affect the epidemiology of typhoid fever in the future, the feasibility of implementing specific catch-up vaccination strategies, and a careful assessment of willingness to pay. Systems for collecting better data on typhoid-specific mortality should also be prioritised. The high-level economic case for TCV immunisation in countries with medium and high incidence of typhoid fever has been made; it is now time to get down to the details of how to best deliver TCVs to save children's lives.

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The authors declare no competing interests.

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Meningitis: a frequently fatal diagnosis in Africa

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In *The Lancet Infectious Diseases*, Mark W Tenforde and colleagues[1] report the mortality findings of the 2004–15 Botswana national meningitis survey. This was a nationwide laboratory-based audit with linkage to the national HIV and death registries. Data from all patients with culture-confirmed pneumococcal and tuberculous meningitis, and all patients with culture-negative meningitis with CSF white cell count (WCC) above 20 cells per µL were included in their analyses, in addition to a random selection of patients with CSF WCC of up to 20 cells per µL. 10-week and 1-year mortality was 47% (112/238) and 49% (117/238) for pneumococcal meningitis, 46% (22/48) and 56% (27/48) for tuberculous meningitis, and 41% (1181/2900) and 49% (1408/2900) for culture-negative meningitis. Most deaths occurred within the first 10 weeks after lumbar puncture. Across the different diagnostic groups 64–76% of patients had documented HIV infection. Cryptococcal meningitis 1-year mortality of 65% was previously reported from this cohort.[2]

Outside of Africa, linkage of multiple national datasets to improve the understanding of meningitis and other diseases happens more often;[3,4] it is exciting to now see this powerful epidemiological method in use with African datasets, in this report and others.[5] Collection of large-scale, high-quality, routine data in electronic databases has great potential to enhance epidemiological assessment of common diseases, diagnostic and management practices, and outcomes, and to direct and prioritise interventions and inform policy, practice, and research.

The high mortality reported by Tenforde and colleagues[1] is similar to the mortality in other meningitis cohorts in Africa,[6–8] although the lack of details regarding presentation and management in this report (eg, clinical signs and symptoms on presentation, history of length of illness before presenting to hospital, antimicrobial therapy, length of treatment, use of adjuvant therapy) limits the ability to evaluate the major health system contributors. Late presentation, reduced access to optimal diagnostics and antimicrobial therapies, suboptimal acute care, and HIV co-infection have been implicated as major contributors in previous reports.[7,9] Of concern is that over the 12-year period covered by Tenforde and colleagues,[1] HIV was still associated with more than two-thirds of meningitis diagnoses and there was no reduction in meningitis mortality over time, despite the scale-up of antiretroviral therapy in Botswana. Reasons for patients continuing to present with complications of advanced HIV (such as meningitis) despite successful antiretroviral therapy programmes include delayed HIV diagnosis and disengagement from antiretroviral care.[10]

A surprising finding was the high mortality in patients with culture-negative meningitis, regardless of the presence of CSF pleocytosis. The authors postulate that this high mortality could be due to missed diagnoses. During the study, tuberculosis culture was done at the request of clinical providers at a central national tuberculosis reference laboratory on 1723 (9%) samples, with acid-fast bacilli microscopy done on 2524 (13%). Together with the low sensitivity of these tests and the suboptimal sample volumes often sent in routine clinical services, these results imply that a proportion of patients with culture-negative meningitis very likely had undiagnosed tuberculous meningitis. The proportion of patients who were treated for tuberculosis could not be established given the study methodology. Additionally, CSF cryptococcal antigen testing was largely unavailable during the study period, potentially resulting in missed diagnoses. Diagnoses of bacterial meningitis were likely also missed in patients who had received antibiotics before lumbar puncture, or due to technical limitations of culture. The indication for lumbar puncture in some patients might also have been prompted by delirium caused by fatal non-neurological infections (such as bacterial sepsis or disseminated tuberculosis), frequent in advanced HIV.[11] This may be particularly relevant for those without CSF pleocytosis.

There is an urgent need for improved rapid diagnostics for meningitis in other low-income and middle-income countries in Africa. Use of better diagnostic modalities, including multipathogen molecular panels, has improved diagnostic yield among patients presenting with meningitis,[12] but there are conflicting opinions about the benefits of routine implementation.[13] Even with the implementation of such testing modalities, more than half of patients with meningitis might not have pathogens detected with available methods in high-income settings.[12,13] In a Ugandan study,[6] implementation of routine liquid medium culture for tuberculosis and the Xpert MTB/Rif assay of CSF from adults with meningitis and negative CSF cryptococcal antigen did not change in-hospital mortality significantly. However, the sensitivity of the second-generation Xpert Ultra assay of CSF has significantly improved.[14]

Better access to existing diagnostics and novel diagnostics alone are unlikely to change long-term outcomes,[6] unless coupled with interventions to ensure earlier presentation, adherence to evidence-based treatment guidelines, and availability of antimicrobials at the facilities where patients present. Adequately trained clinical staff in functional facilities are also required to make a positive impact on outcomes. As countries plan for improvements in health-care delivery, the focus should be on broadening coverage, but also on the key role of improved health services.[15]

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AvG has received grants and travel expenses from Pfizer and Sanofi. GM has research collaborations with Joe Jarvis, an author of the Article.

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Improving clinical management of patients with severe yellow fever

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Published **Online** May 16, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30122-7

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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.