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β-Lactam–Resistant *Streptococcus pneumoniae* Dynamics Following Treatment: A Dose-Response Meta-analysis

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Background. Patient exposure to antibiotics promotes the emergence of drug-resistant pathogens. The aim of this study was to identify whether the temporal dynamics of resistance emergence at the individual-patient level were predictable for specific pathogen-drug classes.

Methods. Following a systematic review, a novel robust error meta-regression method for dose-response meta-analysis was used to estimate the odds ratio (OR) for carrying resistant bacteria during and following treatment compared to baseline. Probability density functions fitted to the resulting dose-response curves were then used to optimize the period during and/or after treatment when resistant pathogens were most likely to be identified.

Results. Studies of *Streptococcus pneumoniae* treatment with β-lactam antibiotics demonstrated a peak in resistance prevalence among patients 4 days after completing treatment with a 3.32-fold increase in odds (95% confidence interval [CI], 1.71–6.46). Resistance waned more gradually than it emerged, returning to preexposure levels 1 month after treatment (OR, 0.98 [95% CI, .55–1.75]). Patient isolation during the peak dose-response period would be expected to reduce the risk that a transmitted pathogen is resistant equivalently to a 50% longer isolation window timed from the first day of treatment.

Conclusions. Predictable temporal dynamics of resistance levels have implications both for surveillance and control.

Keywords. antibiotics; drug resistance; penicillin.

Since the discovery of penicillin, antibiotics have contributed significantly in extending human life expectancy by 23 years [1, 2]. Widespread resistance among common bacterial pathogens and slow development of replacement compounds or alternative therapies threaten these recent gains [3, 4]. It is estimated that approximately 1.27 million annual deaths are attributable to bacterial antimicrobial resistance [5].

Antibiotic resistance is selected for when bacteria are exposed to subtherapeutic levels of antibiotics that would otherwise inhibit their growth or kill them [6], making the remedy itself one of the primary drivers and risk factors for antibiotic resistance [7–10]. The relationship between antibiotics and resistance is dose dependent: Higher antibiotic consumption correlates with more resistant infections [11, 12]. The association between level of antibiotics administered and resistance development has been demonstrated at the bacterial colony level [13], at the individual-patient level [14, 15], and among human populations at the country level [16].

However, resistance is not necessarily a persistent trait of pathogens, and decreased resistance rates have been demonstrated following antibiotic withdrawal both at the individual and community levels [17, 18]. Prolonged treatment to ensure clearing the infection, therefore, comes at the cost of providing more sustained periods over which resistant pathogens have a competitive advantage. This has led to a recent challenge in the dogma of always completing antibiotic courses [19]. For example, randomized controlled trials have shown that shorter treatment schedules for both hospital- and community-acquired pneumonia yield equivalent outcomes to longer courses, but with fewer infection recurrences and reduced rates of antibiotic resistance [20–22]. Understanding the patient-level temporality of resistance emergence and waning thereby offers important insight into prescriptive practice.

Systematic reviews and meta-analyses have provided useful indication of this temporality. Costelloe et al investigated subsequent antibiotic resistance in individuals prescribed antibiotics in primary care, showing a 2.5 increase in odds of resistance within 2 months of treatment for urinary tract infections, which waned to 1.3 within 12 months [15]. However, among

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those treated for respiratory tract infections, the odds of antibiotic resistance remained 2.4 times higher (compared to those not treated with antibiotics) over the whole year [15]. Bakhit et al pooled analyses across bacterial species instead of infection site, showing a 4.2 increase in odds of resistance after receiving penicillin-class treatment for *Streptococcus pneumoniae* within the first week posttreatment, waning to a 1.7 increase in odds after 1 month [14]. A similar trend was found for cephalosporin-class treatment of this pathogen: 2.2 increase in odds within the first week, waning to 1.6 increase in odds after 1 month [14].

To further refine the temporal dynamics of patient-level resistance emergence and waning, here, the odds of antibiotic resistance are modeled over time using a dose-response meta-analysis (DRMA) framework, which incorporates time since antibiotic exposure as a continuous variable [23, 24]. This has the benefit over fixed time intervals (as done in previous meta-analyses) by reducing information loss, thus reducing the risk of distorting exposure-outcome relationships [25, 26]. The aim of this study was to examine the relationship between different antibiotic therapies and the emergence of antibiotic-resistant pathogens over time. To achieve this aim, the meta-analysis conducted by Bakhit et al [14] was updated and the data were reanalyzed using a DRMA [24].

METHODS

The foundation of this study is the systematic review and meta-analysis conducted by Bakhit et al [14] from which the eligibility criteria were adopted along with part of the risk of bias assessment and the included studies. This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [27] (checklist available in Supplementary Material 1).

Study Search and Selection

The study search was updated with a forward citation search using Elsevier's Scopus [28] on 31 October 2019. The basis for the forward citation search consisted of the primary studies included in Bakhit et al [14] and Costelloe et al [15] meta-analyses. No limits were applied to the study search. In case of ambiguities regarding study eligibility at any stage, L. Y. was consulted.

Studies were included if they met the following eligibility criteria: (1) randomized controlled trials (RCTs), quasi-experimental pre–post studies, or prospective cohort studies; (2) compared patients treated with antibiotics vs controls (ie, not treated or prior to treatment with antibiotics); (3) patients were treated in the community or had community-acquired infections; (4) patients received an antibiotic therapy of any class, or combination of classes, for a maximum duration of 14 days; and (5) reported the prevalence or incidence of resistant bacteria among patients, isolates, or specimens over time.

Case reports and conference abstracts were excluded. Studies including patients with hospital-associated, device-related, or persistent infections were excluded; in addition, studies with antibiotic therapies >14 days were excluded.

Data Extraction

The data extraction was done by M. G. and L. F.-K. using an Excel spreadsheet; in case of discrepancies, L. Y. was consulted. The following items were extracted from the studies: Authors and year of publication; patient characteristics (eg, symptomatic or asymptomatic patients, age, proportion of females); study characteristics (eg, study design, recruitment location, duration of study/follow-up); antibiotic exposure (eg, antibiotic class, duration of antibiotic therapy); and bacterial infection (eg, type of bacteria, number of antibiotic-resistant isolates at different time points).

Some studies reported their case counts relative to the total included patients (pathogen carriers and noncarriers) and others to the respective pathogen carriers. Here, only data from participants carrying pathogens were retained in order to describe the burden of resistance among those with infections. In addition, some studies provided data for resistance against multiple antibiotic classes after treatment, but only studies reporting resistance to the treatment antibiotic (so-called primary resistance) were retained.

All antibiotic drugs were classified according to their respective chemical structure. Combined treatments were classified by their active agent in case of an antibiotic and nonantibiotic combination (eg, amoxicillin-clavulanate classified as β-lactam). An antibiotic combination was treated as its own class. Studies that were randomized by design but had data extracted from each arm separately were reclassified as prospective repeated-measures cohort studies (more details in Table 1), as proposed by Bakhit et al [14].

Risk of Bias Assessment

The risk of bias assessment was performed by M. G. using the Cochrane Risk of Bias tool 2.0 [29] for RCTs and Risk of Bias in Nonrandomised Studies of Interventions (ROBINS-I) [30] for nonrandomized studies. To evaluate the risk of bias for cohort studies and longitudinal data, the adapted version developed by Bakhit et al [14] of the ROBINS-I for 3 domains (confounding, missing data, and outcomes) was used (Supplementary Material 2).

Statistical Analyses

The odds ratios (ORs) for carrying resistant bacteria over time were modeled to investigate the temporal relationship between antibiotic intake and resistance. The ORs were estimated as the ratio between the odds of antibiotic resistance at different time

points compared to the odds of antibiotic resistance at baseline —that is, prior to antibiotic therapy or in the control group.

The antibiotic resistance and time data (as a continuous variable) were reanalyzed using a robust error meta-regression method (REMR) [31] for DRMA rather than pooling ORs within time categories as in previous meta-analysis [14]. Time was calculated as the difference in days between the start of the antibiotic treatment (day 0) and the resistance measurement. The median was used for time points that were reported as ranges (eg, 28–30 days). For studies specifying measurement time points as "*x* days after the end of therapy," the time period was added to the therapy duration. To avoid bias, the analysis was additionally sorted by the treatment duration. The REMR method does not require knowledge of the correlation structure of the data within a study, because it stacks included effects as a cluster by study and uses the cluster-robust analysis to obtain a robust standard error, thus treating observations as independent across clusters but correlated within each cluster. Given the results reported in previous meta-analysis, the relationship of resistance over time was not likely to be linear, so the REMR DRMA was fitted with a restricted cubic spline with 3 knots. The number of knots was decided by assessing the fit of the model through the mean squared error and the R-squared. The DRMAs were run using the *remr* module [32] in Stata SE version 14 software (StataCorp, College Station, Texas).

The REMR DRMA used time since first antibiotic as a proxy for "dose," thus producing output that shows how resistance risk increases and then decreases following drug treatment. Fitting these temporal changes in resistance risk to probability distributions enabled estimates for how risk cumulates over different time spans. We made no a priori assumption of the distribution shape and instead fit a range of probability distributions (using a Python library called Reliability [33]) and selected the best fit. These fitted distributions normalize the risk of transmitting resistant pathogens (ie, ensured the area under the curve summed to 1). Knowing how resistance emergence changed over time allowed estimation of how different patient isolation scenarios reduced the risk that a transmitted pathogen was resistant. The first, "naive" scenario measured the duration of isolation required to halve risk that a transmitted pathogen was resistant assuming that isolation was initiated from the first day of treatment. The alternative, "targeted" scenario measured the duration of isolation needed to equivalently impact risk when the isolation window prioritized peak resistance levels.

RESULTS

Yield of Search Strategy

The forward citation search identified a total of 2173 unique records. The title and abstract screening resulted in the exclusion of 2112 records, and 61 articles were included for the full-text screening. An additional 10 articles were identified by hand search, adding up to 71 full-text articles for screening, of which 16 articles were deemed eligible.

Bakhit et al [14] included 26 articles, of which 1 article exceeded the maximum therapy of 14 days and was excluded from our study. Therefore, there were a total of 41 [13, 34–72] articles, reporting findings from 35 different studies. At least 10 data points are required for each DRMA (ie, combination of organism and antibiotic). Studies involving *S. pneumoniae* resistant to either β-lactams or macrolides met this requirement, and 13 studies [35, 36, 38–52] (n = 11 049 participants) were included in the analysis (Figure 1).

Study Characteristics

The study, patients, and treatment characteristics of the retrieved studies are reported in Table 1. The studies included between 58 and 4782 participants, and the study duration ranged between 14 and 180 days. Of the included studies, 3 were RCTs and 10 were prospective cohorts. Nine studies reported data on children, 2 on adults, and 2 studies included children and adults as participants. The symptom status of their patients was reported as symptomatic by 7 studies and as asymptomatic by 3 studies; 2 studies reported on symptomatic and asymptomatic patients, and 1 study did not report the symptom status of their patients. All 13 studies reported on respiratory samples. Eleven studies reported the guideline they used to determine the susceptibility and resistance levels for bacteria. Among these 13 studies that examined *S. pneumoniae*, 8 studies administered β-lactam–class antibiotics, 8 used penicillin, and 5 studies reported macrolide-class antibiotics. The therapy duration was 10 days for β-lactam antibiotics and 1 day for macrolide antibiotics. The unit of analysis was at the patient in all of the studies.

Quantitative Analysis

Eight studies [35, 36, 38–41, 50, 51] (n = 3101) reported a total of 34 primary resistance data points on β-lactam antibiotics in *S. pneumoniae* with a maximum follow-up of 60 days and a therapy duration of 10 days. The relationship between resistance to β-lactams in *S. pneumoniae* and days postexposure revealed a 3.32-fold increase in odds (95% confidence interval [CI], 1.71–6.46) of resistance at day 14 followed by a steady decrease to preexposure level on day 40 (OR, 0.98 [95% CI, .55–1.75]) (Figure 2*A* and Supplementary Material 3).

Eight studies [35, 36, 38–41, 50, 51] (n = 3101) reported a total of 27 primary resistance data points for penicillin treatment of *S. pneumoniae* with a maximum follow-up of 60 days and a therapy duration of 10 days. The results showed a 4.82-fold increase in odds (95% CI, 2.57–9.01) in resistance at day 14, which steadily decreased to a preexposure level on day 40 (OR, 0.72 [95% CI, .41–1.25]) (Figure 2*B* and Supplementary Material 4). The results for primary resistance data on

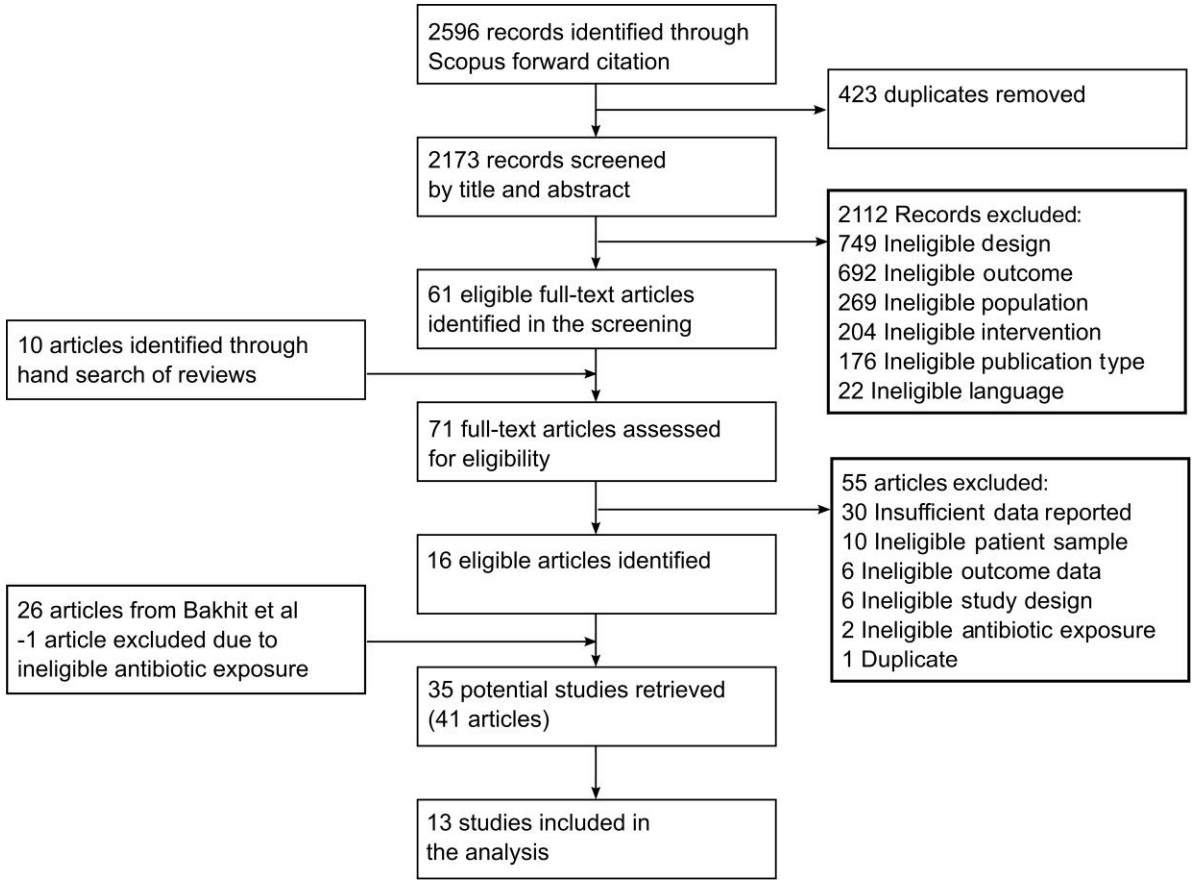

Figure 1. Flowchart for the study screening process.

macrolide antibiotics in *S. pneumoniae* showed a similar trend (see Supplementary Material 5), but with greater uncertainty.

Targeting Surveillance of Resistant Pathogens

Consistent patterns across studies emerged from the dose-response analyses whereby odds of resistance increased to a maximum level on day 14 for the β-lactams (Figure 2). Macrolide treatment studies were also consistent but had peak resistance occurring much later, between days approximately 30 and 60 (see Supplementary Material 5). Knowledge of these temporalities could be used to inform strategically timed sampling to improve estimates of resistance incidence and prevalence. Potentially, this information could also contribute toward temporally targeted isolation of patients with the goal of reducing the risk that transmitted pathogens are drug resistant. The relative reduction in risk that a transmitted pathogen is resistant when isolating patients from the first day of treatment was compared with isolation during the period in which the odds of resistance was found to be highest in the meta-analysis. Both scenarios for β-lactams (including subgroup of penicillin) are shown in Figure 3 (for macrolide treatments of *S. pneumoniae*, see Supplementary Material 5).

Relative to a "naive" approach, a targeted approach reduced the isolation time by about one-third for β-lactam treatments (requiring isolation from days 9 to 19 instead of from days 0 to 15), and by 12.5 days for macrolide treatments of *S. pneumoniae*. The risk of bias for evaluation of the three RCTs resulted in two studies having a high risk of bias and one study having a low risk of bias (Supplementary Material 6). Among the ten cohort studies, the overall risk of bias evaluation resulted in 40% studies having a high risk for bias, 40% having some concern and 20% studies having a low risk of bias. Bias due to confounding in the cohort studies was high in 30% studies and 10% studies had some concern. The bias due to missing data had some concern in 10% of the studies. In 10% of the studies there was high risk for bias in the measurement of outcome and 70% had some concern (Supplementary Material 7).

DISCUSSION

Antibiotic resistance incurs a huge and growing toll in terms of morbidity, mortality, and societal costs [73]. Previous studies have provided evidence of nonlinear temporal trends in the

Table 1. Characteristics of Included Studies: Design and Patients

Author (Year of Publication) [Reference]	Country	No. of Patients	Design	Female Proportion	Age Group/ Symptoms	Study Duration, Days	Sample Site	MoM Resistance/ Guideline	Pathogen Examined	Antibiotic Treatment	Treatment Duration, Days	Unit of Analysis
Chern et al (1999) [46]	Nepal/PED	122	RCT	NA	Child/SaAS	14	Respiratory	Etest/NA	*S. pneumoniae*	Azithromycin	1	Patient
Cohen et al (1999) [38]	France/PED	513	COS-RT	NA	Child/S	42	Respiratory	Agar/NCCLS	*S. pneumoniae*	Amoxicillin-clavulanate	10	Patient
Conradi et al (2007) [39]	Spain/hER	134	COS	0.48	Child/S	44	Respiratory	Agar/CLSI	*S. pneumoniae*	Amoxicillin	10	Patient
Dabernat et al (1998) [40]	France/PED & ENT	426	COS-RT	0.46	Child/S	40	Respiratory	Disk/NCCLS/ EUCAST	*S. pneumoniae*	Cefixime, co-amoxiclav	10, 10	Patient
Ghaffar et al (1999–2002)[a] [41–4341–43]	USA/PED	160	COS-RT	0.45	Child/SaAS	60	Respiratory	Etest & disk/ NCCLS	*S. pneumoniae*	Amoxicillin-clavulanate	10	Patient
Schrag et al (2001) [50]	DR/hOC	795	COS-RT	0.45	Child/S	28	Respiratory	Etest/NCCLS	*S. pneumoniae*	Amoxicillin	10	Patient
Toltzis et al (2005, 2007)[a] [51, 52]	USA/PED	1009	COS-RT	NA	Child/S	30	Respiratory	Etest/NCCLS	*S. pneumoniae*	Amoxicillin	10	Patient
Batt et al (2003)[b] [44]	Tanzania/V	4782	COS	0.56	Child/NA	180	Respiratory	Etest/NA	*S. pneumoniae*	Azithromycin	1	Patient
Brook et al (2005)[b] [35]	USA/OC	58	COS	0.34	Adult/S	14	Respiratory	Broth/NCCLS	*S. pneumoniae*	Amoxicillin, amoxicillin-clavulanate	10, 10	Patient
Brook & Gober (2004)[b] [36]	USA/NA	60	COS	0.28	Child/S	14	Respiratory	Broth/NCCLS	*S. pneumoniae*	Amoxicillin-clavulanate	10	Patient
Burr et al (2014)[b] [45]	Gambia/V	417	COS	0.5	Child & adult/ AS [38]	180	Respiratory	Etest/CLSI	*S. pneumoniae*	Azithromycin	1	Patient
Guchev et al (2004)[b] [47, 48]	Russia/ Vol	1798	RCT	0	Child & adult/ AS	154	Respiratory	Broth/NCCLS	*S. pneumoniae*	Azithromycin	1	Patient
Roca et al (2016)[b] [49]	Gambia/hCC	829	RCT	1	Adult/AS	28	Respiratory	Disk & Etest/CLSI	*S. pneumoniae*	Azithromycin	1	Patient

Abbreviations: Agar, agar dilution; AS, asymptomatic; Broth, broth dilution method; CLSI, Clinical and Laboratory Standards Institute; COS, prospective cohort study design; Disk, disk diffusion; DR, Dominican Republic; ENT, ear, nose, and throat; EUCAST, European Committee on Antimicrobial Susceptibility Testing, hCC, healthcare center; hER, hospital emergency department; hOC, hospital outpatient clinic; MoM, method of measurement; NA, not available; NCCLS, National Committee for Clinical Laboratory Standards; OC, outpatient clinic; PED, pediatric clinic; RCT, randomized controlled trial; RT, randomized trial; S, symptomatic; SaAS, symptomatic and asymptomatic; *S. pneumoniae*, *Streptococcus pneumoniae*; USA, United States; V, villages; Vol, volunteers.

[a]Articles collated into a single study.

[b]Studies retrieved by the study update.

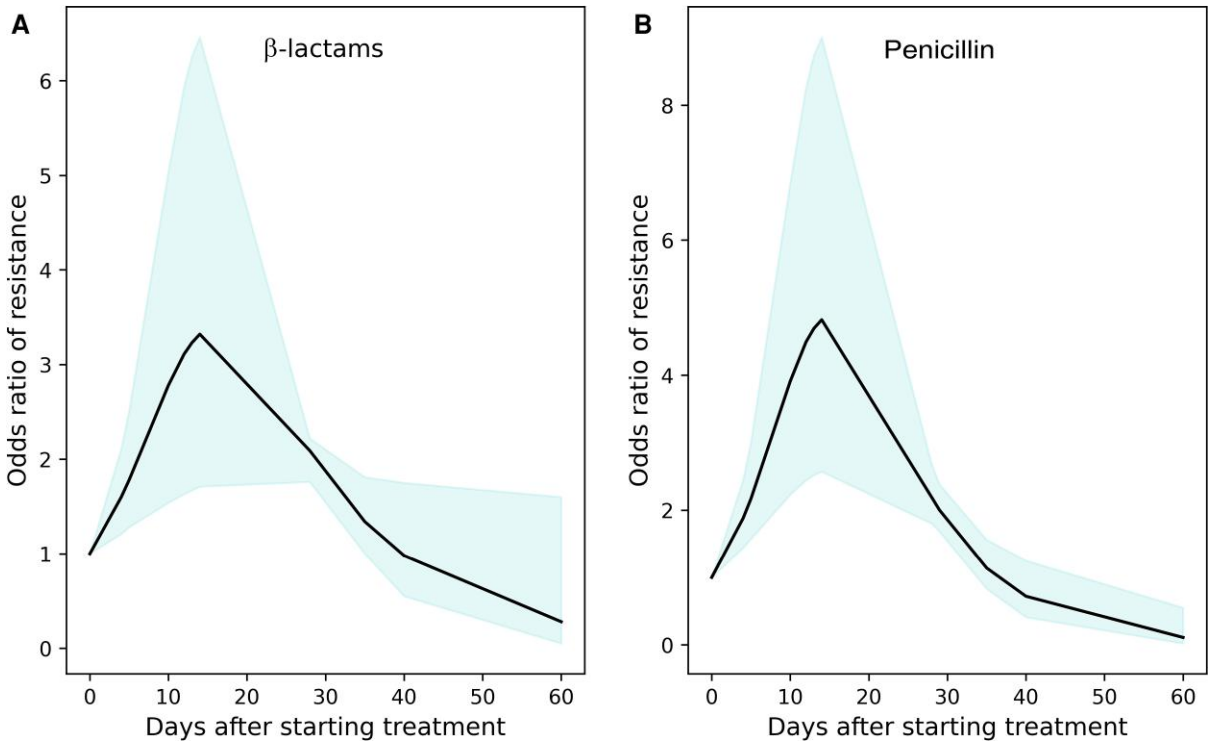

Figure 2. Odds ratios (with 95% confidence intervals) of *Streptococcus pneumoniae* antibiotic resistance to β-lactams (*A*) and penicillin (*B*) over time, as determined by robust error meta-regression.

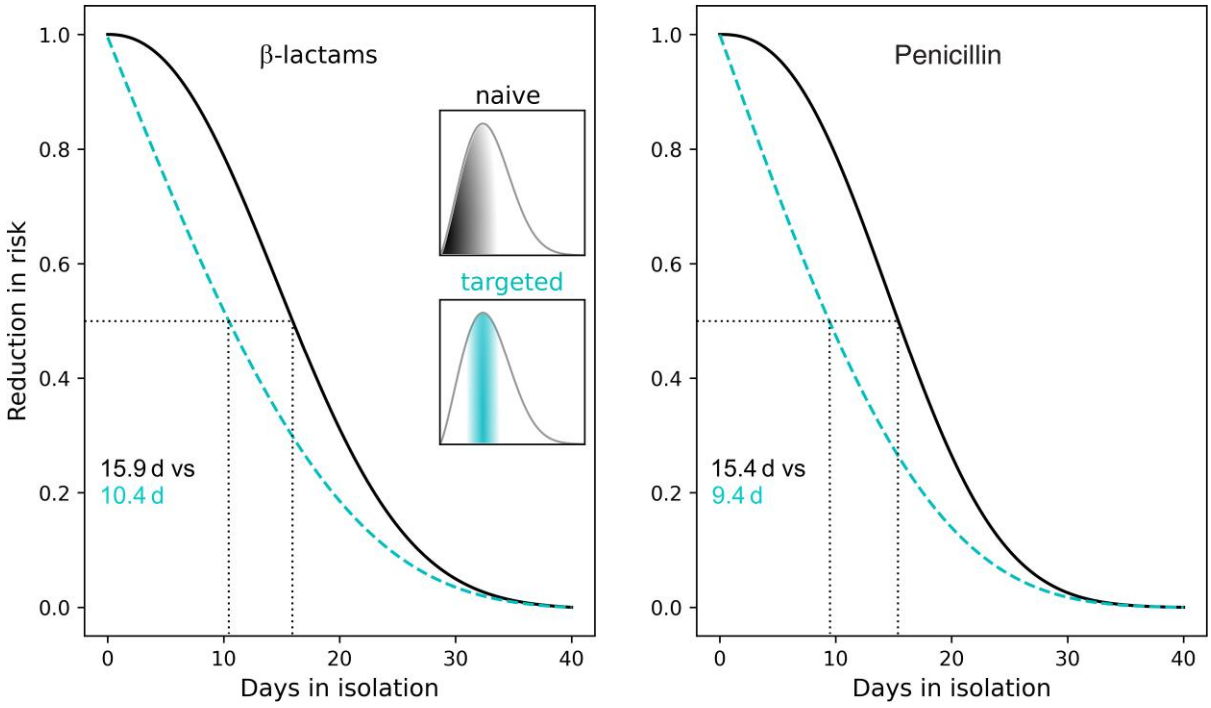

Figure 3. Strategically timed isolation of patients treated for *Streptococcus pneumoniae* infection can reduce the risk that transmitted pathogens are resistant. Alternative isolation windows are shown: time extending from first day of treatment ("naive"; solid line) or during windows of highest resistance risk as identified in the meta-analysis ("targeted"; dashed line). The dotted lines denote the durations of isolation required to halve the risk that transmitted *S. pneumoniae* is drug resistant under the alternative isolation windows.

emergence of resistance among patients following exposure to antibiotics [14, 15]. Using a novel meta-analytical approach [31], this study sought to refine our understanding of the temporality of resistance emergence and waning. After pooling the evidence from 8 studies (n = 3101 participants) an increased risk of resistant *S. pneumoniae* among patients was found, peaking at day 14 for β-lactams and for the penicillin subgroup (4 days after treatment cessation). Evidence is shown for an eventual waning in resistance 30 days following cessation of the antibiotics course, corroborating findings from earlier studies [3, 17, 18].

Identifying consistent dynamics in resistance emergence and waning offers new opportunities for understanding the epidemiology of antibiotic resistance. Surveillance is crucial for tracking resistance spread and in targeting its control. It is 1 of the 5 strategic priorities of the Global Action Plan on antimicrobial resistance [74], and research on resistance is dominated by surveillance reports [75]. A recent report from the Interagency Coordination Group on Antimicrobial Resistance [76] describes several ways in which surveillance can support efforts to reduce antimicrobial resistance: improve detection of the emergence and prevalence of antimicrobial resistance; help guide patient treatment; identify populations at risk; inform policy development; and assess the impact of interventions. Hence, identifying the precise window when patients are most likely to have detectable resistant pathogens improves their detectability and can potentially assist with all of these key features of resistance surveillance.

A more refined understanding of patient-level resistance dynamics also provides new opportunities for strategizing interventions. Stewardship has been the primary means of combatting the spread of resistance, and, while it has proven effective in some settings [77, 78], only a quarter of studies included in a systematic review of interventions to change prescriptive practices in hospitals showed evidence of decreased resistance as a result [79]. Alternative strategies for combatting resistance are needed, and temporally targeted isolation windows may comprise a novel approach. Transmission-based precautions often require physical patient isolation, which may include single-room isolation, an entire isolation ward, or cohorting of a group of patients [80]. Owing to its exaggerated expense, this infection prevention and control strategy is normally reserved for patients infected with multidrug-resistant microorganisms to limit nosocomial transmission to other patients or to healthcare workers [81]. Resistant pathogen transmission risk is a compound of several factors including pathogen burden and patient behavior. Our new findings add a new layer of understanding of how the transmission risk of resistant pathogens changes over the course of infection. Future work should explore combining these factors to inform resistant-infection prevention and control strategies. If predictable temporal dynamics of resistance risk among patients could be exploited to reduce the time required to isolate patients, this would reduce costs associated not only with isolation but also the many adverse impacts that isolation are reported to have [82], including on patient mental health [83]. Since most patients with *S. pneumoniae* infections are not hospitalized, it is possible that the reduction of transmission risk could occur by mask use or "social distancing" during the period of greatest risk.

Strengths of this study include the novel statistical approach, which allowed for time to be treated as a continuous variable instead of being categorized (eg, before vs after, or intervention vs control). This meant that the multiple, longitudinal observations per study could be capitalized upon more effectively for analysis [26, 84]. Limitations of this study include the fact that extracted data from the reviewed studies were insufficient to analyze pathogens other than *S. pneumoniae* and this analysis was restricted to a single antibiotic class with 2 subclasses. It was also not possible to assess the differences between high- and low-dose antibiotics, or between adults and children.

This study identified consistent temporal dynamics in the emergence and waning of drug resistance for specific drug-pathogen combinations. Acknowledging the shortfall in the development of new drugs, the World Health Organization recently reiterated the critical importance of alternative infection control strategies [74]. Implications of predictable dynamics extend beyond improved targeting for future surveillance and highlight a potential novel strategy of temporally optimized patient isolation to reduce transmission of resistant pathogens. Future work will explore alternative data sources beyond published research (eg, hospital records) to investigate the generalizability of the new methods and results presented here to other pathogen-drug class combinations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. L. Y. conceived the study. L. Y. and L. F.-K. directed the study's implementation, designed the analytical strategy, and helped to interpret the findings. M. G. led the literature review, the analysis, and the risk of bias analysis, and helped to prepare the text. All authors contributed to results interpretations and manuscript writing.

Data availability. All data were obtained freely from previously published articles.

Ethical approval. No ethical clearance was needed for this publication because all data were previously published and were anonymized.

Potential conflicts of interest. D. L. P. reports contracts or grants unrelated to this work and paid to institution from Shionogi, Merck, and Pfizer; consulting fees paid to author from Spero Therapeutics, Merck, AMR Action Fund, and QPex; and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events, paid to the author, from Pfizer, bioMérieux, and Merck. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Hutchings MI, Truman AW, Wilkinson B. Antibiotics: past, present and future. Curr Opin Microbiol **2019**; 51:72–80.
2. Nicolaou KC, Rigol S. A brief history of antibiotics and select advances in their synthesis. J Antibiot (Tokyo) **2018**; 71:153–84.
3. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? Nat Rev Microbiol **2010**; 8:260–71.
4. Munita JM, Arias CA. Mechanisms of antibiotic resistance. Microbiol Spectr **2016**; 4. doi:10.1128/microbiolspec.VMBF-0016-2015.
5. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet **2022**; 399:629–55.
6. Aminov RI, Mackie RI. Evolution and ecology of antibiotic resistance genes. FEMS Microbiol Lett **2007**; 271:147–61.
7. Chatterjee A, Modarai M, Naylor NR, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis **2018**; 18:e368–78.
8. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet **2005**; 365:579–87.
9. McCullough AR, Rathbone J, Parekh S, Hoffmann TC, Del Mar CB. Not in my backyard: a systematic review of clinicians' knowledge and beliefs about antibiotic resistance. J Antimicrob Chemother **2015**; 70:2465–73.
10. Olesen SW, Barnett ML, MacFadden DR, et al. The distribution of antibiotic use and its association with antibiotic resistance. eLife **2018**; 7:e39435.
11. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis **2014**; 14:13.
12. Bergman M, Nyberg ST, Huovinen P, Paakkari P, Hakanen AJ. Association between antimicrobial consumption and resistance in *Escherichia coli*. Antimicrob Agents Chemother **2009**; 53:912–7.
13. Lindgren M, Lofmark S, Edlund C, Huovinen P, Jalava J. Prolonged impact of a one-week course of clindamycin on *Enterococcus* spp. in human normal microbiota. Scand J Infect Dis **2009**; 41:215–9.
14. Bakhit M, Hoffmann T, Scott AM, Beller E, Rathbone J, Del Mar C. Resistance decay in individuals after antibiotic exposure in primary care: a systematic review and meta-analysis. BMC Med **2018**; 16:126.
15. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ **2010**; 340:c2096.
16. Seppälä H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med **1997**; 337:441–6.
17. Levin BR. Minimizing potential resistance: a population dynamics view. Clin Infect Dis **2001**; 33(Suppl 3):S161–9.
18. Levin BR. Models for the spread of resistant pathogens. Neth J Med **2002**; 60(7 Suppl):58–64; discussion 64–6.
19. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. BMJ **2017**; 358:j3418.
20. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA **2003**; 290:2588–98.
21. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med **2000**; 162(2 Pt 1):505–11.
22. Dinh A, Ropers J, Duran C, et al. Discontinuing beta-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. Lancet **2021**; 397:1195–203.
23. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol **1992**; 135:1301–9.
24. Zhang C, Jia P, Yu L, Xu C. Introduction to methodology of dose-response meta-analysis for binary outcome: with application on software. J Evid Based Med **2018**; 11:125–9.
25. Bennette C, Vickers A. Against quantiles: categorization of continuous variables in epidemiologic research, and its discontents. BMC Med Res Methodol **2012**; 12: 21.
26. Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. Stat Med **2007**; 26:5512–28.
27. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med **2009**; 6: e1000097.
28. Elsevier. Scopus. Available at: https://www.scopus.com/. Accessed 31 October 2019.
29. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ **2019**; 366:l4898.
30. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ **2016**; 355:i4919.
31. Xu C, Doi SAR. The robust error meta-regression method for dose-response meta-analysis. Int J Evid Based Healthc **2018**; 16:138–44.
32. Furuya-Kanamori L, Xu C, Doi S. REMR: Stata module to implement robust error meta-regression method for dose–response meta-analysis. Available at: https://ideas.repec.org/c/boc/bocode/s458793.html. Accessed 2 September 2020.
33. Reid M. Reliability—a Python library for reliability engineering. Version 0.5.1. Zenodo. Available at: https://zenodo.org/record/3938000#.YIHH3pAzaUk. Accessed 5 February 2021.
34. Brook I. Emergence and persistence of β-lactamase–producing bacteria in the oropharynx following penicillin treatment. Arch Otolaryngol Head Neck Surg **1988**; 114:667–70.
35. Brook I, Foote PA, Hausfeld JN. Eradication of pathogens from the nasopharynx after therapy of acute maxillary sinusitis with low- or high-dose amoxicillin/clavulanic acid. Int J Antimicrob Agents **2005**; 26:416–9.
36. Brook I, Gober AE. Eradication of *Streptococcus pneumoniae* in the nasopharyngeal flora of children with acute otitis media after amoxicillin-clavulanate therapy. Antimicrob Agents Chemother **2004**; 48:1419–21.
37. Cohen R, Bingen E, Varon E, et al. Change in nasopharyngeal carriage of *Streptococcus pneumoniae* resulting from antibiotic therapy for acute otitis media in children. Pediatr Infect Dis J **1997**; 16:555–60.
38. Cohen R, Navel M, Grunberg J, et al. One dose ceftriaxone vs. ten days of amoxicillin/clavulanate therapy for acute otitis media: clinical efficacy and change in nasopharyngeal flora. Pediatr Infect Dis J **1999**; 18:403–9.
39. Conradi AD, Calbo E, Cuchí E, et al. Impact of amoxicillin, associated or not with clavulanic acid, on pharyngeal colonization and selection of *Streptococcus pneumoniae* resistance in children under 5 years of age. Eur J Pediatr **2007**; 166:467–71.
40. Dabernat H, Geslin P, Megraud F, et al. Effects of cefixime or co-amoxiclav treatment on nasopharyngeal carriage of *Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. J Antimicrob Chemother **1998**; 41: 253–8.
41. Ghaffar F, Friedland IR, Katz K, et al. Increased carriage of resistant nonpneumococcal alpha-hemolytic streptococci after antibiotic therapy. J Pediatr **1999**; 135:618–23.
42. Ghaffar F, Muniz LS, Katz K, et al. Effects of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. Clin Infect Dis **2000**; 31:875–80.
43. Ghaffar F, Muniz LS, Katz K, et al. Effects of large dosages of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae*, *Haemophilus influenzae*, nonpneumococcal alpha-hemolytic streptococci, and *Staphylococcus aureus* in children with acute otitis media. Clin Infect Dis **2002**; 34:1301–9.
44. Batt SL, Charalambous BM, Solomon AW, et al. Impact of azithromycin administration for trachoma control on the carriage of antibiotic-resistant *Streptococcus pneumoniae*. Antimicrob Agents Chemother **2003**; 47:2765–9.
45. Burr SE, Milne S, Jafali J, et al. Mass administration of azithromycin and *Streptococcus pneumoniae* carriage: cross-sectional surveys in the Gambia. Bull World Health Organ **2014**; 92:490–8.
46. Chern KC, Shrestha SK, Cevallos V, et al. Alterations in the conjunctival bacterial flora following a single dose of azithromycin in a trachoma endemic area. Br J Ophthalmol **1999**; 83:1332–5.
47. Guchev IA, Gray GC, Klochkov OI. Two regimens of azithromycin prophylaxis against community-acquired respiratory and skin/soft-tissue infections among military trainees. Clin Infect Dis **2004**; 38:1095–101.
48. Guchev IA, Klochkov OI, Ivanitsa GV, Pervov IA, Shturmina SM, Rosman SV. Efficacy and safety of azithromycin prophylaxis of respiratory tract infections in military community [in Russian]. Antibiot Khimioter **2004**; 49:34–42.
49. Roca A, Oluwalana C, Bojang A, et al. Oral azithromycin given during labour decreases bacterial carriage in the mothers and their offspring: a double-blind randomized trial. Clin Microbiol Infect **2016**; 22:565.e1–9.

50. Schrag SJ, Peña C, Fernández J, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA **2001**; 286: 49–56.
51. Toltzis P, Dul M, O'Riordan MA, Toltzis H, Blumer JL. Impact of amoxicillin on pneumococcal colonization compared with other therapies for acute otitis media. Pediatr Infect Dis J **2005**; 24:24–8.
52. Toltzis P, Dul M, O'Riordan MA, Toltzis H, Blumer JL. Comparative effects of single-dose ceftriaxone versus three oral antibiotic regimens on stool colonization by resistant bacilli in children. Pediatr Infect Dis J **2007**; 26:25–30.
53. Bojang E, Jafali J, Perreten V, et al. Short-term increase in prevalence of nasopharyngeal carriage of macrolide-resistant *Staphylococcus aureus* following mass drug administration with azithromycin for trachoma control. BMC Microbiol **2017**; 17:75.
54. Chardin H, Yasukawa K, Nouacer N, et al. Reduced susceptibility to amoxicillin of oral streptococci following amoxicillin exposure. J Med Microbiol **2009**; 58(Pt 8): 1092–7.
55. Eisenblätter M, Klaus C, Pletz MW, et al. Influence of azithromycin and clarithromycin on macrolide susceptibility of viridans streptococci from the oral cavity of healthy volunteers. Eur J Clin Microbiol Infect Dis **2008**; 27:1087–92.
56. Löfmark S, Jernberg C, Jansson JK, Edlund C. Clindamycin-induced enrichment and long-term persistence of resistant *Bacteroides* spp. and resistance genes. J Antimicrob Chemother **2006**; 58:1160–7.
57. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet **2007**; 369:482–90.
58. Malhotra-Kumar S, Van Heirstraeten L, Coenen S, et al. Impact of amoxicillin therapy on resistance selection in patients with community-acquired lower respiratory tract infections: a randomized, placebo-controlled study. J Antimicrob Chemother **2016**; 71:3258–67.
59. Mombelli A, Cionca N, Almaghlouth A, Cherkaoui A, Schrenzel J, Giannopoulou C. Effect of periodontal therapy with amoxicillin-metronidazole on pharyngeal carriage of penicillin- and erythromycin-resistant viridans streptococci. J Periodontol **2016**; 87:539–47.
60. Nyberg SD, Osterblad M, Hakanen AJ, et al. Long-term antimicrobial resistance in *Escherichia coli* from human intestinal microbiota after administration of clindamycin. Scand J Infect Dis **2007**; 39:514–20.
61. Skalet AH, Cevallos V, Ayele B, et al. Antibiotic selection pressure and macrolide resistance in nasopharyngeal *Streptococcus pneumoniae*: a cluster-randomized clinical trial. PLoS Med **2010**; 7:e1000377.
62. Chung A, Perera R, Brueggemann AB, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. BMJ **2007**; 335:429.
63. Crémieux AC, Muller-Serieys C, Panhard X, et al. Emergence of resistance in normal human aerobic commensal flora during telithromycin and amoxicillin-clavulanic acid treatments. Antimicrob Agents Chemother **2003**; 47:2030–5.
64. Dagan R, Leibovitz E, Greenberg D, Yagupsky P, Fliss DM, Leiberman A. Dynamics of pneumococcal nasopharyngeal colonization during the first days of antibiotic treatment in pediatric patients. Pediatr Infect Dis J **1998**; 17:880–5.
65. Eliasson I, Holst E, Mölstad S, Kamme C. Emergence and persistence of beta-lactamase-producing bacteria in the upper respiratory tract in children treated with beta-lactam antibiotics. Am J Med **1990**; 88:51–5s.
66. Gaynor BD, Chidambaram JD, Cevallos V, et al. Topical ocular antibiotics induce bacterial resistance at extraocular sites. Br J Ophthalmol **2005**; 89:1097–9.
67. Morita JY, Kahn E, Thompson T, et al. Impact of azithromycin on oropharyngeal carriage of group A *Streptococcus* and nasopharyngeal carriage of macrolide-resistant *Streptococcus pneumoniae*. Pediatr Infect Dis J **2000**; 19:41–6.
68. Murray BE, Rensimer ER, DuPont HL. Emergence of high-level trimethoprim resistance in fecal *Escherichia coli* during oral administration of trimethoprim or trimethoprim–sulfamethoxazole. N Engl J Med **1982**; 306:130–5.
69. T M PH, et al OK. Emergence of trimethoprim resistance in fecal flora. Antimicrob Agents Chemother **1985**; 28:354–6.
70. Nord CE, Peterson J, Ambruzs M, Fisher AC. Levofloxacin versus azithromycin on the oropharyngeal carriage and selection of antibacterial-resistant streptococci in the microflora of healthy adults. Curr Med Res Opin **2009**; 25:1461–7.
71. Raum E, Lietzau S, von Baum H, Marre R, Brenner H. Changes in *Escherichia coli* resistance patterns during and after antibiotic therapy: a longitudinal study among outpatients in Germany. Clin Microbiol Infect **2008**; 14:41–8.
72. Varon E, Levy C, De La Rocque F, et al. Impact of antimicrobial therapy on nasopharyngeal carriage of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Branhamella catarrhalis* in children with respiratory tract infections. Clin Infect Dis **2000**; 31:477–81.
73. Jit M, Ng DHL, Luangasanatip N, et al. Quantifying the economic cost of antibiotic resistance and the impact of related interventions: rapid methodological review, conceptual framework and recommendations for future studies. BMC Med **2020**; 18:38.
74. World Health Organization. Global action plan on antimicrobial resistance. Geneva, Switzerland: WHO, **2015**.
75. Furuya-Kanamori L, Yakob L. Filling the gaps in global antimicrobial resistance research/surveillance. BMC Infect Dis **2020**; 20:39.
76. Seale AC, Gordon NC, Islam J, Peacock SJ, Scott JAG. AMR surveillance in low and middle-income settings—a roadmap for participation in the Global Antimicrobial Surveillance System (GLASS). Wellcome Open Res **2017**; 2:92.
77. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. Infect Control Hosp Epidemiol **2003**; 24:699–706.
78. de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. Lancet **2000**; 355:973–8.
79. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev **2017**; 2: CD003543.
80. Siegel JD, Rhinehart E, Jackson M, Chiarello L, Health Care Infection Control Practices Advisory Committee. Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control **2007**; 35(10 Suppl 2):S65–164.
81. Landelle C, Pagani L, Harbarth S. Is patient isolation the single most important measure to prevent the spread of multidrug-resistant pathogens? Virulence **2013**; 4:163–71.
82. Kirkland KB, Weinstein JM. Adverse effects of contact isolation. Lancet **1999**; 354: 1177–8.
83. Tarzi S, Kennedy P, Stone S, Evans M. Methicillin-resistant *Staphylococcus aureus*: psychological impact of hospitalization and isolation in an older adult population. J Hosp Infect **2001**; 49:250–4.
84. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ **2006**; 332:1080.