Risk of Acute Liver Injury Associated with the Use of Moxifloxacin and Other Oral Antimicrobials: A Retrospective, Population-Based Cohort Study

James A. Kaye,[1,*] Jordi Castellsague,[2] Christine L. Bui,[3] Brian Calingaert,[3] Lisa J. McQuay,[3] Nuria Riera-Guardia,[2] Catherine W. Saltus,[1] Scott Quinlan,[4] Crystal N. Holick,[4] Peter M. Wahl,[5] Kiliana Suzart,[6] Kenneth J. Rothman,[1] Mari-Ann Wallander,[6] and Susana Perez-Gutthann[2]

[1]Epidemiology, RTI Health Solutions, Waltham, Massachusetts; [2]Epidemiology, RTI Health Solutions, Barcelona, Spain; [3]Epidemiology, RTI Health Solutions, Research Triangle Park, North Carolina; [4]Safety and Epidemiology, HealthCore, Inc., Andover, Massachusetts; [5]Government and Academic Research, HealthCore, Inc., Andover, Massachusetts; [6]Bayer Pharma AG, Global Epidemiology, Berlin, Germany

Study Objective To estimate the incidence and relative risk of a hospitalization or emergency visit for noninfectious liver injury in users of eight oral antimicrobials—amoxicillin, amoxicillin-clavulanic acid, clarithromycin, cefuroxime, doxycycline, levofloxacin, moxifloxacin, telithromycin—compared with nonusers of these antimicrobials.

Design Retrospective, observational cohort study with a nested case-control analysis.

Data Source HealthCore Integrated Research Database.

Patients Adults with continuous health plan enrollment for at least 6 months before study entry who had a new dispensing of a study antimicrobial between July 1, 2001, and March 31, 2009. Cases had diagnoses indicating noninfectious liver injury during follow-up. To control for potentially confounding risk factors, 10 controls at risk for liver injury during follow-up were matched to each case by age, sex, and event date (liver injury date of the case), and analyses were adjusted for medical history, concomitant drugs, and health care service use.

Measurements and Main Results Two physician reviewers (blind to exposure) validated the cases. Among 1.3 million antimicrobial users, we identified 607 cases of liver injury, including 82 cases of severe hepatocellular injury and 11 cases of liver failure. Liver injury incidence in nonusers of study antimicrobials was 35/100,000 person-years (95% confidence interval [CI] 29–42/100,000 person-years). For valid cases, the adjusted relative risk among current users of multiple antimicrobials was 3.2 (95% CI 1.6–6.7). Levofloxacin had the highest relative risk for current single use (3.2, 95% CI 1.8–5.8). Relative risks were also elevated for amoxicillin-clavulanic acid (2.5, 95% CI 1.3–5.0), doxycycline (2.5, 95% CI 1.2–5.2), moxifloxacin (2.3, 95% CI 1.1–4.7), and amoxicillin (2.3, 95% CI 1.1–4.7).

Conclusion The results support a comparatively high adjusted relative risk of liver injury among patients exposed concurrently to multiple antimicrobials and modest elevations in the risk for several antimicrobials used alone; however, we found little evidence of any strong effect of commonly used antimicrobials on the risk of liver injury.

Key Words antiinfective agents, drug-induced liver injury, epidemiology, fluoroquinolones, moxifloxacin, levofloxacin, amoxicillin, telithromycin.

(Pharmacotherapy 2014;34(4):336–349) doi: 10.1002/phar.1367

Acute noninfectious liver injury is rare in the general population, with an estimated incidence of 2.4–14.8 cases/100,000 person-years.[1–7] Antimicrobials are a relatively frequent cause, in part because they are commonly used.[8] The risk of liver injury is particularly high among patients who received isoniazid[9] or pyrazinamide[8] for tuberculosis. Many other antimicrobials, including β-lactams, macrolides, ketolides, fluoroquinolones, sulfonamides, and tetracyclines, have also been implicated.[8]

The present study fulfilled a regulatory requirement related to the potential for hepatotoxicity with use of moxifloxacin, a fluoroquinolone used to treat respiratory, pelvic, skin, and complicated intraabdominal infections. An unpublished United States insurance claims study using the PharMetrics database, with no validation of end points, estimated the risk of severe liver injury requiring hospitalization among moxifloxacin users at 16.9/100,000 prescriptions, more than 2-fold higher than with amoxicillin-clavulanic acid.[10] A warning concerning hepatic toxicity was added to the moxifloxacin U.S. labeling in 2007.[11] In Europe, moxifloxacin was restricted to second-line indications in 2008, and the prescribing information was amended to inform about hepatotoxicity.[12–15]

To assess the risk of noninfectious liver injury associated with the use of moxifloxacin and other commonly prescribed antimicrobials used for similar indications (as agreed in consultation with regulatory authorities), we conducted a retrospective cohort and nested case-control study, controlling for potentially confounding risk factors, and estimated the incidence and relative risk of liver injury among antimicrobial users and nonusers in a broad study population.

Methods

Study Design, Data Source, and Patient Population

We conducted a retrospective, observational cohort study of adults in the HealthCore Integrated Research Database who had a new dispensing of a study antimicrobial between July 1, 2001, and March 31, 2009. To reduce end point misclassification, we included an extensive case validation process.

HealthCore, Inc., is a wholly owned subsidiary of WellPoint, Inc. (Indianapolis, IN), one of the largest health benefits companies in the United States and an independent licensee of the Blue Cross and Blue Shield Association, serving members who are geographically dispersed throughout the United States. Participating insurance plans are based in 14 states, but members of those plans may reside in states different from where their plan is based. Participating insurance plans are geographically dispersed throughout the United States. The database contains fully adjudicated paid claims with dates of service for all emergency department, inpatient, and outpatient encounters for members with eligibility at the time of service, including visits with primary care physicians and specialists. Claims for medical services are associated with diagnoses using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding. Inpatient and outpatient medical records for health plan members with claims data in the database can be abstracted in a deidentified manner for health research purposes. In August 2009, the database contained claims information on 31 million people, mostly insured through employer-based programs. Information from the database has been used extensively in conducting pharmacoepidemiology research[16–20] and it constitutes part of the Sentinel Network developed under mandate of the U.S. Congress to detect and confirm drug safety signals rapidly and quantitatively.[21]

Study Eligibility

Eligible new users of the study antimicrobials were at least 18 years old with continuous health plan enrollment (both medical and prescription

Bayer Pharma AG provided funding to RTI Health Solutions to conduct this study. The contract between RTI Health Solutions and Bayer for the conduct of this study grants the research team all decisions regarding the content of the publication of the results.

Results of this study were presented in part at the 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 23–26, 2012, Barcelona, Spain.

ClinicalTrials.gov Identifier: NCT01434173.

*Address for correspondence: James A. Kaye, RTI Health Solutions, Epidemiology, 1440 Main Street, Suite 310, Waltham, MA 02451-1623; e-mail: cbui@rti.org.

coverage) for 6 months or more before study entry, defined as the first date of dispensing of oral amoxicillin, amoxicillin-clavulanic acid, clarithromycin, cefuroxime, doxycycline, levofloxacin, moxifloxacin, or telithromycin, with no use of any study antimicrobial within the previous 6 months. We omitted parenteral formulations, which had little use in the database, and nonsystemic formulations.

We excluded patients with acute or chronic infectious hepatitis, chronic alcoholism or alcoholic cirrhosis, or human immunodeficiency virus infection or acquired immunodeficiency syndrome before entry. Late pregnancy and the puerperium were temporary exclusions from study person-time. Follow-up terminated with diagnosis of liver injury, occurrence of an exclusion diagnosis, health plan disenrollment, death, or end of the study period, whichever occurred first.

To use resources for case validation efficiently, we randomly sampled from the base population to create new user cohorts approximately the same size as the entire moxifloxacin group at entry. However, because individuals aged over 65 years are underrepresented in the database, we oversampled eligible patients in this age group.

Exposure Classification

We defined "current use" of each antimicrobial as the prescribed duration plus 30 days. "Recent use" extended for 90 days after the end of current use; subsequent time was classified as "nonuse." Patients could again contribute person-time of use if they had a subsequent dispensing of the same antimicrobial. Because antimicrobials are generally prescribed for short periods, most follow-up time would have been classified as nonuse; therefore, we truncated accrual of nonuse person-time after 90 days (i.e., nonuse extended from 121–210 days after the end of prescribed use). This truncation should not bias effect estimates because the background event rate during the subsequent (excluded) nonuse person-time should be similar to that during the nonuse person-time evaluated.

To refine the analysis of each antimicrobial, we defined "current single use" as current use of a study antimicrobial with no current or recent use of any other, "recent single use" as recent use of a study antimicrobial with no current or recent use of any other, "current single use with recent use" as current use of an antimicrobial with recent use of one or more of the others, "current multiple use" as current use of more than one antimicrobial, and "recent multiple use" as recent use of more than one antimicrobial with no current use of another. The referent category was "nonuse" of any study antimicrobial.

Case Screening and Validation

We screened for potential cases based on ICD-9-CM emergency department or hospital discharge claims diagnoses indicating liver injury (570.xx, acute and subacute necrosis of liver; 572.2x, hepatic coma; 573.3x, hepatitis unspecified). Criteria for the primary study outcome, liver injury, were based on those from an international consensus meeting[22]: alanine aminotransferase level more than 2 times the upper limit of normal; total bilirubin level more than 2 times the upper limit of normal; or any increase of aspartate aminotransaminase, alkaline phosphatase, and total bilirubin level with at least one measurement of more than 2 times the upper limit of normal. Severe liver injury was defined according to a modification of Hy's Law criteria[23–25]: alanine aminotransferase level at least 3 times the upper limit of normal and total bilirubin level at least 2 times the upper limit of normal. Liver failure was defined as liver injury with any degree of mental alteration (encephalopathy) and either an increase in prothrombin time or an international normalized ratio more than 2 without anticoagulation, adapted from previous literature[26, 27] Severe liver injury and liver failure cases are subsets of the primary outcome (liver injury).

For validation, the corresponding medical records were abstracted by trained reviewers by using a standardized form to collect anonymized information on liver test results, diagnoses, imaging and pathology results, and deaths (which were also ascertained in the Social Security Administration death master file). Two authoring physicians, blinded to patients' antimicrobial exposure, reviewed the abstracted information. Potential cases were "valid" if they met the liver test criteria and had no excluded diagnosis, "noncases" if the information indicated that they did not meet all case criteria or had any excluded diagnosis, and "uncertain" if the information available was insufficient.[28]

Incidence Estimation

We estimated crude and age-sex–standardized incidence rates and 95% confidence intervals

(CIs) with nonuse person-time as the standard because it reflects the background rate among the study cohort. Standardized incidence rate ratios (by age and sex) and 95% CIs were also calculated.

Case-Control Analysis

Ten controls at risk for liver injury during eligible person-time were matched to each case by age and sex. Each control was randomly selected on the liver injury date of the case (event date) to which it was matched (incidence density sampling).[29] We used conditional logistic regression to estimate odds ratios, representing incidence rate ratios, described herein as relative risks. We controlled for prior liver disease (other than exclusion diagnoses), diseases of the biliary tract or pancreas, concurrent use of potentially hepatotoxic drugs,[23] comorbidities,[30] and measures of health care utilization (hospitalization days, outpatient visits, and unique prescription drugs during the 6 months before the event date).

The main analysis combined valid and uncertain cases (as defined earlier). Separately, we also analyzed only valid cases. Finally, since many cases had diseases that could cause liver test abnormalities unrelated to the study antimicrobials, we also analyzed only cases without such diagnoses.

Human Subjects Protection

The protocol followed current pharmacoepidemiology research guidelines[31, 32] and was granted exemption from informed consent requirements by the RTI International institutional review board.

Results

Study Cohort and Patterns of Antimicrobial Use

We identified 1,299,056 eligible patients. Demographic characteristics at cohort entry are summarized by antimicrobial exposure in Table 1. A smaller proportion of telithromycin users were aged 65 years or older, and smaller proportions of moxifloxacin and levofloxacin users were in the youngest age categories. There were more women than men among users of all antimicrobials.

The numbers of patients and person-years of current and recent use of each of the antimicrobials during follow-up are presented in Table 2. Nearly 14% of patients were currently exposed to more than one study antimicrobial at any time during follow-up.

Altogether, 1,056,239 patients (81.3% of cohort members) contributed nonuse person-time during follow-up, totaling 350,873 person-years; the remaining 18.7% had fewer than 120 days of eligible follow-up time after the end of prescribed use of a study antimicrobial without further use of the same antimicrobial to which they were already exposed or to another study antimicrobial.

Cases of Liver Injury

In screening, we found 715 potential cases of liver injury. Case validation results are shown in Figure 1. Of the 420 cases with adequate records, 312 were valid and 108 were not cases; 295 were of uncertain status (as defined earlier).

Of the 312 valid cases, 82 (26.3%) had sufficiently abnormal liver test results to qualify as cases of severe liver injury, and 11 (3.5%) had liver failure. Medical record review indicated that of the 312 valid cases, 221 (70.8%) had diagnoses that could have caused liver test abnormalities (e.g., cholecystitis, metastatic cancer, congestive heart failure, sepsis) and 63 (20.2%) had diagnoses of noninfectious hepatitis with no other diagnoses that would plausibly cause abnormal liver test results.

Since 74% of potential cases with adequate records were valid, we combined the 312 valid cases with the 295 uncertain cases in the main analyses. Of these 607 cases, 32 (5.3%) were known to have died.

Incidence Estimates

Age-sex–standardized incidence rates/100,000 person-years and rate ratios (compared with nonuse) are reported in Table 3. The rate of liver injury was highest during current use of multiple antimicrobials. Rates during current single use of each antimicrobial were generally higher than corresponding rates during recent single use except for telithromycin, for which the rates were similar (but based on small numbers). Rates during current single use were somewhat higher for levofloxacin, moxifloxacin, and amoxicillin-clavulanic acid than for the other study antimicrobials and were lowest for telithromycin. There were few cases with current

Table 1. Study Population Characteristics and Antimicrobial Exposure at Cohort Entry

Characteristic	Total (n=1,299,056)	Amoxicillin (n=166,888)	Amoxicillin-clavulanic acid (n=178,047)	Cefuroxime (n=151,238)	Clarithromycin (n=156,774)	Doxycycline (n=176,794)	Levofloxacin (n=181,332)	Moxifloxacin (n=176,934)	Telithromycin (n=79,357)	Current Multiple Use (n=31,692)
Age distribution at cohort entry (years)										
18–24	115,695 (8.9)	17,063 (10)	19,137 (11)	16,353 (11)	13,163 (8)	22,200 (13)	9915 (5)	9088 (5)	6905 (9)	1807 (6)
25–34	201,163 (15.5)	26,172 (16)	30,728 (17)	25,212 (17)	24,298 (15)	31,517 (18)	21,759 (12)	22,488 (13)	14,019 (18)	4970 (16)
35–44	280,157 (21.6)	31,535 (19)	39,045 (22)	36,157 (24)	35,898 (23)	35,767 (20)	35,346 (19)	38,069 (22)	20,634 (26)	7644 (24)
45–54	281,850 (21.7)	30,575 (18)	35,450 (20)	34,287 (23)	34,384 (22)	33,201 (19)	41,890 (23)	44,357 (25)	19,801 (25)	7936 (25)
55–64	203,881 (15.7)	21,722 (13)	22,102 (12)	23,855 (16)	21,397 (14)	22,850 (13)	37,214 (21)	36,267 (20)	12,828 (16)	5680 (18)
65–74	125,061 (9.6)	22,521 (13)	19,271 (11)	8343 (6)	18,466 (12)	18,529 (10)	17,476 (10)	14,905 (8)	3406 (4)	2161 (7)
75–84	67,474 (5.2)	13,485 (8)	9080 (5)	4855 (3)	7210 (5)	9772 (6)	12,227 (7)	8396 (5)	1367 (2)	1108 (3)
85+	23,775 (1.8)	3815 (2)	3234 (2)	2176 (1)	1958 (1)	2958 (2)	5505 (3)	3364 (2)	397 (1)	386 (1)
Sex										
Male	567,346 (43.7)	70,661 (42)	81,855 (46)	59,402 (39)	69,917 (45)	78,201 (44)	79,216 (44)	78,494 (44)	33,859 (43)	15,741 (50)
Female	731,710 (56.3)	96,227 (58)	96,192 (54)	91,836 (61)	86,857 (55)	98,593 (56)	102,116 (56)	98,440 (56)	45,498 (57)	15,951 (50)
Calendar year at cohort entry										
2001	46,713 (3.6)	6421 (4)	5687 (3)	9224 (6)	9209 (6)	6963 (4)	4309 (2)	3308 (2)	0 (0)	1592 (5)
2002	89,332 (6.9)	11,954 (7)	11,438 (6)	14,568 (10)	17,475 (11)	12,939 (7)	9781 (5)	8008 (5)	0 (0)	3169 (10)
2003	79,682 (6.1)	10,454 (6)	10,892 (6)	10,678 (7)	15,032 (10)	11,379 (6)	11,069 (6)	7450 (4)	0 (0)	2728 (9)
2004	162,543 (12.5)	22,097 (13)	21,547 (12)	17,205 (11)	20,704 (13)	22,200 (13)	23,105 (13)	19,011 (11)	12,748 (16)	3926 (12)
2005	265,856 (20.5)	32,513 (19)	32,166 (18)	25,981 (17)	30,385 (19)	32,625 (18)	34,861 (19)	29,967 (17)	42,516 (54)	4842 (15)
2006	235,133 (18.1)	29,526 (18)	30,891 (17)	23,700 (16)	24,244 (15)	29,772 (17)	34,834 (19)	34,694 (20)	22,067 (28)	5405 (17)
2007	220,427 (17.0)	27,612 (17)	32,846 (18)	24,866 (16)	21,225 (14)	29,881 (17)	34,520 (19)	42,389 (24)	1937 (2)	5151 (16)
2008	160,072 (12.3)	21,191 (13)	25,759 (14)	19,511 (13)	14,584 (9)	25,180 (14)	23,496 (13)	26,341 (15)	85 (0)	3925 (12)
2009	39,298 (3.0)	5120 (3)	6821 (4)	5505 (4)	3916 (2)	5855 (3)	5357 (3)	5766 (3)	4 (0)	954 (3)

Data are no. (%) of patients.

Patients counted as being exposed to each antimicrobial are those exposed to a single antimicrobial at cohort entry. Patients with current use of more than one antimicrobial at cohort entry are counted only in the column for current multiple use. Because of the sampling plan, the numbers of patients exposed to each of the antimicrobials at entry were similar except for those exposed to telithromycin, which was prescribed considerably less commonly than any of the other drugs.

Table 2. Antimicrobial Exposure During Follow-Up for the 1,299,056 Study Patients

Antimicrobial	No. of Patients	Current Use (Person-Years)[a]	Recent Use (Person-Years)[b]
Amoxicillin	352,614	56,886	109,142
Amoxicillin-clavulanic acid	309,593	45,922	85,272
Cefuroxime	182,786	25,179	47,647
Clarithromycin	245,865	34,524	66,206
Doxycycline	254,535	49,998	65,446
Levofloxacin	331,891	52,383	97,197
Moxifloxacin	226,375	29,937	58,374
Telithromycin	95,887	10,745	24,210
Multiple study antimicrobials[c]	180,116	15,915	40,374

Data in this table are shown for all the patients in the study. However, patients could have had exposure to more than one study drug during their follow-up and thus could be counted in the multiple study antimicrobials group as well as in one or more single antimicrobial lines; therefore, the numbers in the "No. of Patients" column add up to more than the total number of patients in the study.
[a]Current use is defined as the prescribed duration of the antimicrobial plus 30 days.
[b]Recent use is defined as a duration of 90 days after the end of current use of the antimicrobial.
[c]Multiple study antimicrobials is defined as current use of two or more study antimicrobials on the same day or recent use of two or more study antimicrobials on the same day.

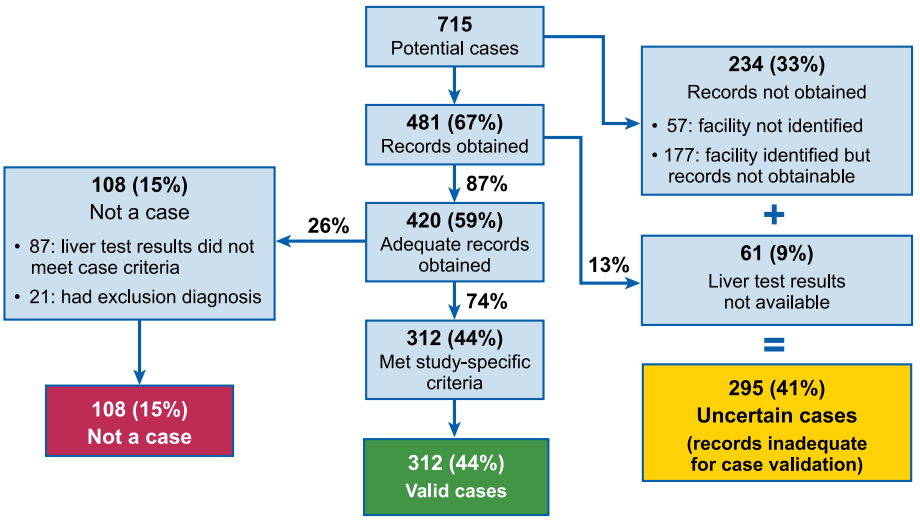

Figure 1. Flow diagram of the case validation results. "Potential" cases met the claims diagnosis screening criteria. Percentages in the boxes refer to the percentage of the total 715 potential cases, whereas percentages outside of boxes refer to percentage of the patients in the preceding box of the flow diagram. Exclusion diagnoses for the 21 potential cases determined not to be valid cases were identified during review of hospital and emergency records. (Patients who had exclusion diagnoses in their claims data were not considered to be potential cases.) "Valid" cases were those confirmed to meet all case definition criteria by review of hospital or emergency department records.

use of a single antimicrobial with recent use of at least one other antimicrobial; these rates were quite variable. Rate ratios (compared with nonuse) mirror all of these findings.

In the stratified analysis, the incidence rate of liver injury during nonuse was lowest among patients aged 25–34 years (11, 95% CI 3.7–26) and increased to a peak among patients aged 85 years or older (137, 95% CI 66–251). The rate among women (37, 95% CI 29–46) was slightly higher than that among men (33, 95% CI 25–44).

The incidence rates and rate ratios for severe liver injury were greater than those for the primary outcome (Table 3). The highest incidence rate was observed for current multiple use; those for recent multiple use were lower than those for current multiple use, and those for current single use were somewhat higher for levofloxacin, moxifloxacin, and amoxicillin-clavulanic acid than for the other antimicrobials.

Case-Control Analyses

Characteristics of the cases and controls are presented in Table 4. Cases were more likely than controls to have a history of chronic diseases, including congestive heart failure, chronic pulmonary disease, diabetes mellitus, renal disease, and malignancy. Severity of concomitant

Table 3. Standardized Incidence Rates and Incidence Rate Ratios of Liver Injury and Severe Liver Injury[a]

		Liver Injury					Severe Liver Injury				
Antimicrobial Exposure	Person-years (n=1,117,323)	Cases (n=607)	Incidence Rate	95% CI	Incidence Rate Ratio	95% CI	Cases (n=82)	Incidence Rate	95% CI	Incidence Rate Ratio	95% CI
Nonuse	350,873	123	35.1	29.1–41.8	REF	REF	9	2.6	1.2–4.9	REF	REF
Current single use											
Amoxicillin	44,555	23	51.0	32.2–77.0	1.45	0.93–2.28	4	9.4	2.5–24.3	3.67	1.12–12.00
Amoxicillin-clavulanic acid	35,529	30	86.0	57.8–123.1	2.45	1.64–3.67	5	13.1	4.2–31.2	5.10	1.70–15.31
Cefuroxime	21,456	14	70.3	37.3–120.2	2.01	1.13–3.56	2	11.5	1.2–41.0	4.48	0.93–21.63
Clarithromycin	25,593	16	64.4	36.3–105.3	1.84	1.08–3.13	1	6.8	0.2–30.8	2.67	0.34–21.06
Doxycycline	42,994	19	46.6	27.9–73.0	1.33	0.82–2.17	3	7.4	1.5–21.5	2.90	0.78–10.75
Levofloxacin	39,974	58	134.3	101.2–175.0	3.83	2.79–5.27	10	22.9	10.8–42.9	8.92	3.59–22.17
Moxifloxacin	24,901	30	116.4	78.4–166.7	3.32	2.22–4.96	3	10.6	2.2–32.1	4.12	1.11–15.22
Telithromycin	9175	3	26.6	5.5–83.1	0.76	0.24–2.38	1	8.9	0.2–56.2	3.45	0.44–27.25
Recent single use											
Amoxicillin	87,527	27	29.0	19.0–42.6	0.83	0.54–1.26	3	3.5	0.7–10.4	1.36	0.37–5.08
Amoxicillin-clavulanic acid	66,390	26	42.4	27.6–62.1	1.21	0.79–1.85	2	3.0	0.3–11.2	1.18	0.25–5.68
Cefuroxime	38,510	12	28.9	14.8–51.5	0.82	0.45–1.50	1	2.1	0.1–14.1	0.83	0.11–6.57
Clarithromycin	48,097	12	25.1	12.9–43.9	0.72	0.39–1.30	1	2.8	0.1–13.7	1.09	0.14–8.59
Doxycycline	54,641	18	31.6	18.6–50.1	0.90	0.55–1.48	1	1.8	0.0–10.2	0.71	0.09–5.64
Levofloxacin	75,615	57	70.9	53.4–92.4	2.02	1.47–2.78	8	10.0	4.3–20.1	3.91	1.50–10.22
Moxifloxacin	46,732	25	52.6	34.0–77.8	1.50	0.97–2.31	5	10.0	3.2–23.7	3.91	1.31–11.70
Telithromycin	19,404	4	29.2	5.0–80.6	0.83	0.24–2.89	0	0.0	0.0–19.3	0.00	0.00 -NE
Current multiple use	15,915	37	234.5	164.8–323.9	6.69	4.63–9.67	7	44.7	18.0–92.5	17.44	6.50–46.84
Recent multiple use	40,374	36	88.4	61.9–122.7	2.52	1.74–3.66	8	19.8	8.5–39.3	7.72	2.98–20.01

CI = confidence interval; NE = not estimable; REF = reference category.

[a]Incidence rates are per 100,000 person-years. Standardization is by age and sex. Data are not shown for 29,068 person-years of exposure in which patients had current use of a single study antimicrobial and concurrent recent use of at least one other study antimicrobial, nor for 37 cases of liver injury (8 of which were severe liver injury) that occurred during this person-time.

Table 4. Characteristics of the Cases and Controls

Characteristic	Cases (n=607)	Controls (n=6070)
Sex		
Male	274 (45)	2740 (45)
Female	333 (55)	3330 (55)
Age (years)		
18–24	23 (4)	230 (4)
25–34	48 (8)	480 (8)
35–44	78 (13)	780 (13)
45–54	129 (21)	1290 (21)
55–64	128 (21)	1280 (21)
65–74	99 (16)	990 (16)
75–84	77 (13)	770 (13)
≥ 85	25 (4)	250 (4)
Event year		
2001	6 (1)	60 (1)
2002	23 (4)	230 (4)
2003	35 (6)	350 (6)
2004	51 (8)	510 (8)
2005	112 (18)	1120 (18)
2006	105 (17)	1050 (17)
2007	117 (19)	1170 (19)
2008	128 (21)	1280 (21)
2009	30 (5)	300 (5)
Comorbidities		
Myocardial infarction	73 (12)	194 (3)
Congestive heart failure	154 (25)	367 (6)
Peripheral vascular disease	71 (12)	257 (4)
Cerebrovascular disease	114 (19)	529 (9)
Dementia	15 (2)	69 (1)
Chronic pulmonary disease	233 (38)	1298 (21)
Rheumatologic disease	41 (7)	141 (2)
Peptic ulcer disease	42 (7)	112 (2)
Mild liver disease	28 (5)	11 (0)
Mild-to-moderate diabetes mellitus	153 (25)	775 (13)
Hemiplegia or paraplegia	9 (1)	29 (0)
Moderate or severe renal disease	86 (14)	152 (3)
Diabetes with complications	47 (8)	166 (3)
Malignancy	164 (27)	565 (9)
Moderate-to-severe liver disease	17 (3)	1 (0)
Metastatic solid tumor	62 (10)	111 (2)

Data are no. (%) of patients.

diseases was specified as in the Deyo-Charlson Comorbidity Index.[30]

The exposure and covariate distributions of the cases and controls and adjusted relative risks for liver injury for both valid and uncertain cases combined (607 cases) are presented in Table 5, Analysis 1. The highest relative risk of any exposure category was associated with current multiple use. Among current single users, the relative risks were somewhat higher for levofloxacin, amoxicillin-clavulanic acid, and amoxicillin than for the other antimicrobials.

Relative risks for liver injury were elevated for prior liver disease, prior disease of the biliary tract or pancreas, congestive heart failure, peptic ulcer disease, metastatic solid tumor, and Deyo-Charlson Comorbidity Index score of 3 or higher. Relative risks of liver injury also increased with increasing number of hospital days, outpatient visits, and unique prescription drugs during the 6 months before the event date.

We restricted a second analysis to only valid cases (312 cases; Table 5, Analysis 2). The pattern of results was similar to that in Analysis 1, but most relative risks were somewhat higher. In this analysis, the relative risk for telithromycin was elevated (with only two exposed cases).

In another approach to control potential confounding, we restricted the analysis to valid cases for which we found no evident cause of abnormal liver test results among their discharge diagnoses (63 cases; Table 5, Analysis 3). Again, the relative risk associated with current multiple use was markedly elevated. Among current single users, the relative risk was highest for telithromycin (based on a single case). The relative risks for levofloxacin, amoxicillin-clavulanic acid, amoxicillin, and moxifloxacin were also elevated; for cefuroxime, clarithromycin, and doxycycline, no cases or only one case occurred in current, singly exposed patients. Due to the smaller number of cases and controls in this analysis, it was not possible to include all components of the Deyo-Charlson Comorbidity Index, but exclusion of cases with diseases such as congestive heart failure and metastatic cancer is expected to accomplish a similar purpose.

Analysis 4 (Table 5) focused on cases of severe liver injury. The patterns were similar to those in previous analyses, with the highest relative risk again observed among patients with current multiple use. Relative risks were elevated for current single use of all the antimicrobials, but were higher for levofloxacin, amoxicillin-clavulanic acid, amoxicillin, and telithromycin than for the others.

Among 11 cases of liver failure, five patients had current or recent single use of levofloxacin, whereas among 607 cases of liver injury overall, only 115 (19%) were so exposed. No liver failure occurred during current or recent single use of moxifloxacin; no cases of liver failure occurred during nonuse, precluding relative risk computation.

Discussion

Automated health databases provide a valuable resource for examining infrequent events like

Table 5. Case-Control Analyses[a]

Category	Analysis 1: Liver Injury				Analysis 2: Valid Cases of Liver Injury			
	Cases, n (%)	Controls, n (%)	OR	95% CI	Cases, n (%)	Controls, n (%)	OR	95% CI
Total no.	607	6070	–	–	312	3120	–	–
Nonuse	123 (20.3)	1680 (27.7)	REF	REF	56 (18)	859 (28)	REF	REF
Current single use								
Amoxicillin	23 (3.8)	287 (4.7)	1.52	0.88–2.62	15 (5)	147 (5)	2.27	1.10–4.66
Amoxicillin-clavulanic acid	30 (4.9)	272 (4.5)	1.54	0.91–2.59	19 (6)	151 (5)	2.53	1.29–4.97
Cefuroxime	14 (2.3)	186 (3.1)	1.04	0.53–2.04	5 (2)	94 (3)	0.85	0.28–2.58
Clarithromycin	16 (2.6)	189 (3.1)	1.34	0.70–2.53	8 (3)	96 (3)	1.79	0.74–4.34
Doxycycline	19 (3.1)	278 (4.6)	1.35	0.76–2.37	13 (4)	139 (4)	2.48	1.18–5.18
Levofloxacin	58 (9.6)	328 (5.4)	1.80	1.16–2.78	33 (11)	162 (5)	3.19	1.75–5.82
Moxifloxacin	30 (4.9)	253 (4.2)	1.31	0.76–2.23	17 (5)	131 (4)	2.29	1.11–4.69
Telithromycin	3 (0.5)	70 (1.2)	0.77	0.21–2.88	2 (1)	35 (1)	1.72	0.36–8.14
Recent single use								
Amoxicillin	27 (4.5)	366 (6.0)	1.26	0.75–2.11	10 (3)	196 (6)	1.24	0.57–2.70
Amoxicillin-clavulanic acid	26 (4.3)	303 (5.0)	1.03	0.59–1.79	13 (4)	167 (5)	0.98	0.44–2.16
Cefuroxime	12 (2.0)	172 (2.8)	0.74	0.36–1.53	6 (2)	99 (3)	0.90	0.33–2.43
Clarithromycin	12 (2.0)	262 (4.3)	0.86	0.44–1.67	6 (2)	126 (4)	1.18	0.46–3.04
Doxycycline	18 (3.0)	266 (4.4)	1.28	0.70–2.35	9 (3)	135 (4)	1.44	0.62–3.38
Levofloxacin	57 (9.4)	357 (5.9)	1.21	0.78–1.87	27 (9)	158 (5)	1.86	0.98–3.55
Moxifloxacin	25 (4.1)	305 (5.0)	0.94	0.55–1.59	12 (4)	171 (5)	0.99	0.47–2.06
Telithromycin	4 (0.7)	88 (1.5)	0.95	0.32–2.82	3 (1)	43 (1)	2.18	0.58–8.12
Current multiple use	37 (6.1)	120 (2.0)	2.46	1.45–4.18	20 (6)	61 (2)	3.23	1.56–6.72
Recent multiple use	36 (5.9)	183 (3.0)	1.28	0.76–2.16	15 (5)	102 (3)	1.37	0.66–2.86
Mean age (yrs)	56.5	56.1	1.02	0.99–1.06	55.0	54.7	1.01	0.96–1.07
Prior liver disease	81 (13.3)	97 (1.6)	2.60	1.59–4.24	32 (10)	64 (2)	1.47	0.74–2.93
Prior disease of biliary tract or pancreas	202 (33.3)	220 (3.6)	7.27	5.47–9.66	105 (34)	122 (4)	7.95	5.34–11.84
Prior or concurrent use of other potentially hepatotoxic drugs	407 (67.1)	3046 (50.2)	1.13	0.88–1.44	205 (66)	1534 (49)	1.14	0.81–1.59
Individual comorbidities of the Deyo-Charlson Comorbidity Index								
Myocardial infarction	73 (12.0)	194 (3.2)	1.29	0.85–1.96	25 (8)	88 (3)	0.92	0.47–1.82
Congestive heart failure	154 (25.4)	367 (6.1)	2.37	1.61–3.50	66 (21)	164 (5)	2.47	1.41–4.33
Peripheral vascular disease	71 (11.7)	257 (4.2)	0.98	0.64–1.50	29 (9)	118 (4)	0.98	0.52–1.86
Cerebrovascular disease	114 (18.8)	529 (8.7)	0.78	0.54–1.11	56 (18)	255 (8)	0.84	0.50–1.40
Dementia	15 (2.5)	69 (1.1)	1.89	0.86–4.17	7 (2)	36 (1)	1.48	0.47–4.71
Chronic pulmonary disease	233 (38.4)	1298 (21.4)	1.02	0.76–1.37	121 (39)	659 (21)	1.20	0.79–1.82
Rheumatologic disease	41 (6.8)	141 (2.3)	1.76	1.06–2.93	17 (5)	67 (2)	1.61	0.74–3.54
Peptic ulcer disease	42 (6.9)	112 (1.9)	1.57	0.93–2.65	24 (8)	56 (2)	2.06	1.01–4.21
Mild liver disease	28 (4.6)	11 (0.2)	2.39	0.84–6.80	8 (3)	7 (0)	0.70	0.12–4.00
Mild-to-moderate diabetes mellitus	153 (25.2)	775 (12.8)	0.77	0.55–1.08	66 (21)	372 (12)	0.77	0.47–1.25
Hemiplegia or paraplegia	9 (1.5)	29 (0.5)	0.53	0.17–1.66	5 (2)	17 (1)	0.78	0.14–4.26
Moderate-to-severe renal disease	86 (14.2)	152 (2.5)	2.12	1.36–3.29	30 (10)	68 (2)	1.50	0.75–2.98

(continued)

Table 5. (continued)

Category	Analysis 1: Liver Injury				Analysis 2: Valid Cases of Liver Injury			
	Cases, n (%)	Controls, n (%)	OR	95% CI	Cases, n (%)	Controls, n (%)	OR	95% CI
Diabetes with complications	47 (7.7)	166 (2.7)	0.88	0.51–1.49	18 (6)	86 (3)	0.78	0.35–1.77
Malignancy	164 (27.0)	565 (9.3)	1.27	0.87–1.86	85 (27)	294 (9)	1.15	0.66–1.99
Moderate-to-severe liver disease	17 (2.8)	1 (0.0)	19.91	1.45–274.02	9 (3)	0 (0)	NE	NE
Metastatic solid tumor	62 (10.2)	111 (1.8)	1.40	0.83–2.38	39 (13)	62 (2)	2.11	1.05–4.24
Acquired immunodeficiency syndrome	0 (0.0)	0 (0.0)	NE	NE	0 (0)	0 (0)	NE	NE
Deyo-Charlson Comorbidity Index score								
0	176 (29.0)	3544 (58.4)	REF	REF	100 (32)	1850 (59)	REF	REF
1–2	159 (26.2)	1724 (28.4)	1.24	0.88–1.75	84 (27)	874 (28)	1.07	0.66-1.72
≥ 3	272 (44.8)	802 (13.2)	1.89	1.06–3.37	128 (41)	396 (13)	1.80	0.77-4.20
No. of hospitalization days								
0	344 (56.7)	5386 (88.7)	REF	REF	197 (63)	2796 (90)	REF	REF
1–3	48 (7.9)	237 (3.9)	1.25	0.81–1.92	20 (6)	101 (3)	0.92	0.46–1.84
≥ 4	215 (35.4)	447 (7.4)	2.10	1.56–2.83	95 (30)	223 (7)	1.72	1.12-2.63
No. of outpatient visits								
0	45 (7.4)	1793 (29.5)	REF	REF	23 (7)	938 (30)	REF	REF
1–5	246 (40.5)	3018 (49.7)	2.20	1.54–3.14	142 (46)	1538 (49)	2.75	1.68–4.51
≥ 6	316 (52.1)	1259 (20.7)	3.04	2.03–4.54	147 (47)	644 (21)	2.77	1.56–4.91
No. of unique prescription drugs								
0–2	36 (5.9)	1222 (20.1)	REF	REF	23 (7)	1538 (49)	REF	REF
3–5	95 (15.7)	1987 (32.7)	1.30	0.85–1.99	142 (46)	644 (21)	1.46	0.80–2.67
6–10	175 (28.8)	1871 (30.8)	2.12	1.37–3.30	147 (47)	312 (11)	2.36	1.27–4.40
≥ 11	301 (49.6)	990 (16.3)	3.33	2.04–5.43	938 (30)	312 (11)	3.58	1.77–7.21

Category	Analysis 3: Restricted Liver Injury				Analysis 4: Severe Liver Injury			
	Cases, n (%)	Controls, n (%)	OR	95% CI	Cases, n (%)	Controls, n (%)	OR	95% CI
Total no.	63	630	–	–	82	820	–	–
Nonuse	13 (21)	162 (26)	REF	REF	9 (11.0)	230 (28.1)	REF	REF
Current use								
Amoxicillin	6 (10)	34 (5)	3.71	1.09–12.70	7 (8.5)	40 (4.9)	6.94	1.88–25.63
Amoxicillin-clavulanic acid	7 (11)	31 (5)	4.03	1.24–13.07	5 (6.1)	41 (5.0)	6.04	1.42–25.72
Cefuroxime	1 (2)	23 (4)	0.40	0.04–4.25	3 (3.7)	23 (2.8)	2.12	0.32–14.09
Clarithromycin	1 (2)	26 (4)	0.88	0.10–7.85	2 (2.4)	25 (3.1)	2.77	0.39–19.69
Doxycycline	0 (0)	32 (5)	0.00	0.00–NE	3 (3.7)	34 (4.2)	2.54	0.48–13.46
Levofloxacin	8 (13)	41 (7)	3.45	1.13–10.57	13 (15.9)	38 (4.6)	7.19	2.05–25.22
Moxifloxacin	5 (8)	32 (5)	2.92	0.82–10.44	3 (3.7)	37 (4.5)	3.10	0.55–17.33
Telithromycin	1 (2)	4 (1)	5.70	0.44–73.74	1 (1.2)	9 (1.1)	5.67	0.41–78.34
Recent single use								
Amoxicillin	0 (0)	42 (7)	0.00	0.00–NE	3 (3.7)	47 (5.7)	2.26	0.47–10.93
Amoxicillin-clavulanic acid	2 (3)	35 (6)	1.00	0.17–5.90	2 (2.4)	41 (5.0)	0.68	0.07–7.13
Cefuroxime	1 (2)	26 (4)	0.87	0.10–7.40	1 (1.2)	30 (3.7)	0.31	0.02–4.59
Clarithromycin	3 (5)	30 (5)	2.18	0.50–9.43	1 (1.2)	28 (3.4)	1.62	0.16–16.26
Doxycycline	3 (5)	18 (3)	2.35	0.48–11.44	1 (1.2)	42 (5.1)	0.80	0.08–7.93
Levofloxacin	2 (3)	28 (4)	0.80	0.13–5.06	8 (9.8)	39 (4.8)	4.92	1.25–19.44
Moxifloxacin	3 (5)	33 (5)	1.07	0.23–4.91	5 (6.1)	56 (6.8)	1.25	0.27–5.71
Telithromycin	2 (3)	6 (1)	15.44	2.27–105.13	0 (0.0)	16 (2.0)	0.00	0.00–NE
Current multiple use	3 (5)	7 (1)	10.87	1.95–60.53	7 (8.5)	13 (1.6)	12.27	2.84–53.04

(continued)

Table 5. (continued)

Category	Analysis 3: Restricted Liver Injury				Analysis 4: Severe Liver Injury			
	Cases, n (%)	Controls, n (%)	OR	95% CI	Cases, n (%)	Controls, n (%)	OR	95% CI
Recent multiple use	2 (3)	20 (3)	1.55	0.28–8.59	8 (9.8)	31 (3.8)	3.86	1.07–13.98
Mean age (yrs)	50.4	49.8	1.07	0.95–1.20	55.7	55.3	1.05	0.94–1.17
Prior liver disease	2 (3)	11 (2)	0.50	0.07–3.67	9 (11.0)	10 (1.2)	1.52	0.39–5.92
Prior disease of biliary tract or pancreas	16 (25)	26 (4)	6.09	2.39–15.50	29 (35.4)	32 (3.9)	9.05	3.74–21.90
Prior or concurrent use of other potentially hepatotoxic drugs	37 (59)	285 (45)	1.10	0.53–2.29	55 (67.1)	380 (46.3)	1.22	0.59–2.51
Individual comorbidities of the Deyo-Charlson Comorbidity Index								
Myocardial infarction	4 (6)	11 (2)	NA[b]	NA[b]	5 (6.1)	21 (2.6)	NA[b]	NA[b]
Congestive heart failure	6 (10)	18 (3)	NA[b]	NA[b]	16 (19.5)	36 (4.4)	NA[b]	NA[b]
Peripheral vascular disease	2 (3)	12 (2)	NA[b]	NA[b]	13 (15.9)	30 (3.7)	NA[b]	NA[b]
Cerebrovascular disease	9 (14)	32 (5)	NA[b]	NA[b]	13 (15.9)	60 (7.3)	NA[b]	NA[b]
Dementia	0 (0)	1 (0)	NA[b]	NA[b]	1 (1.2)	7 (0.9)	NA[b]	NA[b]
Chronic pulmonary disease	18 (29)	114 (18)	NA[b]	NA[b]	34 (41.5)	165 (20.1)	NA[b]	NA[b]
Rheumatologic disease	2 (3)	10 (2)	NA[b]	NA[b]	6 (7.3)	22 (2.7)	NA[b]	NA[b]
Peptic ulcer disease	2 (3)	12 (2)	NA[b]	NA[b]	7 (8.5)	15 (1.8)	NA[b]	NA[b]
Mild liver disease	0 (0)	0 (0)	NA[b]	NA[b]	2 (2.4)	2 (0.2)	NA[b]	NA[b]
Mild-to-moderate diabetes mellitus	10 (16)	60 (10)	NA[b]	NA[b]	17 (20.7)	102 (12.4)	NA[b]	NA[b]
Hemiplegia or paraplegia	0 (0)	2 (0)	NA[b]	NA[b]	1 (1.2)	5 (0.6)	NA[b]	NA[b]
Moderate-to-severe renal disease	0 (0)	9 (1)	NA[b]	NA[b]	7 (8.5)	21 (2.6)	NA[b]	NA[b]
Diabetes with complications	1 (2)	10 (2)	NA[b]	NA[b]	6 (7.3)	32 (3.9)	NA[b]	NA[b]
Malignancy	6 (10)	38 (6)	NA[b]	NA[b]	31 (37.8)	74 (9.0)	NA[b]	NA[b]
Moderate-to-severe liver disease	1 (2)	0 (0)	NA[b]	NA[b]	2 (2.4)	0 (0.0)	NA[b]	NA[b]
Metastatic solid tumor	3 (5)	8 (1)	NA[b]	NA[b]	7 (8.5)	12 (1.5)	NA[b]	NA[b]
Acquired immunodeficiency syndrome	0 (0)	0 (0)	NA[b]	NA[b]	0 (0.0)	0 (0.0)	NA[b]	NA[b]
Deyo-Charlson Comorbidity Index score								
0	31 (49)	411 (65)	REF	REF	23 (28.1)	487 (59.4)	REF	REF
1–2	21 (33)	170 (27)	1.37	0.66–2.84	25 (30.5)	234 (28.5)	1.86	0.84–4.11
≥ 3	11 (17)	49 (8)	1.84	0.59–5.77	34 (41.5)	99 (12.1)	5.20	1.84–14.69
No. of hospitalization days								
0	46 (73)	583 (93)	REF	REF	46 (56.1)	746 (91.0)	REF	REF
1–3	2 (3)	14 (2)	1.14	0.19–7.06	7 (8.5)	26 (3.2)	2.95	0.82–10.59
≥ 4	15 (24)	33 (5)	3.23	1.32–7.90	29 (35.4)	48 (5.9)	3.34	1.41–7.88
No. of outpatient visits								
0	10 (16)	209 (33)	REF	REF	4 (4.9)	262 (32.0)	REF	REF
1–5	38 (60)	308 (49)	1.74	0.72–4.18	45 (54.9)	402 (49.0)	5.07	1.57–16.42
≥ 6	15 (24)	113 (18)	0.87	0.26–2.95	33 (40.2)	156 (19.0)	3.49	0.89–13.65
No. of unique prescription drugs								
0–2	6 (10)	153 (24)	REF	REF	3 (3.7)	163 (19.9)	REF	REF
3–5	14 (22)	223 (35)	1.27	0.41–3.92	15 (18.3)	302 (36.8)	1.46	0.33–6.45
6-10	24 (38)	177 (28)	2.61	0.83–8.20	27 (32.9)	244 (29.8)	3.21	0.72–14.34
≥ 11	19 (30)	77 (12)	2.84	0.75–10.71	37 (45.1)	111 (13.5)	4.53	0.92–22.18

CI = confidence interval; NA = not available; NE = not estimable; OR = odds ratio; REF = reference category.
[a]In addition to the variables shown, Analyses 1 and 2 included variables for current single use with recent use of another antimicrobial (data not shown), whereas in Analyses 3 and 4, current single use of a given study antimicrobial with concurrent recent use of another study antimicrobial was combined with current single use of the antimicrobial to which the patient was currently exposed.
[b]Model was estimated without this variable.

drug-induced liver injury. To our knowledge, this is the first large, population-based study of liver injury among oral antimicrobial users in a relatively unrestricted population including patients with many illnesses, such as cancer and congestive heart failure, which also could cause liver test abnormalities. Indeed, the incidence of liver injury we observed during nonuse (35.1 cases/100,000 person-years) is higher than background incidence rates estimated by other authors who excluded such diagnoses, which range from 2.4–14.8 cases/100,000 person-years.[1–7]

Moreover, the data source provided information on potential confounders, including previous medical diagnoses, use of other drugs, and rates of utilization of health care services.

The highest relative risk of liver injury was associated with current use of multiple antimicrobials. In another study, the risk of liver injury from combined current exposure to nonsteroidal antiinflammatory drugs and other hepatotoxic drugs was more than additive.[33]

Among current users of single antimicrobials, the highest relative risk was associated with exposure to levofloxacin. Fluoroquinolones are known to be associated with an increased risk of liver injury, but it is difficult to discern the relative risk of hepatotoxicity associated with use of specific fluoroquinolones from the published literature. One review reported that hepatotoxicity of moxifloxacin was "not different from what was observed for other fluoroquinolones (excluding trovafloxacin)"[34]; however, the risk of hepatoxicity cited was from a single study that did not quantify moxifloxacin use in the study population.[35] One study[36] reported from the Drug-Induced Liver Injury Network that four cases were attributed to moxifloxacin and one to levofloxacin, but population exposures were not reported, so relative risks were not computed.

The relative risks associated with current single use of moxifloxacin in our primary analysis (1.3, 95% CI 0.76–2.2) and the analysis restricted to valid cases (2.3, 95% CI 1.1–4.7) were both somewhat lower than that reported from the PharMetrics database study (2.58, 95% CI 1.04–6.43).[10] The reference exposure in that study was amoxicillin-clavulanic acid, which itself is associated with an elevated risk of liver injury. Our relative risk estimates would have been lower than those we reported if amoxicillin-clavulanic acid had been the reference exposure.

We found that the incidence of liver injury with current single use of amoxicillin–clavulanic acid was slightly higher than that for amoxicillin alone. Other studies have reported similar findings.[6, 37] Those studies excluded patients with cancer, gallbladder or pancreatic disease, alcohol-related conditions, pregnancy, viral hepatitis, congestive heart failure, and "other well-defined pathology affecting the liver." In our adjusted, matched case-control analysis, odds ratios compared with nonuse were similar for the two drugs. Although this could be due to misclassification or residual confounding, it is expected that in a less restricted population there would be less difference between the rates associated with these two drugs because the attributable cases would represent a smaller proportion of the exposed cases.

We did not find an increased risk of liver injury associated with current or recent single use of telithromycin in our main analysis; we did find an elevated risk in the analysis restricted to cases with no other diagnoses known to cause liver test abnormalities (although the number of cases was small). It is possible that changes in telithromycin labeling during the period of our study, including addition of a warning for liver injury in June 2006,[38] may have resulted in more cautious prescribing of telithromycin to patients with diseases that can cause liver test abnormalities. The varying findings for telithromycin may have resulted from a lower background risk of liver injury during nonuse in the more restricted population than in the main analysis if there were less confounding by contraindication.[39]

The adjusted relative risks for liver injury related to recent use of each antimicrobial in the nested case-control analysis were somewhat lower than the corresponding relative risks for current single use but greater than 1 for some of the study drugs (levofloxacin, amoxicillin, amoxicillin-clavulanic acid, and doxycycline), indicating persistence of liver injury risk more than 30 days after prescribed use ends.

The study has several limitations. "Drug-induced" liver injury is a diagnosis of exclusion; therefore, we focused broadly on liver injury without assuming causality. Relatively few cases did not have other diseases or drug exposures that may have contributed to their risk. Despite improved criteria for diagnosis of liver injury, some cases are undiagnosed and others could be missed by screening claims, so we could have underestimated the true population risk. Information in hospital and emergency department medical records needed to validate liver injury is sometimes incomplete or unavailable. We did not have adequate data to control for the clinical indication for the use of each antimicrobial prescription, so there could be residual confounding by indication. Many antimicrobials are potentially hepatotoxic; our decision about which to include were guided by consideration of their labeled indications, by agreement with regulatory authorities, and by availability in the United States.[40] We studied only oral antimicrobial use, so these results may not be valid for

exposure by other routes of administration. Finally, we cannot carry out additional analyses (e.g., evaluating specific combinations of antimicrobials) because the study funding was related to a specific regulatory obligation, the protocol and analysis plan were specified and agreed to before analyses were carried out, and additional funding was not available to retrieve archived data and carry out exploratory analyses.

Conclusion

This large study evaluating patients with common comorbidities found modest elevations in the risk of validated liver injury associated with some antimicrobials but little evidence of any strong effect of commonly used antimicrobials on the incidence of acute liver injury. We found a comparatively high adjusted relative risk among patients exposed concurrently to multiple antimicrobials.

Acknowledgments

The authors acknowledge helpful contributions to this work by Michelle Therrien for project management, Adele Monroe for medical editing, and Candace Webster for graphics.

References

1. **García Rodríguez LA, Pérez Gutthann S, Walker AM, Lueck L.** The role of non-steroidal anti-inflammatory drugs in acute liver injury. BMJ 1992;305:865–8.
2. **Maggini M, Raschetti R, Agostinis L, Cattaruzzi C, Troncon MG, Simon G.** Use of amoxicillin and amoxicillin-clavulanic acid and hospitalization for acute liver injury. Ann Ist Super Sanita 1999;35:429–33.
3. **García Rodríguez LA, Duque A, Castellsague J, Pérez-Gutthann S, Stricker BH.** A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. Br J Clin Pharmacol 1999;48:847–52.
4. **Sgro C, Clinard F, Ouazir K, et al.** Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002;36:451–5.
5. **Traversa G, Bianchi C, Da Cas R, Abraha I, Menniti-Ippolito F, Venegoni M.** Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ 2003;327:18–22.
6. **de Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA.** Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004;58:71–80.
7. **Andrade RJ, Lucena MI, Fernandez MC, et al.** Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512–21.
8. **Andrade RJ, Tulkens PM.** Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother 2011;66:1431–46.
9. **Derby LE, Gutthann SP, Jick H, Dean AD.** Liver disorders in patients receiving chlorpromazine or isoniazid. Pharmacotherapy 1993;13:353–8.
10. **Food and Drug Administration.** NDA 21-144 Advisory Committee briefing package for Ketek. Appendix H: epidemiology tables. 2006. Available from http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4266b1-01-11-Ketek-appendix-h.pdf. Accessed March 12, 2012.
11. **Food and Drug Administration.** Letter to Bayer Pharmaceuticals Corporation regarding NDA 21-085/S-036 and NDA 21-277/S-030. May 31, 2007. Available from http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/021085s036,021277s030ltr.pdf. Accessed March 12, 2012.
12. **European Medicines Agency.** European Medicines Agency recommends restricting the use of oral moxifloxacin-containing medicines (press release). July 24, 2008. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/08/WC500095423.pdf. Accessed March 12, 2012.
13. **European Medicines Agency.** Annex II: scientific conclusions and grounds for amendment of the summary of product characteristics and package leaflet [for moxifloxacin]. 2008. Available from http://ec.europa.eu/health/documents/community-register/2008/2008071446252/anx_46252_en.pdf. Accessed March 12, 2012.
14. **European Medicines Agency.** Annex III: amendments to summary of product characteristics and package leaflet (relevant sections only). 2008. Available from http://ec.europa.eu/health/documents/community-register/2008/2008071446252/anx_46252_en.pdf. Accessed March 12, 2012.
15. **Bayer Pharma AG.** European summary of product characteristics. Avelox 400 mg film-coated tablets (moxifloxacin hydrochloride). Text revised April 2012. Available from http://www.medicines.org.uk/emc/medicine/11841/SPC/avelox%20400%20mg%20film-coated%20tablets/. Accessed March 12, 2012.
16. **Patorno E, Bohn RL, Wahl PM, et al.** Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010;303:1401–9.
17. **Velentgas P, Amato AA, Bohn RL, et al.** Risk of Guillain-Barré syndrome after meningococcal conjugate vaccination. Pharmacoepidemiol Drug Saf 2012;21:1350–8.
18. **Stephenson JJ, Quimbo RA, Gutierrez B.** Subacute lack of asthma control as a predictor of subsequent acute asthma exacerbation in a managed care population. Am J Manag Care 2010;16:108–14.
19. **Lo Re V 3rd, Haynes K, Ming EE, et al.** Safety of saxagliptin: rationale for and design of a series of postmarketing observational studies. Pharmacoepidemiol Drug Saf 2012;21:1202–15.
20. **Wahl PM, Rodgers K, Schneeweiss S, et al.** Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596–603.
21. **Platt R, Wilson M, Chan KA, Benner JS, Marchibroda J, McClellan M.** The new Sentinel Network—improving the evidence of medical-product safety. N Engl J Med 2009;361:645–7.
22. **Bénichou C.** Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990;11:272–6.
23. **Navarro VJ, Senior JR.** Drug-related hepatotoxicity. N Engl J Med 2006;354:731–9.
24. **Temple R.** Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf 2006;15:241–3.
25. **FDA Working Group.** CDER-PhRMA-AASLD Conference 2000: clinical white paper on drug-induced hepatotoxicity. November 2000. Available from http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm091457.pdf. Accessed March 12, 2012.
26. **Polson J, Lee WM.** AASLD position paper: the management of acute liver failure. Hepatology 2005;41:1179–97.
27. **Lee WM, Stravitz RT, Larson AM.** Introduction to the revised American Association for the Study of Liver Diseases position paper on acute liver failure 2011. Hepatology 2012;55:965–7.
28. **Kaye JA, Castellsague J, Bui CL, et al.** Case screening and validation in a population-based study of antimicrobial use and

acute liver injury (abstract no. 12). Pharmacoepidemiol Drug Saf 2011;20:S5.
29. **Rothman KJ, Greenland S, Lash TL.** Case-control studies. In: Rothman KJ, Greenland S, Lash TL, eds. Modern epidemiology, 3rd edn. Philadelphia: Lippincott Williams & Wilkins, 2008: 111–27.
30. **Deyo RA, Cherkin DC, Ciol MA.** Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–9.
31. **International Society for Pharmacoepidemiology.** Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf 2008;17:200–8.
32. **Food and Drug Administration.** Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets (draft guidance). February 2011. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf. Accessed March 12, 2012.
33. **Perez Gutthann S, García Rodríguez LA.** The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs. Epidemiology 1993;4:496–501.
34. **Van Bambeke F, Tulkens PM.** Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. Drug Saf 2009;32:359–78.
35. **De Valle MB, Av Klinteberg V, Alem N, Olsson R, Bjornsson E.** Drug-induced liver injury in a Swedish University hospital out-patient hepatology clinic. Aliment Pharmacol Ther 2006;24:1187–95.
36. **Orman ES, Conjeevaram HS, Vuppalanchi R, et al.** Clinical and histopathologic features of fluoroquinolone-induced liver injury. Clin Gastroenterol Hepatol 2011;9:517–523.e3.
37. **García Rodríguez LA, Stricker BH, Zimmerman HJ.** Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. Arch Intern Med 1996;156:1327–32.
38. sanofi-aventis U.S. Ketek® (telithromycin) dear healthcare professional letter. March 2011. Available from http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM154544.pdf. Accessed March 12, 2012.
39. **Rothman KJ, Poole C.** A strengthening programme for weak associations. Int J Epidemiol 1988;17:955–9.
40. **Russmann S, Kaye JA, Jick SS, Jick H.** Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: cohort study using data from the UK General Practice Research Database. Br J Clin Pharmacol 2005;60:76–82.