

body, or what the effect of specialised burn wound care would be on the activity of the phages. In-vitro studies have shown a fast and strong inhibitory effect on phage activity by sulfadiazine silver and mupirocin creams.<sup>3</sup>

On the basis of current evidence I would still be prudent in advocating phage therapy as a solution to the global problem of multidrug-resistant bacteria. More high-quality research is needed to answer the questions raised about the use of phages.<sup>4</sup> Jault and colleagues' study shows that phages have some action on the colonisation of bacteria in humans, but whether the efficacy is good enough to have an effect on infection is yet to be shown.

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## Regimen design and pharmacokinetic–pharmacodynamic science: lessons learned

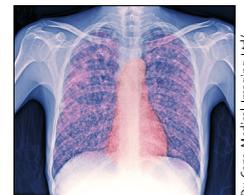
In *The Lancet Infectious Diseases*, Jung-Kyu Lee and colleagues report a study that substituted ethambutol with linezolid during the intensive phase of treatment for pulmonary drug-susceptible tuberculosis.<sup>1</sup> They randomly assigned patients into three groups: standard treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol, or linezolid (instead of ethambutol) at a dose of 600 mg/day for 2 or 4 weeks. The primary endpoint (ie, culture conversion at 8 weeks of treatment) showed no benefit of linezolid over the control.

Shortening tuberculosis therapy is the primary goal of improving tuberculosis treatment, requiring at least one bactericidal and sterilising drug protected by accompanying drugs to prevent acquired drug resistance.<sup>2,3</sup> Gillespie and colleagues previously evaluated whether ethambutol or isoniazid replaced by moxifloxacin in the intensive phase could shorten treatment duration to 4 months. Unfortunately, despite a more rapid decline in bacterial load, non-inferiority for the two moxifloxacin based regimens was not shown.<sup>4</sup> Absence of penetration of moxifloxacin in cavities and pharmacokinetic–pharmacodynamic science might explain the negative outcome of the study.<sup>5,6</sup>

Compared with moxifloxacin, the early bactericidal activity of linezolid is low,<sup>7</sup> making it less likely that using this drug during the intensive phase for 2 weeks or 4 weeks will be of additional value. Although

linezolid potentially possesses sterilising effects,<sup>8</sup> the short period of its use, in the presence of rifampicin makes it unlikely to be effective in this short period of time. As the authors rightly mention, the drug–drug interaction with rifampicin reducing the exposure of linezolid, and the lack of drug exposure measurements make it difficult to estimate whether optimal pharmacokinetic and pharmacodynamic targets were reached. Possibly rifampicin and its enzymatic induction reaching a maximum after approximately 2 weeks might explain the lack of difference in response between 2 and 4 weeks of linezolid. Probably after 2 weeks of linezolid, the linezolid levels fall below a certain threshold, which might result in a static instead of a bactericidal effect. Pharmacokinetic assessment at 2 and 4 weeks during the study could have answered this question.

Determining the dose of linezolid for the treatment of drug-susceptible tuberculosis is challenging, as the majority of evidence on its use is derived from multidrug-resistant-tuberculosis cohorts lacking concomitant use of rifampicin and often also isoniazid. Linezolid drug safety was a serious concern; the authors applied caution when dosing and setting the duration of linezolid use.<sup>9</sup> Concerning the dose, the expected exposure is likely to be sufficient to achieve the target area under the concentration–time curve to minimal inhibitory concentration ratio because the expected linezolid minimal inhibitory concentrations in drug susceptible



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isolates are likely to be low (ie, <1 mg/L). The combination of linezolid and rifampicin was evaluated earlier, and Brown and colleagues showed that a dose of 600 mg/day would achieve the linezolid area under the concentration–time curve to minimal inhibitory concentration ratio of 99 in the presence of rifampicin in 96% of patients.<sup>10</sup> With an optimal dose, the remaining issue is the treatment duration. Clearly, 2–4 weeks is too short as preclinical models showed that a period of at least 6 weeks was required to ensure sterilisation.<sup>11</sup>

Although the trial results did not show treatment-shortening potential, it showed that the addition of linezolid for 4 weeks was well tolerated in patients with drug-susceptible tuberculosis. This study paves the way for the evaluation of new studies, increasing the duration of linezolid treatment to 4 months. Moreover, newer more potent oxazolidinone analogues might bring greater interest to this approach.<sup>12</sup>

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## Public health burden of antimicrobial resistance in Europe



Antimicrobial resistance is one of the greatest challenges of the 21st century. Evaluation of the public health burden of antimicrobial resistance, which is needed to drive policy interventions, is done through estimates of clinical benchmarks (mainly morbidity and crude mortality) and economic indicators (direct costs, use of resources, and drug expenditures). Most of these estimates are restricted to high-income countries and retrieve data to fit the computation models from national surveillance of clinical samples, prevalence or incidence surveys, and retrospective cohorts.<sup>1,2</sup> The high heterogeneity of reporting of surveillance data and the paucity of estimates of the societal effects of antimicrobial resistance (such as reduced productivity due to illness) substantially underestimate the public

health burden. Global estimates are therefore limited in terms of generalisability of results and predictive values.<sup>3</sup>

In *The Lancet Infectious Diseases*, Alessandro Cassini and colleagues<sup>4</sup> measured the health burden of five types of antibiotic-resistant infection (invasive and non-invasive) caused by eight bacteria with 16 resistance patterns in the EU and European Economic Area (EEA). The estimates, presented as disability-adjusted life-years (DALYs), are shocking. The authors estimate that there were 671 689 (95% CI 583 148–763 966) cases of infections with antibiotic-resistant bacteria in 2015, of which 426 277 (63.5%) were associated with health care. These estimates correspond with an incidence of 131 (113–149) infections per 100 000 population and an attributable mortality of 6.44 (5.54–7.48) deaths

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