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The value of single-pathogen antibacterial agents

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As noted by Lewis in a recent Review article (Platforms for antibiotic discovery *Nature Rev. Drug. Discov.* **12**, 371-387 (2013))[1], novel strategies for developing antibiotics are needed, as infections caused by multidrug-resistant organisms (MDROs) are a leading threat to public health[2-4]. Increasingly, industry, academia and regulators have become interested in the concept of relatively small development programmes focused on areas of high unmet need, such as single-pathogen therapies to treat highly resistant or totally resistant bacterial pathogens[4-7]. However, given the small number of cases affected per annum, how such agents could be valued to support development programmes has remained unclear.

To help clarify this issue, we estimated the annual incidence, cost and mortality of infections caused by one of the most concerning antibiotic-resistant pathogens: carbapenem-resistant *Acinetobacter baumannii* (CRAB). We then developed a cost effectiveness model to determine the cost per quality-adjusted life years (QALYs) saved at various costs with a novel, pathogen-specific agent targeting CRAB in comparison with the standard of care (TABLES 1,2; see methods and references in Supplementary information S1 (table)).

Based on published frequencies of hospital-acquired infections, the proportion of such infections caused by *A. baumannii* and the proportion of carbapenem-resistant isolates, we estimated that 22,950 cases of CRAB infection occur annually in the United States and 75,000 globally (in developed nations) (TABLE 1). Based on the number of cases and the cost per case, carbapenem resistance costs health-care systems an annual excess of US$389 million and 4,590 excess deaths in the United States, and an annual excess of $742 million and 15,000 excess deaths globally (TABLE 1).

A cost of $10,000 per course of therapy was used to model QALYs. Net costs per life saved were $15,265 in the United States and $50,549 globally; net costs per life years saved were

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Competing interests statement

B.S. own equity in BioAIM, which is developing immunotherapies for infections. BioAIM provided no financial support for these studies. B.S.'s institute has received consulting fees on his behalf from GlaxoSmithKline, Pfizer, The Medicines Company, Meiji, Adenium, Cardeas, aRigen and Synthetic Biologics and research grants or contracts from Cubist, Pfizer, Esia and Bristol Myers Squibb. B.S. has received speaking honoraria from Cubist. J.H.R. is an employee of AstraZeneca Pharmaceuticals.

$1,908 in the United States and $6,319 globally; and costs per QALYs were $3,180 in the United States and $10,531 globally (TABLE 1).

In sensitivity analyses, even at pricing as high as $30,000 per treatment course, the US cost per QALY remained lower than $50,000, which is a commonly used benchmark for an acceptable cost per QALY against which to set drug pricing[8] (TABLE 2). Costs of therapy below $8,474 (in the United States) or $4,945 (globally) per course resulted in a negative cost per QALY, indicating that the novel therapy reduced health-care costs.

Even if the costs of resistance were zero, and thus there were no health-care savings enabled by reducing those costs using the pathogen-specific therapy (and conservatively not attributing any costs to the standard-of-care therapy), the costs per QALY at a treatment cost of $10,000 per course were only $20,833 in the United States and globally. Varying global health-care costs at 10-60% of US costs had a negligible effect on the global cost per QALY for a novel pathogen-specific agent.

The variable that most affected the model was the excess mortality rate attributable to resistance (that is, with ineffective current therapy, and thus improvable with new, effective therapy). There are extensive reports in the literature to indicate that carbapenem resistance increases the mortality of *A. baumannii* infections (see Supplementary information S1 (table)). In the unlikely event that there is no excess mortality caused by resistance, and a new therapy cannot improve mortality compared to the currently available therapy, the costs per QALY go to infinity (as no life years are saved with the new therapy). To enable more quantitative modelling of the scenario in which there is a minimal survival advantage due to the new therapy, we used only a 1% absolute increase in mortality attributable to carbapenem resistance as the lower bound of the sensitivity analysis. In this case, the cost per QALY at a $10,000 treatment cost was $63,604 in the United States and $210,619 globally. In this scenario, the model becomes extremely sensitive to the cost per treatment course. For example slightly lowering the cost per treatment course to $9,073 (in the United States) or $5,545 (globally) achieves a cost per QALY that is lower than $25,000, even if the absolute increase in mortality that is due to resistance is 1%. Even if the mortality attributable to carbapenem resistance was as low as 2-4%, or the pathogen-specific therapy only reduced mortality by 5-10%, or gained only 0.8-1.6 life years per patient, the costs per QALY remained below the $25,000 cut-off at $10,000 per treatment course.

Thus, a novel, single-pathogen agent focused on CRAB could provide benefits to the health-care system while maintaining costs well below the typical benchmarks used to define cost-effective therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Model variables and sources

Variable	Base case point estimate	Range	Method
Acinetobacter baumannii infections per year	United States: 45,900 Globally: 1,000,000	United States: 41,400–83,000 Globally: 600,000–1,400,000	*
Proportion of carbapenem–resistant cases	50%	15–75%	*
Proportion of global population living in a developed country	15%	10–20%	*
Resulting annual incidence of carbapenem–resistant *A. baumannii* cases	United States: 22,950 Globally: 75,000	NA	‡
Direct health-care cost of resistance per case in the United States (US$)	$16,947	$0–$29,188	*
Percentage of health-care cost due to resistance recovered with effective therapy	50%	25–75%	Estimated
Ratio of global health-care costs to US costs	0.4	0.1–0.6	*
Excess cost of resistant cases per year (millions of US$)	United States: $389 Globally: $742	NA	§
Resistance cost recovered with pathogen–specific therapy per year (millions of US$)	United States: $194 Globally: $371	NA	||
Excess mortality attributable to ineffective therapy	20%	1–30%	*
Excess mortality reduction with effective therapy	50%	25–75%	Estimated
Average life years gained with effective therapy per patient	8	4–16	*
Health utility score of a year of life gained for patient with a resistant pathogen infection	0.6	0.5–0.8	*
Deaths per year due to resistance without pathogen–specific therapy	United States: 4,590 Globally: 15,000	230–6,885 750–22,500	¶
Number of lives saved per year with pathogen–specific therapy	United States: 2,295 Globally: 7,500	115–3,442 375–11,250	#
Net cost per life saved	United States: $15,265 Globally: $50,549	NA	**
Net cost per life year saved (US$)	United States: $1,908 Globally: $6,319	NA	**
Net cost per quality adjusted life year (QALY) saved (US$)	United States: $3,180 Globally: $10,531	NA	**

NA, not applicable.

*See Supplementary information S1 (table) for references and methodological description.

‡Number of *A. baumannii* infections per year multiplied by the proportion of carbapenem-resistant cases, also multiplied by the proportion of the global population living in a developed country for global cases.

§Number of carbapenem-resistant cases multiplied by excess cost of resistance; for global cases, also multiplied by the global health-care costs compared to the United States.

||Excess cost of resistance multiplied by percent of health-care cost due to resistance recovered with effective therapy.

¶Total number of carbapenem-resistant *A. baumannii* cases multiplied by excess mortality attributable to ineffective therapy.

#Deaths per year due to resistance without pathogen-specific therapy multiplied by excess mortality reduction with effective therapy.

** Net cost per life saved is equal to the net cost divided by the number of lives saved per year with the pathogen-specific therapy; net cost per life year saved is equal to the net cost per life saved divided by the average life years gained with the effective therapy per patient (TABLE 1); the net cost per quality-adjusted life year (QALY) is equal to the net cost per life year saved divided by the average quality of life per year gained.

Table 2

Cost-effectiveness sensitivity analysis

Variable (range)	Range of variable in sensitivity analysis	US cost per QALY	Global cost per QALY
Cost of therapy per course	$3,000–$30,000	−$11,403 to $44,846	−$4,052 to $52,197
Direct health-care cost of resistance per case (United States)	$0–$26,913	$20,833 to –$7,201	$20,833 to $4,472
Ratio of global costs to US health-care costs	0.1–0.6	NA	$14,206 to $8,081
Percent of health-care cost recovered with effective therapy	25–75%	$12,007 to –$5,646	$15,682 to $5,380
Excess mortality attributable to ineffective therapy	1–30%	$63,604 to $2,120	$210,619 to $7,021
Excess mortality reduction with effective therapy	25–75%	$6,360 to $2,120	$21,062 to $7,020
Average life years gained with effective therapy per patient	4–16	$6,360 to $1,590	$21,062 to $5,265
Average quality of life per year gained	0.5–0.8	$3,816 to $2,385	$12,637 to $7,898

NA, not applicable; QALY, quality-adjusted life year.