

Nontyphoidal *Salmonella* Infection, Guangdong Province, China, 2012¹

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We used active and passive surveillance to estimate nontyphoidal *Salmonella* (NTS) infection during 2012 in Guangdong Province, China. Under passive surveillance, for every reported NTS infection, an estimated 414.8 cases occurred annually. Under active surveillance, an estimated 35.8 cases occurred. Active surveillance provides remarkable advantages in incidence estimate.

Gastrointestinal illness or diarrhea caused by foodborne pathogens, such as nontyphoidal *Salmonella* (NTS), is a global public health concern (1). Many countries (e.g., the United States, England and Wales, Australia, Canada, Jordan, and Japan) have estimated the incidence of gastrointestinal illness caused by specific pathogens (2–8). However, in China, information is limited about the incidence of specific foodborne pathogens.

In 2003, China initiated a national, internet-based disease reporting system called the National Notifiable Disease Reporting System (NNDRS). This system legally requires routine reporting from all medical institutions and public health units of a list of infectious diseases. In this system, diarrheal pathogens other than *Vibrio cholerae* and *Shigella dysenteriae*, such as *Salmonella* spp., *Escherichia coli*, and *Listeria* spp., are reported as “other infectious diarrhea”; information about etiology is provided as an additional comment (9). Because NNDRS is passive, few reports include laboratory confirmation. According to previous data from passive surveillance, <1,000 NTS cases were reported in Guangdong Province annually since 2009, representing only a small proportion of actual infections.

In 2009, Guangdong Provincial Center for Disease Control and Prevention (Guangdong CDC) established laboratory-based active surveillance for NTS infection. In 2012, this system covered more than half of the Guangdong

Province prefectures, capturing 61.5% of the population served by 27 sentinel hospitals (21 general hospitals and 6 specialized hospitals, including pediatric and gynecologic). In the surveillance system, patients with ≥ 3 loose stools in a 24-hour period plus fever, vomiting, or abdominal pain who visited the sentinel hospitals were enrolled as cases, and fecal samples were collected. The sentinel hospitals were required to forward *Salmonella* isolates to Guangdong CDC, along with epidemiologic data, for analysis. Culture-confirmed cases were then reported to NNDRS with pathogen information. Based on the pyramid model of burden of illness, we used data from active and passive surveillance to estimate NTS infection and to clarify the advantages and disadvantages of each system (2,7,10).

The Study

The estimation requires multiple steps. First, a person must have symptoms severe enough for medical care (multiplier 1). Second, the physician must collect patients' specimens (multiplier 2) and forward them for testing by bacterial culture (multiplier 3). Third, the sample test result must be positive (multiplier 4), and the confirmed case must be reported (multiplier 5) (2,7,8).

To obtain multiplier 1, we conducted a 12-month population-based household survey during March 1, 2012–February 28, 2013 (approved by the Ethics Committee of Guangdong CDC). Respondents were randomly selected from 4 districts in western, eastern, and central Guangdong Province. The case definition was the same as that for active surveillance. We used a standard questionnaire to collect information about diarrhea in the previous 4 weeks. The incidence rate of diarrhea was 0.1081 (95% CI 0.1004–0.1158) episodes/person-year; 38.6% of the household survey respondents with diarrhea sought medical care. Multipliers 2 and 3 were based on data from sentinel hospitals and comprised the overall number of diarrhea cases, samples collected, and samples submitted for culture during the year. A total of 75,583 (45.3%) samples of 166,729 registered diarrhea cases in the sentinel hospitals were collected, of which 22,577 (29.9%) were tested. Laboratories of sentinel hospitals cultured samples for *Salmonella* in accordance with standard pro-

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Table 1. Active and passive surveillance multipliers used to determine the incidence of nontyphoidal *Salmonella* infections, Guangdong Province, China, 2012*

Surveillance steps	Active surveillance			Passive surveillance, by age group, y					
	Overall	General hospitals	Specialized hospitals	Overall	0–4	5–24	25–44	45–64	≥65
Multiplier 1: Patient seeks medical care	2.59	2.59	2.59	2.59	1.25	5.0	8.0	2.0	3.0
Multiplier 2: Physician obtains samples	2.21	2.01	2.31	2.21	2.21	2.21	2.21	2.21	2.21
Multiplier 3: Samples tested for <i>Salmonella</i>	3.35	2.45	6.73	3.35	3.35	3.35	3.35	3.35	3.35
Multiplier 4: Positive laboratory test result	1.14	1.14	1.14	2.07	2.07	2.07	2.07	2.07	2.07
Multiplier 5: Confirmed cases reported	1.64	1.60	1.82	10.45	10.45	10.45	10.45	10.45	10.45
Overall	35.8	23.3	83.7	414.8	200.1	800.6	1,280.9	320.2	480.4

*Incidence is cases per 100,000 persons.

tol provided by the national reference laboratory by using MacConkey agar as plating medium. According to a proficiency testing program, the *Salmonella* isolation sensitivity rate of these laboratories was 87.5% (multiplier 4). The numbers of *Salmonella* isolates identified and reported to NNDRS as NTS infectious diarrhea by all sentinel hospitals yielded the proportion of cases reported (648/1,061, 61.1%) (multiplier 5). We estimated the number of infections using the above 5 multipliers. Thus, active surveillance for each reported NTS infection identified 35.8 cases. We also analyzed multipliers of specialized hospitals (Table 1).

In the population survey-based passive surveillance system, multiplier 1 was the same as for active surveillance. According to a comparison with samples from the submission proportion in a survey of physician-diagnosed diarrhea in Guangdong Province during 2009 (Mann-Whitney test, $p = 0.246$) (11), and a comparison between medical institutions that charged and did not charge for testing (Kolmogorov-Smirnov test, $p = 0.837$), the proportion of samples submitted and tested from active surveillance were also used as estimates of passive surveillance. The average test sensitivity of sentinel laboratories before active surveillance began was used as an estimate of all medical institutions (i.e., the sensitivity of passive surveillance [48.2%]). Using numbers of *Salmonella* isolates in Guangdong Prov-

ince from laboratory data, and number of reported NTS cases by all medical institutions, we determined the proportion of reported NTS was 9.6% (991/10,360). Thus, for each reported NTS case under passive surveillance, 414.8 cases actually occurred. Multipliers of 5 age groups also were presented (Table 1).

To generate a more robust estimate, we conducted uncertainty and sensitivity analyses (online Technical Appendix, <http://wwwnc.cdc.gov/EID/article/22/4/15-1372-Techapp1.pdf>) on passive surveillance data using Monte Carlo simulation (@Risk 6.0; Palisade, Ithaca, NY, USA) (12). We used β distribution to describe the uncertainty of proportions and negative binomial distribution to estimate the number of cases. The sensitivity analysis helped determine factors that provide higher uncertainty in the estimate.

The uncertainty analysis model predicted a 411.9 (95% CI 308.4–592.7) overall multiplier and estimated that 408,499 (95% CI 302,899–591,901) *Salmonella* cases occurred per year when the overall multiplier was applied to the 991 reported NTS cases, resulting in 391.6 (95% CI 290.3–567.4) cases/100,000 persons in 2012. Incidence for 5 age groups was also estimated (Table 2). The rank correlation of various factors in the model showed that patients seeking medical care provided the highest uncertainty in the overall estimate (influence rate 96%) (Figure).

Table 2. Results of Monte Carlo simulation characterizing the uncertainty about the number of cases and the passive surveillance multipliers and the annual reported and estimated cases and incidence of nontyphoidal *Salmonella* infections, Guangdong Province, China, 2012

Age group, y	Annual no. cases, median (95% CI)	Multipliers, median (95% CI)	No. cases		Annual incidence, cases/100,000	
			Reported	Estimated (95% CI)	Reported	Estimated (95% CI)
0–4	87,195 (68,367–138,725)	209.6 (168.5–332.1)	415	87,195 (68,367–138,725)	6.13	1,287.9 (1,009.8–2,049.0)
5–24	222,558 (90,222–1,376,278)	605.3 (248.9–3720.3)	367	222,558 (90,222–1,376,278)	0.90	547.7 (222.0–3387.1)
25–44	119,409 (49,292–488,534)	1038.3 (436.4–4250.9)	115	119,409 (49,292–488,534)	0.32	333.4 (137.6–1,364.1)
45–64	18,577 (11,400–36,234)	320.2 (216.8–603.2)	58	18,577 (11,400–36,234)	0.40	126.6 (77.7–247.0)
≥65	16,421 (8,351–42,273)	457.1 (259.7–1156.5)	36	16,421 (8,351–42,273)	0.56	255.1 (129.7–656.8)
Overall	408,499 (302,899–591,901)	411.9 (308.4–592.7)	991	408,499 (302,899–591,901)	0.95	391.6 (290.3–567.4)

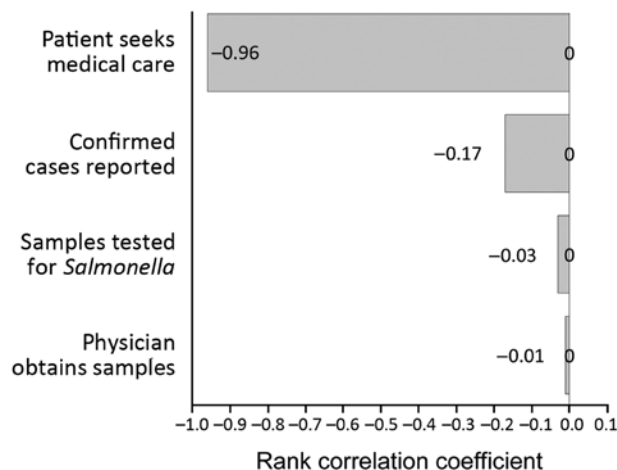


Figure. Rank correlations for the total number of nontyphoidal *Salmonella* cases in the population (tornado diagram), Guangdong Province, China, 2012.

Conclusions

Our estimated NTS incidence was lower than the incidence in China as determined from a literature review (626.5 cases/100,000 persons) (13) but close to that in the United States (352.1 cases/100,000 persons) (3). However, incidences for persons <5 years of age and 5–24 years of age in our study were higher than those for persons in China and the United States, highlighting that *Salmonella* represents a major health problem in Guangdong Province, especially among younger persons. Our estimated active surveillance rate (35.8) of NTS infections per reported case is similar to estimates in the United States (38.6 and 39) (2,10) but different from those for England (3.2), Jordan (278), and Japan (63) (7,8,14). Such differences might be due to differences in methods used and to actual differences in *Salmonella* infections.

With fewer missing cases and less underestimation, active surveillance has lower overall multipliers than passive surveillance, indicating smaller surveillance artifacts and more accurate incidence estimate and presents remarkable advantages over passive surveillance. The estimate for active surveillance also showed that if we seek to reduce uncertainty in the overall estimate, we should first focus on encouraging patients to seek medical care.

Our study provides policymakers in China with a reference for the importance of *Salmonella* incidence and calls for balanced surveillance on both foodborne infections and foods and enlarging active surveillance scales. More surveillance guidelines need to be developed to help physicians identify timing of sampling, tests, and performance. Laws requiring reporting of foodborne diseases and pathogens need to be enacted to increase quantity and quality of reporting. The result suggests that to increase care seeking and sample submission, government health

insurance schemes should be further developed to cover diagnostic tests and treatments of diseases of public health significance.

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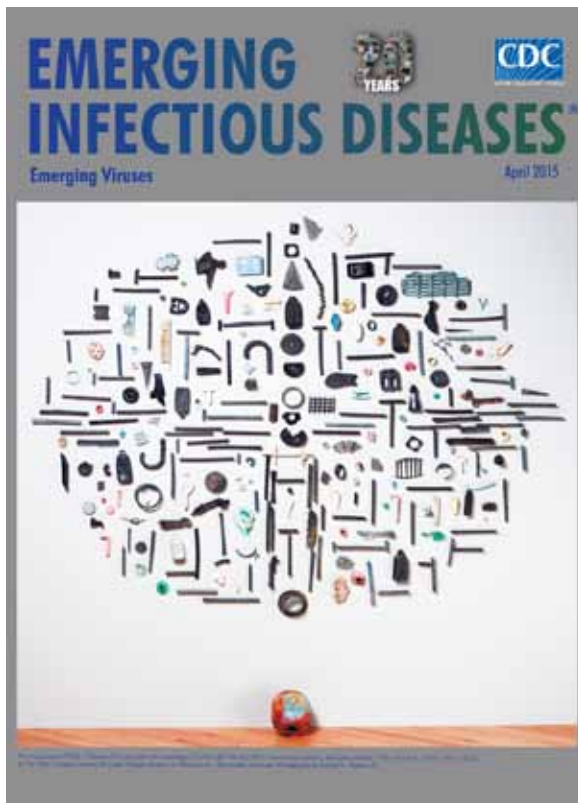
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Nontyphoidal *Salmonella* Infection, Guangdong Province, China, 2012

Technical Appendix

Uncertainty and sensitivity analysis

From data of a population-based survey, we found that 22 (38.6%) of 57 persons with diarrhea reported seeking medical care. From surveillance data, 75,583 of 166,729 registered persons with diarrhea sought medical care in the surveillance hospitals submitting fecal samples; 22,577 of submitted samples tested positive for *Salmonella*; the laboratory test sensitivity was 48.20%; and of the total 10,360 *Salmonella* isolates, 991 were reported in the National Notifiable Disease Reporting System as nontyphoidal *Salmonella*.

In the uncertainty analysis on passive surveillance data using Monte Carlo simulation (I), the β distribution was used to describe uncertainty about proportions (functions and parameters are presented in Technical Appendix Table 1). The negative binomial distribution was used in stepwise fashion to add the number of cases that are missed by the surveillance system due to surveillance artifacts; thus, the total number of cases (N) = no. of cases reported (n) + negative binomial (n, p), $p = p_1 \times p_2 \times p_3 \times p_4 \times p_5$ (p is joint probability).

In the sensitivity analysis, we used variance rates of median and 95% CI of annual cases to describe the influence of the joint probability p ($p = p_1 \times p_2 \times p_3 \times p_4 \times p_5$) on the annual cases estimate (Technical Appendix Table 2). The result indicated that the median of annual cases had more stable results (ranging from -25% to 25%), when the variance rate of joint probability p ranging from -20% to 30%, but had poor stability (30%~45%) when the variance rate of p ranging from -30% to -25%.

The uncertainty of the overall estimate that the input variables (p_1, p_2, p_3, p_4, p_5) provided was described by the rank correlations and presented in descending order in the tornado diagram (Figure). As the figure showed, 4 variables, including patients seeking medical care, confirmed

cases reported, samples tested for *Salmonella*, and physician-obtained samples, provided negative influence on overall estimate of annual cases, means the higher these proportions are, the lower the multipliers, as well as the lower the uncertainty of the annual cases estimate. With the highest influence rate (96%), patients seeking medical care provided the highest uncertainty, and the confirmed cases reported came second (influence rate 17%); samples tested for *Salmonella* and physician-obtained samples provided lower uncertainties, with influence rate <3%.

Study Limitations

Our study has several limitations. First, the samples of the population survey were not totally the same as active surveillance. Second, only a small number of hospitals were included in active surveillance; because the numbers of each surveillance steps were collected separately, the duplicated and invalid samples could not be corrected. Third, we assumed that the behaviors of care seeking were the same between persons with nontyphoidal *Salmonella* and persons with diarrhea. However, salmonellosis may have severer symptoms and longer durations with greater needs of medical care. Forth, some proportions from active surveillance were used as estimate of passive surveillance, as in active surveillance physicians and laboratorians take more initiative in treatment, testing, and reporting, it might have underestimated the real incidence. Finally, only the available data were used to estimate the average test sensitivity in passive surveillance but no specific surveys.

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Technical Appendix Table 1. Uncertainty analysis on passive surveillance data, functions, and parameters, nontyphoidal *Salmonella* Infection, Guangdong Province, China, 2012

Surveillance steps	β Distribution (proportion)		
	Functions	Parameter 1	Parameter 2
Confirmed cases reported	$P_5 \approx \beta (991 + 1, 10360 - 991 + 1)$	992	9370
Laboratory test sensitivity	$P_4 = 0.482$	0.482	0.482
Samples tested for <i>Salmonella</i>	$P_3 \approx \beta (22577 + 1, 75583 - 22577 + 1)$	22578	53007
Physician obtains samples	$P_2 \approx \beta (75583 + 1, 166729 - 75583 + 1)$	75584	91147
Patient seeks medical care	$P_1 \approx \beta (22 + 1, 57 - 22 + 1)$	23	36
Overall (no. cases)	No. cases reported (n) + Negbin (n, p) $p = p_1 \times p_2 \times p_3 \times p_4 \times p_5$		

Technical Appendix Table 2. Influence of the joint probability on the annual estimate of cases, nontyphoidal *Salmonella* Infection, Guangdong Province, China, 2012

Variance rate of joint probability, %	Annual no. cases		Variance rate of median, %
	Median	95% CI	
+30	314,378	233,396–456,756	-23.0
+25	326,783	243,171–472,064	-20.0
+20	340,153	253,116–494,260	-16.7
+15	356,009	263,385–515,700	-12.8
+10	371,944	275,867–537,890	-9.0
+5	388,447	289,986–567,123	-4.9
-5	430,446	317,977–621,347	+6.0
-10	453,821	338,154–658,548	+11.1
-15	480,674	356,927–696,189	+17.7
-20	511,328	378,014–742,446	+25.1
-25*	544,296	402,476–789,619	+33.2
-30	584,342	431,695–844,239	+43.0
Overall	408,499	302,899–591,901	-

*Bold indicates the more stable results (with variance rate of median of -25% to 25%).