lower respiratory tract infections at the Hajj are caused by pneumococci.[4]

To determine the coverage of PPV among British pilgrims, we surveyed 195 UK travelers (aged 1 to 83 years) who attended our temporary clinics in Mecca during the Hajj 2005. The majority were men (91%) and of subcontinental ethnicities (84%). Fifty three (27%) were in an at-risk disease category (25 diabetic, 10 cardiac, and 10 pulmonary patients) and 8 were older than 65 years. Only 10 of 195 British pilgrims (5%) reported PPV immunization. Eight of them were at-risk individuals (5 diabetic, 1 cardiac, 2 elderly patients), equating to a vaccine uptake rate of 15% in at-risk Hajj pilgrims. Among the 195 pilgrims, 30 (15%) were smokers, of whom 7 were at-risk individuals and only 1 was immunized. None of those reporting chronic lung diseases had received the vaccine.

The low uptake of PPV among at-risk adults in our survey, as in other studies, is worrying given the vaccine's benefit in reducing intensive care unit admissions.[1-3] An estimated 55 000 pilgrims from Europe and North America were expected to attend the Hajj pilgrimage by mid December 2007. At least one-fourth of these pilgrims would be eligible for PPV, but it can be extrapolated from the current studies that 85% to 90% of at-risk pilgrims will miss out.[1,2] A sustained effort is needed to improve the uptake of the vaccine among the Hajj pilgrims. There is still time to act in relation to this year's Hajj, and we urge physicians and other health care professionals advising Hajj pilgrims to ensure that those at risk are offered pneumococcal vaccine.

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Risks of Combining Immunosuppressive and Biological Treatments in Inflammatory Bowel Disease

Sorrentino et al[1] report the results of infliximab with low-dose methotrexate for the prevention of postsurgical recurrence of ileocolonic Crohn disease (CD). The authors elected to coadminister methotrexate because it is known to reduce the long-term immunogenicity of infliximab.[2] This is true only with episodic treatment with infliximab. Despite the observation that therapy with concomitant immunosuppressive agents reduces the development of antibodies against biological treatments, the authors have not significantly altered the response to infliximab[3] in the treatment of CD when the agents are administered as an induction course followed by scheduled maintenance treatment. Recently, Maser et al[4] demonstrated that the rate of clinical remission was higher for patients with a detectable trough serum concentration of infliximab compared with patients in whom serum infliximab was undetectable, including those without antibodies (82% vs 6%; $P < .001$). In this study, concurrent immunomodulators did not alter outcomes.[4] A preliminary report from Van Assche et al[5] suggested that the immunosuppressive therapy could be discontinued after 6 months with no effect on the loss of response to infliximab over 2 years. So the concept of combination immunosuppressive therapy needs to be discussed in light of the expanding reports of potential increases in severe infections and neoplasms.[6]

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In reply

We thank Roblin and Phelip for their comment on a timely issue. The recent report of the rare hepatosplenic T-cell lymphoma (HSTCL) in young patients with CD treated with both infliximab and azathioprine or steroids[1] has rightly unleashed a series of doubts regarding the optimal use of biological agents in this and other conditions.[2] How these observations may directly relate to the design of our study[3]—as implied by Roblin and Phelip—is unclear though. While azathioprine by itself has been linked to lymphoma development including HSTCL,[1] recent studies have shown that neither infliximab nor methotrexate, which was used in our study, alone or in combination in CD[4] or in rheumatoid arthritis,[5] appear to be associated with an increased risk of developing lymphomas. In addition, methotrexate alone has never been associated thus far with HSTCL in CD.[1]

The report by Mackey et al[1] on HSTCL is undoubtedly disturbing and should be taken into due consideration. Nev-

ertheless, we should keep in mind that biological agents have been largely used so far in patients with advanced, severe disease, be it rheumatoid arthritis or CD. These patients may be irreversibly bound to develop long-standing complications—including lymphoma and other cancers—driven by inflammation or an intrinsic immune defect regardless of concomitant therapy,[6] therapy which is often sentenced guilty by association. Unfortunately, especially in CD, real measures of disease heterogeneity and progression (such as duration of inflammation before symptom onset) are still lacking, making proper stratification extremely difficult.

A question to be asked is whether the combination of infliximab and immunosuppressives (and more specifically metothrexate) in CD is superior to monotherapy with infliximab alone. Available data indicate that the benefit may be limited to reduction of infusion reactions and increase in serum infliximab levels.[2] Whether the latter effects, directly or indirectly, translate into greater efficacy is unclear. While many advocate the use of immunosuppressives only in episodic infliximab treatment,[2] others suggest that methotrexate may bring a benefit even in maintenance infliximab treatment.[7]

Because there is no established role for methotrexate in prevention of postsurgical recurrence in CD, we do not know whether methotrexate affected the outcome of our study. Preliminary observations suggest that patients who switched to monotherapy with infliximab may do as well as the others (D.S., unpublished data, 2008). A definite answer may only come from a future randomized controlled trial we are planning to conduct that will not include methotrexate and that will target for therapy only patients at high risk of developing recurrence. In the meantime, we believe that our study may open up a new venue for the management of CD. The future challenge is to use this information properly by finding ways to optimize efficacy and the overall risk-benefit ratio.

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