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Improving clinical management of patients with severe yellow fever

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Despite the availability of a highly efficacious vaccine against yellow fever,[1] an unprecedented resurgence of the virus has recently occurred, initially in densely populated urban areas of Angola and the Democratic Republic of the Congo in 2016,[2] and subsequently as an ongoing epizootic disease with sylvatic transmission encroaching on periurban areas in Brazil between 2016 and 2018.[3] Between January, 2016, and June, 2018, 2153 confirmed cases and 744 deaths were recorded in Brazil, with most cases occurring in the southeast region according to the Ministry of Health of Brazil.[4] Yellow fever is feared because severe disease has a high case fatality rate. However, data correlating virological or patient characteristics with death are scarce.

In *The Lancet Infectious Diseases*, Esper Kallas and colleagues[5] report on their clinical experience with patients with yellow fever admitted to intensive care units in two tertiary hospitals in São Paolo City, Brazil. 27 (36%) of 76 patients with laboratory confirmed yellow fever died, highlighting the seriousness of this disease. The authors report on clinical, laboratory, and virological parameters documented on the day of admission and assess their predictive value for mortality. In a multivariate regression model, they found that older age, elevated neutrophil count, elevated liver transaminases, and higher viral load were independently associated with death. All 11 (100%) patients with neutrophil counts of 4000 cells per mL or greater and viral loads of 5·1 $\log_{10}$ copies/mL or greater died (95% CI 72–100).

The strength of this study[5] includes the prospective recruitment of a relatively homogeneous cohort (only two tertiary hospitals involved, recruitment over a short study period, and the same health-care team providing patient care). All patients were infected with the same virus genotype, the modern lineage (sub-lineage 1E) of South American genotype I. Therefore, confounding factors that might have influenced the disease outcome in addition to clinical and laboratory parameters have been minimised, and the study was able to investigate the parameters of interest.

A limitation of this study[5] was that only patients admitted to the intensive care unit were included, thereby skewing the results towards the most severely ill people, and no comparison can be made with patients with a less severe disease course. In fact, most yellow fever infections are asymptomatic or subclinical. Patients with symptomatic disease have fever, headache, chills, muscle pain, and nausea, usually limited to less than a week. Around 10–25% of those with symptomatic yellow fever infection develop severe disease as described in Kallas and colleagues' study, with haemorrhagic manifestations, and heart, kidney, and liver damage, and a case fatality rate of 20–50%.[6] Furthermore, the interval between day of onset and admission might vary considerably depending on host factors, viraemia levels, and other unknown factors. Therefore, additional analysis of the parameters at different timepoints would have been more appropriate, since onset of illness is a more robust and objective parameter than day of admission, especially for the kinetics of the viral load, which are highly time dependent.

Some of the findings of this study are as expected.[5] Older age is also associated with more severe outcomes in other flavivirus infections, including Japanese encephalitis[7] and West Nile encephalitis.[8] Previous studies have identified jaundice, leukocytosis, and high concentrations of hepatic transaminases, bilirubin, and blood urea nitrogen as risk factors for death.[6] However, a potential novel finding is the higher viral load associated with fatal outcomes, suggesting a possible causative role, as has been shown in a hamster model.[9] This finding has implications for improving understanding of the pathogenesis of severe disease and the potential role of early antiviral treatment in mitigating severity.

This study[5] has several other implications. First, predictive markers associated with poor outcome could help triage patients and intensify monitoring and prompt implementation of life-saving interventions, prioritising patients who might benefit from liver transplantation. Second, at a time when already fragile health-care systems are overwhelmed by an influx of patients with yellow fever, as during the Brazil outbreak in 2017–18, application of simple clinical and laboratory evaluations might help improve triage algorithms and resource allocation.

Most importantly, severe cases and fatal outcomes due to yellow fever would not occur if vaccine coverage was high in all at-risk areas. Although overall substantial increases in vaccine coverage have occurred since 1970, notable gaps remain in contemporary coverage within yellow fever risk zones, requiring between 394 million and 473 million more people to be vaccinated to achieve the 80% population coverage threshold recommended by WHO.[10] Until we achieve such high coverage, yellow fever remains a global threat[11] through rapid exportations via travellers, such as in 2016 between Angola and China.[12] The world needs to be better prepared in terms of preventive vaccination, diagnostic capabilities,[13] and improved clinical management. This study[5] is a step towards improving clinical management of patients with yellow fever.

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Novel insights into pneumococcal lineages in the vaccine era

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In *The Lancet Infectious Diseases*, Stephanie Lo and colleagues[1] provide an interesting description of the genetic structure of 3233 pneumococcal strains causing invasive pneumococcal disease in children younger than 3 years from six countries where pneumococcal conjugate vaccines (PCVs) had been implemented.

The implementation of PCVs has been a huge success, with a substantial decrease in the incidence of invasive pneumococcal disease and non-invasive infections, as well as a reduction in antibiotic resistance.[2] Nevertheless, two facts have emerged: we have learned from carriage studies that *Streptococcus pneumoniae* remains a major bacterial species in the nasopharyngeal microbiota of children, because they carry *S pneumoniae* as much as they did before PCV implementation,[3,4] and pneumococci remain one of the leading causes of bacterial infections.[2]

To date, the surveillance programmes that aim to assess the impact of PCVs are mainly based on