EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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# Prescribing of codeine for the treatment of pain in children

Drug utilisation study using IMS electronic health records in Germany and France.

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# 1. PASS information

| | |
|---|---|
| **Title** | Prescribing of codeine for the treatment of pain in children. |
| **Protocol version identifier** | 2.3 |
| **Date of last version of the protocol** | 10 November 2015 |
| **EU PAS Register No:** | Study not registered |
| **Active substance** | Codeine (ATC codes: R05DA04, N02AA59, N02AA79, N02AG, N02B, N02C and M01) |
| **Medicinal product(s):** | Multiple |
| **Study initiator** | EMA/ES/UK |
| **Research question and objectives** | On 28 June 2013 the European Medicines Agency agreed changes to the product information on the use of codeine for pain relief in children.<br><br>The aim of this study is to assess the subsequent impact of the introduced changes to the product information on prescribing patterns for codeine for the treatment of pain in children in Germany and France. This study will inform the PRAC on drug utilisation in the context of the effectiveness of the introduced risk minimisation measures for codeine for the treatment of pain in children.<br><br>This study will be carried out as part of a pilot within the framework of the EU Regulatory Network Strategy for Best Evidence (EMA/508487/2014) that will make use of electronic patient healthcare databases (BIFAP in Spain, CPRD in the UK and IMS in France and Germany). It will therefore also inform on the feasibility of the EU Regulatory Network undertaking studies using a common protocol approach to support the PRAC in its decision making. |
| **Authors** | Karin Hedenmalm for EMA (and colleagues from ES and UK). |

# Marketing authorisation holder

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|---|---|
| Marketing authorisation holder(s) | Multiple |

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## List of Abbreviations

A: Adenoidectomy

ATC: Anatomical Therapeutic Chemical, World Health Organisation classification system for drugs

BNF: British National Formulary

EMA: European Medicines Agency

EHR: Electronic Health Records

EPITT: European Pharmacovigilance Issues Tracking Tool

EU: European Union

GP: General Practitioner, Family Doctor

ICD: International Classification of Diagnosis

MAH: Marketing Authorisation Holder

PRAC: Pharmacovigilance Risk Assessment Committee

T: Tonsillectomy

TA: Tonsillectomy and adenoidectomy

# 2. Responsible parties (EMA)

Project lead: Karin Hedenmalm

Clinical lead: Kevin Blake

Statistical lead: Jim Slattery and Gianmario Candore

Project sign off: Peter Arlett

# 3. Rationale and background

## *3.1. Background*

Codeine is an opium alkaloid, which has been approved via national procedures in the EU Member States. It is marketed both as a single ingredient (plain codeine) and in combination with other substances. It is available in different Member States either as a prescription-only or as an over-the-counter medicine.

Codeine is converted in the body into morphine, which is responsible for the analgesic effect of codeine. The main risk associated with morphine toxicity is respiratory depression, which may be fatal.

In 2012 to 2013 the PRAC undertook an Article 31 review of the risk of life-threatening or fatal respiratory depression in children after ingestion of codeine for the treatment of pain.

Following a review of the evidence, the EMA agreed the following updates to the SmPCs, for codeine-containing products indicated for the treatment of pain:

- Codeine is now only indicated in patients older than 12 years of age for the treatment of acute moderate pain that cannot be relieved by other analgesics such as paracetamol or ibuprofen (alone).
- Codeine should be used at the lowest effective dose for the shortest period of time.
- Codeine is now contraindicated in all paediatric patients (0 - 18 years of age) who undergo tonsillectomy or adenoidectomy for obstructive-sleep-apnoea syndrome and in patients of any age who are known to be CYP2D6 ultra-rapid metabolisers (up to approximately 10% of Caucasians are CYP2D6 ultra-rapid metabolisers, but prevalence differs according to racial and ethnic group), due to an increased risk of developing serious and life-threatening adverse reactions, and in women who are breastfeeding.

Codeine is not recommended for use in children in whom respiratory function might be compromised as this may worsen the symptoms of morphine toxicity.

The aim of this study is to assess the subsequent impact of the updates to the SmPC on prescribing patterns for codeine for the treatment of pain in Germany and France. This study will inform the PRAC on drug utilisation in the context of the effectiveness of the introduced risk minimisation measures for codeine for the treatment of pain in children.

This study will also inform on the feasibility of the EU Regulatory Network undertaking studies using a common protocol approach to support the PRAC in its decision making. Criteria for assessing the results of this pilot study for that purpose will be presented in a separate document.

## *3.2. Targeted risk groups in a drug utilisation study in children*

1. Three groups of children for which codeine is now considered contraindicated for the treatment of pain will be studied in a drug utilisation study:

    - children below the age of 12 years
    - children between 12-18 years of age with non-acute pain or pain that is less than moderate in severity that can be relieved by other analgesics such as paracetamol or ibuprofen alone
    - children undergoing tonsillectomy (T), adenoidectomy (A) or combined tonsillectomy/adenoidectomy (TA) for obstructive sleep apnoea syndrome

2. In terms of studying compliance with the contraindication for children undergoing T, A or TA for obstructive sleep apnoea syndrome, it may not be clear in which cases the procedure was undertaken for obstructive sleep apnoea syndrome as the occurrence of obstructive sleep apnoea may not be well recorded. Therefore, it is considered relevant to study use of codeine in all children with T, A or TA, and to look for the presence of any diagnosis that may indicate obstructive sleep apnoea. Obstructive sleep apnoea may be indicated by a diagnosis of sleep apnoea, snoring or other breathing abnormalities, or hypertrophy of the tonsils or adenoids. It is recognized that obstructive sleep apnoea, which is a risk factor for respiratory depression with codeine, is present before the surgical procedure has been undertaken. For this reason the use of codeine will be studied within a limited period of time both before and after the T, A or TA. Before surgery, codeine may have been prescribed for pain associated with recurrent tonsillitis.

3. In terms of studying compliance with "treatment of acute moderate pain that cannot be relieved by other analgesics such as paracetamol or ibuprofen (alone)", trends in the duration of use and in the proportions of children that have received a prescription for another analgesic during different time periods up to 3 months prior to the prescription of codeine may be considered.

The risk minimisation measures also state that within the approved use of codeine for the treatment of pain in children, the lowest effective dose should be used for the shortest possible time. This may be considered in terms of the overall distribution patterns for prescribed treatment duration and prescribed dose without the need to define thresholds for what constitutes 'lowest effective' and 'shortest possible'.

In addition, the risk minimisation measures state that codeine is not recommended for use in children in whom respiratory function might be compromised. The SmPC text associated with this risk minimisation measure states the following conditions:

- Neuromuscular disorders
- Severe cardiac or respiratory conditions
- Upper respiratory or lung infections
- Multiple trauma or extensive surgical procedures

In case of respiratory infections, it may be difficult to distinguish between the use of codeine for pain or for cough. In the other conditions, it may be difficult to identify when there is a relevant risk of compromised respiratory function. Hence, compliance with these recommendations against use will not be explicitly studied in the present study.

# 4. Research question and objectives

A new drug utilisation study, to measure the impact of the introduced risk minimisation measures for codeine associated with the treatment of pain in children, is proposed as a pilot for the coordination of electronic healthcare records-based studies by multiple Competent Authorities within the framework of the Strategy for Best Evidence (EMA/508487/2014). The study period will start at the beginning of Q1 2010, and end at Q4 2014 or Q2 2015, where available. Trends in prescribing over this time period will be determined to identify any temporal associations with the 2013 referral and its outcomes. A further goal is to assess to what extent the data collected can be used for comparisons between countries.

## *4.1. Table of risk groups to be studied*

**Table 1.** Grouping of children to be included in the drug utilisation study of the effectiveness of introduced risk minimisation measures for codeine for the treatment of pain

| | **All** | **T [1]** | **A [1]** | **TA [1]** | **Not T, A or TA** |
|---|---|---|---|---|---|
| **Total no. of children ≤ 11 years [2]** | | | | | |
| Total no. of children with codeine prescription [3,4] | | | | | |
| Within 3 days before | | | | | NA |
| Within 3 days after | | | | | NA |
| 4-7 days before | | | | | NA |
| 4-7 days after | | | | | NA |
| 8-30 days before | | | | | NA |

| | | | | | |
|---|---|---|---|---|---|
| 8-30 days after | | | | | NA |
| > 30 days before | | | | | NA |
| > 30 days after | | | | | NA |
| **Total no. of children 12-18 years** [2] | | | | | |
| Total no. of children with codeine prescription [3] | | | | | |
| Within 3 days before | | | | | NA |
| Within 3 days after | | | | | NA |
| 4-7 days before | | | | | NA |
| 4-7 days after | | | | | NA |
| 8-30 days before | | | | | NA |
| 8-30 days after | | | | | NA |
| > 30 days before | | | | | NA |
| > 30 days after | | | | | NA |

T= tonsillectomy, A = adenoidectomy, TA = tonsillectomy and adenoidectomy, NA = not applicable

For events or prescriptions that run across time periods, the start date determines in which time period the event/prescription is counted.

[1] The proportion of children with a concomitant (two time windows will be investigated: within 12 months prior to surgery and any time prior to surgery) diagnosis of sleep apnoea (ICD code G47.3), snoring (ICD code R06.5) or other breathing abnormalities (ICD codes R06.0, R06.1, R06.2, R06.3), or hypertrophy of the tonsils or adenoids (ICD codes J35.1, J35.2, J35.3) will be identified and presented by age group and use of codeine.

[2] All patients that were active (i.e. had at least one consultation) or all patients that were registered with a general practitioner (GP) that is considered to be up to standard in terms of data collection. Patients ≥ 12 months of age must have at least one year of previous follow up in the database to be included.

[3] Prescriptions of other analgesics during 90 days before the codeine prescription will be recorded.

## *4.2. Use of codeine*

Codeine is available as plain codeine, and as combinations with other substances, e.g. analgesics, expectorants, and muscle relaxants. Codeine is broadly used in three different therapeutic areas:

- Treatment of pain
- Treatment of cough
- Treatment of diarrhoea

This study is intended to capture the use of codeine for pain, and not for cough or diarrhoea. In order to capture the use of codeine for pain, the following sets of combinations of codeine with other active substances will be considered to concern the use of codeine for pain:

- Codeine in combination with other analgesics or non-steroidal anti-inflammatory agents, e.g. ibuprofen, acetylsalicylic acid or paracetamol (with or without caffeine) (ATC codes N02AA59, N02B, M01)
- Other codeine combinations not considered above (e.g. ATC code N02C for codeine in combination with an antihistamine and an analgesic)

The following sets of combinations of codeine with other active substances will not be considered to concern the use of codeine for pain:

- Codeine in combination with menthol, sympathomimetics, antitussives, expectorants, antihistamines (without analgesic or non-steroidal anti-inflammatory agent), or herbal cough ingredients (ATC codes R05C, R05D and R05F)
- Codeine in combination with antispasmodic agents or antidiarrhoeals (ATC codes N02AG, A03)

Plain codeine (ATC code R05DA04) will be considered to concern the use of codeine for both pain and cough. See section 5.3 for more details about the analysis.

# 5. Research methods

## *5.1. Study design*

Descriptive study based on electronic health record (EHR) databases.

## *5.2. Setting and data sources*

See Appendix 1.

## *5.3. Variables*

The use of codeine will be analysed in accordance with table 1 in section 4.1. It is proposed to present results for codeine for the treatment of pain in the following groups, see section 5.6:

- Total codeine for the treatment of pain
- Oral solutions with plain codeine
- Other oral dosage forms for plain codeine (tablets, capsules)
- Each of the codeine combination products in section 4.2

If feasible, patient records for all patients 0-18 years with a prescription of plain codeine will be reviewed to determine to what degree oral solutions and other oral dosage forms of plain codeine are used in the pain indication. Otherwise, the analysis will be based on a review of random samples.

## *5.4. Study size*

This study is a descriptive analysis of EHR data. No sample size or statistical precision calculation is performed.

## *5.5. Data management*

Data extraction will be performed in IMS Disease Analyser and SAS Enterprise Guide 6.1. Data analysis will be performed in SAS Enterprise Guide 6.1.

## *5.6. Data analysis*

This analysis is descriptive in nature. In each country the following will be investigated:

- The total prevalence over time (6-monthly and quarterly),) of use of codeine for pain in children by age group (≤11 years and 12-18 years) and gender, as measured by the unique number of children with a prescription of codeine for the treatment of pain and, presented as all codeine products for the treatment of pain, followed by oral solution plain codeine products, other oral plain codeine products, and the different types of combination products containing codeine (see section 4.2), and the denominator being based on children registered or active children (see Appendix 2 for examples of figures).
    - Separate prevalence estimations for total use of codeine for pain will be calculated for children that have undergone tonsillectomy (T), adenoidectomy (A) or combined tonsillectomy/adenoidectomy (TA), and for children that have not undergone these procedures. The prevalence estimations will use as denominator 1) all children in the respective age group and 2) only those children in the respective age group that up to the time point of the data included in the analysis have undergone/not undergone the respective procedures.
    - Prevalence estimations for total use of codeine for pain will also be calculated for children that have undergone T, A or TA for obstructive sleep apnoea syndrome, see section 4.1.
- For children that have undergone tonsillectomy (T), adenoidectomy (A) or combined tonsillectomy/adenoidectomy (TA), different time windows for use of codeine in relation to the procedure will also be investigated, see section 4.1.
- The duration of use will be analysed descriptively by treatment episode and by total treatment duration; mean (standard deviation), median ($25^{th}$ to $75^{th}$ percentiles) and range, including an analysis of whether the duration of use varies by
    - Age group (≤11 years and 12-18 years)
    - Gender
    - T, A, TA and no T, A or TA
    - Type of codeine product (see section 5.3)
    - Time (trends before and after the introduced risk minimisation measures will be explored)
- The dose or total amount prescribed will be analysed descriptively by age group (≤11 years and 12-18 years) and expressed as mg; mean (standard deviation), median ($25^{th}$ to $75^{th}$ percentiles) and range, including an analysis of whether the dose varies by
    - Gender
    - T, A, TA and no T, A or TA
    - Type of codeine product (see section 5.3)
    - Time (trends before and after the introduced risk minimisation measures will be explored)
- The proportion of all children with a codeine prescription that had another analgesic prescribed within 3 days, 4-7 days, 8-14 days, 15-30 days and 31-90 days before the codeine prescription, in view of the contraindication "treatment of acute moderate pain that cannot be relieved by other analgesics such as paracetamol or ibuprofen (alone)", will be analysed descriptively, including an analysis of whether this proportion varies by

- Age group (≤11 years and 12-18 years)
- Gender
- T, A, TA and no T, A or TA
- Type of codeine product (see section 5.3)
- Time (trends before and after the introduced risk minimisation measures will be explored)

### *5.7. Limitations of the research methods*

The primary data sources are electronic health records entered by physicians and collected by computer software. The data recorded are governed by healthcare systems and policies.

A patient is only uniquely identified within a practice. A patient is recorded multiple times and is not recognised as the same patient if he/she visits several practices. There is no requirement to register with a primary care physician in Germany or France, but in France, patients must choose and visit a GP before going to a specialist to get reimbursement (except for paediatricians, gynaecologists, ophthalmologists). In Germany, patients may visit a specialist physician practice without a referral from a GP. However, if the GP has referred a patient to a specialist, information about the referral is available in the electronic health records.

In Germany, recording of a diagnosis is mandatory for statutory billing purposes. It is not mandatory to record a diagnosis in France.

The dates recorded in the databases are typically those on which an action took place, and not necessarily the dates of a specific event. For example, a GP may record on a date of visit that a patient has undergone TA, but the date of the TA may not be provided. Prescribing information can only be obtained from the physicians included in the database. Furthermore, it is not possible to follow all prescriptions in the same patient if he/she also receives prescriptions from other practices or a hospital physician. Data is recorded at the prescription level; hence it is unknown whether the patients have visited the pharmacy to dispense the treatment.

Limitations of the study concern, in particular

- Incomplete recording of or uncertain dates for T, A or TA or other concomitant diagnoses
- Incomplete recording of prescriptions of analgesics due to prescribing by physicians not included in the databases. This is likely to be the case during the perioperative phase of T, A or TA
- Insufficient data to be able to assess the level of pain or the acuteness of pain
- Missing data especially on duration

## 6. Plans for communicating study results

The study including the final protocol and results will be registered in the ENCePP E-Register of Studies http://www.encepp.eu/encepp/studiesDatabase.jsp which currently serves as the EU PAS register referred in the Module VIII of the good pharmacovigilance practices (GVP) on post-authorisation studies. PRAC will be kept informed of the progress of the pilot and the results.

## Appendix 1 -

## IMS databases

In the IMS databases, the therapeutic use of codeine products is indicated through ATC codes. ATC codes that start with N02 or M01 are used for products that are indicated for the treatment of pain. However, plain codeine has an ATC code for cough, R05DA04, which is used for both the cough indication and the pain indication[1]. Codeine products for the treatment of pain will be identified by searching for substance name and by selecting products with an ATC code that begins with N02B, N02C or M01, and the ATC code R05DA04.

In the IMS databases, a patient is only recognized as the same patient in the same practice. This needs to be taken into account when analysing data, correcting as needed for the proportion of patients that change physician.

### *Strengths and limitations of IMS Disease Analyser[2]*

- The IMS Disease Analyser maintains data collected through a representative panel of general practitioners (GPs) in each of the study countries. In Germany, data is also collected by representative panels of specialist physicians.
- Prescription records are the most complete set of data in IMS Disease Analyser. However, prescriptions in hospital and in settings other than those included in IMS Disease Analyser will be missing. The information in IMS is captured at prescription level, i.e. it is not known to what extent the patients have visited the pharmacy to have the prescription dispensed.
- Variations in healthcare systems among individual countries
  - Registration of patients with a GP is not a requirement of the national healthcare system in France. However, patients must choose and visit a GP before going to a specialist to get reimbursement (except for paediatricians, gynaecologists, ophthalmologists).
  - In Germany the national healthcare insurance system allows patients to visit a physician of choice whenever a medical need emerges, which results in possible information gaps in the patient's medical records maintained by any given physician, including those contributing data to the German database of IMS Disease Analyser.

### *IMS Germany*

Anonymised patient medical records are collected since 1992 through a representative panel of internists (GPs and specialists in internal medicine) and other specialist physicians in computerized practices throughout Germany[3]. The sampling of participating physicians is stratified for specialist group, region, and age of physician. The database contains information related to the participating physicians and their practices, and patient data. The patient data is structured into three parts:

[1] For the classification of codeine please see http://www.whocc.no/atc_ddd_index/?code=R05DA04&showdescription=yes

[2] A comprehensive bibliography of the studies conducted with IMS Disease Analyser databases, including validation studies in selected therapeutic areas is available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Researchers/IMS_bibliography.pdf

[3] Becher H, Kostev K, Shröder-Bernhardi D. Validity and representativeness of the "Disease Analyzer" patient database for use in pharmacoepidemiological and pharmacoeconomic studies. Int J Clin Pharmacol Ther 2009; 47 (10): 617-26.

- General data such as ID, age, gender, insurance, laboratory test results and risk factors. Only risk factors that are considered relevant for the diagnosis are collected.
- Diagnoses in original text, dates, ICD 10 and read codes including co-morbidities, referrals and hospitalizations
- Drug therapy including dates, product and quantity prescribed, ATC code and active substance, dosage (and pack size and number of packs), co-prescriptions, treatment costs and therapy switches. At least 70 % of drug therapies have a recorded diagnosis (indication for treatment).

The sampling of physicians ensures that patients may be considered as representative for the speciality of the physician over the different regions in Germany. In Germany, 83 % of practices are single physician practices. The rest of the practices have multiple physicians.

In Germany the national healthcare insurance system allows patients to visit a physician of choice whenever a medical need emerges, which results in possible information gaps in the patient's medical records maintained by any given physician, including those contributing data to the German database of IMS Disease Analyser. For the health care of their child parents often choose to consult a paediatrician directly. Recording of a diagnosis is mandatory in Germany for statutory billing purposes. Patients in Germany can be enrolled in certain disease management programs, like diabetes. Medicinal products can only be prescribed by active substance name if there are generics. Codeine is listed underneath the Betäubungsmittelgesetz in Germany. Dispensing of codeine generally require a prescription order from a physician or the discretion of the pharmacist.

It is of importance to select the categories of physicians who are responsible for most of the prescriptions in IMS Disease Analyser as all patients with a certain treatment in IMS may not necessarily be representative for all patients with that treatment in Germany due to a variation in the percentage of physicians included in IMS Disease Analyser between specialties. The patient population of GPs in Disease Analyser has been found to be broadly representative of the German population in terms of gender and age distribution, except for children. A total of ca. 13.7 million patients are recorded in IMS Germany in the last 3 years.

For this analysis, GPs and other specialist physicians that prescribe codeine in children, e.g. paediatricians will be included.

***IMS France***

Anonymised patient medical records are collected since 1997 through a representative panel of GPs. The physician sample represents ca 2 % of physicians, and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). In France, all practices are single physician practices.

Registration with a GP is not a requirement of the national healthcare system in France, but patients must choose and visit a GP before going to a specialist to get reimbursement (except for paediatricians, gynaecologists, ophthalmologists). Recording of a diagnosis by GPs is not mandatory in France. Medicinal products can be prescribed by active substance name even if there are no generics. Most preparations containing codeine in France do not require a prescription by a physician.

IMS France contains less information about the physicians practices compared with IMS Germany. IMS France does not contain information about risk factors such as BMI or smoking or laboratory values of the patients. Furthermore, IMS France does not contain information about the certainty of a diagnosis, referral to a specialist, hospitalisations or sick notes.

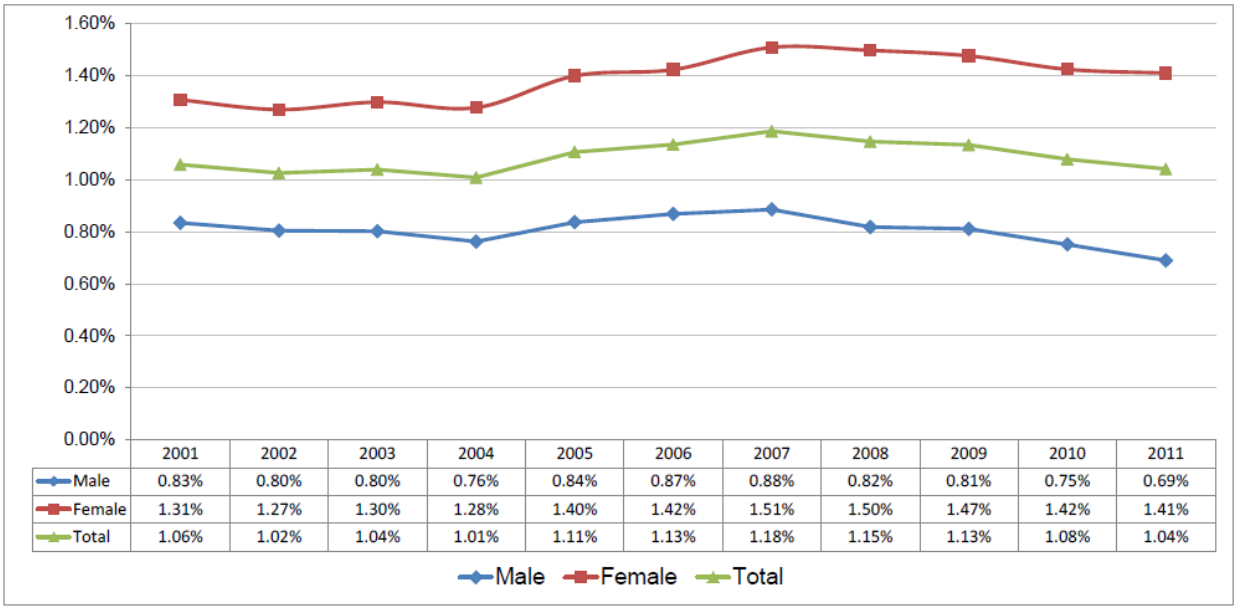
The age distribution of patients has been shown to be similar to France social security data (SNIIRAM)[4]. Ca 2.5 million patients are recorded in IMS France in the last 3 years.

[4] Information provided by IMS Health.

## Appendix 2

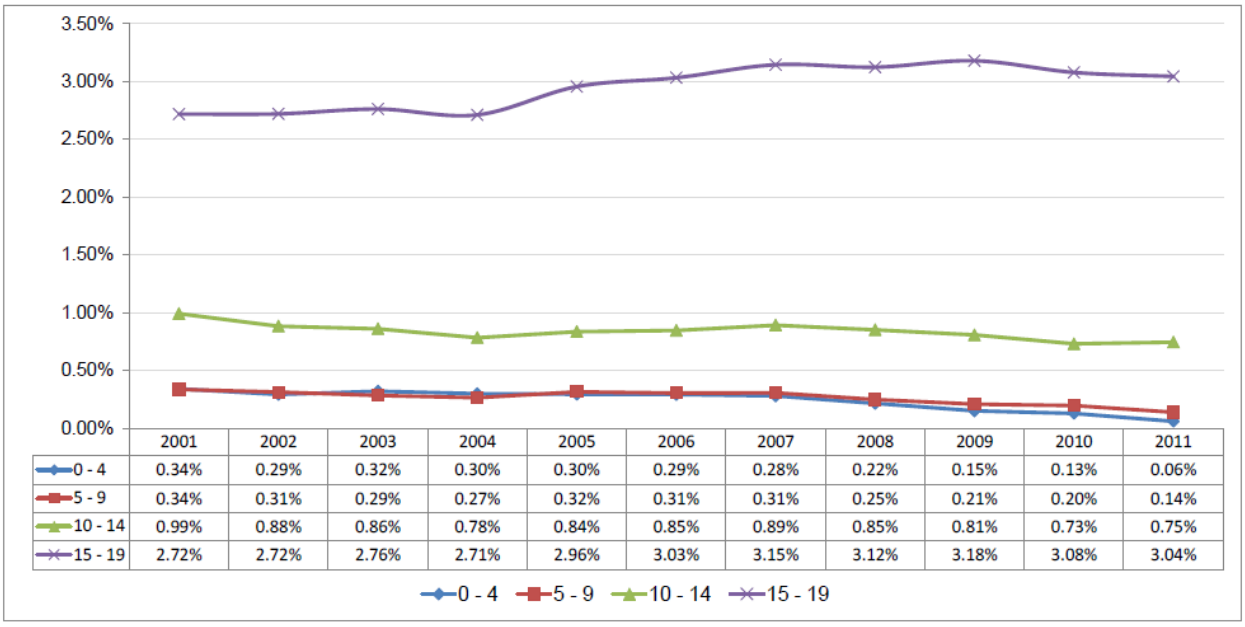
## Mock figure examples

### Gender stratified prevalence by year




| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Male | 0.83% | 0.80% | 0.80% | 0.76% | 0.84% | 0.87% | 0.88% | 0.82% | 0.81% | 0.75% | 0.69% |
| Female | 1.31% | 1.27% | 1.30% | 1.28% | 1.40% | 1.42% | 1.51% | 1.50% | 1.47% | 1.42% | 1.41% |
| Total | 1.06% | 1.02% | 1.04% | 1.01% | 1.11% | 1.13% | 1.18% | 1.15% | 1.13% | 1.08% | 1.04% |

### Age group stratified prevalence by year




| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 - 4 | 0.34% | 0.29% | 0.32% | 0.30% | 0.30% | 0.29% | 0.28% | 0.22% | 0.15% | 0.13% | 0.06% |
| 5 - 9 | 0.34% | 0.31% | 0.29% | 0.27% | 0.32% | 0.31% | 0.31% | 0.25% | 0.21% | 0.20% | 0.14% |
| 10 - 14 | 0.99% | 0.88% | 0.86% | 0.78% | 0.84% | 0.85% | 0.89% | 0.85% | 0.81% | 0.73% | 0.75% |
| 15 - 19 | 2.72% | 2.72% | 2.76% | 2.71% | 2.96% | 3.03% | 3.15% | 3.12% | 3.18% | 3.08% | 3.04% |

**Gender and age group stratified prevalence**