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Hazards of widespread use of erythromycin for preterm prelabour rupture of membranes

Sir—The widespread, and often inappropriate,[1] use of broad-spectrum antibacterial drugs has led to the emergence of many antibiotic-resistant organisms. Erythromycin-resistant organisms are increasingly reported and include Group B streptococcus, the most common cause of early-onset neonatal sepsis.[2] Furthermore, early-life exposures are recognised as an important factor in the immunological health of children. S Murch[3] suggested that the significant rise in childhood allergy in developed countries may be related to abnormal initial gut colonisation of infants as a result of obstetric and neonatal practices.

The ORACLE 1 study by Sara Kenyon and colleagues[4] is the only randomised controlled study to assess the use of erythromycin, co-amoxiclav, or both for preterm prelabour rupture of membranes. The investigators found that use of these antibiotics did not lead to a significant reduction in the composite primary outcome measure and its components (neonatal death, chronic lung disease, and major cerebral abnormality on ultrasound scan) when all mothers and babies were included in the analyses. A subgroup analysis of singletons only showed that fewer women had the composite primary outcome in the erythromycin group than in the other groups. Kenyon and co-workers recommended erythromycin for preterm prelabour rupture of membranes. However, in an accompanying Commentary, Mary Hannah[5] argued that use of erythromycin should be limited to specific situations in which benefits clearly outweigh risks. There have been no studies of the microbiological effects of erythromycin in mothers and babies.

In the UK, obstetric units in the Thames region were surveyed 1 year after publication of the ORACLE 1 study to find out if the Kenyon and colleagues' recommendations had affected erythromycin-prescribing practice. 32 of 45 hospitals surveyed had a protocol for antibiotic prescription in preterm prelabour rupture of membranes. The antibiotic chosen most frequently was erythromycin (erythromycin in 22 hospitals, penicillin in five, co-amoxiclav in two, ampicillin in one, and cephradine in one). 16 units adopted erythromycin use after publication of the ORACLE 1 study—11 had previously used co-amoxiclav, five had used penicillin, and one had not used antibiotics.

Of the 45 units, four used erythromycin rarely or never (less than once per week), 34 units prescribed erythromycin 1–5 times a week, and six units prescribed it 5–10 times a week. No unit reported prescribing erythromycin for more than ten patients per week. From these data, we estimate that between 60 and 230 mothers per week are prescribed erythromycin just within the Thames region.

Despite this increasing use of erythromycin for preterm prelabour rupture of membranes, many questions remain unanswered—for example, the potential for drug resistance, the emergence of unusual organisms, and the possible disruption of early colonising bacteria and subsequent effect on child health. The benefits of erythromycin for chronic lung disease and brain damage are unclear and follow-up studies are needed. In the meantime, widespread use of a broad-spectrum antibiotics may eliminate protective commensal flora, especially in the gut, and encourage antimicrobial resistance and the emergence of unusual and invasive bacterial strains, an issue already highlighted by WHO, the European Union, and the UK's Department of Health. Alteration of neonatal gut flora to more pathogenic species is potentially harmful. ORACLE 1 is an excellent and instructive study, but the potential benefits of erythromycin for preterm prelabour rupture of membranes must be balanced with the potential hazards of widespread use of broad-spectrum antibiotics.

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El Niño and drought in southern Africa

Sir—Extreme phases of the El Niño Southern Oscillation (ENSO) have been linked to precipitation anomalies in many areas of the world.[1] Precipitation can increase during warm (El Niño) or cold (La Niña) ENSO events in some areas, whereas in others drought might be more likely. For example, in southern Africa droughts tend to happen in the December to March rainy season after onset of an El Niño event.[1]

The 1997–98 El Niño event was the largest this century; it was predicted with a high degree of certainty, and this prediction was used systematically by the international community to prepare societies for climatic extremes. Decision-makers in southern Africa knew about the possibility of region-wide rainfall below normal levels.[2] However, although many of the climate anomalies typical of an El Niño event took place around the globe,[3] the feared devastating drought in southern Africa did not happen.

The present status of sea-surface temperatures in the tropical Pacific Ocean indicate a moderate El Niño event (http://iri.columbia.edu). Any climatic and socioeconomic effects of this event will arise in southern Africa in the first half of 2003.

The 1997–98 experience notwithstanding, southern Africa is a drought-prone region, in which disasters associated with drought have historically had a significant association with the occurrence of El Niño.[4] We assessed the historical patterns of drought disasters during El Niño events in the region. We obtained the number of years (during 1980–2001) in which drought disasters were recorded for every country in southern Africa (Botswana, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe) from the EMDAT global disaster

history database (http://www.cred.be). With a logistic regression model, we compared the likelihood of drought disaster occurrence during the El Niño dissipation year with the likelihood at other times. We recorded a 120% increase in probability of drought disaster in the year after El Niño onset (p=0·0005). Health consequences of previous drought emergencies have included rapid increases in morbidity and mortality related to malnutrition, diarrhoeal diseases (including cholera), and measles.

Understandably, the climate community in southern Africa has been reluctant to make dire drought warnings after the 1997–98 experience. However, parts of southern Africa are already in a precarious state. The region is presently the subject of a US$611 million United Nations appeal (http://www.reliefweb. int). On the basis of the present El Niño, good rains are unlikely to bring respite to the region in the coming (2002–03) season. It is precisely this combination—high probability of a hazard event coupled with high vulnerability—that is a recipe for disaster.[5]

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Bridges to Iran

Sir—Allon Friedman admonishes Stuart Spencer and David Sharp for being naive in their description of a visit to Iran (Nov 23, p 1694).[1] Like Chris Burns-Cox (Nov 23, p 1694)[2] we visited Iran, and provided a training workshop for staff at the Ministry of Health in Tehran, sponsored by WHO. Attendees were young, articulate, and intelligent, and Ministry staff open and welcoming. Women respect the dress code—most wear the chador in public—but this outfit conceals their bodies, not their faces or minds. The professional women we dealt with were direct with us, and were prepared to speak their mind on any issue. These women think they are misrepresented in the Western media.

Iran is a young country with great internal tensions between clerics and reformers. The Iranian government has sponsored some internal and external actions that no enlightened person can lend support to. So have many other governments.

People who visit Iran are left with a feeling of hope that a progressive democratic Islamic republic can emerge if the true aspirations of most people can be realised. Moral support, education, and trade will aid this, not the cynical condemnation meted out by Friedman.

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Cause of death among passengers on the *Titanic*

Sir—I would like to re-examine the cause and manner of death among the passengers on the *Titanic*.

On April 14, 1912, at 2340 h, the ship struck an iceberg and sank off the Newfoundland Coast in the North Atlantic ocean. The temperature of the water was −2·2°C. There were 2201 people aboard, and all 1489 people who fell into the water were recorded as having drowned. There were 3560 lifebelts aboard the ship, so presumably all those who died were wearing lifebelts; 712 people were able to leave the ship in lifeboats. The rescue ship *Carpathia* arrived at the site in 1 h 50 min. The crew were able to rescue everyone on board the lifeboats, but all the others were left for dead, even though they were presumably floating with their heads above water. Keatinge[1] states that, in the official report, the cause of the ship's sinking took precedence over the question of cause and manner of death.

Orlowski[2] has found 17 cases of good outcome after drowning and hypothermia when appropriate resuscitative measures, including rewarming and cardiopulmonary resuscitation, were available. Full recovery is possible in many who have been ruled as dead, even after submersion of up to 40 min.[3] The *Titanic* passengers were only exposed to hypothermia and not to cold-water inhalation into the lungs. Aspiration might have occurred after they became unconscious. Therefore, the primary cause of death was immersion hypothermia with its attendant consequences, and not drowning as recorded in the official report.

The current consensus of opinion is that patients should not be considered dead until they return to near normal core temperature and do not respond to cardiopulmonary resuscitation.[3] Many of the presumed dead were probably alive. The above factors must be incorporated into decision making before pronouncing dead someone who is pulled out of the water in any circumstances.

Finally, using the International Classification of Diseases,[4] I hereby reclassify the cause and manner of death in the victims of the *Titanic* disaster as "accidental hypothermia" (code 991.6) and "accident to water craft causing submersion" (code E830), respectively.

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DEPARTMENT OF ERROR

A new NOS2 *promoter polymorphism associated with increased nitric oxide production and protection from severe malaria in Tanzanian and Kenyan children*—In this Mechanisms of disease article by M R Hobbs and colleagues (Nov 9, p 1468), the reference column in Figure 4 (p 1473) should read, from top to bottom: "This paper, This paper, 9, 11, 11, 10, 10, This paper, 11, 29".

Lysosomes and drug resistance in malaria—In this Commentary by David Warhurst and colleagues (Nov 16, p 1527), reference 16 should have read "Martiney JA, Cerami A, Slater AFG. Verapamil reversal of chloroquine-resistance in the malaria parasite *Plasmodium falciparum* is specific for resistant parasites and independent of the weak base effect. *J Biol Chem* 1995; **270:** 22393–98." The reference in the text should have read "was predicted by Martiney et al[16] in 1995." The e-mail address for the corresponding author should have read "(e-mail: David.Warhurst@lshtm.ac.uk)".