Investing in antibiotics to alleviate future catastrophic outcomes: what is the value of having an effective antibiotic to mitigate pandemic influenza?

Abstract

Over ninety-five percent of post-mortem samples from the 1918 pandemic, which caused 50 to 100 million deaths, showed bacterial infection complications. The introduction of antibiotics in the 1940s has since reduced the risk of bacterial infections, but growing resistance to antibiotics could increase the toll from future influenza pandemics if secondary bacterial infections are as serious as in 1918, or even if they are less severe. We develop a valuation model of the option to withhold wide use of an antibiotic until significant outbreaks such as pandemic influenza or foodborne diseases are identified. Using real options theory, we derive conditions under which withholding wide use is beneficial and calculate the option value for influenza pandemic scenarios that lead to secondary infections with a resistant *Staphylococcus aureus* strain. We find that the value of withholding an effective novel oral antibiotic can be positive and significant unless the pandemic is mild and causes few secondary infections with the resistant strain or if most patients can be treated intravenously. Although the option value is sensitive to parameter uncertainty, our results suggest that further analysis on a case-by-case basis could guide investment in novel agents as well as strategies on how to use them.

Key words: real options analysis; insurance value; antibiotics; antibiotics resistance; pandemic influenza; secondary bacterial infections

1. Introduction

In the past four hundred years, roughly three influenza pandemics have spread across the world each century, killing millions of people (Potter, 2001). The most recent pandemic influenza prior to the introduction of antibiotics in 1942 was the 1918 (H1N1) pandemic, also known as the 'Spanish Flu.' It was the most devastating pandemic historically, infecting a third of the world's population and killing 50 to 100 million people (Johnson & Mueller, 2002). Postmortem samples showed that over ninety-five percent of deaths in the 1918 pandemic were complicated by a bacterial infection (Morens, Taubenberger, & Fauci, 2008), and had antibiotics been available in 1918, many deaths could have been averted (Brundage, 2006; Handel, Longini, & Antia, 2009; Chien, Levin, & Klugman, 2012). Since then, experience and science have taught us more about influenza viruses and pandemics (1957, 1968, and 2009), and we have developed tools, such as better infection control, vaccines, antivirals, and antibiotics, to prepare for and combat future pandemics.

Despite the significant research on previous pandemics undertaken in the 21st century, it is difficult to predict the timing and scale of the next pandemic. Influenza A viruses continually evolve through accumulated mutations over time (antigenic drift) and also by less frequent but more drastic antigenic changes that occur when different sub-types infect a single cell (antigenic shift). Pandemic influenza occurs when a novel influenza A sub-type emerges or an old one—not recently in cycle—remerges in an immunologically naïve human population (Webby & Webster, 2001). These changes are unpredictable, making future pandemics inevitable, and their timing and scale unknown (Webby & Webster, 2001; Taubenberger & Morens, 2010).

The World Health Organization (WHO) and several countries have developed pandemic preparedness plans, which include maintaining stocks of antivirals, antibiotics, and vaccines to minimize the impact of future pandemics (e.g., US Department of Health and Human Services, 2005; Department of Health, 2011a; WHO, 2009). Supporting these plans, the breadth of literature on the value and cost-effectiveness of stockpiling vaccines and antivirals has increased in the 21st century (Velasco et al., 2012 and herin; Germann, Kadau, Longini, & Macken, 2006; Attema, Lugnér, & Feenstra, 2010; Halder, Kelso, & Milne, 2014). However, the economic value of stockpiling or conserving the effectiveness of antibiotics remains unexplored despite the high morbidity and mortality caused by secondary bacterial infections.

Maintaining a stockpile of antibiotics will not be an effective strategy for prepardness if the antibiotics are not effective. The emergence of multi-drug resistant and pandrug-resistant (PDR), untreatable infections and the alarm bells of a potential postantibiotic era emphasize the value of protecting our investment in effective antibiotics, whether existing or in the development pipeline (Souli, Galani, & Giamarellou, 2008; McGann et al., 2016; Chen, 2017; Laxminarayan et al., 2013). In a world with prevalent PDR bacterial infections, treatment costs increase significantly, cuts and scrapes can be life-threatening, and common surgical procedures and cancer chemotherapy may lead to unacceptably high rates of untreatable infections (Teillant, Gandra, Barter, Morgan, & Laxminarayan, 2015; ECDC & EMEA, 2009). In the event of a significant influenza pandemic, secondary infections caused by prevalent PDR bacteria could be catastrophic. Ensuring effective antibiotics in the future is a public health priority, and only two novel classes of antibiotics have been introduced since the 1970s (Coates, Halls, & Hu, 2011).

A possible strategy for managing a newly developed antibiotic is to withhold its wide use to conserve its effectiveness until a later time, when it potentially provides higher benefits. The benefits, or value, we garner in the future by this delay are the opportunity cost of foregoing the antibiotic's use for a time. This value is pertinent to antibiotics because increasing their use today may improve the effectiveness of the existing portfolio of drugs available to treat infections, but with the irreversible cost of reduced effectiveness for treating an uncertain number of future infections. Antibiotic effectiveness decreases because their use leads to selection pressure for resistant microbial strains, giving these strains competitive advantage (Davies & Davies, 2010), and even if resistance is reversible by reducing consumption, the process would be slow, costly, and easily reversed (Andersson & Hughes, 2010).

The literature on valuing new antibiotics provides a framework to estimate their expected net present value (NPV) (Sertkaya et al., 2014), but it fails to capture the irreversible effect of resistance and the value new antibiotics contribute to having effective treatment options in the future. Traditional NPV analysis assumes the decision to invest is a now-or-never one and does not consider delaying investing, or in our case introducing the wide use of an antibiotic. However, real options theory has studied the impact of irreversibility and uncertainty on the value of delaying investment and maintaining flexibility (Myers, 1977; McDonald & Siegel, 1986; Dixit & Pindyck, 1994; Trigeorgis, 1996). Real options valuation has roots in corporate

finance, but its application has extended to other fields, including a growing literature on real options analysis in healthcare investment and health technology assessment (e.g., Palmer & Smith, 2000; Driffield & Smith, 2007; Eckermann & Willan, 2008; Attema et al., 2010; Meyer & Rees, 2012; Wernz, Gehrke, & Ball, 2015; Thijssen & Bregantini, 2017). The real options framework has also been implemented and studied in the context of pest resistance (Wesseler, 2003; Mbah, Forster, Wesseler, & Gilligan, 2010) and assessing policy changes (Leitzel & Weisman, 1999; Beckmann, Soregaroli, & Wesseler, 2006; Wesseler & Zilberman, 2014).

Studies on delaying access to treatment highlight additional values that underpin a real options framework for considering either immediately offering or delaying access to antibiotics (Littmann, Buyx, & Cars, 2015). Eckermann & Willan (2008) show that the option to delay introduction to collect additional evidence may be preferable to adopting health technologies when the decision is irreversible. Wesseler & Zilberman (2014) develop an option model to demonstrate how political economy can drive delaying introducing a Vitamin A deficiency reducing technology. Other authors have raised ethical issues related to delaying access to treatment, including intragenerational and intergenerational justice (Dawson & Verweij, 2007) and the trade-off between patient autonomy and drug control (Coleman, Jaramillo, Reis, & Selgelid, 2010). The common theme is that these studies assess trade-offs between immediate and delayed treatment.

In this paper, we apply real options theory and develop a framework for assessing trade-offs to estimate the value of investing in developing and conserving an antibiotic to mitigate the burden of bacterial infections during pandemic influenza. A similar model can be applied to value the availability of effective antibiotics in other potential scenarios, such as regional outbreaks of PDR bacteria in healthcare settings that force shutting down intensive care units, outbreaks of foodborne resistant infections in the community, or simply when resistant bacteria are more prevalent in the community. We focus on pandemic influenza because several countries already maintain a stockpile in preparation, but these stockpiles will not be effective if the antibiotics are not effective. Furthermore, the high burden over a short period can stress the health system and other sectors of the economy. In the following section, we derive the theoretical solution and study threshold rules for when investing in an antibiotic and withholding its use until an outbreak is beneficial. We numerically estimate the value for scenarios of pandemic influenza in the United Kingdom (UK).

2. Model: option value of conserving antibiotics

We assume the novel antibiotic is available at time $t_0 = 0$, and its development cost is I. At time t_1, which is uncertain, an outbreak of infections caused by PDR bacteria is identified. A decision maker, such as the UK Department of Health, needs to decide whether to widely introduce the antibiotic at t_0 or withhold its wide use until t_1, when the benefits may be higher. We model both policies' NPVs, with costs and benefits related to the new antibiotic that accrue over time discounted at the annual rate μ. The difference between the policies' NPVs represent the value of the option to conserve the antibiotic's effectiveness until the outbreak is identified. We define this value as the 'option value.' Since the novel antibiotic is available at time t_0 in both policies (i.e., investment in the antibiotic is not delayed in either policy), the investment cost I does not impact the option value of conserving effectiveness.

2.1. Policy A: Withhold wide use of antibiotic

Use of the novel antibiotic is held off until a significant outbreak is detected at an uncertain point in time, t_1 (Figure 1). The model for Policy A calculates the value to invest in developing an antibiotic conserved until detecting the outbreak.

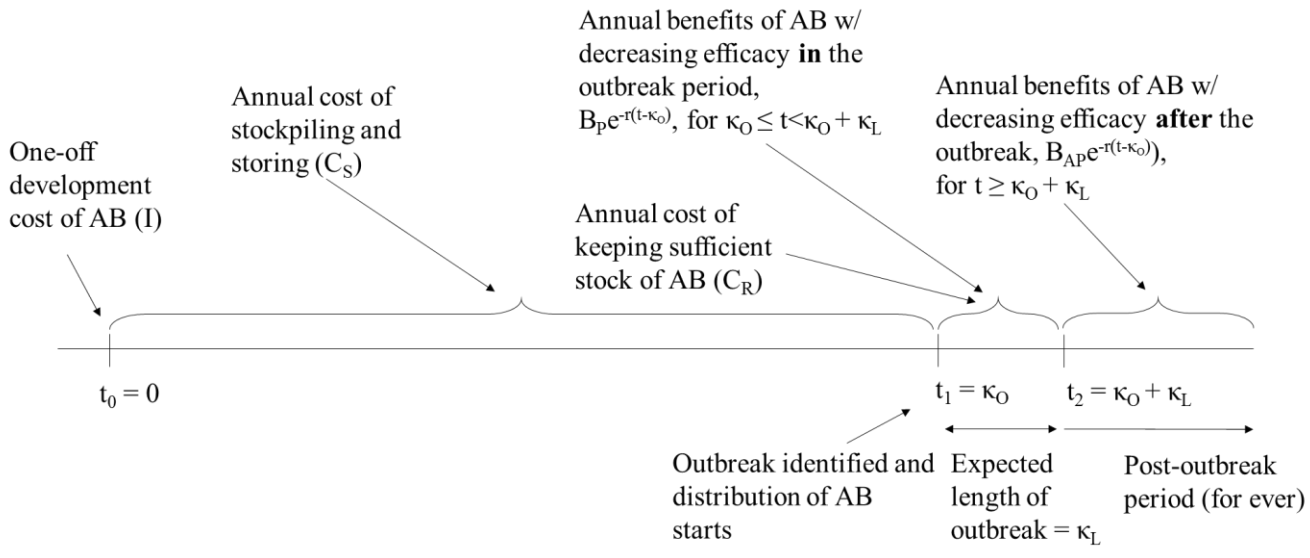


Figure 1. Policy A.

148 The annual costs of stockpiling and storing the antibiotic (C_S) are incurred starting at $t_0 = 0$.
149 The outbreak is expected to occur κ_O years after the antibiotic has been developed (i.e., at
150 time $t_1 = \kappa_O$). We model the uncertainty related to the start of the outbreak by letting κ_O
151 follow the exponential distribution $g(\kappa_O) = h_O e^{-h_O \kappa_O}$, with $E(\kappa_O) = 1/h_O$, where h_O denotes
152 the hazard rate. The outbreak duration, κ_L, is exponentially distributed with $k(\kappa_L) = h_L e^{-h_L \kappa_L}$
153 and $E(\kappa_L) = 1/h_L$, where h_L is the hazard rate.
154
155 The stockpile maintenance and distribution costs during the outbreak are C_R. The availability
156 of the novel antibiotic during the outbreak leads to benefits (B_P) that include the avoided
157 economic costs that would have been incurred in the absence of the antibiotic.
158
159 When the antibiotic is introduced, bacterial resistance to the drug emerges and spreads. We
160 model the decrease in effectiveness of the novel antibiotic by discounting the treatment
161 benefits at the annual rate of decay r. Thus, the effective annual benefits of the new antibiotic
162 during the outbreak are $B_P e^{-r(t-\kappa_O)}$, for $\kappa_O \le t < \kappa_O + \kappa_L$.
163
164 After the outbreak (i.e., after $t_2 = \kappa_O + \kappa_L$), the antibiotic provides annual benefits of
165 $B_{AP} e^{-r(t-\kappa_O)}$. The post-outbreak benefits represent the antibiotic increasing the effectiveness of
166 the portfolio of antibiotics available to treat infections. At this point, we no longer withhold
167 and stockpile the antibiotic.
168
169 Using the functional forms for the distribution of uncertain times κ_O and κ_L specified above,
170 we obtain the present value net benefits of Policy A as follows (Appendix A presents the
171 derivations):
172
173 Pre-outbreak costs of stockpiling and storing are

$$\frac{C_S}{\mu + h_O}, \tag{1}$$

174 benefits – costs during the outbreak are

$$\frac{h_O}{\mu + h_O}\left(\frac{B_P}{r + \mu + h_L} - \frac{C_R}{\mu + h_L}\right), \tag{2}$$

175 benefits after the outbreak are

$$\frac{h_O h_L B_{AP}}{(\mu + h_O)(r + \mu)(r + \mu + h_L)}, \tag{3}$$

176 and the NPV of Policy A is

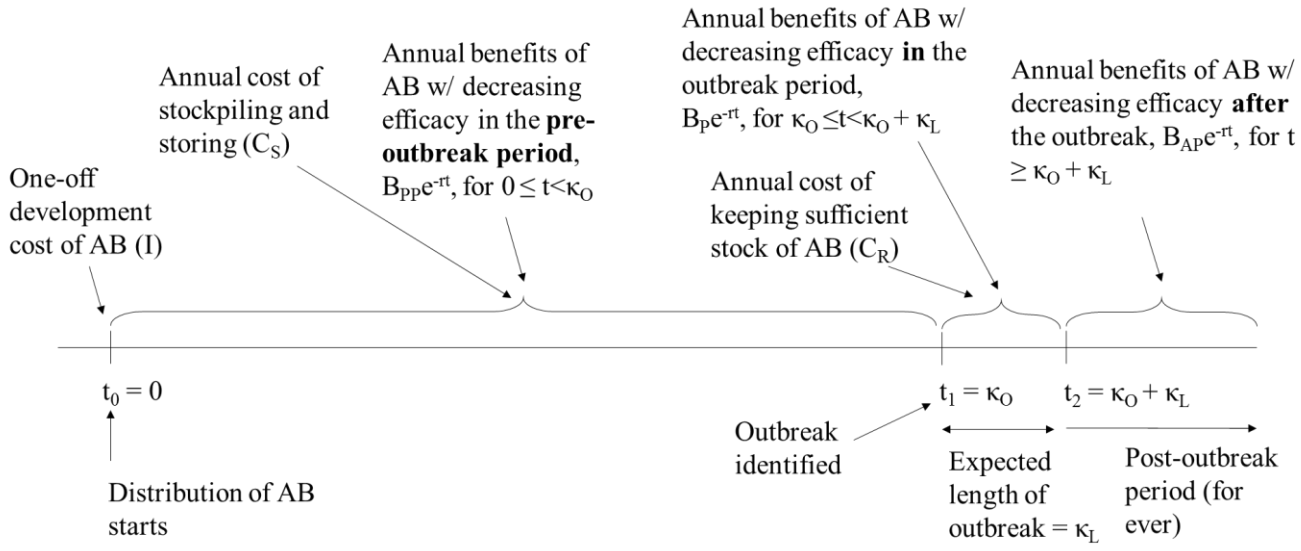
$$-I - (1) + (2) + (3). \tag{4}$$

177

178 ## 2.2. Policy B: immediately introduce antibiotic

179 The antibiotic is launched and is immediately part of the existing portfolio of antibiotics at

180 $t_0 = 0$ (Figure 2).



181

182 **Figure 2. Policy B.**

183

184 The annual costs of stockpiling and storing the novel antibiotic (C_S) are incurred from $t_0 = 0$

185 until the outbreak at t_1. The benefits from immediate release are a more diverse portfolio of

186 antibiotics in the pre-outbreak period, which provides an annual benefit of $B_{PP} e^{-rt}$, for

187 $0 \leq t < \kappa_O$.

188

189 After the outbreak is identified at $t_1 = \kappa_O$ and until it is over at $t_2 = \kappa_O + \kappa_L$, costs for

190 stockpile maintenance and distribution (C_R) are accrued. The annual benefits of the novel

191 antibiotic during the outbreak, $B_P e^{-rt}$, for $\kappa_O \leq t < \kappa_O + \kappa_L$, account for the decreasing

effectiveness due to resistance. The discounted annual benefits after the outbreak (i.e., after $t_2 = \kappa_O + \kappa_L$) are $B_{AP}e^{-rt}$.

The present value net benefits in each period of Policy B (derivations in Appendix A) are as follows:

benefits – costs before the outbreak are

$$\frac{B_{PP}}{\mu + r + h_O} - \frac{C_S}{\mu + h_O}, \tag{5}$$

benefits – costs during the outbreak are

$$\frac{h_O B_P}{(r + \mu + h_O)(r + \mu + h_L)} - \frac{h_O C_R}{(\mu + h_O)(\mu + h_L)}, \tag{6}$$

benefits after the outbreak are

$$\frac{h_O h_L B_{AP}}{(r + \mu)(r + \mu + h_O)(r + \mu + h_L)}, \tag{7}$$

and the NPV of Policy B is

$$-I + (5) + (6) + (7). \tag{8}$$

2.3. Option value

The option value of conserving effectiveness is the difference between expressions (4) and (8).

2.4. Parameters thresholds

We now investigate the conditions under which the option value is positive and withholding immediate wide use of the antibiotic is beneficial. After simplifications, the condition $NPV_A > NPV_B$ implies

$$\frac{B_{PP}}{B_P + \frac{h_L}{r + \mu} B_{AP}} < \frac{rh_O}{(\mu + h_O)(r + \mu + h_L)}. \tag{9}$$

Note that the right-hand side of inequality (9) is always non-negative (as all parameters are non-negative) and less than unity.

To consider the ratio of potential pre-outbreak benefits to ones during the outbreak, we further assume benefits after the outbreak—and after the novel antibiotic has been introduced in both policies A and B—are negligible (i.e., $B_{AP} \approx 0$). Inequality (9) then reduces to

$$\frac{B_{PP}}{B_P} < \frac{rh_O}{(\mu + h_O)(r + \mu + h_L)}. \quad (10)$$

Letting $\frac{rh_O}{(\mu + h_O)(r + \mu + h_L)} = m$, we can interpret condition (10) as the maximum ratio of pre-outbreak to outbreak benefits ($\frac{B_{PP}}{B_P}$) for which withholding wide use of an antibiotic (Policy A) is more beneficial than using it immediately (Policy B).

Because $\partial m/\partial r > 0$, the maximum value of the threshold is when $r \to \infty$, producing $m = \frac{h_O}{\mu + h_O}$. Similarly, because $\partial m/\partial h_O > 0$, when $h_O \to \infty$, then $m = \frac{r}{r + \mu + h_L}$, Finally, since $\partial m/\partial h_L < 0$, the maximum value of *m* is when $h_L \to 0$, producing $m = \frac{rh_O}{(\mu + h_O)(r + \mu)}$.

Note that in the extreme cases, when $r = 0$ or $h_O = 0$, inequality (10) reduces to $\frac{B_{PP}}{B_P} < 0$, which cannot hold because benefits are positive. Therefore, when $r = 0$ or $h_O = 0$, $NPV_A < NPV_B$. Intuitively, if no resistance to antibiotics builds up ($r = 0$), then we always choose to introduce the antibiotic immediately after its development. Similarly, if expected time to the outbreak approaches infinity ($h_O = 0$), we always choose immediate introduction.

3. Application scenario details

3.1. Influenza pandemic scenario

We based our pandemic scenarios on the UK preparedness plan assumptions (Department of Health, 2007, 2011a) but made specific assumptions regarding prevalence of bacterial infections (see Table 1). In the base-case, we assumed that the influenza pandemic will lead to secondary bacterial infections in 20% of cases (Brundage, 2006; Morens et al., 2008), with

10% of these infections caused by a resistant *Staphylococcus aureus* strain (Morens et al., 2008; Oswald, Shooter, & Curwen, 1958; Louria, Blumenfeld, Ellis, Kilbourne, & Rogers, 1959; Schwarzmann, Adler, Sullivan, & Marine, 1971). Though *S. aureus* represented only 8% of bacterial pathogens in autopsies of the 1918 pandemic, it was predominant in the 1957 pandemic potentially because resistance to tetracycline and streptomycin was becoming widespread (Morens et al., 2008; Department of Health, 2011b). We assumed the base-case scenario hazard rate (h_O) is 1/150 (see Appendix B).

The prevalence of secondary bacterial infections in community and healthcare settings would stress the healthcare system. Available oral antibiotics may not effectively treat infections with the resistant *S. aureus* strain, and individuals infected with the strain would require hospitalization. Though we assumed intravenous (IV) therapy exists, the increased volume of cases would overburden the health system, leading to deaths and increased economic costs. Previous estimates suggested that hospital capacity may only meet 20% to 25% of expected demand at the pandemic peak (Department of Health, 2007), and exacerbating the situation, the risk of secondary bacterial infections may be greater in healthcare settings then in the community, particularly in the case of a pathogen such as resistant *S. aureus*, which is prevalent in this setting (Nin et al., 2011; European Centre for Disease Prevention and Control, 2017). We modelled three levels of IV therapy coverage: 20%, 50%, and 80%.

Table 1 provides details on the base-case scenario and on more mild and severe scenarios; Appendix B describes the scenario parameter choices in more detail.

Table 1. Pandemic influenza scenarios

	Base-case	Mild scenario	Severe scenario	Sensitivity distribution †	Source for assumptions
Pandemic influenza					
Pandemic hazard rate (h_O)	1/150	3/100	1/500	Lognormal (1/500, 1/100, 1/20)	(Potter, 2001)
Pandemic attack rate ‡	35%	25%	50%	Beta (15%, 30%, 50%)	(Potter, 2001; Ferguson et al., 2006; Department of Health, 2007, 2011a)
Pandemic duration ($1/h_O$)	15 weeks	15 weeks	15 weeks	Lognormal (5, 15, 52 weeks)	(Potter, 2001; Taubenberger & Morens,

					2010; Department of Health, 2007, 2011a)
Pandemic overall case fatality rate (CFR), including secondary bacterial infections	1%	0.04%	2.5%	Beta (0.02%, 0.5%, 2%) §	(Department of Health, 2007, 2011a; US Department of Health and Human Services, 2005)
Secondary bacterial infections					
Percent develop secondary bacterial infections ‡	20%	10%	30%	Beta (10%, 20%, 35%)	(Brundage, 2006; Morens et al., 2008; Department of Health, 2007, 2011a)
Percent of bacterial infections caused by *S. aureus* resistant to existing oral antibiotics ‡	10%	1.25%	20%	Beta (0%, 2%, 20%)	(Morens et al., 2008; Department of Health, 2011b; Oswald et al., 1958; Louria et al., 1959; Schwarzmann et al., 1971)
CFR for *S. aureus* secondary bacterial infections	30%	20%	30%	Beta (15%, 25%, 35%)	(Department of Health, 2011a; Oswald et al., 1958)
Proportion of secondary infections that can be treated intravenously ‡¶	20%, 50%, and 80%	50% and 80%	20% and 50%	Lognormal (10, 40, 500 thousand)	Authors' assumption

† Distribution used in Latin-Hypercube Sampling Partial Rank Correlation Coefficient sensitivity analysis. Percentiles the distribution was fitted to are provided in parentheses: 2.5%, 50%, and 97.5%.

‡ Used to estimate avertable cases and deaths by the novel antibiotic.

§ Overall CFR only affects models that consider economic losses due to absenteeism from work, which is a function of the number of deaths. Additionally, the sensitivity range for overall CFR does not include deaths due to the infections caused by the resistant *S. aureus* strain.

¶ We assume that antibiotics can be administered intravenously, but this is not a viable route because of health system constrains during epidemics. The sensitivity range is in terms of total capacity to intravenously treat the secondary infections with the resistant *S. aureus* strain instead of percent covered; the percent covered is then calculated depending on the size of the pandemic.

We assumed the novel oral antibiotic can effectively treat the resistant infections and alleviate the burden on the health system. However, *S. aureus* has been quick to develop

resistance to novel antibiotics historically (Chambers & DeLeo, Frank R., 2009; Grundmann, Aires-de-Sousa, Boyce, & Tiemersma, 2006). In the base-case, we assumed that when in use, the antibiotic effectiveness treating infections caused by the resistant *S. aureus* strain decayed at the annual rate (r) 0.02 (Table 2). This means that 10 years after the antibiotic's introduction and wide use it would no longer treat 18% of infections effectively (see Appendix B for comparison with the speed *S. aureus* developed resistance historically).

3.2. Costs

We considered the costs of developing (I) and stockpiling (C_S) the novel antibiotic, including the cost of wastage, misdiagnosis, and empirical treatment that is likely due to the volume of patients. We ignored the costs of distributing antibiotics (C_R) during the pandemic, which are small compared to potential burden averted by the novel antibiotic (see 3.3 Benefits) and are incurred in both Policy A and Policy B. Future costs were discounted at 3.5%. Table 2 provides the costs and benefits (further explained in Appendix B).

Table 2. Costs and benefits

	Base-case	Sensitivity range[†]	Source for assumptions
Antibiotic			
Out-of-pocket cost of developing an antibiotic (I)	$1.1 billion		(Sertkaya et al., 2014; DiMasi, Grabowski, & Hansen, 2016)
Stockpile size	1 million	Lognormal (0.2, 1, 5 million)	(Siddiqui & Edmunds, 2008; Lugnér & Postma, 2009)
Stockpile storage cost per course per year	$1	Truncated normal ($0.20, $1.00, $1.90)	
Population level effectiveness rate of decay when in use (r)	0.02	Lognormal (0.004, 0.015, 0.050)	(Grundmann et al., 2006 and herin; Chambers & DeLeo, Frank R., 2009)
Disease Burden costs [‡]			
Value of statistical life	$2.4 million	Truncated normal ($1.8, $2.4, $3.0 million)	(Department for Transport, 2017)

Cost of hospitalization per patient	$5,000	Truncated normal ($2, $5, $8 thousand)	(Lode, 2007; NICE, 2014; Rozenbaum, Mangen, Huijts, van der Werf, & Postma, 2015)
Economic benefits			
a §	0, 27		Fit based on (Smith, Keogh-Brown, Barnett, & Tait, 2009; Keogh-Brown, Smith, Edmunds, & Beutels, 2010)
u §	0, 0.30		Fit based on (Smith et al., 2009; Keogh-Brown et al., 2010)
Averted burden when there is no pandemic (annual)			
Hospital days	300,000	Truncated normal (200, 300, 400 thousand)	Authors' assumption
Other			
Discount rate	3.5%		

Costs are in US$ 2015.

† Distribution used in Latin-Hypercube Sampling Partial Rank Correlation Coefficient sensitivity analysis. Percentiles the distribution was fitted to are provided in parentheses: 2.5%, 50%, and 97.5%.

‡ Disease burden costs are represented as benefits—from averted burden by the novel antibiotic—in the model.

§ Shape parameter in function of percent Gross Domestic Product loss in terms of mortality (see the Appendix). We evaluate each scenario without economic losses averted (i.e., *a* and *u* are both 0) and with economic losses averted.

3.3. Benefits

We estimated the benefits before (B_{PP}), during (B_P), and after the pandemic (B_{AP}) based on the avertable burden by the novel antibiotic, including hospitalization, deaths, and economic losses. Prior to pandemic influenza, the healthcare system would not be overburdened and individuals could be treated intravenously in healthcare facilities. However, the novel oral antibiotic would reduce the length of stay in hospitals and prevent hospitalization, averting hospital days and associated costs in Policy B (Table 2).

The avertable burden during the pandemic depends on the number of secondary infections caused by the resistant *S. aureus* strain (Table 1). We assumed that the novel oral antibiotic would not be more effective treating infections caused by the resistant strain than IV administered antibiotics, and therefore the oral antibiotic would not avert additional deaths among patients that could alternatively be treated by IV therapy. However, the availability of oral therapy would reduce their hospitalization. Among patients that the health system would not have had the capacity to treat with IV administered antibiotics, the oral antibiotic would avert both hospitalizations and deaths. We conservatively assumed the oral antibiotic does not avert losses to the economy in the base-case scenario, but we do consider potential impact on economic losses in the sensitivity analysis.

The benefits decayed according to *r* when policy dictated the oral antibiotic's wide use. Benefits were further discounted at 3.5%.

3.4. Sensitivity analysis

Alternative scenarios were constructed to explore influenza pandemics of differing magnitude (Table 1). We set the hazard rate for the mild scenario at 3/100 per year and for the severe scenario at 1/300 per year. We did not consider low capacity to treat (20% of patients) with IV administered antibiotics in the mild pandemic scenario, and we did not consider high capacity to treat (80% of patients) in the severe scenario; scenarios which seemed unreasonable.

We also estimated the option value accounting for economic losses averted in addition to hospitalizations and deaths averted. Based on a general equilibrium model of influenza pandemic in the UK, we assumed an S-shaped curve representing percent Gross Domestic Product (GDP) loss in terms of the mortality rate—a high number of deaths during the pandemic triggers absenteeism from work, which drives economy losses (Smith et al., 2009) (see Appendix B and C for details).

Lastly, we explored the relative sensitivity of the option value model to parameters using Latin Hypercube Sampling (LHS) and conducting a Partial Rank Correlation Coefficient (PRCC) analysis. The sampling distributions are provided in Table 1 and in Table 2. Parameters with large absolute PRCC values that are statistically significant (t-test) are most

influential (See Appendix B for more detail). We further explored the most important parameters and examined how they impact the option value threshold for the influenza pandemic application.

4. Application results

4.1. Base-case

In the base-case pandemic scenario approximately 455,000 individuals developed secondary bacterial infections with the *S. aureus* strain resistant to all oral options but the novel antibiotic. The strain caused approximately 68,000 deaths when we assumed the healthcare system had the capacity to intravenously treat 50% of patients infected with it (30% of all pandemic related deaths). The strain caused 27,000 deaths if capacity was set to 80% and 109,500 deaths if it was 20%.

Figure 3 shows the option value for different scenarios. When IV therapy capacity during the pandemic was set to 50% or 20%, withholding wide use proved to be fruitful, providing a value of $578 million and $2.2 billion respectively. However, introducing the novel antibiotic prior to identifying the pandemic would have been the better strategy if 80% of patients infected with the strain could not be treated intravenously. The value of waiting until the pandemic was identified was -$1.1 billion in this case.

4.2. Alternative scenarios

If the pandemic proved to be mild, withholding the novel antibiotic prior to the pandemic was not beneficial (Figure 3), even though the hazard rate for this scenario was significantly higher. In the mild pandemic scenario 6,500 individuals died, and the resistant *S. aureus* strain was responsible for either 800 (80% coverage) or 2,000 deaths (50% coverage), depending on IV therapy coverage. The option value was approximately -$1.3 billion for both IV therapy coverage levels.

Withholding wide use of the novel antibiotic until the severe pandemic scenario provided significant value despite the low hazard rate. In this scenario, the pandemic CFR was set to 2.5% and deaths caused by infections with the resistant *S. aureus* strain represented 36%

(57.5%) of these deaths when IV therapy covered 50% (20%) of patients. The option value was $2.1 billion ($4.7 billion) when IV therapy covered 50% (20%) of patients.

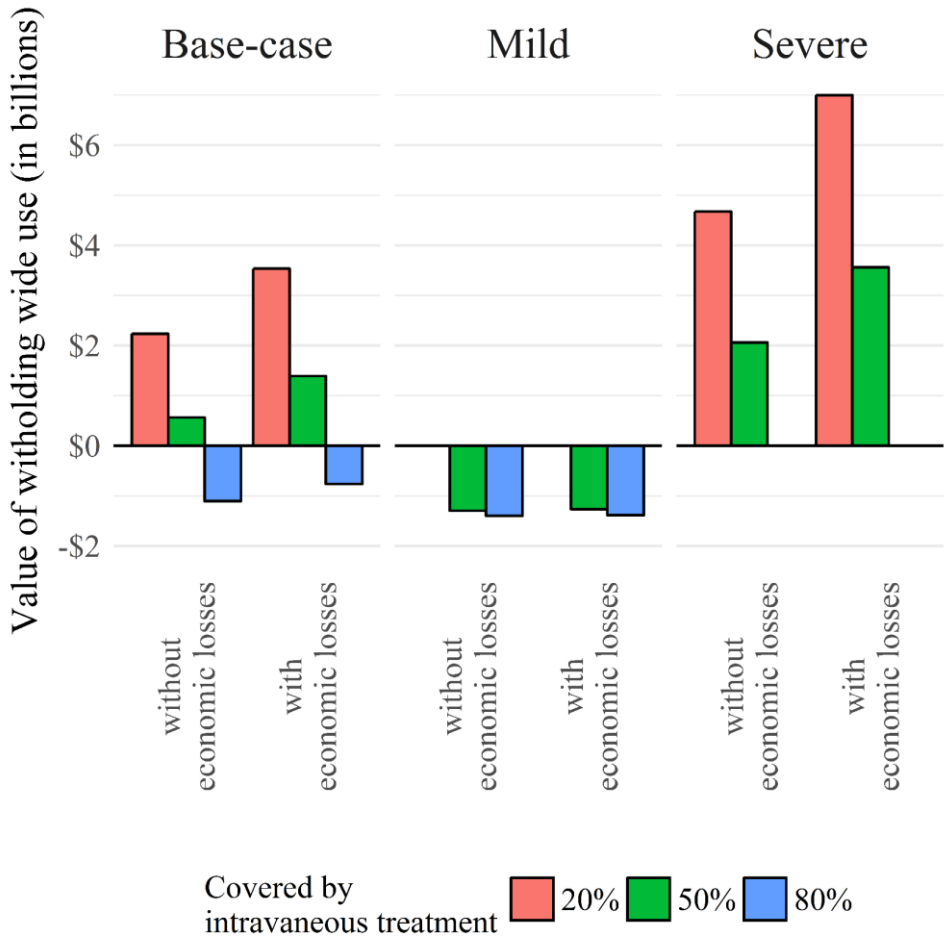


Figure 3. Value of withholding a novel oral antibiotic until pandemic influenza is identified.

4.3. Economic losses

The option value was higher if we considered economic losses. In the mild pandemic scenario, benefits due to economic losses averted were insignificant, and withholding wide use until the pandemic remained unattractive. Withholding wide use until the base-case pandemic also remained unattractive if 80% of patients could be treated by IV therapy. However, the value increased by 141% (57%) when IV coverage was 50% (20%). In the severe scenario the value increased by 73% (50%) when IV coverage was 50% (20%).

4.4. Model sensitivity to parameters

Table 3 shows the results from the PRCC sensitivity analysis. As expected,

a higher pandemic hazard rate (PRCC = 0.581, p<0.0001), a larger pandemic (PRCC = 0.279, p<0.0001), and a higher antibiotic decay rate (PRCC = 0.578, p<0.0001) increased the value of withholding wide use of the novel antibiotic. The most important parameter influencing potential benefits during the pandemic was the portion of secondary bacterial infections caused by the resistant strain (PRCC = 0.790, p<0.0001). The most influential parameter negatively correlated with the option value was the cost of hospitalization (PRCC = -0.622, p<0.0001). A longer pandemic duration (PRCC = -0.305, p<0.0001) reduced the value due to resistance spreading and due to discounting further into the future; we did not consider the shock impact of a high number of deaths over a short duration, which likely would have increased the negative impact of the pandemic duration hazard rate.

Table 3. Partial rank correlation coefficient (PRCC) sensitivity analysis

Parameter	PRCC	p-value
Antibiotic stockpiling costs	0.000	0.94337
Hospitalization costs	-0.622	0.00000
Value of statistical life	0.052	0.00000
Hospital days averted during non-pandemic period	-0.409	0.00000
Pandemic hazard rate	0.581	0.00000
Pandemic period hazard rate (1/mean duration)	-0.305	0.00000
Pandemic attack rate	0.279	0.00000
Pandemic case fatality rate (not including deaths caused by resistant *S. aureus* strain)	0.071	0.0000
Percent develop secondary	0.260	0.00000
Portion of bacterial infections that are *S. aureus* strain resistant to existing oral antibiotics	0.790	0.00000
Secondary infections with resistant *S. aureus* strain case fatality rate	0.116	0.00000
Capacity to treat intravenously	-0.199	0.00000
Antibiotic decay rate	0.578	0.00000

100,000 Latin Hypercube samples were drawn. Parameter distributions are presented in Table 1 and 2.

4.5. Option value thresholds

In this section we vary the most influential parameters to determine under what conditions Policy A, the option to withhold wide use of the novel antibiotic, is beneficial. We then also use equation (10) to consider the maximum ratio of benefits pre-pandemic to post-pandemic for Policy A to be beneficial.

Figure 4 plots the impact of the pandemic—captured by varying the percent of secondary bacterial infections that are caused by the resistant *S. aureus* strain—against other influential parameters. In each panel, all other parameters were set to the base-case without economic losses averted and IV therapy coverage at 50%. When we set the hazard rate (Panel A) to 3/100 per year, the cut-off point at which withholding the antibiotic was beneficial (the value of waiting = 0) was when the resistant strain caused approximately 2% of secondary infections and 14,000 avertable deaths. For hazard rates 1/100, 1/300, or 1/500 per year, the corresponding cut-off points were approximately 4.5%, 11.7%, or 18.0% of secondary infections.

When we set the novel antibiotic annual rate of decay (Panel B) to 0.02, the cut-off point was approximately 6.3% of secondary infections caused by the resistant strain (~43,000 avertable deaths). The lowest rate of decay for which withholding the antibiotic was beneficial was 0.0067, and it was only beneficial when more than 19.7% of secondary infections were caused by the resistant bacteria (~134,000 avertable deaths).

When we set the cost of hospitalization (Panel C) to below $2,000, the resistant strain had to cause more than 2.3% of secondary infections for Policy A to be beneficial. When we set the cost to $5,000 or $10,000 the cut-off point was 5% and 12.7% of secondary infections respectively. If 100,000 hospital days were averted (Panel D) in the year the antibiotic was first introduced during the pre-pandemic period (and slightly less each following year as the antibiotic decayed), the cut-off point would be 2% of secondary infections, and if it was 300,000 or 500,000 hospital days averted, the cut-off points would be 6.3% (~43,000 avertable deaths) and 10.7% (~73,000 avertable deaths) respectively.

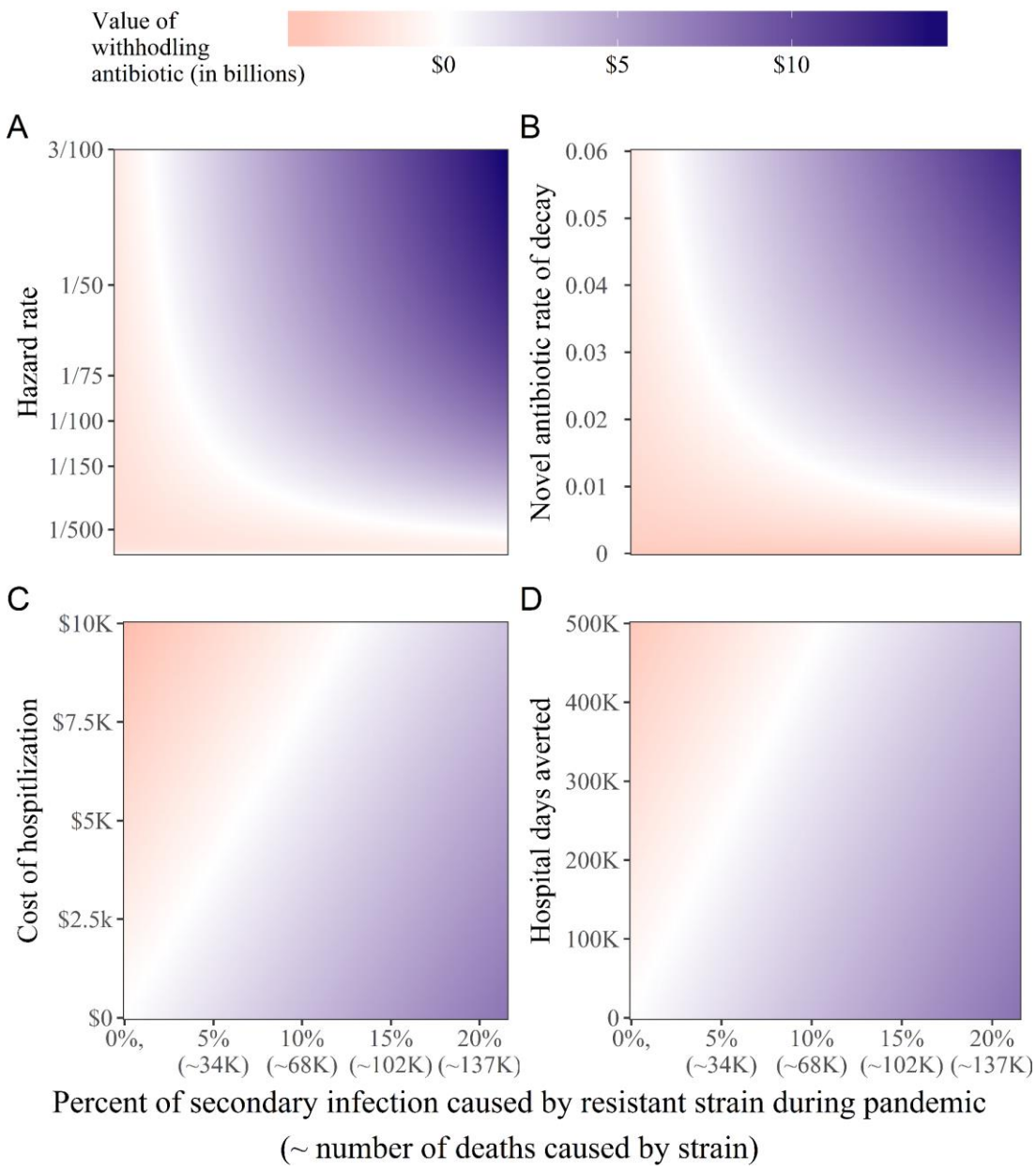


Figure 4. Sensitivity of the option value model to influential parameters.

Finally, we use the base-case values of parameters on the right-hand side of inequality (10) to calculate the threshold

$$\frac{B_{PP}}{B_P} < \frac{0.02 \times \frac{1}{150}}{\left(0.035 + \frac{1}{150}\right)\left(0.02 + 0.035 + \frac{52}{15}\right)} \approx 0.001.$$

Our base-case values indicate withholding wide use of the antibiotic will be a preferred strategy if the annual benefits during the pandemic are at least 1000 times greater than the

annual pre-pandemic benefits. In the mild and severe pandemic scenarios, the annual benefits during the pandemic would need to be at least 380 and 3,000 times greater than the pre-pandemic ones respectively.

4.6. Discussion

The literature assessing the value and cost-effectiveness of antibiotics assumes introducing antibiotics is a now-or-never decision (e.g., Sertkaya et al., 2014) despite the inherent value of the option to delay antibiotics' use to slow down emergence and spread of resistance. We developed a model based on real options theory to estimate the value of delaying antibiotic introduction. The closest work to our model is by Attema et al. (2010), who use a real options framework to value investment in stockpiling an antiviral drug for an influenza pandemic with uncertain timing. In their model, the economic value derives from the option to delay investing in their stockpile, but we additionally value delaying the spread of resistance to our treatment. The effectiveness of the precautionary measure (i.e., the stockpile) is endogenous in our model. Attema et al. assume uncertainty follows a Brownian motion. Our goal was to provide a closed-form solution that can be simply calculated for different antibiotics and indications without requiring simulation. Incorporating antimicrobial resistance in our model introduced additional complexity that prevented us from arriving at a close-form solution, and therefore we assumed exponentially distributed uncertainty. We derived a theoretical condition under which withholding wide use of the antibiotic would be a preferred option from a benefit-cost perspective as compared to using the antibiotic immediately. We empirically quantified the threshold value for the condition to withhold, and we estimated the option value for stockpiling and withholding wide use of a novel oral antibiotic until detecting an influenza pandemic that potentially overwhelms the healthcare system in the UK.

Pandemic influenza preparedness provides a clear example of when conserving antibiotic effectiveness for a specific indication provides value to society. If the background prevalence of resistant bacterial strains—mostly carried asymptomatically in the community—is high, pandemic influenza can lead to a wave of secondary infections with few treatment options. Even if prevalence in the community is not high, transmission of resistant strains in healthcare facilities that are accommodating an influx of patients can be high, similarly leading to resistant secondary infections. The acute pressure on the healthcare system could

overwhelm providers to the point they cannot sufficiently treat all patients during the peak of the pandemic, even if IV antibiotic therapy exists. Without an effective option to quell rising demand for an orally-administered antibiotic in primary care services, a high number of cases and deaths and knock-on effects on the economy caused by absenteeism could be devastating. Interventions that mitigate these outcomes will undoubtedly hold value. The health economics literature found pharmaceutical interventions such as vaccines and antivirals and non-pharmaceutical interventions such as school-closures cost-effective in many circumstances (Velasco et al., 2012). Effective antibiotics are unlikely to reduce the number of cases in an influenza pandemic, but they are likely to reduce severe illness and deaths, and therefore, potentially absenteeism (Chien et al., 2012).

We found that protecting our hypothetical oral antibiotic until detecting pandemic influenza can provide significant value. However, if the pandemic is mild or if the prevalence of the resistant pathogen is non-existent, the population would be better off either using the antibiotic earlier or continuing to wait until a more significant event occurs. We assumed a prevalent *S. aureus* strain resistant to all oral options except for the hypothetical drug. A few novel agents for treating methicillin-resistant *S. aureus* were approved in the last decade, including linezolid, which can be administered orally, and additional investigational agents are in the pipeline (Rodvold & McConeghy, 2014). Our hypothetical antibiotic can represent one of these drugs, but since experience has taught us that *S. aureus* quickly develops resistance to novel agents, our model may also be used as a decision tool, whether to invest in a new drug.

If we wait until no options are available before deciding to invest in novel drugs, we may be too late. Having effective antibiotics is critical for preventing outbreaks in healthcare settings forcing shutting down wards and for reducing the impact and costs of disastrous events such as significant influenza pandemics (Brundage, 2006), food-borne infection outbreaks (Newell et al., 2010), or natural disasters (Ligon, 2006). These events are unpredictable, and it is unlikely that scientists and pharmaceuticals will have sufficient time to develop new effective drugs when they strike.

Ignoring the opportunity cost to delay the introduction of novel antibiotics and conserve their effectiveness will narrow investments in antibiotics to ones that provide immediate value and will presuppose a strategy of immediate wide use, and this will leave the population

unprepared. When the risks for significant events that will require effective antibiotics are sufficiently low, we may be better off not investing in a new drug when other options are available, but ignoring the benefits of the option to delay increases the likelihood that we will not be prepared even if the risks are sufficiently high.

Decisions on investment in antibiotics need to consider both immediate values and the value to delay. Immediately introducing an approved agent will be the optimal choice in many cases. For example: agents that treat infections with a high burden and limited treatment options; agents that add significant value by increasing the diversity of an existing portfolio and slowing resistance spread; and agents that provide significant value enabling other medical procedures, including surgery and chemotherapy.

Our model is a simplification. We only consider one significant event (i.e., one pandemic influenza) occurring, we do not consider transmission dynamics, and we assume that resistance to the novel antibiotic increases at a constant rate when it is widely used. These assumptions can be relaxed in future models and simulations. Furthermore, a positive value in our model does not imply private firms have incentive to invest in antibiotic development. Providing a rational for this would require a broader regulatory and risk sharing framework, and this is an area for future work. We apply our model to a pandemic influenza scenario leading to secondary bacterial infections; however, reparametrizing the model it can be applied to other outbreaks.

The results we present in our worked example suggest that considering the option value of delaying introducing antibiotics is important for making decisions to invest in antibiotics. Governments globally will need to consider this value as we move to new business models for encouraging antibiotics research and development (R&D) and promoting stewardship; experts globally are pushing for a delinked model for antibiotics, in which healthcare systems pay a flat annual fee instead of pharmaceutical revenues relying on volume of sales (Towse et al., 2017; Department of Health, 2017). This provides the healthcare system the opportunity to devise strategies for antibiotics use. For certain antibiotics it may be obvious that introducing the antibiotic today will be optimal, but in other cases comparing the values an antibiotic provides can guide investment in novel agents as well as strategies on how to use them.

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Figure Legends

Figure 1. Policy A. The antibiotic is available at t_0, but is held off until the outbreak is detected.

Figure 2. Policy B. The antibiotic is available at t_0 and is widely introduced immediately.

Figure 3. Value of withholding a novel oral antibiotic until pandemic influenza is identified. The values without economic losses include deaths and hospitalizations averted. Economic losses are based on an S-shaped curve relating percent GDP loss to mortality, which triggers higher rates of absenteeism. We consider different levels of capacity for the healthcare system treating patients intravenously: 20%, 50%, and 80% in the base-case, 50% and 80% when the pandemic scenario is mild, and 20% and 50% when it is severe. Parameters for the base-case, mild, and severe scenarios are provided in Table 1 and Table 2.

Figure 4. Sensitivity of the option value to influential parameters. The x-axis is the percent of secondary infections caused by the resistant *S. aureus* strain; the approximate number of avertable deaths by an effective oral antibiotic are in parentheses. The y-axes are A) the annual hazard rate of the base-case pandemic influenza scenario, B) the novel antibiotic annual rate of decay when the antibiotic is widely used, C) the cost of hospitalization, and D) the number of hospital days averted annually when the antibiotic is widely used during the non-pandemic period. In each panel, all other parameters are set to the base-case without economic losses averted (see Table 1 and Table 2).