6 July 2021
EMA/758630/2021

EU collaborative study: Changes in alternative treatments for pain and cough in children after introduction of risk minimisation measures for codeine

Final Report

Details	
Participating organisations	ANSM, France NOMA, Norway AEMPS, Spain EMA, European Medicines Agency
Associated regulatory procedure	Article 31 referrals of Directive 2001/83/EC as amended on Codeine-containing medicines concluded in 2013 and 2015

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2021. Reproduction is authorised provided the source is acknowledged.

Table of Contents

1. Rationale and background

Following a benefit-risk review of the use of codeine for the treatment of pain relief in children (EMEA/H/A-31/1342), risk minimisation measures (RMM) were introduced in June 2013 to manage the risk of serious adverse events including serious and fatal respiratory depression. In April 2015, another review on the use of codeine for the treatment of cough or cold in paediatric patients (EMEA/H/A-31/1394) led to the adoption of similar RMM.

The following changes were applied to sections 4.1, 4.2 and 4.3 of the Summary of Product Characteristics (SmPC) of codeine-containing products indicated in the treatment of pain relief in children:

- Section 4.1 Therapeutic indications:
    - *Codeine is indicated in children older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).*
- Section 4.2 Posology and method of administration:
    - *Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240 mg. The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.*
    - *Paediatric population:*
        - *Children aged 12 years to 18 years: The recommended codeine dose for children 12 years and older should be [Dose range to be completed nationally] every 6 hours when necessary up to a maximum dose of codeine 240 mg daily. The dose is based on the body weight (0.5-1 mg/kg).*
        - *Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).*
- Section 4.3 Contraindications:
    - *In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).*

The following changes were introduced in sections 4.2 and 4.3 of the SmPC of codeine-containing products indicated in the treatment of cough or cold in paediatric patients:

- Section 4.2 Posology and method of administration:
    - *Paediatric population:*
        - *Children aged less than 12 years: Codeine is contraindicated in children below the age of 12 years for the symptomatic treatment of cough and/or cold (see sections 4.3).*
        - *Children aged 12 years to 18 years: Codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough and/or cold (see section 4.4).*
- Section 4.3 Contraindications:
    - *In children below the age of 12 years for the symptomatic treatment of cough and/or cold due to an increased risk of developing serious and life-threatening adverse reactions.*

In order to assess the effectiveness of these RMM, a collaborative study was performed with the participation of three National Competent Authorities (NCAs) (Agence Nationale de securité du médicament et des produits de santé (ANSM) in France, Statens Legemiddelverket (NOMA) in Norway and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) in Spain) and the European Medicines Agency (EMA). The study had two main objectives: one was to analyse the use of codeine over time including before and after the introduction of the RMM, and the other was to look at the effect they had on the use of opioid and non-opioid alternative medicinal products in children.

The use of codeine, opioid and non-opioid analgesics and antitussives will heavily depend on the indications for which these medicines are prescribed in each country. An overview of the indications for the different treatments in the participating Member States is provided in Table 1 of the Annex A.

2. Study objectives

This study addresses the following objectives:

1) To describe the use of codeine, alternative analgesics and antitussives between 2010 and 2017 (included) in patients below 18 years of age in France, Norway, Germany, Spain and the United Kingdom as applicable;

2) To assess whether the codeine referrals for the treatment of pain and cough or cold were associated with any changes in the use of alternative analgesics, antitussives in this patient population after each regulatory procedures (referred to later as “post-intervention”) compared to before (“pre-intervention”).

The prevalence of use of the different treatments are described in this study based on the trends of prescriptions in the five participating Member States.

3. Study milestones

Study milestones	Dates
Common study protocol agreed	March 2020
Data extracted by database holders	June-September 2020
Data analysed by EMA research staff	September 2020 – January 2021
results of analyses communicated to each database holder for comments	September to December 2020
Study results presented to the PRAC Interest Group on Impact of Pharmacovigilance	January 2021
Final study report presented to PRAC	July 2021

4. Study methods

4.1. Study design

Five patients’ cohorts were defined to analyse the trends in prescriptions of the treatments of interest over time in the participating Member States. An Interrupted time series (ITS) regression analysis was

performed to assess whether the regulatory actions taken as a result of the codeine referrals in 2013 and in 2015 were associated with a statistically significant change in the use of these treatments.

4.2. Study population

The patient population consisted in all patients under the age of 18 years, with a particular focus on children below 12 eligible to be exposed to codeine or any of the alternative analgesics or antitussives of interest included in our study.

4.3. Study period

We studied the use of codeine, alternative analgesics and antitussives in patients below 18 years of age, between 2010 and 2017 (included) in France, Germany, Norway, Spain and the United Kingdom as applicable.

The study time period between 01/01/2010 and 31/12/2017 provided 14 quarterly (3 calendar months) data points before and 18 quarterly data points after the intervention related to the pain relief indication (June 2013); and 22 quarterly data points before and 10 quarterly data points after the intervention related to the treatment of cough or cold (April 2015). The earliest date of the regulatory intervention was defined as 28/06/2013 for the pain relief indication, and 24/04/2015 for the cough and cold indication.

4.4. Study exposure

The following exposure groups were investigated: 1) Codeine containing products; 2) Opioid antitussives; 3) Opioid analgesics; 4) Non-opioid analgesics and 5) Non-opioid antitussives. Four* or five cohorts were generated from each database accordingly. The products included in each exposure group and sub-groups can be consulted in Table 2 of the Annex A.

* Considering that codeine containing products are not authorised in Norway for cough or cold indications, Norwegian data were omitted from the analysis for the second referral procedure. Moreover, as non-opioid antitussives are not subject to prescription in Norway, they are not recorded in NorPD, and can therefore not be studied in this database.

The prevalence of use was measured at the level of prescribing and was calculated as the number of children with a prescription for the drug of interest (patient numerator) in relation to all children in the population denominator during each respective time period.

4.5. Databases

The following databases were included in the study:

- Databases recording drug use at prescription level: IMRD-Germany, and IMRD-UK;
- Databases recording drug use at dispensing level: BIFAP (Spain), NorPD (Norway) and SNDS (France). For the purposes of analysing the data, the date of dispensing is taken as being the same as the date of prescription (for the medicines to be dispensed, they must have first been prescribed) and from hereon will be referred to as prescriptions.

None of the databases capture over the counter (OTC) medicines. More details on each of the five systems are presented below.

4.5.1. SNDS (ex SNIIRAM)

The French National Health Data System database (SNDS) includes all French residents' health-related expenses. In France, individuals have a health insurance coverage plan, which varies according to the person's occupational status. Only claims reimbursed from the general health insurance plan (which covers private and public employees and the unemployed, accounting for 77% of the population) were considered because of their availability and quality. In the SNDS database, an anonymous unique subject identifier links information from different data sources: PMSI (the national hospital and discharge database), DCIR (the national health insurance claims database), and CepiDC (the national exhaustive database for the medical causes of death).

The DCIR database includes individual information on sociodemographic characteristics, outpatient medical care, laboratory tests, and dispensed drugs. It also contains information about the presence of any severe or costly medical condition (per the International Classification of Disease, Tenth Revision [ICD-10] codes).

The PMSI database contains details of all private and public hospital admissions and discharges for either inpatient stays or ambulatory care. Data on diagnoses, treatments, and surgical procedures provided during hospital stays are also accessible.

4.5.2. Norwegian prescription database (NorPD)

NorPD is a national database with information on dispensed prescriptions back to 2004. Sales of OTC medicines are not captured. Information on age and gender is available for patients with a prescription. The indication is also recorded in case of reimbursed medications. The patient denominator is obtained from population statistics.

4.5.3. IMRD-Germany database

The IMRD-Germany database contains anonymised electronic medical records data from a representative panel of physicians since 1992 (general practitioners (GPs) and specialists). The sampling of participating physicians is stratified for specialist groups, regions, and age. IMRD-Germany contains patient records including diagnoses, prescriptions, referrals, hospitalisations and sick notes. The sampling of physicians ensures that patients are representative for each speciality across regions in Germany with 83% of practices being single physician practices. As registration with a GP is not a requirement in Germany, patients with a consultation during the time period will be used as denominator in prevalence calculations. The GP patient population is broadly representative of the German population in terms of gender and age distribution, except for children, as parents may choose to visit a paediatrician directly. Both GPs and paediatricians have been included in the study and analysed separately.

4.5.4. BIFAP

BIFAP is a longitudinal population-based database of anonymised medical patient records from primary care physicians, including GPs and paediatricians from nine Spanish regional healthcare systems. BIFAP started in 2003 and includes electronic health records after 2001. Practices in BIFAP include around 20% of the Spanish population. In Spain, most of the population is registered with a primary care physician (PCP) who acts as gatekeeper of the healthcare system. Participation of practices in BIFAP is voluntary and conditional upon meeting standard quality criteria.

Most treatments use recorded is obtained at dispensing level considering the whole study period (2010-2017). However, a transition from paper based prescribed medication to directly routed e-prescriptions (with accessibility to dispensing information) is observed in BIFAP according to gradual e-prescription implementation in Spain (from 2011). The fact that the first or consecutive prescriptions of a specific study are paper based or dispensing drugs would largely depend on the study period and the availability of e-prescription in the patient's practice during this time. In 2018, around 70% of the system has changed to an e-prescription-dispensation system.

4.5.5. IMRD-UK database

The IMRD-UK database contains electronic primary care medical records extracted from over 500 general practices across the United Kingdom covering approximately 6% of the population. The data is representative of the population in terms of age, deprivation, and geographical distribution and linked via an anonymous patient ID number allowing patients to be followed longitudinally over time. Diagnoses, symptoms, procedures, and other relevant health information are recorded using the Read Code clinical classification system, a hierarchical classification system.

4.6. Data extraction

A data extraction plan document and an Excel file with table shells were developed to lay down definitions and ensure a consistent approach to the data extraction for each database and to the analysis process. The aggregate table shells were completed by each participating NCA (ANSM, NOMA, AEMPS) and EMA (for German and UK data). The information was then sent to EMA as applicable for analysis at central level.

4.7. Data analysis

Trends in prescriptions of the treatments of interest were first plotted graphically using quarterly time periods before and after the interventions (Figures).

Interrupted time series (ITS) regression analyses were then performed when applicable to assess whether the regulatory actions taken as a result of the codeine referrals in 2013 and in 2015 were associated with a statistically significant change in trend of prescriptions of these treatments. More specifically, ARIMA models were used, adjusting for potential autocorrelation as indicated with the Durban-Watson statistic and pre-intervention trend, to assess a slope change from the baseline trend to the post-intervention trend (sustained effect), and a level change associated with the intervention time points (immediate effect). The quarterly time period that includes the time point of the regulatory intervention was categorised as time before the regulatory action due to the fact that any deterministic changes in trend would only take effect after the regulatory action.

The fit of the selected model was assessed through a visual inspection of the white noise and IACF (Inverse Autocorrelation Function) plots.

Two separate analyses were performed for each regulatory intervention and for the two previously defined numerators: at patient level and at prescription level (sensitivity analyses). All analyses were performed using SAS. The prevalence of use was measured at the level of prescribing and was calculated as the number of children with a prescription for the drug of interest (patient numerator) in relation to all children in the population denominator during each respective time period.

4.8. Ethical approval of the study

Upon agreement of the study protocol, the participating NCAs requested ethical approval at national level as applicable.

5. Results

This section describes the results of the prevalence of use in children of codeine, alternative analgesics and antitussives before and after the codeine referrals for pain relief and cough or cold indications in each of the participating cohorts. The Figures presented in this report relate to children below 12 years of age due to codeine's contraindication in this age group for the aforementioned indications. The results for children aged 12 and above can be consulted in the Annex B.

5.1. Referral on pain relief indication (June 2013)

5.1.1. Use of codeine containing products

The use of codeine in the five participating Member States is presented in Figure 5.1.1 (trends in prescribing) and Table 5.1.1 (statistical measures: interrupted time series).

Before the referral on pain relief indication:

A decreasing trend is visible in Spain and the United Kingdom prior to the referral while the use of codeine seems to increase in France and slightly increase in Norway (not statistically significant – Table 5.1.1).

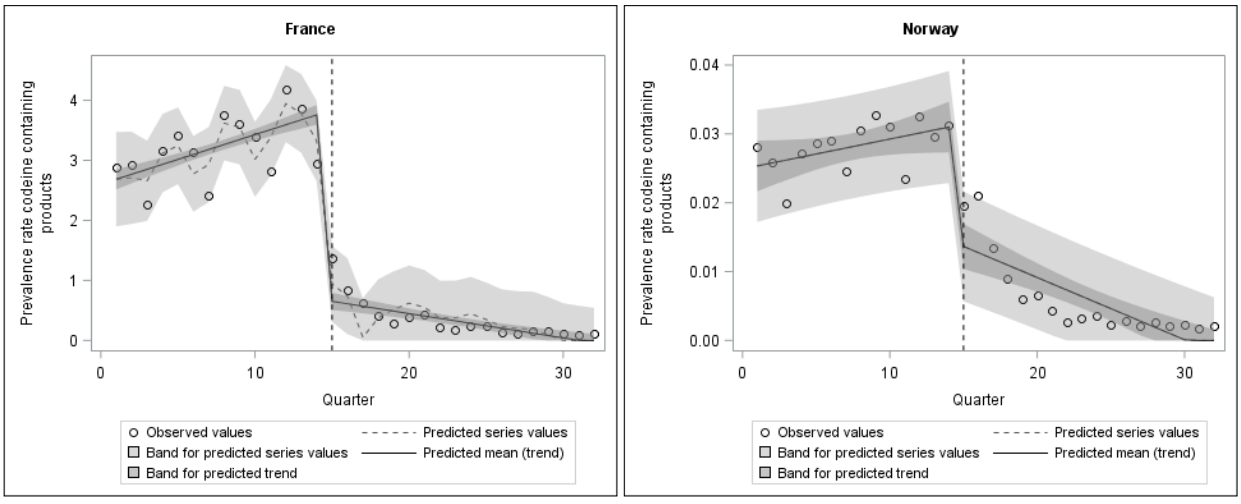
Immediately after the referral:

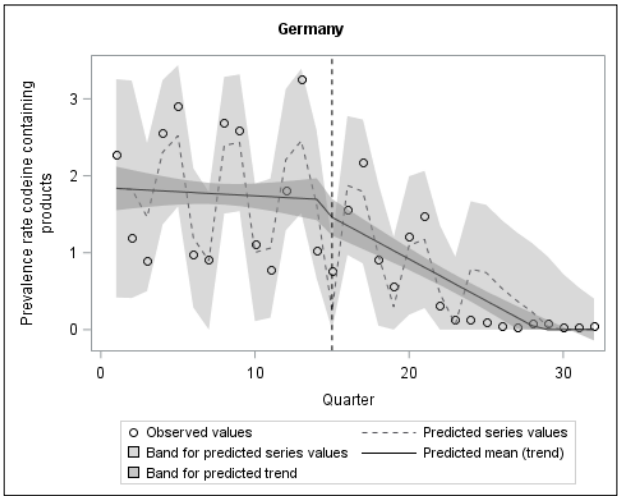
A decrease in the use of codeine containing products post-intervention compared with the baseline prescribing trends is reported for all countries, with a significant drop in France and Norway (Table 5.1.1).

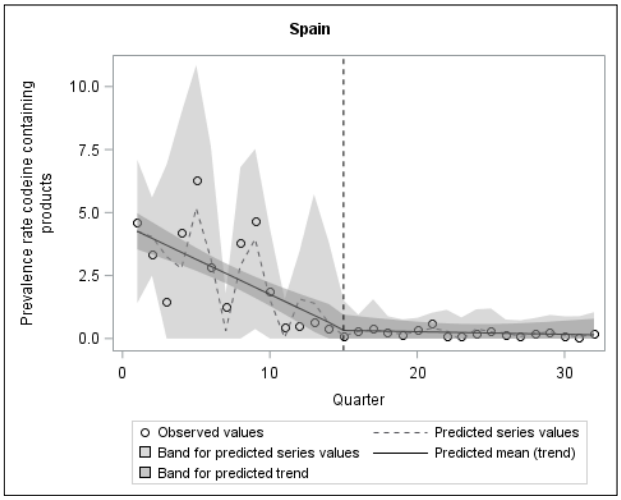
Later after the referral:

A continuous decrease is observed in all five countries post-intervention reaching near null prevalence.

Figure 5.1.1 Quarterly (n=32) trends in codeine containing products in France, Norway, Germany, Spain and United Kingdom between 1 January 2010 and 31 December 2017







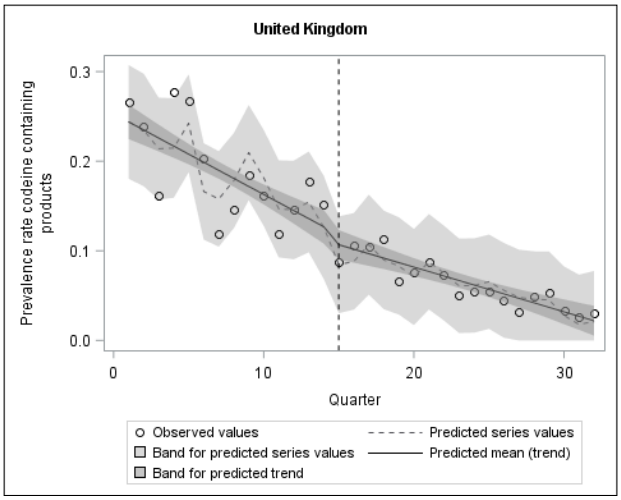


Table 5.1.1 Results of interrupted time series analysing for trends in codeine containing products in population <12 years of age after the pain referral (June 2013) in France, Norway, Germany, Spain and United Kingdom
Statistically significant increases and decreases are highlighted in blue bold font.

	Pre-intervention trend and p-value		Change in level immediate after regulatory measure and p-value after June 2013		Change in trend postintervention compared with the baseline prescribing trend and p-value	
	Change	p-value	Change	p-value	Change	p-value
France	0.0824	<.0001	-3.0664	<.0001	-0.1231	<.0001
Norway	0.0004	0.0751	-0.0164	<.0001	-0.0013	<.0001
Germany	-0.0108	0.5582	-0.1265	0.5196	-0.0977	<.0001
Spain	-0.2659	<.0001	-0.2395	0.6417	0.2468	0.0040
United Kingdom	-0.0089	<.0001	-0.0151	0.2651	0.0040	0.0091

Note on children aged 12 and above (Annex B): The general trends in prescribing of codeine containing products in the five participating Member States are similar as in children below 12, but the prevalence of use is higher.

5.1.2. Use of alternative treatments

The use of alternative analgesics in the five participating Member States is presented in Figure 5.1.2 and Table 5.1.2.

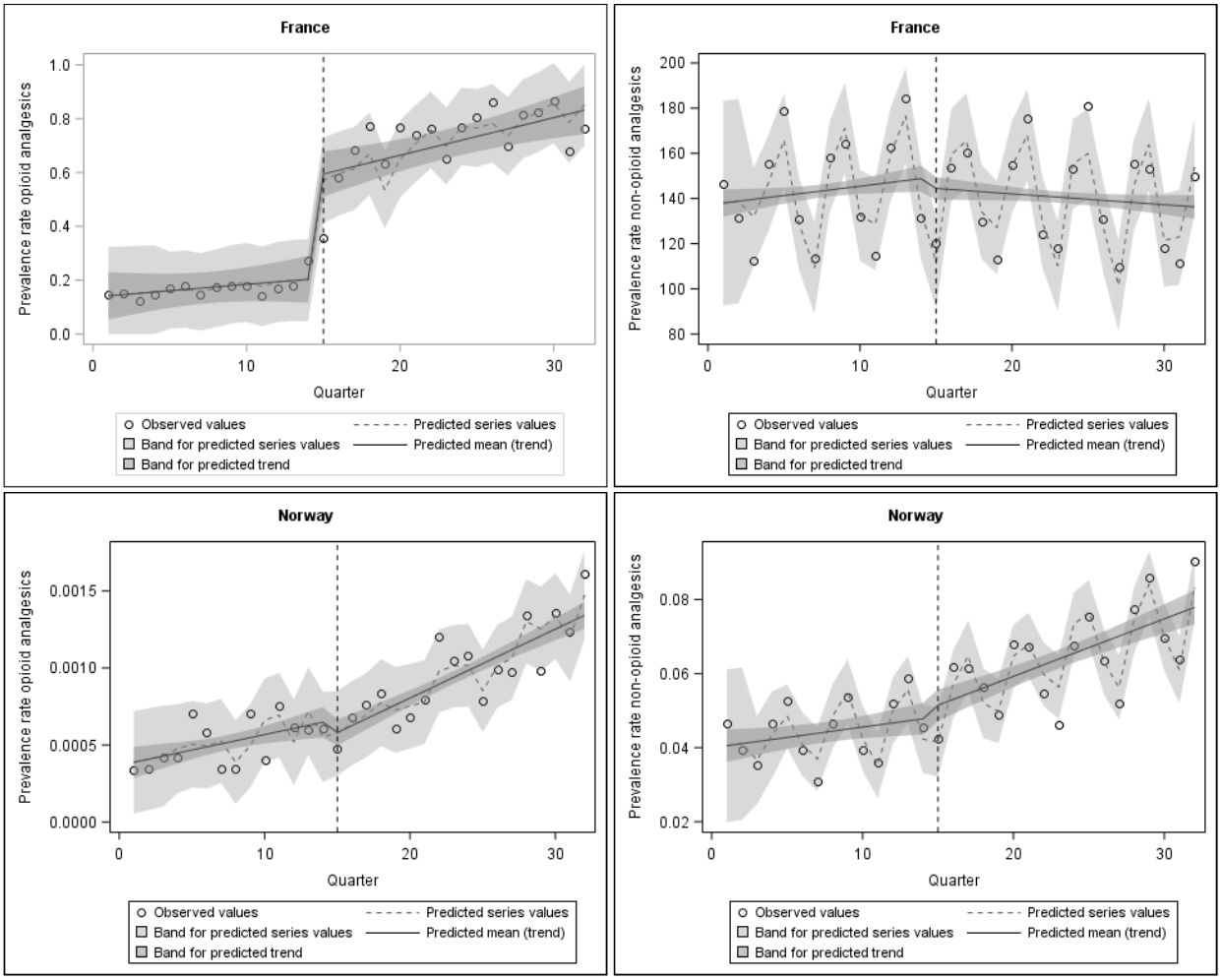
Other opioid analgesics:

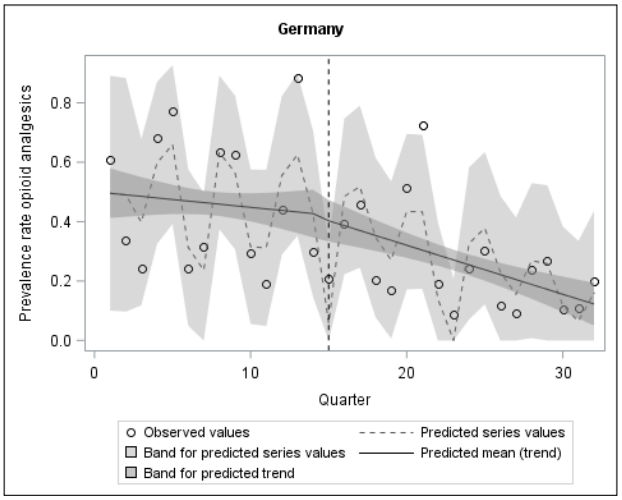
A significant uptake in France and the United Kingdom, and a slight increase in Spain and Norway can be seen over time, while a slight decrease is noted in Germany.

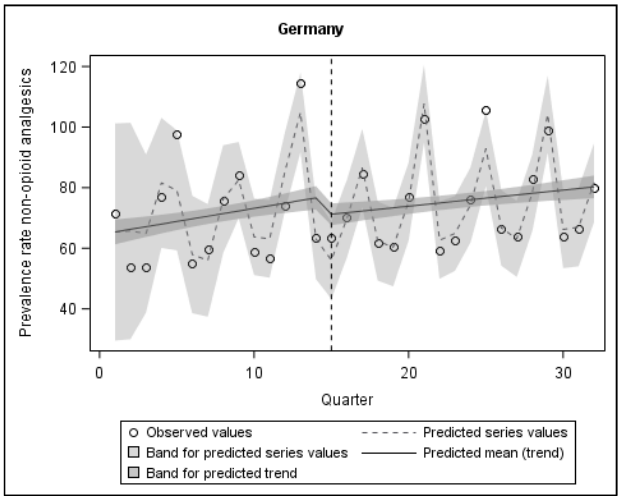
Non-opioid analgesics:

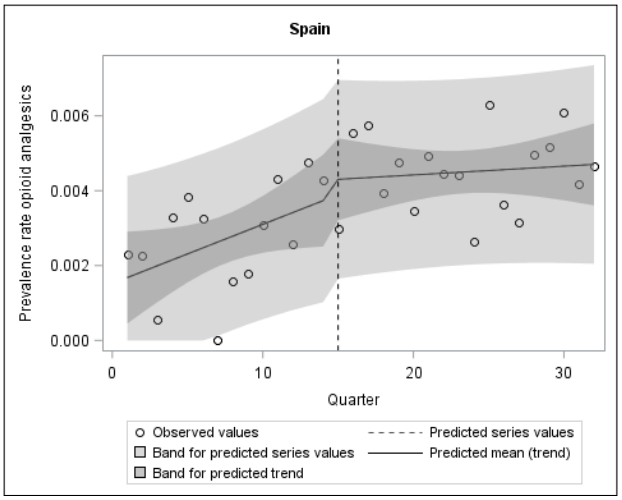
A significant increase is visible in Norway and Germany, whereas a significant decrease is observed in France and the United Kingdom (slight decrease in Spain).

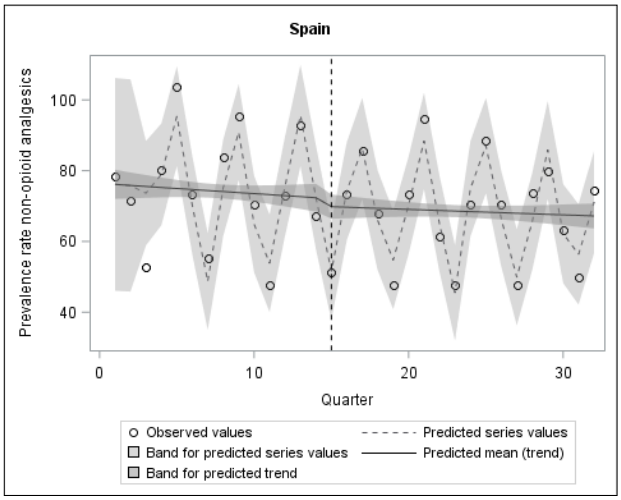
Figure 5.1.2 Quarterly (n=32) trends in alternative medicines in France, Norway, Germany, Spain and United Kingdom between 1 January 2010 and 31 December 2017

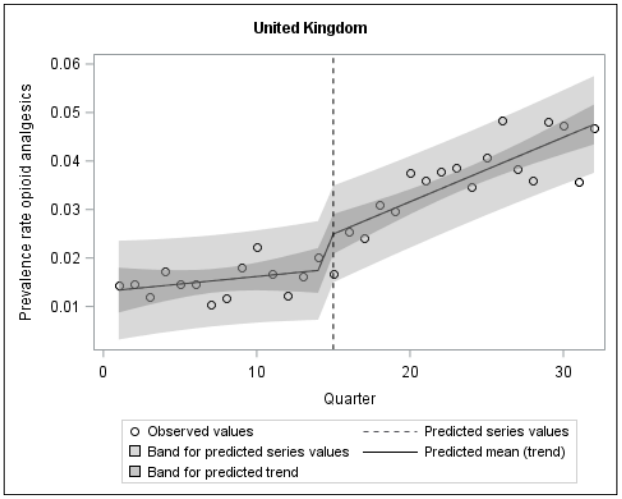



Germany
Prevalence rate opioid analgesics
0.0
0.2
0.4
0.6
0.8
0
10
20
30
Quarter
Observed values
Predicted series values
Band for predicted series values
Predicted mean (trend)
Band for predicted trend


Germany
Prevalence rate non-opioid analgesics
40
60
80
100
120
0
10
20
30
Quarter
Observed values
Predicted series values
Band for predicted series values
Predicted mean (trend)
Band for predicted trend


Spain
Prevalence rate opioid analgesics
0.000
0.002
0.004
0.006
0
10
20
30
Quarter
Observed values
Predicted series values
Band for predicted series values
Predicted mean (trend)
Band for predicted trend


Spain
Prevalence rate non-opioid analgesics
40
60
80
100
0
10
20
30
Quarter
Observed values
Predicted series values
Band for predicted series values
Predicted mean (trend)
Band for predicted trend


United Kingdom
Prevalence rate opioid analgesics
0.01
0.02
0.03
0.04
0.05
0.06
0
10
20
30
Quarter
Observed values
Predicted series values
Band for predicted series values
Predicted mean (trend)
Band for predicted trend

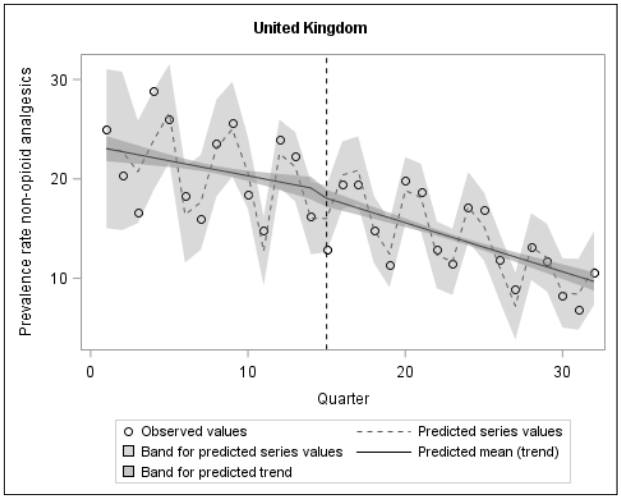

United Kingdom
Prevalence rate non-opioid analgesics
10
20
30
0
10
20
30
Quarter
Observed values
Predicted series values
Band for predicted series values
Predicted mean (trend)
Band for predicted trend

Table 5.1.2 Results of interrupted time series analysing for trends in alternative medicine in population <12 years of age after the pain referral (June 2013) in France, Norway, Germany, Spain and United Kingdom
Statistically significant increases and decreases are highlighted in blue bold font.

	Pre-intervention trend and p-value		Change in level immediate after regulatory measure and p-value after June 2013		Change in trend postintervention compared with the baseline prescribing trend and p-value	
	Change	p-value	Change	p-value	Change	p-value
Opioid Analgesics						
France	0.0047	0.3427	0.3773	**<.0001**	0.0092	0.1767
Norway	0.00001	0.0057	-0.0001	0.1313	0.0001	**0.0027**
Germany	-0.0052	0.3344	-0.0076	0.8948	-0.0112	0.0789
Spain	0.0001	0.0531	0.0005	0.5179	-0.00013	0.1668
United Kingdom	0.0003	0.2978	0.0061	0.0580	0.0010	**0.0080**
Non-Opioid Analgesics						
France	0.8287	0.0425	-3.8306	0.3618	-1.3088	**0.0068**
Norway	0.0005	0.0333	0.0021	0.3750	0.0009	**0.0060**
Germany	0.8637	0.0008	-5.9269	**0.0160**	-0.3321	0.2506
Spain	-0.289	0.2833	-2.3838	0.4021	0.1348	0.6595
United Kingdom	-0.3039	0.0013	-0.5470	0.5306	-0.1881	**0.0272**

Note on children aged 12 and above (Annex B): While the prevalence of use of opioid analgesics is higher than for children under 12, it is lower for non-opioid analgesics in all countries except in Norway. The overall prescribing trends are consistent across both age groups within each participating Member State over time, except for opioid analgesics in the United Kingdom.

5.2. Referral on cough or cold indications (June 2015)

5.2.1. Use of codeine containing products

As codeine containing products are not authorised in Norway for cough or cold indications, Norwegian data are not included in this section.

A continuous decrease before and after the referral on cough or cold indications can be observed in all four remaining Member States until reaching extremely low prevalence (close to 0) (Figure 5.2.1 and Table 5.2.1).

Figure 5.2.1 Quarterly (n=32) trends in codeine containing products in France, Germany, Spain and United Kingdom between 1 January 2010 and 31 December 2017

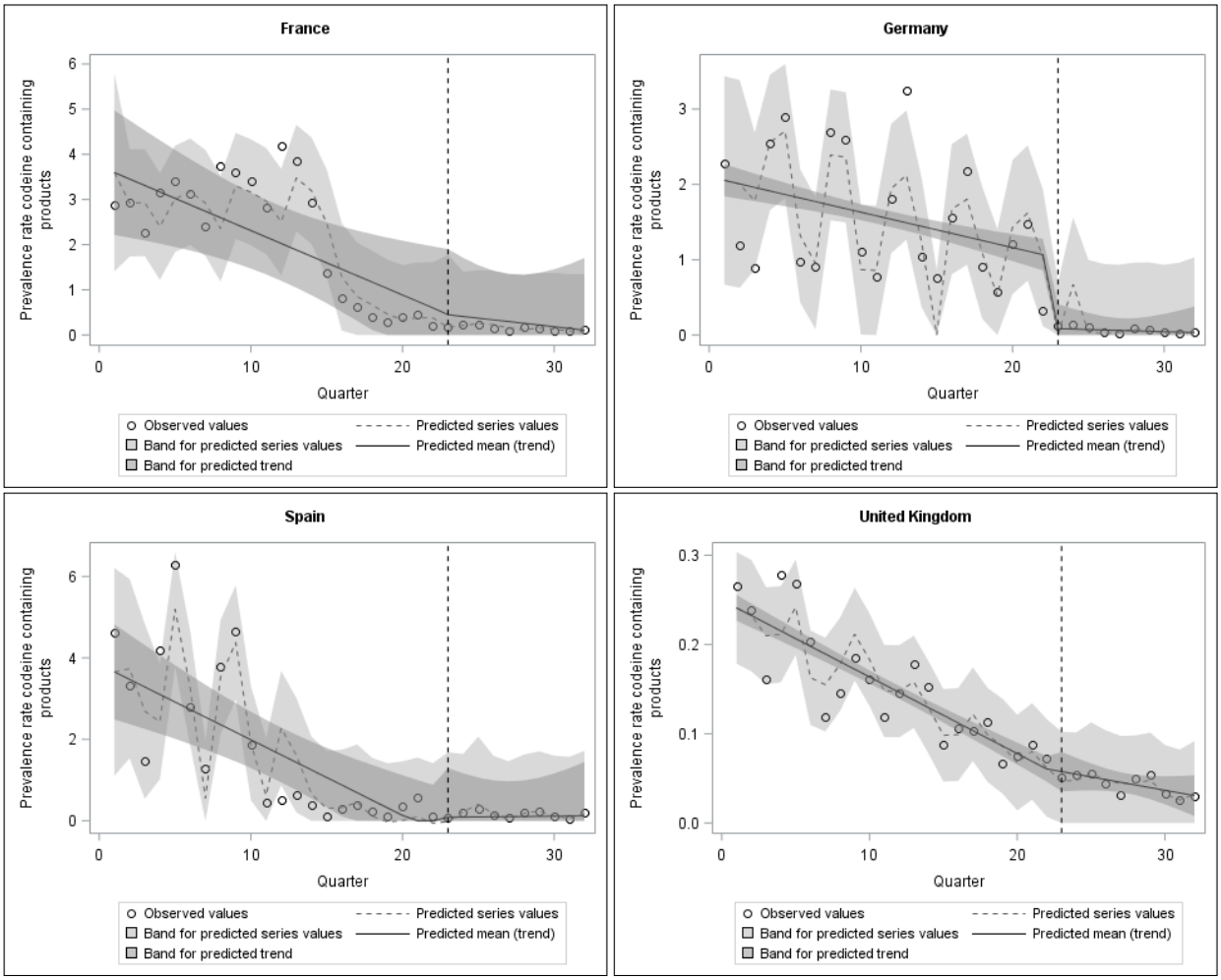


Table 5.2.1 Results of interrupted time series analysing for trends in codeine containing products in population <12 years of age after the cough or cold referral (April 2015) in France, Germany, Spain and United Kingdom
Statistically significant increases and decreases are highlighted in blue bold font.

	Pre-intervention trend and p-value		Change in level immediate after regulatory measure and p-value after April 2015		Change in trend postintervention compared with the baseline prescribing trend and p-value	
	Change	p-value	Change	p-value	Change	p-value
France	-0.1427	**0.0087**	-0.1114	0.8612	0.1045	0.4562
Germany	-0.0470	**<.0001**	-0.9776	**0.0002**	0.0414	0.2090
Spain	-0.1855	**0.0001**	0.3214	0.5810	0.1892	0.1182
United Kingdom	-0.0085	**<.0001**	0.00001	0.9974	0.0056	0.0144

Note on children aged 12 and above (Annex B): The same decreasing trends can be seen in older children, except in Germany and Spain where the use of codeine seems to flatten over time. The prevalence of use remains higher than in children below 12.

5.2.2. Use of alternative treatments

The use of alternative antitussives in the four Member States is shown in Figure 5.2.2 and Table 5.2.2.

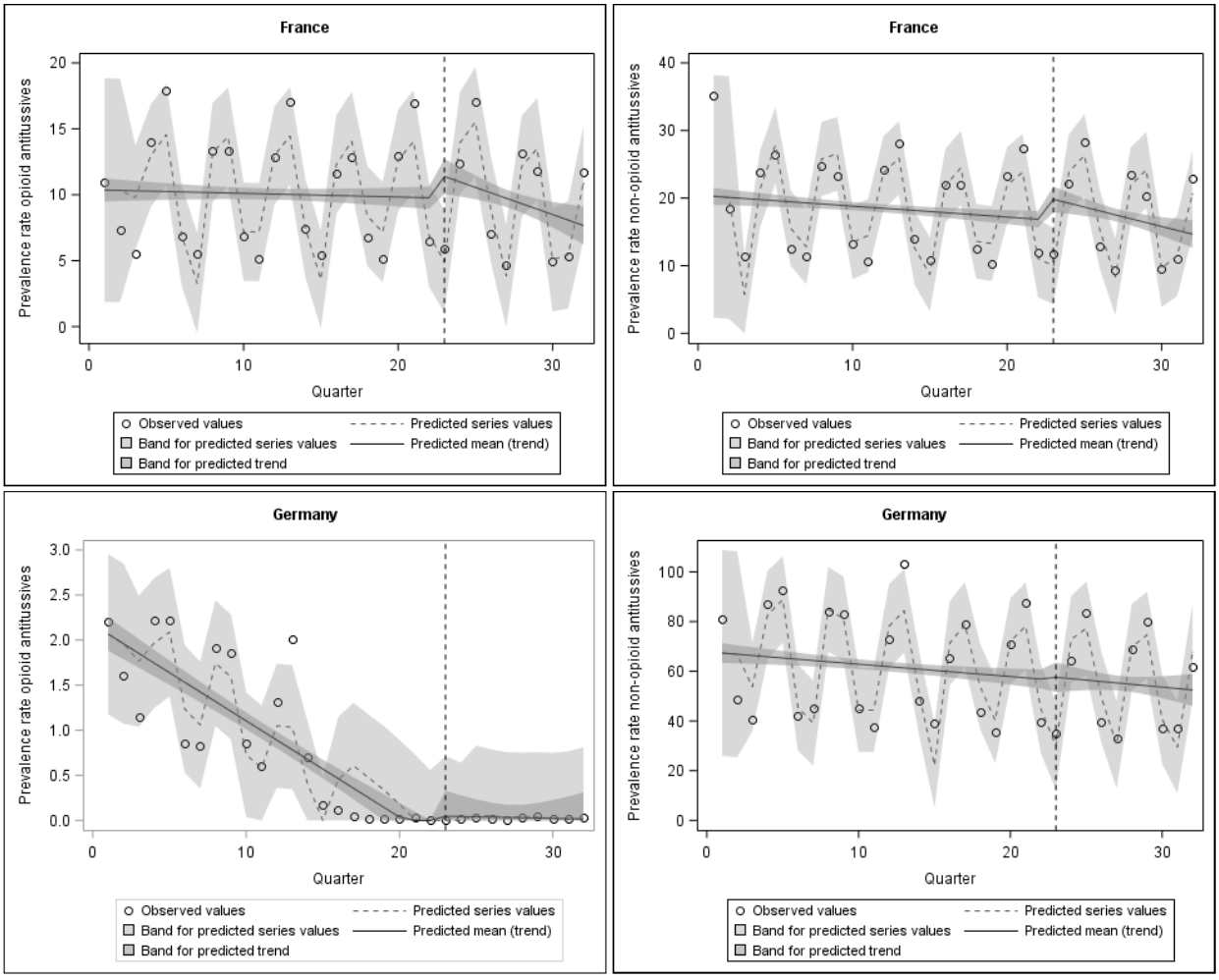
Other opioid antitussives:

An immediate uptake in the use of other opioids antitussives in France after the referral is then followed by a decrease in prescriptions over time. For the other Member States, the prevalence of use tends to flatten towards 0. A change in trend post-intervention compared with the baseline prescribing trend was reported in Germany.

Non-opioids antitussives:

The same pattern as for the opioid antitussives can be seen in France (immediate update followed by a decrease over time in the use of these treatments). A continuous decrease is visible in Germany and the United Kingdom, while in Spain the trend is close to no use.

Figure 5.2.2 Quarterly (n=32) trends in alternative medicines in France, Germany, Spain and United Kingdom between 1 January 2010 and 31 December 2017



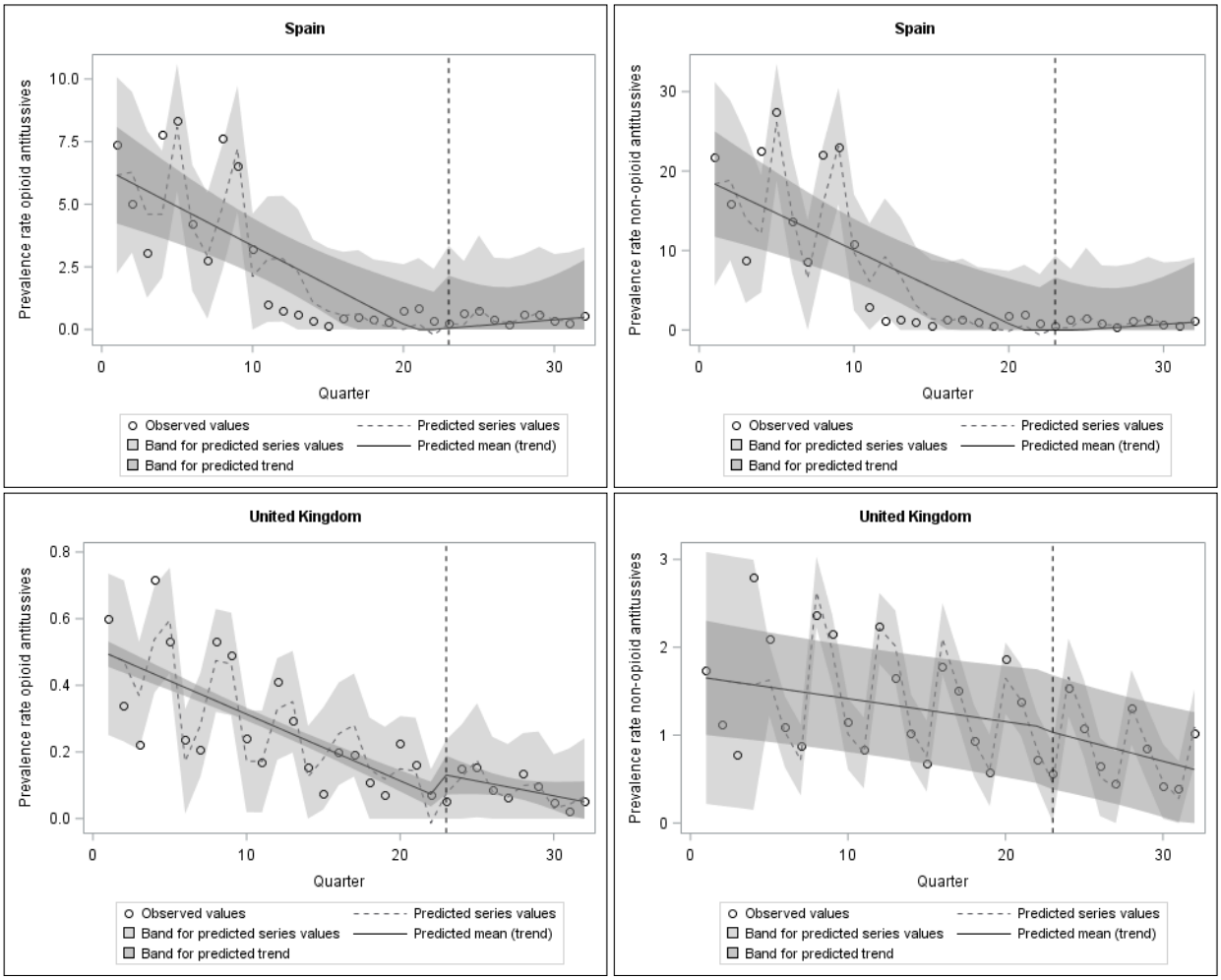


Table 5.2.2 Results of interrupted time series analysing for trends in alternative medicine in population <12 years of age after the cough referral (April 2025) in France, Germany, Spain and United Kingdom
Statistically significant increases and decreases are highlighted in blue bold font.

	Pre-intervention trend and p-value		Change in level immediate after regulatory measure and p-value after June 2013		Change in trend postintervention compared with the baseline prescribing trend and p-value	
	Change	p-value	Change	p-value	Change	p-value
Opioid Antitussives						
France	-0.0278	0.4313	2.0267	0.0357	-0.3854	0.0071
Germany	-0.1069	<.0001	0.2281	0.2502	0.1035	0.0009
Spain	-0.3128	0.0001	0.4197	0.7030	0.3604	0.0929
United Kingdom	-0.0200	<.0001	0.0661	0.1100	0.0111	0.0636
Non-Opioid Antitussives						
France	-0.1609	0.0031	3.5102	0.0120	-0.4108	0.0383
Germany	-0.4987	0.0036	1.2935	0.7561	-0.0715	0.9053
Spain	-0.9250	0.0005	0.7129	0.8215	1.0568	0.1252
United Kingdom	-0.0262	0.0230	-0.0226	0.8406	-0.0208	0.3582

Note on children aged 12 and above (Annex B): The trends in prescribing of other opioid antitussives are similar to those for children under 12 in France, Germany and the United Kingdom. No changes in

prescribing of these treatments are visible after the referral in Spain where the prevalence is higher than in the younger population.

The prescriptions pattern of non-opioids antitussives is consistent with children under 12 years of age in France, Germany, Spain and the United Kingdom.

6. Discussion

6.1. Observations on prevalence of use and prescribing trends across age groups and Member States (Annex B for children ≥ 12)

This section should be read in conjunction with the Annex B that presents the prevalence of use of codeine, alternative analgesics and alternative antitussives in children aged 12 to 18 years. Throughout the study period, the use of codeine in the five participating Member States decreases overall in children under 18 years of age, until reaching extremely low (or no) prevalence in children below 12. Such decrease can even be observed prior to the launch of the referral on pain relief indication in some countries[1]. The prevalence of use remains higher in children 12 years and above than in children below 12 but can highly differ between countries hinting at different clinical practices across Member States (e.g. predicted means in December 2017 in children above 12 of 0.08 in Norway and 5 per 100 person years in Spain).

In line with codeine, the use of opioid alternative medicines remains higher in children 12 and above compared to younger children, while the use of non-opioid alternatives is higher in children below 12 throughout the study period in all countries. For analgesics, the use of non-opioids alternatives remains higher than opioid alternatives in all Member States.

Important differences in patterns of use of alternative treatments can be observed between the two age groups and between Member States. These emphasise some variabilities in national clinical practices adopted by the five countries in parallel to the RMM imposed on codeine containing products, e.g.:

- Non-opioid analgesics: predicted mean in December 2017 of 140 per 100 person years in children below 12 and 80 per 100 person years in children 12 and above in France, compared to <1 in Norway;
- Opioid antitussives: predicted mean in December 2017 of about 8 to 10 per 100 person years in France in both age groups compared to nearly 0 in all other countries;
- Non-opioid antitussives: predicted mean of approximately 50 and 25 per 100 person years in both age groups respectively in Germany compared to close to 0 in Spain and the United Kingdom.

It is however important to note that prescribing trends for all these alternative medicines are consistent throughout the study period between the two age groups within each individual Member State.

6.2. Switching patterns

Changes to prescribing trends of alternative medicines observed across the participating Member States following the referrals lead to assumptions on switching patterns towards the use of opioid

[1] Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death; Ciszkowski et al. N Engl J Med 2009; 361:827-828: https://www.nejm.org/doi/full/10.1056/nejmc0904266#article_citing_articles

analgesics in France, Norway and the United Kingdom, and towards the use of non-opioid analgesics in Norway and Germany for pain management in children under 12 years of age.

As the study did not aim at assessing the prescribing trends at individual substance level, it is difficult to point out which of the substances have benefited from a switch from codeine. However, Table 2 in the Annex A provides an overview of the numbers of prescriptions and their proportion (%) within each treatment groups and sub-groups. We can see for example that tramadol (including in combination with non-opioids products) is the main alternative opioid analgesic used across all Member States, while prescribed ibuprofen (Norway, Germany and Spain) and paracetamol (France and the United Kingdom) appear to stand out as non-opioid analgesics.

The overall use of alternative opioid antitussives decreases or flattens over time after the referral on cough and cold indications where these products are authorised in parallel to the use of codeine, approaching extremely low prevalence in most countries (except in France for both age groups). This leads us to assume that no switching occurred towards these substances. The same applies to non-opioid antitussives, but their use in France and Germany remains much higher than in the other Member States.

The variability in prescribing trends of alternatives across Member States and across the two age groups may be influenced by national reimbursement status and/or clinical guidelines or recommendations.

6.3. Contextualisation of the results

France: The marketing of the only plain codeine containing product authorised for pain relief in children (Codenfan®) was ceased by the MAH in 2013 following the results of the referral, which explains the immediate drop in the use of codeine containing products after the first referral. This is associated with an increase in the use of other opioid analgesics such as tramadol (from 3 years of age) or even morphine according to certain conditions as recommended by French competent authorities for the management of intense pain in children[2]. It is therefore assumed that prescribers switched to these treatments for intense pain.

Norway: According to this study, the restrictions on codeine led to a significant decrease in its use, associated with a significant increase in the use of both opioid and non-opioid analgesics in children. Besides, a Norwegian study[3] using the same database (NorPD) reported only a very small increase in tramadol followed by morphine and oxycodone between 2011 and 2015, as well as a slightly higher increase in the use of paracetamol (which is most probably underestimated due to its OTC status as for the non-steroidal anti-inflammatory agents). The different findings between these two studies may be explained by a different timespan, by the methods applied and by the treatments' groups' categorisation. In any case, the use of codeine, opioid/non-opioid analgesics and opioid antitussives is in general extremely low in Norway.

Since codeine has never been authorised for cough and cold in Norway, no communication following the EU regulatory procedure concluded in 2015 was issued at national level. It is therefore assumed that the agreed RMM did not have any impact on the use of opioid and non-opioid antitussives.

[2] HAS: https://www.has-sante.fr/jcms/c_2010340/en/prise-en-charge-medicamenteuse-de-la-douleur-chez-l-enfant-alternatives-a-la-codeine
https://www.sfpediatrie.com/sites/www.sfpediatrie.com/files/medias/documents/prise_en_charge_medicamenteuse_de_la_douleur_chez_lenfant_alternatives_a_la_codeine_-_fiche_memo.pdf
[3] Olav Magnus S. Fredheim et al. published in the Journal of Norske Legeforening:
https://tidsskriftet.no/2017/05/originalartikkel/utlevering-av-analgetika-til-barn-og-etter-nye-anbefalinger-om-kodein

Germany: The decrease in codeine use following the pain referral did not have a significant impact on opioid analgesics which remain at a low prevalence[4] throughout the study. However, an increased use of non-opioid analgesics is visible, meaning that health care professionals may have switched from codeine to this type of products including paracetamol (acetaminophen) and ibuprofen.

Spain: Codeine is mainly prescribed in Spain for respiratory infections (89.5%) instead of pain relief (2.3%), which explains the seasonal pattern with peaks in the winter over the entire time period (Table 3) also visible for the alternative treatments (Figure 6.3 in the Annex A). However, the peaks appear to be lower from Q1 2013 compared to the previous years. This is due to a change in the national reimbursement status that became effective on the 1st September 2012[5] for a list of medicinal products indicated in a wide range of minor symptoms like cough or cold. Most of the products excluded from reimbursement concern those categorised in groups 1, 2 and 5 of our study (Annex A Table 2). As a consequence, a similar decreasing pattern in the number of prescriptions can be observed between 2011 and 2012 in both age groups: codeine-containing products (group 1) dropped by 64%, opioid antitussives (group 2) by 93%, and non-opioid antitussive (group 5) by 89%.

United Kingdom: The use of codeine and antitussives started to decrease before 2013 and continue to go down after the two referral procedures to reach hardly any use. A steep increase is visible in the use of opioid analgesics in children below 12 after the pain referral, assuming that patients were switched from codeine to these medications. This switch might have been triggered by the overall warning of the harm of codeine containing products in 2009[1]. In addition, back in 2010, the United Kingdom Commission on Human Medicines advised[6] that OTC liquid medicines containing codeine should not be used for cough suppression in people under 18[7], which might have also contributed to the early decrease in use of these products.

6.4. Limitations

As the study was performed in prescriptions databases, the results do not take account of OTC medications. The use of non-opioid medicinal products presented in this report is therefore most probably under-estimated. While our study shows a decrease in their use over time in some Members States (e.g. non-opioid analgesics in France and the United Kingdom, non-opioid antitussives in France, Germany and the United Kingdom), it may actually increase over the counter. It is therefore not possible to guarantee that the decrease in the use of codeine has not also led to an increase in use of OTC non-opioid medicines. Switches to opioid alternatives would not be impacted by this aspect, since most of these products are dispensed under prescription.

The specific indications for which codeine was used were not considered in the analysis, nor was the prevalence of use of individual alternative substances. It is therefore difficult to ascertain which substances were precisely used instead of codeine.

6.5. Lessons learnt from the codeine pilot impact study

Three NCAs participated with EMA to the study. Teleconferences were organised as needed to take stock at each step of the study and to facilitate exchanges when clarifications where needed. The whole process worked well thanks to very good interactions between the different parties involved and

[4] https://onlinelibrary.wiley.com/doi/full/10.1002/j.1532-2149.2011.00093.x
[5] Confer to the Resolution of the Spanish Ministry of Health (Resolución de 2 de agosto de 2012 de la Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia, por la que se procede a la actualización de la lista de medicamentos que quedan excluidos de la prestación farmacéutica en el Sistema Nacional de Salud. (https://www.boe.es/eli/es/res/2012/08/02/(2))
[6] https://www.gov.uk/drug-safety-update/codeine-containing-liquid-over-the-counter-medicines
[7] https://www.gov.United Kingdom/drug-safety-update/codeine-containing-liquid-over-the-counter-medicines

strong expertise on the characteristics of the national datasets. The common data extraction plan was consistently used by the three NCAs and EMA, allowing the data to be retrieved in a structured format, and simplifying data pooling and analysis centrally by EMA.

The overall time needed for this pilot study (from the development of/agreement on the documentation, the data extraction, the statistical analysis and the finalisation of the general report) was however a challenge. As no specific deadline had been formally agreed with the PRAC Impact Group (IG), individuals involved may not have regularly allocated time to work on the project, as participation was on voluntary basis. Moreover, unforeseen circumstances leading to high workload (e.g. COVID-19 pandemic) created a shift in priorities that contributed to a lengthy process. In order to address this challenge, it is recommended that for future similar projects:

- Specific deliverables and timelines are officially agreed with the PRAC IG. These should only be amended based on clear justification(s) that should be tracked accordingly;
- Regular oral updates are planned and provided to the PRAC IG to take stock on the study status, and to give the opportunity to all members to raise questions and/or provided clarifications on any aspects of the study as applicable.

7. Conclusion

This study shows that the risk minimisation measures introduced following the first referral procedure on the pain indication in children had an impact to different extents across the participating countries on the use of codeine containing products and alternative treatments. While a significant drop in the use of codeine is visible after the referral in France and Norway (slight decrease in Germany), prescribing of codeine started to decrease before the regulatory intervention in Spain and the United Kingdom and continued steadily afterwards to reach very low or near null prevalence (particularly in children below 12). Nevertheless, this general decrease in use leads to the assumption that overall, healthcare professionals seem to have followed the measures adopted at EU level, and switched prescribing patterns for pain management in children towards opioid analgesics like tramadol in France, Norway and the United Kingdom, and towards the use of non-opioid analgesics like prescribed ibuprofen and paracetamol in Norway and Germany. In Spain, the decrease in codeine use was triggered by a change in reimbursement status of these products prior to the 2013 referral. The RMM did not translate into a noteworthy changing trend in the use of opioids and non-opioids analgesics after 2013, nor in opioids and non-opioids antitussives after 2015.

In parallel, the overall use of both opioid and non-opioid antitussives started to decrease prior to the referral on cough and cold indication in children under 18 years of age, indicating that the 2015 regulatory procedure did not have a significant impact on the prescribing patterns of alternative medicinal products in this indication.

The project proved to be a success in terms of the interactions between the three NCAs involved and EMA. This fruitful collaboration led to the development of a clear protocol and data extraction plan that were commonly applied by each analyst leading to a structured information gathering that facilitated a centralised analysis.

This exercise was very useful to identify points to consider for the improvement of the process for future EU collaborative studies.