investigation (figure 1) and 0·85 (0·81–0·89, I^2=95·6%) for passive case finding. Restricting pooled analysis to confirmed active tuberculosis, the pooled estimates would be 0·08 (0·05–0·12, I^2=93.5%) for household contact investigation and 0·92 (0·88–0·95, I^2=93·5%) for passive case finding. Such findings may highlight the key role of passive case finding in the control of tuberculosis.[3]

The public-health impact of household contact investigation is expected to be sustantially lower than that of passive case finding. The incubation period of tuberculosis varies from a few weeks to a few decades and household contact investigation focuses on examination at only one point of time. Additionally, most infected hosts do not develop disease. Thus, it may be more cost effective for low-income and middle-income countries to spend limited public-health resources on improving accessibility of a patient-friendly health-care infrastructure[4] and on increasing public awareness of tuberculosis, upon which passive case finding heavily relies. The feasibility of achieving the case detection target of 70% by passive case finding has been substantiated by early studies in India, which showed that 70% of people with smear-positive tuberculosis had symptoms and sought health care.[5]

In conclusion, although household contact investigation may be considered in low tuberculosis incidence, high-income countries,[6] the available evidence from meta-analysis does not favour household contact investigation in low-income and middle-income countries. The importance of improving case detection among symptomatic patients self-reporting to health services cannot be over-emphasised.[3]

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Efficacy and safety of cefepime

A Review by Dafna Yahav and colleagues[1] found that cefepime compared with other beta-lactam antibiotics was associated with increased all-cause mortality, a difference driven by the febrile neutropenia subset of patients (risk ratio [RR] 1·26, 95% CI 1·08–1·49).

To better understand these differences and to determine if infectious or non-infectious causes impacted the mortality results, we reviewed the 19 studies comprising the neutropenic fever subset of these data. Whenever possible, the actual articles were obtained from the FDA website or through medical library holdings. Where abstracts were the only information available or data within the published literature were not adequate to answer all questions, every attempt was made to contact the original authors. Studies were specifically reviewed for data including number of deaths in each arm and causes of death.

For these 19 studies, complete cause of death information was obtained for 11 and partial cause of death information for two. These 13 studies included 64% of the all-cause neutropenic deaths in Yahav and colleagues' paper. Review of causes of death among these patients found no marked differences between cefepime and beta-lactam comparator for any infectious cause (table 1). A higher proportion of patients died secondary to progression of their underlying disease in the cefepime arm compared with the other beta-lactam arm. Furthermore, no patients were determined to have died directly as a result of receiving therapy with any agent, including cefepime (references 2–14, and personal communication with the lead author of reference 4).

	Cefepime deaths (%)	Beta-lactam comparator deaths (%)
Progression of underlying disease	27 (36)	10 (22)
Invasive fungal infection	6 (8)	6 (14)
Bacterial infection	9 (12)	5 (11)
Unknown sepsis	23 (31)	19 (42)
Renal failure	2 (3)	0
Hepatic failure	1 (1)	0
Haemorrhage/cerebral vascular accident	4 (6)	3 (7)
Other (pulmonary embolism, heart failure, myocardial infarction)	2 (3)	2 (4)
Total	74	45

Table 1: **Causes of death for cefepime and beta-lactam antibiotic comparators**[2-14]

Yahav et al propose two explanations in their paper for increased deaths in the cefepime arm: unrecognised cases of non-convulsive status epilepticus/encephalopathy or inadequate antimicrobial effects. Our review of the available causes of death did not find unrecognised cases of non-convulsive status epilepticus/encephalopathy among the study patients. More substantial discussion of increased altered mental status would have been expected if these cases were more frequently reported; however, this was not seen. The second explanation on the potential for inadequate antimicrobial response is refuted by the authors' own statement earlier in the paper that microbiologic failure was not significantly different between the cefepime and comparator arms (RR 0·92, 95% CI 0·84–1·02).[1]

We believe that practitioners have the right and the responsibility to question and review data presented in a meta-analysis, especially if those data challenge our normal conceptions about medical practice. As evidenced by the recently released FDA memo concerning their safety review of cefepime, acquisition of the data used by Yahav and colleagues has been difficult and has yet to be completed. If a government body cannot obtain the necessary information to complete their analysis in a reasonable period of time, how is the everyday practitioner to make prescribing decisions based upon the meta-analysis?[15]

Taken without critical examination, the meta-analysis published by Yahav and colleagues seems to implicate cefepime as the cause of higher mortality compared with that among patients treated with other beta-lactam antibiotics. In an era with limited development of new antimicrobials for resistant Gram-negative organisms, agents like cefepime have a very important role. Losing cefepime as a major antimicrobial for the treatment and prophylaxis of complicated infections would have a profound impact on both pharmacy and medicine. Experience with cefepime is extensive and there is a considerable literature to support the safety and efficacy of this drug for many serious infections. We must be careful not to place too much weight on a meta-analysis without substantial biologic plausibility.

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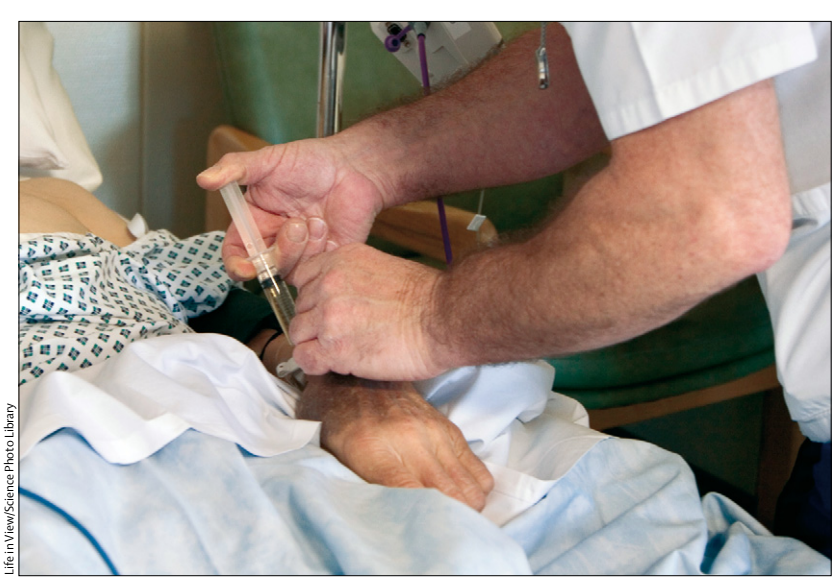
Authors' reply

All-cause mortality is the primary outcome when assessing treatment of severe infections because it is the most objective outcome and encompasses efficacy, adverse events, and superinfections. The main purpose of treating patients with severe infections is to prevent death.

Cause-specific mortality might have delineated better differences between treatment regimens, avoiding dilution with outcomes that are unrelated to infection and its consequences. However, the cause of death cannot be established clinically in most cases. In cancer patients many causes of death commonly co-exist, including underlying malignancy, background diseases, thrombocytopenia, fungal infections, chemotherapy, and other drug-related adverse events. The final event remains mostly undiagnosed without post-mortem studies. In much less complex situations the correlation between clinical and post-mortem-established causes of death was poor.[1–3] Among patients with haematological malignancies, clinician's cause of death was reclassified by an expert panel in more than 50% of cases.[4] Infection-related mortality, frequently reported in trials of febrile neutropenia, is a subjective outcome, liable to impression and interpretation. We certainly welcome the quest for truth following our systematic review. However, clinical assessment of the cause for death is probably not the way. Rather, responsible recording of sponsored trials should provide all-cause mortality data for all trials conducted to date. All-cause mortality should be compared, accounting for the adequacy of allocation concealment and whether intention-to-treat analysis was done in the trial.



Life in View/Science Photo Library

Non-infection-related causes for death should be distributed equally between trial arms in randomised controlled trials. Trent Towne and colleagues claim that more patients treated with cefepime died due to their underlying disease. If this was true, patient allocation must have been unbalanced at baseline, since the only difference between trial arms was the antibiotic given. This can probably occur with imperfect allocation concealment in trials testing a new antibiotic. But then, where is the evidence on the efficacy and safety of cefepime?

We did not base our conclusions on the outcome of microbiological eradication, defined in the subgroup of patients with microbiologically documented infection. The outcome of microbiological eradication does not encompass all patients with the disease and the selection of patients may be biased. Within this subgroup, microbiological eradication does not well represent the outcome that is relevant to the individual patient, since adverse events and superinfections are ignored.

In summary, our Review[5] reported all-cause mortality data extracted from 41 trials including 7388 patients. All-cause mortality was significantly higher with cefepime (RR 1·26, 95% CI 1·08–1·49, p=0·005). Although we could not explain the increased mortality, considering the significance of the results and the wide variety of alternative antibiotic treatments, we believe that it is reasonable to reconsider the use of cefepime until the US Food and Drug Administration reaches a definite conclusion concerning the safety of cefepime.[6]