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ORIGINAL ARTICLE

A Theoretical Framework to Quantify the Tradeoff Between Individual and Population Benefits of Expanded Antibiotic Use

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Abstract

The use of antibiotics during a disease outbreak presents a critical tradeoff between immediate treatment benefits to the individual and the long-term risk to the population. Typically, the extensive use of antibiotics has been thought to increase selective pressures, leading to resistance. This study explores scenarios where expanded antibiotic treatment can be advantageous for both individual and population health. We develop a mathematical framework to assess the impacts on outbreak dynamics of choosing to treat moderate infections not treated under current guidelines, focusing on cholera as a case study. We derive conditions under which treating moderate infections can sufficiently decrease transmission and reduce the total number of antibiotic doses administered. We identify two critical thresholds: the Outbreak Prevention Threshold (OPT), where expanded treatment reduces the reproductive number below 1 and halts transmission, and the Dose Utilization Threshold (DUT), where expanded treatment results in fewer total antibiotic doses used than under current guidelines. For cholera, we find that treating moderate infections can feasibly stop an outbreak when the untreated reproductive number is less than 1.42 and will result in fewer does used compared to current guidelines when the untreated reproductive number is less than 1.53. These findings demonstrate that conditions exist under which expanding

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treatment to include moderate infections can reduce disease spread and the selective pressure for antibiotic resistance. These findings extend to other pathogens and outbreak scenarios, suggesting potential targets for optimized treatment strategies that balance public health benefits and antibiotic stewardship.

Keywords Antibiotic resistance · Dynamical modeling · Epidemiology · Public health interventions · Cholera · Threshold analysis · Reproductive number

1 Introduction

The global rise in antibiotic resistance poses a significant public health threat, leading the World Health Organization (WHO) to issue a warning that the world is "running out of antibiotics". Chinemerem Nwobodo et al. (2022); Organization et al. (2017) The emergence of antibiotic resistance adds complexity to the clinical challenge of ensuring that the right antibiotic is prescribed to the right patient at the right dose for the right duration, to maximize benefits and minimize harm. Doron and Davidson (2011); Joseph and Rodvold (2008) Antibiotic resistance necessitates balancing the potential benefits and risks of antibiotic use for individual patients alongside broader implications for public health. In some cases, antibiotic prescribing has clear benefits for patients that outweigh any public health concerns (e.g., life-threatening bacterial sepsis). In other cases, antibiotic prescribing has no benefits for patients (e.g., viral infections) while the potential individual harms are multi-fold: 1 in 5 patients experience side effects from antibiotics (Tamma et al. 2017; Scott Fridkin et al. 2014); antibiotics have been shown to disrupt the gut microbiome, particularly in children where it can lead to conditions such as obesity (Liu et al. 2021); and may increase an individual's risk of developing future antibiotic-resistant infections (Mo et al. 2023; Magill et al. 2014). For these situations, individual and public health benefits align and it is easy to strongly recommend antibiotic avoidance. The complexity arises in less clear-cut scenarios where the benefits to individuals are unclear. For example, in travelers' diarrhea most patients recover without antibiotics; however, antibiotics can reduce the duration of symptoms, which, for some individuals, may be important (CDC 2022). In these cases, it is necessary to balance the individual benefit of reducing the duration of symptoms against the potential individual harms associated with broad-spectrum antibiotics, as well as public health harms including the development of antibiotic resistance. While antibiotics are a cornerstone of control for many infectious diseases, discussion of the population-level benefits of antibiotic prescribing is often absent from the discourse. Here, we discuss scenarios under which prescribing antibiotics benefits public health by reducing both transmission and selective pressure for antibiotic resistance (Fig. 1). We suggest that prescribing antibiotics to an individual reduces disease transmission enough to reduce the overall size, duration, or existence of an outbreak. In this scenario, individual level harms are reduced as well the overall number of antibiotic doses used at the population level.

Here, we demonstrate a mechanism by which antibiotic use can offer population-level benefits through reduced transmission as a result of antibiotic treatment. That is, treating highly infectious individuals who may not require treatment to recover

can reduce overall disease transmission, resulting in fewer total cases and/or fewer total antibiotic doses over the course of an outbreak. We explore this using cholera as a case study. Cholera, caused by the bacterium *Vibrio cholerae*, is a significant public health concern responsible for 1.3-4 million cases and 21,000-143,000 deaths annually worldwide (WHO 2022; Ali et al. 2015). Although most people infected with cholera do not develop symptoms, cholera can cause catastrophic diarrhea leading to potentially lethal dehydration. Since 2020, there has been a large increase in the number of cholera outbreaks, and these outbreaks have higher fatality rates than previously observed (Cholera - Global situation 2023).

The development of antibiotic resistance in cholera is a major concern that governs current antibiotic treatment recommendations (GTFCC 2018) which reserve antibiotics for patients with severe illness who are at highest risk of death without antibiotic treatment (WHO 2022). Patients with moderate illness generally experience self-limited symptoms that resolves with appropriate supportive care, and receive only a modest benefit from antibiotics primarily through reduction in symptom duration (GTFCC 2018; Cash et al. 1974; Greenough et al. 1964; Leibovici-Weissman et al. 2014; Lindenbaum et al. 1967). Although individuals with moderate infection may not individually be more infectious than severe cases, collectively, they can significantly contribute to onward transmission of the disease (Weil et al. 2009). In these patients, antibiotic treatment can reduce shedding duration by up to 90% (GTFCC 2018; Leibovici-Weissman et al. 2014). Without antibiotic treatment, an infected individual can shed cholera for up to 10 days (WHO 2022). Consequently, cholera provides an important opportunity to explore the tradeoffs between antibiotic utilization at both individual and population levels.

Mathematical models are a common tool both for exploring the effects of antibiotic use and for exploring the dynamics of cholera. Models of the population-level effects of antibiotic use are common in research of antibiotic resistance (Niewiadomska et al. 2019), including models of antibiotic stewardship programs (Caudill and Wares 2016). While modeling studies have found that pharmaceutical interventions affecting antibiotic-resistant, healthcare-associated pathogens can be cost-effective due to their transmission-reducing effects in a population (Allel et al. 2024), including decolonization of asymptomatic carriers (Robotham et al. 2011; Nelson et al. 2010; Toth et al. 2021a), these studies tend to focus on healthcare associated infections and cost-saving results, rather than the impacts on disease dynamics. Mathematical models have been instrumental in advancing the understanding of cholera transmission dynamics (Capasso and Paveri-Fontana 1979; Chao et al. 2014; Fung 2014). Models of cholera transmission reflect the diversity of acquisition sources, with some modeling only direct transmission and others including both direct and indirect (environmentally mediated) transmission (Capasso and Paveri-Fontana 1979; Chao et al. 2014). A key application of cholera models has been to evaluate the impact of interventions, particularly those related to water, sanitation, and hygiene (WASH) initiatives and vaccination campaigns (Posny et al. 2015; Sun et al. 2017; Chao et al. 2011; Fitria and Syafi'i 2019; Cai et al. 2020; Tuite et al. 2010; Lemos-Paiao et al. 2017). Such models have provided critical insights into the effectiveness, timing, and optimal frequency of these interventions. However, less attention has been paid to modeling the impact of antibiotic interventions for cholera (Mushanyu et al. 2024; Ahmed et al. 2024).

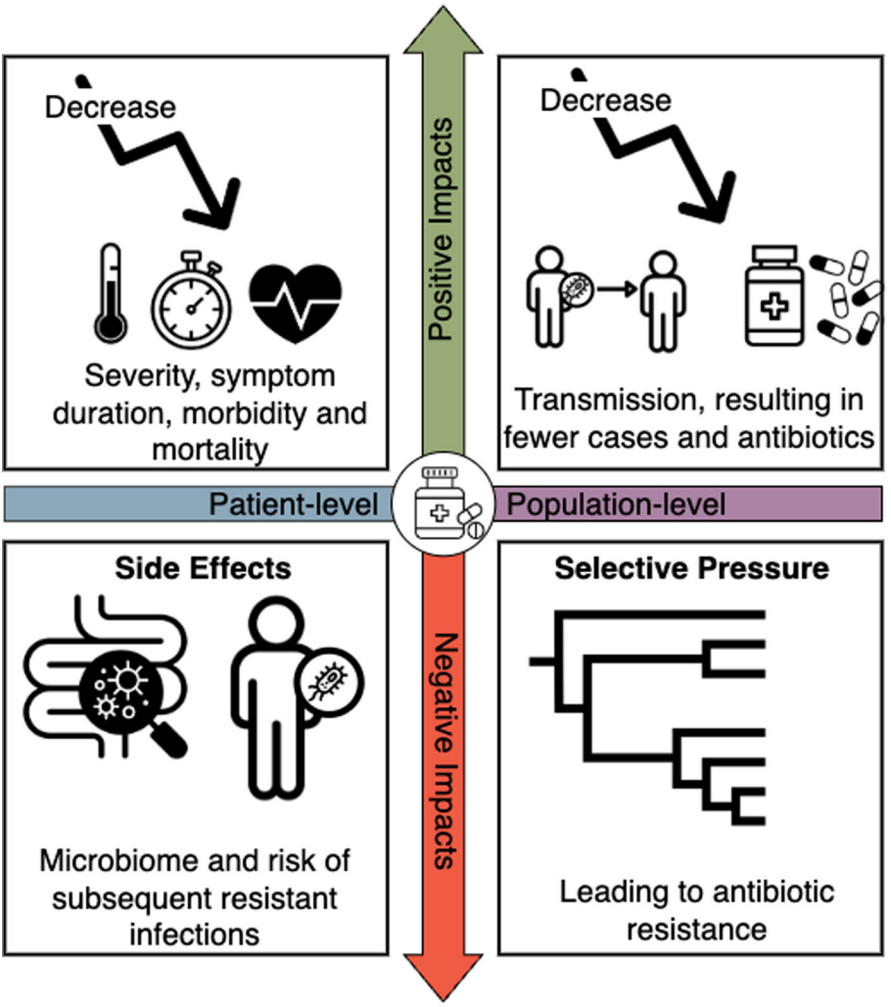

Fig. 1 Schematic of individual and population-level harms and benefits of antibiotic use. The horizontal axis describes the individual (patient-level) and population-level impacts and the vertical axis describes the benefits (positive impacts) and harms (negative impacts) of antibiotic usage

In this paper, we analytically solve for two thresholds to characterize these trade-offs and use simulation to identify the conditions under which expanded antibiotic treatment to include moderate cholera infections presents a population-level benefit by reducing cholera transmission, outbreak persistence, and total antibiotic use.

2 Methods

2.1 Model

The authors declare that there is no associated data and code is available on GitHub (https://github.com/UT-IDDynamics/Cholera_Threshold).

To examine the tradeoffs between the individual- and population-level impacts of expanding antibiotic treatment, we analytically evaluate an extension of a *Susceptible-Exposed-Infected-Removed* (SEIR) model (Fig. 2). Here we explore the effectiveness of expanded antibiotic treatment at the population-level and assume that the individual-level benefit arises from reduction in symptom severity and duration. To do this, we compare the final size of the outbreak and the total number of doses given under different treatment scenarios, as well as the impact of these treatment decisions on outbreak emergence and spread.

We model disease dynamics by dividing the population into the following compartments: Susceptible (S), Exposed (E), Infected (I), and Removed (R); and further subdivide these compartments to capture the structure essential for our questions. To track disease outcomes more effectively, we differentiate the removed class (indicated by a purple hashed box in Fig. 2) by treatment status and death: Recovered untreated (R_{un}), Recovered treated with antibiotics (R_{abx}), or Dead (D).

We subdivide the infected compartment by symptom class, treatment seeking behavior, and shedding (Table 1). We split the infected compartment into three groupings by symptom classification, denoted with the following subscripts: Asymptomatic infections ($_A$), Moderately symptomatic infections (which we call moderate infections) ($_M$), and Severely symptomatic infections (which we call severe infections) ($_S$). Asymptomatic infections do not cause noticeable symptoms but patients may still transmit. Moderate infections cause mild symptoms and patients may know that they are infected, but in the case of cholera, do not experience high fluid loss. Severe infections cause more serious symptoms, like heavy fluid loss, with an associated high risk of death if not treated promptly with re-hydration and/or antibiotics.

We subdivide the moderate and severe infectious compartments based on whether or not they present to healthcare: seeking treatment ($_T$) or not seeking treatment (untreated) ($_U$). Because asymptomatic individuals do not experience symptoms, we assume that they never seek treatment and thus do not subdivide this compartment by treatment. We assume that those with severe infections are much more likely to seek treatment due to the dire nature of their symptoms, while only some individuals with moderate infections seek treatment.

Individuals shed at different rates based on symptom severity. Asymptomatic individuals shed less overall, whereas individuals who are untreated or have not yet received treatment shed at a higher rate ($_{sy}$). Once symptoms resolve, moderate and severe infections maintain shedding for up to 10 days without antibiotic treatment ($_{sh}$). WHO (2022) We assume that all severely infected individuals receive antibiotic treatment ($_{abx}$) and remain in a cholera treatment facility until shedding has resolved before they are discharged; thus we assume they do not contribute to transmission after treatment. On the other hand, because moderate infections do not require hospitaliza-

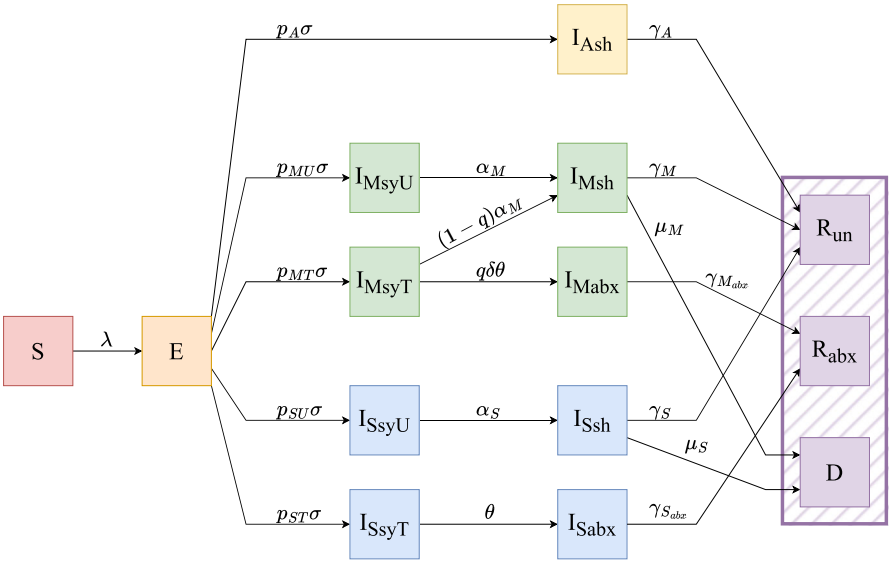

Fig. 2 Compartmental model of cholera transmission dynamics. Each compartment represents a different epidemiological class. All individuals begin in the susceptible class (S), and become exposed (E) at rate λ. From E, individuals become infectious (I) and, based on their symptoms, follow one of five different paths (Supplement 4 further describes rates $p_A\sigma$, $p_{MU}\sigma$, $p_{MT}\sigma$, $p_{SU}\sigma$, $p_{ST}\sigma$). Post-infection, individuals are removed in one of three ways (purple hatching: R_{un}, R_{abx}, D). Breaking down the transition from exposure to infectiousness, exposed individuals become asymptomatically infected (I_{Ash}) at rate $p_A\sigma$, are never eligible for treatment, and recover at rate γ_A to the recovered, untreated compartment (R_{un}). Exposed individuals become infected with moderate symptoms (I_{MsyT} or I_{MsyU}) at rate $p_{MT}\sigma$ or $p_{MU}\sigma$ depending on whether or not they seek treatment. Moderately infected individuals who do not seek treatment (I_{MsyU}) recover from symptoms at rate α_M and continue to shed (I_{Msh}) until they fully recover at rate γ_M to the recovered, untreated compartment (R_{un}), or they die at rate μ_M, moving to the dead compartment (D). Moderately infected individuals who seek treatment (I_{MsyT}) may or may not receive treatment based on the model scenario. Treatment seeking patients with moderate infections receive treatment and recover from symptoms at rate $q\delta\theta$ or do not receive treatment and recover from symptoms at rate $(1-q)\alpha_M$. Moderate infections who receive treatment continue to shed (I_{Mabx}) for a shorter duration than those not receiving treatment, and fully recover at rate $\gamma_{M_{abx}}$ to the recovered, treated compartment (R_{abx}). Treatment seeking patients with moderate infections who do not receive treatment recover from symptoms and continue to shed (I_{Msh}) until they fully recover at rate γ_M to the recovered, untreated compartment (R_{un}), or they die at rate μ_M, moving to the dead compartment (D). Exposed individuals become severely infected (I_{SsyU} or I_{SsyT}) at rate $p_{SU}\sigma$ or $p_{ST}\sigma$ depending on whether or not they seek treatment. Severely infected individuals who do not seek treatment (I_{SsyU}) recover from symptoms at rate α_S and continue to shed (I_{Ssh}) until they fully recover at rate γ_S to the recovered, untreated compartment (R_{un}), or they die at rate μ_S, moving to the dead compartment (D). All individuals with severe infections who seek treatment (I_{SsyT}) receive treatment with antibiotics at rate θ. Those with severe infections who receive treatment continue to shed (I_{Sabx}); however, they remain hospitalized until symptoms resolve and therefore do not contribute to transmission. They then fully recover at rate $\gamma_{S_{abx}}$ to the recovered, treated compartment (R_{abx}). Full model equations can be found in Supplement 4

tion alongside re-hydration, we assume they are able to transmit to others, although we assume that when treated ($_{abx}$), moderate infections shed at a far lower rate per unit time than untreated severely infected individuals.

Table 1 Summary of infected states and their properties

State	Symptoms	Treatment	Shedding
I_{Ash}	Asymptomatic	Not seeking care, not treated	Full Asymptomatic ($\nu_A\beta$)
I_{MsyU}	Moderate	Not seeking care, not treated	Full Moderate ($\nu_M\beta$)
I_{MsyT}	Moderate	Seeking care, may receive antibiotic (*)	Full Moderate ($\nu_M\beta$)
I_{Msh}	Moderate Post-symptom	May have sought care, but do not receive antibiotic (*)	Reduced Moderate ($\nu_M\nu_{sh}\beta$)
I_{Mabx}	Moderate	Seen and treated with antibiotic	Minimal Moderate ($\nu_M\nu_{abx}\beta$)
I_{SsyU}	Severe	Not seeking care, not treated	Full Severe (β)
I_{SsyT}	Severe	Seeking care, will be treated with antibiotic	Full Severe (β)
I_{Ssh}	Severe Post-symptom	Not seeking care, not treated	Reduced Severe ($\nu_{sh}\beta$)
I_{Sabx}	Severe	Seen and treated with antibiotic	None

This study focuses on states denoted with (*). The shedding column includes the associated term in the force of infection in Eq. (1), illustrating the reductions in transmission relative to the shedding caused by severely symptomatic untreated infections (β).

2.1.1 Force of Infection

In this model, we define β as the rate of transmission by severely symptomatic infections and describe the transmission potential of all other infectious compartments relative to severely symptomatic infections. We do this because for cholera, untreated, severely symptomatic individuals shed the most per unit time and are thus the most infectious. As previously described, we assume that treatment with antibiotics, natural recovery, or infections with lower symptom severity all reduce transmissibility. We use different values of the parameter ν to represent the relative modification of infectiousness for individuals in these groups compared to untreated, severely symptomatic infections (Table 2). While each ν can take on any positive value dependent on the disease of interest, for cholera, we assume that $\nu \in [0, 1]$ to represent a proportional reduction in transmission. Individuals belonging to multiple groups multiply the values for each group.

The force of infection, λ, sums the contributions to transmission of all of the infected classes, except severely infected individuals who have received treatment ($I_{S_{abx}}$), and is given by:

$$\lambda = \beta(I_{S_{syU}} + I_{S_{syT}}) + \nu_{sh}\beta I_{S_{sh}} + \nu_A\beta I_{A_{sh}} + \nu_M\beta(I_{M_{syU}} + I_{M_{syT}}) + \nu_{sh}\nu_M\beta I_{M_{sh}} + \nu_M\nu_{abx}\beta I_{M_{abx}}. \quad (1)$$

Table 2 Model parameters and definitions, grouped by related parameters with subscripts to differentiate among symptom classifications, treatment, and shedding status

Parameter	Description
λ	Force of infection
β	Transmission rate
N	Population size (use 1 to study proportion)
p_A, p_{MU}, p_{MT}, p_{SU}, p_{ST}	Proportion of exposed who become asymptomatic moderately symptomatic, or severely symptomatic – these sum to 1 (Supplement 4)
σ	Rate of symptom development – inverse of latent period
$\nu_{sh}, \nu_A, \nu_M, \nu_{abx}$	Infectiousness relative to untreated severe symptoms of natural recovery, asymptomatic, moderate symptoms and antibiotic treatment
$\gamma_A, \gamma_M, \gamma_{M_{abx}}$, $\gamma_S, \gamma_{S_{abx}}$	Recovery rate for asymptomatic, moderate moderate treated with antibiotics, severe severe treated with antibiotics
μ_M, μ_S	Death rate for moderate, severe
θ	Treatment rate – inverse of time to treatment
δ	Relative reduction of θ for moderate infection relative to severe
α_M, α_S	Rate at which symptoms resolve without antibiotic treatment (moderate, severe)
q	Moderate infection treatment effort

See Table 3 for parameter values used in the simulations.

2.1.2 Proportion of Moderate Infections Treated

To study the impact of treating moderate infections, we define the proportion of moderate infections that receive treatment as M_{abx}. M_{abx} is the fraction of departure rates from $I_{M_{sy}T}$ to the treatment states and depends on the treatment effort (q), recovery rate with antibiotic treatment (α_M), and recovery rate without antibiotic treatment ($\delta\theta$) (Table 2). M_{abx} is given by

$$M_{abx} = \frac{q\delta\theta}{(1-q)\alpha_M + q\delta\theta}\,. \tag{2}$$

Because q, defined as the relative effort in treating moderate infections compared to treating severe infections, is difficult to measure in an outbreak setting, we rearrange for q in terms of the more easily measured M_{abx} to present model outputs. Rearranging, we find:

$$q = \frac{\alpha_M M_{abx}}{\alpha_M M_{abx} + \delta\theta(1-M_{abx})} \tag{3}$$

Table 3 Model parameters values used in simulation with citations used to generate estimates

Parameter	Value	Range	Citation
$\mathcal{R}_0$	1.15	1.01−1.29	(Morris 2011; Phelps et al. 2018)
p_A	0.75	0.65−0.85	(Bertuzzo et al. 2011; Hartly et al. 2011)
p_{MU}	0	0−0	(Bertuzzo et al. 2011; Hartly et al. 2011; Weil et al. 2009)
p_{MT}	0.175	0.09−0.28	(Bertuzzo et al. 2011; Hartly et al. 2011; Weil et al. 2009)
p_{SU}	0.023	0.01−0.03	(Bertuzzo et al. 2011; Hartly et al. 2011; Weil et al. 2009)
p_{ST}	0.052	0.04−0.05	(Bertuzzo et al. 2011; Hartly et al. 2011; Weil et al. 2009)
σ	0.69	0.62−0.77	(Azman et al. 2013)
ν_{sh}	0.45	0.30−0.60	(Greenough et al. 1964; Lindenbaum et al. 1967; Wallace et al. 1968)
ν_A	0.25	0.15−0.35	see below
ν_M	0.60	0.45−0.75	see below
ν_{abx}	0.50	0.30−0.70	see below
γ_A	0.20	0.10−0.30	(Greenough et al. 1964; Lee et al. 2017; Lindenbaum et al. 1967; Wallace et al. 1968)
γ_M	0.14	0.07−0.21	(Greenough et al. 1964; Lee et al. 2017; Lindenbaum et al. 1967; Wallace et al. 1968)
$\gamma_{M_{abx}}$	1	1−1	(Greenough et al. 1964; Lee et al. 2017; Lindenbaum et al. 1967; Wallace et al. 1968)
γ_S	0.06	0.02−0.11	(Greenough et al. 1964; Lee et al. 2017; Lindenbaum et al. 1967; Wallace et al. 1968)
$\gamma_{S_{abx}}$	1	1−1	(Greenough et al. 1964; Lee et al. 2017; Lindenbaum et al. 1967; Wallace et al. 1968)
μ_M	0.01	0.01−0.01	(WHO 2022)
μ_S	0.90	0.46−1.55	(Lindenbaum et al. 1967)
θ	2.66	1.33−3.98	varies based on policies
δ	0.50	0.50−0.50	varies based on policies
α_M	0.30	0.20−0.40	(Greenough et al. 1964; Lindenbaum et al. 1967)
α_S	0.20	0.10−0.30	(Greenough et al. 1964; Lindenbaum et al. 1967)

Note that $\mathcal{R}_0$ is used to solve for β using Eq. (5).

Both q and M_{abx} range from 0 to 1, where treating no moderate infections with antibiotics corresponds to $q = M_{abx} = 0$ (status quo), and treating all moderate infections that seek care corresponds to $q = M_{abx} = 1$.

2.1.3 Cholera-Specific Assumptions

Several specific assumptions follow from our focus on cholera. First, the current guideline for treating cholera cases is to reserve antibiotics for severely symptomatic individuals who would be likely to die without such treatment. GTFCC (2018) Under

these guidelines, no moderately symptomatic infections are treated with antibiotics ($M_{abx} = 0$). Our study question explores the effects of increasing the proportion of moderates treated, M_{abx}.

Next we assume that treatment with antibiotics reduces the transmission potential of an infected individual by reducing the duration of shedding in stool by 80-90%. GTFCC (2018); Cash et al. (1974); Greenough et al. (1964); Leibovici-Weissman et al. (2014); Lindenbaum et al. (1967) Additionally, since symptoms severity is correlated with shedding volume, we assume lower severity infections are less transmissible. Greenough et al. (1964); Lindenbaum et al. (1967) We use ν_{sh} (0.450) and ν_{abx} (0.500) to capture the reductions in shedding after symptoms resolve from natural recovery and from antibiotic treatment, respectively. For a comprehensive list of parameter values, see Table 3. These reductions apply to moderate and untreated severe infections, as we assume severe infections remain hospitalized until symptoms and shedding has resolved and therefore do not shed in the community. Finally, we denote the reduction in infectiousness of asymptomatic and moderate infections relative to severe infections by ν_A and ν_M, respectively.

2.2 Basic and Control Reproductive Numbers

The reproductive number for a disease provides a population-level threshold for transmission. When the reproductive number is above 1, a disease will invade and persist and below 1 it will die out. We use this threshold condition to explore when expanded treatment may result in an outbreak dying out, by reducing the reproductive number below 1. Because we are interested in comparing the current treatment guidelines with expanded treatment guidelines, we calculate two reproductive numbers: the reproductive number under the current treatment guidelines, which we call, $\mathcal{R}(\mathrm{q} = 0)$, and the reproductive number under the expanded treatment guidelines, which we call, $\mathcal{R}(\mathrm{q})$. Both are measures of transmission potential for an infectious disease, capturing the average number of secondary infections from a single infected individual. Sharma et al. (2023)

From equation (SI 1), $\mathcal{R}(\mathrm{q})$ sums the contribution from each infection class (labelled in Eq. (4)) to the number of new infections in each generation, proportional to the total population (N) (Diekmann et al. 2010). We find

$$\mathcal{R}(\mathrm{q}) = \beta N \left(\underbrace{\frac{p_A \nu_A}{\gamma_A}}_{I_{A_{sh}}} + \underbrace{\frac{p_{MU} \nu_M}{\alpha_M}}_{I_{M_{syU}}} + \underbrace{\frac{p_{MT} \nu_M}{(1-q)\alpha_M + q\delta\theta}}_{I_{M_{syT}}} + \underbrace{\left(p_{MU} + p_{MT} \frac{(1-q)\alpha_M}{(1-q)\alpha_M + q\delta\theta} \right) \frac{\nu_{sh} \nu_M}{\gamma_M + \mu_M}}_{I_{M_{sh}}} \right)$$

$$+ \underbrace{p_{MT}\frac{q\delta\theta}{(1-q)\alpha_M + q\delta\theta}\frac{\nu_{abx}\nu_M}{\gamma_{M_{abx}}}}_{I_{M_{abx}}}$$

$$+ \underbrace{\frac{p_{SU}}{\alpha_S}}_{I_{S_{syU}}} + \underbrace{\frac{p_{ST}}{\theta}}_{I_{S_{syT}}} + \underbrace{p_{SU}\frac{\nu_{sh}}{\gamma_S+\mu_S}}_{I_{S_{sh}}} + \underbrace{p_{ST}\frac{\nu_{abx}}{\gamma_{S_{abx}}}}_{I_{S_{abx}}}\Bigg) \tag{4}$$

To find the reproductive number for the special case of no treatment, we substitute $q = 0$ into Eq. (4) and find $\mathcal{R}(\mathrm{q} = 0)$ to be

$$\begin{aligned}\mathcal{R}(\mathrm{q}=0) = \beta N \Bigg(& \frac{p_A\nu_A}{\gamma_A} \\ & + (p_{MU}+p_{MT})\left(\frac{\nu_M}{\alpha_M} + \frac{\nu_{sh}\nu_M}{\gamma_M+\mu_M}\right) \\ & + \frac{p_{SU}}{\alpha_S} + \frac{p_{ST}}{\theta} \\ & + p_{SU}\frac{\nu_{sh}}{\gamma_S+\mu_S} + p_{ST}\frac{\nu_{abx}}{\gamma_{S_{abx}}}\Bigg)\end{aligned} \tag{5}$$

2.3 Outbreak Final Size

We compare the effectiveness of expanded antibiotic treatment on the final outbreak size, defined as the total proportion of infections over the course of the outbreak (i.e., the asymptotic state of the system). Kermack et al. (1997); Miller (2012) To do this, we separate the final size based on disease outcome and treatment status. We compare the number of untreated infections ($R_{un\infty}$), infections treated with antibiotics ($R_{abx\infty}$), and people who die (D_∞) as well as the proportional final sizes $r_{un\infty} = R_{un\infty}/N$, $r_{abx\infty} = R_{abx\infty}/N$, and $d_\infty = D_\infty/N$. These can be summed to find the overall final size of the outbreak, $r_\infty = r_{un\infty} + r_{abx\infty} + d_\infty$.

Using the proportion of the population that remain susceptible at the completion of the outbreak (s_∞), we derive equations (details in SI § 4) for the proportion of infections that were untreated ($r_{un\infty}$), the proportion of infections that were treated ($r_{abx\infty}$), and the proportion of infections that died (d_∞).

$$r_{un\infty} = \left(\frac{\alpha_M\gamma_M}{\gamma_M+\mu_M}\left(\frac{\sigma p_{MU}}{\alpha_M} + \frac{\sigma p_{MT}}{(1-q)\alpha_M+q\delta\theta}\right) + \sigma p_A + \frac{\sigma p_{SU}\gamma_S}{\gamma_S+\mu_S}\right)\frac{1}{\mathcal{R}}\left(-\ln(s_\infty)\right) \tag{6}$$

$$r_{abx\infty} = \left(q\delta\theta\left(\frac{\sigma p_{MT}}{(1-q)\alpha_M+q\delta\theta}\right) + \sigma p_{ST}\right)\frac{1}{\mathcal{R}}\left(-\ln(s_\infty)\right) \tag{7}$$

$$d_\infty = \left(\frac{\alpha_M\mu_M}{\gamma_M+\mu_M}\left(\frac{\sigma p_{MU}}{\alpha_M} + \frac{\sigma p_{MT}}{(1-q)\alpha_M+q\delta\theta}\right) + \frac{\sigma p_{SU}\mu_S}{\gamma_S+\mu_S}\right)\frac{1}{\mathcal{R}}\left(-\ln(s_\infty)\right) \tag{8}$$

To understand the impact of treating moderate infections on the total proportions of infections and doses used in an outbreak, we numerically solve these final size

Equations (Eqs. 6–8) and vary the proportion of moderately infected individuals treated (M_{abx}) from 0 to 1 and calculate the final size (r_∞) using R Statistical Software (R Core Team 2021).

3 Results

Our analysis reveals two critical two-dimensional thresholds in the parameters $\mathcal{R}(\mathrm{q}=0)$ and M_{abs} that summarize the relationship between antibiotic treatment and outbreak control. The first threshold occurs when expanded antibiotic treatment reduces the effective reproductive number ($\mathcal{R}(\mathrm{q})$) below 1, thereby halting the outbreak. We call this the Outbreak Prevention Threshold (OPT). The second threshold occurs when expanded treatment to include treating moderate infections reduces the number of antibiotic doses used over the course of the outbreak below that with the current treatment guidelines. We call this the Dose Utilization Threshold (DUT).

3.1 Outbreak Prevention Threshold (OPT)

To derive the OPT, we identify the conditions where expanded treatment reduces $\mathcal{R}(\mathrm{q})$ below 1, stopping transmission. We define the OPT as the values of $\mathcal{R}(\mathrm{q}=0)$ and M_{abx} for which an outbreak can be stopped with treatment of some proportion of moderate infections. For sufficiently large $\mathcal{R}(\mathrm{q}=0)$, even treating all moderate infections will not reduce $\mathcal{R}(\mathrm{q})$ below 1. We define $\mathcal{R}_{opt}$ to be the maximum value of $\mathcal{R}(\mathrm{q}=0)$ for which an outbreak can be feasibly stopped. To do this, we solved Eq. (4) for $\mathcal{R}(\mathrm{q})=1$, since $\mathcal{R}_{opt}$ occurs when $\mathcal{R}(q=1)=1$. We then used Eq. (2) to find values of M_{abx} from q.

Using the mean value of each cholera parameter in the model, we show that $\mathcal{R}_{\mathrm{opt}}=1.42$. That means that for outbreaks with $\mathcal{R}(\mathrm{q}=0)\leq\mathcal{R}_{\mathrm{opt}}=1.42$, expanding antibiotic treatment to include moderate infections from the onset of the outbreak would prevent the outbreak from emerging and spreading. Because $\mathcal{R}_{opt}$ describes the maximum value of $\mathcal{R}(\mathrm{q})$ for which treating all moderate infections contains the outbreak, for lower values of $\mathcal{R}(\mathrm{q})$, outbreak containment can be achieved by treating a smaller proportion of moderate infections.

The relationship between the proportion of moderate infections treated and the percent of the population infected (Fig. 3A) is shown in Fig. 3. Each curve that intersects the horizontal axis represents an $\mathcal{R}(\mathrm{q}=0)$ value that can be reduced below 1 by treating some proportion of moderates. The proportion of moderates needed to contain the outbreak is given by the value where the curve intersects the horizontal axis. For curves that do not intersect the horizontal axis, even treating all moderate infections with antibiotics will not reduce $\mathcal{R}(\mathrm{q})$ below 1.

3.2 Dose Utilization Threshold (DUT)

We define the DUT as the values of $\mathcal{R}(\mathrm{q}=0)$ and M_{abx} for which treating both moderate and severe cases with antibiotics results in fewer doses used over the course

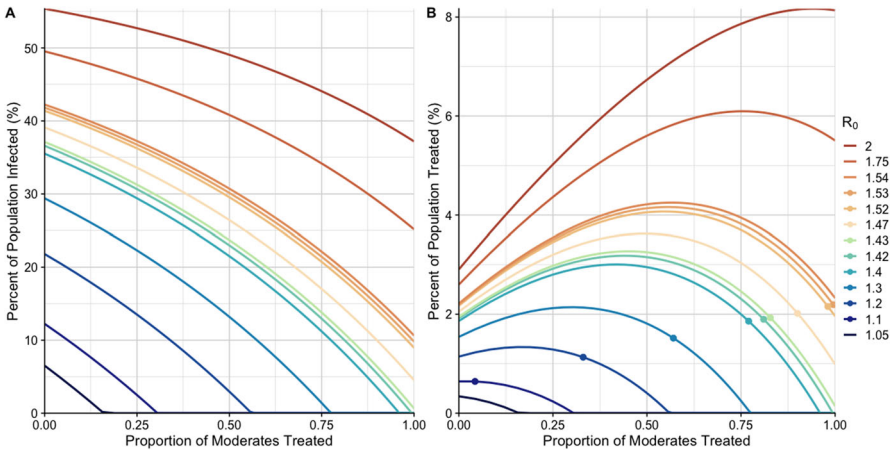

Fig. 3 The final size (**A**) and proportion of total population treated (**B**) plotted against M_{abx} in a cholera outbreak for different values of $\mathcal{R}(\mathrm{q}=0)$. Each curve corresponds to a different value of $\mathcal{R}(\mathrm{q}=0)$, representing different outbreak scenarios of varying severity and transmissibility. **A** The percent of the population infected, regardless of severity of infection or treatment status, over an outbreak (r_∞). **B** The percent of the population that receive antibiotics, including moderate and severe infections, over the course of an outbreak ($r_{abx\infty}$). Dots indicate the proportion of moderates that need to be treated to cross the Dose Utilization Threshold (DUT), for each value of $\mathcal{R}(\mathrm{q}=0)$. Lines without points indicate that $\mathcal{R}(\mathrm{q}=0) > \mathcal{R}_{dut}$ (Color figure online)

of the outbreak when compared to treating severe cases alone, where $\mathcal{R}_{dut}$ is the maximum value of $\mathcal{R}(\mathrm{q}=0)$ for which this occurs. To derive the DUT, we use the final size equations, Eqs. (6), (7), and (8). We identify the conditions under which expanding treatment can reduce the total number of doses used over the course of an outbreak. This can occur even if transmission is not completely halted and an outbreak still persists.

Mathematically, we solve for when $r_{abx\infty}$ (evaluated when $q=0$) is greater than $r_{abx\infty}$ (evaluated when $q\neq 0$). To find the threshold value for where this occurs, we set $r_{abx\infty}(q=0)=r_{abx\infty}(q\neq 0)$, which results in the following equation

$$\begin{aligned}&(\sigma\, p_{ST})\,\frac{1}{\mathcal{R}(\mathrm{q}=0)}\ln(s_\infty(\mathcal{R}(\mathrm{q}=0)))\\&=\left(q\delta\theta\left(\frac{\sigma\, p_{MT}}{(1-q)\alpha_M+q\delta\theta}\right)+\sigma\, p_{ST}\right)\frac{1}{\mathcal{R}(\mathrm{q})}\ln(s_\infty(\mathcal{R}(\mathrm{q}))).\end{aligned}\tag{9}$$

We numerically solve for $\mathcal{R}_{dut}$, because this equation is not analytically tractable, as Eq. (9) is an implicit function of $\mathcal{R}(\mathrm{q}=0)$. For cholera we found $\mathcal{R}_{dut}=1.53$. Like the OPT, for lower values of $\mathcal{R}(\mathrm{q})$ a reduction in doses can be achieved by treating a smaller proportion of moderate infections. The relationship between the proportion of moderates treated and the number of doses of antibiotics used is shown in Fig. 4.

While treating more cases (high M_{abx}) will always reduce the number of cases in the outbreak (Fig. 3A), the non-monotonic relationship between proportion of moderates treated and the number of doses of antibiotics used over the outbreak

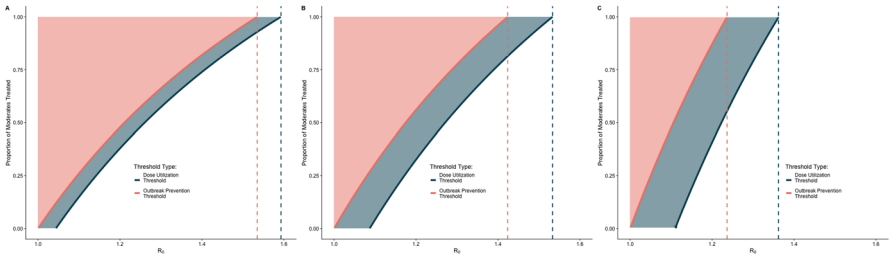

Fig. 4 Plot of the threshold values for dose reduction (DUT) and outbreak prevention (OPT), by $\mathcal{R}(\mathrm{q} = 0)$, for each proportion of moderates treated (M_{abx}), at **A** low, **B** mean, and **C** high values of parameters. For a each value of $\mathcal{R}(\mathrm{q} = 0)$, the pink curve shows the OPT of $\mathcal{R}(\mathrm{q} = 0)$ and M_{abx}, the shaded region above the curve shows all combinations of $\mathcal{R}(\mathrm{q} = 0)$ and M_{abx} in which treating moderate infections reduces the effective reproductive number, $\mathcal{R}(\mathrm{q})$, below 1. The dotted red line indicates $\mathcal{R}_{opt}$ for cholera. The blue curve shows the DUT of $\mathcal{R}(\mathrm{q} = 0)$ and M_{abx}, the shaded region above the curve shows all combinations of of $\mathcal{R}(\mathrm{q} = 0)$ and M_{abx} in which fewer doses are given overall with expanded treatment. The dotted blue line indicates $\mathcal{R}_{dut}$ for cholera. Outside of these regions, in the white space, there is no outcome improvement (Color figure online)

leads to an increase in the total number of doses used when when a small proportion of moderate infections are treated. However, as the proportion of moderate infections treated increases, the number of doses used decreases, and, for values of $\mathcal{R}(\mathrm{q} = 0) \leq \mathcal{R}_{dut} = 1.53$, drops below the number of doses used when treating no moderate infections (indicated by the points in Fig. 3B). For outbreaks with very high values of $\mathcal{R}(\mathrm{q} = 0)$, treating moderate infections substantially increases the total number of doses given as the reduction in transmission from treatment is insufficient to compensate for the large number of infected individuals (illustrated by $R_0 = 2$ in Fig. 3B).

4 Discussion

It has previously been thought that there is an unavoidable tradeoff between the utilization of antibiotics and the evolutionary risk of developing antibiotic resistance. Here we identify scenarios where antibiotic use creates a population-level benefit, thus benefiting both the individual and the population. The key mechanism is that antibiotics reduce the duration of shedding in treated individuals thereby reducing transmission and the total number of cases. We find cases where treating more patients with antibiotics can reduce the total number of doses used during an outbreak, thus reducing the selective pressures for the development of antibiotic resistance, and even cases where there are population benefits of treating people who would recover adequately without treatment.

Here, we present a theoretical framework for finding the conditions under which treating moderate infections with antibiotics reduces the total number of doses used in an outbreak (which we term the Dose Utilization Threshold, or DUT) as well as when treating moderate infections completely stops an outbreak before it can take off (the Outbreak Prevention Threshold, or OPT). These two thresholds depend on two key

measurable quantities, $\mathcal{R}(\mathrm{q}=0)$ and M_{abx}. When treating all moderate infections ($M_{abx}=1$), we specify $\mathcal{R}_{opt}$ and $\mathcal{R}_{dut}$ as the maximum value of $\mathcal{R}(\mathrm{q})$ for which these thresholds occur. When considering other values of M_{abx}, the OPT and the DUT describe when these population-level benefits can be achieved by treating a smaller proportion of moderates for lower values of $\mathcal{R}(\mathrm{q})$. However, if $\mathcal{R}(\mathrm{q}=0)$ is larger than the DUT, the benefits of treating moderate infections is lost and the total number of doses given out over the course of the outbreak increases. This suggests that in some circumstances, it is better to not treat moderate infections if it is not certain that a threshold can be met due to concerns with public health infrastructure or compliance, for example.

Using cholera as case study, we found the conditions under which these thresholds occur. For cholera, we compute $\mathcal{R}(\mathrm{q}) \leq \mathcal{R}_{\mathrm{opt}} = 1.42$, below which treating moderate infections can reduce the effective reproductive number below 1, stopping the outbreak before it can spread. Similarly, when $\mathcal{R}(\mathrm{q}=0) \leq \mathcal{R}_{dut} = \mathbf{1.53}$, treating moderate infections results in fewer doses used over the course of the outbreak than under current treatment guidelines. Because the range of reproductive numbers for cholera outbreaks is 1.1−2.7 (Morris 2011; Phelps et al. 2018), only outbreaks with low to intermediate values of $\mathcal{R}(\mathrm{q}=0)$ can benefit from expanded antibiotic treatment. Further, since the relationship between the proportion of moderates treated and the number of doses used is non-monotonic, failure to treat a sufficient proportion of moderates treated may increase the number of doses used over the outbreak. The relationship between the proportion of moderates treated and the percent of the population infected is monotonical, any increase in the proportion of moderates treated reduces the percent of the population infected. Thus, careful evaluation of an outbreak setting, particularly with respect to community transmission (magnitude of $\mathcal{R}(\mathrm{q}=0)$), is essential prior expanding antibiotic treatment eligibility. In this paper, we solve for $\mathcal{R}_{opt}$ and $\mathcal{R}_{dut}$ under just three parameter values, high, mean, and low. Ahmed et al. (2024), uses a similar model and simulates over the whole range of parameter values to evaluate the outbreak settings under which treating moderately symptomatic infections is a viable outbreak control method.

When $\mathcal{R}(\mathrm{q}=0) \leq \mathcal{R}_{dut}$, it is imperative to identify and treat sufficient moderate infections, particularly in the context of cholera, as many moderately infected individuals may not seek treatment. This is particularly true because the current treatment guidelines of reserving antibiotic treatment for severe infections may discourage treatment seeking behavior by those with more moderate cases. Therefore, even giving antibiotics to all moderate infections who present for treatment (as we do in our model, Table 3) may not be sufficient to achieve the population-level benefits identified by our model. However, since individuals with moderate infections do not receive treatment under current guidelines, it is unknown how many would seek care if they qualified for antibiotic treatment under expanded access. This strategy may require proactively aiming to treat individuals who may not typically seek care and altering public messaging to encourage them to seek care. Further study is required to determine how treatment-seeking behavior may change should the policy change.

Our model relies on several simplifying assumptions, including that there is no heterogeneity in susceptibility. Our approach also relies on the assumption that severity is not transmitted; cases derived from moderate infections are equally likely to be

severe as those derived from severe infections. For the sake of analytic tractability, we assume that cholera is directly transmitted. We have also made a simplifying assumption by grouping infections into just three symptomatic classes. Additionally, because we specifically model an outbreak setting, we assume individuals who recover from cholera do not become susceptible again during our simulation. A potentially valuable extension of these results may be to adapt this model to include loss of immunity to model endemic transmission dynamics. Because symptoms exist on a continuum, exploring a more granular division may help to further stratify the moderately symptomatic class by shedding and target the most infectious moderate infections for treatment. In our cholera case study, we used average reported parameter values and present a high and low scenario in the supplement. Additional sensitivity analysis could be used to determine which parameters have the greatest and most consistent influence on the threshold values and highlight them for future study. Our analysis evaluates only case counts and antibiotic use, neglecting other tradeoffs due to the economic costs of treatment (Toth et al. 2021b).

While we tailored our model equations to the specifics of cholera, this theoretical framework may be valuable for other pathogens. A similar framework has been considered in the context of Carbapenem-resistant Enterobacterales (CRE) and decolonization in healthcare settings, where surveillance and testing strategies could be used to treat colonized individuals before they become infected, in parallel to the moderately symptomatic cholera patients considered here (Toth et al. 2021b). Similarly, for viruses such as influenza, this framework could aid in determining optimal strategies by balancing the tradeoff between testing and treatment. Here, factors such as cost-effectiveness (Smith and Roberts 2002) and the development of resistance (Patterson-Lomba et al. 2013) can play significant roles, as treatment strategies rely on individual vulnerability and susceptibility, as well as timing treatment before suspected symptom onset. This could be modeled to study scenarios in which it may be more beneficial to treat all cases as opposed to requiring a positive test for treatment. For HIV, particularly before the development of advanced antiretroviral therapies, healthcare providers had to balance side effects, patient compliance, and resistance concerns when trying to prevent HIV transmission prior to positive HIV test results. Chesney et al. (2000); Johnson et al. (2011) In such scenarios, our framework could help optimize the balance between side effects and compliance. While we propose that our framework may be applicable to other disease systems, in this paper we structure our model and tailor our assumptions specifically to cholera. Exploring how the thresholds identified in this manuscript may vary over a wider range of diseases or biologically reasonable parameters would require restructuring the model to accommodate disease-specific assumptions.

In conclusion, this study provides a new lens through which to view antibiotic use during infectious disease outbreaks, specifically highlighting the population-level benefits that can arise from expanding antibiotic treatment to include moderate infections. By shifting the emphasis from individual patient outcomes to broader population

impacts, our findings challenge traditional approaches to antibiotic prescribing and propose a more strategic and context-sensitive framework for antibiotic stewardship.

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Author Contributions CRL, SMA, FRA and LTK developed and analyzed the model, CRL, SMA, DT, JRR, VMV, FRA and LTK drafted the manuscript. CRL, SMA, DT, JRR, VMV, FRA and LTK have all read and approved the manuscript.

Declarations

Conflict of interest The authors declare that they have no Conflict of interest.

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