The year in review

July 2021–June 2022

Welcome to UMC

The last year at UMC has again seen considerable work related to COVID-19. But alongside all that we have continued to move forward in other areas. In particular, I encourage you to read about our progress with the Identification of Medicinal Products standards, online learning courses, and vigiGroup in this report. And while that has been happening, we have also been planning for the next few years, for a fit-for-purpose organisation post-COVID; using the new insights and skills developed for remote learning and work combined with how we worked before to create more value than ever.

UMC, as part of its day-to-day operations, now covers not only medicines, but also to a much greater extent vaccines. You can see that change within our services (signal assessment, education), solutions (tools and products) and research.

One of our key priorities for the next couple of years will be to further clarify the place of UMC in the global pharmacovigilance landscape, in terms of the respective roles of all the stakeholders in the field of drug risk management. With public health decision-makers and regulators on one side, and scientific experts on the other, UMC belongs very much with the latter. Our ambition is to create a body of excellence aiming to offer customised technical and scientific support to WHO and its Programme for International Drug Monitoring (PIDM), but also to develop innovative tools and solutions and conduct high-level research. A good collaboration platform with WHO, including regular meetings to enhance the alignment of our deliverables to the WHO PIDM and its members, is already in place.

All our current work and future aspirations rely on the dedicated staff across the entire UMC organisation who have responded with skill and imagination to the many scheduled and unexpected demands made on them over the year. You can find out about our work on an ongoing basis by tuning in to our social media channels for regular news.

The death last April of Sten Olsson, one of UMC's founding staff members, affected not only everyone here, but resonated around the world; so many people got in touch to share their memories and condolences. His spirit of internationalism, good humour and collaboration, based on solid scientific questioning is a legacy we are proud to inherit.

I hope you enjoy reading about UMC in the following pages, and naturally you can contact us to let us know your response to this report or to our involvement in pharmacovigilance generally. We hope to hear from, and meet, many of you over the coming year.

Birgitta Linder
Acting Chief Executive Officer

Highlights of the year

- A prototype mobile app to facilitate vaccine reporting to VigiFlow with offline capability
- 3 projects to create efficient signal detection and assessment within large case series
- UMC organised the 2021 MedSafetyWeek campaign on the theme of vaccines
- 14 signals published in VigiLyze, accessible to pharmacovigilance centres in the WHO Programme for International Drug Monitoring
- UMC's online learning portfolio extended with courses on regulatory aspects of pharmacovigilance, and Drug-Induced Liver Injury
- Mongolia, Gambia, Burundi, Central African Republic, and Guinea-Bissau full members of the WHO Programme for International Drug Monitoring
- New search and viewing functionalities in WHODrug Insight to facilitate investigation of similar product names
- Papers published on research methods and new signals
- Pharmacovigilance course training materials updated and offered to a greater number of national centre staff
- Resumption of face-to-face WHODrug user group meetings
- An upgrade for VigiAccess
- VigiBase passed 30 million ICSRs
- Refinement and real-world use of our vigiGroup cluster analysis method for case series identification in VigiBase
- Increased audience for MedSafetyWeek, *Uppsala Reports* magazine, and Drug Safety Matters podcast

Resources for pharmacovigilance practice

UMC provides resources for pharmacovigilance practice via access to information as well as tools and services for members of the WHO PIDM and the wider pharmacovigilance community. This allows countries to transform data into improved clinical practice. UMC develops and spreads knowledge about scientific methods and best practices, and provides guidance on the use of data management and analysis tools.

VigiBase

VigiBase is the unique WHO global database of reported potential side effects of medicinal products, and is continuously updated. Alongside its data management and quality assurance tools, the VigiBase system is linked to standard international medical and drug classifications. These enable structured data entry, retrieval, and analysis at different levels of precision and aggregation – vital for effective and accurate analysis. Member countries of the WHO Programme for International Drug Monitoring (WHO PIDM) have been submitting reports to VigiBase since 1968.

VigiFlow

VigiFlow is a web-based pharmacovigilance management system with streamlined easy-to-follow workflows that use integrated standardised medical terminologies such as WHODrug Global and MedDRA. Many members of the WHO PIDM use VigiFlow as their complete pharmacovigilance system, or part of such a system. Workflow support is aligned to pharmacovigilance processes to optimise collection, triage, and assessment of cases. Workloads can be allocated by delegating cases to pharmacovigilance units within a national network.

VigiLyze

VigiLyze is a signal detection and management tool that uses insights into the safer use of medicines from members of the WHO PIDM as a starting point for efficient quantitative signal detection. It supports national signal management processes, including qualitative assessments.

An important new project

The Identification of Medicinal Products (IDMP) standards developed by the International Organization for Standardization aims to create a universal framework of structured, coded data that uniquely identify and describe all key aspects of medicinal products. As the WHO Collaborating Centre for International Drug Monitoring, UMC has been proposed as the global maintenance organisation for Pharmaceutical Product Identifiers (PhPID), with the goal of generating and publishing unique identifiers. This requires expertise in handling global drug information, in collaboration with stakeholders around the world. In October 2021, UMC was a founding member of the working group for global implementation of the IDMP standards and maintenance of global identifiers.

In parallel, the UNICOM project – "Up-scaling the global univocal identification of medicines" – is an EU initiative for implementing IDMP standards. UMC has been involved in UNICOM deliverables to use IDMP for coding of ICSRs and for medicinal product dictionary use, and has presented global substance identifiers and PhPID at webinars to stakeholders.

VigiBase contained (30 June 2022)

31,326,511

ICSRs

out of which

4,928,051

ICSRs were from **low- and middle-income countries**

Working with WHO

The UMC Signal Management team has observer status in the Advisory Committee on Safety of Medicinal Products (ACSoMP) and Global Advisory Committee on Vaccine Safety (GACVS), where it provided WHO with decision-making material within those committees. UMC staff are in regular contact with the pharmacovigilance team at WHO HQ on a range of issues including providing tools and services to existing and potential member countries, training, and signal work.

Reporting and access

Over the year, UMC developed an updated version of primary eReporting as well as an industry eReporting service with coding support for MedDRA and WHODrug to facilitate reporting and analysis at national regulatory authorities. There was new support for safety profiling via a line listing in VigiFlow and compliance with EMA's EudraVigilance, to ensure compatibility when the EMA makes E2B R3 mandatory. UMC also upgraded the publicly available summary statistics tool VigiAccess.

In the March 2022 release of WHODrug Global, three modifications to meet regulatory expectations and technical developments were rolled out:

- To accommodate a more granular naming of substances, the substance name field was extended to 250 characters.
- The casing of drug names in the C3 format was unified to standardise the appearance of drug names bearing the same drug code.
- Country codes and names were updated, to harmonise with ISO 3166-1.

Responding to users' needs, UMC created new search and viewing functionalities in WHODrug Insight to facilitate investigation of differences between similar product names, thus speeding up coding decisions and supporting the creation of customised drug groupings (CDGs).

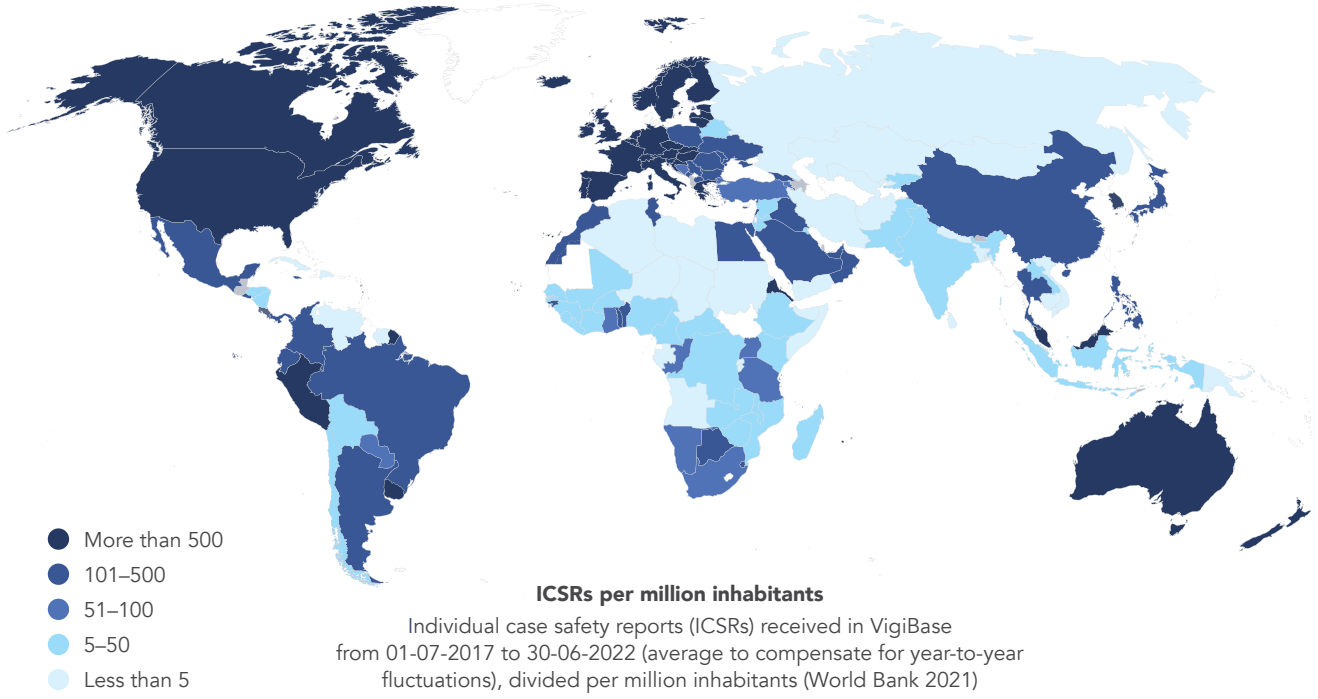
In WHODrug Koda, UMC's drug coding engine, a new version of the API was released with streamlined functionality. The output from the API now includes all available ATC codes and texts for each coded WHODrug record per the B3 format, as well as Preferred Name.

Each release of WHODrug Global Chinese is updated with new drug information in Chinese, focussing on generic synonym names. Over the year, a Chinese language version of the standardised drug groupings (SDGs) was also developed.

WHODrug User Group

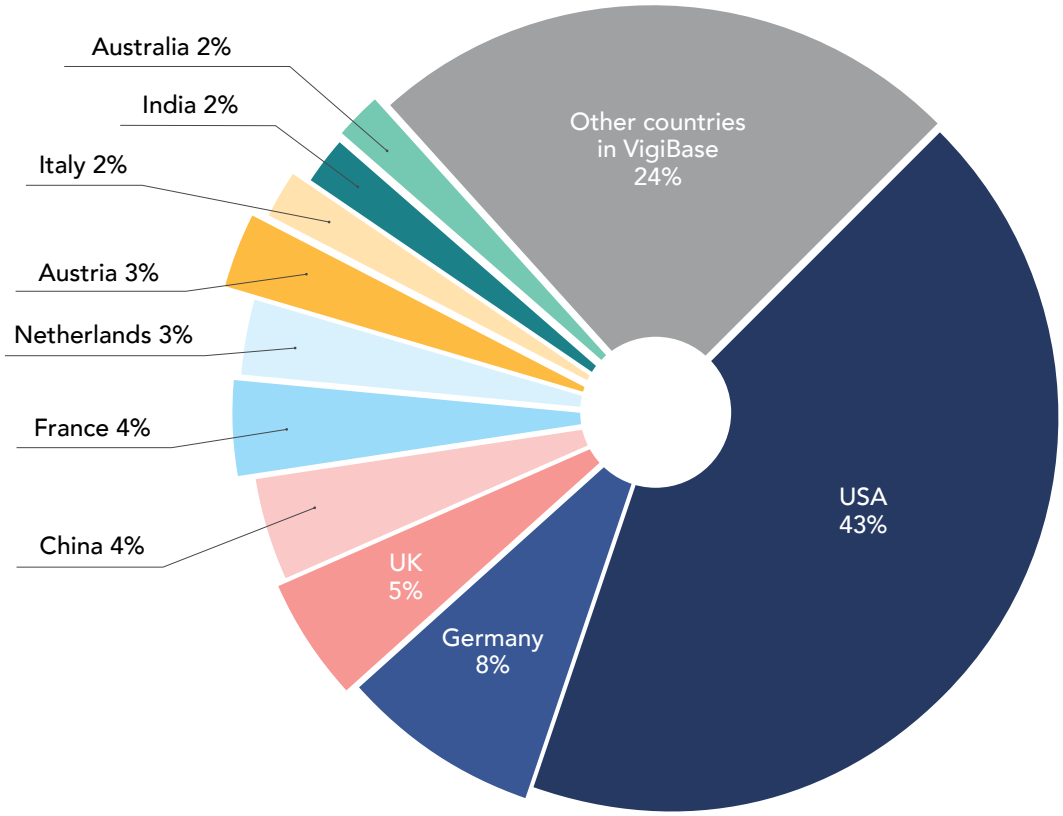
User Group meetings continued as virtual events and webcasts: three in the second half of 2021 (one specifically for Republic of Korea, one for Japan), and three in the first half of 2022 (one for India, another just for EU countries). Eleven webinars took place covering topics such as new functionality in WHODrug, SDGs, WHODrug Link Korea, WHODrug Global Chinese, and coding challenges.

Quantity of ICSR reporting



ICSRs per million inhabitants

Individual case safety reports (ICSRs) received in VigiBase from 01-07-2017 to 30-06-2022 (average to compensate for year-to-year fluctuations), divided per million inhabitants (World Bank 2021)



Country distribution for ICSRs received over the year

Country distribution in VigiBase for ICSRs received during the past 12 months, as of 30-06-2022

Scientific development

Another busy year for signals and safety monitoring of COVID vaccines, scientific method development and evaluation, and further research on cluster analysis and de-identification.

The Research department continued method development for vigiGroup to assist in signal detection work. Ongoing projects include decision support for the identification of case reports for manual review, a narrative search engine that will recognise reports with certain characteristics, and a duplicate detection tool for vaccine reports.

The WHO CC department, meanwhile, continued the safety monitoring of COVID-19 vaccines and medicines in close collaboration with UMC's external clinical experts and WHO.

Research projects

Scientists from several UMC teams worked together on three projects to develop tools for more efficient signal assessment within large case series (see under "Master theses" for the project on duplicate detection for COVID-19 vaccines). The development and application of vigiGroup has been a key focus area for UMC's researchers over the past few years. vigiGroup is used to discover distinct patterns in data from adverse event reports based on all recorded signs, symptoms, and diagnoses, and group together reports describing similar clinical conditions – offering new, complementary ways of evaluating data from such reports. UMC published the paper describing the current version of the method and its systematic evaluation in terms of stability and clinical coherence of the patterns it generates ("Consensus clustering for case series identification and adverse event profiles in pharmacovigilance"). Additional research was performed to further extend the capability to evaluate such methods and possibly improve vigiGroup, resulting in a poster at the 2022 ICPE conference and a joint paper with the Netherlands Pharmacovigilance Centre Lareb ("Post-marketing Safety Profile of Vortioxetine Using a Cluster Analysis and a Disproportionality Analysis of Global Adverse Event Reports"). Finally, staff evaluated a video abstract to communicate the methodology to a broader audience and presented at the ISoP annual meeting.

Other projects included one on the automated de-identification of case narratives, with a focus on recognition and redaction of person names, and another (published in *Drug Safety*) to evaluate UMC's drug coding engine WHODrug Koda for its coding performance on adverse event reports from VigiBase, in terms of level of automation and coding quality. Work began on two ongoing projects related to decision-support for prioritising case reports and the narratives search engine. A poster was prepared for ICPE 2022 of a scoping review of signals published in scientific and "grey" literature.

Signals

Fourteen signals were published in VigiLyze, accessible to all pharmacovigilance centres within the WHO PIDM. The majority of these focused on interactions connected to COVID-19 vaccines, and two concerned medicines. One signal was published in a scientific journal, "COVID-19 vaccines and appendicitis", and a review article was accepted for publication, "Global safety monitoring of COVID-19 vaccines: how pharmacovigilance rose to the challenge".

See page 10 for more information on efforts related to the safety monitoring of COVID-19 vaccines.

Master theses

UMC hosted several MSc thesis projects during the year: one on a duplicate detection tool for vaccine reports, "Free-text Informed Duplicate Detection of COVID-19 Vaccine Adverse Event Reports", and one on the possibility of using chemical similarity between drugs to predict label changes, where the chemical properties of drugs are typically only considered in the later phase of the signal management process. For the latter, incorporating this information earlier could complement data on disproportionate reporting to help screen for potential signals to investigate further. The results were promising, showing the highest level of performance when chemical information and disproportionality were used together. Two students on the professional Master's programme in pharmacovigilance and drug regulations at the University of Verona, Italy investigated 'The impact of web and mobile apps for spontaneous reporting'. Their preliminary study was based on comparisons of the use of the COVID-19 vaccine safety surveillance apps from Italy, Germany, and UK.

European collaboration

UMC increased its involvement in the European Health Data & Evidence Network (EHDEN), a multidisciplinary collaboration between 22 European partners from academia, industry, regulators, and others, to improve health outcomes by facilitating analysis of health data in electronic patient records. Building on previous research, UMC leads the assessment of how real-time analysis of observational data from these sources, alongside the analysis of individual case reports, may enhance signal detection and assessment. Preparations began for a "study-a-thon" in Uppsala later in 2022.

Communications, promotion and advocacy

UMC continues to take the lead in the promotion of good pharmacovigilance practice and advocacy of better communication to improve patient safety around the world.

Both the podcast and the magazine received new logos and graphic redesigns.

UMC's communications department continuously creates and delivers original content across multiple media platforms, producing ad-hoc campaigns and materials to promote emerging UMC initiatives and assist others with their communication and training needs.

Uppsala Reports magazine published articles regularly on its dedicated website and in two issues collecting features and news, sent to thousands of subscribers. The Drug Safety Matters podcast and UMC's social media channels have all increased their following and improved the quality of their output.

For the sixth year UMC organised the annual MedSafetyWeek, convening a planning team, and providing support and materials for the campaign, the theme of which was to encourage patients and healthcare professionals to report all side effects, especially those associated with vaccines. UMC invited the entire WHO PIDM network to participate, and 67 national regulatory agencies joined in along with six supporting organisations, including the European Medicines Agency, the International Society of Pharmacovigilance, and the Pan American Health Organisation. Participants shared three animations – translated into their local language and including their logo – across Twitter, LinkedIn, Facebook, Instagram, and YouTube, reaching a total of 85.9 million people. The animations were translated into 38 languages.

Web and social media

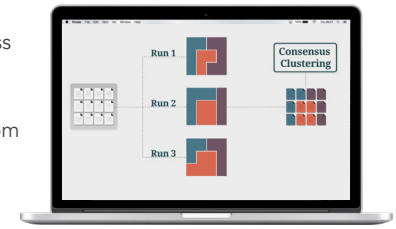
UMC's social media channels are growing steadily and have gained more than 47,000 followers across LinkedIn, Facebook, Twitter, and YouTube – an increase of 34% from the previous year.

Relevant content and regular updates to UMC's website who-umc.org have ensured a 15% year-on-year increase in website traffic, with the most visited pages relating to WHODrug, UMC's educational offerings, and VigiBase.

UMC participated in a high-level webinar series organised by the Centre of Regulatory Excellence (CoRE) at Duke NUS Medical School, Singapore. The event, "Safety signal detection and analysis for COVID-19 vaccines at the Uppsala Monitoring Centre", featured five UMC experts explaining the significance of spontaneous reporting and the role of VigiBase in understanding the safety profile of medicines and vaccines.

UMC released 10 podcast episodes. Over the year, there were 9,377 podcast downloads, on average 780 per month – double the previous year.

A digital campaign to promote UMC's new clustering algorithm vigiGroup was vital in bringing a complex scientific method to life and increasing engagement and understanding. The campaign reached over 50,000 people across our channels, with vigiGroup posts and content displaying high levels of interest and discussion. The effectiveness of a vigiGroup information video was evaluated in a survey of 80 participants from UMC's online community, with overwhelmingly positive feedback.



Internal communications

The intranet is the cornerstone of UMC's digital work environment, keeping around 100 staff updated on recent activities and new policies and providing easy access to internal documents and processes. The top news feed was regularly updated, while the team news and announcement sections had frequent notices posted directly by staff members, testifying to the value of the intranet as an information-sharing and community-building platform in which staff play an active role.

Building capacity and support for member countries

As a WHO Collaborating Centre, UMC supports WHO's overall strategies for pharmacovigilance capacity building. Education and training in pharmacovigilance concepts and practice are central to this.

UMC supports national pharmacovigilance centres in its capacity as the WHO Collaborating Centre for International Drug Monitoring. In the last year, to consolidate what UMC provides to WHO and programme members, a new department was created focused on the collaborating centre role and related tasks. Customised training aligned with current and anticipated needs, and based on the concept of learning paths, was offered, integrating the teaching of cognitive, process, and tools skills.

The WHO programme continued to grow and during the period Mongolia, Gambia, Burundi, Central African Republic, and Guinea-Bissau became full members. Many countries use UMC tools for reporting (VigiFlow) and analysis (VigiLyze).

The Signal Management and Education & Training teams fulfilled training requests from WHO for pharmacovigilance and signal detection knowledge training, delivered online to staff at WHO India and WHO HQ in Geneva.

For the 2019 face-to-face course in Uppsala, there were 30 participants from 18 countries. In contrast, since the end of 2020, after the transition from face-to-face to online learning, pharmacovigilance education has been delivered to 170 professionals from 64 countries, with courses in both English and Spanish.

Based on evaluations, the UMC annual pharmacovigilance course training materials were updated and offered to national centre staff from the autumn of 2021. The materials build on the previous annual course through six consecutive courses, both self-paced and instructor-led.

In winter and spring of 2022, the online courses were reshaped to five independent self-paced courses introducing key strategies, concepts, terminology, and tools for the effective collection, handling, and analysis of adverse event reports, and to a broader audience. These are available in English, with most in Spanish. UMC's education portfolio was extended, first with a course on regulatory aspects of pharmacovigilance, and through an online Drug-Induced Liver Injury (DILI) course, developed in collaboration with CIOMS, based on sections of a CIOMS consensus document on DILI.

UMC's new learning management system (LMS) was fully implemented to serve as a hub for all online courses. It also facilitates interactive exercises, knowledge checks (quizzes), and reflective exercises.

UMC contributed to 16 online training events, in collaboration with WHO, CIOMS, ISoP, and KIDS, among others.

PV and COVID-19 vaccines

UMC continued to develop its tools to support members of the WHO Programme for International Drug Monitoring in AEFI recording, processing, and analysis as the COVID-19 pandemic progressed.

UMC has continually monitored the ICSRs coming into VigiBase and thus the safety of medicines and vaccines globally. In response to the COVID-19 pandemic two in-depth analyses were requested by WHO regarding Guillain-Barré syndrome and Glomerulonephritis/Nephrotic syndrome connected to the COVID-19 vaccines. An urgent request from WHO concerned safety data analysis, seriousness, and fatal cases in specific batches of a vaccine.

For WHO's Global Advisory Committee on Vaccine Safety (GACVS), UMC provided materials and reports, and analysed fatal cases of myocarditis, pregnancy outcomes, menstrual disorders, and infertility for COVID-19 vaccines. For WHO's Advisory Committee on Safety of Medicinal Products (ACSoMP), in COVID-19 medical treatments, UMC provided reports on paxlovid, remdesivir, and molnupiravir, the latter focusing on serious cases. To support the monitoring of the adverse event profile of COVID-19 drugs and vaccines, related products and substances in WHODrug Global were added on a continual basis and made available daily in WHODrug Insight.

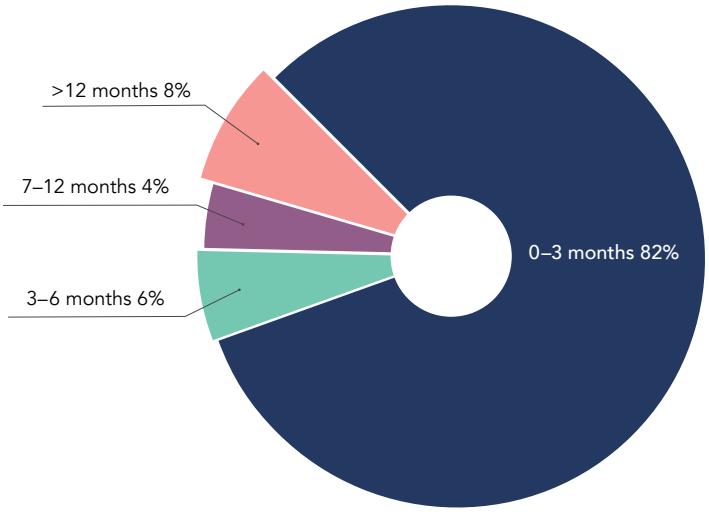
UMC worked to further strengthen its product support with three key projects, involving collaboration with WHO:

- VigiMobile, a prototype mobile app – an addition to the e-reporting suite – to facilitate vaccine reporting to VigiFlow with offline capability
- Interoperability from other immunisation systems to VigiFlow
- Development of a vaccine-specific training environment to support WHO in AEFI surveillance training

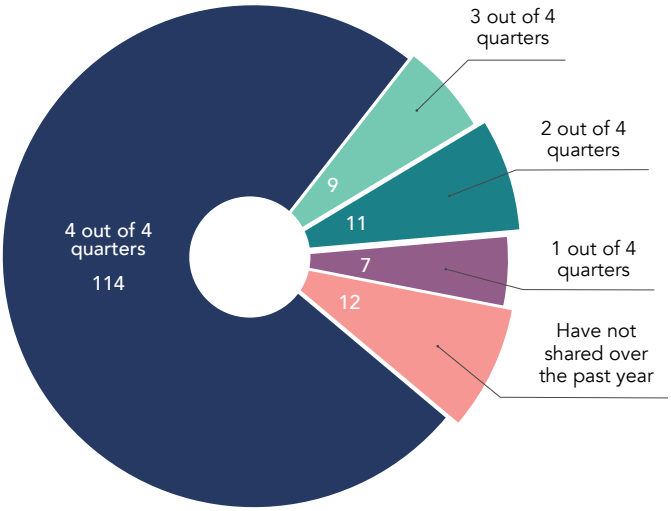
UMC staff have been involved in drafting new WHO performance indicators for countries planning to follow the Immunization Agenda 2030; UMC's role was to provide data to WHO that they will use to develop performance indicators, and compare with reporting to VigiBase based on number of Serious AEFIs per 100,000 population.

Frequency of ICSR reporting

Frequent submissions of new ICSRs are critical to detect signals and take appropriate action at an early stage. Member countries are expected to submit ICSRs to UMC on a regular basis; preferably **more than once a month**, but **at least every quarter**.

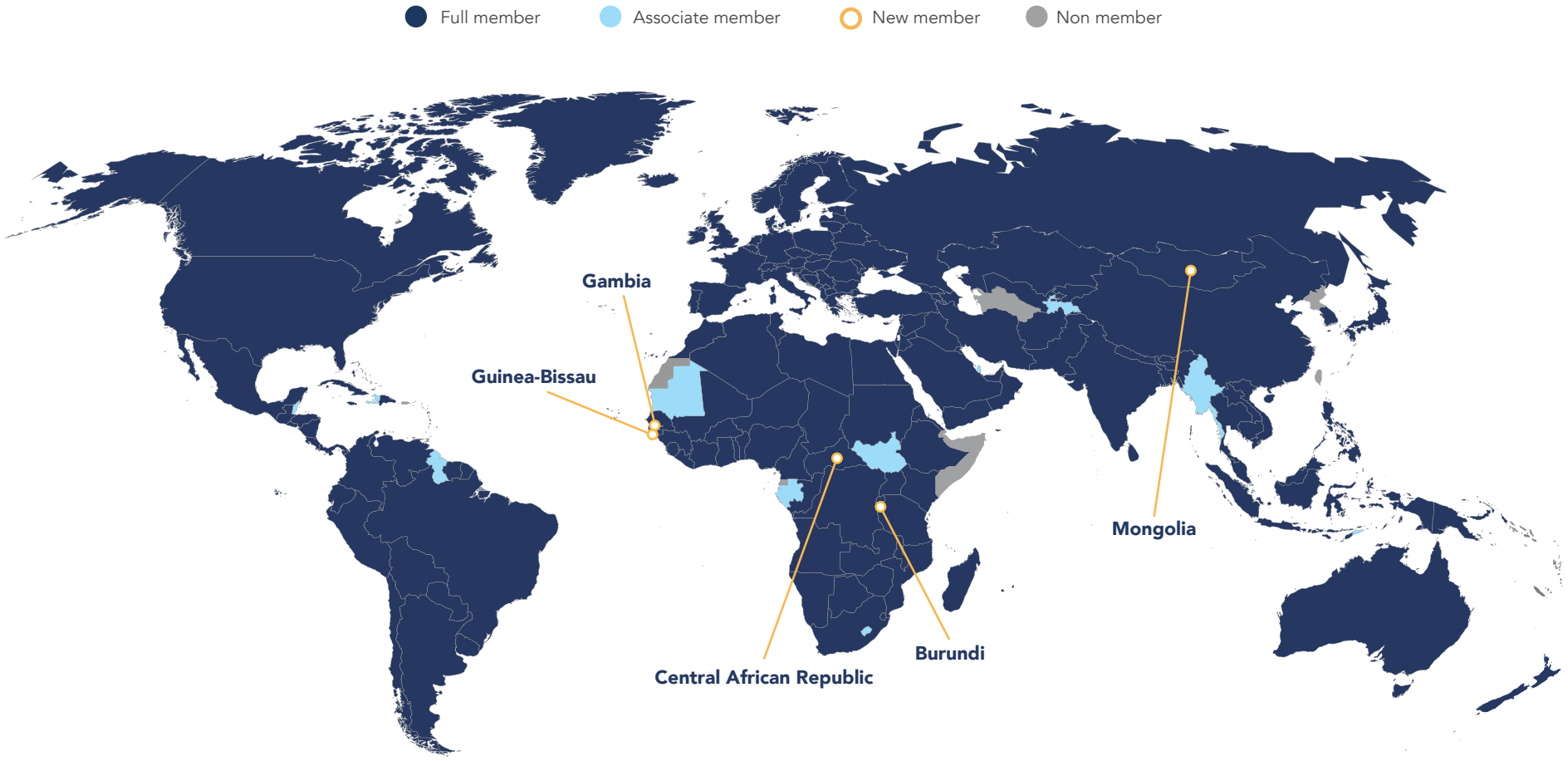


Time since last submission
Countries distributed according to time elapsed since last submission of ICSRs to VigiBase as of 30 June 2022. 81% of member countries shared ICSRs with the WHO PIDM in the last quarter.



Number of countries submitting ICSRs in VigiBase, by quarter
114 countries have shared data in VigiBase all four quarters during the period 1 July 2021 to 30 June 2022.

Members of the WHO Programme for International Drug Monitoring



A global network

Technical and operational support to member countries of the WHO PIDM is a core UMC activity, including guidance on becoming, and being, a member of the WHO PIDM. During 2021–2022 agencies from these countries joined: Mongolia, Gambia, Burundi, Central African Republic and Guinea-Bissau. Organisations joining the WHO PIDM receive an introduction to UMC pharmacovigilance tools and ongoing support. As of 30 June 2022, the WHO PIDM had 152 full members and 20 associate members.

UMC publications

Papers published in journals

Appendicitis as a possible safety signal for the COVID-19 vaccines

Vaccine: X. Volume 9, December 2021, 100122

Joseph Mitchell, Qun-Ying Yue

Consensus clustering for case series identification and adverse event profiles in pharmacovigilance

Artificial Intelligence in Medicine. Volume 122, December 2021, 102199

G. Niklas Norén, Eva-Lisa Meldau, Rebecca E. Chandler

Fatal adverse events of dabigatran combined with aspirin in elderly patients: An analysis using data from VigiBase

Frontiers in Pharmacology, section Cardiovascular and Smooth Muscle Pharmacology, 22 December 2021

Qingxia Zhang, Qian Ding, Suying Yan and Qun-Ying Yue

Post-Marketing Safety Profile of Vortioxetine Using a Cluster Analysis and a Disproportionality Analysis of Global Adverse Event Reports

Drug Safety (2022)

Corine Ekhart, Florence van Hunsel, Eugène van Puijenbroek, Rebecca Chandler, Eva-Lisa Meldau, Henric Taavola and G. Niklas Norén

Indapamide-Induced Rhabdomyolysis: An Evaluation of Case Reports in VigiBase Using the Bradford Hill Criteria

Drugs – Real World Outcomes, Vol 9, 189–198 (2022)

Qun-Ying Yue, Pia Caduff Janosa

Automated Drug Coding Using Artificial Intelligence: An Evaluation of WHODrug Koda on Adverse Event Reports

Drug Safety, Vol 45, p549–561 (2022)

Eva-Lisa Meldau, Shachi Bista, Emma Rofors and Lucie M. Gattepaille

Montelukast and Nightmares: Further Characterisation Using Data from VigiBase

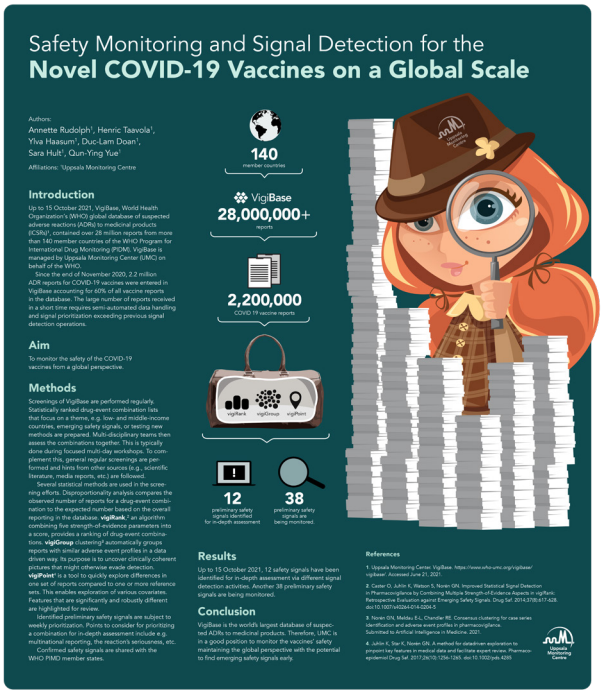
Drug Safety, Vol 45, 675–684 (2022)

Sarah Watson, Elenor Kaminsky, Henric Taavola, Marian Attalla and Qun-Ying Yue

Fatal adverse events of rivaroxaban combined with aspirin: an analysis using data from VigiBase

European Journal of Clinical Pharmacology, Vol 78, 1521–1526 (2002)

Qingxia Zhang, Qian Ding, Suying Yan & Qun-Ying Yue



Posters

Remdesivir during the COVID-19 pandemic

Elena Rocca, Oskar Gauffin, Ruth Savage, Sara Hedfors Vidlin, Birgitta Grundmark (ICPE 2021)

Montelukast and nightmare

Qun-Ying Yue, Marian Attalla, Henric Taavola, Sara Watson, Elenor Kaminsky (ICPE 2021)

Safety monitoring and signal detection for the novel COVID-19 vaccines

Annette Rudolph, Henric Taavola, Ylva Haasum, Duc-Lam Doan, Sara Hult, Qun-Ying Yue (ISoP 2021)

Exploring the safety profiles of the COVID-19 vaccines in VigiBase using vigiGroup

Nils Erlanson, Jim Barrett, Lucie Gattepaille, Carlos Melgarejo, Joseph Mitchell and Qun-Ying Yue (ISoP 2021)

AI-powered drug coding with WHODrug Koda

Eva-Lisa Meldau, Shachi Bista, Emma Rofors, Lucie Gattepaille (ISoP 2021)