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ADVERSE EVENT REPORTING IN DRUG-RESISTANT TUBERCULOSIS FACILITIES IN SOUTH AFRICA:

RESULTS FROM A NATIONAL SURVEY

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Human and Social Capabilities
Human Sciences Research Council

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Definitions

- **Pharmacovigilance** - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects and all other problems related to medicines' (WHO. 2002a. The importance of pharmacovigilance: safety monitoring of medicinal products. United Kingdom: WHO)

- **Expanded definition of pharmacovigilance** – To include medication errors, counterfeit or substandard medication, lack of efficacy of medication, the misuse or abuse of medication and the interaction between medications and include the surveillance of herbal products, other traditional and complimentary medication, biologicals, vaccines, blood products and medical devices (WHO. 2015. WHO Pharmacovigilance Indicators: a practical manual for the assessment of pharmacovigilance systems. France: WHO Press)

Background

- Post-marketing pharmacovigilance is essential to understand the effectiveness of medication in large diverse populations that cannot be achieved during clinical trials
- This relies on healthcare professionals to report through spontaneous reporting systems
- Drug-resistant tuberculosis (DR-TB) involves complicated treatment which is often influenced by adverse effects of medication
- New drugs (bedaquiline, delamanid and pretomanid) and repurposed drugs (linezolid, clofazimine) – emphasises further need for pharmacovigilance
- Adverse effects reportedly well documented in terms of incidence – reporting to regulatory bodies using standard reporting form is unclear
- There is a dearth of information on pharmacovigilance and reporting frequencies in South Africa

Background

- National pharmacovigilance systems that monitor harms associated with drugs used to treat TB are best placed to protect patient safety, particularly when new drugs are introduced
- Scaling up of treatment will results in more persons with diverse ages, sex, ethnicity and comorbidities being exposed to anti-TB medication, thus increasing the risk of adverse reactions manifesting

Background

- 1940s – thiocetazone was used as a treatment for TB
- Reports of Stevens-Johnson syndrome emerged and eventually the causal relationship was well established
- However, in spite of the risk, thiocetazone continued to be used in low-income countries due to its low cost
- In the late 1980s and early 1990s reports of Stevens-Johnson syndrome and toxic epidermal necrolysis were emerging in HIV-positive patients receiving thiocetazone and there was a high fatality rate
- Thiocetazone was replaced by ethambutol 1991 and is now reserved for uncommon cases

Common adverse reactions with medication used to treat drug resistant TB

Drug	Adverse reactions
Terizidone	Neurological effects (anxiety, confusion, depression, **PSYCHOSIS**, aggression, irritability, paranoia) Headache, vertigo, drowsiness, speech difficulties, tremor, **CONVULSIONS**, coma
Moxifloxacin	Seizures (rare) but may occur in patients with underlying CNS condition, **STEVENS-JOHNSON SYNDROME**, anaphylaxis
Levofloxacin	Severe persistent diarrhoea (uncommon), **CNS EFFECTS**, blood dyscrasias, hepato-biliary disorders, renal and urinary disorders
Ethionamide	Gynaecomastia (rare), impotence (rare), amenorrhoea (rare)
Pyrazinamide	Dose-related **HEPATOTOXICITY**
Ethambutol	Dose-related **OCULAR TOXICITY**, hyperuricemia,
Isoniazid	Potentially fatal **HEPATOTOXICITY**, dole-related **NEUROTOXICITY** (more common in malnourished patients)

Common adverse reactions with medication used to treat drug resistant TB

Drug	Adverse reactions
Clofazimine	**SKIN DISCOLOURATION**, reddening of urine, sweat, sputum or faeces. Dose-related gastrointestinal adverse reactions
Para-amino salicylic acid (Paser)	Hypothyroidism
Linezolid	Fungal infections, **BLOOD DYSCRASIAS**, **BLURRED VISION**, tinnitus,
Bedaquiline	Gastrointestinal adverse reactions, **PROLONGED QT INTERVAL**, hepatic disorders

Primary Aim

To understand the current adverse event reporting practices in specialised DR-TB treatment facilities in South Africa and develop appropriate interventions if needed

OBJECTIVES:

- understand experiences of healthcare professionals in adverse event reporting;
- map out the current adverse event reporting practices and identify best practices (based on successful reporting of adverse events);
- analyse quality of adverse event reporting according to minimum requirements of National Pharmacovigilance Centre (NPC);
- understand the activities of NGOs working in pharmacovigilance and their linkages to regulatory authorities; and
- develop an intervention plan based on findings.

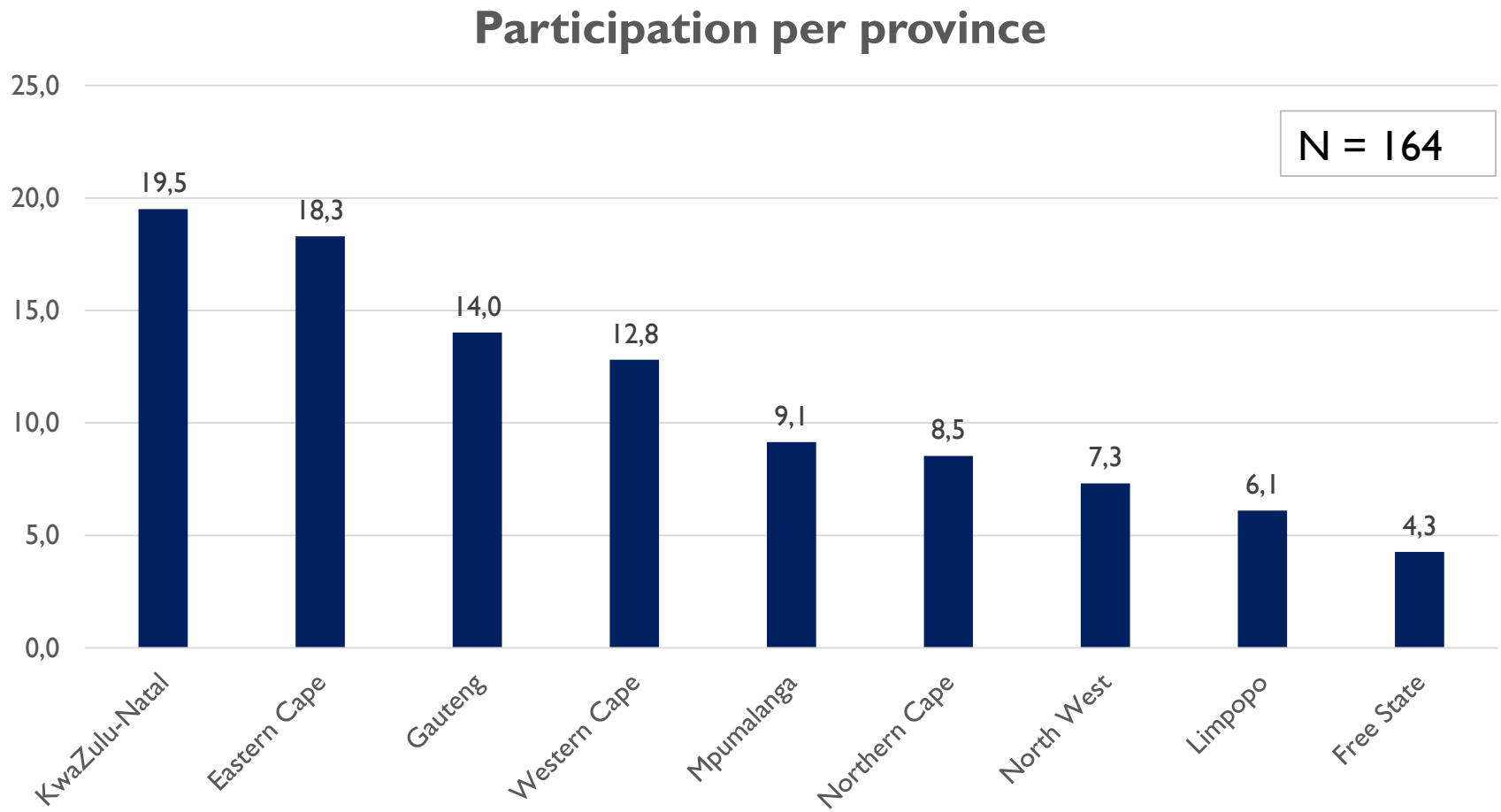
Methodology

- Descriptive and cross sectional in nature
- Structured interviews focusing on knowledge, beliefs and practices (target population – doctors, nurses, pharmacists, quality assurance managers, operational managers, facility managers at Centres of Excellence)
- Review of completed adverse event reports over the last six months (January to June 2019) (approximately 15% to 20% of completed reports will be audited to ensure minimum required information is available)
- Engagement with NGOs identified to be involved with strengthening pharmacovigilance processes and their activities
- Study sites have been selected in each province

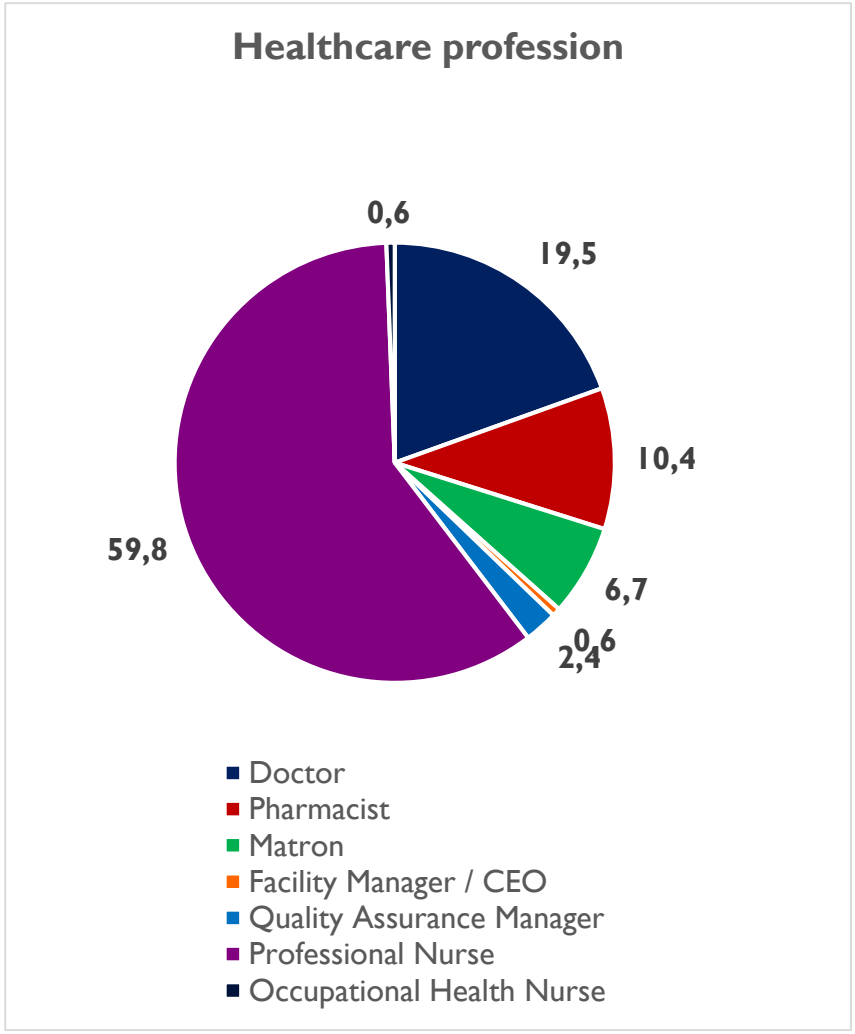
Ethical clearance

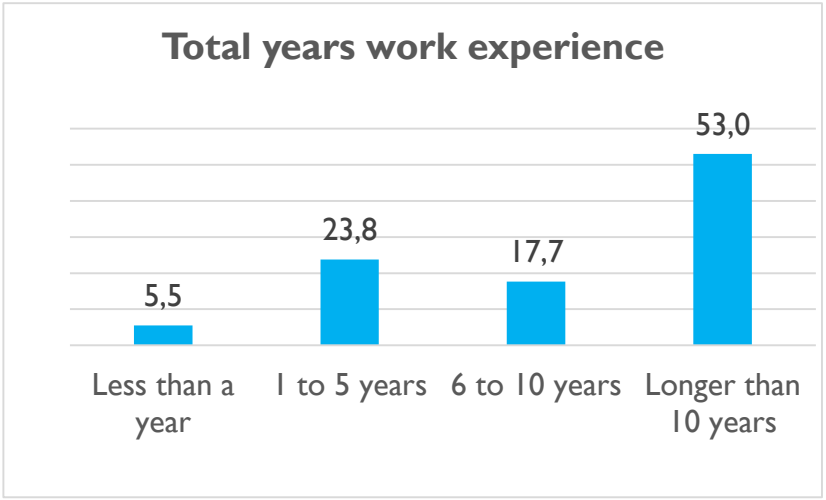
- Ethics approval was obtained from the Human Sciences Research Council (Reference: 6/22/08/18) and all Provincial Ethics Committees
- Permission and/or support from relevant districts/hospitals were obtained prior to planning and visiting selected sites

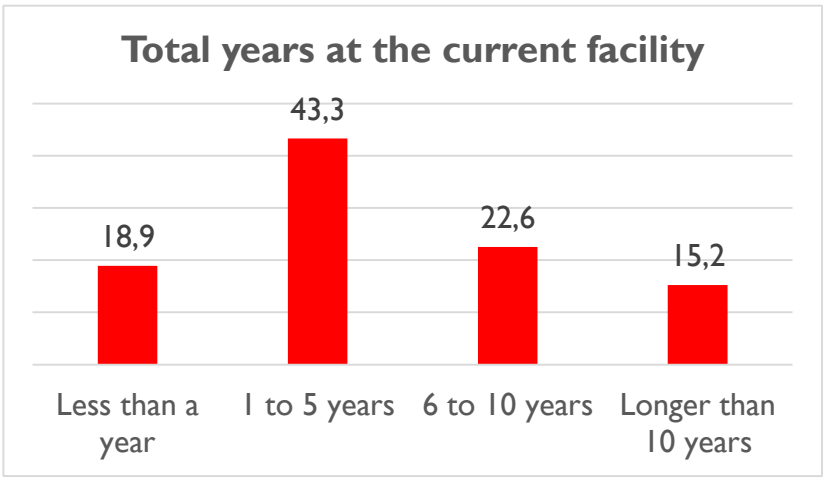
Results – Study participation



Results - Demographics



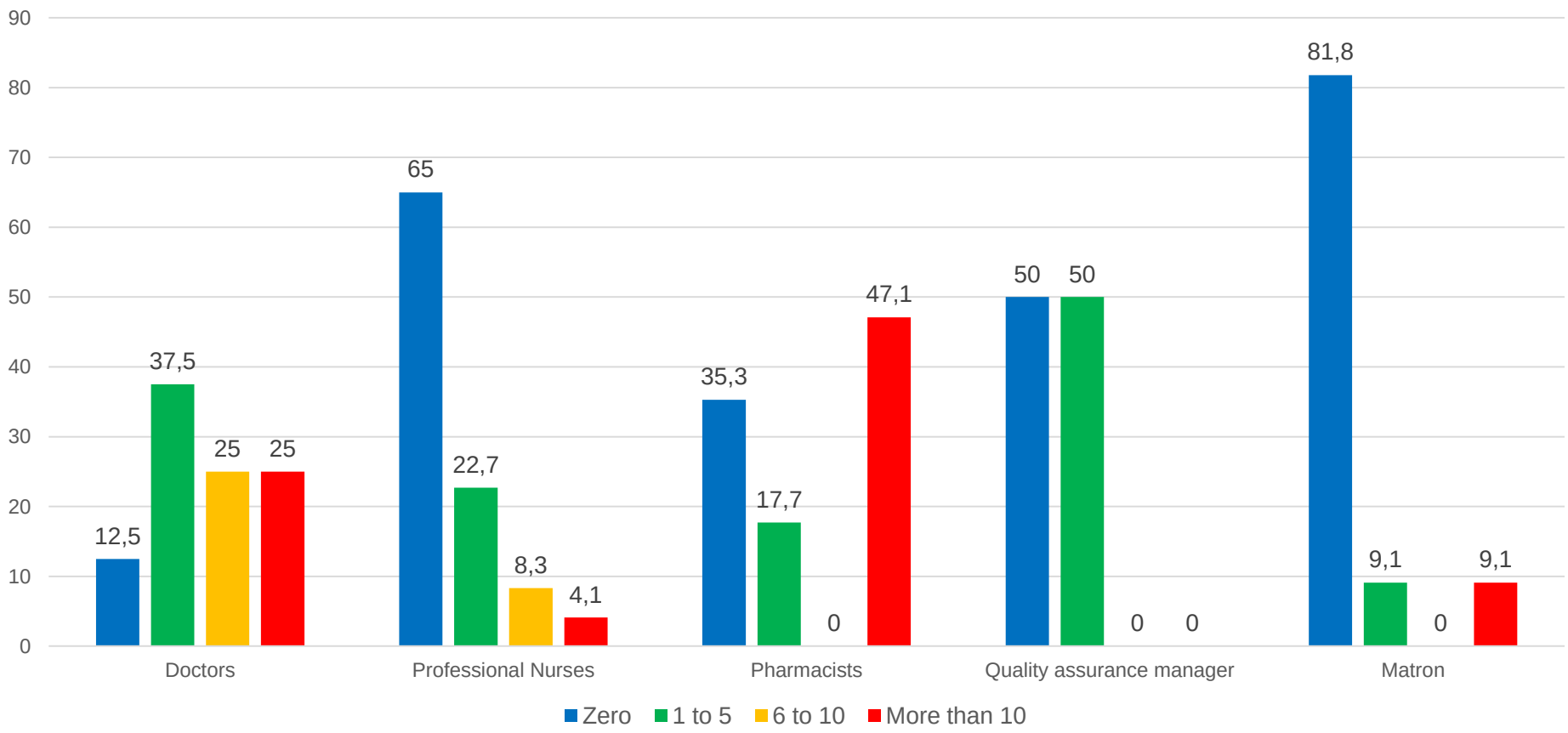




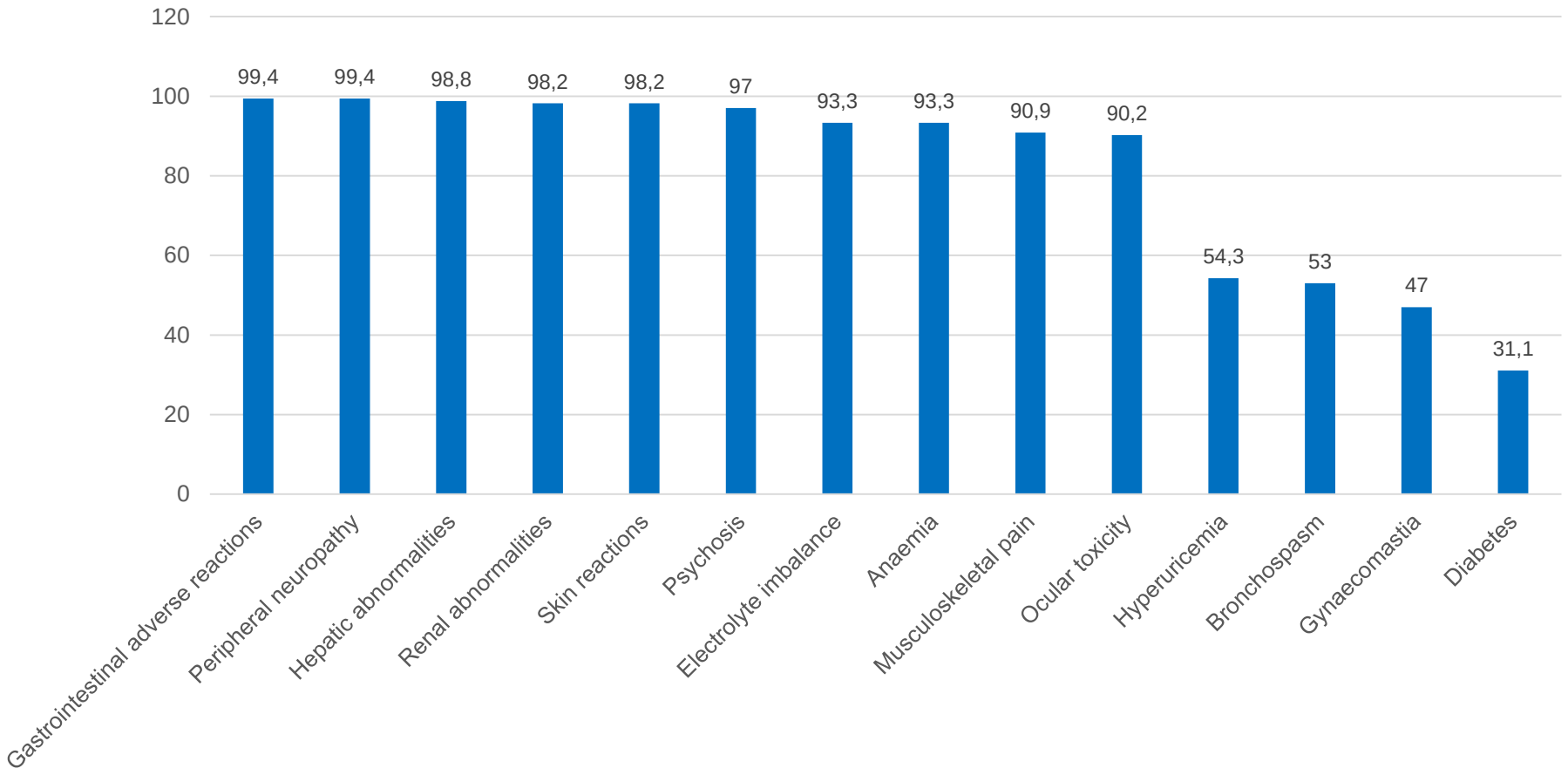
Results – Adverse event reporting

Question	Yes
Received training in adverse event reporting in the last 12 months	44.5% (n = 73)
Is adverse event reporting necessary	99.4% (n = 163)
Is adverse event reporting your responsibility	98.8% (n = 162)
Have you reported an adverse event in the last six months	53.7% (n = 88)

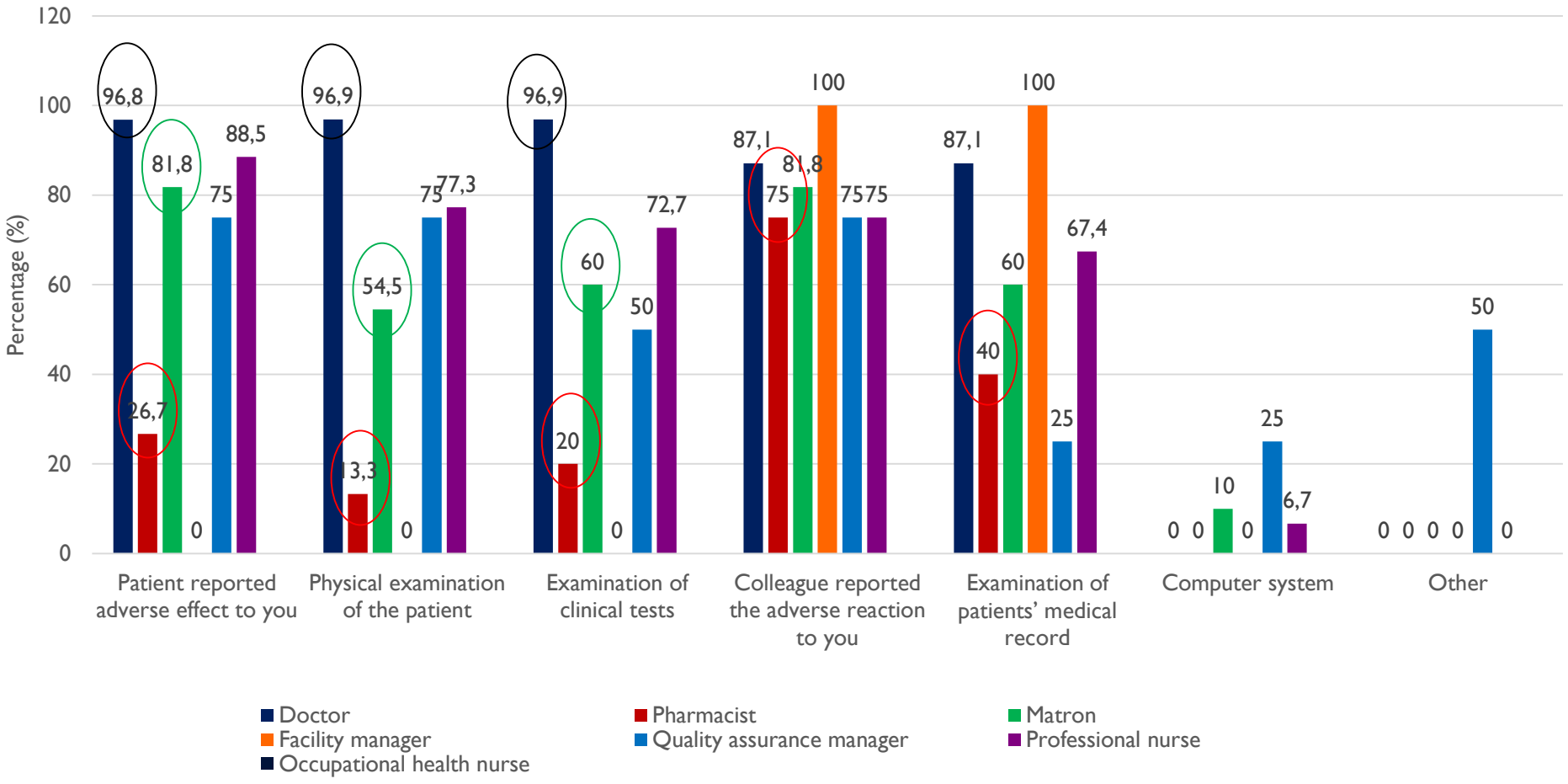
Number of adverse event forms completed by profession



Knowledge of common adverse reactions caused by medication used to treat drug resistant TB

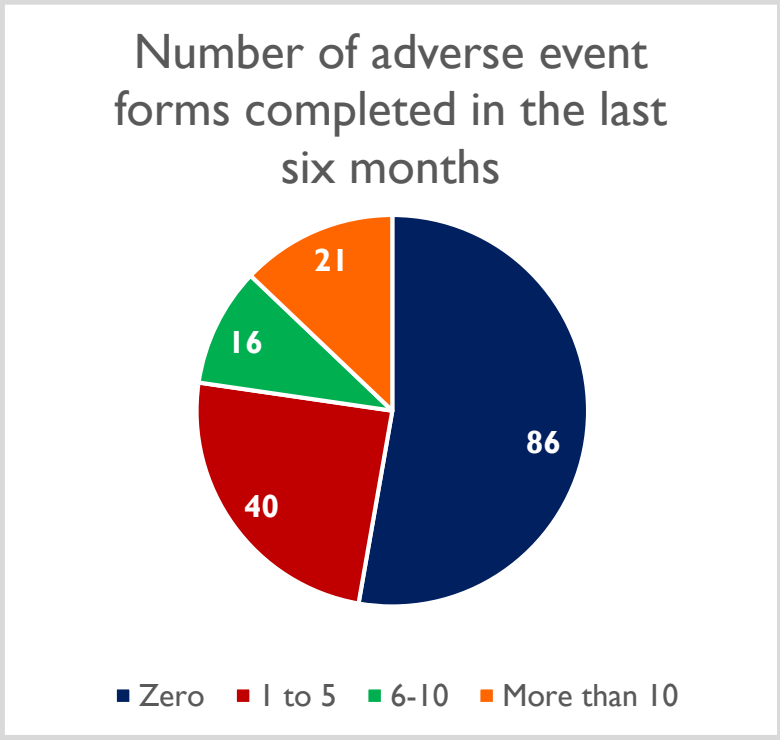


Results - Adverse event identification

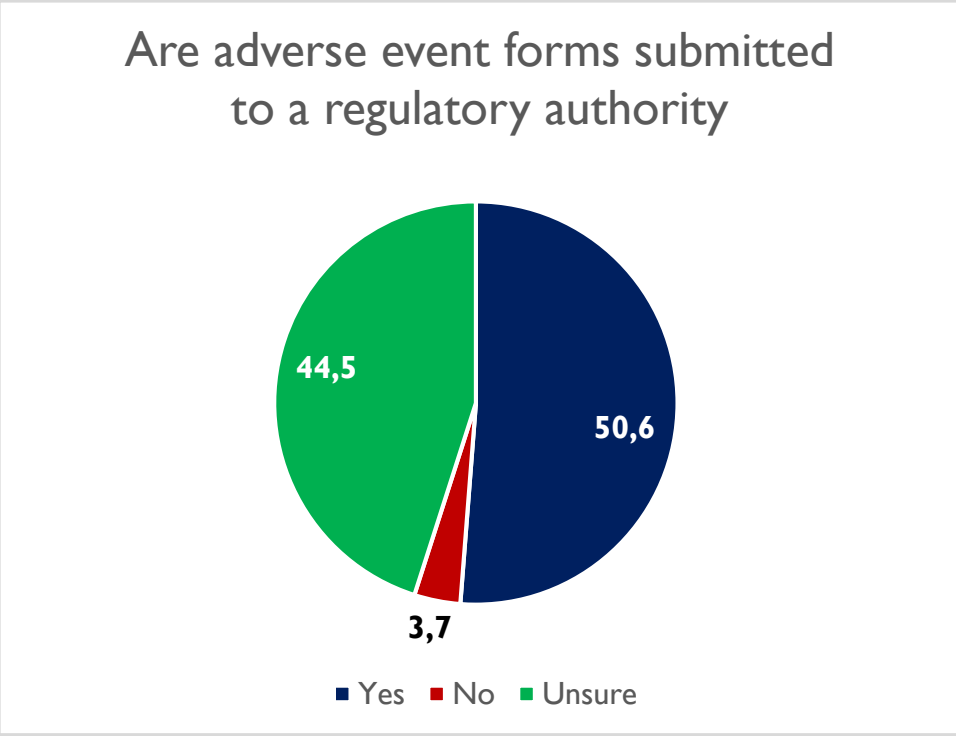


Results – Adverse events at facility

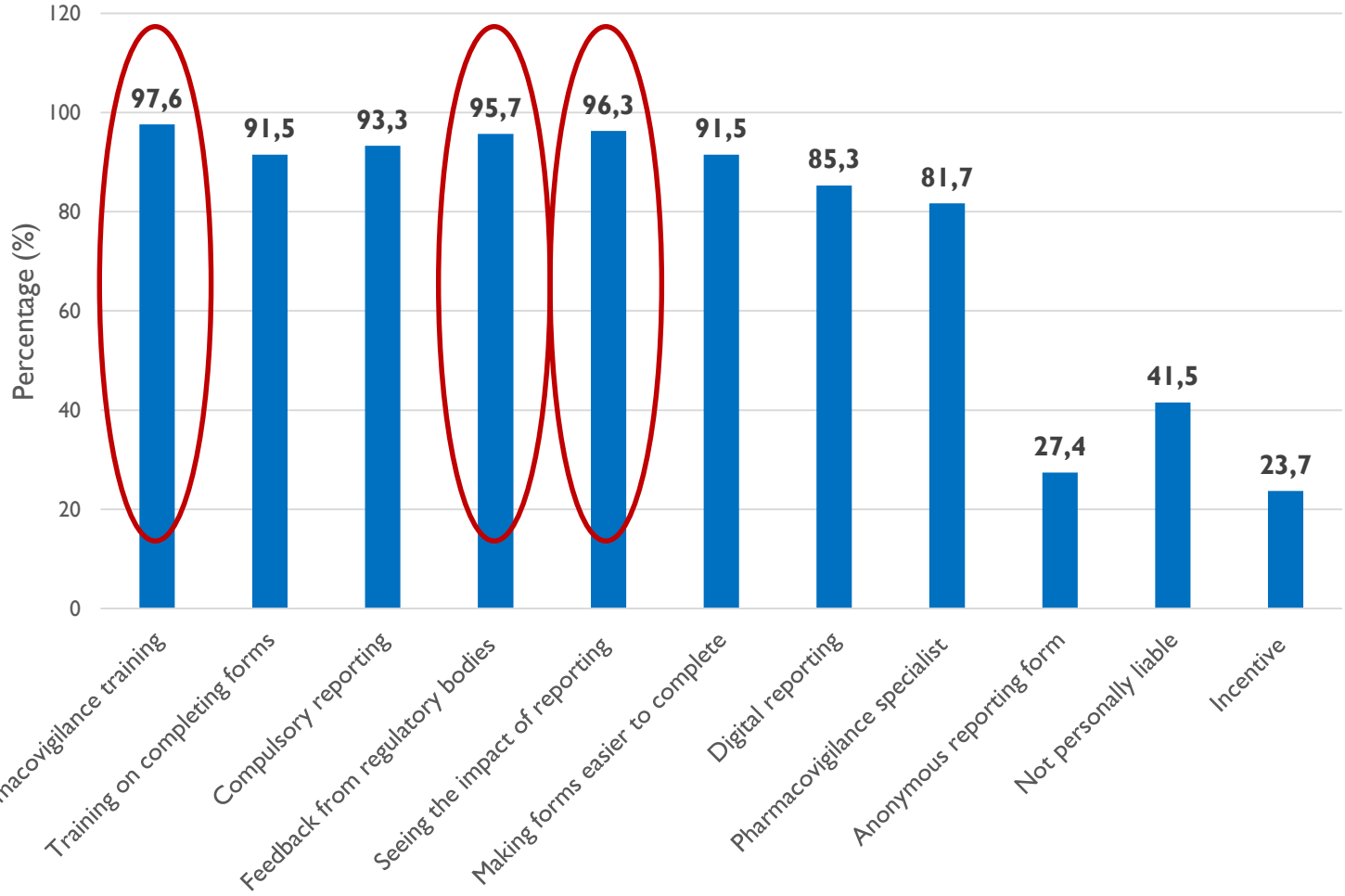
Is there an active PTC at your facility?	
Yes	56.7%



I have reported the management and outcome of an adverse event	
Agree	50.6%



Results – Factors that would encourage adverse event reporting



- Adverse event report forms were reviewed using a checklist of the required information as stipulated by SAHPRA and National Pharmacovigilance Centre (1/2)

Audit form

Province: _____ 1 = EC, 2 = WC, 3 = KZN, 4 = GP, 5 = MP, 6 = NC, 7 = NWP, 8 = LP, 9 = FS

Facility: _____

Checklist	Yes	No
Facility name		
Sub-district/district		
Province		
Patient details		
Initials		
Age		
Gender		
Weight		
Height		
Allergies		
DR-TB registration number		
Hospital number		
Pregnant		
Gestational age		
HIV		
Status		
On ART		
ART start date		
Current ARV regimen		
CD4 count and date		
Viral load and date		
Concomitant conditions		
TB Medication		

- Adverse event report forms were reviewed using a checklist of the required information as stipulated by SAHPRA and National Pharmacovigilance Centre (2/2)

TB Medication		
TB medicines listed		
Dose		
Route		
Date started		
Date stopped or dose reduced		
Reason for stopping or reduction		
Manufacturer		
Batch/expiry date		
Suspect herbal medication		
Adverse drug reaction		
Date of onset of reaction		
Date reported		
Morbidity or mortality report		
Laboratory results		
Adverse drug reaction		
Date observed		
Suspected drug		
Intervention		
Patient outcome		
Narrative of ADR		
Reported by		

Completed by	
Date completed (dd/mm/yyyy)	
Signature	

Results – Adverse event report forms

Variable	Completed
HIV status	46.2% (n = 36)
On ART	28.2% (n = 22)
Current ART regimen	24.4% (n = 19)
Concomitant conditions	10.3% (n = 8)

Recommendations 1/2

- Standardization of the adverse event report forms across facilities;
- Evaluate various methods of incorporating the form into the daily routine or standard patient examination;
- Train all staff working with DR-TB patients (including non-RNs, social workers, physiotherapists, pharmacists, CHWs) regarding adverse event reporting and its value as part of a national intervention;
- Implement a pre/post assessment of the training intervention (for research purposes);
- Implement a formal audit for operational management purposes;

Recommendations 2/2

- Consolidate guidelines from SAHPRA and NPC concerning the reporting of adverse reactions associated with TB and HIV;
- Clarify which health professionals can complete these forms;
- Encourage feedback from the NPC on reports received;
- Encourage the use of digital applications for reporting which will eventually replace paper-based reports and
- Encourage PTC meetings at all study sites and provide training on basic analysis of reports in the facility and how they can be used at a facility level.

Conclusions

- Health professionals showed good knowledge of the common adverse reactions associated with DR-TB medication
- Translation of that knowledge into action was challenging though
- A clear need for training and regular refresher courses on pharmacovigilance
- Specific training on completing adverse event report forms to empower health professionals and encourage reporting
- Inclusion of reporting health facilities in a feedback process
- Multidisciplinary interaction with patients would improve overall quality of DR-TB care
- Facilities need to be motivated to revive and engage PTCs
- Utilise facility-generated pharmacovigilance data to inform clinical practice.

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- Site staff and respondents

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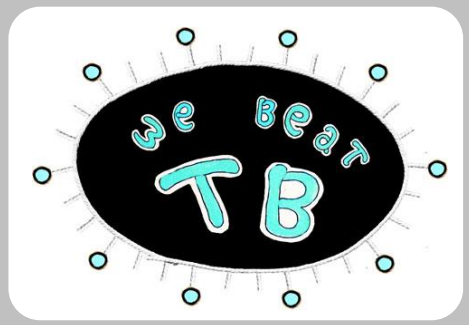

Thank you

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