

Table S1 | Methods and references for data

Variable	Rationale and methods	References
<i>A. baumannii</i> infections per year	<p>A study of the US National Healthcare Safety Network (NHSN) found that <i>A. baumannii</i> causes 2.7% of hospital acquired infections in the US annually.¹ The US Centers for Disease Control and Prevention contemporaneously estimated that 1.7 million hospital acquired infections occur per year in the US.² Thus, a reasonable base case estimate of the number of cases of <i>A. baumannii</i> infection per year in the US is 45,900 (Table 1). Sensitivity analyses were generated by extrapolation from other datasets. Several European national surveillance studies found that median <i>A. baumannii</i> infection rates were 1.8 to 3.6 per 1,000 ICU-days.³⁻⁵ Given 23 million ICU days per year in the US,⁶⁻⁸ other reasonable estimates for the number of <i>A. baumannii</i> cases per year in the US are 42,000–84,000 (23 million × 1.8 (or 3.6)/1000). Thus, the base case was set at 45,900 cases with a range of 42,000–84,000 per year in the US (Table 1).</p> <p>Two separate calculations provided estimates for the number of global cases. The US possesses 4.5% of the world’s population.⁹ Hence, a base case estimate of 45,900 cases in the US projects to approximately 1,000,000 cases per year globally (Table 1). As a second estimate, national surveillance data from Thailand identified 14,000 cases of <i>A. baumannii</i> per year.¹⁰ Thailand has 0.98% of the world’s population, extrapolating to 1.4 million cases per year globally. Thus the base case estimate of global cases of <i>A. baumannii</i> was 1 million, with a sensitivity range of +/- 400,000 (given an upper bound estimate of 1.4 million cases). Finally, 15% of the world population resides in developed countries.¹¹ Thus total global cases were multiplied by 0.15 to calculate numbers of cases in developed countries, representative of a potential market for a pathogen-specific therapy (Table 1).</p>	1-4,9,10,12
Proportion carbapenem-resistant	Carbapenem-resistance rates for <i>A. baumannii</i> have been rising dramatically over the past decade in the US and globally, with data from 2011–2012 revealing in excess of 50–60% resistance. ¹³⁻¹⁶ The base case estimate of carbapenem resistance was set at 50% to be conservative relative to recent publications, with sensitivity analyses run at 15 to 75% (Table 1).	13–16
Proportion of global population living in a developed country	15% of the world population resides in developed countries. ¹¹ Thus total global cases were multiplied by 0.15 to calculate numbers of cases in developed countries, representative of a potential market for a pathogen-specific therapy (Table 1).	11
Direct healthcare cost of resistance per case in US	Several articles have described the impact of carbapenem-resistance on costs of <i>A. baumannii</i> infections. In one article, cases caused by imipenem-resistant strains had markedly increased length of hospital stay and costs, but the differences	17–20

	<p>became non-significant when adjusted for confounding factors.¹⁷ In contrast, other studies have found significant increases in healthcare costs of carbapenem-resistant versus susceptible <i>A. baumannii</i> infections despite adjustment.¹⁸⁻²¹ In the most recent study in which careful matching was conducted, the cost of resistant hospital-acquired infections, including those caused by <i>A. baumannii</i>, was found to be \$15,626 (95% CI \$4,339–\$26,913) more than matched cases caused by susceptible strains of the same pathogens. The latter number was adjusted to 2013 dollars using the CPI, resulting in a base case figure of \$16,947, with an upper bound sensitivity of used as the US base case estimate, with sensitivity analyses run ranging from no extra cost to \$29,188 per case (Table 1). Global costs of resistance were adjusted down by 60% compared to US costs, as described in the methods.</p>	
<p>Ratio of global healthcare costs to US costs</p>	<p>In the base case, global resistance costs were assumed to be 40% of the US costs based on the median relative overall healthcare costs of other developed countries compared to the US.²² Sensitivity analyses were run using the range of international costs relative to the US (since the US had the highest costs in the database). Because costs differed between the US and other countries, costs were separately calculated for US cases and non-US global cases and then summed together to generate the total global costs.</p>	<p>22</p>
<p>Excess mortality attributable to ineffective therapy</p>	<p>Mortality rates for carbapenem-resistant <i>A. baumannii</i> infections are well described. However, it is the mortality rate attributable to resistance that is potentially reducible by availability of new therapy to which the organism is not resistant. Mortality attributable to resistance was estimated by comparing mortality rates of initially ineffective versus effective therapy for carbapenem-resistant <i>A. baumannii</i>.²³⁻²⁶ In calculating the mortality attributable to ineffective therapy, we focused on studies in which absolute mortality rates were presented (as opposed to relative rates), since relative increases calculated by regression analyses do not allow inclusion of an actual mortality rate in the model.</p> <p>A recent study from Columbia reported not finding a statistically significant increase in mortality attributable to carbapenem-resistance in <i>A. baumannii</i> by multivariate analysis.²⁷ However, the authors concluded that their study was underpowered to detect the difference since the point estimate (95% confidence interval) of the relative increase in mortality was 1.45 (0.74–2.87). Thus this study could not conclude that there was no impact on mortality of carbapenem-resistance, and the point estimate and majority of the confidence interval are consistent with the absolute increases in mortality we modeled. The same authors subsequently conducted a systematic review and meta-analysis of other studies and found that overall, carbapenem resistance was associated with a greater than doubling of mortality compared to carbapenem-susceptible <i>A.</i></p>	<p>23–27</p>

	<i>baumannii</i> . ²¹ Nevertheless, to be conservative, we set the lower bound of the confidence interval for increase in mortality attributable to inadequate therapy to 1%.	
Average life years gained with effective therapy per patient and health utility score of a year of life gained for patient with resistant pathogen infection	There are no published data on average number of additional life-years of patients who survive <i>A. baumannii</i> infection, nor for quality of life during those years. Therefore, data were used from studies of patients with severe sepsis/septic shock or acute respiratory distress syndrome, which are also severe infections with high morbidity and mortality, and which can be caused by <i>A. baumannii</i> , to provide a base case and range for sensitivity testing (Table 1). ²⁸⁻³¹	28–31

References

1. Hidron, A. I. *et al.* NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect. Control Hospital Epidemiol.* 29, 996-1011 (2008).
2. Klevens, R. M. *et al.* Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep.* 122, 160-166 (2007).
3. Rodriguez-Bano, J. *et al.* Clinical features and epidemiology of *Acinetobacter baumannii* colonization and infection in Spanish hospitals. *Infect. Control Hospital Epidemiol.* 25, 819-824 (2004).
4. Agodi, A. *et al.* Building a benchmark through active surveillance of intensive care unit-acquired infections: the Italian network SPIN-UTI. *J. Hospital Infect.* 74, 258-265 (2010).
5. Martins, A. F. *et al.* High endemic levels of multidrug-resistant *Acinetobacter baumannii* among hospitals in southern Brazil. *Am. J. Infect. Control* 40, 108-112 (2012).
6. Halpern, N. A. & Pastores, S. M. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Crit. Care Med.* 38, 65-71 (2010).
7. Barnato, A. E. *et al.* Prioritizing the organization and management of intensive care services in the United States: the PROMIS Conference. *Crit. Care Med.* 35, 1003-1011 (2007).
8. Zimmerman, J. E., Kramer, A. A., McNair, D. S., Malila, F. M. & Shaffer, V. L. Intensive care unit length of stay: Benchmarking based on Acute Physiology and Chronic Health Evaluation (APACHE) IV. *Crit. Care Med.* 34, 2517-2529 (2006).
9. U.S. & World Population Clocks. (2012). <<http://www.census.gov/main/www/popclock.html>>.
10. Dejsirilert, S., Tiengrim, S., Sawanpanyalert, P., Aswapokee, N. & Malathum, K. Antimicrobial resistance of *Acinetobacter baumannii*: six years of National Antimicrobial Resistance Surveillance Thailand (NARST) surveillance. *J. Med. Assoc. Thailand* 92, S34-S45 (2009).
11. World Population Data Sheet 2012. (2012). <<http://www.prb.org/Publications/Datasheets/2012/world-population-data-sheet/fact-sheet-world-population.aspx>>.
12. Hospital Utilization (in non-Federal short-stay hospitals). (2012). <<http://www.cdc.gov/nchs/fastats/hospital.htm>>.

13. Chung, D. R. *et al.* High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am. J. Respir. Crit. Care Med.* 184, 1409-1417 (2011).
14. Koh, T. H. *et al.* Acinetobacter calcoaceticus-Acinetobacter baumannii complex species in clinical specimens in Singapore. *Epidemiol. Infect.* 140, 535-538 (2012).
15. Jaggi, N., Sissodia, P. & Sharma, L. Acinetobacter baumannii isolates in a tertiary care hospital: Antimicrobial resistance and clinical significance. *J. Microbiol. Infect. Dis.* 2, 57-63 (2012).
16. Shlaes, D. M., Sahm, D., Opiela, C. & Spellberg, B. Commentary: The FDA Reboot of Antibiotic Development. *Antimicrob. Agents Chemother.* 57, 4605-4607 (2013).
17. Lautenbach, E. *et al.* Epidemiology and impact of imipenem resistance in Acinetobacter baumannii. *Infect. Control Hospital Epidemiol.* 30, 1186-1192 (2009).
18. Lee, N. Y. *et al.* Clinical and economic impact of multidrug resistance in nosocomial Acinetobacter baumannii bacteremia. *Infect. Control Hospital Epidemiol.* 28, 713-719 (2007).
19. The cost of antibiotic resistance: effect of resistance among *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* on length of hospital stay. *Infect. Control Hospital Epidemiol.* 23, 106-108 (2002).
20. Neidell, M. J. *et al.* Costs of healthcare- and community-associated infections with antimicrobial-resistant versus antimicrobial-susceptible organisms. *Clin. Infect. Dis.* 55, 807-815 (2012).
21. Lemos, E. V. *et al.* Carbapenem resistance and mortality in patients with Acinetobacter baumannii infection: systematic review and meta-analysis. *Clin. Microbiol. Infect.* ePub, (2013).
22. Health expenditures per capita, public and private expenditure, OECD countries, 2010. (2012). <<http://www.oecd.org/unitedstates/BriefingNoteUSA2012.pdf>>.
23. Kwon, K. T. *et al.* Impact of imipenem resistance on mortality in patients with Acinetobacter bacteraemia. *J. Antimicrob. Chemother.* 59, 525-530 (2007).
24. Joung, M. K. *et al.* Impact of inappropriate antimicrobial therapy on outcome in patients with hospital-acquired pneumonia caused by Acinetobacter baumannii. *J Infect* 61, 212-218, (2010).
25. Esterly, J. S. *et al.* Impact of carbapenem resistance and receipt of active antimicrobial therapy on clinical outcomes of Acinetobacter baumannii bloodstream infections. *Antimicrob. Agents Chemother.* 55, 4844-4849 (2011).
26. Huang, S. T. *et al.* Risk factors and clinical outcomes of patients with carbapenem-resistant Acinetobacter baumannii bacteremia. *J. Microbiol. Immunol. Infect.* 45, 356-362 (2012).
27. Lemos, E. V. *et al.* Impact of carbapenem resistance on clinical and economic outcomes among patients with Acinetobacter baumannii infection in Colombia. *Clin. Microbiol. Infect.* ePub, (2013).
28. Davidson, T. A., Caldwell, E. S., Curtis, J. R., Hudson, L. D. & Steinberg, K. P. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *JAMA* 281, 354-360 (1999).
29. Heyland, D. K., Hopman, W., Coe, H., Tranmer, J. & McColl, M. A. Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. *Crit. Care Med.* 28, 3599-3605 (2000).
30. Manns, B. J., Lee, H., Doig, C. J., Johnson, D. & Donaldson, C. An economic evaluation of activated protein C treatment for severe sepsis. *N. Engl. J. Med.* 347, 993-1000 (2002).
31. Quartin, A. A., Schein, R. M., Kett, D. H. & Peduzzi, P. N. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA* 277, 1058-1063 (1997).