reduction was more important for the total number of days at the day-hospital (–34%, 205 *vs* 309) than for the number of inpatient days at the university hospital (–10%, 553 *vs* 615). The total number of unscheduled consultations was 12% lower in the co-trimoxazole group than in the placebo group (3744 *vs* 4265). There were 348 days in hospital and 1717 unscheduled consultations per 100 person-years in the co-trimoxazole group, versus 430 and 1984 in the placebo group. Thus, in our population and under our standard of care, co-trimoxazole prophylaxis could be roughly estimated to have saved 82 days in hospital and 267 consultations per 100 person-years, in addition with all related unscheduled complementary examinations and curative treatments. The overall cost of these two latter factors was about eight times higher than that of hospital admissions.

Accurate cost-effectiveness analyses should take into account other factors (eg, numbers of unemployed days). Our trial did not have the best designs to allow such analyses, because our conditions of care (consultations, medications, examinations and hospitalisations free of charge, and examinations not routinely used in other community clinics) differed from the usual conditions of Côte d'Ivoire where patients have to pay for all services. We thus fully agree with Christopher Hudson and Timothy Roach that cost-effectiveness analysis still needs to be done in resource-poor settings where co-trimoxazole prophylaxis could be recommended. These analyses, which need to document the number of hospital admissions and consultations according to diagnostic category, could also help establish whether to recommend the large-scale use of co-trimoxazole prophylaxis at early stages of HIV-1-infection, at more advanced ones, or not to recommend it, depending on the local spectrum of HIV-1-related infections.

In Côte d'Ivoire, a recent national consensus statement recommended that co-trimoxazole prophylaxis should be systemically proposed to all HIV-1-infected adults at WHO clinical stages 2, 3, or 4, and that these recommendations should be adapted in the future, depending on the evolution of bacterial susceptibility to co-trimoxazole.[1] If resistance of pneumococci and non-typhi salmonella becomes as frequent in Côte d'Ivoire as in Malawi, future statements will be likely to favour an advanced co-trimoxazole chemo-prophylaxis, to focus on parasitic infections that are common in patients with low CD4 cell counts. The results of our early prophylaxis trial should not mask the efficacy of co-trimoxazole in the prevention of toxoplasmosis at more advanced stages. Although Richard Brindle argues that "the choice of co-trimoxazole seems to have been based more on its historical use . . . than on the microbiology of HIV-1-associated infections in Africa", the "historically"-proven efficacy of co-trimoxazole against toxoplasmosis, together with the spectrum of severe morbidity related to HIV-1-infection in Côte d'Ivoire, were part of our decision to chose co-trimoxazole. Trimethoprim alone cannot be considered as the first-line toxoplasmosis primary prophylaxis.

We share the concerns of Richard Brindle, and Martin Boeree and their colleagues about the spread of bacterial and parasitic resistance. However, co-trimoxazole has been widely used in Africa for a long time, and both bacterial resistance to co-trimoxazole and *P falciparum* resistance to sulphadoxine-pyrimethamine exist in African settings where co-trimoxazole prophylaxis is not introduced. Thus, it is likely that co-trimoxazole will continue to be widely prescribed, and that susceptibility will continue to drop, even if co-trimoxazole prophylaxis is not recommended widely. Before this resistance becomes widespread, should co-trimoxazole be reserved for a non-HIV-related use in Africa? We believe that this question should be carefully discussed, together with the risk of "therapeutic nihilism" mentioned by Motasim Badri and colleagues.

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1 Société Ivoirienne de Pathologie Infecieuse et Tropicale. Cotrimoxazole en prophylaxie des infections opportunistes chez les patients infectés par le VIH en Côte d'Ivoire. Abidjan, 19 Février 1999.

Oral contraceptives and risk of hip fractures

Sir—Karl Michaëlsson and colleagues' data (May 1, p 1481)[1] from a large case-control study from Sweden indicate an inverse relation between use of oral contraceptives and the risk of hip fractures, which, if confirmed, would have major public-health implications.

We examined this issue with data from a case-control study of hip fractures undertaken in Italy between 1983 and 1992.[2,3] Cases were 279 women aged 29–74 years (median age 62), admitted to a network of teaching and general hospitals in the greater Milan area. Controls were 1861 women, aged 25–74 (median age 55) admitted for non-traumatic conditions to the same network of hospitals.

Ever use of oral contraceptives was reported by ten (4%) cases and 167 (9%) controls, corresponding to a multivariate odds ratio of 0·98 (95% CI, 0·47–2·03). The odds ratio was 1·04 (0·42–2·55) for women who had used oral contraceptives for 2 years or longer. Among ever users of hormone replacement therapy the odds ratio was 0·53 (0·23–1·19).

Our study does not lend support to the existence of a consistent relation of hip-fracture risk with use of oral contraceptives. Given the low frequency of users, our study had limited power to detect a potential association between exogenous oestrogens and hip fractures. Nevertheless our risk estimates accord with a reduced risk in users of hormone replacement therapy.[4,5] This finding is consistent with a short-term influence of oestrogen on bone mass.[4,5]

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1 Michaëlsson K, Baron JA, Farahmand BY, Persson I, Ljunghall S. Oral-contraceptive use and risk of hip fracture: a case-control study. *Lancet* 1999; **353:** 1481–84.
2 La Vecchia C, Negri E, Levi F, Baron JA. Cigarette smoking, body mass and other risk factors for fractures of the hip in women. *Int J Epidemiol* 1991; **20:** 671–77.
3 Parazzini F, Tavani A, Ricci E, LaVecchia C. Menstrual and reproductive factors and hip fractures in post menopausal women. *Maturitas* 1996; **24:** 191–96.
4 Felson DT, Zhang Y, Hannan MT, et al. The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 1993; **329:** 1141–46.
5 Ettinger B, Grady D. The waning effect of postmenopausal estrogen therapy on osteoporosis. *N Engl J Med* 1993; **329:** 1192–93.

Mannose-binding lectin and meningococcal disease

Sir—Martin Hibberd and colleagues (March 27, p 1049)[1] report that genetic variants of mannose-binding lectin (MBL) are associated with increased susceptibility to meningococcal disease in two separate studies, one with controls admitted to hospital with non-infectious disorders and the other with healthy controls recruited in the community.

Further analysis of the data reveals two additional interesting results. The first is the hospital and community control groups differ in allele frequency for the codon 52 *MBL* variant (0·024 *vs* 0·045) and codon 54 variant (0·066 *vs* 0·141). Combining the two variants gives an odds ratio of 0·43 (p=0·0002). The second result is that the codon 57 variant, measured only in the hospital study, seems to have a protective rather than a harmful effect (allelic odds ratio 0·36, p=0·04). If these differences do not reflect ethnic biases in the control group (racial differences in MBL variants are well described),[2,3] they suggest that: codon 52 and 54 variants may protect against the non-infectious disorders in the hospital controls; and that the codon 57 variant, which is most common among Africans,[2,3] has an opposite effect on meningococcal disease outcome to codon 52 and 54 variants. Are Hibberd and colleagues able to shed any light on these observations?

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1 Hibberd ML, Sumiya M, Summerfield JA, Booy R, Levin M, and the Meningococcal Research Group. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. *Lancet* 1999; **353:** 1049–53.
2 Lipscombe RJ, Sumiya M, Hill AV, et al. High frequencies in African and non-African populations of independent mutations in the mannose binding protein gene. *Hum Mol Genet* 1992; **1:** 709–15.
3 Turner MW. Mannose-binding lectin: the pluripotent molecule of the innate immune system. *Immunol Today* 1996; **17:** 532–40.

Sir—Martin Hibberd and colleagues[1] report an increased frequency of *MBL* variant alleles causing dominant decrease in the MBL serum concentration in English patients with meningococcal disease. In 1993, we reported a lack of association with low serum concentrations of MBL and tendency to meningococcal serogroup B (n=74) or serogroup C (n=25) disease in Norwegian patients (52 females) aged 12–21 years compared with controls.[2] These patients also took part in a national, randomised trial of vaccine efficacy against serogroup B meningococcal disease, which comprised 171 800 students in Norwegian secondary school[3] and 54 000 military recruits. 119 individuals of the study population developed meningococcal disease during the 3-year observation period. Serum samples from 13 fatal cases were not available for the investigation. Among the 106 survivors, serum samples were taken from the 99 included patients, which were collected at least 6 months after the onset of disease.

Because of the complexity of the MBL polymorphisms,[4] our serum measurement may not adequately reflect the MBL polymorphisms in the patients, which could explain the discrepancy between our results and those of Hibberd and colleagues. Therefore, our patients were asked to donate an additional blood sample for DNA analysis; 75 of the previously included patients agreed to take part in the genetic study. The overall frequency of *MBL* variant alleles in the patients with meningococcal disease was almost identical to that found in Norwegian controls (0·19 and 0·21, respectively,* which lends support to the conclusion in our earlier study.[2] There were an excess of *MBL*-variant-alleles homozygotes, in the English patients, but no excess in the Norwegian patients (1·3% *vs* 3% in the controls). In addition, no association was found with an *MBL* promoter allele in position −221 (*X*/*Y*), which is also associated with low MBL serum concentrations. Stratification in receipt of active vaccine versus placebo did not change the overall conclusion.

The discrepancies between the English and the Norwegian studies are not clear. It may be argued that we studied only survivors and, thus, missed fatal cases who might have been deficient in MBL. However, in the English study, the patients homozygous for *MBL* variant alleles had a lower mortality rate and less use of intensive care than their MBL competent counterparts, which argues against such a bias in our patients.

The English study comprised one hospital-based study (n=194, mean age 3·5 years) and one community-based study (n=72, mean age 15 years). In the Norwegian study the median age was 16 years. However, with stratification according to genotype, carriers of *MBL* variant alleles tended to be younger when they contracted meningococcal disease than those homozygous for the normal allele (median age 15 years and 17 years, respectively; Mann-Whitney, p=0·05). The *MBL* variant allele frequency in those below 16 years was 0·25, compared with 0·15 in those 16 years or older (Fisher's p=0·06). This result indicates that MBL may have an immune protective role against meningococcal disease in young patients, whereas it is less important in the older patients. This could partly explain the differences between the English and Norwegian findings.

Thus, the *MBL* variant alleles did not contribute to the overall protection against meningococcal disease in Norwegian patients, but an age-dependent effect seems possible and needs to be further investigated, for example, in the community-based part of the study by Hibberd and colleagues.

*Full data available from authors, on request.

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1 Hibberd ML, Sumiya M, Summerfield JA, Booy R, Levin M, and the Meningococcal Research Group. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. *Lancet* 1999; **353:** 1049–53.
2 Garred P, Michealsen TE, Bjunc G, Thiel S, Svejgaard A. A low serum concentration of mannan-binding protein is not associated with serogroup B or C meningococcal disease. *Scan J Immunol* 1993; **37:** 468–70.
3 Bjune G, Høiby EA, Grønneby JK, et al. Effect of outer membrane vescicle vaccine against group B meningococcal disease in Norway. *Lancet* 1991; **2:** 1093–96.
4 Garred P, Madsen HO, Svejgaard A. Genetics of human mannan-binding protein. In: Ezekowitz RAB, Sastry K, Reid KBM, eds. Collectins and innate immunity, Austin, TX: RG Landes Company, 1996: 139–64.
5 Madsen HO, Garred P, Thiel S, et al. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. *J Immunol* 1995; **155:** 3013–20.