Quinolone Resistance Is Associated with Increased Risk of Invasive Illness or Death during Infection with *Salmonella* Serotype Typhimurium

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In a registry-based cohort study, we determined the risk of invasive illness or death associated with infection with quinolone-resistant *Salmonella* serotype Typhimurium. We linked data from the Danish surveillance registry of enteric pathogens with data from the Danish civil registration system and 2 national health registries. Of 1323 patients infected with *Salmonella* Typhimurium, 46 (3.5%) were hospitalized due an invasive illness within 90 days of infection, and 16 (1.2%) died within 90 days of infection. After adjustment for age, sex, and comorbidity, infection with quinolone-resistant *Salmonella* Typhimurium was associated with a 3.15-fold (95% confidence interval, 1.39–7.10-fold) higher risk of invasive illness or death within 90 days of infection, compared with that observed for infection with pansusceptible strains.

In developed countries, nontyphoidal *Salmonella* strains develop drug resistance primarily in response to selective pressure from antibiotics used in food animals [1]. Of particular concern is the emergence of resistance to clinically important antibiotics such as fluoroquinolones, which were introduced into veterinary medicine in Europe during the late 1980s and in the United States in 1995. Although this group of antimicrobial drugs plays a key role in human medicine and *Salmonella* bacteria are a leading cause of foodborne infection in many countries, the clinical consequences of resistance have not yet been well characterized. The objective of the present registry-based cohort study was to determine the risk of the most severe outcomes of *Salmonella* infection—invasive illness and death—associated with quinolone-resistant *Salmonella* serotype Typhimurium, compared with that associated with pansusceptible *Salmonella* Typhimurium.

Quinolone-resistant *Salmonella enterica* usually contain chromosomal point mutations that result in alterations of the A subunit of DNA gyrase. It has been demonstrated that single chromosomal point mutations are sufficient to cause an amino acid change and to result in nalidixic acid resistance. Strains with such a mutation are currently defined as strains with decreased susceptibility to fluoroquinolones according to NCCLS breakpoint concentrations. However, there have been documented therapeutic failures suggesting that fluoroquinolones may have reduced efficacy in the treatment of an infection caused by nalidixic acid–resistant *Salmonella* Typhimurium [2–4]. In the present report, “quinolone resistance” refers to strains resistant to the first-generation quinolone, nalidixic acid.

**Methods.** For our study, we obtained data from the Danish surveillance registry of enteric pathogens, the Danish civil registration system (CRS), the national registry of patients (NRP), and the cancer registry. Bacterial foodborne infections are diagnosed at our institute (Statens Serum Institut [SSI], Copenhagen, Denmark) and at 10 local clinical microbiology laboratories. SSI is notified of positive findings and records them in the surveillance registry of enteric pathogens. If on >1 occasion a *Salmonella* serotype is obtained from the same patient during a period of up to 6 months, only the first positive sample is registered. In 1995, monitoring for antimicrobial resistance in *Salmonella* Typhimurium was initiated as part of the laboratory-based surveillance system in Denmark. During 1995–1996, only a sample of strains were tested for antimicrobial susceptibility, but, from 1997 on, all *Salmonella* Typhimurium strains received at SSI have been tested for antimicrobial susceptibility. In the present study, we included all *Salmonella* Typhimurium isolates examined from 1 January 1995 to 31 December 2000. Isolates were tested by tablet diffusion with Neosensitabs (Rosco) on Danish blood agar (SSI Diagnostica).

All live-born children and citizens of Denmark are assigned a personal identification number within the CRS that uniquely identify every single person. Demographic data, including vital status, emigration/immigration information, and address of residence, are kept in this system. For every patient infected with *Salmonella* Typhimurium, we randomly selected 10 per-
sons from the CRS, matched for age, sex, and county of residence, who were alive on the date on which the sample had been received for the corresponding patient. We obtained information on date of death or emigration for the patients and for the sample of the general population. Finally, data were obtained from the NRP on all hospital admissions, outpatient clinic visits, and discharge diagnoses within the time span of up to 5 years before entry in the study and up to 3 months after entry. This allowed us to control for preexisting illness (comorbidity) and to determine the risk of invasive illness. The NRP contains data on all patients discharged from somatic departments since 1 January 1977 and on outpatient visits since 1 January 1995. Diagnoses are coded according to the International Classification of Diseases (ICD) 8 or ICD 10 (from 1993).

The matched sample composed of 10 people from the general population per each patient was used to calculate a comorbidity index, as described by Charlson et al. [5]. Using data from the NRP and the cancer registry, we first calculated the relative mortality associated with the different diagnostic groups included in the comorbidity index (metastatic cancer, hematologic malignancies, HIV infection, liver diseases, etc.). The index was defined as the logarithm of this relative mortality. For each patient, a comorbidity weight was then calculated as the sum of the indices corresponding to the number and severity of coexisting illnesses.

To estimate the relative risk of death or invasive illness associated with quinolone resistance, we used a proportional-hazards model. The outcome variable was time to invasive illness or death, up to 90 days after diagnosis. Data were stratified by age and sex. After the comorbidity weights were included, the difference in risk between quinolone-resistant and pansusceptible Salmonella Typhimurium infections was beyond that attributable to underlying illnesses (figure 1).

**Results.** Of 3724 culture-confirmed Salmonella Typhimurium infections reported during the study period, a positive match to the CRS was obtained for 3703 (99.5%). Of these, 2522 isolates (68.0%) were tested for antimicrobial susceptibility. A total of 1244 (49.3%) were pansusceptible, 104 (4.1%) were quinolone resistant, and 1174 (46.6%) were quinolone susceptible but were resistant to at least 1 other drug. The group of

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Proportion (%) of infections resulting in invasive illness or death</th>
<th>RR (95% CI) [P] of invasive illness or death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Quinolone resistant</td>
<td>7/79 (8.86)</td>
<td>2.00 (0.94–4.25) [0.070]</td>
</tr>
<tr>
<td>Pansusceptible</td>
<td>55/1244 (4.42)</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>62/1323 (4.69)</td>
<td>...</td>
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</table>

**NOTE.** CI, confidence interval.
quinozolone-susceptible strains resistant to at least 1 other drug was very heterogeneous, and, due to the scope of the present study, this group was not included in the final analysis. Of the quinozolone-resistant *Salmonella Typhimurium* isolates, 49 (47.1%) were resistant to at least 5 other drugs (ampicillin, chloramphenicol, streptomycin, sulphonamide, and tetracycline; i.e., R-type ACSSuTNx); 47 (45.2%) were resistant to a least 1 other drug and were not R-type ACSSuTNx; and 8 (7.7%) were resistant to quinozolone only.

Twenty-five patients infected with R-type ACSSuTNx strains were part of an outbreak traced back to swine herds [4] and were excluded, leaving 79 patients infected with quinozolone-resistant strains and 1244 patients infected with pansusceptible strains. None of the patients had >1 positive finding of *Salmonella* Typhimurium infection during the study period.

Twenty (25.3%) and 347 (27.2%) patients infected with quinozolone-resistant or pansusceptible *Salmonella Typhimurium* strains, respectively, had a history of preexisting illness. There was no significant difference in comorbidity between quinozolone-resistant strains and pansusceptible strains (P = .962). The median age of all patients was 31 years (range, 0.04–91.3 years; interquartile range [IQR], 10.8–49.2 years).

A total of 46 (3.5%) patients were hospitalized due to diagnosis of an invasive illness within 90 days of infection, and an additional 16 (1.2%) patients died within 90 days of infection. Most (52 [83.9%]) of these 62 patients had their adverse event within the first 30 days of infection. The proportion of patients with invasive illness or fatal outcome was dependent on age. Among patients with either of these outcomes, the median age was 64 years (range, 0.15–89.4 years; IQR, 34.3–77.0 years).

Overall, before the data were adjusted for age, sex, and comorbidity, patients infected with quinozolone-resistant *Salmonella Typhimurium* had a 2.00-fold (95% confidence interval [CI], 0.94–4.25-fold; P = .070) increased risk of invasive illness or death within 90 days of infection, compared with that for patients infected with a pansusceptible strain. After the data were adjusted for age, sex, and comorbidity, the relative risk of invasive illness or death increased to 3.15 (95% CI, 1.39–7.10; P = .0058) (table 1).

**Discussion.** At present, fluoroquinolones are the drug of choice for the empirical treatment of serious intestinal and extraintestinal *Salmonella* infection in adults. Resistance to these drugs will reduce the efficacy of early empirical treatment and may limit therapeutic choice in the management of severely ill patients with culture-confirmed infection. In the present study, we present new estimates of the risk of invasive illness or death associated with quinozolone-resistant *Salmonella Typhimurium* infection; nearly 5% of the patients died or were admitted to the hospital due to invasive illness associated with *Salmonella* Typhimurium infection, and the patients infected with quinozolone-resistant *Salmonella Typhimurium* had an adjusted 3.15-fold higher risk (table 1) of invasive illness or death within 90 days of infection than did the patients infected with pansusceptible *Salmonella Typhimurium*. At present, it is impossible to determine whether this excess risk of adverse outcome can be fully explained by reduced efficacy of treatment, because data on antimicrobial-drug use were not available in this registry-based study.

In a previous study, we found that infection with quinozolone- and multidrug-resistant *Salmonella Typhimurium* was associated with increased mortality up to 2 years after infection [6]. However, that study included patients who were part of the previously mentioned outbreak of *Salmonella Typhimurium* DT104 R-type ACSSuTNx, and it is possible that the outbreak resulted in a higher average inoculum, which may have contributed to the death of some of these individuals [4]. A recent study from the United States suggests that infection with resistant *Salmonella* strains may be associated with an increased risk of invasive illness [7]. Taken together, these studies suggest that antimicrobial resistance—and, in particular, quinozolone resistance—in *Salmonella* strains is associated with adverse effects on human health. Given that antimicrobial resistance in *Salmonella* strains in developed countries is largely a consequence of the use of antimicrobial drugs in food animals, the use of fluoroquinolones in food animals should be either discontinued or severely restricted.

**Acknowledgment**

We thank Peter Gerner-Smidt and Katharina E. P. Olsen of the National Reference Center for Enteric Pathogens, Department of Bacteriology, Mycology and Parasitology, Statens Serum Institut.

**References**