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UPPSALA Reports

Strengthening Pharmacovigilance Systems in Resource-Limited Countries

TRENDING TOPICS

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A blueprint for strengthening pharmacovigilance systems in resource-limited countries burdened by poverty related diseases.

POVERTY RELATED DISEASES (PRDs) affect large parts of the population in low- and middle-income countries (LMIC) necessitating the development of new and improved medicines and vaccines to fight these diseases. In 2021 in sub-Saharan Africa (SSA), 20.1 million people were accessing antiretroviral treatment, yet HIV still accounted for 420,000 deaths.[1a] The burden of tuberculosis continued to be high with 2.5 million new cases and 501,000 deaths, and an estimated 234 million cases of malaria occurred with 593,000 deaths.[1a]

However, new medicines and vaccines are being used by patients based on limited information about their safety. Since many of the new medicines and vaccines preventing or treating PRDs will be deployed mainly in LMICs, it is vital that these countries develop robust pharmacovigilance systems to monitor their safety.

The PhArmacoVIgilance Africa – PAVIA - project aimed to improve both the National Medicines Regulatory Authorities' (NMRA) capacity to conduct pharmacovigilance and to strengthen collaboration with Public Health Programmes (PHPs) with a focus on the National Tuberculosis Programme (NTP) for reporting, sharing and analysing safety data on multidrug-resistant tuberculosis (MDR-TB) medicines. The national tuberculosis control programmes in the four project countries had started introducing new and repurposed drugs for this indication based on a limited number of small trials, partially through donations. To monitor post-introduction safety, these programmes were implementing active drug-safety monitoring and management (aDSM), a system developed and recommended by the Global Tuberculosis Department of the WHO.[2a] aDSM aimed to collect (mainly serious) adverse events related to treatment with these new and repurposed drugs, and report these within and between national tuberculosis control programmes and to the WHO but not, or not systematically, to their country's NMRA.[1b,2b,2c] The project aimed to use the NTP as a model for similar collaborations with other PHPs. Producing a blueprint[1b] for strengthening pharmacovigilance systems in resource limited countries by improving engagement with PHPs has been the single most important deliverable of PAVIA.

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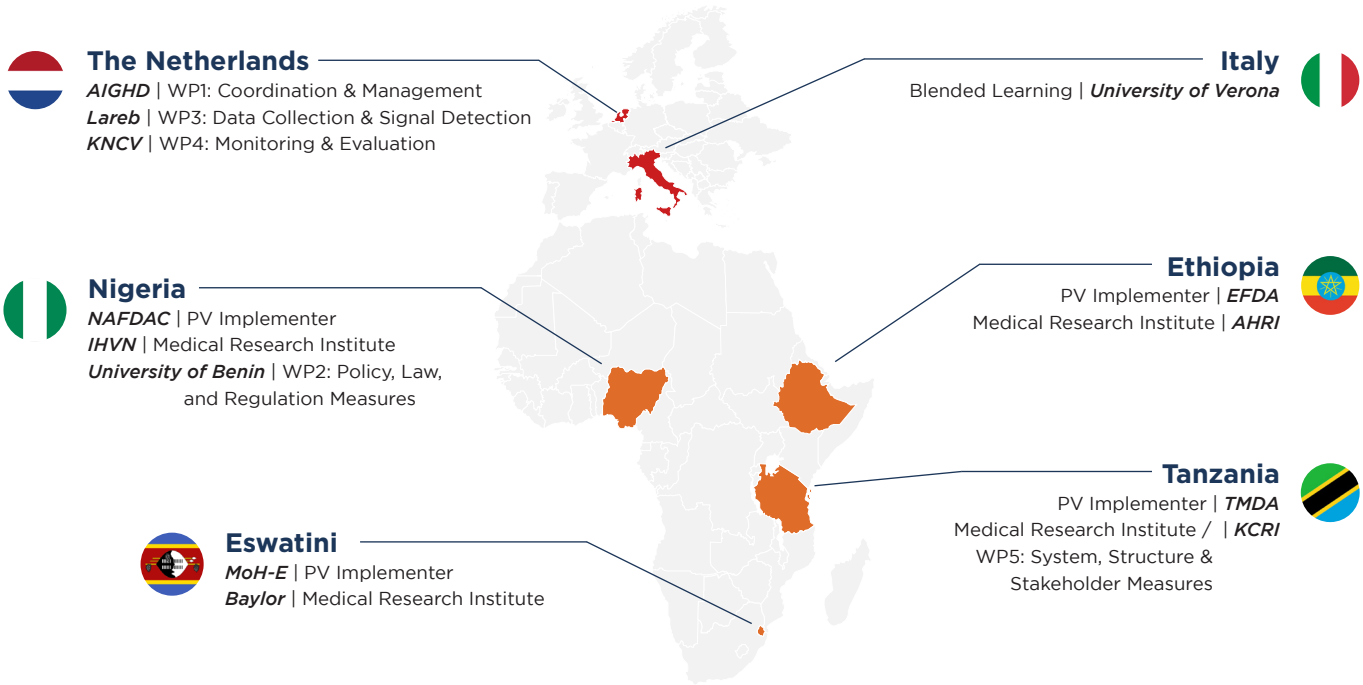
PAVIA ID

The PAVIA project, developed, implemented and evaluated in 2018-2022 in Eswatini, Ethiopia, Nigeria and Tanzania, set out to help address these issues in the African context. Funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), supported under the European Union's Framework Programme for Research and Innovation Horizon 2020, PAVIA was a collaboration of NMRAs and medical research institutes (MRIs) in these four African countries together with PV, infectious disease control and health systems expert organizations in Nigeria, Italy and The Netherlands.

The PAVIA project was structured by five Work Packages (WPs), notably the Policy, Law and Regulation Measures, Data collection and signal detection, including Data Management Measures and System, Structure, and Stakeholder Measures WPs.

PAVIA aimed to bring down hurdles both in the capacity of NMRAs to conduct PV and in the collaboration and safety reporting between PHPs and NMRAs.

Overview of PAVIA partners and their key role in the project.



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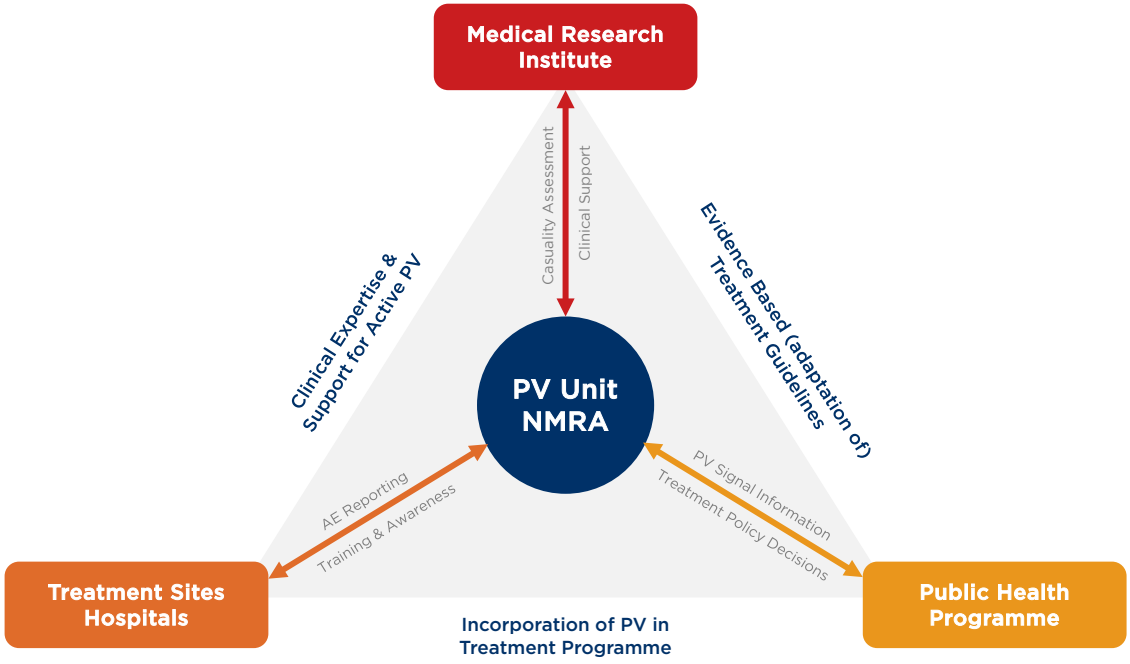
The PAVIA project established collaborative triangles within each project country, utilising the combined experience and expertise of the local NMRA, NTP and a Medical Research Institute (MRI).

PAVIA Triangle Model



What hampers NMRAs in SSA to deliver reliable PRDs benefit-risk analysis?

1. NMRAs' capacity is often restricted by various factors such as legal, financial, human resources expertise and experience, technical infrastructure for PV
2. Underreporting of adverse events incl. adverse events following immunisation (AEFIs) for vaccines, lead to limited safety data collected
3. The provision of PRDs, including vaccines, is deployed by an array of organisations such as multinational pharmaceutical companies, non-profit organizations and Foundations, Government and Public Health Agencies, Regional and International Organizations (e.g., the African Union or the World Health Organization). PRDs are generally not delivered by marketing authorization holders (MAHs), but usually by PHPs. Whereas MAHs are legally bound to systematic collection and sharing of data on the safety of their products, PHPs often are not
4. Although in some SSA countries risk-management plan requirements are defined, the regulatory framework is rather scarce in most countries, especially as regards specific requirements for post-marketing signal management.

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During the PAVIA project, a model to improve the national pharmacovigilance system in SSA & LMICs was developed to enable reliable benefit-risk analysis of PRDs by NMRAs consisting of best practices and lessons learned, as depicted in Table 1.

Table 1: Establish robust PV systems in LMICs

Best practices	Prerequisites (lessons learned) for a strong pharmacovigilance system in LMICs
Create a strong legal basis	**Dedicated PV policy and a set of laws and regulations** • A national PV system should be supported by a strong national PV centre to enable enforcement of legislation • A strong legal mandate includes the anchoring of a national PV system in Acts and Regulations • Larger countries will need to create sub-national structures to bring PV to all levels of national PHPs
Provide technical tools to improve ADR reporting	**Electronic tools, whether locally developed or sourced internationally:** • Availability and quality of internet access should be considered when developing and introducing tools • Efficient data flows may offer several options for reporting, including paper forms, mobile phone applications and web-based reports, while avoiding double reporting • Ideally PV data should be fed into a single central PV database
Set-up and implement strong processes	• Identification of safety signals and management of risks by NMRAs • Outcomes shared with PHPs to enable timely revision of treatment guidelines
Invest in training	**Dedicated training of health care workers and PV centre staff, especially with respect to aDSM, is critical** • Health care worker training should focus on improving awareness and knowledge of ADR reporting • Blended learning courses (self-learning and classroom) are effective • PV centre staff training should be tailored to the staff's needs and may focus on data analysis and risk assessment • Training should be structured to support PV system, enabling healthcare workers to identify potential drug safety issues and report these to the national PV • Provide feedback to health care workers on their ADR reports is essential
Set-up strong partnerships	**Engagement of partners, including PHPs, universities and medical research institutes, professional organisations and non-governmental organizations, is critical** • Create awareness among healthcare workers and PHP staff working on specific diseases, providing support to data analysis and reporting and conducting PV research and training

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Create a strong legal base

How decentralization might affect ADR reporting: Tanzania [1b]

To promote the importance of PV and the reporting of ADRs in particular, TMDA needed to reach individual health care professionals and patients at the local health facility level. For this reason, the PV system in Tanzania makes use of sub-national structures. The NMRA in Tanzania, TMDA, has zonal offices and each of these have a zonal PV coordinator who coordinates all PV activities in the zone, including collection and data entry of ADR reports into the Tanzanian database VigiFlow. Each zonal office is in turn responsible for a number of regional PV centres. The regional PV centres, usually incorporated in regional referral hospitals, are not part of the TMDA structure.

Revising the PV regulations to increase the responsibilities of PHPs regarding PV: Nigeria

Not all medicinal products used within PHPs are officially registered for medicinal use in the countries where they are deployed. For such products, PHPs can request a waiver from the drug regulatory authority. The Good PV Practice Regulations, prescribe clear roles and responsibilities to MAHs with respect to PV. There was, however, an issue with medicinal products deployed by PHPs that had not yet been registered in Nigeria. These unregistered medicinal products had no MAH, and, therefore, no organisation could be held responsible for fulfilling the PV obligations stipulated in the Regulation. This issue was resolved in the revised national PV policy (2020) by stipulating the following:

- It shall be mandatory for all MAHs, including all PHPs, to report ADRs
- PHPs shall appoint a Qualified Person responsible for PV (QPPV). The QPPV shall establish an effective system for detecting ADRs associated with the medicines used in their programs and reporting these ADRs to the national PV centre

As such, PHPs are now responsible for the safety monitoring of the unregistered medicinal products they deploy. The goal is to promote the importance of PV within the PHPs and increase funding for PV activities.

Provide technical tools [1b]

During the PAVIA project, Nigeria's NAFDAC has:

- Made VigiFLow their main database, replacing the old database in Excel;
- Introduced e-reporting and the MedSafety app which directly forwards reports to VigiFlow without manual data-entry;
- Removed the backlog of reports which enables real time monitoring of the safety of drugs; and
- Increased the number of reports sent to the global database at the Uppsala Monitoring Centre (80% of all reports received by NAFDAC are currently forwarded to the Uppsala Monitoring Centre).

N.B. VigiFLow is an E2B compatible database, maintained by the Uppsala Monitoring Centre. VigiFlow also supports exchange of reports with the global WHO database (VigiBase). VigiLyze is an analysis tool used to analyse the data in the VigiFlow database.

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PrimeVigilance, having a pool of SMEs around the globe and being involved in risk-based minimization of post-market safety surveillance activities from high income countries (HICs) and LICs can support SSA PHPs and new MAHs in the implementation of bespoke solutions. These solutions enable effective safety data collection and benefit-risk analyses, as well as delivery of functional PV systems with an action-based feedback loop to patients and healthcare providers (HCPs).

The process consists of a systematic analysis of the distribution chain, outlining reporting responsibilities across different regions or countries, harnessing the Smart Safety Surveillance approach [3, 5] and raising awareness of the importance of safety data collection through tailored training offered to HCPs, patients & industry.

PrimeVigilance has been actively involved in developing education materials and conferences in LICs regions, namely in North Africa and Latin America, and can consolidate similar campaigns in SSA.

Our experts:

- assess the global dynamics that impact organisations e.g., biosimilar and vaccine clinical development, licensure evergreen initiatives, review and registration progress of medicinal products in HICs and LICs,
- leverage existing data platforms, analysis tools and work-sharing networks, and
- monitor the regulatory framework e.g., in Tanzania, the Personal Data Protection Act of 2022 (PDPA) went into effect in May 2023,[6] and The Personal Data Protection Processing Regulations which define the obligations of data controllers and data processors and related security standards during collection and processing of personal data, went into effect in July 2023,[7]

so, you can plan and operate effectively to best utilize limited resources.

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