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Original Research

Bayesian hierarchical model of ceftriaxone resistance proportions among *Salmonella* serotype Heidelberg infections

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ABSTRACT

The National Antimicrobial Resistance Monitoring System (NARMS) at the Centers for Disease Control and Prevention tracks resistance among *Salmonella* infections. The annual number of *Salmonella* isolates of a particular serotype from states may be small, making direct estimation of resistance proportions unreliable. We developed a Bayesian hierarchical model to improve estimation by borrowing strength from relevant sampling units. We illustrate the models with different specifications of spatio-temporal interaction using 2004–2013 NARMS data for ceftriaxone-resistant *Salmonella* serotype Heidelberg. Our results show that Bayesian estimates of resistance proportions were smoother than observed values, and the difference between predicted and observed proportions was inversely related to the number of submitted isolates. The model with interaction allowed for tracking of annual changes in resistance proportions at the state level. We demonstrated that Bayesian hierarchical models provide a useful tool to examine spatio-temporal patterns of small sample size such as those found in NARMS.

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1. Introduction

Antimicrobial-resistant nontyphoidal *Salmonella* (hereafter referred to as *Salmonella)* is a serious threat to public health (CDC, 2013). Although most *Salmonella* infections are self-limited, treatment with antibiotics is recommended for severe infections, such as bacteremia and meningitis. Third-generation cephalosporins (e.g., ceftriaxone) are one of the recommended antibiotics when treatment is indicated.

The National Antimicrobial Resistance Monitoring System (NARMS) at the Centers for Disease Control and Prevention (CDC) has tracked resistance patterns among enteric pathogens from humans since 1996. NARMS is a collaboration among CDC, the U.S. Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state and local public health departments. Since 2003, NARMS has included health departments from all 50 states, covering over 300 million persons. Participating public health laboratories submit every 20th nontyphoidal *Salmonella* isolate to the CDC NARMS laboratory and include available information regarding age, sex, specimen source, and *Salmonella* serotype (CDC, 2013). Each year, NARMS reports the proportion of *Salmonella* isolates with resistance to antimicrobial agents, such as ceftriaxone, for the most common serotypes.

Understanding the annual and regional patterns of resistant infections, such as increases, decreases, and regional concentrations, is important for designing public health policies to control antibiotic resistance. For Heidelberg and many *Salmonella* serotypes, however, only a few isolates are submitted for testing per year by many states. Furthermore, states might have no isolate submission for some years, especially for less common serotypes, resulting in

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Table 1
Summary of annual submission of *Salmonella* Heidelberg to NARMS by states.

Year	5th percentile	25th percentile	Median	Mean	75th percentile	95th percentile	Missing percent (%)	Total
2004	1.00	1.00	2.00	2.68	3.00	7.10	29	91
2005	1.00	1.75	2.00	3.84	4.25	12.60	33	123
2006	1.00	1.00	2.00	3.09	3.00	7.80	31	102
2007	1.00	1.00	2.00	2.97	2.00	10.80	31	98
2008	1.00	1.00	2.00	2.84	3.00	6.00	48	71
2009	1.00	1.00	2.00	3.15	3.50	5.00	44	85
2010	1.00	1.00	1.00	2.36	2.00	9.40	48	59
2011	1.00	1.00	2.00	3.14	3.75	6.95	54	69
2012	1.00	1.00	1.50	2.00	3.00	4.00	58	40
2013	1.00	1.00	1.00	2.68	2.75	8.95	54	59

gaps in annual estimated resistance. The sparse and missing data of yearly submission by state (hereafter state-year, respectively) pose a challenge for assessing spatio-temporal changes in resistance. Direct estimation of area-specific resistance proportions based on small samples is unreliable with unacceptably large variance. To improve the precision of estimates, indirect estimation has been proposed, which uses the data collected from other sampling units (Hidiroglou, 2007). This is sometimes referred to as small area estimation. Bayesian hierarchical modeling is a useful technique for small area estimation because it improves estimation by borrowing information from other sampling units.

In this study, we developed Bayesian hierarchical models for estimation of spatio-temporal patterns of antimicrobial resistance. Our objective was to address sparse data issues in NARMS to improve estimation of resistance proportions. We illustrate the application using NARMS data on ceftriaxone resistance in *Salmonella* serotype Heidelberg. Our ultimate goal was to provide improved estimates of NARMS state-year resistance proportions that could be combined with incidence data from overall *Salmonella* surveillance to estimate incidence rates of resistant infections.

2. Methods

2.1. Data

For *Salmonella* isolates, susceptibility to agents representing 8–9 classes of antimicrobial agents are tested. Minimum inhibitory concentrations (MICs) were determined by broth microdilution (Sensititer; Trek Diagnostics, Westlake, OH, USA) and interpreted by using criteria from the Clinical and Laboratory Standards Institute when available (CDC, 2016). We defined ceftriaxone resistance as MIC $> 4\,\mu$g/mL. We used 2004–2013 NARMS data on ceftriaxone resistance in *Salmonella* Heidelberg from the 48 contiguous states of the United States (excluding Hawaii and Alaska).

The number of isolates of *Salmonella* Heidelberg by state was small (on average 2–3 isolates per state) and were sparse for estimating resistance proportions (Table 1). There was a steady decrease in submission since 2005. Out of 480 state-year pairs, 43% (207) had no submitted isolate, 23% (109) had only 1 isolate. There were 96 ceftriaxone-resistant Heidelberg isolates of 797 isolates tested, resulting in an overall resistance proportion of 12.0%.

2.2. Bayesian hierarchical models (BHM)

The number of resistant isolates $n_{s,t}$ at state s and year t was assumed to be binomially distributed with unknown parameter $p_{s,t}$

$$n_{s,t} \sim B(p_{s,t}, T_{s,t})$$

where $p_{s,t}$, was the unobserved proportional resistance, and $T_{s,t}$ was the number of isolates tested in state s at year t. For these cases with missing $T_{s,t}$, we imputed $T_{s,t}$ as either the average of the yearly submission rates (estimated from the years with observed submissions for state s) or one if the former was not available. The latter minimized the influence of the assumption of imputation on posterior estimates. The corresponding missing $n_{s,t}$ was estimated by Bayesian hierarchical model as unknown parameters.

We constructed Bayesian hierarchical models treating state and year as random effect. We compared four models with different assumptions of interaction between state and year effect.

2.2.1. Main effect model

This model only accounted for main effect with no interaction between state and year

$$\log\left(\frac{p_{s,t}}{1-p_{s,t}}\right) = \alpha + v0_t + v_t + u0_s + u_s$$

where α is intercept, $v0_t$ and v_t are unstructured and structured year effects, and $u0_s$ and u_s are unstructured and structured state effects.

For unstructured α, $v0_t$, and $u0_s$, normal priors were applied with zero means and precision parameters τ as follows:

$$\alpha \sim N(0, \tau_\alpha)$$
$$v0_t \sim N(0, \tau_{v0})$$
$$u0_s \sim N(0, \tau_{u0})$$

The exchangeable priors of $v0$, and $u0$ allowed borrowing strength globally among all years and all states. We included the temporally structured effect v_t, to borrow strength from the precedent years:

$$v_t \sim N(0, \tau_{vt}) \quad (t = 1)$$
$$v_t \sim N(v_{t-1}, \tau_{vt}) \quad (t > 1)$$