Supplementary Data

1. Choice of comparator drug and information related to data source

Choice of comparator drug - oxytetracycline

Our aim in the causal analysis part of this study was to obtain a comparator population that was (1) similar to the exposed population in terms of health and health-seeking characteristics and (2) was not exposed to a potential hepatotoxin at the start of follow-up. The hepatotoxicity of oxytetracycline itself was not a focus of this study, apart from that it was known to have low hepatotoxicity, so people exposed to it would be likely to experience a risk of liver injury events similar to completely unexposed people. This would allow us to estimate a relative risk of liver injury associated with flucloxacillin use that was as close as possible to the relative risk one would estimate if comparing flucloxacillin users to a group of completely unexposed people with similar health and health-seeking profiles.

Data source - CPRD

The UK Clinical Practice Research Datalink (CPRD Gold, hereafter referred to as CPRD), contains anonymised data on patients from over 625 NHS primary care practices from across the UK (approximately 12 million total patients). Information is recorded by general practitioners or other health centre staff as part of routine clinical care, and data quality checks at the database headquarters ensure that each practice contributing data maintains "up-to-standard" data.[1] In addition to the routinely collected data from primary care consultations, information from some secondary sources that has been provided to primary care clinicians (such as major diagnoses made in hospital) may also be recorded. The database has been collecting data since 1987, and has recently been shown to be broadly representative of the UK population.[2] Epidemiological research has been performed using the database for over 20 years (generating over 1000 publications),[3] and the validity of many diagnoses recorded in the database has been shown to be high.[1]

Patient records for study cohorts are extracted from the database based upon the presence of standardised diagnostic codes (Read codes) or, if defining a cohort by drug exposure, British National Formulary (BNF) drug product or substance codes. Searchable dictionaries of all diagnostic and drug prescription terms used in the database are provided, with each record including a specific code and the corresponding descriptive term. Based on the diagnostic or prescription codes selected from the dictionaries, electronic health records can be obtained for all patients who have any of the codes of interest during a period of interest. Data are extracted from the database as a number of separate data files, each containing a different type of data, with the information relevant to any particular patient identified via a unique patient identifier (patient id).

It is usual to ensure that study particpiants all have a minimum prescription history (e.g. 6 months as used in this study) prior to their inclusion in the study, in oder to ensure that the date of prescription for the drug(s)

of interest (index date) is as accurate as possible (people who have recently registered may have all legacy diagnoses and prescriptions entered into the system on one date, that represents only the date at which the person was first registered into the system).

2. List of exclusion terms (with their Read codes)

This list was prepared in order to select patients who had any of the following in the 6 months prior to their index date for exclusion: any documented liver disease, jaundice, alcoholism, malignant neoplasm of the liver/gallbladder/pancreas, cholelithiasis, viral hepatitis, chronic liver disease, cirrhosis, congestive heart failure, hepatitis following blood transfusion, HIV, rheumatoid arthritis, sarcoidosis, systemic lupus or inflammatory bowel disease. The diagnostic terms in this list were selected based upon a review of 12 studies[4-15] identified by a systematic literature review performed for a previous study on liver injury[16]. Final review of the included exclusion terms was performed by a member of the study team who is a General Practitioner and Professor in Clinical Epidemiology (LS).

Term	*READ code in lowercase (lc)*
[v]contact with and exposure to viral hepatitis	zv01b00
[v]personal history of alcoholism	zv11300
[v]personal history of malignant neoplasm of liver	zv10015
[v]screening for alcoholism	zv79100
[v]screening for rheumatoid arthritis	zv7y100
[v]viral hepatitis carrier	zv02600
[x]acute alcoholic drunkenness	eu10011
[x]alcoholic dementia nos	eu10711
[x]alcoholic hallucinosis	eu10511
[x]alcoholic jealousy	eu10512
[x]alcoholic paranoia	eu10513
[x]alcoholic psychosis nos	eu10514
[x]chronic alcoholic brain syndrome	eu10712
[x]chronic alcoholism	eu10212
[x]dementia in human immunodef virus [hiv] disease	eu02400
[x]hiv disease result/haematological+immunologic abnorms,nec	ayucb00
[x]hiv disease resulting in multiple infections	ayuc300
[x]hiv disease resulting in other non-hodgkin's lymphoma	ayuc600
[x]hiv disease resulting in other specified conditions	ayucc00
[x]hiv disease resulting/other infectious+parasitic diseases	ayuc400
[x]other and unspecified cirrhosis of liver	jyu7100
[x]other cholecystitis	jyu8100
[x]other cholelithiasis	jyu8000
[x]other crohn's disease	jyu4000
[x]other forms of systemic lupus erythematosus	nyu4300
[x]other seropositive rheumatoid arthritis	nyu1100
[x]other specified acute viral hepatitis	ayub000
[x]other specified rheumatoid arthritis	nyu1200
[x]other ulcerative colitis	jyu4100

Term	*READ code in lowercase (lc)*
[x]rheumatoid arthritis+involvement/other organs or systems	nyu1000
[x]sarcoidosis of other and combined sites	cyu0600
[x]sequelae of viral hepatitis	ayuj900
[x]seropositive rheumatoid arthritis, unspecified	nyu1g00
[x]unspecified human immunodeficiency virus [hiv] disease	ayucd00
[x]viral hepatitis	ayub.00
accidental poisoning by alcoholic beverages	t900.00
acute alcoholic hepatitis	j611.00
acute alcoholic intoxication in alcoholism	e230.00
acute alcoholic intoxication in alcoholism nos	e230z00
acute alcoholic intoxication in remission, in alcoholism	e230300
acute alcoholic intoxication, unspecified, in alcoholism	e230000
acute angiocholecystitis	j650100
acute cholecystitis	j650.00
acute cholecystitis nos	j650z00
acute cholecystitis unspecified	j650000
acute congestive heart failure	g580000
acute emphysematous cholecystitis	j650200
acute gangrenous cholecystitis	j650400
acute polyarticular juvenile rheumatoid arthritis	n043100
acute suppurative cholecystitis	j650300
acute viral hepatitis nos	a70z100
alcohol dependence with acute alcoholic intoxication	e230.11
alcoholic cardiomyopathy	g555.00
alcoholic cirrhosis of liver	j612.00
alcoholic dementia nos	e012.11
alcoholic encephalopathy	f11x011
alcoholic fatty liver	j610.00
alcoholic fibrosis and sclerosis of liver	j612000
alcoholic gastritis	j153.00
alcoholic hepatic failure	j613000
alcoholic hepatitis	j617.00
alcoholic liver damage unspecified	j613.00
alcoholic myopathy	f394100
alcoholic paranoia	e015.00
alcoholic polyneuropathy	f375.00
alcoholic psychoses	e01..00
alcoholic psychosis nos	e01z.00
alcoholics anonymous	13y8.00
Alcoholism	e23..11
alcoholism counselling	z4b1.00
arthropathy in crohn's disease	n031100
arthropathy in ulcerative colitis	n031000
aversion therapy - alcoholism	8g32.00
bacterial portal cirrhosis	j615d00
benign neoplasm of gallbladder	b715200
benign neoplasm of liver	b715000
benign neoplasm of liver and biliary ducts	b715.00
bile duct calculus + acute cholecystitis - obstruct nos	j643z00

Term	*READ code in lowercase (lc)*
bile duct calculus + acute cholecystitis and no obstruction	j643000
bile duct calculus + acute cholecystitis and obstruction	j643100
bile duct calculus + other cholecystitis - obstruction nos	j644z00
bile duct calculus + other cholecystitis and obstruction	j644100
bile duct calculus with acute cholecystitis	j643.00
bile duct calculus with other cholecystitis	j644.00
bile duct calculus without cholecystitis nos	j645z00
bile duct calculus without cholecystitis with obstruction	j645100
bile duct calculus without cholecystitis, no obstruction	j645000
bile duct calculus without mention of cholecystitis	j645.00
biliary cirrhosis	j616.00
biliary cirrhosis nos	j616z00
biliary cirrhosis of children	j616200
bmast - brief michigan alcoholism screening test	zra1111
brief michigan alcoholism screening test	zra1100
capsular portal cirrhosis	j615600
carcinoma gallbladder	b160.11
carcinoma in situ of liver	b808000
carcinoma in situ of liver and biliary system	b808.00
carcinoma in situ of liver or biliary system nos	b808z00
carcinoma in situ of pancreas	b80z000
cardiac portal cirrhosis	j615700
cdai - crohn's disease activity index	zr3s.11
cerebellar ataxia due to alcoholism	f144000
cerebral degeneration due to alcoholism	f11x000
cholecystitis nos	j651z00
cholelithiasis	j64..00
cholelithiasis nos	j64z.00
cholelithiasis nos	j64zz00
cholelithiasis with obstruction nos	j64z100
cholelithiasis without obstruction nos	j64z000
chronic alcoholic brain syndrome	e012000
chronic alcoholic hepatitis	j617000
chronic alcoholism	e231.00
chronic alcoholism in remission	e231300
chronic alcoholism nos	e231z00
chronic cholecystitis	j651000
chronic congestive heart failure	g580100
chronic liver disease nos	j61z.00
chronic viral hepatitis	a707.00
chronic viral hepatitis b with delta-agent	a707000
chronic viral hepatitis b without delta-agent	a707100
chronic viral hepatitis c	a707200
chronic viral hepatitis, unspecified	a707x00
cirrhosis - non alcoholic	j615.00
cirrhosis and chronic liver disease	j61..00
cirrhosis of liver nos	j615z13

Term	*READ code in lowercase (lc)*
congenital viral hepatitis	q409.00
congestive heart failure	g580.00
congestive heart failure due to valvular disease	g580400
congestive heart failure monitoring	662t.00
continuous acute alcoholic intoxication in alcoholism	e230100
continuous chronic alcoholism	e231100
crohn's disease	j40..11
crohn's disease activity index	zr3s.00
crohn's disease nos	j40z.11
crohn's disease of the ileum nos	j400400
crohn's disease of the ileum unspecified	j400300
crohn's disease of the large bowel nos	j401z00
crohn's disease of the small bowel nos	j400z00
crohn's disease of the terminal ileum	j400200
cryptogenic cirrhosis of liver	j615z12
cystic fibrosis related cirrhosis	c370800
cytomegaloviral hepatitis	a785200
delivery of rehabilitation for rheumatoid arthritis	7p20300
diffuse nodular cirrhosis	j615300
disease activity score 28 joint in rheumatoid arthritis	38dz000
disease activity score in rheumatoid arthritis	38dz.00
drug-induced systemic lupus erythematosus	n000200
episodic acute alcoholic intoxication in alcoholism	e230200
episodic chronic alcoholism	e231200
exacerbation of crohn's disease of large intestine	j401200
exacerbation of crohn's disease of small intestine	j400500
exacerbation of ulcerative colitis	j410400
except rheumatoid arthritis qual indicator: informed dissent	9hr1.00
except rheumatoid arthritis quality indicator: pt unsuitable	9hr0.00
exception reporting: rheumatoid arthritis quality indicators	9hr..00
fatty portal cirrhosis	j615400
fh: alcoholism	1282.00
fh: crohn's disease	12e5.00
fh: gallbladder disease	12e4.11
fh: rheumatoid arthritis	12i1.00
fh: ulcerative colitis	12e2.11
fibrosing alveolitis associated with rheumatoid arthritis	n04y012
flare of rheumatoid arthritis	n040t00
florid cirrhosis	j612.11
gallbladder calculus with acute cholecystitis	j640.00
gallbladder calculus with acute cholecystitis - obst nos	j640z00
gallbladder calculus with acute cholecystitis + obstruction	j640100
gallbladder calculus with acute cholecystitis +no obstruct	j640000
gallbladder calculus with other cholecystitis	j641.00
gallbladder calculus with other cholecystitis - obstruct nos	j641z00

Term	*READ code in lowercase (lc)*
gallbladder calculus with other cholecystitis + obstruct	j641100
gallbladder calculus with other cholecystitis +no obstruct	j641000
gallbladder calculus without cholecystitis and obstruct nos	j642z00
gallbladder calculus without mention cholecystitis + obstruc	j642100
gallbladder calculus without mention cholecystitis +no obstr	j642000
gallbladder calculus without mention of cholecystitis	j642.11
gallbladder calculus without mention of cholecystitis	j642.00
gallstones	j64..15
glycogenosis with hepatic cirrhosis	c310400
h/o: alcoholism	1462.00
h/o: gallbladder disease	14c7.11
h/o: rheumatoid arthritis	14g1.00
h/o: ulcerative colitis	14c4.11
hepatic granulomas in sarcoidosis	j63a.00
hepatoblastoma of liver	b150100
history of viral hepatitis	141f.00
hiv disease complicating pregnancy childbirth puerperium	l179.00
hiv disease result/haematological+immunologic abnorms,nec	a788u00
hiv disease resulting in burkitt's lymphoma	a789600
hiv disease resulting in candidiasis	a789200
hiv disease resulting in cytomegaloviral disease	a789100
hiv disease resulting in kaposi's sarcoma	a789500
hiv disease resulting in lymphoid interstitial pneumonitis	a789900
hiv disease resulting in multiple infections	a789400
hiv disease resulting in multiple malignant neoplasms	a789800
hiv disease resulting in mycobacterial infection	a789000
hiv disease resulting in pneumocystis carinii pneumonia	a789300
hiv disease resulting in pneumocystis jirovecii pneumonia	a789311
hiv disease resulting in unspecified malignant neoplasm	a788w00
hiv disease resulting in wasting syndrome	a789a00
hiv disease resulting/unspcf infectious+parasitic disease	a788x00
hiv infection with persistent generalised lymphadenopathy	a788200
hiv positive	43c3.11
husband alcoholic	13l3.13
hypertrophic portal cirrhosis	j615500
indian childhood cirrhosis	j615812
infectious cirrhosis nos	j615h00
inflammatory bowel disease	j4...12
[d]jaundice (not of newborn)	r024.00
[d]jaundice	r024111
obstructive jaundice nos	j66y600

Term	*READ code in lowercase (lc)*
o/e – jaundiced	2274.11
jaundice – symptom	1675.11
[d]icterus nos	r024100
yellow/jaundiced colour	1675.00
o/e - jaundiced colour	2274.00
[d]jaundice (not of newborn) nos	r024z00
juvenile arthritis in crohn's disease	n045300
juvenile arthritis in ulcerative colitis	n045400
juvenile portal cirrhosis	j615800
juvenile rheumatoid arthritis	n045500
juvenile rheumatoid arthritis - still's disease	n043.00
juvenile rheumatoid arthritis nos	n043z00
korsakoff's non-alcoholic psychosis	e040.11
korsakov's alcoholic psychosis	e011000
korsakov's alcoholic psychosis with peripheral neuritis	e011100
laennec's cirrhosis	j612.12
liver abscess and sequelae of chronic liver disease	j62..00
liver metastases	b577.11
lung disease with systemic lupus erythematosus	h57y400
macronodular cirrhosis of liver	j615z11
malignant neoplasm gallbladder and extrahepatic bile ducts	b16..00
malignant neoplasm gallbladder/extrahepatic bile ducts nos	b16z.00
malignant neoplasm of body of pancreas	b171.00
malignant neoplasm of gallbladder	b160.00
malignant neoplasm of head of pancreas	b170.00
malignant neoplasm of liver and intrahepatic bile ducts	b15..00
malignant neoplasm of liver and intrahepatic bile ducts nos	b15z.00
malignant neoplasm of liver unspecified	b152.00
malignant neoplasm of other specified sites of pancreas	b17y.00
malignant neoplasm of pancreas	b17..00
malignant neoplasm of pancreas nos	b17z.00
malignant neoplasm of specified site of pancreas nos	b17yz00
malignant neoplasm of tail of pancreas	b172.00
malignant neoplasm other gallbladder/extrahepatic bile duct	b16y.00
mast - michigan alcoholism screening test	zra1.11
meningitis due to sarcoidosis	f013.00
michigan alcoholism screening test	zra1.00
monarticular juvenile rheumatoid arthritis	n043300
multilobular portal cirrhosis	j615100
multiple cranial nerve palsies in sarcoidosis	f326300
munich alcoholism test	zrau.00
myopathy due to rheumatoid arthritis	f396400
myopathy due to sarcoidosis	f396500
myositis in sarcoidosis	n233200
neoplasm of uncertain behaviour of liver	b903000
neoplasm of uncertain behaviour of liver and biliary passage	b903.00

Term	*READ code in lowercase (lc)*
nephrotic syndrome in systemic lupus erythematosus	k01x400
non-alcoholic cirrhosis nos	j615z00
non-alcoholic fatty liver	j61y100
o/e - alcoholic breath	2577.11
oesophageal varices in alcoholic cirrhosis of the liver	g852300
oesophageal varices in cirrhosis of the liver	g852200
orofacial crohn's disease	j08z900
other alcoholic dementia	e012.00
other alcoholic psychosis	e01y.00
other alcoholic psychosis nos	e01yz00
other cholecystitis	j651.00
other cholecystitis os	j651y00
other non-alcoholic chronic liver disease	j61y.00
other non-alcoholic chronic liver disease nos	j61yz00
other rheumatoid arthritis of spine	n040100
other sequelae of chronic liver disease	j62y.00
other specified viral hepatitis with coma	a704.00
other specified viral hepatitis with hepatic coma nos	a704z00
other specified viral hepatitis without coma	a705.00
other specified viral hepatitis without mention of coma nos	a705z00
pauciarticular juvenile rheumatoid arthritis	n043200
pigmentary cirrhosis of liver	c350012
polyneuropathy in rheumatoid arthritis	f371200
polyneuropathy in sarcoidosis	f374900
portal cirrhosis	j615.11
portal cirrhosis unspecified	j615y00
portal fibrosis without cirrhosis	j61y300
primary biliary cirrhosis	j616000
primary carcinoma of liver	b150000
primary malignant neoplasm of liver	b150.00
primary malignant neoplasm of liver nos	b150z00
pulmonary sarcoidosis	h57y200
regional enteritis - crohn's disease	j40..00
rheumatoid arthritis	n040.00
rheumatoid arthritis - multiple joint	n040s00
rheumatoid arthritis and other inflammatory polyarthropathy	n04..00
rheumatoid arthritis annual review	66hb000
rheumatoid arthritis of 1st mtp joint	n040k00
rheumatoid arthritis of acromioclavicular joint	n040400
rheumatoid arthritis of ankle	n040f00
rheumatoid arthritis of cervical spine	n040000
rheumatoid arthritis of dip joint of finger	n040a00
rheumatoid arthritis of distal radio-ulnar joint	n040600
rheumatoid arthritis of elbow	n040500
rheumatoid arthritis of hip	n040b00
rheumatoid arthritis of knee	n040d00
rheumatoid arthritis of lesser mtp joint	n040l00
rheumatoid arthritis of mcp joint	n040800
rheumatoid arthritis of other tarsal joint	n040j00
rheumatoid arthritis of pip joint of finger	n040900
rheumatoid arthritis of sacro-iliac joint	n040c00

Term	*READ code in lowercase (lc)*
rheumatoid arthritis of shoulder	n040200
rheumatoid arthritis of subtalar joint	n040g00
rheumatoid arthritis of talonavicular joint	n040h00
rheumatoid arthritis of wrist	n040700
rheumatoid arthritis particle agglutination test	43b9.00
rheumatoid arthritis screen	68f1.00
rheumatoid arthritis screening test	43c6.00
sarcoidosis	ad5..00
sarcoidosis of inferior turbinates	ad54.00
sarcoidosis of lung	ad50.00
sarcoidosis of lung with sarcoidosis of lymph nodes	ad52.00
sarcoidosis of lymph nodes	ad51.00
sarcoidosis of skin	ad53.00
secondary biliary cirrhosis	j616100
secondary malignant neoplasm of liver	b577.00
secondary malignant neoplasm of liver	b153.00
sequelae of viral hepatitis	ae23.00
seronegative rheumatoid arthritis	n040p00
seropositive errosive rheumatoid arthritis	n047.00
seropositive rheumatoid arthritis, unspecified	n04x.00
slam - systemic lupus activity measure	zrq8.11
suspected gallstones	1j5..00
systemic lupus activity measure	zrq8.00
systemic lupus erythematosus	n000.00
systemic lupus erythematosus disease activity index	zrq9.00
systemic lupus erythematosus nos	n000z00
systemic lupus erythematosus with organ or sys involv	n000300
systemic lupus erythematosus with pericarditis	n000400
toxic liver disease with fibrosis and cirrhosis of liver	j635600
ulcerative colitis	j410100
ulcerative colitis and/or proctitis	j41..12
unspecified chronic alcoholism	e231000
unspecified viral hepatitis	a70z.00
viral (serum) hepatitis b	a703.00
viral hepatitis	a70..00
viral hepatitis a with coma	a700.00
viral hepatitis b with coma	a702.00
viral hepatitis c with coma	a704000
viral hepatitis c without mention of hepatic coma	a705000
viral hepatitis carrier	65q7.00
viral hepatitis comp pregnancy, childbirth & the puerperium	l176500
viral hepatitis screening test	4jrf.00
viral hepatitis without hepatic coma	a709.00
xanthomatous portal cirrhosis	j615c00

3. Case definition

3a Diagnostic terms indicating liver injury

(a) Search terms used to search for relevant diagnostic terms in CPRD diagnosis dictionary

Inclusion terms
Search based on the word "liver" *liver* AND (*biopsy* OR *necrosis* OR *disease* OR * enlarged* OR *disorder*)
Search based on the word "hepatic" *hepatic* AND (*failure* OR *coma* OR encephalopathy*)
Other search terms *cholesta*, *jaundice*, *icterus*, *cholangitis*, *other gall bladder disorders*, *cholaemia*, *yellow atrophy*, *hepatitis*
Terms excluded during search to increase specificity
fetal, *hepatitis a*, *hepatitis b*, *hepatitis c*, *hepatitis e*, *hepatitis g*, *delive*, *pregn*, *neonat*, *perinatal*, *viral*, *virus*, *congenital*, *autoimmune*

Note 1: * represents a wildcard, which means that any text can be present in this position
Note 2: the search was set to look for words after the word "AND" on either side of the main search term (e.g. both "liver biopsy" and "biopsy liver" would be searched for)

(b) CPRD terms selected following search

Term	*READ code (lc)*
toxic liver disease with cholestasis	j635000
[d]jaundice (not of newborn)*	r024.00
hepatitis unspecified	j633.00
[d]jaundice*	r024111
obstructive jaundice nos*	j66y600
hepatitis unspecified nos	j633z00
o/e – jaundiced*	2274.11
jaundice – symptom*	1675.11
[d]icterus nos*	r024100
yellow/jaundiced colour*	1675.00
o/e - jaundiced colour*	2274.00
[d]jaundice (not of newborn) nos*	r024z00
infective hepatitis	a701.11
other liver disorders	j63..00
chronic hepatitis	j614.00
chronic aggressive hepatitis	j614200
acute alcoholic hepatitis	j611.00
other specified liver disorder nos	j63yz00
[d]cholaemia nos	r024000
acute hepatic failure	j600000
o/e - liver grossly enlarged	25g4.00
alcoholic hepatitis	j617.00
open wedge biopsy of lesion of liver	7804200
Cholangitis	j661.00
biopsy of liver nec	780b000
liver disorder nos	j63z.00
primary sclerosing cholangitis	j661700
chronic hepatitis nos	j614z00
toxic hepatitis	j633000
recurrent cholangitis	j661200

Term	*READ code (lc)*
acute hepatitis – noninfective	j600100
o/e -liver moderately enlarged	25g3.00
hepatic failure	j62y.13
needle biopsy of liver nec	780a112
toxic liver disease with chronic persistent hepatitis	j635300
alcoholic hepatic failure	j613000
hepatitis non a non b	a705400
fh: hepatitis	12e3.11
subacute hepatitis – noninfective	j601100
encephalopathy – hepatic	j622.11
hepatic coma	j622.00
chronic persistent hepatitis	j614000
calculus of bile duct with cholangitis	j646.00
[x] hepatic failure	j625.00
liver abscess due to cholangitis	j620100
other specified liver disorder	j63y.00
subacute hepatic failure	j601000
nonspecific reactive hepatitis	j63y100
other cholangitis	j661y00
other non-alcoholic chronic liver disease nos	j61yz00
ascending cholangitis	j661400
percutaneous transvascular biopsy of lesion of liver	780a000
toxic liver disease with hepatic necrosis	j635100
hepatic failure as a complication of care	sp14200
toxic liver disease	j635.00
toxic liver disease with chronic active hepatitis	j635500
toxic liver disease with acute hepatitis	j635200
acute hepatic failure due to drugs	j635700
acute necrosis of liver	j600.00
toxic liver disease, unspecified	j635x00
other non-alcoholic chronic liver disease	j61y.00
toxic liver disease with fibrosis and cirrhosis of liver	j635600
sclerosing cholangitis unspecified	j661900
other sequelae of chronic liver disease	j62y.00
acute and subacute liver necrosis	j60..00
chronic cholangitis	j661100
recurrent hepatitis	j614300
acute yellow atrophy	j600200
chronic hepatitis unspecified	j614y00
acute necrosis of liver nos	j600z00
hepatic failure nos	j62y.11
subacute necrosis of liver	j601.00
cholangitis nos	j661z00
central haemorrhagic necrosis of liver	j636.00
toxic liver disease with chronic lobular hepatitis	j635400
menghini needle biopsy of liver	780a111
acute and subacute liver necrosis nos	j60z.00
toxoplasma hepatitis	ad05.00
cholangitis lenta	j661500
chronic lobular hepatitis	j614400
subacute yellow atrophy	j601200
subacute necrosis of liver nos	j601z00

Term	*READ code (lc)*
endoscopic ultrasound examination liver biopsy lesion liver	780f000
obliterative cholangitis	j661600
sheeba needle biopsy of liver	780a113

*****Terms/codes required for an individual to be a symptom-defined case. For laboratory-confirmed cases, the individual could have any of the codes in this list (provided they also had a laboratory test results indicative of DILI).

3b Comparison of selected cases with the RUCAM/CIOMS causality assessment method

For each of the cases we collected information on the type of liver injury, whether exposure was first or second, time from drug intake until reaction onset, presence of alcohol or pregnancy as a risk factor, age >=55 as a risk factor, presence and nature of concomitant therapy, whether non drug-related causes had been ruled out and prescribing information related to flucloxacillin hepatotoxicity in order to test each case against the RUCAM/CIOMS criteria for assessing causality of drug-induced liver injury.[17] Additional information that this method can use relates to course of the reaction (i.e. how the patient improved over the following 180 days) and response to re-administration, data that was not available within CPRD. The RUCAM/CIOMS causality method uses all of this information to derive a score, which is converted into the following categories:

- ≤0: Excluded ADR*
- 1-2: Unlikely ADR
- 3-5: Possible ADR
- 6-8: Probable ADR
- ≥9: Highly probable ADR

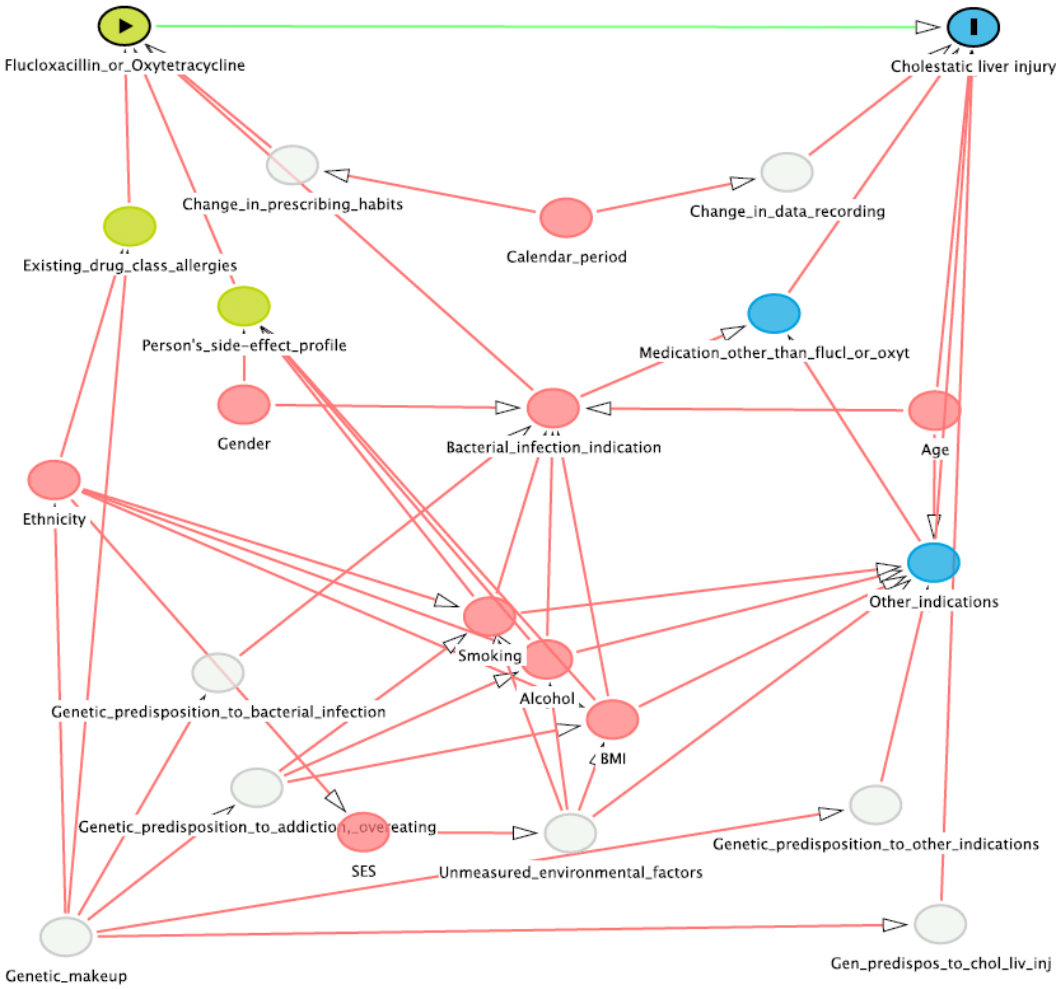
*ADR caused by drug of interest

Given that information on course of the reaction or response to re-administration was not available to us, the highest score that any of our cases could attain was an 8 (Probable ADR).

4. Selection and management of covariates, and handling of missing data

a. Selection and management of covariates

A causal diagram was used in order to inform the selection of covariates.[18] This was prepared using the DAGittty graphical tool for analyzing causal diagrams,[19] and is reproduced below.



Age and gender have been suggested as risk factors for flucloxacillin-induced liver injury,[14, 20, 21] and are included as part of the CPRD patient (demographic) data file. A categorical age variable was created with ten year categories.

The role of ethnicity has not been previously studied, and was considered important due to a likely genetic susceptibility to flucloxacillin-induced liver injury.[22, 23] Ethnicity codes based on the 2001 UK census data were used to search the CPRD additional files,[24] in order to assign ethnicity to the cohort, as a 5-category variable. If no ethnicity records were found in CPRD for a patient, the HES records of any patients that were HES-linked were also searched for ethnicity information. Any patients who did not have ethnicity information in CPRD or HES were assigned to an "Unknown" category.

BMI, alcohol intake and SES are likely to be associated with indications requiring flucloxacillin (such as cellulitis) and with susceptibility to liver-related conditions. CPRD smoking status is recorded as non-, ex-, current and unknown. CPRD alcohol status is recorded as never, ex-, current (not-otherwise-specified), ≤2 or less units/day, 3-6 units/day, >6 units per day, and unknown. A categorical BMI status variable was created with categories of <20, 20-25, 25+, and unknown. Smoking, alcohol and BMI status were assigned according

to the classification of the nearest date prior to the index date (if no prior status, the status from the nearest post-index date was used). SES information is not part of the standard CPRD database, and was obtained separately as linked data. This was provided by CPRD as an Index of Multiple Deprivation score based upon individual patient postcode, and as a practice level score based upon practice postcode (both variables consisting of 5 categories representing quintiles of score). A dedicated SES variable was created for the study and populated with the patient-level score, unless this was missing, in which case the practice-level score was used. This linked SES data was only available for practices in England.

Calendar period was included in order to assess if changes in prescribing habits or recording of outcomes occurred over time (for example, improved automation of the system for capturing liver test results within CPRD over time). A calendar time-period variable was created with categories spanning 3-year periods.

The possible impact of the use of other drugs associated with liver injury was assessed by looking for prescriptions for other drugs that occurred before the end of follow-up for the patient and up to 1 month before the index date. A variable was created with three categories: 0=no use of other drugs, 1=use of drugs thought to cause liver injury at a frequency lower than flucloxacillin, 2=use of drugs thought to cause liver injury at a frequency higher than flucloxacillin. The list of drugs and categorisation was based upon a systematic literature review of epidemiological studies of drug-induced liver injury performed for a previous study on liver injury,[16] combined with information from three reviews relating to drug-induced liver injury[25-27] and from the LIVERTOX website.[28] The drugs included NSAIDs, other antibiotics, antidepressants and antifungals, and a full list of therapies is provided below.

Drug substance	*Frequency category* *(category=less frequent unless marked)*
acebutolol hydrochloride/hydrochlorothiazide	
allopurinol	
aluminium hydroxide/bismuth subnitrate/magnesium carbonate/sodium bicarbonate/deglycyrrhizinised liquorice	
amiloride hydrochloride/hydrochlorothiazide	
amiodarone hydrochloride	
amitriptyline hydrochloride	
amitriptyline hydrochloride/perphenazine	
amlodipine	
amlodipine besilate	
amlodipine besilate/hydrochlorothiazide/olmesartan medoxomil	
amlodipine besilate/olmesartan medoxomil	
amlodipine besilate/valsartan	
amoxicillin sodium	
amoxicillin sodium/potassium clavulanate	More frequent

Drug substance	*Frequency category* *(category=less frequent unless marked)*
amoxicillin trihydrate	
amoxicillin trihydrate/potassium clavulanate	More frequent
ampicillin	
ampicillin sodium	
ampicillin trihydrate	
aspirin	
aspirin/aloxiprin/caffeine citrate	
aspirin/caffeine	
aspirin/caffeine/citric acid/sodium bicarbonate/paracetamol	
aspirin/codeine phosphate	
aspirin/ethoheptazine citrate/meprobamate	
aspirin/isosorbide mononitrate	
aspirin/papaveretum	
aspirin/paracetamol	
aspirin/paracetamol/caffeine	
atenolol/amiloride hydrochloride/hydrochlorothiazide	
atorvastatin calcium	
atorvastatin calcium trihydrate	
auranofin	
azathioprine	More frequent
bacampicillin	
benzoyl peroxide/clindamycin phosphate	
benzoyl peroxide/erythromycin	
betahistine dihydrochloride	
bezafibrate	
bisoprolol fumarate/hydrochlorothiazide	
bupropion hydrochloride	
captopril	
carbamazepine	More frequent
carmustine	
cefalexin	
cefuroxime	
cefuroxime axetil	
cefuroxime sodium	
celecoxib	
cetirizine hydrochloride	
chlorambucil	
chlorothiazide	
chlorpromazine embonate	More frequent
chlorpromazine hydrochloride	More frequent
chlortetracycline hydrochloride	
chlortetracycline hydrochloride/tetracycline hydrochloride/demeclocycline hydrochloride	
chlortetracycline hydrochloride/triamcinolone acetonide	

Drug substance	*Frequency category* *(category=less frequent unless marked)*
cimetidine	
cinnarizine	
ciprofloxacin	
ciprofloxacin hydrochloride	
ciprofloxacin lactate	
clarithromycin	
clindamycin hydrochloride	
clindamycin phosphate	
clobetasone butyrate/oxytetracycline calcium/nystatin	
clomethiazole	
clomethiazole edisilate	
clomipramine hydrochloride	
clopidogrel	
clopidogrel hydrogen sulphate	
cloxacillin	
clozapine	
codeine phosphate/aspirin	
cyclophosphamide	
cyclophosphamide monohydrate	
cyproheptadine hydrochloride	
danazol	
desogestrel/ethinylestradiol	
dexibuprofen	
dexketoprofen trometamol	
dextromethorphan hydrobromide	
dextromethorphan hydrobromide/ephedrine hydrochloride	
dextromethorphan hydrobromide/menthol	
dextromethorphan hydrobromide/pseudoephedrine hydrochloride	
dextromethorphan hydrobromide/terpin hydrate/menthol/pumilio pine oil/eucalyptus oil	
dextromethorphan hydrobromide/triprolidine hydrochloride	
dextropropoxyphene hydrochloride	
dextropropoxyphene hydrochloride/paracetamol	
dextropropoxyphene napsylate	
diazepam	
diclofenac diethylammonium	
diclofenac epolamine	
diclofenac potassium	
diclofenac sodium	
diclofenac sodium/misoprostol	
diflunisal	
digoxin	
dimenhydrinate/cinnarizine	

Drug substance	*Frequency category* *(category=less frequent unless marked)*
diphenhydramine hydrochloride/dextromethorphan hydrobromide	
diphenhydramine hydrochloride/menthol/dextromethorphan hydrobromide	
dipyridamole/aspirin	
disulfiram	
dosulepin hydrochloride	
doxazosin mesilate	
doxycycline hyclate	
doxycycline monohydrate	
drospirenone/estradiol hemihydrate	
drospirenone/ethinylestradiol	
duloxetine hydrochloride	
dydrogesterone/estradiol	
enalapril maleate	
enalapril maleate/hydrochlorothiazide	
erythromycin	
erythromycin ethyl succinate	
erythromycin lactobionate	
erythromycin stearate	
erythromycin/isotretinoin	
erythromycin/tretinoin	
erythromycin/zinc acetate	
escitalopram oxalate	
esomeprazole magnesium	
esomeprazole magnesium dihydrate	
esomeprazole magnesium trihydrate	
esomeprazole sodium	
estradiol	
estradiol acetate	
estradiol hemihydrate	
estradiol valerate	
estradiol valerate/norethisterone	
estradiol/levonorgestrel	
estradiol/norethisterone acetate	
estrone/estriol/estradiol	
ethinylestradiol	
ethinylestradiol/cyproterone acetate	
ethinylestradiol/etonogestrel	
etodolac	
etoricoxib	
ezetimibe/simvastatin	
fenofibrate	
fenofibrate micronised	
fenoprofen calcium	
flucloxacillin magnesium	

Drug substance	*Frequency category* *(category=less frequent unless marked)*
flucloxacillin magnesium/ampicillin trihydrate	
flucloxacillin sodium	
flucloxacillin sodium/ampicillin trihydrate	
fluconazole	
fluphenazine decanoate	
fluphenazine enantate	
fluphenazine hydrochloride	
fluphenazine hydrochloride/nortriptyline hydrochloride	
flutamide	
fluvastatin sodium	
fosinopril sodium	
fosphenytoin sodium	
gabapentin	
gemcitabine hydrochloride	
gestodene/ethinylestradiol	
glibenclamide	
glimepiride	
griseofulvin	
haloperidol	
haloperidol decanoate	
halothane	
hydrochlorothiazide	
hydrochlorothiazide/amlodipine besilate/olmesartan medoxomil	
hydrochlorothiazide/amlodipine/olmesartan medoxomil	
hydrochlorothiazide/captopril	
hydrochlorothiazide/irbesartan	
hydrochlorothiazide/losartan potassium	
hydrochlorothiazide/metoprolol tartrate	
hydrochlorothiazide/olmesartan medoxomil	
hydrochlorothiazide/quinapril hydrochloride	
hydrochlorothiazide/telmisartan	
hydrochlorothiazide/valsartan	
hydrocortisone/nystatin/oxytetracycline calcium	
ibuprofen	
ibuprofen lysine	
ibuprofen sodium dihydrate	
ibuprofen/codeine phosphate	
ibuprofen/levomenthol	
ibuprofen/paracetamol	
ibuprofen/phenylephrine hydrochloride	
ibuprofen/pseudoephedrine hydrochloride	
imipramine hydrochloride	
infliximab	
interferon beta-1a	

Drug substance	*Frequency category* *(category=less frequent unless marked)*
iproniazide	
irbesartan	
irbesartan/hydrochlorothiazide	
isoflurane	
isoniazid	More frequent
itraconazole	
ketoprofen	
ketoprofen/omeprazole	
ketorolac trometamol	
lamotrigine	
leflunomide	
levocetirizine dihydrochloride	
levofloxacin	
levofloxacin hemihydrate	
levonorgestrel	
levonorgestrel/ethinylestradiol	
linagliptin/metformin hydrochloride	
lisinopril	
lisinopril/hydrochlorothiazide	
lithium carbonate	
lithium citrate	
losartan potassium/hydrochlorothiazide	
loxapine succinate	
lysine acetylsalicylate/metoclopramide hydrochloride	More frequent
medroxyprogesterone acetate/estradiol valerate	
mefenamic acid	
meloxicam	
mepivacaine hydrochloride/nicotinamide/polyestradiol phosphate	
mercaptopurine	
metformin	
metformin hydrochloride	
metformin hydrochloride/rosiglitazone maleate	
metformin hydrochloride/saxagliptin hydrochloride	
metformin hydrochloride/sitagliptin phosphate	
metformin hydrochloride/vildagliptin	
methyldopa anhydrous	
methyldopate hydrochloride	
methyltestosterone	
methyltestosterone/pemoline/yohimbine hydrochloride	
metoclopramide hydrochloride	More frequent
metoclopramide hydrochloride/paracetamol	More frequent
metoprolol tartrate/hydrochlorothiazide	

Drug substance	*Frequency category* *(category=less frequent unless marked)*
mianserin hydrochloride	
minocycline hydrochloride	
nabumetone	
nandrolone decanoate	
naproxen	
naproxen sodium	
naproxen/esomeprazole	
nefazodone hydrochloride	
nevirapine	
nevirapine anhydrate	
nevirapine hemihydrate	
nitrofurantoin	
nomegestrol/estradiol hemihydrate	
norelgestromin/ethinylestradiol	
norethisterone acetate/estradiol	
norethisterone acetate/ethinylestradiol	
norethisterone/ethinylestradiol	
norfloxacin	
norgestimate/ethinylestradiol	
olanzapine	
olanzapine embonate monohydrate	
olmesartan medoxomil/amlodipine besilate	
olmesartan medoxomil/hydrochlorothiazide	
omeprazole	
omeprazole magnesium	
omeprazole sodium	
orlistat	
oxandrolone	
oxymetholone	
oxytetracycline dihydrate	
oxytetracycline hydrochloride	
oxytetracycline hydrochloride/hydrocortisone	
paracetamol/caffeine/aspirin	
paracetamol/dextropropoxyphene hydrochloride	
paracetamol/ibuprofen	
paracetamol/metoclopramide hydrochloride	More frequent
paracetamol/promethazine hydrochloride/dextromethorphan hydrobromide	
paracetamol/pseudoephedrine hydrochloride/doxylamine succinate/dextromethorphan hydrobromide	
paroxetine hydrochloride	
perphenazine	
phenoxymethylpenicillin potassium	
phenylbutazone	
phenytoin	
phenytoin sodium	

Drug substance	*Frequency category* *(category=less frequent unless marked)*
pimozide	
pioglitazone hydrochloride	
pioglitazone hydrochloride/metformin hydrochloride	
piroxicam	
piroxicam betadex	
pivampicillin	
polymyxin b sulphate/trimethoprim	
prochlorperazine maleate	
prochlorperazine mesilate	
propafenone hydrochloride	
pseudoephedrine hydrochloride/dextromethorphan hydrobromide	
pseudoephedrine hydrochloride/ibuprofen	
pseudoephedrine hydrochloride/levomenthol/diphenhydramine hydrochloride/dextromethorphan hydrobromide	
pseudoephedrine hydrochloride/triprolidine hydrochloride/dextromethorphan hydrobromide	
pyrazinamide/rifampicin/isoniazid	More frequent
quetiapine fumarate	
racemic camphor/aspirin/methyl salicylate/menthol	
ranitidine bismuth citrate	
ranitidine hydrochloride	
repaglinide	
rifampicin	
rifampicin/isoniazid	More frequent
risperidone	
rofecoxib	
rosiglitazone maleate	
rosiglitazone maleate/metformin hydrochloride	
sertraline hydrochloride	
simvastatin	
simvastatin/ezetimibe	
sodium aurothiomalate	
sodium fusidate	
sodium fusidate/hydrocortisone acetate	
sodium valproate	More frequent
spironolactone/chlorothiazide	
stanozolol	
sulfamethoxazole/trimethoprim	
sulindac	
sulpiride	More frequent
talampicillin hydrochloride	
tamoxifen citrate	
telmisartan/hydrochlorothiazide	

Drug substance	*Frequency category* *(category=less frequent unless marked)*
tenoxicam	
terbinafine	
terbinafine hydrochloride	
terfenadine	
testosterone	
testosterone enantate	
testosterone phenylpropionate/testosterone propionate/testosterone decanoate/testosterone isocaproate	
testosterone propionate	
testosterone propionate/testosterone phenylpropionate/testosterone isocaproate	
testosterone undecanoate	
tetracycline hydrochloride	
thioridazine	
thioridazine hydrochloride	
ticlopidine hydrochloride	
timolol maleate/hydrochlorothiazide/amiloride hydrochloride	
tolbutamide	
tolmetin sodium	
triamterene/hydrochlorothiazide	
trifluoperazine hydrochloride	
trimethoprim	
trimethoprim/sulfamethoxazole	
trimipramine maleate	
valproate semisodium	More frequent
valsartan/amlodipine besilate	
valsartan/hydrochlorothiazide	
vildagliptin/metformin hydrochloride	
zinc sulphate/lithium succinate	

b. Handling of missing data

In order to allow multivariable analysis of the association between flucloxacillin and liver injury (compared with oxytetracycline), missing data were accounted for using multiple imputation by chained equations, assuming a missing at random (MAR) model of missingness.[29] All the variables included in Table 2 were included in the imputation model, in addition to outcome status. Five imputed datasets were created and combined for analysis, and the results of complete records analysis and multiple imputed analysis were tabulated as part of the results.

5. Supplementary Data Results Tables

Table S1 - For the 1-90 period from first prescription: (1) the number of cases of liver injury within people prescribed flucloxacillin or oxytetracycline (2) the median time from first recorded flucloxacillin prescription until case assignment and (3) characteristics of symptom-defined and laboratory-confirmed liver injury cases in the exposed to flucloxacillin group

	Flucloxacillin or oxytetracycline	Flucloxacillin-only		
Case definition[1]	**Number of (potential) liver injury cases: number subsequently identified as flucl- or oxyt-induced (%)[2]**	**Time from first prescription until case assignment** Median in days (25 - 75%)	**Characteristics of cases**	
Symptom-defined	266:183 (68%)	38 (27 – 47)	Liver-related diagnosis	N=169
			jaundice – symptom	66 (39%)
			obstructive jaundice nos	36 (21%)
			[d]jaundice	27 (16%)
			o/e – jaundiced	20 (12%)
			[d]jaundice (not of newborn)	14 (8%)
			yellow/jaundice colour	3 (2%)
			[d]icterus	2 (1%)
			o/e – jaundiced colour	1 (1%)
			Rash or pruritus	11 (7%)
			Eosinophilia (n=55)[3]	11 (20%)
Laboratory -confirmed	149: 108 (72%)	40 (32 – 48)	Liver-related diagnosis	N=102
			jaundice – symptom	36 (35%)
			obstructive jaundice nos	18 (18%)
			o/e – jaundiced	14 (14%)
			[d]jaundice	13 (13%)
			[d]jaundice (not of newborn)	7 (7%)
			hepatitis unspecified nos	4 (4%)
			yellow/jaundice colour	3 (3%)
			toxic liv disease with cholestasis	2 (2%)
			o/e – jaundiced colour	1 (1%)
			hepatitis unspecified	1 (1%)
			hepatitis non a non b	1 (1%)
			acute hepatitis – noninfective	1 (1%)
			acute hepatic failure	1 (1%)
			Type of liver injury	
			hepatocellular	33 (31%)
			cholestatic[4]	75 (69%)
			Rash or pruritus	7 (7%)
			Eosinophilia (n=48)	9 (19%)

Note 1: Symptom based only: electronic record contains a diagnostic code for any jaundice-related symptom within 90 days of index prescription. Laboratory-confirmed: any of the diagnostic codes listed in supplementary data section 3 present within 90 days of the liver-related diagnosis, and liver test results indicating drug-induced liver injury (according to Aithal ref) present within 90 days either side of this diagnosis (but not before the index prescription). Both definitions: all other more likely causes of the liver symptoms ruled out by clinician review of full electronic health record in the 6-month period before the index prescription. **Note 2:** All within the 90-day period after the index prescription. Potential: people identified as symptom-based or laboratory-confirmed cases of liver injury prior to review of electronic record for other more likely causes. **Note 3:** Eosinophilia classified by an eosinophil count of >0.5 10^9/l, based upon.[30] Only a proportion of all cases had blood eosinophil count measured, indicated by (n=number who were tested). **Note 5:** Of the cholestatic cases, 41 (55%) were pure cholestatic, with the remaining 34 (45%) mixed hepatocellular-cholestatic.

Table S2: Comparison of multiple imputation analysis with a complete records analysis for variables with missing data in the flucloxacillin (compared with oxytetracycline) and liver injury cohort: crude risk ratios for laboratory-confirmed liver injury

				Multiple imputation[1] used to account for missing data		Complete records analysis	
		# with outcome n=76	People[2] N=1046699	Crude Risk Ratio (CI[3])	p-value[4]	Crude Risk Ratio (CI)	p-value
Smoking status	Non-smoker	30	467185	1	0.006	1	0.006
(missing n=21755)	Current smoker	11	260101	0.64 (0.32 – 1.27)		0.66 (0.33 – 1.31)	
	Ex-smoker	34	297658	1.74 (1.08 – 2.85)		1.78 (1.09 – 2.91)	
BMI	<20	2	59374	1	0.399	1	0.193
(missing n=141633)	20 – 25	29	303273	2.33 (0.46 – 11.79)		2.84 (0.68 – 11.90)	
	25+	39	542419	1.78 (0.34 – 9.18)		2.13 (0.52 – 8.84)	
Alcohol intake	Non-drinker	4	117896	1		1	0.052
(missing n=146511)	Ex-drinker	1	33858	0.78 (0.09 – 7.06)	0.089	0.87 (0.10 – 7.70)	
	Current NOS	4	33304	3.51 (0.78 – 15.86)		3.54 (0.89 – 14.16)	
	2 or less u/d	22	169725	3.59 (1.16 – 11.16)		3.82 (1.32 – 11.09)	
	3/6 u/d	34	465597	2.02 (0.70 – 5.80)		2.15 (0.76 – 6.07)	
	>6 u/d	5	79808	1.84 (0.51 – 6.68)		1.85 (0.50 – 6.88)	
Socioeconomic status	1 (Highest SES)	17	186791	1	0.905	1	0.881
(missing n=235614)	2	14	175506	0.90 (0.46 – 1.76)		0.88 (0.43 – 1.78)	
	3	14	167976	0.95 (0.49 – 1.83)		0.92 (0.45 – 1.86)	
	4	12	158966	0.79 (0.38 – 1.61)		0.83 (0.40 – 1.74)	
	5 (Lowest SES)	7	121846	0.68 (0.24 – 1.90)		0.63 (0.26 – 1.52)	
Ethnicity[5]	White	46	534142	1	0.402	1	0.998
(missing n=389411)	Other than white	1	17497	0.29 (0.03 – 2.57)		0.31 (0.04 – 2.23)	
	Not Stated	9	85336	1.27 (0.62 – 2.56)		1.22 (0.60 – 2.50)	

Note 1: Multiple imputation with chained equations. Imputation model included all variables presented in this table plus age, gender, date of index prescription, outcome status, exposure status and concomitant prescriptions for other causes of liver injury. **Note 2:** Number of people prescribed either flucloxacillin or oxytetracycline. **Note 3:** 95% confidence interval. **Note 4:** p-value results for LRT of an association over all categories of the variable. **Note 5:** Categories combined due to insufficient numbers of events in original ethnicity categories (shown in Table 2) to allow multiple imputation.

Table S3: Comparison of multiple imputation with using a complete records approach for variables with missing data in the flucloxacillin (compared with oxytetracycline) and liver injury cohort: crude risk ratios for symptom-defined liver injury

				Multiple imputation[1] used to account for missing data		Complete records analysis	
		# with outcome	People[2]	Crude Risk Ratio (CI[3])	p-value[4]	Crude Risk Ratio (CI)	p-value
		n=129	N=1046699				
Smoking status	Non-smoker	48	467137	1	<0.001	1	0.001
(missing n=21755)	Current smoker	23	260078	0.85 (0.52 – 1.39)		0.86 (0.52 - 1.41)	
	Ex-smoker	56	297602	1.83 (1.25 – 2.69)		1.83 (1.25 - 2.69)	
BMI	<20	8	59366	1	0.078	1	0.028
(missing n=141633)	20 – 25	54	303219	1.26 (0.55 – 2.82)		1.32 (0.63 - 2.78)	
	25+	58	542361	0.76 (0.36 – 1.62)		0.79 (0.38 - 1.66)	
Alcohol intake	Non-drinker	11	117885	1	0.054	1	0.069
(missing n=146511)	Ex-drinker	3	33855	0.92 (0.27 – 3.14)		0.95 (0.26 - 3.40)	
	Current NOS	7	33297	2.11 (0.78 – 5.66)		2.25 (0.87 - 5.81)	
	2 or less u/d	34	169691	2.03 (1.04 – 3.98)		2.15 (1.09 - 4.24)	
	3/6 u/d	52	465545	1.10 (0.56 – 2.14)		1.20 (0.62 - 2.29)	
	>6 u/d	9	79799	1.13 (0.48 – 2.66)		1.21 (0.50 - 2.92)	
Socioeconomic status	1 (Highest SES)	23	186768	1	0.846	1	0.956
(missing n=235614)	2	22	175484	1.05 (0.61 – 1.80)		1.02 (0.57 - 1.83)	
	3	23	167953	1.21 (0.71 – 2.06)		1.11 (0.62 - 1.98)	
	4	17	158949	0.87 (0.43 – 1.74)		0.87 (0.46 - 1.63)	
	5 (Lowest SES)	16	121830	1.20 (0.66 – 2.19)		1.07 (0.56 - 2.02)	
Ethnicity[5]	White	78	534064	1	0.282	1	0.065
(missing n=389411)	Other than white	1	17497	0.18 (0.02 – 1.55)		0.18 (0.03 – 1.30)	
	Not Stated	13	85232	0.97 (0.52 – 1.79)		1.04 (0.58 - 1.88)	

Note 1: Multiple imputation with chained equations. Imputation model included all variables presented in this table plus age, gender, date of index prescription, outcome status, exposure status and concomitant prescriptions for other causes of liver injury. **Note 2:** Number of people prescribed either flucloxacillin or oxytetracycline. **Note 3:** 95% confidence interval. **Note 4:** p-value results for LRT of an association over all categories of the variable. **Note 5:** Categories combined due to insufficient numbers of events in original ethnicity categories (shown in Table 2) to allow multiple imputation.

6. Example of calculation of revised numbers needed to treat for an *HLA-B*5701* predictive genetic test (see [31] for original calculations)

<u>For the over 70 year olds (incidence of 45/100000)</u>:

- Pre-test probability=45/100 000*100=0.045
- Post test probability for a positive test is 0.045*14.5=0.6525% (14.5 is the Likelihood ratio for a positive test)[31]
- Post test probability for a negative test is 0.04*0.14=0.0056% (0.14 is the Likelihood ratio for a negative test)[31]
- Assuming 7% carrier frequency and a population of 100 000[31]
    - 7000 * 0.006525=45.675
    - 93000*0.000063=5.859
- Absolute risk reduction= 45.675-5.859=39.816
- Number of 70 year olds needed to screen to prevent 1 case=100 000/39.816=**2512**

7. The ten most common diagnostic terms entered on the first day of prescription for either flucloxacillin or oxytetracycline

Oxytetracycline		**Flucloxacillin**	
Diagnostic term	**%[1]**	**Diagnostic term**	**%[1]**
Acne vulgaris	8	Cellulitis NOS	5
C/O: a rash	6	Skin and subcutaneous tissue infections	5
Rosacea	3	Infected insect bite	3
C/O - cough	3	Impetigo	3
Acne rosacea	3	Infected sebaceous cyst	3
Cough	2	Dressing of wound	2
Intertrigo	2	C/O: a rash	2
Chest infection NOS	2	Folliculitis	2
Acute sinusitis	2	Boil NOS	2
Chest infection	2	Furuncle - boil	2

Note 1: % of people who had this diagnostic code on the date of their first prescription

8. Supplementary Data - References

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