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SCIENCE MEDICINES HEALTH

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# Extended Annex 2 - Portfolio of use cases

This portfolio provides examples of RWD studies conducted against the various use case categories during the period covered by the 1st and the 2nd real-world evidence report, from September 2021 to February 2024.

- **Design and feasibility of planned studies**

| **Use case 1 (1st report): PDCO – Prevalence of hypereosinophilia (EUPAS45202)** | |
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| **Problem statement** | The applicant for a medicinal product developed for the treatment of patients with eosinophilic asthma, requested a partial PIP waiver for children younger than 6 years of age. The applicant claimed that studies would not be feasible as the condition is too rare in this age group. Contrasting data was available indicating very low prevalence in a European database and higher prevalence (suggesting that the study might be feasible) in a US database.<br>To decide on the waiver request, the PDCO requested additional European data to better inform the feasibility of clinical trials in children with hypereosinophilic syndrome (HES). |
| **Research question/ objective** | The study aimed to describe the yearly prevalence of HES in children aged 0-5 and 6-11 years in Europe. |
| **Findings** | An analysis in IQVIA™ Disease Analyzer France and Germany showed that cases with possible HES were rare in children aged 0-5 years with an estimated yearly prevalence between 0.0 and 6.2 per million children, and no child below the age of 6 years had a confirmed HES diagnosis. Possible HES was somewhat less rare in children aged 6-11 years with an estimated yearly prevalence between 0.0 and 74.6, and a single child was identified with confirmed HES. These results were based on a paediatric population of around 30,000-60,000 children per age group per year in France and around 200,000-380,000 children per age group per year in Germany. Results of this study are consistent with the lower end of the estimates of the published literature. |
| **How was this useful?** | The results supported the applicant claims and supplemented the available scarce evidence in the scientific literature. The results supported the PDCO decision to grant a waiver for children below 6 years of age and since the analysis was performed in a short period of time, another request to the applicant could be avoided. |

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| Use case 2 (1st report): PDCO – Prevalence of palmoplantar psoriasis (EUPAS104293) | |
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| **Problem statement** | The PDCO received a request for a full PIP waiver in relation to a product intended for the treatment of palmoplantar psoriasis on the grounds that the disease does not occur in children. The PDCO asked for a study to estimate the prevalence of the condition in children in order to verify the applicant's claim. |
| **Research question** | The study aimed to describe the population level prevalence of palmoplantar and pustular psoriasis in children by age group during the last 10 years. |
| **Findings** | The prevalence of palmoplantar psoriasis in the two age groups (0-11 years and 12-17 years) was consistent across all the databases used, and typically being around 2 per 100,000 persons. The trend for prevalence of palmoplantar psoriasis over time in children seems to be stable or slightly increasing.<br>The prevalence of pustular psoriasis was highly variable between databases with no consistency between countries, age group or across time. This is suggestive of variation in coding practice, changes in diagnostic criteria or diagnostic coding. |
| **How was this useful?** | The results informed PDCO the decision making on the acceptability of a full product specific waiver for palmoplantar psoriasis. The PDCO also appreciated the analysis of the limitations of the RWD study which was helpful for the interpretation of the results. |

- **Support the evaluation of incidence and prevalence of diseases (Disease epidemiology)**

| Use case 3 (1st report): COMP – Prevalence of narcolepsy (EUPAS48036) | |
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| **Problem statement** | During the review of an initial orphan designation request for a medicinal product intended for the treatment of narcolepsy, an analysis of in-house RWD was requested to understand the evolution of the prevalence rate since the H1N1 vaccination campaign and the finding of an increased risk of narcolepsy in children and adolescents. |
| **Research question** | What is the yearly prevalence of narcolepsy between 2011 and 2019, stratified by sex and age group? |
| **Findings** | An analysis of the data available in IQVIA™ Disease Analyser France and Germany showed stable annual prevalence rates in France (between 0.77 and 0.98 per 10,000) during the observation period, whereas prevalence steadily increased over time in Germany (from 1.83 per 10,000 in 2011 to 3.16 per 10,000 in 2029). The observed rates in France were lower than the previously published prevalence of 2.1-2.6 per 10,000 persons in the literature and hence considered to be underestimated in the database. However, the findings in Germany were in line with estimates previously reported in the global literature (2.5-5 per 10,000 persons). |
| **How was this useful?** | The results provided up-to-date prevalence of narcolepsy in two European countries that was useful to support discussions during the review process. |

| Use case 4 (1st report): DARWIN EU® - Prevalence of rare blood cancers in Europe (EUPAS50800) | |
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| **Problem statement** | Substantial uncertainty surrounds the prevalence of rare blood cancers. Using real-world data, brought together as part of DARWIN EU®, we aimed to estimate the prevalence of rare blood cancers to assess whether they still meet the threshold to be classified as a rare disease. |
| **Research question** | What is the prevalence of rare blood cancers in Europe, specifically, of follicular lymphoma, diffuse Large B-Cell Lymphoma, multiple myeloma, chronic lymphocytic leukaemia, acute myeloid leukaemia and acute lymphocytic leukaemia? |
| **Findings** | As of the 1 January 2020, 5-year partial prevalence estimates for ALL ranged between 0.44 (0.44 to 0.44) and 0.65 (0.65 to 0.65) per 10,000. Estimates for AML ranged between 0.72 (0.72 to 0.72) and 1.03 (1.03 to 1.03). Estimates for CLL ranged between 2.83 (2.83 to 2.83) and 4.13 (4.13 to 4.13). Estimates |

| Use case 4 (1st report): DARWIN EU® - Prevalence of rare blood cancers in Europe (EUPAS50800) | |
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| | for DLBCL ranged between 0.47 (0.47 to 0.47) and 1.73 (1.73 to 1.73). Estimates for FL ranged between 0.90 (0.90 to 0.90) and 2.83 (2.83 to 2.83). Lastly, estimates for MM ranged between 2.15 (2.15 to 2.15) and 4.27 (4.27 to 4.27).<br>Complete prevalence was higher than partial prevalence, more than double the 5-year partial prevalence of CLL for example, while 2-year partial prevalence was substantially lower. Estimates were typically higher for older age groups except for ALL. The relationship between sex and prevalence varied depending on the study outcome. Increasing trends over calendar time were more typically seen for complete prevalence compared to partial prevalence. |
| **How was this useful?** | The study provides estimates of prevalence from five European countries to inform decision making, among others, on orphan designations for these disease areas. |

| Use case 5 (1st report): PRAC – DARWIN EU®: Use of valproate-containing medicinal products in women of childbearing potential (EUPAS50789) | |
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| **Problem statement** | Vaproic acid/valproate-containing medicines (VPA) are first-line treatment for generalised tonic - clonic seizures (epilepsy) and adjunctive therapies in other types of seizures. They are also used as second-line treatments or adjuncts for the treatment of bipolar disorder, and for migraine prevention. Valproic acid is a teratogen, with prenatal exposure carrying a substantial risk of neurodevelopmental impairment and congenital malformations in the child. Therefore, its use in women of childbearing age (WCBP) is restricted to prevent valproate exposure during conception and pregnancy. |
| **Research question** | The objectives of this study were:<br>1. To characterise the prevalence and incidence of use of valproate, valproate containing medicines, and alternative therapies among women aged 12 to 55 years of age, stratified by calendar year and age<br>2. To characterise the use of valproic acid or valproate containing medicines among women aged 12 to 55 years of age, stratified by indication, calendar year and age. |
| **Findings** | The incidence of new use of VPA amongst women 12 to 55 years decreased over the period 2010-2021 for all analysed datasets: ACI VARHA, CPRD GOLD, IPCI, SIDIAP, IQVIA Belgium LTD, and IQVIA Germany DA, from a maximum of 250 new users per 100,000 person years in 2010 to less than 89 in 2021. The median age in these cohorts of women ranged between 40 and 43 years. Healthcare utilisation was high with the median number of visits ranging between 5 in IQVIA Germany DA and 29 in CPRD. Anxiety and depressive disorders were frequent comorbidities, with 20%-39% and 16%-44% having a history of these before treatment start. The level of prescription of contraceptives was highest in CPRD GOLD, followed by IQVIA Belgium LPD, IPCI and lowest in SIDIAP and IQVIA Germany DA. Use of hormonal contraception varied greatly across age groups, with highest levels of prescriptions being observed in women between 15-39 compared to lower rates in the >50- and 12–14-year age groups.<br>At the population level, the prevalence of use of VPA among women of childbearing age has declined since 2015 in all data sources. Incidence rates declined over the same period in all four databases. Conversely, alternative antiepileptics have increased in uptake in the same period, with gabapentinoids showing a more obvious increasing trend. |
| **How was this useful?** | The study results provide recent data on drug utilisation of valproate in WCBP, further to the implementation of risk minimisation measures by the PRAC. The study can be repeated in the future, and when necessary, with an accelerated timetable due to the re-use of the existing analytical pipeline. |

| Use case 6 (2nd report): CAT FWC – Spinal muscular atrophy (SMA): natural history of disease and treatment patterns (EUPAS50476) | |
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| **Problem statement** | The natural course of SMA, diagnostic criteria and standard of care are expected to have evolved significantly since the approval of disease modifying therapies (DMTs). Recent studies have reported disease trajectories that significantly differ from the known natural history of SMA. An update on natural history of SMA would help regulators with the assessment of new therapies in this area. |
| **Research question** | The study aimed to investigate SMA patients' course of disease and standards of care delivery over time in multiple European countries including the newly available disease-modifying therapies in real-world settings. The study used patient registry data from six SMA registries. |
| **Findings** | Among the 2,188 patients with SMA across all registries overall, the greatest number of patients were identified from the Germany and Austria registry (31.8%), and the lowest from Sweden (8.0%). The breakdown for the other registries was 18.0% in the UK and Ireland, 15.9% in Czech Republic, 14.6% in Spain and 11.7% in Belgium. Among the 2,188 patients, 1,321 were classified as treated, 847 were never treated.<br>Overall, SMA type 1 represented 19.7% of patients, SMA type 2, 41.8% and SMA type 3, 35.6% of patients. There was an almost equal split between male (51.6%) and female (48.4%) patients in the overall SMA population. Registry time coverage varied with Germany, Austria registry, and UK and Ireland registries covering 15 years (2008 to 2023) while Belgium covering only 4 years (2018 to 2021). The observed duration of follow-up ranged from 42 months (in Czech Republic and Slovakia) to 104.5 months (Sweden). 1321 (61.3%) patients have been treated with at least one DMT. Among treated group, 75.9% treated at least once with Spinraza. Overall, 29.7% of patients were lost to follow-up; 55.9% being among never treated patients. |
| **How was this useful?** | Use of multiple registries in rare diseases provided complementary information and allowed analysis of an unprecedented number of SMA patients. The study showed a treatment uptake over time.<br>Once the data were analysed, the extent of missing data was important for many variables and was notable among never treated patients. In never treated patients, it may suggest a less regular and accurate follow up and/or an under report of data in such patients, alongside the fact that 55.9% of those untreated were lost to follow-up.<br>Improving the data accuracy and quality, reducing the missingness, identifying essential variables that are mandatory - e.g. registry entry date, diagnosis date, presymptomatic and others - could help greatly answering key questions for the SMA community and regulatory decision making. These different elements plead for a common dictionary for SMA Registries across Europe with Regulators. |

| Use case 7 (2nd report): PDCO – DARWIN EU – Natural history of dermatomyositis (DM) and polymyositis (PM) in adults and paediatric populations (EUPAS107454) | |
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| **Problem statement** | As part of paediatric investigation plans (PIP), the PDCO often needs to evaluate paediatric extrapolation plans. These plans outline the objectives, methodological approaches, and planned analysis of existing or to be generated data to inform decision-making on similarity of disease and response to treatment between paediatric and reference adult populations.<br>The role of RWD to potentially generate additional evidence that informs and might help reduce uncertainty around the extrapolation framework is not well known.<br>A study on the epidemiology, diagnostic criteria as well as drug utilisation in dermatomyositis and polymyositis and their juvenile forms was considered useful to help address that knowledge gap. |
| **Research question** | The overall objective of this study was to describe and characterise dermatomyositis (DM), polymyositis (PM) and their juvenile forms (JDM and JPM), in terms of prevalence, natural history of the disease, disease severity, and treatment patterns. |

| Use case 7 (2nd report): PDCO – DARWIN EU – Natural history of dermatomyositis (DM) and polymyositis (PM) in adults and paediatric populations (EUPAS107454) | |
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| **Findings** | We identified 3,969 DM patients, 2,541 PM patients, 333 JDM patients and 32 JPM patients. Most of the patients for all the conditions were women, around 60-70% in most cases, with a median age of 50-60 years old across data sources for DM and PM. JDM median age of diagnosis across data sources was around 9-13 years old.<br>Period complete prevalence of DM and PM in adults (>18 years old) increased or was stable over time in all databases. Prevalence of DM was slightly higher than PM for all databases and ranged from 7 per 100,000 in one database from Spain to 40 per 100,000 in another database from Estonia at the end of the study. Prevalence for PM at the end of the study ranged from 0.5 per million in the Spanish database to 3 per million in the Estonia database. Looking at juvenile forms, JPM was very rare, with prevalences of less than 0.05 per million children in primary care databases. JDM was slightly more frequent but still with lower incidence than adult forms, with prevalence estimates at the end of the study period ranging from 0.2 per million in a UK database (0.3 per million in a German database) to 1 per million in a French hospital database. Most of these cases of JDM occurred in patients aged 13 to 18.<br>In most databases, biomarkers such as C-reactive Protein (CRP), Erythrocyte sedimentation rate (ESR) and aspartate aminotransferase (AST) showed higher testing in the months before and after diagnosis of DM and PM. Testing of specific auto-antibodies can be seen in hospital databases. As for clinical manifestations, the highest was the occurrence of muscle pain; 14% and 15% for DM and PM, respectively. For JDM and JPM, the number of individuals with clinical manifestations and complications was less than 5.<br>Adult DM and PM showed similar patterns in treatment use. The most used drug class one month before cohort entry were glucocorticoids. Their use increased notably in the 3 months after the index date and decreased afterwards. Use of disease-modifying anti-rheumatic drugs (DMARDS) was low before index but increased in the months following diagnosis and for up to 3 years after. Some use of biologics and immunoglobulins was seen in databases with hospital information, especially in the 3 months to 3 years after diagnosis. |
| **How was this useful?** | The results of this study helped contextualise several aspects for the discussion and evaluation by the committee. Prevalence estimates for PM and DM were consistent with previous studies. The observed disease manifestations for both diseases (including muscle weakness/pain, dysphagia, and interstitial lung disease) aligned with the latest clinical criteria recognised by European and American guidelines (EULAR/ACR). Testing in contributing databases aligned with diagnostic criteria in these guidelines, including inflammation markers, liver and muscle enzymes, and specific autoantibodies observed only in hospital and biobank datasets. Treatments prescribed in European real-world data for PM/DM aligned with the recent recommendations. |

- **Drug utilisation**

| Use case 8 (1st report): SAWP - Angiotensin II receptor blocker (ARB) use in paediatric population (EUPAS104305) | |
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| **Problem statement** | In order to support a SAWP advice procedure, EMA offered to provide up-to-date data on the use of angiotensin II receptor blockers (ARBs) in children with arterial hypertension, occurrence of primary vs. secondary hypertension in children by age group as well as risk factors for this disease that would help to understand if secondary causes of hypertension are more common in younger children below the age of 6 years. |
| **Research question** | The study aimed to describe the population level prevalence of arterial hypertension in the paediatric population, the main risk factors (looking at medical history of the patients) and the use of ARBs in this population. |
| **Findings** | Most children identified in the databases (IQVIA™ Disease Analyser France and Germany and IMRD UK) with hypertension had received a diagnosis of |

| Use case 8 (1st report): SAWP - Angiotensin II receptor blocker (ARB) use in paediatric population (EUPAS104305) | |
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| | presumed primary hypertension. Only a small proportion had a diagnosis of secondary hypertension.<br>Large differences, up to around 20-fold, were identified between the databases in the yearly prevalence of arterial hypertension in children 2-17 years (in Germany around 6-7.8 per 1000 children, in the UK around 0.2-0.4 per 1000 children, and in France 0.5-0.8 per 1000 children). Prevalence increased with increasing age and was highest in children 13-17 years and lowest in children 2-5 years. Only few children with a history of arterial hypertension received treatment with an ARB. The highest proportion was observed in the UK (14.3%), followed by France (5.7%) and Germany (1.5%).<br>Risk factors for hypertension varied between the three countries, both in terms of history of diseases or conditions, and in terms of treatment with drugs that increase blood pressure. |
| **How was this useful?** | The study provided helpful insights in the use of ARBs and causes of hypertension across different paediatric age groups. |

| Use case 9 (1st report): DARWIN EU® - Use of Antibiotics in the 'Watch' category of the WHO AWaRe classification (EUPAS103381) | |
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| **Problem statement** | The inappropriate use of antibiotics can lead to the development of antimicrobial resistance (AMR). The WHO "Watch list" includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. |
| **Research question/ Objectives** | The objectives of this study were to investigate the incidence and prevalence of use of antibiotics (from the WHO Watch list) and to explore duration of antibiotic use as well as indication for antibiotic prescribing/dispensing. |
| **Findings** | This study included five data sources from the Netherlands, United Kingdom, Spain, Germany and France. 10Amongst the listed antibiotics, 78 were prescribed in at least one of the data sources during the study period. Of the prescribed antibiotics, few had an incidence rate > 100/100,000 person-years (PY). Those antibiotics with the highest incidence rates were the same within the databases with, for instance, high prescribing (amongst top 3) of ciprofloxacin in all 4 primary care databases. Other drugs frequently prescribed in primary care were clarithromycin, fosfomycin and azithromycin with some variation amongst the data sources. In secondary care, higher use of ceftriaxone, vancomycin and meropenem was observed.<br>In some databases, an increase in incidence rate over time was observed for ceftriaxone, cefuroxime, piperacilline-tazobactam and vancomycin. For azithromycin, different patterns were observed by database with an increase in IMASIS (ES) and SIDIAP (ES) up to 2018 and 2020 respectively, a decrease in IPCI (NL) and stable use in CPRD GOLD (UK) and CHUBX (FR). A decrease or steady state in incidence rate was observed for the fluoroquinolones. Other antibiotics for which the incidence rate clearly decreased over time were pheneticillin, oxytetracycline, erythromycin and clarithromycin. The prevalence analysis was in line with the incidence rates with highest use for azithromycin, ciprofloxacin, clarithromycin, and fosfomycin.<br>Antibiotic use was lower in children than in adults and use increased with age. For some of the antibiotics, use was also high in children or young adults such as macrolides, second generation cephalosporins and tetracyclines. In primary care databases, the median duration of treatment ranged around a week and was shorter in hospital databases. With regard to the indication of use, there was a high proportion of prescriptions/dispensing with unknown indication (i.e., presence of a disease code but not belonging to any of the infection classes that had been generated) or missing indication (no disease code around the prescription/dispensing). |

| Use case 9 (1st report): DARWIN EU® - Use of Antibiotics in the 'Watch' category of the WHO AWaRe classification (EUPAS103381) | |
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| **How was this useful?** | The study provides important data on the long-term trends in utilisation of many antibiotics at risk of AMR, spanning primary and secondary care settings in five European countries over 10 years. The analysis can be repeated with an accelerated timetable with additional antibiotics and additional data sources, as and when necessary to inform regulatory decision making.<br>PRAC welcomed the utillity of the results as additional evidence from European countries in the monitoring of antibiotics use as part of the work on antimicrobial resistance, allowing supervision of antibiotics across healthcare settings and countries. PRAC considered these results in the context of the ongoing review of the EMA commissioned impact study on fluroquinoloones use after the referral (EUPAS37856) see section 3.4.4. In addition, the CMDh, the Infectious Diseases Working Party (IDWP), and members of the joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) showed great interest in the study results and possible future repititions. |

| Use case 10 (2nd report)PDCO – DARWIN EU – Treatment patterns of drugs used in adult and paediatric population with systemic lupus erythematosus (SLE) (EUPAS106436) | |
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| **Problem statement** | PDCO noted that there are several products targeted to treat paediatric lupus in the pipeline and the conduct of clinical trials in the paediatric population is hampered by competitive recruitment. As an example, belimumab was recently authorised for treatment of SLE above 5 years but it is not yet clear what the uptake is in clinical practice. Besides it would be important to understand the overall current treatment patterns in paediatric SLE and how it differs from adults. |
| **Research question** | The study aimed to describe demographic and clinical characteristics of patients with SLE and also the treatment patterns after diagnosis, both in paediatric and adult population. |
| **Findings** | We included between 699 and 5,964 patients for the new diagnosis cohort, out of which between 13 and 255 paediatric patients.<br><br>In the paediatric SLE cohort, 66% to 83% were female, with median age of 12 to 16 years. The most common comorbidities were asthma (6-15%), pneumonia (10-13%), anxiety (8-13%), and other autoimmune disease (3-16%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (35-38%) and systemic antibacterials (25-45%). In the adult SLE cohort, 80% to 88% were female, with median age of 49 to 54 years. The most common comorbidities were other autoimmune disease (9-35%), hypertension (15-27%), anxiety/depressive disorder (6-27%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (13-57%) and systemic antibacterials (8-53%).<br><br>Among the paediatric cohort, the most frequent treatments within the first year of diagnosis were hydroxychloroquine (9-62%), glucocorticoids (12-62%), and mycophenolate mofetil (5-46%) across all databases. Among the adult cohort, the most frequent treatments within the first year of diagnosis were hydroxychloroquine (13-49%) and glucocorticoids (18-42%).<br><br>In paediatric patients using hydroxychloroquine, median duration was 8 to 501 days, median initial daily dose ranged from 199 to 300 mg, median cumulative dose ranged from 20,000 to 116,600 mg. For prednisone/prednisolone, median duration was 13 to 246 days, median initial daily dose ranged from 10 to 60 mg.<br><br>In adult patients using hydroxychloroquine, median duration was 4 to 485 days, median initial daily dose ranged from 13 to 400 mg, median cumulative dose ranged from 600 to 130,051 mg. For prednisone/prednisolone, median duration was 4 to 111 days, median initial daily dose ranged from 2 to 40 mg. |

| Use case 10 (2nd report)PDCO – DARWIN EU – Treatment patterns of drugs used in adult and paediatric population with systemic lupus erythematosus (SLE) (EUPAS106436) | |
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| **How was this useful?** | The study confirmed that the characteristics of SLE patients in both paediatric and adult cohort were similar with respect to majority being female, and frequently used medications. As expected, the most frequent treatments were hydroxychloroquine and glucocorticoids in both groups, with a higher proportion of these treatments being used in paediatric patients, as adults were treated with a wider range of treatments such as methotrexate.<br>The low number of paediatric patients with SLE and especially hospitalised patients with SLE precluded full details on treatment patterns and we had only limited insight into belimumab and rituximab use. |

- **Safety studies**

| Use case 11 (1st report): PRAC - Immune thrombocytopenia in children receiving tetravalent vaccines (EUPAS104290) | |
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| **Problem statement** | The combined vaccine diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed), also referred to as DTaP-IPV, is indicated for primary vaccination in infants and for booster in children who have previously received a primary vaccination. The diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed), reduced antigens content, also referred to as TdaP-IPV, is indicated for re-vaccination of children (≥4 years). Further to a signal of immune thrombocytopenia (ITP) with these combined childhood vaccines, a RWD study was conducted to support the related PRAC assessment. |
| **Research question** | The study aimed to describe: (a) the use of the vaccines in the general population and changes over time, and (b) incidence rates for ITP in the general and exposed population across three European databases: IMRD UK, IQVIA™ Disease Analyser France and Germany. |
| **Findings** | Children 0-2 years and 3-6 years had the highest population rates of immune thrombocytopenia in the main analysis in all three databases. In IMRD UK database, most children vaccinated with DTaP-IPV or TdaP-IPV were 3-6 years of age. During 90 days of follow-up a higher-than-expected incidence of immune thrombocytopenia was observed in vaccinated children in this age group, which could support the possibility that immune thrombocytopenia could be an adverse event of the vaccines. However, alternative explanations cannot be ruled out. Similar findings were not observed in this age group in Germany or France databases, but more vaccinated children in Germany and France were in the older age groups 7-11 years and 12-17 years. |
| **How was this useful?** | The study results were taken into account during the review of the signal. While the PRAC noted the higher incidence of ITP in vaccinated children 3-6 years of age, in absence of a comparative analysis of exposed versus unexposed subjects (which was not possible since a meaningful unexposed cohort could not be identified), this finding was not considered to support a causal association. This was supported by an EudraVigilance analysis (EVDA) which showed that the vast majority of ITP cases occurs within the age group 2 month to 2 years. |

| Use case 12 (1st report): PRAC – Comirnaty and vulval ulceration (EUPAS50609) | |
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| **Problem statement** | During routine signal detection, cases of genital ulceration (including vulval ulceration, vaginal ulceration, vulvovaginal ulceration, genital ulceration) in close temporal association to Comirnaty vaccination were identified. To support the assessment of a potential causal relationship, a RWD study was conducted using the primary care databases available to EMA. |
| **Research question** | The objectives of the study were to: (a) describe the use of the vaccine in the general population, and (b) estimate incidence rates of vulval ulceration in the |

| Use case 12 (1st report): PRAC – Comirnaty and vulval ulceration (EUPAS50609) | |
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| | general and exposed female population. In addition, a self-controlled case series (SCCS) was conducted to further explore a possible association. |
| **Findings** | The study was conducted in IMRD UK and THIN® Spain, which had sufficient exposure data. The study found no difference in post-vaccination incidence rates of vulval ulceration compared to the background incidence rates either 30 or 90 days after receiving the first dose of Comirnaty vaccine, or after receiving the second or third doses. Similar results were obtained for other COVID-19 vaccines (Spikevax and Vaxzevria). The SCCS analyses also found no increase in the incidence rate of vulval ulceration in the period after vaccination.<br>However, confidence intervals of the incidence rates were relatively wide due to a limited number of follow-up years in each stratum analysed. This implies that the study is lacking power to provide an adequate precision in the estimates. |
| **How was this useful?** | The study results were considered helpful in absence of reliable background incidence in literature, which made an O/E analysis unfeasible. While likely underpowered (limited number of follow-up years), the study helped putting into perspective the reporting rate of vulval ulceration after vaccination and supported the PRAC conclusion that at the moment there is not sufficient evidence to conclude a causal association between vulval ulceration and Comirnaty exposure. |

| Use case 13 (1st report): PRAC - Cutaneous T-cell lymphomas in patients with severe atopic dermatitis (EUPAS50516) | |
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| **Problem statement** | During the assessment of a PSUR for dupilumab (Dupixent) the PRAC noted an increased reporting rate of cases of cutaneous T-cell lymphoma (CTCL). It is however also known that CTCL is more common in patients with atopic dermatitis (AD), which is one of the approved indications for Dupixent. While a study on the association of CTCL and use of Dupixent was not feasible with the primary care databases available to EMA (due to insufficient outcomes being recorded for exposed patients), an alternative analysis of cases occurring in the general population and patients with (severe) AD was possible. |
| **Research question** | The study aimed at describing the population incidence rates of CTCL, patient-level incidence rates of CTCL following diagnosis of AD, and patient-level incidence rates of CTCL following treatment for severe AD. Severity of AD was defined based on use of systemic immunosuppressive medicines. The study was designed to match as closely as possible a study presented by the marketing authorisation holder using OPTUM, a large claims database in the United States. |
| **Findings** | Analyses using IMRD UK and IQVIA™ Disease Analyzer Germany showed that the incidence rate of CTCL was higher in patients with AD diagnosis in comparison to the general population (four-fold in the UK and seven fold in the German database, which also includes data from specialist practices). In the UK, event rates in patients with AD who initiated treatment for severe AD were also higher compared to all subjects with AD (around three-fold higher in UK). No difference was seen for patients with AD versus severe AD in Germany. |
| **How was this useful?** | The EMA study confirmed the findings of the OPTUM study which also indicated high incidence of CTCL in particular in patients with severe atopic dermatitis irrespective of treatments received. The results helped the PRAC reach the position that most cases of CTCL may be explained as misdiagnosis of AD, coexistence of AD and CTCL, or as a consequence of natural evolution of prior long-standing AD and that currently no causal association between dupilumab treatment and CTCL could be established based on the overall evidence. |

| Use case 14 (1st report): CHMP – DARWIN EU®: Serious adverse events in patients with severe asthma (EUPAS103936) | |
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| **Problem statement** | During the evaluation of the safety results of a clinical trial in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to |

| Use case 14 (1st report): CHMP – DARWIN EU®: Serious adverse events in patients with severe asthma (EUPAS103936) | |
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| | contextualise these differences, a non-interventional study was requested to generate background rates of selected health outcomes in patients with severe asthma, with a disease definition that follows recently conducted clinical trials. The results of this study may inform future drug-related safety assessments in severe asthma population. |
| **Research question** | The objectives of this study are:<br>(i) To estimate the rate of mortality due to any cause stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021.<br>(ii) To estimate the rate of mortality due to fatal infections stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021.<br>(iii) To estimate the rate of mortality due to cardiovascular events stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021.<br>(iv) To estimate the incidence rate of serious cardiovascular events (but not necessarily leading to death) stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021 |
| **Findings** | The study is ongoing |
| **How was this useful?** | The study is ongoing |

| Use case 15 (2nd report): PRAC – In-house – Incidence rates of pemphigus and pemphigoid following COVID-19 vaccines (EUPAS50715) | |
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| **Problem statement** | During routine signal detection activities, cases of pemphigus and pemphigoid in close temporal association to the Comirnaty, Spikevax and Vaxzevria vaccinations were identified in EudraVigilance and the scientific literature. To support assessment of this signal, an in-house study was proposed to generate estimates on incidence rates for pemphigus and pemphigoid in the general and vaccine-exposed population across those electronic health record databases available within the Agency with data on COVID-19 vaccines. |
| **Research question** | This study aimed to describe:<br>1. Comirnaty, Spikevax and Vaxzevria vaccine exposure: overall and stratified by sex, age, and year;<br>2. Incidence rates of new onset pemphigus or pemphigoid in the general population: overall and stratified by sex, age, and year;<br>3. Incidence rates of new onset pemphigus or pemphigoid following exposure to Comirnaty, Spikevax or Vaxzevria vaccines stratified by number of doses.<br>In an exploratory analysis, a Self-controlled Case Series (SCCS) design was used to investigate whether there is an association between exposure to COVID-19 Vaccines and pemphigus/pemphigoid. |
| **Findings** | Description of the vaccine coverage in Spain and the UK was in line with expectation. Differences in the post-vaccination standardised incidence rate for pemphigoid or pemphigus were observed in the UK but not Spain when compared to a historic background population for Comirnaty and Vaxzevria vaccines. An association between exposure to Comirnaty and increased relative incidence of pemphigoid or pemphigus was observed in just one sensitivity analysis. Similar associations were found for Spikevax in Spain and for Vaxzevria, but all results had wide confidence intervals. |
| **How was this useful?** | When considering the totality of the available evidence, the Rapporteurs concluded that that there was insufficient evidence to establish a causal association for all three vaccines. However, it was decided that further monitoring was warranted with ongoing reviews for all new emerging data on pemphigus and pemphigoid after all three COVID-19 vaccines. The in-house study offered supportive evidence that was highly appreciated. |

| Use case 16 (2nd report): ECDC/ETF – FWC – Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 years in the Nordic countries (EUPAS48979) | |
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| **Problem statement** | Following safety concerns about myocarditis and pericarditis with Comirnaty and Spikevax vaccines, PRAC concluded in July 2021 that these events can very rarely occur and recommended listing them in the Product Information (PI) of the two vaccines. Concerns regarding the risk of vaccine-associated thromboembolic events in adults were raised in relation to Vaxzevria and Jcovden: in April 2021, PRAC concluded that a causal relationship between both vaccines and thrombosis in combination with thrombocytopenia (TTS) was at least a reasonable possibility, resulting in the update of the PI. This study was initiated to better characterise the risk of these outcomes in children and adolescents, both after vaccination and after COVID-19 infection. |
| **Research question** | The purpose of the study was to assess the association between COVID-19 vaccines and paediatric safety outcomes in children/adolescents in the Nordic countries: myocarditis/pericarditis; thromboembolic and thrombocytopenic outcomes; autoimmune hepatitis, juvenile rheumatoid arthritis and Guillain-Barré syndrome juvenile rheumatoid arthritis, multiple sclerosis and type 1 diabetes. |
| **Findings** | The study included 5,098,625 subjects aged from 5 to 19 years from Denmark, Finland, Norway and Sweden between Jan 2021-Oct 2022. Myocarditis, pericarditis, and thromboembolic events were rare after vaccination with Comirnaty. An association between Comirnaty and myocarditis was observed in the 28-day main risk period after 1 dose (RR 2.75, 95% CI, 1.92-3.95), 2 doses (RR 2.81, 95% CI, 1.94-4.07), and 3 doses (RR 5.30, 95% CI, 2.24-12.53) in contemporary cohort analyses. An association with pericarditis was observed in the 28-day main risk period after 2 doses (RR 2.58, 95% CI, 1.44-4.63) and 3 doses (RR 6.24, 95% CI, 0.81-47.85). There was no robust association with new onset of autoimmune hepatitis, Guillain-Barré syndrome, or type 1 diabetes, as well as with flares of juvenile rheumatoid arthritis, multiple sclerosis and type 1 diabetes. |
| **How was this useful?** | The study generated reassuring evidence on the safety of COVID-19 vaccination in children and adolescents, in which serious adverse events were very rare, and provided important methodological considerations to support the planning of future safety studies with immune-mediated outcomes and the evaluation of the evidence from such studies. |

| Use-case 17 (2nd report): PRAC – in-house – Association between exposure to GLP-1 receptor agonists and risk of suicide-related and self-harm-related events (EUPAS1000000052) | |
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| **Problem statement** | A safety signal concerning a potentially increased risk of suicidal ideation and self-injurious ideation associated with the use of GLP-1 receptor agonists (GLP-1a) semaglutide and liraglutide was raised by the Icelandic Medicines Agency after the review of 3 individual case reports. Liraglutide and semaglutide are both authorized for controlling type-2 diabetes mellitus (T2DM) as well as for weight management in obese individuals, while other GLP-1a are only recommended for T2DM. Both T2DM and obesity are potential risk factors for depression and suicidality. The biological mechanism by which GLP-1a could modify the risk of self-harming/suicidal ideation is not clear. The PRAC requested MAHs to review available evidence for all members of the GLP-1a class. In parallel, the EMA conducted an observational new-user, active comparator cohort study to estimate the causal association between GLP-1a and the risk of self-harming and suicidal ideation in T2DM. |
| **Research question** | To compare the incidence of self-harming and suicidal ideation between a cohort of T2DM patients who initiated GLP-1a and a cohort of T2DM patients who initiated SGLT-2 inhibitors (SGLT-2i) without having used any drug from these classes previously. |
| **Findings** | The study used data from IQVIA™ Medical Research Data (IMRD) UK. The unadjusted analysis showed a ~60% higher incidence rate of self-harming |

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| | /suicidal ideation among diabetic GLP-1a initiators compared to SGLT-2i initiators in both intention-to-treat analysis (where patients in both cohorts were followed regardless of discontinuing or switching the baseline treatment) and on-treatment analysis (where patients were censored at baseline treatment discontinuation or switch to the comparator treatment). The difference could be explained by a higher incidence of obesity and psychiatric disease history (including depression) among GLP-1a initiators, since after adjusting for baseline differences between treatment cohorts, the contrast dropped very close to the null (hazard ratio ~1.1, with a lower 95% confidence limit ~0.8). Several sensitivity analyses, where the definition for treatment discontinuation was changed and adjustment for post-baseline selection bias was applied, were consistent with the main analysis. |
| **How was this useful?** | The EMA study results were included in the signal assessment report and were mostly in line with other findings presented in the report. The conclusion of the report was that the combined evidence does not support an increased risk of self-harming/suicidal ideation associated with GLP-1a treatment and no update to the product information is warranted. See also PRAC meeting highlights, April 2024. |

| **Use-case 18 (2nd report): ECDC/ETF, PRAC, PDCO – FWC – Safety monitoring of COVID-19 vaccines in European countries (*Covid-Vaccine-Monitor - CVM*) (EUPAS39798, EUPAS42504, EUPAS42467)** | |
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| **Problem statement** | Large scale COVID-19 vaccination campaigns started to be rolled out across Europe in January 2021, triggering the need for comprehensive safety monitoring to complement routine pharmacovigilance activities and non-interventional studies conducted by Member States and vaccine manufacturers, as well as the need for readiness to address emerging safety concerns. This led EMA to support a large, 2-year COVID-19 vaccine safety research programme embedding: prospective and retrospective evidence generation; a framework for the assessment of safety signals including data sources across Europe; and methodological research. |
| **Research questions** | 1) Cohort-event monitoring to generate incidence rates of solicited and unsolicited suspected adverse drug reactions (ADRs) reported by vaccinated persons through active prospective surveillance in general population and special populations (pregnant/lactating persons, children/adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection)<br>2) Secondary use of EHR data from 9 data sources in 5 countries were used to evaluate the following issues:<br>• Incidence of multi-inflammatory syndrome (MIS) pre/post COVID-19 vaccination in children<br>• Association between COVID-19 vaccines and myocarditis/pericarditis (to contribute to signal evaluation/PRAC).<br>• Incidence of COVID-19 disease by severity and vaccine uptake in paediatric populations (to support PDCO assessment of PIPs for therapeutic products for paediatric patients with COVID-19 symptomatic infections) |
| **Findings** | 1) Cohort-event monitoring (primary data collection)<br>Results provided safety evidence after primary and 1st booster vaccination, combining self-reported data from 642,632 vaccinees in 13 countries The proportion of reported serious ADRs and AESIs was low (<0.9%) across the different cohorts and vaccine brands. Solicited ADRs were common (reported in >50% of the population), especially injection site reactions. Results were in line with data from clinical development and confirmed the overall safety profile of the vaccines.<br>2) Secondary use of data<br>a. The multisystem inflammatory syndrome(MIS) analyses included 650,731 children aged 0-17 years. For data sources lacking MIS information, Kawasaki disease (KD) codes were used. KD and MIS were both very rare, and no post-vaccination cases were observed in the study period Jan |

| Use-case 18 (2nd report): ECDC/ETF, PRAC, PDCO – FWC – Safety monitoring of COVID-19 vaccines in European countries (*Covid-Vaccine-Monitor - CVM*) (EUPAS39798, EUPAS42504, EUPAS42467) | |
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| | 2020-Oct 2021 (where only few children were vaccinated). KD incidence increased >10-fold after COVID-19 diagnosis. Results updated in 2023 confirmed the very rare incidence of MIS. It is recommended to combine KD and MIS codes due to the challenges of estimating MIS incidence with specific codes.<br>b. Myocarditis/pericarditis: >35 million individuals were included (57,4% received at least one COVID-19 vaccine dose). Baseline incidence of myocarditis was low. Myocarditis incidence rate ratios(IRR) were elevated after vaccination in those aged <30 years, after both Pfizer vaccine doses (IRR = 3·3, 95%CI 1·2-9.4; 7·8, 95%CI 2·6-23·5, respectively) and Moderna vaccine dose 2 (IRR = 6·1, 95%CI 1·1-33·5). An effect of AstraZeneca vaccine dose 2 could not be excluded (IRR = 2·42, 95%CI 0·96-6·07). Pericarditis was not associated with vaccination in this analysis.<br>c. COVID-19 in children/adolescents: the study population comprised 4,447,460 including 368,706 at-risk with comorbidities that increase the risk of COVID-19 severe illness. Incidence of non-severe COVID-19 was highest during Omicron in Dec. 2021/Jan. 2022 (27-143 cases/100 PY). In subjects without risk factors, incidence rates varied between 70-240 cases/100 PY and dropped substantially (0-1/100 PY) for severe COVID-19 (hospitalisation, intensive care unit admission, and death after COVID-19). Severe COVID-19 accounted for <1.5% of cases overall. Understanding of COVID-19 severity in this population may contribute to Paediatric Investigation Plans for COVID-19-related or other therapeutic products in at-risk children. |
| **How was this useful?** | The project demonstrated that large EU collaborations for vaccine safety monitoring at EU level are feasible. The cohort event monitoring study allows to obtain near real-time evidence directly from vaccinated subjects, which plays an important role during public health emergencies. The *ad hoc* studies using EHR data confirmed findings from independent research, including additional evidence such as on the role of COVID-19 infection for MIS and peri/myocarditis.<br>Lessons learnt will support future pandemic preparedness and may also inform safety monitoring outside of public health emergencies |

- **Clinical management**

| Use case 19 (2nd report): CHMP – DARWIN EU – Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH) (EUPAS106052) | |
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| **Problem statement** | An application was submitted for a new marketing authorisation for a fixed-drug combination treatment of two therapies for pulmonary arterial hypertension (PAH). The applicant initially proposed a comparative effectiveness study based on their own registry datasets, but this was abandoned for technical reasons. However, the Rapporteur's team considered useful to try to perform a study in the DARWIN EU network. The objective was to describe the actual use of mono- and combined therapies in patients with PAH, specifically for combination of interest and also for the respective classes: endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE-5Is).<br>The final aim was to establish if a comparative effectiveness study could be done using DARWIN EU. |
| **Research question** | The purpose of the study was to estimate the proportion of PAH patients initiating treatment with ERAs or PDE-5Is (as monotherapy or in combination), duration |

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| | of prescription and sequences of treatments and the proportion of treated patients experiencing specific outcomes(cardiovascular hospitalisation, all-cause hospitalisation, and death) after initiating treatment with ERAs and PDE-5Is. |
| **Findings** | A study was performed in 4 countries (Estonia, France, Germany and UK). 9,474 patients with incident PAH were characterised by age, sex, symptoms, comorbidity, co-prescribed medications and use of PDE-5is and ERAs. Monotherapy was most frequent therapy (either PDE-5is or ERAs) but there was some use of the combination of other ERAs (mostly bosentan) and PDE-5Is (mostly tadalafil) was identified. The specific combination of drugs of interest was not used/prescribed in the databases. |
| **How was this useful?** | The results of the study were included in the clinical efficacy section of the assessment report as supportive evidence to complement evidence provided by the MAH and from the literature. |

| **Use case 20 (2nd report): HTA/Payers – DARWIN EU – Multiple myeloma: patient characterisation, treatments and survival in the period 2012-2022 (EUPAS105033)** | |
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| **Problem statement** | The rarity of multiple myeloma makes it challenging to have a clear picture across Europe of the characteristics of these patients at the time of diagnosis, the different therapies they receive in subsequent lines and their overall survival. The goal of this study was to inform these aspects, which are important from the point of view of HTA bodies and payers to provide context and help understand how new medicines may add value for patients. |
| **Research question** | This specific study aimed at describing demographic and clinical characteristics of multiple myeloma (MM) patients at the time of diagnosis, as well as therapies to treat MM (including combinations and sequences) and overall survival. |
| **Findings** | The study identified more than 30,000 newly diagnosed patients of MM in six databases from five different European countries (Estonia, France, Germany, The Netherlands and Spain). While the results varied across data sources, general findings included:<br>*Characterisation at the time of diagnosis:* The median age was around 70 years, with approximately half of the patients being female. The most frequent co-morbidities were hypertension, renal impairment, and hyperlipidemia. In younger age groups, the most common ones were anxiety, depression and asthma. The most frequently used co-medications were medicines for acid related disorders, agents acting on the renin-angiotensin system, and lipid modifying agents.<br>*Treatments received within one year of diagnosis:* More than 50% of patients received glucocorticoids, with dexamethasone and prednisone being the most prescribed. Other therapies included (in decreasing order of usage): proteasome inhibitors, chemotherapies, immunomodulatory imide drugs and monoclonal antibodies.<br>*Survival:* Results were quite heterogenous, with 5-year survival rates ranging from 49% to 78% across different data sources. |
| **How was this useful?** | This is the first of two use cases for HTA bodies/ payers piloting use of RWE generated via DARWIN EU. The feedback received was positive, especially regarding the speed of study execution and large amount of useful data for a rare disease, allowing to better understand what data is available and which questions can be studied via the network. It also confirmed that some information may still need to be derived from RCTs. |

- **Effectiveness**

| **Use case 21 (2nd report): ECDC/ETF – FWC – Effectiveness of heterologous and booster COVID-19 vaccination in 5 European countries, in children and adults (EUPAS47725)** | |
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| **Problem statement** | At the time of this study, evidence from studies on heterologous vaccination suggested that the combination of mRNA and viral vector vaccines produces acceptable levels of SARS-CoV-2 antibodies and a higher T-cell response, compared to homologous vaccination. However, the use of two different mRNA |

| Use case 21 (2nd report): ECDC/ETF – FWC – Effectiveness of heterologous and booster COVID-19 vaccination in 5 European countries, in children and adults (EUPAS47725) | |
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| | vaccines was less well studied. Therefore, additional real-world evidence was needed on the effectiveness of heterologous vaccination in large populations. |
| **Research question** | What is the comparative VE of completed heterologous primary schedule of COVID-19 vaccination in preventing severe COVID-19 in the general adult population, compared to a completed homologous primary schedule?<br>This study also includes other populations (adolescents), other comparisons (e.g., completed heterologous primary schedule vs. no vaccination; completed homologous primary schedule vs. no vaccination; completed primary schedule plus booster vs. completed primary schedule only), other outcomes (COVID-19 related death, non-severe COVID-19) and other time periods (to explore waning of effectiveness over time). |
| **Findings** | The study used data sources from Italy, Spain, the Netherlands and the United Kingdom. For the main research question, only Spanish data sources could be used. No difference was found between homologous and heterologous primary regimen regarding their effectiveness in preventing severe COVID-19 in the adult population. The confidence interval included 0 in both data sources (comparative VE in BIFAP was 9% (95%CI -137; +65) and 40% in SIDIAP (95%CI -102; +82)). Results of the other analyses (other populations, other comparisons, other outcomes, and waning) can be found in the report. |
| **How was this useful?** | The results of this study supported the effectiveness of mixing different vaccine brands in the primary schedule and contributed to the overall published body of evidence on the effectiveness of COVID-19 vaccination. |

| Use case 22 (2nd report): ETF/ECDC – FWC – Effectiveness and safety of MVA-BN vaccination against mpox in at-risk individuals in the United States (USMVAc) (EUPAS104386) | |
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| **Problem statement** | After the 2022 mpox outbreak was declared a public health emergency by WHO in July 2022, the indication of the 3rd generation smallpox vaccine MVA-BN (Imvanex) was extended to the prevention of mpox in adults, based on limited clinical experience and evidence primarily derived from non-clinical data. Therefore, there was a need for effectiveness and safety data to support public health and regulatory decision-making. The USMVAc study was initiated in the US where the vaccine had large uptake (Jynneos, authorised for emergency use in August 2022). |
| **Research question** | To assess the effectiveness and safety of the MVA-BN vaccine against mpox among men-who-have-sex-with-men (MSM) and transgender women (the populations most affected by mpox) through secondary use of data aggregated from HealthVerity's administrative healthcare data between 1 April 2021 and 31 December 2022. |
| **Findings** | Fully vaccinated subjects (2 doses ≥28 days apart) were initially matched with five unvaccinated subjects on calendar date, age, US region, and insurance type using coarsened exact matching to assign an index date in the unvaccinated group. Subjects were followed from index date (14 days after the second dose) until death or data end to ascertain mpox occurrence. After propensity score adjustment, vaccine effectiveness against mpox disease was 89% (95% CI: 12%, 99%) among those fully vaccinated; 64% (95% CI: 40%, 78%) for any dose; and 70% (95% CI: 44%, 84%) for a single dose. No safety events were observed (in either vaccinated or unvaccinated comparator group) using the primary risk window of 14 days. One pericarditis adverse event was observed when the risk window was extended to 28 days. Results were consistent with existing US evidence, suggesting that completing the 2-dose schedule is associated with a reduced risk of mpox disease in MSM and transgender women. |
| **How was this useful?** | This study provided evidence to complement SEMVAc study and its additional analyses using retrospective target trial emulation (TEMVAc) once available. This combined approach is aimed at increasing the robustness of evidence generation, to ultimately contribute to the totality of evidence supporting the favourable benefit/risk profile of the MVA-BN vaccine, and support readiness in case of future mpox outbreaks. |