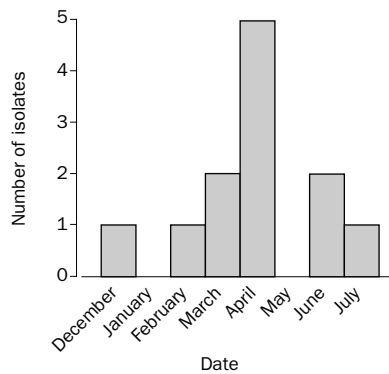




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Rate of isolation of *C. tropicalis* between December, 2001, and July, 2002

agents, fluorouracil and cyclophosphamide had been administered to all infected patients. We therefore examined sealed vials of these two drugs. We were able to grow *C. tropicalis* from the three batches of fluorouracil available in the hospital pharmacy. We informed the manufacturers of our findings and the drug was recalled across Pakistan. All patients who had received the contaminated drug are being followed up.

Routine surveillance led to the prompt control of a possible outbreak of nosocomial fungal infection in an immunocompromised population. Furthermore, iatrogenic infections across the country were prevented because of the timely withdrawal of the drug from the market.

Unfortunately, little attention is paid to infection control in developing countries. Reasons for such neglect include apparent associated high cost of surveillance, inadequate microbiological support, paucity of trained infection-control personnel, lack of hand-washing facilities, and poor quality-control measures of pharmaceutical companies.^{4,5} Moreover, absence of record keeping in drug prescribing with a non-existing patient tracking system makes it impossible to gather reliable data.⁴

Our findings reinforce the need for active and effective infection control activity and systems for notification of adverse drug events at a national level. We urge international agencies to encourage and to lend support to such programmes, particularly in countries with a primitive health-care infrastructure.

We thank Elizabeth M Johnson for her assistance and support, and for her help in examination of specimens.

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SARS transmission: language and droplet production

Sir—Severe acute respiratory syndrome (SARS) is transmitted via droplets spread by infected individuals. Droplets are generated when patients cough and, to a lesser extent, when they talk during the early stages of disease. I believe that the efficiency of transmission of SARS by talking might be affected by the language spoken.

As of mid June, 2003, the number of probable cases of SARS in Japan remained zero, whereas there were more than 70 cases diagnosed in the USA.¹ There were about 3·1 million Japanese travellers to mainland China, Hong Kong, and Taiwan in 2000,² and about 2·3 million US citizens visited these areas in 2001.³ With such large numbers of visitors from Japan and USA, why have no Japanese visitors contracted the virus? Here, I propose a hypothesis.

The Chinese language has an aspiration/non-aspiration pronunciation system: the consonants p, t, k, q, ch, and c, when placed in front of vowels, are pronounced with a strong breath, by contrast with b, d, g, j, zh, and z. In English, but not in Japanese, p, t, and k are pronounced with a similar accompanying exhalation of breath. Furthermore, the p sound is not used as frequently in Japanese as in English. Aspiration could produce droplets.

A Chinese attendant in a souvenir shop probably speaks to American tourists in English, and to Japanese tourists in Japanese. If the shop assistant is in the early stages of SARS and has no cough, I believe American tourists would, hence, be exposed to the infectious droplets to a

greater extent than would Japanese tourists.

I thank Professors S Yabuki, Yokohama City University, and T Kohno, Otsuma Women's University, for discussions on cultural and linguistic aspects of Chinese and American people.

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Uncertainty in SARS epidemiology

Sir—Oliver Razum and colleagues (May 17, p 1739)¹ rightly describe the difficulty inherent in fitting cumulative case data for severe acute respiratory syndrome (SARS) to exponential functions and then extrapolating the resulting curve.² There are additional subtleties involved in these calculations that, if not understood, can lead to misleading conclusions.

The basic reproduction number, R_0 , is defined as the expected number of cases in the next disease generation caused by the index case in a naive population.³ This number provides a threshold criterion for an infectious agent to invade. Put simply, if R_0 is greater than 1, there are more cases in the next disease generation, and an epidemic will occur. Thus, R_0 is defined for an infectious agent in a particular population. In less formal settings, R_0 is sometimes thought of as an intrinsic property of an infectious agent.

How should one estimate R_0 for SARS? In Hong Kong, Vietnam, Thailand, Toronto, and Singapore, the first disease generation after the index case produced more than one secondary case, but in a few households, there were no secondary cases.⁴ Worldwide attention and infection control after the identification of initial cases probably reduced the number of cases per case in subsequent disease generations. Thus, the cumulative case data provide only very limited information

about the intrinsic growth rate of SARS epidemics in the absence of control. In fact, cumulative case data reflect more information about subsequent disease generations, and little information about the index case. The proper conclusion from the cumulative case data for SARS is that the reproductive number R_0 , a general term for the number of cases per case, has been near 1 over the course of an epidemic, including the generations before and after control. What was happening before control?

Infectious disease epidemics are birth-death processes, so an exponential model is the proper basis from which to reason, not a linear one; the geometric mean is the proper statistic of measure of the growth rate, not the arithmetic mean. We note that the cumulative number of cases is linear when $R_0=1$, but one should not choose a linear model to reason about epidemics, a priori, any more than one should use a linear model to compute the future value of an annuity.

Assuming conditions remain the same and R_0 is really less than 1, control measures will eventually eradicate SARS, but it may take several generations. However, conditions may change: transmission rates may be seasonal, the virus may mutate, or the efficacy of infection control may wane as people's fear subsides. Most seriously, if the number of active cases gets very large, it might limit the amount of resources that can be devoted to control, per case, and the epidemic may escape control. If we are lucky, control will succeed and we will never know how bad things might have been.

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Age of diagnosis of cystic fibrosis

Sir—We appreciated the Seminar on cystic fibrosis by Ratjen and Doring (Feb 22, p 681),¹ in which they drew attention to age of diagnosis in most patients. Age is of interest to us, because we cared for a man in whom cystic fibrosis was diagnosed at age 65 years.

The patient underwent genetic testing after his grandniece was diagnosed with the disorder. She presented as a young girl with failure to thrive, recurrent pulmonary infections, had positive sweat tests, and was homozygous for the delF508 mutation. Both parents were heterozygous for this mutation, but her mother's sister tested heterozygous for the R117H mutation. Further family testing of the girl's maternal grandmother showed she was a compound heterozygote for delF508 and R117H. This woman had two brothers: one died, but had diabetes mellitus and chronic liver disease of unknown cause during life. The other was our patient.

In November, 1977, aged 43 years, our patient underwent appraisal for child adoption. He and his wife were infertile; only she had undergone investigation thereof. Systematic inquiry noted an alcohol intake of at least 40 units a week over many years, and examination established hepatosplenomegaly. Liver test results were bilirubin 15 $\mu\text{mol/L}$ (normal range 5–17), albumin 37 g/L (40–48), alkaline phosphatase 141 IU/L (20–90), aspartate transaminase 27 IU/L (5–20), γ -glutamyl transpeptidase 378 IU/L (5–38), and prothrombin time 18 s (12.5–14.5).

After 4 months, our patient's employer requested independent investigation of hyperglycaemia and hepatosplenomegaly. Despite abstinence from alcohol, liver test results were largely unchanged. Cirrhosis was evident on liver biopsy specimen, but features of acute-on-chronic ethanolic liver disease, namely steatosis, Mallory's hyaline, and lobular neutrophil infiltration, were absent. Other potential causes of chronic liver disease were eliminated on the basis of normal blood work, negative serological findings, and stains on the biopsy sample. Barium contrast radiography showed oesophageal varices.

In 2000, genotyping showed that the patient was a compound heterozygote for delF508 and R117H. When we met him in 2001, he had limited vision (diabetic retinopathy), difficulty gaining weight (61.1 kg), loose stools, and continuing evidence of chronic liver

disease. He had no lung symptoms and confirmed being a lifelong non-smoker. Small-bowel function was normal, but a pancreatic function (fluorescein dilaurate) test result was borderline. Before enzyme supplements could be established he developed pneumonia and died.

Post-mortem examination showed secondary biliary cirrhosis, splenomegaly, small oesophageal varices, bronchopneumonia bilaterally, renal papillary necrosis, and diabetic nephropathy. The pancreas was completely devoid of exocrine, and to a lesser extent endocrine, tissue. Pancreatic ducts were strikingly dilated as a result of dense eosinophilic mucin plugging.

This case is notable for the age at which cystic fibrosis was diagnosed. The absence of lung symptoms almost certainly contributed to this delay. Moreover, despite evidence to the contrary, ethanol (alone) was assumed to have caused liver disease. Presence of both diabetes mellitus and infertility at that time (1978) could have allowed the diagnosis to be made, although genetic testing did not exist then.

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Trading ideology for dialogue: an opportunity to fix international aid for health?

Sir—Ines Périn and Amir Attaran (April 5, p 1216)¹ are wrong to posit that the continued ill health of poor people is the consequence of “ephemeral aid trends”. The factors that result in high degrees of ill health in the developing world are far more complex than they suggest. Changing approaches to use of development aid to improve health systems in developing countries are not the result of donor ideologies but are largely reactions to emerging evidence of what works and what does not in improving the performance of health systems.

Périn and Attaran's ideal health aid model, if ever adopted, would be a disaster for the poorest. To understand why we need look no further than the evidence already emerging from the *Global Fund for AIDS, Malaria, and Tuberculosis* that the authors draw our attention to—money diverted to