

infections. The spread of CTX-M-positive bacteria considerably changes the way we think about treating community-acquired infections and limits the oral antibiotics that may be administered. This finding has major implications for treating children, who should not be given fluoroquinolones and tetracyclines.

The observation that different *bla*<sub>CTX-M</sub> alleles, located on plasmids of different sizes, were involved in clinical infections caused by distinct *E. coli* clones implies that CTX-M enzymes may become widespread in the community. A possible association of *bla*<sub>CTX-M</sub> genes with insertion sequences like *ISEcp1B* might have contributed to the enhanced expression and mobilization of *bla*<sub>CTX-M</sub> genes among *E. coli* isolates (7). The apparent dissemination of CTX-M producers could represent a substantial barrier in the treatment of community-acquired infections. Additionally, severely ill patients treated in the outpatient setting may transmit such resistant organisms to hospitalized patients.

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## Age and Transmissible Spongiform Encephalopathies

**To the Editor:** Bacchetti (1) notes “Our findings suggest that the possibility should not be discounted that biological factors peaking in the third decade of life may promote variant Creutzfeldt-Jakob disease (vCJD) prion replication and consequent development of disease.” Such age specificity of disease risk may be a general feature of transmissible spongiform encephalopathies, which suggests that a general mechanism should be sought. A likely candidate for this mechanism is senescence-related immune system defects.

In a study of scrapie outbreaks in

four sheep flocks, the incidence of clinical cases peaked in sheep 2–3 years of age, despite very different forces -of- infection at work and very large differences in disease incidence (2). Similar age specificity has been observed in cattle infected with bovine spongiform encephalopathy (3), which is believed to be the causal agent of variant Creutzfeldt-Jakob disease. There is evidence that an age-specific peak in prevalence also occurs in chronic wasting disease, a laterally transmitted spongiform encephalopathy of North American cervids, specifically elk, mule deer, and white-tailed deer. For example, data on prevalence of chronic wasting disease in mule deer (Figures 4B and 4A of [4]) suggest the existence of age-specific peaks. In aggregate, these observations suggest that a general mechanism might produce the marked decline in disease risk as age increases.

In 1979, Dickinson and Outram (5) conjectured that, in some experiments, scrapie responsiveness is the opposite of what one normally expects with an infection, “raising the possibility that, far from being inimical, some part of the host’s immune system is essential and may even play the role of a Trojan Horse for these agents when infection occurs by a peripheral route.” This theory appears well founded for transmissible spongiform encephalopathies in general. Disease-associated forms of resistant prion protein (PrP<sup>Res</sup>) are likely transported from the gut to lymphoid tissue by cells such as migrating intestinal dendritic cells (6). Once in the lymphoid tissue PrP<sup>Res</sup> appears to be amplified by follicular dendritic cells (6) and then enters the nervous system. Defects in either the complement pathway or follicular dendritic cells result in resistance to peripheral scrapie infection (7,8), and this resistance likely occurs for peripheral transmissible spongiform encephalopathy infections in general.

Both in vitro and in vivo animal and human studies demonstrate age-related declines in both humeral and cellular components of the immune system (9). In old (23 months) mice, the normal functioning of follicular dendritic cells appears to be strongly impaired when compared with young mice (10); according to researchers, "Antigen transport was defective and only a small fraction of antigen transport sites developed." (10). Furthermore, follicular dendritic cells were ultrastructurally atrophic, retained little antigen, and produced no iccosomes. By interfering with normal follicular dendritic cell function, age likely has the same effect on transmissible spongiform encephalopathies as has been observed due to dedifferentiation of follicular dendritic cells (8). Senescence of the immune system function could interfere with transmissible spongiform encephalopathy pathogenesis in other ways as well, such as impairing migrating intestinal dendritic cells or complement pathways involved in complexing PrP<sup>Res</sup> to follicular dendritic cells.

This hypothesis could be readily tested by intracerebral versus peripheral PrP<sup>Res</sup> challenge of young versus old animals. Because the intracerebral challenge bypasses the immune system portal, old, peripherally challenged animals should show a disproportionate reduction in disease risk if immune system senescence is important in regulating pathogenesis.

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## SARS Epidemiology Modeling

**To the Editor:** To assess the effectiveness of intervention measures during the recent severe acute respiratory syndrome (SARS) pandemic, Zhou and Yan (1) used Richards model, a logistic-type model, to fit the cumulative number of SARS cases reported daily in Singapore, Hong Kong, and Beijing. The key to using mathemati-

cal models for SARS epidemiology is understanding the models (2). In the Richards model (1), the function  $F(S)$  in the model was described as measuring "the effectiveness of intervention measures." The parameters in  $F(S)$ , namely, the maximum cases load  $K$  and the exponent of deviation  $a$ , depict the actual progression of the epidemic as described by the reported data. In other words, the parameter estimates are used to quantify end results of the intervention measures implemented during the outbreaks. Simply put, the all-important question of "what if?" was not answered by their result. To gauge the effectiveness of intervention measures, one should consider a more complicated model with variable maximum case load and growth rate ( $r$ ) that highlights the time-varying nature of an epidemic and its dependence on the intervention measures implemented during the epidemic.

Predicting the trend of an epidemic from limited data during early stages of the epidemic is often futile and sometimes misleading (3). Nevertheless, early prediction of the magnitude of an epidemic outbreak is immeasurably more important than retrospective studies. But how early is too early? Intuitively, the cumulative case curve will always be S-shaped and well-described by a logistic-type model. The essential factor is the time when the inflection of the cumulative case curve occurs, i.e., the moment when a rapid increase in case numbers is replaced by a slower increase. Since the inflection point, approximated by  $t_m$  (1), dictates the point in time when the rate of increase of cumulative case numbers reaches its maximum, the moment marks the key turning point when the spread of the disease starts to decline. As long as the data include this inflection point and a time interval shortly after, the curve fitting and predicting future case number will be reasonably accurate.

To illustrate this point more pre-