

1 Investing in antibiotics to alleviate future catastrophic
2 outcomes: what is the value of having an effective
3 antibiotic to mitigate pandemic influenza?
4

5 **Abstract**

6
7 Over ninety-five percent of post-mortem samples from the 1918 pandemic, which caused 50
8 to 100 million deaths, showed bacterial infection complications. The introduction of
9 antibiotics in the 1940s has since reduced the risk of bacterial infections, but growing
10 resistance to antibiotics could increase the toll from future influenza pandemics if secondary
11 bacterial infections are as serious as in 1918, or even if they are less severe. We develop a
12 valuation model of the option to withhold wide use of an antibiotic until significant outbreaks
13 such as pandemic influenza or foodborne diseases are identified. Using real options theory,
14 we derive conditions under which withholding wide use is beneficial and calculate the option
15 value for influenza pandemic scenarios that lead to secondary infections with a resistant
16 *Staphylococcus aureus* strain. We find that the value of withholding an effective novel oral
17 antibiotic can be positive and significant unless the pandemic is mild and causes few
18 secondary infections with the resistant strain or if most patients can be treated intravenously.
19 Although the option value is sensitive to parameter uncertainty, our results suggest that
20 further analysis on a case-by-case basis could guide investment in novel agents as well as
21 strategies on how to use them.

22
23 Key words: real options analysis; insurance value; antibiotics; antibiotics resistance;
24 pandemic influenza; secondary bacterial infections

26 **1. Introduction**

27 In the past four hundred years, roughly three influenza pandemics have spread across the
28 world each century, killing millions of people (Potter, 2001). The most recent pandemic
29 influenza prior to the introduction of antibiotics in 1942 was the 1918 (H1N1) pandemic, also
30 known as the ‘Spanish Flu.’ It was the most devastating pandemic historically, infecting a
31 third of the world’s population and killing 50 to 100 million people (Johnson & Mueller,
32 2002). Postmortem samples showed that over ninety-five percent of deaths in the 1918
33 pandemic were complicated by a bacterial infection (Morens, Taubenberger, & Fauci, 2008),
34 and had antibiotics been available in 1918, many deaths could have been averted (Brundage,
35 2006; Handel, Longini, & Antia, 2009; Chien, Levin, & Klugman, 2012). Since then,
36 experience and science have taught us more about influenza viruses and pandemics (1957,
37 1968, and 2009), and we have developed tools, such as better infection control, vaccines,
38 antivirals, and antibiotics, to prepare for and combat future pandemics.

39
40 Despite the significant research on previous pandemics undertaken in the 21st century, it is
41 difficult to predict the timing and scale of the next pandemic. Influenza A viruses continually
42 evolve through accumulated mutations over time (antigenic drift) and also by less frequent
43 but more drastic antigenic changes that occur when different sub-types infect a single cell
44 (antigenic shift). Pandemic influenza occurs when a novel influenza A sub-type emerges or
45 an old one—not recently in cycle—reemerges in an immunologically naïve human population
46 (Webby & Webster, 2001). These changes are unpredictable, making future pandemics
47 inevitable, and their timing and scale unknown (Webby & Webster, 2001; Taubenberger &
48 Morens, 2010).

49
50 The World Health Organization (WHO) and several countries have developed pandemic
51 preparedness plans, which include maintaining stocks of antivirals, antibiotics, and vaccines
52 to minimize the impact of future pandemics (e.g., US Department of Health and Human
53 Services, 2005; Department of Health, 2011a; WHO, 2009). Supporting these plans, the
54 breadth of literature on the value and cost-effectiveness of stockpiling vaccines and antivirals
55 has increased in the 21st century (Velasco et al., 2012 and herin; Germann, Kadau, Longini, &
56 Macken, 2006; Attema, Lugnér, & Feenstra, 2010; Halder, Kelso, & Milne, 2014). However,
57 the economic value of stockpiling or conserving the effectiveness of antibiotics remains
58 unexplored despite the high morbidity and mortality caused by secondary bacterial infections.

59

60 Maintaining a stockpile of antibiotics will not be an effective strategy for preparedness if the
61 antibiotics are not effective. The emergence of multi-drug resistant and pandrug-resistant
62 (PDR), untreatable infections and the alarm bells of a potential postantibiotic era emphasize
63 the value of protecting our investment in effective antibiotics, whether existing or in the
64 development pipeline (Souli, Galani, & Giamarellou, 2008; McGann et al., 2016; Chen,
65 2017; Laxminarayan et al., 2013). In a world with prevalent PDR bacterial infections,
66 treatment costs increase significantly, cuts and scrapes can be life-threatening, and common
67 surgical procedures and cancer chemotherapy may lead to unacceptably high rates of
68 untreatable infections (Teillant, Gandra, Barter, Morgan, & Laxminarayan, 2015; ECDC &
69 EMEA, 2009). In the event of a significant influenza pandemic, secondary infections caused
70 by prevalent PDR bacteria could be catastrophic. Ensuring effective antibiotics in the future
71 is a public health priority, and only two novel classes of antibiotics have been introduced
72 since the 1970s (Coates, Halls, & Hu, 2011).

73

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

84

85 The literature on valuing new antibiotics provides a framework to estimate their expected net
86 present value (NPV) (Sertkaya et al., 2014), but it fails to capture the irreversible effect of
87 resistance and the value new antibiotics contribute to having effective treatment options in
88 the future. Traditional NPV analysis assumes the decision to invest is a now-or-never one and
89 does not consider delaying investing, or in our case introducing the wide use of an antibiotic.
90 However, real options theory has studied the impact of irreversibility and uncertainty on the
91 value of delaying investment and maintaining flexibility (Myers, 1977; McDonald & Siegel,
92 1986; Dixit & Pindyck, 1994; Trigeorgis, 1996). Real options valuation has roots in corporate

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

101

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

113

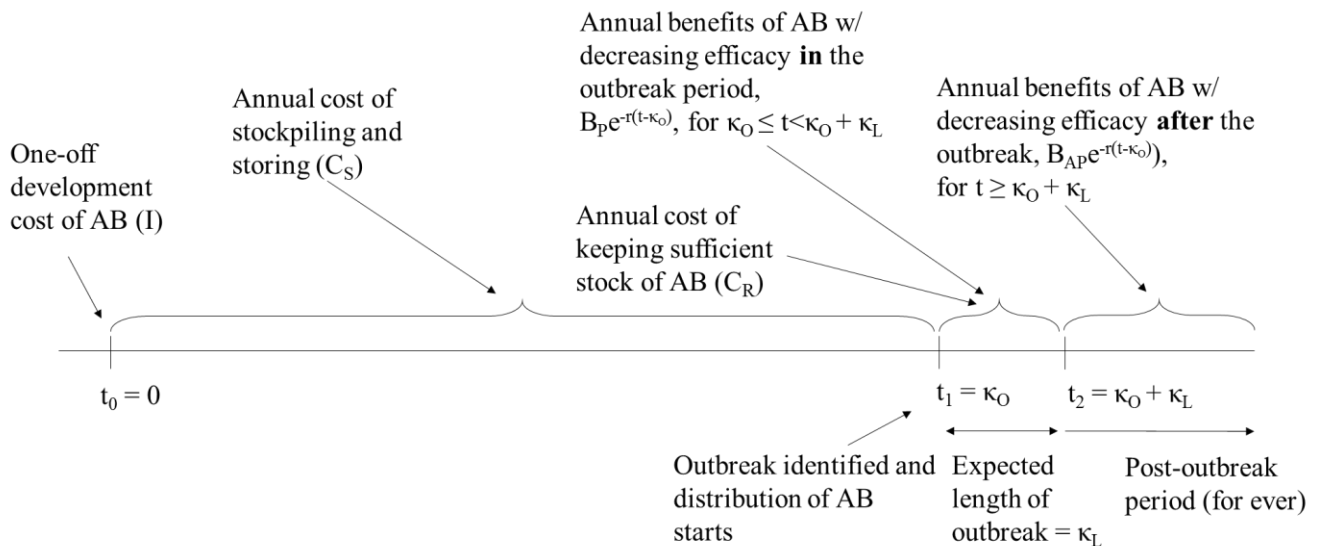
114 In this paper, we apply real options theory and develop a framework for assessing trade-offs
115 to estimate the value of investing in developing and conserving an antibiotic to mitigate the
116 burden of bacterial infections during pandemic influenza. A similar model can be applied to
117 value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

128 **2. Model: option value of conserving antibiotics**

129 We assume the novel antibiotic is available at time $t_0 = 0$, and its development cost is I . At
 130 time t_1 , which is uncertain, an outbreak of infections caused by PDR bacteria is identified. A
 131 decision maker, such as the UK Department of Health, needs to decide whether to widely
 132 introduce the antibiotic at t_0 or withhold its wide use until t_1 , when the benefits may be
 133 higher. We model both policies' NPVs, with costs and benefits related to the new antibiotic
 134 that accrue over time discounted at the annual rate μ . The difference between the policies'
 135 NPVs represent the value of the option to conserve the antibiotic's effectiveness until the
 136 outbreak is identified. We define this value as the 'option value.' Since the novel antibiotic is
 137 available at time t_0 in both policies (i.e., investment in the antibiotic is not delayed in either
 138 policy), the investment cost I does not impact the option value of conserving effectiveness.
 139

140 **2.1. Policy A: Withhold wide use of antibiotic**

141 Use of the novel antibiotic is held off until a significant outbreak is detected at an uncertain
 142 point in time, t_1 (Figure 1). The model for Policy A calculates the value to invest in
 143 developing an antibiotic conserved until detecting the outbreak.
 144



145
 146 **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 $\kappa_o \leq t < \kappa_o + \kappa_L$.

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

$$\frac{C_S}{\mu + h_o}, \quad (1)$$

174 benefits – costs during the outbreak are

$$\frac{h_o}{\mu + h_o} \left(\frac{B_p}{r + \mu + h_L} - \frac{C_R}{\mu + h_L} \right), \quad (2)$$

175 benefits after the outbreak are

$$\frac{h_o h_L B_{AP}}{(\mu + h_o)(r + \mu)(r + \mu + h_L)}, \quad (3)$$

176 and the NPV of Policy A is

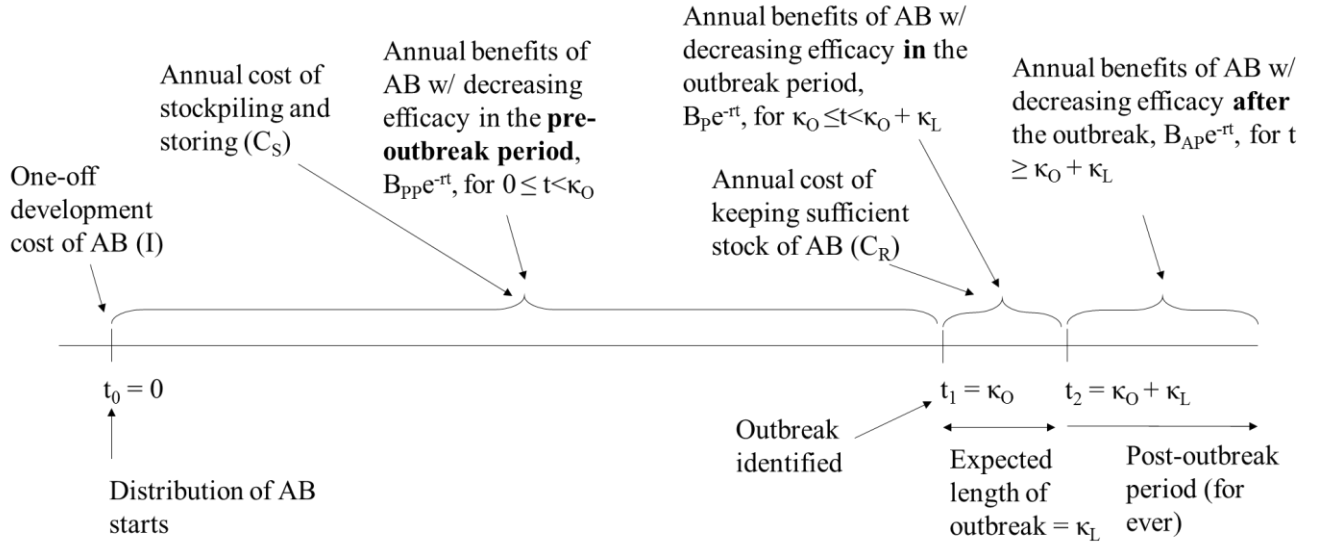
$$-I - (1) + (2) + (3). \quad (4)$$

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

192 effectiveness due to resistance. The discounted annual benefits after the outbreak (i.e., after
 193 $t_2 = \kappa_O + \kappa_L$) are $B_{AP}e^{-rt}$.

194

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

197

198 benefits – costs before the outbreak are

$$\frac{B_{PP}}{\mu + r + h_O} - \frac{C_S}{\mu + h_O}, \quad (5)$$

199 benefits – costs during the outbreak are

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

200 benefits after the outbreak are

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

201 and the NPV of Policy B is

$$-I + (5) + (6) + (7). \quad (8)$$

202

203 **2.3. Option value**

204 The option value of conserving effectiveness is the difference between expressions (4) and
 205 (8).

206

207 **2.4. Parameters thresholds**

208 We now investigate the conditions under which the option value is positive and withholding
 209 immediate wide use of the antibiotic is beneficial. After simplifications, the condition

210 $NPV_A > NPV_B$ implies

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

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

213

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

$$\frac{B_{PP}}{B_P} < \frac{rh_o}{(\mu + h_o)(r + \mu + h_L)} \quad (10)$$

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

220

221 Because $\partial m / \partial r > 0$, the maximum value of the threshold is when $r \rightarrow \infty$, producing

$$222 \quad m = \frac{h_o}{\mu + h_o}. \text{ Similarly, because } \partial m / \partial h_o > 0, \text{ when } h_o \rightarrow \infty, \text{ then } m = \frac{r}{r + \mu + h_L}, \text{ Finally,}$$

223 since $\partial m / \partial h_L < 0$, the maximum value of m is when $h_L \rightarrow 0$, producing

$$224 \quad m = \frac{rh_o}{(\mu + h_o)(r + \mu)}.$$

225

226 Note that in the extreme cases, when $r = 0$ or $h_o = 0$, inequality (10) reduces to $\frac{B_{PP}}{B_P} < 0$,

227 which cannot hold because benefits are positive. Therefore, when $r = 0$ or $h_o = 0$,

228 $NPV_A < NPV_B$. Intuitively, if no resistance to antibiotics builds up ($r = 0$), then we always

229 choose to introduce the antibiotic immediately after its development. Similarly, if expected

230 time to the outbreak approaches infinity ($h_o = 0$), we always choose immediate introduction.

231

232 **3. Application scenario details**

233 **3.1. Influenza pandemic scenario**

234 We based our pandemic scenarios on the UK preparedness plan assumptions (Department of

235 Health, 2007, 2011a) but made specific assumptions regarding prevalence of bacterial

236 infections (see Table 1). In the base-case, we assumed that the influenza pandemic will lead

237 to secondary bacterial infections in 20% of cases (Brundage, 2006; Morens et al., 2008), with

238 10% of these infections caused by a resistant *Staphylococcus aureus* strain (Morens et al.,
 239 2008; Oswald, Shooter, & Curwen, 1958; Louria, Blumenfeld, Ellis, Kilbourne, & Rogers,
 240 1959; Schwarzmann, Adler, Sullivan, & Marine, 1971). Though *S. aureus* represented only
 241 8% of bacterial pathogens in autopsies of the 1918 pandemic, it was predominant in the 1957
 242 pandemic potentially because resistance to tetracycline and streptomycin was becoming
 243 widespread (Morens et al., 2008; Department of Health, 2011b). We assumed the base-case
 244 scenario hazard rate (h_o) is 1/150 (see Appendix B).

245
 246 The prevalence of secondary bacterial infections in community and healthcare settings would
 247 stress the healthcare system. Available oral antibiotics may not effectively treat infections
 248 with the resistant *S. aureus* strain, and individuals infected with the strain would require
 249 hospitalization. Though we assumed intravenous (IV) therapy exists, the increased volume of
 250 cases would overburden the health system, leading to deaths and increased economic costs.
 251 Previous estimates suggested that hospital capacity may only meet 20% to 25% of expected
 252 demand at the pandemic peak (Department of Health, 2007), and exacerbating the situation,
 253 the risk of secondary bacterial infections may be greater in healthcare settings than in the
 254 community, particularly in the case of a pathogen such as resistant *S. aureus*, which is
 255 prevalent in this setting (Nin et al., 2011; European Centre for Disease Prevention and
 256 Control, 2017). We modelled three levels of IV therapy coverage: 20%, 50%, and 80%.

257
 258 Table 1 provides details on the base-case scenario and on more mild and severe scenarios;
 259 Appendix B describes the scenario parameter choices in more detail.

260

261 **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,

Pandemic overall case fatality rate (CFR), including secondary bacterial infections	1%	0.04%	2.5%	Beta (0.02%, 0.5%, 2%) [§]	2010; Department of Health, 2007, 2011a) (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 <i>S. aureus</i> 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; Schwarzmman et al., 1971)
CFR for <i>S. aureus</i> 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 constraints 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.

262

263

264

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

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

271

272 3.2. Costs

273 We considered the costs of developing (I) and stockpiling (C_S) the novel antibiotic,
 274 including the cost of wastage, misdiagnosis, and empirical treatment that is likely due to the
 275 volume of patients. We ignored the costs of distributing antibiotics (C_R) during the
 276 pandemic, which are small compared to potential burden averted by the novel antibiotic (see
 277 3.3 Benefits) and are incurred in both Policy A and Policy B. Future costs were discounted at
 278 3.5%. Table 2 provides the costs and benefits (further explained in Appendix B).

279

280 **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.

281

282 3.3. Benefits

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

289

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

300

301 The benefits decayed according to r when policy dictated the oral antibiotic's wide use.

302 Benefits were further discounted at 3.5%.

303

304 **3.4. Sensitivity analysis**

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

311

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

318

319 Lastly, we explored the relative sensitivity of the option value model to parameters using
320 Latin Hypercube Sampling (LHS) and conducting a Partial Rank Correlation Coefficient
321 (PRCC) analysis. The sampling distributions are provided in Table 1 and in Table 2.

322 Parameters with large absolute PRCC values that are statistically significant (t-test) are most

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

326

327 **4. Application results**

328 **4.1. Base-case**

329 In the base-case pandemic scenario approximately 455,000 individuals developed secondary
330 bacterial infections with the *S. aureus* strain resistant to all oral options but the novel
331 antibiotic. The strain caused approximately 68,000 deaths when we assumed the healthcare
332 system had the capacity to intravenously treat 50% of patients infected with it (30% of all
333 pandemic related deaths). The strain caused 27,000 deaths if capacity was set to 80% and
334 109,500 deaths if it was 20%.

335

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

342

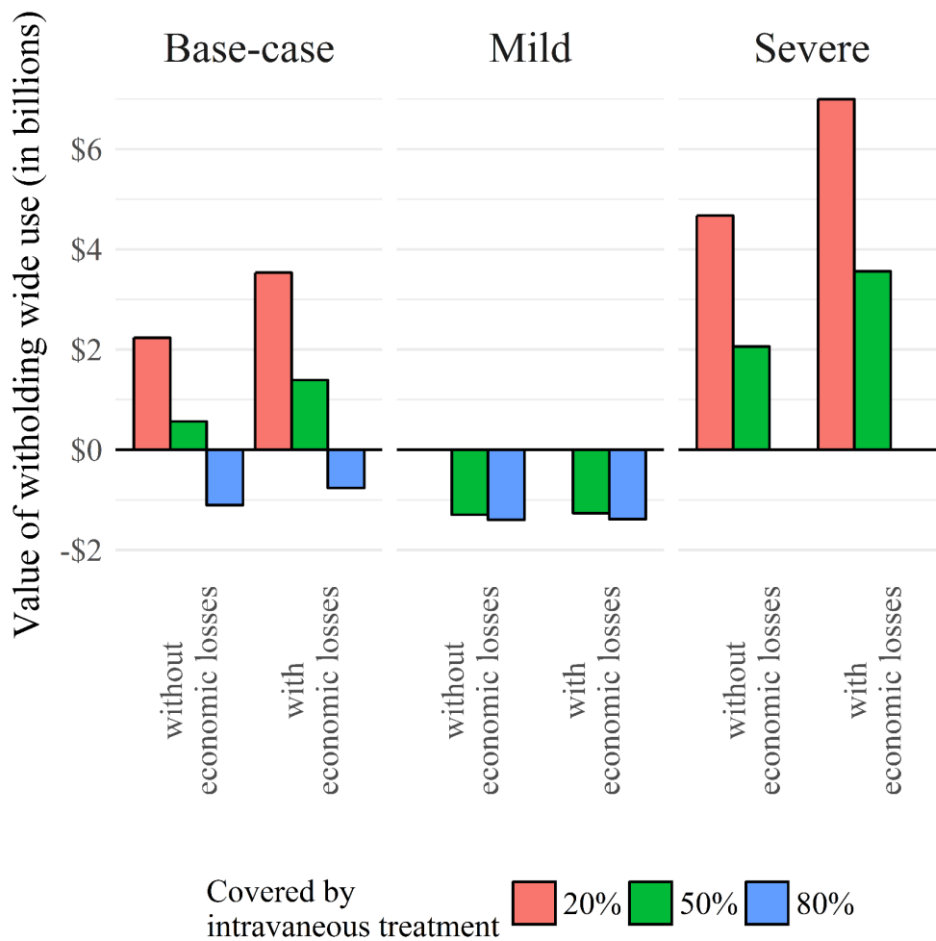
343 **4.2. Alternative scenarios**

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

350

351 Withholding wide use of the novel antibiotic until the severe pandemic scenario provided
352 significant value despite the low hazard rate. In this scenario, the pandemic CFR was set to
353 2.5% and deaths caused by infections with the resistant *S. aureus* strain represented 36%

354 (57.5%) of these deaths when IV therapy covered 50% (20%) of patients. The option value
 355 was \$2.1 billion (\$4.7 billion) when IV therapy covered 50% (20%) of patients.
 356



357
 358 **Figure 3. Value of withholding a novel oral antibiotic until pandemic influenza is identified.**

359
 360 **4.3. Economic losses**

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

367
 368 **4.4. Model sensitivity to parameters**

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

370 a higher pandemic hazard rate (PRCC = 0.581, $p < 0.0001$), a larger pandemic (PRCC = 0.279,
 371 $p < 0.0001$), and a higher antibiotic decay rate (PRCC = 0.578, $p < 0.0001$) increased the value
 372 of withholding wide use of the novel antibiotic. The most important parameter influencing
 373 potential benefits during the pandemic was the portion of secondary bacterial infections
 374 caused by the resistant strain (PRCC = 0.790, $p < 0.0001$). The most influential parameter
 375 negatively correlated with the option value was the cost of hospitalization (PRCC = -0.622,
 376 $p < 0.0001$). A longer pandemic duration (PRCC = -0.305, $p < 0.0001$) reduced the value due to
 377 resistance spreading and due to discounting further into the future; we did not consider the
 378 shock impact of a high number of deaths over a short duration, which likely would have
 379 increased the negative impact of the pandemic duration hazard rate.

380

381 **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 <i>S. aureus</i> strain)	0.071	0.00000
Percent develop secondary	0.260	0.00000
Portion of bacterial infections that are <i>S. aureus</i> strain resistant to existing oral antibiotics	0.790	0.00000
Secondary infections with resistant <i>S. aureus</i> 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.

382

383 **4.5. Option value thresholds**

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

388

389 Figure 4 plots the impact of the pandemic—captured by varying the percent of secondary
390 bacterial infections that are caused by the resistant *S. aureus* strain—against other influential
391 parameters. In each panel, all other parameters were set to the base-case without economic
392 losses averted and IV therapy coverage at 50%. When we set the hazard rate (Panel A) to
393 3/100 per year, the cut-off point at which withholding the antibiotic was beneficial (the value
394 of waiting = 0) was when the resistant strain caused approximately 2% of secondary
395 infections and 14,000 avertable deaths. For hazard rates 1/100, 1/300, or 1/500 per year, the
396 corresponding cut-off points were approximately 4.5%, 11.7%, or 18.0% of secondary
397 infections.

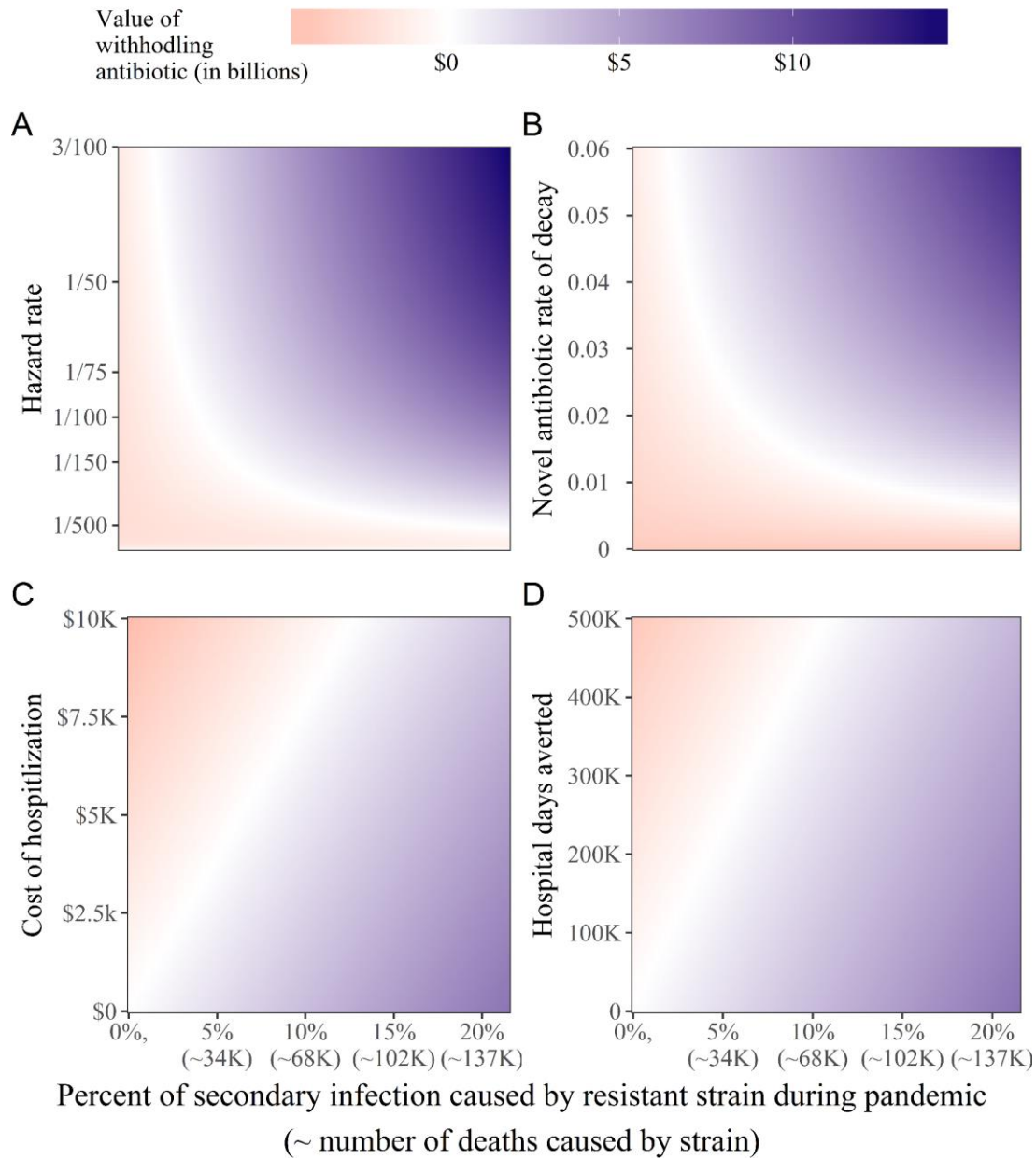
398

399 When we set the novel antibiotic annual rate of decay (Panel B) to 0.02, the cut-off point was
400 approximately 6.3% of secondary infections caused by the resistant strain (~43,000 avertable
401 deaths). The lowest rate of decay for which withholding the antibiotic was beneficial was
402 0.0067, and it was only beneficial when more than 19.7% of secondary infections were
403 caused by the resistant bacteria (~134,000 avertable deaths).

404

405 When we set the cost of hospitalization (Panel C) to below \$2,000, the resistant strain had to
406 cause more than 2.3% of secondary infections for Policy A to be beneficial. When we set the
407 cost to \$5,000 or \$10,000 the cut-off point was 5% and 12.7% of secondary infections
408 respectively. If 100,000 hospital days were averted (Panel D) in the year the antibiotic was
409 first introduced during the pre-pandemic period (and slightly less each following year as the
410 antibiotic decayed), the cut-off point would be 2% of secondary infections, and if it was
411 300,000 or 500,000 hospital days averted, the cut-off points would be 6.3% (~43,000
412 avertable deaths) and 10.7% (~73,000 avertable deaths) respectively.

413



414

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

416

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

418 calculate the threshold

419

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

420

421 Our base-case values indicate withholding wide use of the antibiotic will be a preferred

422 strategy if the annual benefits during the pandemic are at least 1000 times greater than the

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

426

427 **4.6. Discussion**

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

448

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

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

466
467 We found that protecting our hypothetical oral antibiotic until detecting pandemic influenza
468 can provide significant value. However, if the pandemic is mild or if the prevalence of the
469 resistant pathogen is non-existent, the population would be better off either using the
470 antibiotic earlier or continuing to wait until a more significant event occurs. We assumed a
471 prevalent *S. aureus* strain resistant to all oral options except for the hypothetical drug. A few
472 novel agents for treating methicillin-resistant *S. aureus* were approved in the last decade,
473 including linezolid, which can be administered orally, and additional investigational agents
474 are in the pipeline (Rodvold & McConeghy, 2014). Our hypothetical antibiotic can represent
475 one of these drugs, but since experience has taught us that *S. aureus* quickly develops
476 resistance to novel agents, our model may also be used as a decision tool, whether to invest in
477 a new drug.

478
479 If we wait until no options are available before deciding to invest in novel drugs, we may be
480 too late. Having effective antibiotics is critical for preventing outbreaks in healthcare settings
481 forcing shutting down wards and for reducing the impact and costs of disastrous events such
482 as significant influenza pandemics (Brundage, 2006), food-borne infection outbreaks (Newell
483 et al., 2010), or natural disasters (Ligon, 2006). These events are unpredictable, and it is
484 unlikely that scientists and pharmaceuticals will have sufficient time to develop new effective
485 drugs when they strike.

486
487 Ignoring the opportunity cost to delay the introduction of novel antibiotics and conserve their
488 effectiveness will narrow investments in antibiotics to ones that provide immediate value and
489 will presuppose a strategy of immediate wide use, and this will leave the population

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

494

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

501

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

511

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

523

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745

746 **Figure Legends**

747

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

750

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

752

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

760

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