One must use extreme caution in accepting the published trial data as proof of the concept of B-cell-driven pathogenesis in multiple sclerosis. Indeed, most authors of this paper were also involved with the clinical trial of B-cell-targeted treatment with atacicept that was terminated by the sponsor because of serious worsening of disease in the treated groups (ClinicalTrials.gov NCT00642902).

The lessons from the clinical trial of natalizumab[4] seem to have been forgotten too quickly: nearly a quarter of more than 200 patients with natalizumab-induced progressive multifocal leukoencephalopathy are dead and most of the rest are severely disabled by the drug rather then their disease. Quo vadis multiple sclerosis?

I declare that I have no conflicts of interest.

Abhijit Chaudhuri
chaudhuria@gmail.com

Essex Centre for Neurological Sciences, Oldchurch Hospital, Romford RM7 0BE, UK

1 Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled multicentre trial. *Lancet* 2011; **378:** 1779–87.
2 Harigai M, Tanaka Y, Maisawa S. Safety and efficacy of various dosages of ocrelizumab in Japanese patients with rheumatoid arthritis with an inadequate response to methotrexate therapy: a placebo controlled double blind parallel group study. *J Rheum* 2012; **39:** 486–95.
3 Phadke JG. Survival pattern and cause of death in multiple sclerosis: results from an epidemiological survey in north east Scotland. JNNP 1987; **50:** 523–31.
4 Chaudhuri A. Lessons for clinical trials from natalizumab in multiple sclerosis. *BMJ* 2006; **332:** 416–19.

Authors' reply

We agree with Abhijit Chaudhuri that a phase 2 proof-of-concept study cannot provide definite evidence about the safety profile of a new compound. What we reported is that the benefit/risk profile noted over 48 weeks and in a limited number of patients was positive. Our paper concludes by underlining the need for larger and longer-term studies to better inform the benefit/risk profile of ocrelizumab.

Indeed the death of a patient is always a reason for concern, but an independent pathological review by external experts concluded that the patient who died in our study did not show any signs of viral infection. Whether the systemic acute inflammatory reaction noted in this patient had a causal relation with ocrelizumab treatment has not been established.

The lack of evidence for a dose response in this proof-of-concept study does not allow us to conclude one way or the other whether "escalation of B-cell depletion by immunotherapy alters the natural course of multiple sclerosis". As a side note, although the primary analysis of this study did not show a clear dose response, a later post-hoc analysis indicated a dose response in patients with highly active multiple sclerosis and—together with data collected in studies of ocrelizumab in rheumatoid arthritis—suggests that ocrelizumab 600 mg might be the lowest effective dose in multiple sclerosis.

Finally, the failure of atacicept in the treatment of relapsing multiple sclerosis[1] underlines the notion that not all B-cell-directed treatments are beneficial. Failed trials are—although regrettable—a strong stimulus for further research and for refinement of our concepts of pathogenesis and treatment. On closer inspection there are substantial differences in the mode of action of atacicept and ocrelizumab that certainly need to be discussed when the atacicept trial results are fully published.

The short-term efficacy shown in our proof-of-concept study of ocrelizumab compares well with that of other compounds used for the treatment of multiple sclerosis and certainly provides ample motivation to do larger and longer-term studies in an informative phase 3 programme to further explore the benefit/risk profile of this humanised monoclonal antibody in multiple sclerosis.

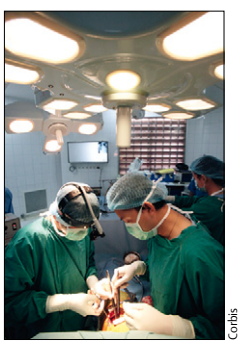
We declare that we have no conflicts of interest other than those stated in the original paper.

**Ludwig Kappos, David Leppert, Jeroen Timmermann, Robert Glanzman, Stephen Hauser*
lkappos@uhbs.ch

Department of Neurology, University Hospital Basel, 4031 Basel, Switzerland

1 Kappos L, Hartung H-P, Freedman MS, et al. ATAMS: a randomized trial of the B-cell-targeting agent atacicept in patients with relapsing multiple sclerosis. *Multiple Sclerosis J* 2011; **17** (suppl 10): S40 (abstr).

Interventional cardiology and cardiac surgery in Cambodia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WHO and other international organisations decree that facilities and treatments provided by donors to developing countries should correspond to the economic realities of those countries. We would like to highlight and defend a sophisticated yet sustainable technology transfer programme that we have operated, against these principles, in paediatric cardiac surgery and interventional cardiology in Cambodia.

The five Kantha Bopha Children's Hospitals in Cambodia have admitted more than 1 million severely sick children over the past 20 years and treated more than 10 million sick children in their outpatient clinics. The Kantha Bopha Hospitals care for 85% of all sick Cambodian children. All treatment is free of charge.

109 100 severely sick children were admitted to hospital in 2010: 58 267 in Phnom Penh and 50 833 in Siem Reap Angkor. In the Kantha Bopha Hospitals in Phnom Penh, 376 children died (0·64%), of whom 53 (14%) had an untreatable pulmonary complication caused by a congenital heart defect. In other words, the disease with the highest mortality rate in the Kantha Bopha Hospitals is now congenital heart malformation.

But many more have died as a consequence of a heart malformation. In 2010, 272 children with severe pulmonary problems as a consequence of heart malformation had to be admitted to the intensive-care unit. 53 died (20%). The other 219 children were discharged still in

a critical state, and their parents were told that they could not be saved. They died later at home.

This is the reason why we have installed in Siem Reap Angkor, as a logical step to reduce the mortality rate, interventional cardiology for closure of patent ductus arteriosus and atrial and ventricular septal defects, dilation of pulmonary and aortic stenoses, and cardiac surgery for more complex congenital malformations via a partnership involving the teams of the University Children's Hospital Zurich, Switzerland; Chaîne de l'Espoir, Paris, France; and Fondation le Petit Coeur, Zurich. This strategy is based on epidemiological data and translates the will to decrease mortality in severely sick children in a sustainable way.

We declare that we have no conflicts of interest.

*Beat Richner, Chour Sok, O Kretschmar, Rene Pretre, Gerard Babatasi, *Antoine Lafont*
antoine.lafont@inserm.fr

Kantha Bopha Hospitals, Siem Reap, Cambodia (BR); Chaine de l'Espoir, 75014 Paris, France (CS, GB, AL); University Children's Hospital Zurich, Zurich, Switzerland (OK); and Fondation le Petit Coeur, Zurich, Switzerland (RP)

Rising maternal deaths in London, UK

UK maternal mortality remained relatively static between 1983 and 2008, varying from 9·8 to 13·1 direct and indirect maternal deaths per 100 000 maternities (pregnancies resulting in livebirth at any gestation or stillbirth occurring at or after 24 weeks).[1] In 2010, the Local Supervising Authority (LSA) and NHS London noted an apparent rise in maternal deaths in London and commissioned a review (covering Jan 1, 2009, to June 30, 2010) from the Centre for Maternal and Child Enquiries (CMACE). This review found London's maternal mortality rate to be substantially higher than that of the rest of the UK: 19·3 per 100 000 maternities (95% CI 14·0–26·6) versus 8·6 per 100 000 maternities (7·1–10·5).[2]

CMACE has been suspended since April, 2011. Thus, to investigate trends further, we retrieved information from the past ten London LSA Annual Reports to the Nursing and Midwifery Council. Deaths were categorised as direct, indirect, coincidental, and late, and verified with CMACE. Before 2005, the LSA reports contained no information on deaths. 2010–11 data could not be cross-checked with CMACE. We found a 27% increase in births in London, from 106 071 maternities in 2001 to 134 544 in 2011, and a rise in maternal mortality between 2005 and 2011 (figure).

Maternal death is associated with extremes of maternal age, obesity, social deprivation, black and minority ethnicity, late access to health care, in-vitro fertilisation, and multiple pregnancy—all factors pertaining to London's childbearing population.[2] Although many determinants of life-threatening pregnancy complications exist before conception, and numbers of deaths in individual units are inevitably small, maternal mortality is regarded as a sensitive measure of health-care quality. In 2008, London's maternity services were found wanting by comparison with the rest of the UK.[3] Over the same decade that witnessed mergers, reconfigurations of maternity services, and site closures, London has seen falls in hospital standardised mortality ratios and summary hospital-level mortality indicators.[4] However, since maternity measures do not always feature in NHS reports, our finding demands urgent attention.

Increases in maternal mortality have been reported in several high-income countries including Austria, Canada, Denmark, the Netherlands, Norway, and the USA,[5] although improved detection might be implicated. With a background of increasing deliveries and complexity, rising mortality could reflect worsening demographic and medical risk in the pregnant population, excessive strain on the health-care system, or both.

Especially in the absence of CMACE, maternity service provision in the UK must be closely monitored and aligned to need and evidence. New thinking and more innovative public health measures, supported by government policy, might be required to address maternal risk.

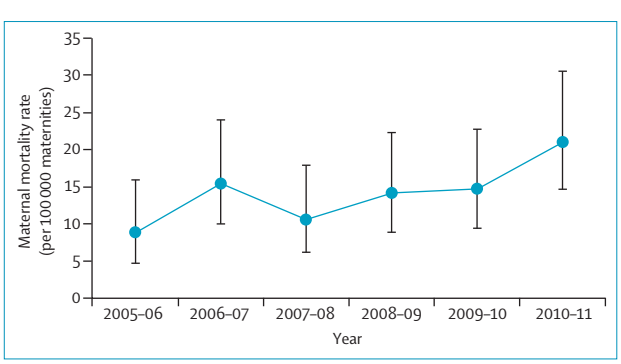

Figure: **Maternal mortality, London, 2005–11**
Rate per 100 000 maternities, with 95% CIs. Source: London Local Supervisory Authority reports.

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**Susan Bewley, Angela Helleur*
susan.bewley@kcl.ac.uk

Women's Health Academic Centre, King's Health Partners, St Thomas' Hospital, London SE1 7EH, UK (SB); and NHS London, London, UK (AH)

1 CMACE, Lewis G. Saving mothers' lives: reviewing maternal deaths to make motherhood safer, 2006–2008. The eighth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118**(suppl 1): 1–203.

2 Centre for Maternal and Child Enquiries. A review of maternal deaths in London, January 2009–June 2010. http://www.london.nhs.uk/publications/independent-publications/independent-reports/a-review-of-maternal-deaths-in-london-january-2009-june-2010 (accessed Dec 9, 2011).

3 Healthcare Commision. Towards better births: a review of maternity services in England. http://webarchive.nationalarchives.gov.uk/20110504133205/http:/www.cqc.org.uk/_db/_documents/Towards_better_births_200807221338.pdf (accessed March 21, 2012).

4 Dr Foster Intelligence. Inside your hospital. Dr Foster hospital guide 2001–2011. http://drfosterintelligence.co.uk/wp-content/uploads/2011/11/Hospital_Guide_2011.pdf (accessed Dec 9, 2011).

5 Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet* 2010; **375:** 1609–23.