The risk of acute liver injury associated with the use of antibiotics. A methodological comparison across epidemiological data sources

First published: 04/09/2012

Last updated: 02/07/2024

Study Finalised

Administrative details

EU PAS number

EUPAS2353

Study ID

28775

DARWIN EU® study

No

Study countries

- ☐ Denmark
- ☐ Germany
- ☐ Netherlands

- [ ] Spain
- [ ] United Kingdom

Study description

The studies described in this protocol are all performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Work Package 2 and Working Group 1. The primary aim of these studies is to develop, test and disseminate methodological standards for the design, conduct and analysis of Pharmacoepidemiological (PE) studies applicable to different safety issues and using different data sources. To achieve this, results from PE studies on 5 key Drug / adverse events (D-AEs) pairs performed in different databases will be evaluated. The Use of antibiotics associated with the risk of acute liver injury is one of the key D-Ae pair of interest. Therefore, emphasis will be on the methodological aspects of the studies in this protocol and not on the clinical consequences of studying the association under investigation.

Study status

Finalised

Research institutions and networks

Institutions

Fundación Centro Español de Investigación Farmacoepidemiológica (CEIFE)

- [ ] Spain

First published: 15/03/2010

Last updated: 15/02/2024

Institution | Not-for-profit | ENCePP partner

Electronic Health Records (EHR) Research Group, London School of Hygiene & Tropical Medicine (LSHTM)

United Kingdom

First published: 19/04/2010

Last updated: 30/10/2024

Institution | Educational Institution | ENCePP partner

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 23/05/2024

Institution | Educational Institution | ENCePP partner

Fundación Centro Español de Investigación Farmacoepidemiológica (CEIFE)

Spain

First published: 15/03/2010

Last updated: 15/02/2024

Institution | Not-for-profit | ENCePP partner

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | EU Institution/Body/Agency | Not-for-profit | Regulatory Authority | ENCePP partner

Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS) Spain, Lægemiddelstyrelsen (DKMA) Denmark, Ludwig-Maximilians-Universität-München (LMU Muenchen) Germany, European

Medicines Agency (EMA) United Kingdom, Amgen United Kingdom, LSHTM United Kingdom

Networks

PROTECT

- [ ] Belgium
- [ ] Denmark
- [ ] France
- [ ] Germany
- [ ] Italy
- [ ] Netherlands
- [ ] Poland
- [ ] Spain
- [ ] Sweden
- [ ] Switzerland
- [ ] United Kingdom

First published: 26/06/2013

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Network

Contact details

Study institution contact

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Primary lead investigator

Ana Ruigomez

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 19/08/2009

Actual: 19/08/2009

Study start date

Planned: 03/10/2011

Actual: 03/10/2011

Date of final study report

Planned: 01/02/2013

Actual: 01/07/2013

Sources of funding

- EU institutional research programme
- Pharmaceutical company and other private sector

More details on funding

Amgen, AstraZeneca, Genzyme, GSK, MerckSerono, Novartis, Roche, Pfizer, Innovative Medicines Initiative (IMI)

Study protocol

PROTECT_WP2Final Protocol_AntibLiver_Amend2_July2012.pdf (483.48 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Disease epidemiology

Other

If ‘other’, further details on the scope of the study

Analysis of discrepancies in results between different databases

Data collection methods:

Secondary use of data

Main study objective:

To assess the association between the use antibiotics and the risk of acute liver injury with different study designs across different primary care databases and to compare the results between databases, across designs to evaluate the impact of design/database/population differences on the outcome of the studied association.

Study Design

Non-interventional study design

Case-control

Cohort

Other

Non-interventional study design, other

Case-crossover, Self-controlled case series, Descriptive study = description of exposure and/or outcome in the whole database during a defined period of time

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(J01) ANTIBACTERIALS FOR SYSTEMIC USE

ANTIBACTERIALS FOR SYSTEMIC USE

Medical condition to be studied

Liver injury

Population studied

Short description of the study population

Patients of all ages with an active or died registration status during the study period of January 1st 2004 to December 31st 2009. Patients must have attained one year of enrolment with the GP and one year of computerized prescription history.

Age groups

- Infants and toddlers (28 days – 23 months)
- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

55700000

Study design details

Data analysis plan

Descriptive study of the primary study population including all ages, from 1 Jan 2004 to 31 Dec 2009). Prevalence of antibiotic (AB) use stratified by age, by sex, by indication, by number of prescriptions and by AB class. Incidence of first-time liver failure by age, by sex per calendar year. Retrospective Cohort study: estimates of incidence rate ratios and 95% confidence intervals of acute liver injury associated with current AB as compared to non-use with Poisson regression adjusted by age/sex/ and calendar year categories. Case Control Study: estimates of relative risk and 95% confidence intervals using unconditional logistic regression. Age, sex, calendar year, and other variables will be introduced in the model to control for potential confounding. Case-crossover analysis estimates of the odds of having an event (liver injury while exposed to antibiotic drugs will be compared with the odds of having liver injury while unexposed.

Documents

Study publications

Udo R, Tcherny-Lessenot S, Brauer R, Dolin P, Irvine D, Wang Y, Auclert L, Juha…

Brauer R, Ruigómez A, Klungel O, Reynolds R, Feudjo Tepie M, Smeeth L, Douglas …

Brauer R, Douglas I, Garcia Rodriguez LA, Downey G, Huerta C, de Abajo F, Bate …

Ruigomez A, Brauer R, Rodríguez LG, Huerta C, Requena G, Gil M, de Abajo F, Dow…

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

THIN® (The Health Improvement Network®)

Clinical Practice Research Datalink

Danish registries (access/analysis)

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

Data sources (types)

Administrative healthcare records (e.g., claims)

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown