Meeting South Africa's Pharmacovigilance Challenges in the Face of Rapidly Increasing Public Health Treatment Programmes

2016

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Submitted in fulfillment of the requirements for the degree of Doctor of Philosophy in the School of Pharmacy, College of Health Sciences, University of KwaZulu-Natal, Westville for the degree of Doctor of Philosophy in Pharmacy.

This is a thesis in which the chapters are written as a set of discrete research publications, with an overall introduction and final summary. Typically these chapters will have been published in internationally recognised, peer-reviewed journals.

This is to certify that the contents of this thesis are the original work of Mukesh Dheda

As the candidate's supervisor, I have approved this thesis for submission.

Supervisor:

Name of Supervisor; Dr F Oosthuizen

Signature: _____ Date: _____

ABSTRACT

Background

Among South Africa's (SA's) many public health challenges, having the largest treatment programmes globally is a significant challenge. The latter requires a robust pharmacovigilance (PV) programme. The purpose of this study was to conduct a review of the PV landscape in SA to meet the PV challenge of these treatment programmes.

Aims and Objectives

The aim of this study was to explore the decentralised PV approach to support key public health programmes. The specific objectives were firstly, to trace and reconstruct the history of PV activities to date. Secondly, to benchmark the current PV activities through an appropriate baseline assessment. Thirdly, to determine the impact of a PV training intervention. And finally, to evaluate the effectiveness of a low cost SA-specific PV strategy implemented in response to major public health challenges, namely HIV/AIDS and tuberculosis, through analysis of the data collected.

Methodology

This thesis followed a mixed methods approach including a literature survey, a structured questionnaire-based evaluation (baseline and before- and after-training assessments) and finally a retrospective review of ADR reports.

Results

The study reviewed published and grey literature to reconstruct the evolution of pharmacovigilance in SA. Through a baseline assessment in Eastern Cape Province, it also demonstrated areas that need strengthening and provided recommendations of simple, cost-effective interventions to close these gaps in that province, as well as generally in SA.

Training, a key intervention recommended, was also tested and the study found a positive shift in knowledge gained by healthcare professionals (HCPs) from a one-day pharmacovigilance training intervention ($p<0.002$). Finally, a retrospective analysis of ADR data collected was conducted. Among others, this revealed the effectiveness of this low cost PV programme in detecting top causative agents, most common ADRs and their incidence across gender.

Conclusions

This study provided a review of the PV landscape in SA. The findings have the potential to inform treatment guidelines. Scaling up the methods used herein has the

potential to detect trends that can be acted upon to reduce morbidity and mortality from large public health treatment programmes, especially in low-income settings.

DECLARATION- I PLAGIARISM

I, Mukesh Dheda, declare that;

1. The research reported in this thesis, except where otherwise indicated, is my original research.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

4. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

    a. Their words have been re-written but the general information attributed to them has been referenced.
    b. Where their exact words have been used, then their writing has been placed in italics or inside quotation marks, and referenced.

5. This thesis does not contain text, graphics or tables copied and pasted from the internet, unless specifically acknowledged, and the source being detailed in the thesis and in the references sections

A detailed contribution to publications that form part and/or include research presented in this thesis is stated (include publications submitted, accepted, in press and published).

Signed: _____

DECLARATION- II LIST OF PUBLICATIONS

PUBLISHED

1. Dheda, M. Perspectives on the Emergence of Pharmacovigilance in Public Health Programmes in South Africa, *Pharmaceutical Medicine*, August 2016, Volume 30, Issue 4, pp 213-219, DOI 10.1007/s40290-016-0150-x, http://link.springer.com/article/10.1007/s40290-016-0150-x

   Contributions:
   Dheda M : main contributor, contributed by doing all the research and literature search, compilation and writing of the manuscript.

2. Dheda M, Kambafwile H, Oosthuizen F, Bakor A, Soka A, and Malangu N. A cross-sectional baseline assessment of the pharmacovigilance systems, processes and challenges faced by healthcare professionals in three South African districts prior to pharmacovigilance training and programme roll-out. Accepted for publication. *PULA*: Botswana Journal of African Studies Vol. 30, No. 1, 2016.

   Contributions:
   a. Dheda, M.: main contributor, contributed by doing the design, literature search, compilation and writing of the manuscript.
   b. Oosthuizen, F.: supervisor.
   c. Kambafwile, H.: edited and reviewed the final manuscript.
   d. Soka, A.: facilitated the collection of the data and review of the final manuscript.
   e. Bakor, A.: facilitated the collection of the data and review of the final manuscript.
   f. Malangu, N.: edit and review of the final manuscript.
   g. Field officers from International Training and Education Center for Health, South Africa (I-TECH SA) that collected information using a structured questionnaire on a tablet.

SUBMITTED

1. Dheda M. A Positive Response Shift in the Evaluation of a One-day Pharmacovigilance Training of Healthcare Professionals. Submitted to the International Journal of Risk & Safety of Medicine.

   Contributions:
   a. Dheda, M.: main contributor, contributed by literature search, compilation, preparation, data analysis, interpretation and writing of the manuscript.
   b. Oosthuizen, F.: supervisor.
   c. Kambafwile, H.: edited and reviewed the final manuscript.

2. Dheda M, Kambafwile H, Moorhouse M, Mukudu H, WB Plummer, Oosthuizen F. Descriptive Analysis of ART and TB Therapy ADRs received from Implementation of Pharmacovigilance in Public Health Programmes in South Africa. Submitted to the Journal of the International AIDS Society.

Contributions:

a. Dheda, M.: main contributor, contributed by literature search, compilation, preparation, data analysis, interpretation and writing of the manuscript.
b. Oosthuizen, F.: supervisor.
c. Kambafwile, H.: contributed to the project by editing and review of the manuscript.
d. Mukudu, H.: contributed to the project by data analysis and interpretation of results.
e. Moorehouse, M.: contributed to the project by interpretation of clinical component of the results.
f. Plummer, WB.: contributed to the project by editing and reviewing of the manuscript.

ACKNOWLEDGEMENTS

It is with great satisfaction that I wish to express my sincere appreciation to the many people who supported me in the successful completion of this thesis. My deepest appreciation is expressed to all those who assisted me directly or indirectly. I wish to thank:

The National Department of Health, for giving permission to use their data. The Provincial Departments of Health for helping to pave the way, organisationally and administratively, to allow its HCPs to be part of this decentralised pharmacovigilance programme to improve quality of care in HIV/AIDS and TB patients.

My supervisor, Dr Frasia Oosthuizen for her continued encouragement, motivation, patience and guidance.

My colleagues and dear friends Drs Wallis Best-Plummer and Henry Kambafwile for their advice and comic relief.

My family for serving as a constant source of motivation to complete the thesis.

The University of KwaZulu-Natal for institutional support and being the vehicle for the completion of my degree.

I would also like to acknowledge the efforts of my team at the National Department of Health and the Pharmacovigilance Centre for Public Health Programmes for assistance and support throughout this period.

Last but not least, I would like to thank each and every participant who took part in this project.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ADRs	Adverse Drug Reactions
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral treatment
ARV	Antiretroviral
AZT	Zidovudine
CCMT	Comprehensive Care, Management and Treatment of HIV and AIDS
CHC	Community Healthcare Centre
d4T	Stavudine
EC	Eastern Cape
EDL	Essential Drug List
EFV	Efavirenz
EML	Essential Medicine List
FDC	Fixed dose combination
FPPR	Food Control, Pharmaceutical Trade and Product Regulatory Authority
FTC	Emtricitabine
HAART	Highly Active Anti-retroviral Therapy (HAART)
HCPs	Healthcare professionals
HIV	Human immunodeficiency virus
HPCSA	Health Professions Council of South Africa
IEC	Information, education and communication
INH	Isoniazid
I-TECH SA	International Training and Education Center for Health, South Africa
KZN	KwaZulu-Natal
M/XDR TB	Multi/ extreme drug resistant tuberculosis
MCC	Medicines Control Council
MEDUNSA	Medical University of South Africa
MIC	Medicines Information Centre
MRA	Medicines Regulatory Authority
MRPs	Medicine related problems

NADEMC	National Adverse Drug Event Monitoring Centre
NDoH/ NDOH	National Department of Health
NGOs	Non-governmental organisations
NNRTI	Non nuclear reverse transcriptase inhibitors
NPC	National Department of Health's Pharmacovigilance Centre for Public Health Programmes
NVP	Nevirapine
PDoH	Provincial Department of Health
PHC	Primary Healthcare Centre
PMTCT	Prevention of mother to child transmission
PrEP	Pre-exposure prophylaxis
PV	Pharmacovigilance
SA	South Africa
STG	Standard Treatment Guidelines
SWP	Sector-Wide Procurement
TB	Tuberculosis
TDF	Tenofovir
TDF/FTC/EFV	tenofovir/emtricitabine/efavirenz
UMC	Uppsala Monitoring Centre
UNAIDS	United Nations Programme on HIV/AIDS
USA	United States of America
WHO	World Health Organisation

CHAPTER 1

1.0 GENERAL INTRODUCTION

1.1.1 Background

The burden on communicable and non-communicable diseases, is exacerbated by the burden of the twin diseases of acquired immune deficiency syndrome (AIDS) and tuberculosis (TB), cited as the first and third leading causes of morbidity and mortality in South Africa (SA)[1]. In addition, there is a considerable economic burden that these diseases impose[2]. It is for this reason that the South African government emphasised the need for a comprehensive pharmacovigilance (PV) programme as an integral part of its Comprehensive Care, Management and Treatment of Human immunodeficiency virus (HIV) and AIDS (CCMT) in 2004[3]. A comprehensive PV programme initially began with a pilot project in the Mpumalanga province of SA in 2010 and has now been rolled out into six provinces[4].

1.1.2 Clinical and Economic Burden of Adverse Drug Reactions

Adverse drug reactions (ADRs) are significant causes of morbidity and mortality globally[5]. Literature suggests that 6% of all hospital admissions can be attributed to ADRs[6,7]. A meta-analysis of 39 prospective studies from hospitals in the United States of America (USA) reported that ADRs may be the fourth to sixth leading cause of death in hospitalised patients, with serious ADRs occurring in 6.7% and fatal ADRs in 0.32% of the hospitalised cases[8,9].

ADRs are not only associated with morbidity and/or mortality; they can impose a considerable economic burden. They have been associated with a greater length of hospital stay which may consequently lead to increased healthcare costs. A study in the USA reported 47.4 billion dollars being spent on drug-related admissions[2]. Another study estimated that the total costs, including lost income, lost household production, disability and healthcare costs, due to preventable ADRs was between 17 billion to 29 billion United States Dollars (USD). ADRs may also lead to patients defaulting treatment, poor adherence and/or loss of confidence in healthcare systems[7]. ADRs

have a more significant impact on a public health system in low-income countries and yet they are preventable[10]. In SA, 1 in 12 admissions have been reported to be due to ADRs as well as up to 16% deaths[11], [12].

1.1.3 A Brief History of Pharmacovigilance

Pharmacovigilance (PV) has been defined by the World Health Organisation (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems"[13]. PV plays a crucial role in the study of medicine safety[14].

In 1957, the thalidomide disaster opened up the issue of drug safety for the public and healthcare professionals (HCPs)[15]. It brought to the fore, the importance of systematic surveillance of medicines for ADRs[16]. The thalidomide tragedy led many countries to set up observational systems for early detection of potential ADRs associated with pharmacotherapy[17]. The WHO programme of monitoring of ADRs that began in 1968 with ten founder members, has now increased to 125 full member countries[18].

In a review of post-marketing withdrawals of medicinal products due to ADRs, it was found that 462 medicinal products were withdrawn from the market between 1953 and 2013[19]. The most common reason for withdrawal was hepatotoxicity. This has serious implications for SA that has the burden of the twin diseases of HIV and TB, requiring treatment with medicines having a high incidence of hepatotoxicity, and a higher risk for patients co-infected with HIV and TB[20].

Both the HIV and TB programmes are national medicine safety concerns and were not getting the attention they deserved. In August 2012, a workshop was held among key stakeholders (National Department of Health (NDoH), academics and other non-governmental organisations) in SA to prioritise these concerns[21]. The workshop identified PV issues facing the HIV and TB programmes to be key shortcomings and suggested that PV should be reviewed in terms of its performance in meeting their objectives[21]. This gave the impetus needed to strengthen the National Department of Health's Pharmacovigilance Centre for Public Health Programmes (NPC), which

became functional with the appointment of a director for the centre in October 2014. The director was tasked to develop a PV programme capable of giving inputs to treatment policy decision-making and improved patient care, prioritising HIV and TB. Hence, to assist the director in making informed and innovative improvements to the programme the undertaking to read for a PhD.

Pharmacovigilance in SA was previously only regulatory. It has now been expanded into two complementary units featuring a broad-based, collaborative public health programme of research and monitoring of ADRs as well as health worker training on the one hand and regulatory PV on the other, (Figure 1). Regulatory PV is performed by the Food Control, Pharmaceutical Trade and Product Regulation Authority (FPPR, formerly known as the Medicines Regulatory Authority). It is a statutory regulatory authority responsible for medicines registration and safety monitoring with a focus on pharmaceutical companies. The programmatic component was established to close the lacuna around linkage with public health facilities and patients. It falls under the NDoH. This combination between the two components created a more comprehensive approach as it also included interaction not only between the two components, but other key stakeholders such as academia among others. The new structure gives NPC the ability to provide feedback to ADR reporters, facilities and provinces in the public health sector.

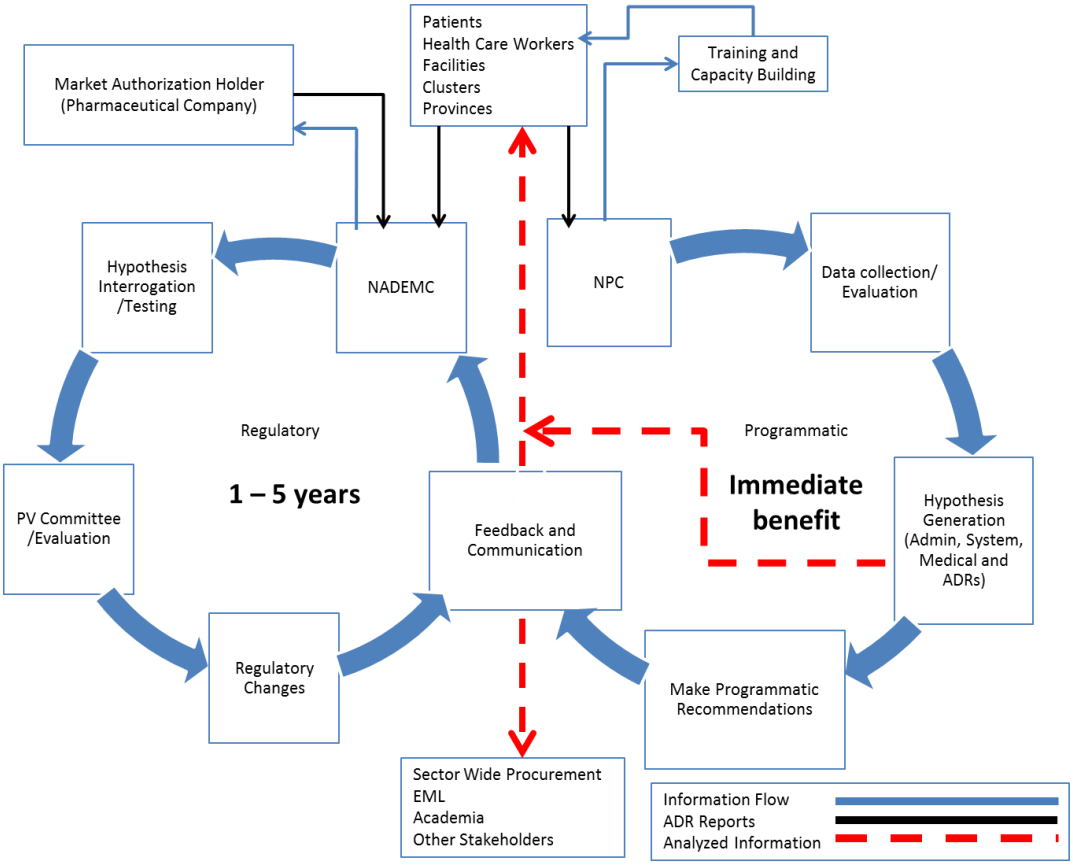

Figure 1: Overall PV activity syncing the regulatory and programmatic activities

1.1.4 Reporting of Adverse Drug Reactions (ADRs)

Simply described, an ADR is an unintended response from taking a medicine[22]. It has also been defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of disease, or for the modification of physiological function [23].

There are two major systems of reporting in PV. These are passive reporting and active surveillance systems. The passive reporting system, also known as spontaneous reporting system, remains the most common form of reporting. In this system, there are no active measures taken to find ADRs other than encouragement of healthcare professionals (HCPs) and others to report the safety concerns[24]. The active surveillance system on the other hand, is a dynamic surveillance system that actively takes measures and force HCPs to detect and report ADRs[25].

Most of the PV systems around the world depend on spontaneous reporting systems to collect information about ADRs, where the reports are submitted on a voluntary basis from the reporters (HCPs). Thereafter, the information is entered into a database which is assessed regularly for signal generation[26]. Spontaneous reporting is considered the cheapest and easiest mechanism by which to collect PV data. Unfortunately, a number of systematic weaknesses have been documented, the most notable being underreporting of ADRs from HCPs and other stakeholders. Although well documented in some developed countries, research around underreporting and the quality of reports are not well documented in SA.

At a workshop in August 2012, it was established by key stakeholders that in the short-to-medium term that spontaneous reporting be the approach for public health PV programmes. There was also general agreement that active surveillance is a costly and labour intensive approach that was not appropriate for the SA context[21]. However, like other systems globally, SA suffers from ADR under-reporting from all cadres of HCPs.

The number of reports received by the Medicines Control Council (MCC) and NPC (currently averaging 50 to 75 reports per million inhabitants per year, since 2010 to 2014) is lower than the recommendations of the WHO Program for International Drug Monitoring (200 reports per million inhabitants per year)[27]. The numbers are steadily increasing with the introduction of the decentralised PV programme that has added 1000 reports or 20 reports per million inhabitants per year in 2016.

At the time this study was conceptualised, there were no studies that mapped the evolution of PV in SA giving past, present and possible future perspectives as well as suggesting potential interventions that would reduce under-reporting and/or develop systems and interventions that speak to SAs current public health challenges.

1.2 Problem Statement

South Africa has the largest antiretroviral treatment (ART) programme globally as well as one of the largest TB programme (including multi/extreme drug resistant (M/XDR)

TB). Apart from the TB and HIV/AIDS, there are other rapidly expanding programmes such as the expanded programme for immunisation, national pregnancy exposure registry and birth defect surveillance and the use of long term contraceptives such as subdermal (etonogestrel) implant in family planning. Successful treatment interventions of these programmes are seriously threatened by ADRs which may result in treatment defaulting and serious downstream threats such as multidrug resistance. It is therefore imperative that a critical assessment of the current PV activities in SA is conducted from a national perspective. This is the first time in SA that a national review is being conducted.

Increased PV activities in SA have the potential of decreasing medicine related problems (MRPs) and can positively impact on the country's economy by reduced hospitalisations, reduced expenditure on expensive regimen switches and/or other treatment programmes[27]. It can reduce work opportunity cost lost directly through decreased morbidity and mortality as well as increased quality of life and economic productivity.

South Africa uses PV as the primary method to collect information about ADR occurrences in its treatment programmes. The effectiveness and success of this PV system depends highly on the participation of all HCPs and it also relies upon the degree of co-operation and communication between these professions.

As in most of the PV system around the world, SA's PV also suffers from the problem of ADR under-reporting. ADRs reports from Africa only account for less than one percent of the global ADR reports, with SA providing the largest number of these reports[28]. These reports also differ from the rest of the world with regards to the type of medicines reported[28].

1.4 Aim

The aim of this study was to explore the decentralised pharmacovigilance (PV) approach to support key public health programmes in SA.

1.5 Specific objectives

The specific objectives of this research were four-fold as follows:

- To trace and reconstruct the history of PV activities to date.
- To benchmark current PV activities through an appropriate baseline assessment.
- To determine the impact of a PV training intervention.
- To evaluate the effectiveness of a low cost SA-specific PV strategy implemented in response to the major public health challenges, namely HIV/AIDS and tuberculosis, through analysis of the data collected.

1.6 Significance of the Study

1) This study may provide healthcare policy makers and planners with information on the current ADR reporting status among healthcare professionals in SA.
2) It will provide information that can be used for future evaluation or reconstruction of public health PV.
3) The study is the first of its kind in SA that will evaluate the factors that could possibly affect ADRs reporting among HCPs. It will provide support mechanisms and feedback linkages with the formation of mini PV centre and ongoing professional development in its various phases of training.
4) It will provide suggestions to improve reporting by health professionals.

The study provides the NDoH and other stakeholders with knowledge about the current situation of ADRs reporting and thus enabling them to discuss the suitable methodology to improve reporting processes. It will determine the actual interventions required in improving ADRs reporting through verifying the possible factors leading to underreporting in SA. Information about ADR reporting such as knowledge, awareness and practice and barriers have to be assessed and the needs associated with these factors have to be identified. This will provide valuable data on the issues of PV and ADRs reporting which may be utilised to improve and further evolve the PV system.

1.7 Conflict of Interest

In order to avoid conflict of interest, the hats of the researcher and director of the National PV Centre were separated by ensuring no interference with interpretation of the results as obtained. Furthermore, the authorships and/or field work included other role players and collaborators (including those external to the NDoH PV Centre). The data collected, as well as interpretation thereof, involved other role players and this is in itself is a safeguard preserving the integrity of the research.

1.8 Overview of the Thesis

This thesis is composed of six chapters, including this chapter, and each chapter stands as a separate chapter:

Chapter 1: This chapter is the introductory chapter that provides an overview of the research presenting the general flow of the whole research project and organisation of the thesis. Furthermore, it outlines briefly the rationale, aims and objectives of the study and the possible impact of the research.

Chapter 2: (Published work)
Presented in the format requested by the journal.
A paper entitled "Perspectives on the Emergence of Pharmacovigilance in Public Health Programmes in South Africa" has been published in the Journal of *Pharmaceutical Medicine*.

This article provides past, current and future perspectives of PV in SA's public health programmes. It discussed events that led SA to reconceptualise it's PV system in treatment programmes. It discussed the decentralised approach to PV that seeks to improve the quality of patient care at the point of care.

Chapter 3: (Published work)

Presented in the format requested by the journal.

The manuscript accepted for publication is entitled "A Cross Sectional Mixed-Method Baseline Assessment of Pharmacovigilance Systems, Processes and Challenges Faced by Healthcare Professions in Three South African Districts Prior to Pharmacovigilance Training and Programme Roll-Out" in *PULA: Botswana Journal of African Studies*.

This baseline assessment was conducted in order to document the knowledge, awareness and practice of PV systems among public healthcare professionals (HCPs) to understand the strategies required for roll-out of a PV programme. The baseline assessment indicated the need for an appropriate training intervention of all relevant HCPs to bridge the shortfalls identified and ensure a successful implementation of the decentralised programme.

Chapter 4: (Manuscript Submitted and under review)

Presented in the format requested by the journal.

The manuscript is currently under review entitled "A Positive Response Shift in the Evaluation of a One-day Pharmacovigilance Training of Healthcare Professionals" has been submitted to The International Journal of Risk & Safety of Medicine.

This article aimed to identify gaps and evaluate the impact of a one-day pharmacovigilance training of healthcare professionals in SA. It found an increase in healthcare professionals' knowledge regarding pharmacovigilance after the training. However, despite this increment, it is clear that certain aspects of the overall training need to be re-emphasised to have an even greater impact.

Chapter 5: (Manuscript Submitted and under review)

Presented in the format requested by the journal.

The manuscript is currently under review entitled "Descriptive Analysis of ADRs from the National Department of Health's Pharmacovigilance Centre for Public Health Programmes in South Africa" has been submitted to Journal of the International AIDS Society.

The paper describes analysis of post-training data collected from the programme. It found areas where the PV programme needs to be strengthened as well as the successes the programme has achieved. It also detected the top causative agents causing safety issues in the HIV and TB programmes, the most common ADRs, as well as the difference in rate of ADRs experienced by males and females.

This pharmacovigilance programme was found to have the potential to extract important data that may inform HIV and TB programme treatment guidelines, identify trends and generate hypotheses to be further investigated.

Chapter 6: Conclusion: This chapter describes the general conclusions drawn from the various findings in this study, identifies possible study limitations and highlights recommendations for future work.

1.9 References

1. Bradshaw D, Groenewald P, Laubscher R, Nannan N, Nojilana B, Norman R, et al. Initial burden of disease estimates for South Africa, 2000. South African Med J. 2003;93(9):682–8.
2. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. [Internet]. Vol. 155, Archives Of Internal Medicine. 1995. p. 1949–56. Available from: https://pallas2.tcl.sc.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=7575048&site=ehost-live
3. NDoH. Operational Plan for Comprehensive HIV and Aids Care, Management and Treatment for South Africa. 2003;(October):1–40.
4. Dheda M. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga as pilot province for national roll- out. J AIDS HIV Res. 2013;5(9):357–65.
5. Franklin B, Vincent C, Schachter M, Barber N. The Incidence of Prescribing Errors in Hospital Inpatients [Internet]. Vol. 28, Drug Safety. London; 2005. p. 891–900. Available from: http://dx.doi.org/10.2165/00002018-200528100-

00005

6. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj [Internet]. 2004;329(7456):15–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15231615http://www.bmj.com/cgi/reprint/329/7456/15.pdf%5Cnhttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC443443/pdf/bmj329000015.pdf
7. Zolezzi M, Parsotam N. Adverse drug reaction reporting in New Zealand: implications for pharmacists. Ther Clin Risk Manag [Internet]. 2005;1(3):181–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18360558%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1661625
8. Muehlberger N, Schneeweiss S, Hasford J. Adverse drug reaction monitoring—cost and benefit considerations. Part I: frequency of adverse drug reactions causing hospital admissions. Pharmacoepidemiol Drug Saf [Internet]. 1997;6(S3):S71–7. Available from: http://2-i
9. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies [Internet]. Vol. 279, J Am Med Assoc. 1998. p. 1200–5. Available from: http://dx.doi.org/10.1001/jama.279.15.1200
10. Ayani I, Aguirre C, Gutiérrez G, Madariaga A, Rodríguez-SasiańN JM, Martínez-Bengoechea MJ. A cost-analysis of suspected adverse drug reactions in a hospital emergency ward. Pharmacoepidemiol Drug Saf. 1999 Dec;8(7):529–34.
11. Mouton JP, Njuguna C, Kramer N, Stewart A, Mehta U, Blockman M, et al. Adverse Drug Reactions Causing Admission to Medical Wards. A Cross-Sectional Survey at 4 Hospitals in South Africa. Medicine (Baltimore). 2016;95(19):1–10.
12. Mouton JP, Mehta U, Parrish AG, Wilson DPK, Stewart A, Njuguna CW, et al. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. British Journal of Clinical

Pharmacology. 2015. p. 818–26.

13. WHO Policy Perspectives on Medicines. Pharmacovigilance: ensuring the safe use of medices [Internet]. Geneva; 2004. Available from: http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf [accessed on 31 oct 2016]
14. Herdeiro MT, Figueiras A, Polónia J, Gestal-Otero JJ. Influence of pharmacists' attitudes on adverse drug reaction reporting: A case-control study in Portugal. Drug Saf. 2006;29(4):331–40.
15. McBride WG. Thalidomide and congenital abnormalaties. Lancet. 1961;271.
16. World Health Organization. The Importance of Pharmacovigilance - Safety Monitoring of medicinal products. Who [Internet]. 2002;1–52. Available from: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf
17. Meyboom RH, Egberts a C, Gribnau FW, Hekster Y a. Pharmacovigilance in perspective. [Internet]. Vol. 21, Drug safety. 1999. p. 429–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10612268
18. Uppsala Monitoring Centre public service pharmacovigilance WHO programme members [Internet]. WHO Health Organisation; Available from: http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442 accessed 20 Sep 2016
19. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med [Internet]. 2016;14(1):10. Available from: http://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0553-2%5Cnhttp://www.biomedcentral.com/1741-7015/14/10
20. Lima MF, Melo HR. Hepatotoxicity induced by antituberculosis drugs among patients coinfected with HIV and tuberculosis. Cad Saude Publica. 2012;28(4):698–708.
21. Mehta U, Dheda M, Steel G, Blockman M, Ntilivamunda A, Maartens G, et al. Strengthening pharmacovigilance in South Africa. 2014;104(2):104–6.
22. Harmonisation IC on. ICH HARMONISED TRIPARTITE GUIDELINE GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) GUIDELINE FOR

GOOD CLINICAL PRACTICE. 1996;(step 4 version):1–53.

23. WHO Technical Report No 498 (1972). 1972;1–48.
24. Edwards IR. Spontaneous reporting - Of what? Clinical concerns about drugs. Br J Clin Pharmacol. 1999;48(2):138–41.
25. Huang YL, Moon J, Segal JB. A comparison of active adverse event surveillance systems worldwide. Drug Saf. 2014;37(8):581–96.
26. Waller P. Introduction of pharmacovigilance. Chapter 4. The process of pharmacovigilance [Internet]. Wiley; 2009. Available from: http://onlinelibrary.wiley.com/doi/10.1002/9781444316766.ch4/chapter accessed 20 Jun 2019
27. Rosli R, Ming LC, Aziz NA, Manan MM. A Retrospective Analysis of Spontaneous Adverse Drug Reactions Reports Relating to Paediatric Patients. 2016;1–18. Available from: http://dx.doi.org/10.1371/journal.pone.0155385
28. Ampadu HH, Hoekman J, Bruin2. ML de, Pal SN, Olsson S, Daniele S, et al. Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World : Analyses of Spontaneous Reports. Drug Saf. 2016;39(4):335–45.

Introductory Notes to Manuscript One /Chapter Two

“Perspectives on the emergence of pharmacovigilance in public health programmes in South Africa" provides a systematic review of the literature in the field of pharmacovigilance relevant to the South African context. It outlines the evolution of pharmacovigilance in public health programmes in South Africa, and offers a perspective on its future.

The review includes relevant aspects of the history and status of pharmacovigilance in the public health sector in South Africa. These include information from minutes of committee meetings, emails, structural plans and proposals submitted at various stages of its evolution.

Furthermore, it provides guidance to the developing and strengthening of a decentralised pharmacovigilance centre. A process that uses current public health structures to capacitate healthcare professionals (HCPs) to detect, assess and prevent adverse drug reactions (ADRs). HCPs also benefit by increasing their knowledge and receiving feedback from their monthly meetings to discuss ADRs emanating from their practices the ground level. At a national level the National Department of Health’s Pharmacovigilance Centre for Public Health Programmes (NPC) has implemented a process of continual training and retraining with feedback to the reporters.

The author is also the director of the NPC. In order to prevent the article being presented from a departmental point of view or conclusions not consistent with the department’s policies being ameliorated, each aspect of this article was closely managed. Each stage of the paper process up to the publication stage; study design, implementation, analysis, interpretation, conclusion and publication was not allowed to proceed until consensus was reached by the supervisor.

CHAPTER 2

Pharm Med (2016) 30:213–219
DOI 10.1007/s40290-016-0150-x

REVIEW ARTICLE

Perspectives on the Emergence of Pharmacovigilance in Public Health Programmes in South Africa

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Published online: 11 June 2016

Abstract Pharmacovigilance in South Africa was formalised in 1987 with the creation of the first pharmacovigilance centre in Africa. This pharmacovigilance centre subsequently became a full member of the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring in 1992. In 2004, pharmacovigilance received a major boost with the roll-out of the South Africa antiretroviral treatment (ART) programme and the establishment of a National Pharmacovigilance Centre for Public Health Programmes (NPC) within the National Department of Health (NDOH). The NPC's activities maintain a special focus on public health pharmacovigilance, monitoring patient safety in important treatment programmes such as TB, HIV and others. In comparison, pharmacovigilance, assessing the risk–benefit profile of registered medical products in both the pre- and post-approval periods, continues to be conducted by the Medicines Control Council (MCC). This article provides past, current and future perspectives of pharmacovigilance in the South African public health programmes. These were informed by the review of published articles, international and regional reports, health law and policy documents, as well as strategic plans and reports from within the South African NDOH. South Africa now understands that the benefit–harm ratio of medicines is a dynamic variable that has to be monitored continuously. Reconceptualising the pharmacovigilance system in South Africa to focus on treatment programmes and individual patients has gradually set the stage for a holistic system and established a decentralised but structured and highly participative national pharmacovigilance programme that significantly benefits public health and patient care.

Key Points

South Africa has reconceptualised its pharmacovigilance programme in response to specific public health challenges.

Decentralisation of pharmacovigilance activities has improved the level of individual patient care in the country.

Pharmacovigilance continues to evolve in South Africa and this article offers a perspective on its future development.

1 Introduction

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [1]. It is a dynamic discipline based on sound scientific principles and is integral to effective clinical practice. Pharmacovigilance plays a vital role in ensuring that healthcare professionals (HCPs), at times together with the patient, can make informed decisions when it comes to choosing a medicine for treatment [2]. It is the outcome of the implied willingness of HCPs to ensure the safety of their patients. As such, it is a discipline that extends the implementation of the principle of "first do no harm" towards a wider, systematic application in clinical practice. In order to prevent or reduce harm to patients, and thus improve public health, mechanisms for evaluating and monitoring the

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health pharmacovigilance system that were exchanged between the national pharmacovigilance coordinator, various colleagues and stakeholders were also included in the review to establish the relative occurrence of events in the absence of published materials.

medicine for treatment [2]. It is the outcome of the implied willingness of HCPs to ensure the safety of their patients. As such, it is a discipline that extends the implementation of the principle of "first do no harm" towards a wider, systematic application in clinical practice. In order to prevent or reduce harm to patients, and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical practice are vital. Consequently, pharmacovigilance has been considered the master key to monitoring medicine safety [3].

Although several developed countries have had major achievements in pharmacovigilance to date, South Africa, like most other low- to middle-income countries, is only now catching up. The impetus for this is multidimensional. Factors include the mandatory requirement of the pharmaceutical industry to report adverse drug reactions (ADRs), the country's exposure to a large number of phased clinical trials, a shift in national policies, the involvement/support of donor partners via various non-governmental organisations (NGOs) and the existence of large treatment programmes such as the HIV/AIDS antiretroviral treatment (ART) programme [4, 5]. In particular, the accelerated roll-out of the ART programme underscored the need to study and understand the idiosyncrasies of the local context to ensure successful implementation of pharmacovigilance at acceptable local and international standards. This article seeks to outline the evolution of pharmacovigilance in public health programmes in South Africa, and offer a perspective on its future.

2 Literature Review

In order to reconstruct the evolution of pharmacovigilance in South Africa, systematic searches of online literature sources and a detailed review of available relevant policy documents in the National Department of Health (NDOH) were conducted from 1 January 1987 to 30 September 2015. Search terms such as 'pharmacovigilance', 'South Africa', 'drug safety', 'medicine safety', 'antiretroviral therapy', 'pharmaceutical regulation in South Africa', 'supply chain pharmacovigilance' and 'tuberculosis drug safety' were entered into PubMed, and websites of the NDOH, Health Practitioners Council of South Africa (HPCSA), South African Pharmacy Council and the Medicines Control Council (MCC). Reviewed documents sourced within the South African NDOH included the Medicines and Related Substances Control Act 101 of 1965 (amended), the 2011/2012 Global Fund for HIV/AIDS proposal and subsequent operational plan [13] and ADR reporting guidelines [6]. Communications and emails concerning the development of the decentralised public health pharmacovigilance system that were exchanged between the national pharmacovigilance coordinator, various colleagues and stakeholders were also included in the review to establish the relative occurrence of events in the absence of published materials.

3 Pharmacovigilance Pathways in South Africa

3.1 Events Leading to the Formation of the National Pharmacovigilance Centre for Public Health Programmes (NPC)

The establishment of the National Adverse Drug Event Monitoring Centre (NADEMC) in Cape Town in 1987, by the South African NDOH Medicines Regulatory Authority (MRA) [now re-named the Food Control, Pharmaceutical Trade and Product Regulatory Authority (FPPR)], is acknowledged as the start of pharmacovigilance activities at a national level in South Africa [7, 8]. Application was soon made for full membership of the WHO Collaborating Centre for International Drug Monitoring/Uppsala Monitoring Centre (UMC). The UMC is an independent organisation, established in 1978, that operates under WHO principles to detect and analyse ADR signals in case reports submitted by member countries, facilitate information exchange between the WHO and national ADR centres, conduct pharmacovigilance research, develop training tools and software and publish pharmacovigilance information [9]. In accordance with an agreement between the WHO and the Government of Sweden, the WHO Headquarters maintains responsibility for policy issues on drug monitoring, while the operational responsibility rests with the UMC [9]. Unfortunately, owing to the existing sanctions placed on South Africa due to its then apartheid policies, membership to the WHO Drug Monitoring Programme was denied at that time. Following the release of Nelson Mandela in 1990 and the first lifting of sanctions in 1991 [10], the way was paved for membership to the WHO Drug Monitoring Programme. In 1992, having met the prescribed criteria, such as the quality and technical compatibility of its reporting format, as well as the minimum number of Individual Case Safety Report submissions (commonly referred to as spontaneous ADR reports in South Africa), South Africa became a full member of the UMC, sharing the honour of being the first African full members along with Morocco [11].

Documentation from the minutes of NDOH meetings informs that a pharmacovigilance committee, in the form of an advisory committee to the MCC, was subsequently formed by the MCC in 2002. The committee's mandate was to advise on the pharmacovigilance aspects of medicines, their production and registration, in addition to

overseeing the work of the NADEMC. In May 2003, the committee developed guidelines for ADR reporting primarily by the pharmaceutical industry and other agencies with statutory obligations to report drug safety information to the MCC [6, 12]. Then, in November 2003, the South African government approved the Operational Plan for the Comprehensive Care, Management and Treatment of HIV and AIDS (CCMT) and released it in 2004 [13]. This was timely, as Chapter XIII of the CCMT operational plan emphasised the need for a comprehensive pharmacovigilance programme as an integral part of the ART roll-out [13]. It further recognised that, in spite of ongoing mandatory monitoring of pharmaceutical companies as part of their applications during clinical trials and/or drug registration, the reporting of ADRs for all medicines had been poor, and remained limited from individual practitioners.

The operational plan for the CCMT acknowledged that, in the face of the rapidly growing epidemic, antiretroviral (ARV) registration both around the world and in South Africa had been fast-tracked. The consequent risk of unknown or poorly documented adverse medicinal effects, and drug–drug, drug–food and drug–traditional medicine interactions in the consuming South African population thus had to be investigated [13]. To achieve this, a robust local pharmacovigilance system, resourced by appropriately trained and competent HCPs who were likely to recognise and report ADRs, was urgently needed. This pharmacovigilance system would also closely monitor ART safety and counter the potential impact of ARV-related adverse effects on the South African population [13].

Based on documents and emails from the pharmacovigilance unit of the MRA, pursuant to the CCMT operational plan, and alongside the ART roll-out in 2004, two new pharmacovigilance centres were brought into a collaborative network in order to provide data to the MRA and MCC on ART safety (Fig. 1). The new centres were the Medical University of South Africa (MEDUNSA) and the Bloemfontein Pharmacovigilance Centre at the University of the Free State. These centres were to work on pharmacovigilance for adult and herbal medicines and paediatric and pregnant patients, respectively, as stated in their memorandums of understanding with the NDOH. The pharmacovigilance unit and HIV cluster of NDOH supported the initial phases of pharmacovigilance activities at MEDUNSA and the University of the Free State Centre in 2004/2005. Similarly, as it was already operational at that time, the NDOH also provided funding for the Medicines Information Centre (MIC) at the University of Cape Town in order to strengthen monitoring of medicine safety, support pharmacovigilance activities and provide information to healthcare workers. NDOH's oversight of pharmacovigilance activities at these centres declined with time, and by 2011, albeit to varying degrees, their operation was largely administered by their parent universities.

From 1987 to 2004 therefore, the pharmacovigilance programme appeared to be neither designed nor extended to include drug safety monitoring in clinical settings. Similarly, since it primarily managed drug regulation and medicine registration, it did not take into consideration issues arising from the daily management of patients in various treatment programmes [14] (Fig. 2). Furthermore, it seemed to face major challenges such as a lack of funding, lagging commitment from the necessary authorities, low capacity and poor infrastructure. Against the backdrop of the immensity of the potential ART ADR problem in South Africa, and the recognition of the need to re-conceptualise the national pharmacovigilance programme, the framework for the decentralised pharmacovigilance programme was formulated, as highlighted in proposals and operational plans to NDOH. As a result, the National Pharmacovigilance Centre for Public Health Programmes (NPC), an independent centre under the HIV/AIDS, TB, Maternal and Child Health branch of the NDOH, was established in 2004 and became fully functional in October 2014 with the appointment of its first director.

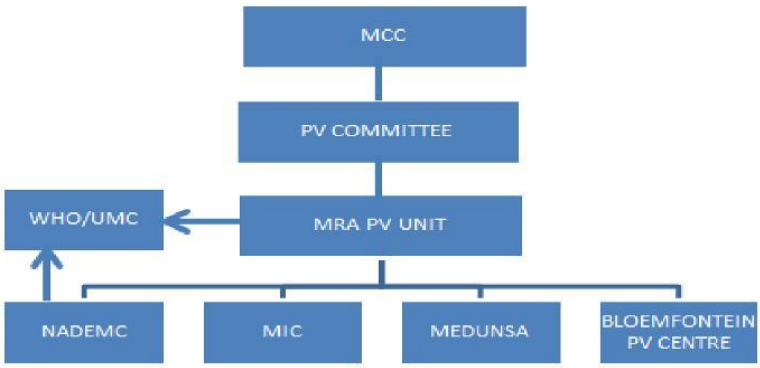

Fig. 1 Collaboration centres of the national pharmacovigilance programme. *MCC* Medicines Control Council, *MEDUNSA* Medical University Of Southern Africa, *MIC* Medicine Information Centre, *MRA* Medicines Regulatory Authority, *NADEMC* National Adverse Drug Event Monitoring Centre, *PV* pharmacovigilance, *UMC* Uppsala Monitoring Centre, *WHO* World Health Organization

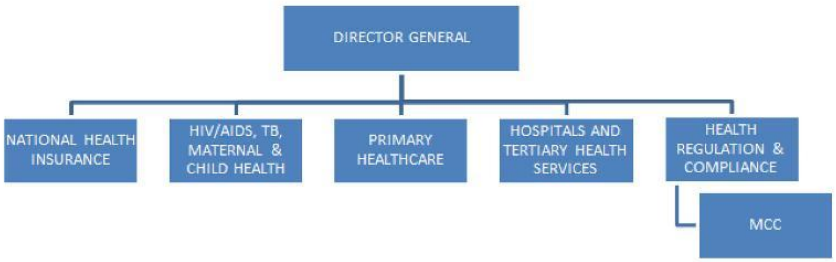

Fig. 2 NDOH organisational structure. *MCC* Medicines Control Council, *NDOH* National Department of Health, *TB* tuberculosis

3.2 Current National Pharmacovigilance Activities in South Africa

The regulatory aspects of pharmacovigilance (i.e. signal detection, ensuring provision of safe, efficacious and quality medicines, postmarketing surveillance, instituting appropriate remedial action where necessary and establishing the risk–benefit profile of all registered medical products) continues to be carried out by both the FPPR and the MCC [15]. On the other hand, pharmacovigilance at treatment sites in public health programmes is coordinated by the NPC (Fig. 3). This approach to pharmacovigilance in public health programmes targets post-regulatory approval, medicine-related problems, as well as other issues including HCP training in pharmacovigilance together with the management and prevention of ADRs. Although initially focused on anti-TB and ARV drug safety, it will be subsequently expanded to include other chronic disease programmes such as hypertension, diabetes mellitus, etc. NPC further aims to minimise medicine-related morbidity and mortality, limit the downstream adverse economic implications of medicine use and inform both the selection of and access to safe and effective essential medicines [5].

The NPC has a focused vision and effective strategy for implementing this new pharmacovigilance system in South Africa. Key components of this strategy include generating a stakeholder tracking system, initiating and/or consolidating formal relationships with existing pharmacovigilance units in the NDOH, strengthening relations with Chief Directorates such as Sector-Wide Procurement (SWP), engaging Provincial Departments of Health (PDOHs), expanding support of the current and planned ART pregnancy registries, collaborating with academic institutions and incorporating pharmacovigilance programmes, particularly those associated with NGOs, into the national database of ADR reports. Benefits that have accrued from this strategy to date include the development of cooperative working relationships with PDOHs in Limpopo, Free State, North West, Eastern Cape,

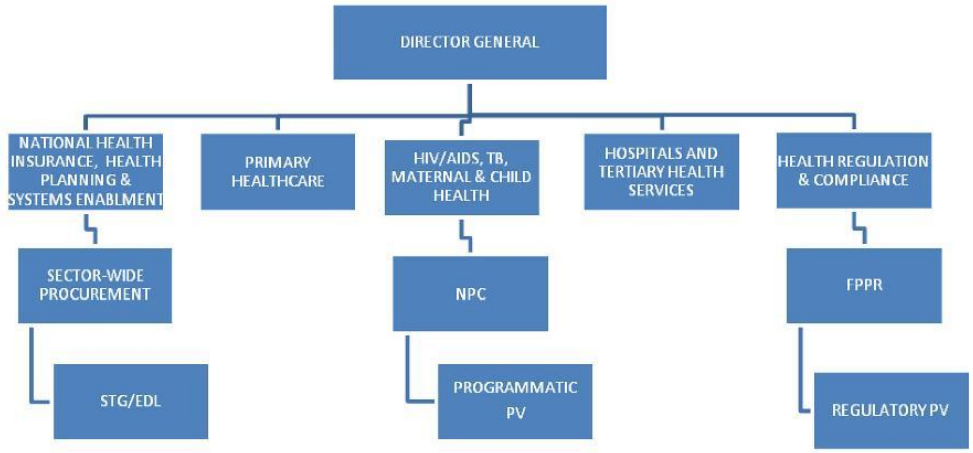

Fig. 3 Pharmacovigilance in public health programmes and pharmacovigilance centres conducting regulatory monitoring within the NDOH. *EDL* Essential Drug List (now renamed EML [Essential Medicine List]), *FPPR* Food Control, Pharmaceutical Trade and Product Regulatory Authority (formerly MRA [Medicines Regulatory Authority]), *NDOH* National Department of Health, *NPC* National Pharmacovigilance Centre for Public Health Programmes, *PV* pharmacovigilance. *STG* standard treatment guidelines

Mpumalanga, Northern Cape and Gauteng, as the new pharmacovigilance programme has been rolled out. Likewise, the close collaborations between the NPC and the pregnancy registry in KwaZulu-Natal and the subdermal contraceptive implant programmes with the Maternal Health cluster in NDOH have led to augmented public health programmes. The NDOH 2014/15–2018/19 Strategic Plan [15] places medicine procurement under the authority of the National Health Insurance, Health Planning and Systems Enablement branch that is responsible for rational medicine use and access to quality, safe and cost-effective essential medicines and pharmaceutical commodities. Standard treatment guidelines and essential medicines list (STG/EML) activities fall under the SWP. Consequently, consultations between the NPC and SWP will create avenues for monitoring and evaluation of ADRs from essential medicines and feedback within the procurement processes. Finally, to support pre-service and in-service training of HCPs in pharmacovigilance, the NPC is reviewing available pharmacovigilance training options and consulting with academic institutions to identify the best approaches for training HCPs needing to be upskilled in this discipline.

Falling under the HIV/AIDS and STIs and Maternal and Child Health branches, the NPC therefore has specific objectives for pharmacovigilance in clinical practice, public health institutions and programmes. These include the following [13, 16]:

- Improving appropriate ADR reporting by all facilities, and optimising the quality of reporting through provision of training on how to report and manage ADRs at primary healthcare (PHC) level.
- Evaluating the impact of ART and TB ADRs on patient quality of life.
- Devising strategies to minimise the economic impact of ADRs on the public health system.
- Identifying, assessing and communicating any new safety concerns associated with the use of ARVs and other medicines.
- Supporting regulatory and public health programmes through informed decision making based on information generated from the decentralised pharmacovigilance programme.
- Minimising the impact of misleading or unproven associations between adverse events and medicines including complimentary and African traditional medicines.
- Establishing an early warning system for resistance to antimicrobials, especially ARVs.
- Ascertaining the safety of medicines in pregnancy.

3.3 The Decentralised Pharmacovigilance Programme

The new robust, decentralised, patient-centred pharmacovigilance process has been successfully piloted in Mpumalanga and North West provinces, and is being rolled out in the Eastern Cape, Northern Cape, Limpopo and Gauteng at present [16, 17].

As was previously reported [4, 5] the purpose of decentralisation is to bring pharmacovigilance closer to PHC practice. Pharmacovigilance clusters consisting of multidisciplinary HCP teams of doctors, nurses, pharmacists, social workers, laboratory technicians and dieticians are formed at healthcare facilities, and meet monthly to discuss effective interventions and case management strategies per individual patient case. The formation of clusters is not prescriptive, and the provinces, districts, hospitals and clinics decide what works best in their context. Clusters are often formed where systems exist between hospitals and clinics, such as up and/or down referrals of patients, or where geographic proximity allows [4]. Decentralisation also increases general interest in medicines and medicine-related problems among clinic staff. As a result, decentralised structures create a smaller and more effective safety feedback loop that allows faster information flow back to reporters, thereby enhancing patient care. In addition to this, the clusters have the important task of informing other HCPs about ADRs with a focus on the reporting of these.

Whenever ADRs are suspected and investigated, a copy of each case report is faxed to the NPC to analyse for ADR signals and inclusion in the national database. Trends are monitored from this database generating important safety information to be circulated back to the reporting HCPs or clusters, as well as more broadly through bulletins, newsletters, internal memoranda or publication in peer-reviewed journals (Fig. 4).

3.4 Future Perspectives on Pharmacovigilance in Public Health Programmes in South Africa

A properly working pharmacovigilance system is essential for medicines to be used safely. In turn, it benefits all parties including HCPs, regulatory authorities, pharmaceutical companies and the consumers. Having therefore considered the problems and challenges facing the development of a robust pharmacovigilance system for South Africa, the NPC has developed the following short- and medium-term goals for country-wide implementation of decentralised pharmacovigilance:

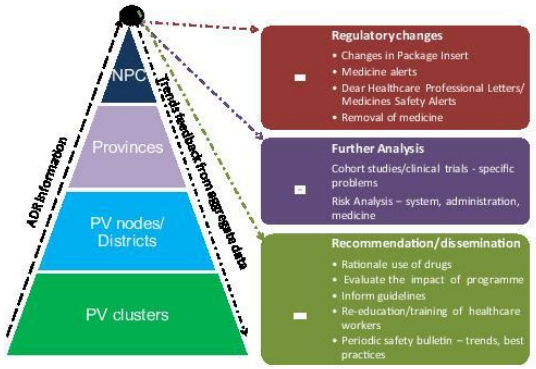

Fig. 4 Information flow in the decentralised pharmacovigilance public health programme. *ADR* adverse drug reactions, *NPC* National Pharmacovigilance Centre for Public Health Programmes, *PV* pharmacovigilance

1. A follow-up high-level stakeholders' forum to review the progress made in the implementation of the five core principles previously identified as building blocks for the national public health pharmacovigilance system during the pharmacovigilance gap-analysis workshop held in August 2012 [18]. Since this engagement is an opportunity to align new and existing stakeholders towards an identified group of common pharmacovigilance goals, the forum will also provide an opportunity for charting the next phase of public health pharmacovigilance roll-out through plans founded on a broad-based consultative process.
2. Strengthening the NPC with trained scientific and medical assessors. As an ongoing activity, intensive training will be provided in all aspects of pharmacovigilance to officials working both within the NDOH's pharmacovigilance unit as well as those in the various pharmacovigilance clusters around the country.
3. Advocating for standardised ADR reporting by all stakeholders using forms compatible with the new NPC ADR report form. This new form is dynamic, uncomplicated, easy to use, and available to all PHC centres and practicing HCPs. This should encourage reporting by all registered hospitals (both private and governmental), teaching hospitals, drug information centres and pharmacies throughout the country.
4. Engaging and/or building the capacity of academic and research institutions to educate and train future medical doctors, pharmacists, nurses and other HCPs on pharmacovigilance. At present, substantive pharmacovigilance training is not readily available at medical training institutions across South Africa. The NPC will therefore encourage the incorporation of pharmacovigilance as a strong component in existing academic curricula, so that proper theoretical and practical training can enhance student HCPs' abilities to recognise ADRs and foster a culture of reporting. The NPC will further engage academia and/or other appropriately qualified/experienced stakeholders on strategies around continued in-service training for HCPs to enhance the pharmacovigilance programme's sustainability.
5. Collaborating and creating linkages with organisations for enhancing drug safety. With advancements in information technology, there has been the emergence of new opportunities for national and international collaborations that can enhance postmarketing surveillance programs and increase drug safety [19, 20]. The WHO Programme for International Drug Monitoring provides an excellent forum for collaboration of WHO member states in pharmacovigilance and for harmonising postmarketing surveillance.
6. Developing software programs for collection and analysis of data sets, determining trends of drug usage in key disease areas, patient compliance, medication errors and drug interactions leading to ADRs.
7. Introducing patient reporting via computer and cell phones directly into the NPC's pharmacovigilance database.
8. Standardising effective indigenous protocols for treating ADRs into algorithms that can be reviewed by clinical and academic stakeholders involved in protocol and policy development, then where possible, implemented these in public health programmes.

4 Conclusions

Recently, pharmacovigilance has risen to the fore in research programmes, academia and industry. Since clinical trials involve only smaller numbers and selected groups of patients, less common adverse events are often unknown at the time when a medicine enters the market. Also, because of ethical limitations, the effects of medicines in organ-impaired patients and special populations like pregnant women and children are not studied extensively in clinical trials.

Consequently, post-marketing pharmacovigilance has gained much importance, since it uses tools such as data mining and case report investigations to explore the relationships between medicines and ADRs. Early detection of signals from both clinical trials and postmarketing surveillance studies is critical for risk identification associated with medicinal products. Signal detection and proactive risk management add new dimensions to the field of pharmacovigilance, and as evolving disciplines, require

ongoing refinement to increase their applicability to public health in South Africa.

The public health pharmacovigilance programme is a decentralised approach to pharmacovigilance that seeks to improve the quality of patient care at the point of care. Optimised patient care also requires a strong commitment to pre- and in-service functional pharmacovigilance education of all HCPs. Although only in South African public hospitals and clinics at present, the potential benefits could see pharmacovigilance education expanding into the private sector in the future. It is hoped that, as the conversations between the NPC and other agencies influencing pharmacovigilance practice in the private and public sector intensify, there will be a consolidation of the seemingly fragmented pharmacovigilance programmes across South Africa, starting with the harmonisation of data collection tools, and culminating with a holistic pharmacovigilance system.

Acknowledgments The author would like to acknowledge all the healthcare providers and administrators who have contributed to the successful evolution of the pharmacovigilance field in South Africa, and in particular to the success of decentralised pharmacovigilance as the new approach to managing ADRs in patients.

Compliance with Ethical Standards

Funding This work was not funded.

Conflict of interest Mukesh Dheda is the Director of the National Pharmacovigilance Centre for Public Health Programmes based at the National Department of Health in South Africa.

References

1. WHO Policy Perspectives on Medicines. Pharmacovigilance: ensuring the safe use of medicines. 2004. http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf. Accessed 2 Dec 2015.
2. Harmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. Eur J Clin Pharmacol. 2008;64(8):743–52.
3. Jeetu G, Anusha G. Pharmacovigilance: a worldwide master key for drug safety monitoring. J Young Pharm. 2010;2(3):315–20.
4. Dheda M. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga as pilot province for national roll-out. J AIDS HIV Res. 2013;5(9):357–65.
5. Dheda M, Distefano K, Sunduzwayo K, Williams F, Kambafwile H. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga success and moving forward. J AIDS HIV Res. 2013;5(9):370–9.
6. South African National Department of Health. Reporting of post-marketing adverse drug reactions to human medicinal products in South Africa. Guideline 2.11 Version 1.0. 2003.
7. Strengthening Pharmaceutical Systems (SPS) Program. Safety of medicines in Sub-Saharan Africa: assessment of pharmacovigilance systems and their performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington: Management Sciences for Health; 2011.
8. Essack SY, Schellack N, Pople T, van der Merwe L, Suleman F, Meyer JC, Gous AG, Benjamin D. Antibiotic supply chain and management in human health. S Afr Med J. 2011;101:562–6.
9. Uppsala Monitoring Centre. The WHO Programme. Introduction to the WHO Programme for International Drug Monitoring. 2015. http://www.who-umc.org/DynPage.aspx?id=98080&mn1=7347&mn2=7252&mn3=7322. Accessed 2 Dec 2015.
10. Sanctions Against South Africa Lifted. In: CQ Almanac 1991, 47th edn. Washington, DC: Congressional Quarterly; 1992. p. 478–79. http://library.cqpress.com/cqalmanac/cqal91-1111124. Accessed 2 Dec 2015.
11. Uppsala Monitoring Centre. WHO Programme members. http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442. Accessed 9 May 2016.
12. South African National Department of Health. Reporting of post-marketing adverse drug reactions to human medicinal products in South Africa. Guideline 2.33 Version 1.0. 2003.
13. South African National Department of Health. Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa. Department of Health 2012/13 Annual Report; 2003. RP: 237/2012 ISBN: 978-0-621-41127-0.
14. Department of Health. National antenatal sentinel HIV and syphilis prevalence survey in South Africa 2011 report. South Africa: Department of Health; 2011.
15. South African National Department of health strategic plan 2014/15–2018/19, RP: 37/2014. ISBN: 978-0-621-42474-4.
16. Decentralized HIV/AIDS and TB pharmacovigilance in South Africa: Mpumalanga province success and moving forward. Submitted to the South African NDoH, Pretoria, South Africa.
17. National Pharmacovigilance Centre. August 2014, Decentralized Pharmacovigilance Report for Northwest Province.
18. Mehta U, Dheda M, Steel G, Blockman M, Ntilivamunda A, Maartens G, Pillay Y, Cohen K. Strengthening Pharmacovigilance in South Africa. S Afr Med J. 2014;104:104–6.
19. The Erice declaration. On communicating drug safety information. Prescrire Int. 1998;7:191.
20. The European Parliament and the Council of the European Union. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;2004(L136):34–57.

Document Linking Chapter 2/ Manuscript 1 to Chapter 3/ Manuscript 2

Chapter two (2) presented "Perspectives on the Emergence of Pharmacovigilance in Public Health Programmes in South Africa," published in the Journal of Pharmaceutical Medicine.

This chapter traced the past, current and future perspectives of pharmacovigilance (PV) in South Africa's (SA's) public health programmes. It discussed events that led to SA's current PV system. This study was a review of the literature based on published and grey literature from a national perspective. Consequently, another study in a form of a baseline PV assessment from a district perspective was designed to benchmark PV activities.

Chapter three (3), published in the PULA: Botswana Journal of African Studies and herein presented in the format requested by the journal, was a study entitled "A Cross Sectional Mixed-Method Baseline Assessment of Pharmacovigilance Systems, Processes and Challenges Faced by Healthcare Professions in Three South African Districts Prior to Pharmacovigilance Training and Programme Roll-Out". This baseline assessment was conducted in order to document the knowledge, awareness and practice of PV systems among public healthcare professionals (HCPs) to understand the strategies required for roll-out of a PV programme. The baseline assessment indicated the need for an appropriate training intervention of HCPs to bridge the shortfalls identified and to ensure a successful implementation of the decentralised programme.

CHAPTER 3

Understanding of pharmacovigilance systems, processes and challenges faced by healthcare professionals in three Eastern Cape districts

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Abstract

This baseline assessment was conducted in order to document the knowledge, awareness and practice of pharmacovigilance systems among public healthcare professionals (HCPs) in the Eastern Cape (EC) Province of South Africa, as a key to understanding the strategies required for the roll-out of a pharmacovigilance programme. A semi-structured, researcher-administered questionnaire was used to interview seven key informants and 53 HCPs. Informal conversations and observations were also conducted with various other HCPs to supplement the collected information. Findings from this baseline assessment revealed limited knowledge, awareness and practice around pharmacovigilance systems and processes among HCPs and key informants. They further highlighted gaps that can inform planning for training in the province. In conclusion, the baseline assessment found gaps that indicate the need for an appropriate training intervention of all relevant HCPs impacted by the roll-out of the decentralised pharmacovigilance programme in order to ensure the successful implementation of the programme in the EC Province of South Africa.

Key words: decentralised pharmacovigilance, ADRs, Eastern Cape, pharmacovigilance systems and processes.

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Introduction

In addition to their benefits, medicines may cause harm in the form of Adverse Drug Reactions (ADRs). An ADR is defined as a response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or the modification of physiological function (WHO, 2002). ADRs are major problems and leading causes of mortality and morbidity globally (Lazarou et al, 1998; Classen et al, 1997; Mouton et al, 2015; Mouton et al, 2016).

Pharmacovigilance is defined as "the science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems". Its implementation is crucial in minimising the harm that may result from medicines (WHO, 2002). This is particularly important in South Africa, which has the largest antiretroviral therapy (ART) programme globally, one of the highest TB burdens, a multi-ethnic population as well as a high rate of use of herbal and complementary medicines.

The National Pharmacovigilance Centre for Public Health Programmes (NPC) was established by the South African National Department of Health in 2004. Through its work, it identified the lack of correct knowledge, right attitudes and perception of HCPs toward pharmacovigilance as a bottle-neck to the establishment of a robust pharmacovigilance programme. In order to document this, the NPC conducted this baseline study whose main aim was to obtain a snap-shot of pharmacovigilance systems, processes and activities in the Eastern Cape Province in order to inform interventions. The Eastern Cape Province, in particular, its districts of Amathole, Chris Hani, and Alfred Nzo, were chosen because the national pharmacovigilance programme had not been rolled out in these areas.

Methods and materials

This was a study based on a researcher-administered questionnaire as well as inevitable informal conversations and observations with various other HCPs during this process. Participants included key informants from provincial and district levels of administration as well as HCPs from healthcare facilities and the same tool was utilized to guide the interviews. Purposive sampling was used to identify the key informants while convenience sampling was used to enroll HCPs into the study. The HCPs were chosen from three randomly selected healthcare facilities within each district so that participants came from a hospital, a community health centre (CHC) and a primary healthcare (PHC). The survey was conducted over four days from the 20th July to the 23rd July 2015 in the three districts, Amathole, Chris Hani and Alfred Nzo. The sample included medical doctors, pharmacists, pharmacy assistants and professional nurses. In total, seven key informants and 53 HCPs were enrolled in the study. Data were collected using a researcher-administered, semi-structured, tablet-based questionnaire. Prior to administration, the tool and tablets were pretested and piloted in order to identify questions that don't make sense to participants, or problems with the tools. Two field workers, an adult male and an adult female, administered the questionnaires to respondents who consented to participate after being briefed about the study's objectives. A boardroom or an empty office was used to conduct the interview privately. A tablet pre-loaded with the questions was used; respondents were first

shown how to use it; then they were requested to punch in their answers to questions as they popped up. All interviews took place during working hours. The data captured from the tablet were synchronised directly with an online electronic database; hence, the dataset so constituted was exported to Microsoft Excel for analysis of socio-demographic characteristics and professional categories.

Ethics approval for the study was obtained from the Human Sciences Research Council Ethics Committee(Reference Number REC 1/19/11/14 dated 29 Jan 2015) and permission to use data was obtained from the National Department of Health.

Results

Findings from healthcare professional interviews

All the HCPs in the district were invited to participate, but only 53 participated. Of these, 18 (34.0%) were from Alfred Nzo, 11 (20.8%) from Amathole, and 24 (45.3%) from Chris Hani as shown in Table 1.

Socio-demographic characteristics

Table 1: Gender characteristics of HCPs

Gender	***Total N=53***	***Alfred Nzo N=18***	***Amathole N=11***	***Chris Hani N=24***
	N (%)	*N (%)*	*N (%)*	*N (%)*
Male	14 (26.4)	3 (16.7)	4 (36.4)	7 (29.2)
Female	39 (73.6)	15 (83.3)	7 (63.6)	17 (70.8)

Overall, the majority of participants were in the 50-59 age category. However, there were some differences in that in Chris Hani District, most of the participants were aged 30 to 59 years old; whilst in Amathole, young adults of 18-29 years old and those 50-59 years old were in equal numbers as shown in Table 2.

Table 2: Age distribution of respondents

Age categories (years)	***Total N=53***	***Alfred Nzo N=18***	***Amathole N=11***	***Chris Hani N=24***
	N (%)	*N (%)*	*N (%)*	*N (%)*
18 – 29	11 (20.8)	3 (16.7)	4 (36.4)	4 (16.7)
30 – 39	12 (22.6)	3 (16.7)	2 (18.2)	7 (29.2)
40 – 49	9 (17.0)	2 (11.1)	1 (9.1)	6 (25.0)
50 – 59	20 (37.7)	10 (55.6)	4 (36.4)	6 (25.0)
60+	1 (1.9)	0 (0.0)	0 (0.0)	1 (4.2)

Professional categories of respondents and types of facilities

The majority of respondents were nurses followed by medical doctors and pharmacists; though, in Chris Hani District, 25% of respondents were pharmacy assistants as reported in Table 3.

Table 3: Professional categories of respondents

Categories	***Total (N=53)*** *N (%)*	***Alfred Nzo (N=18)*** *N (%)*	***Amathole (N=11)*** *N (%)*	***Chris Hani (N=24)*** *N (%)*
Doctor	15 (28.3)	5 (27.8)	4 (36.4)	6 (25.0)
Nurse	24 (45.3)	9 (50.0)	5 (45.5)	10 (41.7)
Pharmacist	9 (17.0)	2 (11.1)	1 (9.1)	2 (8.3)
Pharmacy assistant	5 (9.4)	2 (11.1)	1 (9.1)	6 (25.0)

By type of health facility, the majority of respondents were based in hospitals, while others worked at primary health clinics and community health centres (Table 4).

Table 4: Respondents by facility type

Facility type	***Total (N=53)*** *N (%)*	***Alfred Nzo (N=18)*** *N (%)*	***Amathole (N=11)*** *N (%)*	***Chris Hani (N=24)*** *N (%)*
Community Health Clinic	15 (28.3)	4 (22.2)	4 (22.2)	7 (29.2)
Primary Health Care	8 (15.1)	12 (66.7)	6 (54.6)	12 (50.0)
Hospital	30 (56.6)	2 (11.1)	1 (9.1)	5 (20.8)

Knowledge and understanding of ADRs

For purposes of these results, "knowledge" refers to information or awareness gained through experience; whereas "**understanding"** is deeper as it comes from identification or realising the importance and/or interpretation or view of pharmacovigilance.When asked to identify terms related to ADRs, overall 35 (66.0%) stated that it 'is a patient response to a drug'. Others referred to an ADR as 'unintended effect', or 'unexpected effect' or as a 'noxious or negative effect' as reported in the figure below.

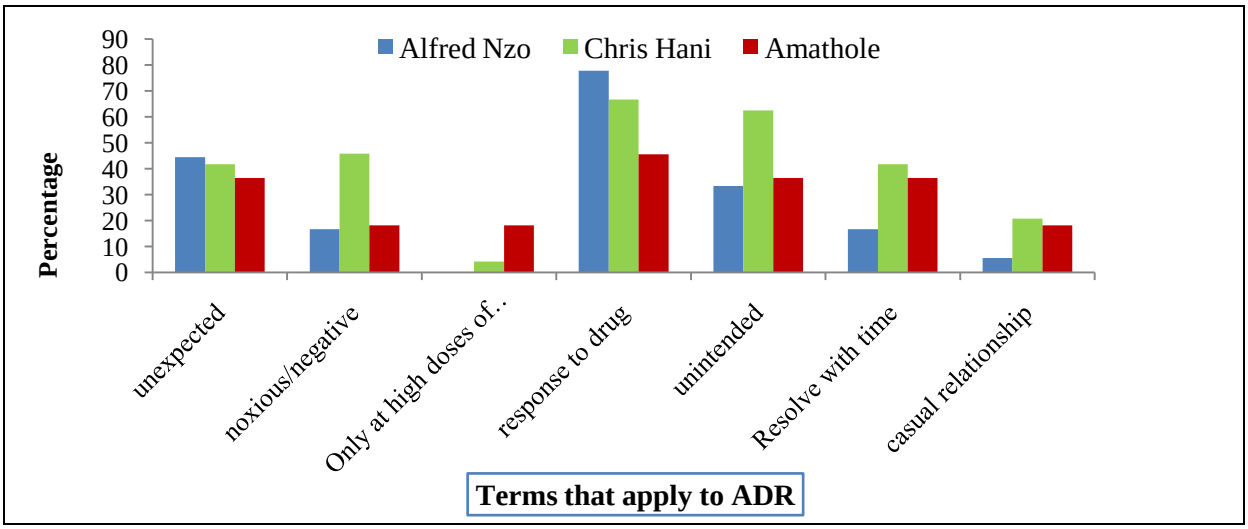

Figure 1: Summary of responses from districts on HCP understanding of the term ADR

Furthermore, approximately 45% of the respondents from each district were aware of the availability of an ADR protocol (Figure 2).

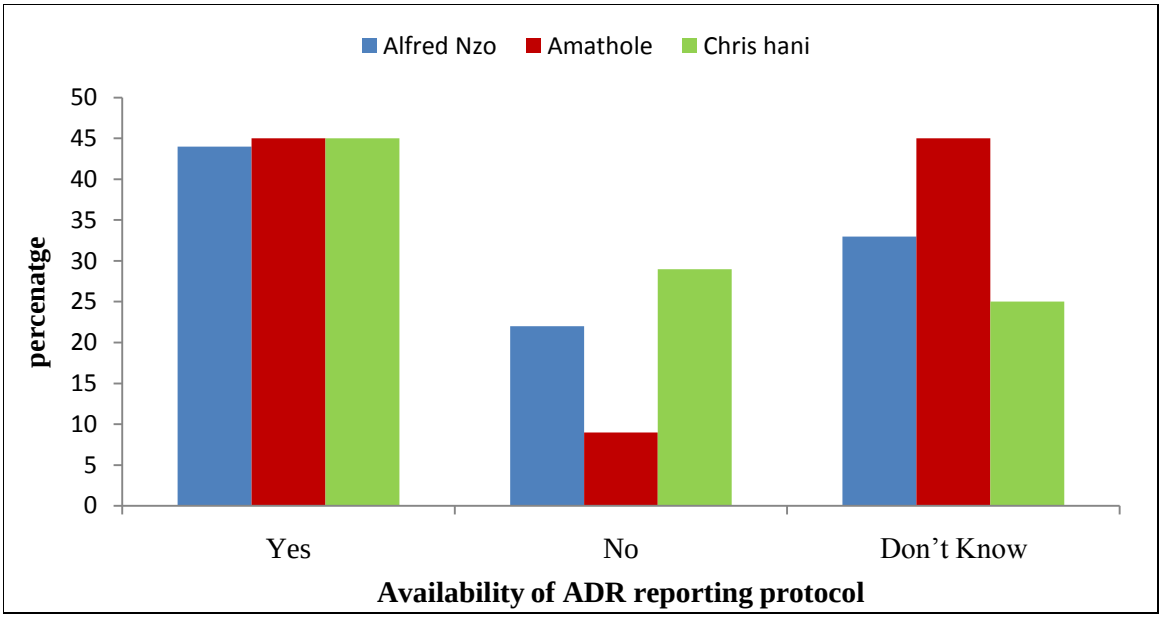

Figure 2: Awareness on the availability of a protocol for ADR reporting in the selected three districts of the Eastern Cape Province

Commonly observed ADR conditions in the province

Table 5: Commonly reported ADRs

Symptoms	***Total (N=53)***	***Alfred Nzo (n=18)***	***Amathole (N=11)***	***Chris Hani (N=24)***
	Number of respondents that observed the symptoms			
	N (%)	*N (%)*	*N (%)*	*N (%)*
Stevens Johnson Syndrome	29 (54.7)	7 (38.9)	10 (90.1)	12 (50.0)
Back pain	18 (34.0)	5 (27.8)	4 (36.4)	9 (37.5)
Fat redistribution	18 (34.0)	6 (33.3)	5 (45.5)	7 (29.2)
Dizziness	17 (32.1)	7 (38.9)	1 (9.1)	9 (37.5)
Pain/tingling/numbness	17 (32.1)	3 (16.7)	5 (45.5)	9 (37.5)
Unusual bleeding	14 (26.4)	3 (16.7)	2 (18.2)	9 (37.5)
Anaemia	12 (22.6)	3 (16.7)	2 (18.2)	7 (29.2)
Headache	11 (20.8)	3 (16.7)	3 (27.3)	5 (20.8)
Insomnia	11 (20.8)	3 (16.7)	3 (27.3)	5 (20.8)
Enlarged breasts	10 (18.9)	4 (22.2)	1 (9.1)	5 (20.8)
Fatigue	10 (18.9)	2 (11.1)	4 (36.4)	4 (16.7)
Fever	10 (18.9)	3 (16.7)	3 (27.3)	5 (20.8)
Heartburn	10 (18.9)	4 (22.2)	0 (0.0)	6 (25.0)
Nausea	10 (18.9)	1 (5.6)	4 (36.4)	5 (20.8)
Appetite loss	10 (18.8)	3 (16.7)	4 (36.4)	3 (12.5)
Abdominal pain	9 (17.0)	3 (16.7)	2 (18.2)	4 (16.7)
Diarrhoea	9 (17.0)	3 (16.7)	0 (0.0)	6 (25.0)
Renal failure	9 (17.0)	4 (22.2)	2 (18.2)	3 (12.5)
Jaundice	8 (15.1)	2 (11.1)	3 (27.3)	3 (12.5)
Vomiting	8 (15.1)	3 (16.7)	3 (27.3)	2 (8.3)
Difficulty breathing	7 (13.2)	3 (16.7)	0 (0.0)	4 (16.7)
Constipation	4 (7.6)	2 (11.1)	1 (9.1)	1 (4.2)
Rash	4 (7.6)	2 (11.1)	1 (9.1)	1 (4.2)
Persistent muscle pain	4 (7.5)	2 (11.1)	1 (9.1)	1 (4.2)
Chills	3 (5.7)	0 (0.0)	2 (18.2)	0 (0.0)
Depression	3 (5.7)	1 (5.6)	0 (0.0)	6 (25.0)
Cough	1 (1.9)	0 (0.0)	1 (9.1)	0 (0.0)
Loss of libido	1 (1.9)	0 (0.0)	1 (9.1)	0 (0.0)

The most common ADRs cited were Stevens-Johnson syndrome, back pain, fat redistribution, dizziness and peripheral neuropathy. In total, 28 ADRs were cited (Table 5).

Post-ADR protocol for patient Care

A higher percentage of the respondents from Amathole district, as compared with the other two, were not aware of the availability and existence of a post-ADR patient care protocol (Figure 3).

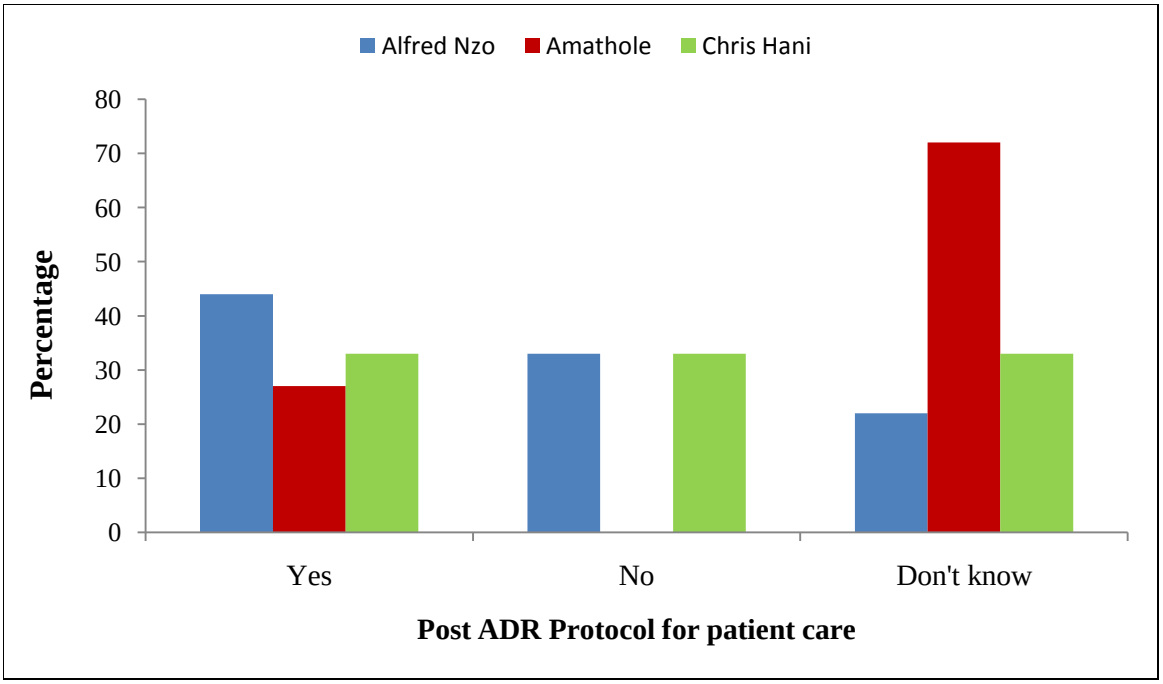

Figure 3: Awareness, by district, of the availability of a protocol for patient care following the report of a suspected or confirmed ADR.

Pharmacovigilance programme

Between 27% and 34% of participants reported a formal pharmacovigilance programme at their facility (Figure 4). The remaining participants either reported no existence of a formal programme (average 37.7%) or that they had no knowledge of any formal programme (average 30.2%).

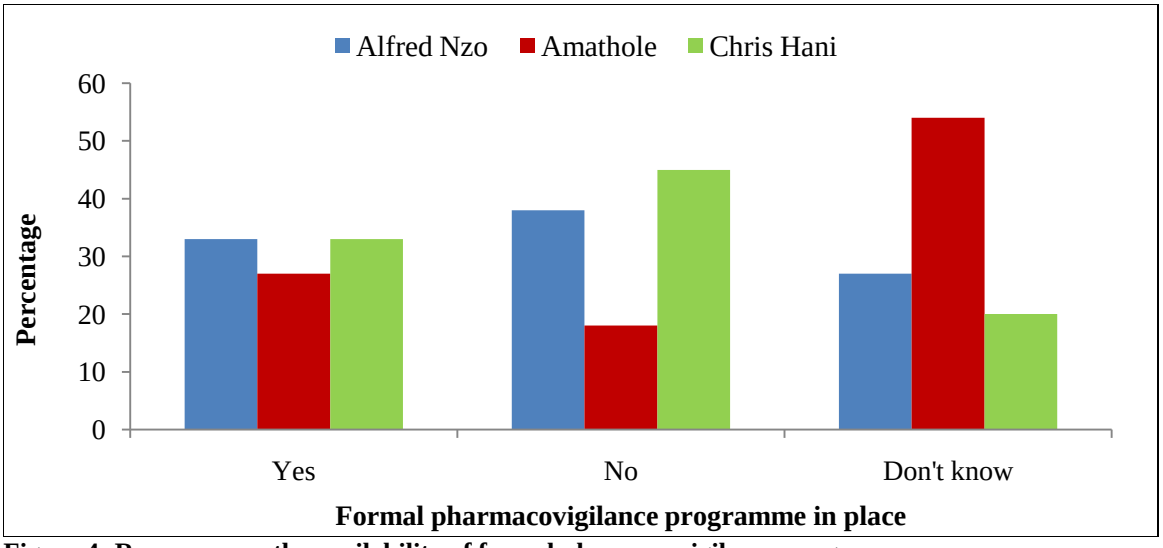

Figure 4: Responses on the availability of formal pharmacovigilance programme

Pharmacovigilance training needs

When asked about specific training needs in pharmacovigilance, it is noteworthy that no respondent mentioned the need to be trained in the detection and reporting of ADRs (Table 6).

Table 6: Training needs to improve ADR reporting

Training area	***n***	***%***
ADR reporting regulations in South Africa	39	73,6
Effective communication and risk management in pharmacovigilance	35	66,0
ADR Alerting Conditions	31	58,5
Understanding common serious ADRs to ART	28	52,8
Counseling patients to address side effects of ART	27	50,9
Causality Assessment in pharmacovigilance	19	35,8
Adherence to ART	19	35,8
Decentralised pharmacovigilance for Public Health	18	34,0
ADR Detection and Reporting by healthcare professionals	0	0,0

As shown in Table 6, more than half of respondents stated that they needed to be trained. This training included topics such as regulations about ADR reporting, risk communication and management, ADRs alerting conditions (premonitions), understanding of serious ADRs and how to counsel patients about ADRs experienced.

ADR Reporting

The majority of respondents (N=49, 92.5%) stated that ADRs are reported. Among them, 39 (73.6%) indicated that observed ADRs were only reported internally within their facilities; nine (17.0%) stated that ADRs are reported both internally and to external agencies; and one (1.9%) stated that reporting was done to external agencies only. In this group, the frequency of reporting as described as follows: 20 (41.7%) always, 6 (12.5%) usually, 13 (27.1%) sometimes, and 9 (18.8%) rarely. It is noted that while four (7.6%) persons did not report any identified ADRs at all.

Factors influencing ADR reporting

When asked about factors that facilitated reporting, the most cited reason for reporting an ADR was the level of seriousness (17, 32%) followed by the HCP's obligation to report (16, 30.2%) as reported below (Table 7).

Table 7: Factors influencing ADR reporting

Factors mentioned	*Total (N=53)*		*Alfred Nzo (N=18)*		*Amathole (N=11)*		*Chris Hani (N=24)*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
The intensity and severity of patient symptoms	17	32,1	3	16,7	4	36,4	10	41,7
My responsibility/obligation to do so as a health worker professional	16	30,2	6	33,3	2	18,2	8	33,3
My confidence in the suspected diagnosis	12	22,6	5	27,8	3	27,3	4	16,7
My position in my organization	11	20,8	1	5,6	2	18,2	8	33,3
Availability of ADR forms	10	18,9	4	22,2	2	18,2	4	16,7
Familiarity with the process for reporting suspected ADRs internally.	10	18,9	3	16,7	1	9,1	6	25,0
The availability of time to make a report	6	11,3	1	5,6	1	9,1	4	16,7
Unstated	2	3,8	0	0,0	1	9,1	1	4,2

Findings from key informants

Due to the unpredicted unavailability of some personnel, out of the 15 planned key informant interviews, only seven took place. These were as follows: 2 in Alfred Nzo, 3 in Amathole and 2 in Chris Hani. These key informants were provincial and district mid- to senior-level managers. They were asked questions on issues such as the existence of ADR reporting protocols, data flow systems and usefulness of ADR data, the perceived reporting culture among HCPs, the burden of care on the health system due to ADRs, likely pharmacovigilance training needs for HCPs and finally, possible approaches for managing ADR patient outcomes.

It is interesting to note that the key informants confirmed the existence of protocols for ADR reporting in their districts or the province, but acknowledged underreporting by HCPs. They also acknowledged the disadvantage to the health system of not knowing the true burden of morbidity due to ADRs in the absence of valid data. When probed further about underreporting of ADRs, they cited negative attitudes and unavailability of time as completing forms was time-consuming. They also cited lack of feedback on reports submitted. Other reasons cited were collated as follows:

- Limited HCP knowledge about ADRs
- Reluctance to report for fear of negative consequences on reporter
- Infrequency of the observed incidence of ADRs
- Transport challenges making it difficult to deliver and collect completed forms from CHC/PHC
- Unavailability of reporting forms at clinics
- Competing healthcare priorities
- Overwhelmed clinical staff due to high patient numbers
- The general lack of awareness of ADR reporting by clinicians
- No culture of reporting
- No legal requirement for HCPs to report

Discussion

A baseline assessment is a key tool in the preparatory stages preceding the implementation of a new programme. It enables gathering information for planning and strategising a proposed intervention(s). The results of this assessment have revealed several challenges to the successful introduction of the decentralised pharmacovigilance programme in the Eastern Cape Province and highlighted key issues needing attention.

Knowledge and understanding of ADRs

Although the majority of HCPs had some knowledge of terms applicable to the description of an ADR, this knowledge varied from district to district with the gap in positive knowledge about ADRs being greatest between the Chris Hani and the Amathole respondents. This finding concurs with what was reported in a study from KwaZulu-Natal (Nlooto and Sartorious, 2015). However, since respondents from all districts failed to consistently choose the best descriptive terms for ADRs, the results clearly show that upgrading and standardising knowledge and understanding of ADRs by HCPs in this province must be prioritised.

A similar study investigating HCP knowledge, experience and challenges of reporting ADRs also revealed that scanty reporting was a result of poor knowledge and limited experiences of HCPs (Parrella et al., 2013). This approach is therefore expected to produce a positive change in ADR reporting by HCPs and optimise the introduction of the decentralised pharmacovigilance programme.

Commonly reported ADRs

The most commonly encountered ADRs were Stevens Johnsons Syndrome, peripheral neuropathy, fat redistribution and back pain, all consistent with the drugs commonly used in the national ART programme. Despite the opinion of some key informants that the lack of reporting is a consequence of the HCPs' lack of knowledge about ADRs, this finding highlights the existence of a good level of knowledge about common ADRs to ART (Nlooto and Sartorius, 2015). It also suggests that one approach to improving reporting would be to build upon their existing knowledge and increase HCPs confidence in reporting with supplementary knowledge about assessing, understanding and managing a wider range of ADRs.

Training of health professionals

Findings in this study are consistent with previous reports about the importance of continued training of HCPs in South Africa (Letlape et al, 2014). They suggest that in-service training is crucial for HCPs. This is particularly important for the decentralised pharmacovigilance programme as evidenced by the findings of this survey. Other studies have likewise accentuated the importance of strengthening the HCP's knowledge and understanding of the processes of identification and reporting of ADRs at facility levels (Anderson et al, 2011; Parrella et al, 2013).

Pharmacovigilance programmes and ADR reporting systems

A greater proportion of HCPs across the districts were not aware of either the availability of an ADR protocol for patient care following reporting of an ADR or a pharmacovigilance programme at their facility. This lack of awareness and lack of shared pharmacovigilance information potentially compromises the quality of patient care. In order to cultivate a robust pharmacovigilance programme, it is imperative that information on pharmacovigilance systems, processes and guidelines in districts and provinces are clearly communicated to HCPs (WHO, 2004; Malangu, 2014).

Further, the value of the system must be continuously reiterated through feedback to HCPs on ADR trends and updates in ADR management strategies (Mehta et al, 2014). The findings from key informant interviews highlighted the commonality of the negative HCP attitude to identifying and reporting ADRs across the districts despite the presence of some system for reporting. The findings provide a context for understanding the responses of the HCPs and structuring the proposed intervention to complement provincial and district-level strategies and objectives (Van Grootheest and De Jong-van den Berg, 2005).

Monitoring the number of ADR reports in any treatment programme is a key outcome useful in evaluating the implementation success of a pharmacovigilance programme. The many reported challenges to ADR reporting by HCPs draw attention to specific activities and interventions that can be resolved through targeted training and the creation of clear and reporting protocols and paradigms (Jacob et al, 2013; Zhang et al, 2014). However, this baseline study has identified specific areas for intervention that should facilitate a smooth introduction of the new pharmacovigilance programme with the HCPs of the Eastern Cape.

Limitations of the Study

This baseline survey had several limitations. The cadre and number of participants could not be obtained as envisaged on account of challenges encountered at district level as there are many vacancies and even when available, they were unable to participate in the study due to other commitments. Furthermore, the sample size was small and thus not representative of all HCPs in the province. Additionally, the limited timeframe for the exercise to be completed meant that there was no alternative day to re-visit the field for additional interviews (Yin, 2013). However, the findings have provided insights of what ought to be considered in planning and implementing a pharmacovigilance system in the province. Finally, the scope of this particular analysis was quantitative excluding qualitative data obtained using the tool as well as that obtained through informal conversations.

Conclusion

This baseline assessment study has provided information for development of a training intervention in the Eastern Cape Province. It has offered a snap-shot of the knowledge, awareness and practice of pharmacovigilance in the target districts. The findings of this study, will inform the national programmatic pharmacovigilance efforts. They contribute meaningfully to the ability of the National Department of Health to develop

an appropriate training intervention for the decentralised pharmacovigilance programme provincially.

Acknowledgements
This baseline research was supported by the International Training and Education Centre for Health (I-TECH), through funding from the US Department of Health Resources and Services Administration (HRSA), Cooperate Agreement U91HA06801. The authors would also like to acknowledge the National Department of Health, National Pharmacovigilance Centre, the Provincial Government and District Management Teams in Eastern Cape Province. The content of this report represent the views of the authors and do not represent those of HRSA, the US Government and/or those of the National Department of Health of South Africa.

Conflict of Interests

In order to avoid conflict of interest, the two obligations namely researcher and director of the National PV Centre were separated by ensuring no interference with interpretation of the results as obtained. Furthermore, the authorships and/or field work included other role players and collaborators (including those external to the NDoH PV Centre, acknowledgements section refers). Therefore, the data collected, as well as interpretation thereof involved other role players and this is in itself is a safeguard preserving the integrity of the research.

References

Anderson, C., Krska, J., Murphy, E., & Avery, A. The importance of direct patient reporting of suspected adverse drug reactions: A patient perspective. *British Journal of Clinical Pharmacology*. 2011; 72(5):806-22 http://doi.org/10.1111/j.1365-2125.2011.03990.x

Classen, D. C., Pestotnik, S. L., Evans, R. S., Lloyd, J. F., & Burke, J. P. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *Journal of the American Medical Association.*1997; 277(4), 301-306

Dheda, M. Perspectives on the Emergence of Pharmacovigilance in Public Health Programmes in South Africa. *Pharmaceutical Medicine,* 2016; 30(4), 213–219.

Jacob, D., Marrón, B., Ehrlich, J., & Rutherford, P. A. Pharmacovigilance as a tool for safety and monitoring: a review of general issues and the specific challenges with end-stage renal failure patients. *Drug Healthcare Patient Safety,* 2013; 5: 105-112.

Lazarou, J., Pomeranz, B. H., Corey, P. N. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *Journal of the American Medical Association,* 1998; 279(15), 1200-1205.

Letlape Herman, R., Koen Magdalena, P., Coetzee Siedine, K., Koen, V. The exploration of in-service training needs of psychiatric nurses. *Health SA Gesondheid*, 2014; 19(1): 1-9.

Malangu, N. Pharmacovigilance in South Africa: Undocumented undergraduate training and practice. *World Journal of Pharmaceutical Sciences* 2014; 2 (3), 210-212

Mehta, U., Dheda, M., Steel, G., Blockman, M., Ntilivamunda, A., Maartens, G., ... & Cohen, K. Strengthening pharmacovigilance in South Africa.*South African Medical Journal*2014; 104(2): 104-106.

Mouton, J. P., Njuguna, C., Kramer, N., Stewart, A., Mehta, U., Blockman, M., … Cohen, K. Adverse Drug Reactions Causing Admission to Medical Wards. *Medicine.*2016; 95(19): e3437.

Mouton, J. P., Ushma, M., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., … Cohen, K. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. *British journal of Clinical Pharmacology.*2015; 80(4): 818-826.

Nlooto, M., & Sartorius, B. Differences in awareness and practice of adverse event reporting among doctors, nurses, pharmacists and post-basic pharmacist assistants in HIV clinical practice in the eThekwini Metropolitan Health district, South Africa.*Pula: Botswana Journal of African Studies.*2015; 28(1), 90-104.

Parrella, A., Braunack-Mayer, A., Gold, M., Marshall, H., Baghurst, P., Iskander, J., DeStefano, F. Healthcare providers' knowledge, experience and challenges of reporting adverse events following immunisation: a qualitative study. *BMC Health Services Research.*2013: 13(1): 313.

Van Grootheest, A. C., De Jong-van den Berg, L. T. W. The role of hospital and community pharmacists in pharmacovigilance. *Research in Social and Administrative Pharmacy.*2005; 1(1): 126-133.

World Health Organisation. Safety of Medicines. http://apps.who.int/iris/bitstream/10665/67378/1/WHO_EDM_QSM_2002.2.pdf 2002. [Accessed 27 July 2017]

World Health Organization. The Importance of Pharmacovigilance - Safety Monitoring of medicinal products. WHO, 1–52. http://doi.org/10.1002/0470853093 2002. [Accessed 27 July 2017]

World Health Organization. Guidelines on safety monitoring of herbal medicines in pharmacovigilance systems.http://apps.who.int/medicinedocs/documents/s7148e/s7148e.pdf [Accessed 27 July 2017]

Yin, R. K. . Case study research: Design and methods. Sage publications.Thousand Oaks, 2013. 4th ed. 2009, pp. 240

Zhang, L., Wong, L. Y., He, Y., Wong, I. C. Pharmacovigilance in China: current situation, successes and challenges.*Drug safety. 2014; 37(10): 765-770.*

Document Linking Chapter 3/ Manuscript 2 to Chapter 4/ Manuscript 3

After conducting "A Cross Sectional Mixed-Method Baseline Assessment of Pharmacovigilance Systems, Processes and Challenges Faced by Healthcare Professions in Three South African Districts Prior to Pharmacovigilance Training and Programme Roll-Out" presented in Chapter three, the researcher then proceeded to design and conduct an intervention. The latter was in the form of a one-day didactic training.

Herein therefore, Chapter 4 presents a study entitled "Investigation of the Effect of a One-day Pharmacovigilance Training of Healthcare Professionals" This study aimed to measure the impact of this one-day training as a response to the findings presented in Chapter 3.

It found an increase in healthcare professionals' knowledge regarding pharmacovigilance after the training. However, despite this increment, it is clear that certain aspects of the overall training need to be re-emphasised to have an even greater impact.

CHAPTER 4

Investigation of the Effect of a One-day Pharmacovigilance Training of Healthcare Professionals

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Abstract

Introduction

A key objective of the decentralised pharmacovigilance programme is to increase the knowledge of in-service Healthcare Professionals on pharmacovigilance to enable them to develop a habit and practice of reporting adverse drug reactions. It is imperative to evaluate the impact of the training offered, as it is a key component of the national decentralised pharmacovigilance programme.

Objectives: The aim of this study was to evaluate the impact of a one-day decentralised pharmacovigilance programme training of healthcare professionals on pharmacovigilance in South Africa.

Methods: Self-administered structured, pre- and post-training questionnaires were retrospectively reviewed.

Results: The healthcare professionals' knowledge regarding pharmacovigilance in South Africa significantly increased after the one-day training intervention ($P < 0.002$). There was an increase in the number of correct answers to every question, albeit to varying degrees. However, despite this incremental increase, it is clear that various aspects of the overall training need to be re-emphasised to have an even greater impact.

Conclusion

There is a strong indication of a positive shift in knowledge gained albeit to varying degrees.

Introduction

Pharmacovigilance (PV) is the science and activities related to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) or any other drug-related problem.[1] The National Department of Health's (NDoH's) Pharmacovigilance Centre for Public Health Programmes (NPC) in South Africa established in 2004 embarked on a programme to decentralised PV in 2010. Currently, the focus of this programme is on the management of ADRs in public health programmes such as HIV and TB. To date, 2919 healthcare professionals (HCPs) were trained in seven of South Africa's nine provinces[2]. These include 169 physicians, 618 pharmacists, 1317 Nurses and 798 allied healthcare professionals.

Spontaneous reporting by HCPs has been shown to play an important role in identifying drug safety issues[3]. However, underreporting of ADRs has been a real and persistent problem for PV programmes. In order to improve the reporting rate, it is important to educate the HCPs about PV approaches, its tools and its impact on both the cost and quality of patient care. Ideally, the most appropriate time to train HCPs would be during the undergraduate training. In the South African context, PV has not been a very strong component of undergraduate training, or if it exists, it remains largely undocumented[4].

Given the background of insufficient PV training of undergraduates, the in-service training of HCPs as part of the decentralised PV programme is a very positive development. A key objective of the decentralised PV programme is to increase the knowledge of in-service HCPs on PV and ADRs and to enable them to develop a habit and practice of reporting spontaneously. As this in-service training is a key component

of the NDoH decentralised PV programme, it is imperative that the impact of the training is evaluated.

The aim of this investigation was to assess the impact of a one-day PV training provided during the roll-out of the PV programme.

METHODS

Design

This is a descriptive before and after study

Study Setting

The setting for this study is in South African public health facilities, specifically in Pixley ka Seme and Namaqualand districts of Northern Cape Province, where PV training was conducted between February and March 2015. All healthcare professionals in the two districts were invited to attend the training through a memorandum from the Provincial Head of Department. In particular, the training was aimed at HCPs without previous pharmacovigilance training. The training is expected to contribute to professional development and increase in PV knowledge of the participants. Participants are then expected to apply this to their practice and also to cascade the knowledge gained to other HCPs in their facilities who could not attend the training.

Training Intervention

One-day didactic training sessions, delivered by NPC staff, were held to introduce the theory and practice of PV together with the various systems and processes involved in PV practice in South Africa. NPC organised the training. Four hours of theory, interspersed with four hours of discussion and ADR reporting practice, was given to groups of between 30 and 50 participants. The participants were made up of a heterogeneous assortment of doctors, nurses and pharmacists but also included a few social workers and laboratory technicians.

Sample Size Determination and Sampling Technique

As the study population was small, all the participants that came for training were surveyed.

Data Collection Instrument

To compare the knowledge levels before and after training, a peer-reviewed, structured, self-administered questionnaire was developed for use as a pre-test/post-test tool. Prior to administration, the tool and tablets were pretested and piloted with three staff members at the NDoH in order to identify questions that didn't make sense to participants, or identify problems with the tool and/or tablet.

The objective of this investigation was to measure the impact of the training. The tool had sixteen items and used both open and closed questions. This study used twelve relevant quantitative questions (questions 2 to 13) that related directly to the aims of the study.

Data Analysis

All collected data were captured in Microsoft Excel (Microsoft Corp, Redmont, WA, USA) and exported to STATA 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP) for the statistical analysis. The numbers of correct answers for each question before and after the training were the variables of interest. Descriptive analyses were run to determine proportions of correct and wrong answers per question and the overall correct answers. One sample test of proportions was employed to determine differences between the results for each question of the questionnaire as well as the overall results. A p value less than 0.05 was considered statistically significant.

Ethical Considerations

Full ethical approval for the study was obtained from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (HSS/1328/016D), and permission to use the data was obtained from the South African National Department of Health.

Results

Gender

All the HCPs in the district were invited to participate, but only 137 HCPs were trained, and 129 were included in the analysis (Table 1). Eight HCPs that came in late for training and only completed a post-test questionnaire, were excluded from the analysis. Proportionally, 32.6% (42) were male whereas 67.4% (87) were female.

Table 1: Gender and Professional Categories Trained

Gender	***Total N=129***	***Cadre***
	N (%)	
Male	42 (32.6)	Physicians 3 (2.3) Nurses 22 (17.1) Pharmacists 8 (6.2) Other 9 (6.97)
Female	87 (67.4)	Physicians 1 (0.78) Nurses 65 (50.4) Pharmacists 6 (4.65) Other 15 (11.63)

Professional categories

The majority of the HCPs trained were nurses (87; 65 females, 22 males). Others were 4 physicians (1 female, 3 males), 14 pharmacists (6 females, 8 males) and 24 "other" healthcare workers (15 females, 9 males). The "other" healthcare workers constituted pharmacy assistants, counsellors, laboratory personnel and data capturers.

Responses to Questions Pre- and Post-training

The statistics of the responses to the questions in the tool are presented in Table 2.

Table 2: Responses to questions in the pre- and post-test (n = 129).

		Pre-Test	Post-Test	
Question number	**Questions**	**Correct answers (%)**	**Correct answers (%)**	**Test of proportion *p* value**
Pharmacovigilance Concepts and Theory				
2	Which objective of pharmacovigilance do you think is most important	80 (62)	98 (76)	<0.01
5	All of the following are threats to national ADR reporting in SA except...	31 (24)	41 (31.8)	0.05
7	Which of the following persons should NOT attend meetings of the PV committee	72 (55.8)	109 (84.5)	<0.01
9	Which of the following is a requirement for proper reporting of an ADR to a PV centre	66 (51.2)	104 (80.6)	<0.01
10	Which of the following is/are true about spontaneous reporting of ADRs	63 (48.8)	70 (54.3)	0.25
12	Which of the following does not determine the increased concern about drug safety	32 (24.8)	33 (25.6)	0.8
13	Which of the following does not support ethical PV	37 (28.7)	39 (30.2)	0.8
Systems and processes in pharmacovigilance and its decentralization				
3	Which of the following is/are responsible for monitoring Adverse Drug Reactions in South Africa	9 (7)	11 (8.5)	<0.01
4	What do you think would be the main advantage of decentralised PV in SA	76 (58.9)	78 (60.5)	0.64
6	Within a decentralised PV programme, where would assessments of ADR interventions be discussed	12 (9.3)	96 (74.4)	<0.01
8	Which of the following should NOT be a goal of the decentralised system of PV in SA	23 (17.8)	31 (24.0)	0.11
11	Which represents a logical flow of information about ADRs in a decentralised PV system	65 (50.4)	80 (62)	0.01
	TOTAL PERCENTAGE	**36.6**	**51**	0.002
	TOTAL NUMBER	**566**	**790**	

Discussion

Gender and Professional Characteristics

The majority of HCPs who attended the training and responded to the pre- and post-test were nurses followed by "other" healthcare workers, pharmacists and physicians in that order. This information is of considerable interest when seeking to request permission for the proportions of HCPs to attend training. The proportions trained were found to be representative of the proportions of HCPs in districts.

Responses to the Pre- and Post-training Questionnaires

A heterogeneous mixture of questions on PV and the systems and processes involved in PV practice were asked in the pre and post-test. The result of these tests did not show any specific trends that favoured either an increase in the knowledge of the concept of PV or an increase in the knowledge of systems and processes. However, there was an overall positive shift in improved knowledge for each of the questions asked, albeit to varying amounts.

In some areas where there were only small increases in the knowledge gained (Questions 2,9,11 and 12). These were flagged for consideration. This may be due to contamination of the testing instrument, where there may be some ambiguity or misunderstanding with the question/s, and/or areas of weakness in the training. The latter may result from a gap between materials delivered versus specific questions asked. This discussion is grouped into two areas:

1. Pharmacovigilance concepts and theory (Questions 2, 5, 7, 9, 10, 12, 13))
2. Systems and processes in pharmacovigilance and its decentralisation (Questions 3, 4, 6, 8, 11)
3. Questions 1, 14, 15 and 16 did not form part of this quantitative analysis as they are part of another study

Pharmacovigilance Concepts and Theory

Which objective of pharmacovigilance do you think is most important? (Question 2 in Questionnaire)

The participants were tested for their knowledge and awareness of the primary aim of pharmacovigilance which is patient safety before (n = 80, 62%) and after the training (n = 98, 76%). The results showed a statistically significant improvement (p = <0.01). Healthcare providers need to understand that with every medicinal product comes its own benefit-harm scale, and that they should always ensure the medicine used is more beneficial.

All of the following are threats to national ADR reporting in South Africa EXCEPT? (Question 5 in Questionnaire)

The participants were taught the importance of reporting ADRs to understand that medicines safety data has to be collated, aggregated and analysed in order to pick up signals. That there was not a significant improvement in the before (n = 31, 24%) and after responses (n = 41, 31.8%) (p = 0.05) is an indication that the training needs more emphasis on the adverse consequences of underreporting on PV.

Which of the following persons should NOT attend meetings of the PV committee? (Question 7 in Questionnaire)

The participants were tested for their awareness about who should be present in the cluster and/or pharmacovigilance committee meetings. Based on the programmatic recommendations, the patient should not form part of the committee. Before the training, only 72 participants (55.8%) answered correctly to this question. After the training, the number of correct answers increased significantly (n = 109, 84.5%, p < *0.01*).

Which of the following is a requirement for proper reporting of an ADR to a PV centre? (Question 9 in Questionnaire)

The correct answer to this question provided information on the awareness of trainees of the importance of a properly and fully completed an ADR form. Sixty six (51.4%) of the trainees gave correct answers before the training which increased significantly to 104 (80.6) ($p < 0.01$) just after the PV training.

Which of the following is/are true about spontaneous reporting of ADRs? (Question 10 in Questionnaire)

The spontaneous reporting system is the easiest and cheapest to establish and presently, it is the bedrock of the current decentralised PV programme in SA[5]. Before the training, 63 participants (48.8%) gave the correct answer which slightly increased to 70 participants (54.3%) after the training, an increase that was not statistically significant ($p = 0.25$). These results suggest that more training and information on the methods of reporting in pharmacovigilance be given.

Which of the following does not determine the increased concern about drug safety? (Question 12 in Questionnaire)

Pharmacovigilance and drug safety concerns have recently come into the spotlight on account of the rapid scale up of ART (pre-exposure prophylaxis [PrEP], revised guidelines to include universal test and treats among others) as well as multidrug resistant tuberculosis (MDR-TB), concerns around co-morbidities and prevalence of traditional medicines use[6]. HCPs are required to understand the reasons for the increased concerns. That there was no significant increase ($p = 0.8$) between before ($n = 32$, 24.8%) and after the training ($n = 33$, 25.6%) is of great concern. This training going forward should be revised to include materials that will put more emphasis on these growing concerns in large treatment programmes.

Which of the following does not support ethical PV? (Question 13 in Questionnaire)

The training gives information on confidentiality, patient education and handling of patient personal identifier information when reporting . Unfortunately, there was no significant difference ($p = 0.8$) in the correct responses given before ($n = 37$, 28.7%)

and after (*n* =39, 30.2%) the training. This is an indication that more emphasis needs to be placed on ethical consideration in training going forward.

Systems and processes in pharmacovigilance and its decentralisation

Which of the following is/are responsible for monitoring Adverse Drug Reactions in South Africa? (Question 3 on Questionnaire)

Since 1987, the Medicines Control Council (MCC) of South Africa has been the regulatory body responsible for monitoring the safety of all medicinal products used in South Africa. In 2004, the SA NDoH formed the NPC[(7)]. The participants were tested for their awareness of the existence of the latter and the former bodies. Before the training, only nine participants (7%) were aware of either of the two bodies responsible for monitoring ADRs in South Africa. After the training, although a statistically significant result (p = <0.01) was found, the number only increased to 11 (8.5%). The results obtained, with a mere increase of two, suggest that the component of understanding the PV systems and processes in SA is still poorly understood. It is proposed therefore that this component of the training be reinforced in the future and that more information, education and communication material be distributed in public health.

What do you think would be the main advantage of decentralised PV in SA? (Question 4 in Questionnaire)

The decentralised pharmacovigilance programme was established in June 2011 and is currently being rolled-out into Mpumalanga, Northwest, Eastern Cape, Northern Cape, Limpopo, parts of KwaZulu Natal and the Free State provinces. This question tested the awareness of the participants on the programme with regard to the purpose of a decentralised PV programme. The results, 76 correct answers before (58.9%) and 78 (60.5%) after did not increase significantly (p = 0.64). What was interesting, however was the fact that a large number of participants (>59%) clearly understood the main advantage of a decentralised pharmacovigilance process. During the training, information relating to the advantages of decentralising PV in public health, especially in the era of HIV/AIDS and MDR-TB, and the benefits of the resulting rapid decision-

making in rational medication use in patient treatment and management were emphasised.

Within a decentralised PV programme, where would assessments of ADR interventions be discussed? (Question 6 in Questionnaire)

The decentralised PV programme is constituted of pharmacovigilance clusters and/or mini pharmacovigilance centers[8]. The latter and the former are formed between facilities that have existing referral lines and/or proximity. The clusters themselves are multidisciplinary platforms that include doctors, pharmacists, nurses and other para-medical staff such as laboratory personnel and counsellors. It is within these structures that pharmacovigilance activities are expected to the take place. These clusters form the backbone of the decentralised programme and trainees are expected to clearly understand their role in the overall programme. Comparatively, before (n = 12, 9.3%) and after the training (n = 96, 74.4%) the awareness by HCPs increased significantly ($p < 0.01$). This gives an indication that participants really understood their enhanced role in the decentralised PV programme post training.

Which of the following should NOT be a goal of the decentralised system of PV in SA? (Question 8 in Questionnaire)

The question about the goals of pharmacovigilance was answered correctly by 23 (17.8%) of the trainees before and 31 (24%) after the training. The score did not increase significantly after the training ($p = 0.11$).

Which represents a logical flow of information about ADRs in a decentralised PV system? (Question 11 in Questionnaire)

The correct answer to this question provided information on the awareness of trainees around PV systems and flow of data/information. 65 (50.4%) of the trainees gave correct answers before the training which increased significantly to 80 (62%) ($p < 0.01$) just after the PV training. This, together with the increase in knowledge of their enhanced role in the decentralised PV programme, is a positive signs for both the training and the programme.

General comments

The HCPs overall knowledge about PV significantly increased after the training ($p < 0.002$). The increase was for every question, albeit to varying degrees. However, despite this increment, it is clear that various aspects of the overall training need to be re-emphasised to have an even greater impact.

It has been previously shown that healthcare professionals knowledge about PV was inadequate in some countries and it was reported that ADR reporting's increased after the training[9–12]. Therefore, healthcare professionals' training is very important to increase ADR reporting.

The training of HCPs in PV has been conducted before. However, this is the first study of the impact of the training currently provided to HCPs in the SA public health system. Overall, the knowledge of HCPs increased soon after the training. However, a further study needs to be conducted to establish whether this increase remains steady in the long term.

Studies have shown that HCPs have limited knowledge about PV resulting in low spontaneous ADR reporting rates. One of the reasons for this was an inadequate knowledge of how to report ADRs[13–15]. This therefore highlights the importance of appropriate PV training.

Limitations

One limitation of the study is the mode of assessing the impact which depended on the respondent's ability to recall if they had prior knowledge of PV, which may be subject to recall bias. Furthermore, a truly representative sample was not achieved since HCPs were not selected from each of the five districts or indeed provinces of SA. Thirdly, selection bias may occur as respondents who were more interested in PV may have been the only ones who attended the workshop, as it was not compulsory. Fourthly,

long term knowledge retention was not conducted. Furthermore, individual's and HCP cadre's gain in knowledge was not coded to link the pre- and post-training data. Finally, a before-after design is sometimes considered to be a weak design when evaluating effects of interventions.

Conclusion

This study investigated the impact of a one-day PV training provided during the roll-out of the PV programme. There is a strong indication of a positive shift in knowledge gained albeit to varying degrees. It has also highlighted areas of training that needs further strengthening. As the impact of training was evaluated shortly after the intervention, it is suggested that long term knowledge retention, as well as its translation into increased quality and quantities of reports be investigated.

References

1. WHO Policy Perspectives on Medicines. Pharmacovigilance: ensuring the safe use of medices [Internet]. Geneva; 2004. Available from: http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf [accessed on 31 Oct 2016]
2. NDoH. Global Fund for HIV/AIDS, TB and Malaria. Pretoria; 2015, Presentaion by Pharmacavogilance Centre for Public Health.
3. Begum SS, Mansoor M, Mahadevamma L KB. Tools to improve reporting of adverse drug reactions - A review. Int J Pharm Sci Rev Res [Internet]. 2013;23(1):262–5. Available from: http://globalresearchonline.net/journalcontents/v23-1/49.pdf\nhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013720628 [Accessed on 27 July 2017]
4. Malangu N. Pharmacovigilance in South Africa: Undocumented undergraduate training and practice. World J Pharm Sci Pharmacovigil South Africa. 2014;210–2.
5. Dheda M. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga as pilot province for national roll- out. Journal of AIDS and HIV

Research. 2013;5(9):357–65.

6. Clayden P, Collins S, Frick M, Harrington M, Horn T, Jefferys R, et al. 2016 Pipeline Report [Internet]. London; 2016. Available from: http://i-base.info/htb/wp-content/uploads/2016/07/2016-Pipeline-Report.pdf [Accessed on 27 July 2017]

7. Dheda M. Perspectives on the Emergence of Pharmacovigilance in Public Health Programmes in South Africa. Pharmaceut Med [Internet]. 2016;30(4):213–9. Available from: http://dx.doi.org/10.1007/s40290-016-0150-x Accessed on 27 July 2017]

8. Dheda M, Distefano K, Williams F, Kambafwile K. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga Success & Moving Forward. Journal of AIDS and HIV Research 2013;5(5). Available from: http://www.academicjournals.org/JAHR

9. Naritoku DK, Faingold CL. Development of a therapeutics curriculum to enhance knowledge of fourth-year medical students about clinical uses and adverse effects of drugs. Teach Learn Med [Internet]. 2009;21(2):148–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19330694

10. Shankar PR, Subish P, Mishra P, Dubey AK. Teaching pharmacovigilance to medical students and doctors. Indian J Pharmacol [Internet]. 2006;38(5):316–9. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-33749590380&partnerID=40&md5=38907165fbb72bfd53eee72b94feffcf Accessed on 27 July 2017]

11. Rehan HS, Vasudev K, Tripathi CD. Adverse drug reaction monitoring: knowledge, attitude and practices of medical students and prescribers. The National Medical Journal of India. 2002; 15(1): 24–6.

12. Hema NG, Bhuvana KB, Sangeetha. Pharmacovigilance: The extent of awareness among the final year students, interns and postgraduates in a government teaching hospital. J Clin Diagnostic Res. 2012;6(7 SUPPL.):1248–53.

13. Oshikoya KA, Senbanjo IO, Olufemi AO. Interns' knowledge of clinical pharmacology and therapeutics after undergraduate and on-going internship training in Nigeria: a pilot study. BMC Medical Education [Internet]. 2009; 9: 50 Available from: http://www.medilam.ac.ir/LinkClick.aspx?fileticket=7qP2yO-n-pM=&tabid=9423 Accessed on 27 July 2017]

14. Hardeep, Bajaj JK RK. Survey on the Knowledge, Attitude and the Practice of Pharmacovigilance Among the Health Care Professionals in a Teaching Hospital in Northern India. J Clin Diagnostic Res. 2013;7(1):97–9.

15. Pedrós C, Vallano A, Cereza G, Mendoza-Aran G, Agustí A, Aguilera C, Danés I, Vidal X AJ. An intervention to improve spontaneous adverse drug reaction

reporting by hospital physicians: a time series analysis in Spain. Drug Saf; 2009; 32 (1):77–83.

ATTACHMENT 1

NATIONAL PHARMACOVIGILANCE CENTRE: DECENTRALISED PHARMACOVIGILANCE PROGRAMME
PRETEST

INSTRUCTIONS: This pretest is being administered anonymously by the National Pharmacovigilance Center (NPC) to determine the level of awareness about pharmacovigilance among persons participating in the first training session of the provincial rollout of the programme of decentralised pharmacovigilance. You are requested to answer these questions to the best of your knowledge and experience..

WHERE RELEVANT, SELECT THE BEST RESPONSE GIVEN.

PERSONAL CODE:	**GENDER:** ☐Male ☐ Female

1. What do you understand about pharmacovigilance?

2. Which objective of pharmacovigilance do you think is MOST important?

A. To facilitate early detection of Adverse Drug Reactions (ADRs) and other drug-induced problems
B. To calculate the incidence of ADRs
C. To identify predisposing factors to ADRs.
D. To identify unrecognized ADRs

3. Which of the following is/are responsible for monitoring Adverse Drug Reactions in South Africa? (**You may choose more than 1 response**).

- ☐ National Comprehensive Care, Management and Treatment HIV/AIDS & TB Programme Unit (CCMT)
- ☐ Medicines Control Council
- ☐ Health Professions Council of South Africa
- ☐ South African Pharmacy Council
- ☐ South African Nursing Council
- ☐ South African Medical Council
- ☐ National Pharmacovigilance Center
- ☐ National Adverse Drug Event Monitoring Center

4. What do you think would be the MAIN advantage of decentralised pharmacovigilance in South Africa?

A. Improved patient care at the point of identification of ADRs
B. To implement spontaneous reporting of ADRs
C. To replace the MRA system of pharmacovigilance
D. To increase reporting of ADRs

5. All of the following are threats to national ADR reporting in South Africa EXCEPT?

A. Underreporting by health care providers, patients and other parties
B. Absence of an ADR problem among patients
C. Lack of a National policy for mandatory ADR reporting
D. Parallel reporting of ADRs to agencies independent of the NDOH

6. Within a decentralised pharmacovigilance program, where would assessments of ADR interventions be discussed?

A. At the level of the provincial DOH
B. At meetings of the clusters
C. At meetings of the pharmacovigilance committees
D. At meetings of the National Pharmacovigilance Center

7. Which of the following persons should not attend meetings of the pharmacovigilance committee?

A. The Doctor
B. The Patient
C. The Nurse
D. The Social Worker

8. Which of the following should NOT be a goal of the decentralised system of pharmacovigilance in South Africa?

A. To increase central management of ADRs by the National Pharmacovigilance Center
B. To improve ADR reporting and the quality of the reports
C. To inform national treatment guidelines
D. To encourage districts to formulate their own specific ADR prevention strategies

9. Which of the following IS a requirement for proper reporting of an ADR to a pharmacovigilance center?

A. A fully completed ADR Form
B. A telephone call or email to the National Pharmacovigilance Center
C. Full personal details of the patient
D. Prior reporting and review of the proposed ADR by the provincial DOH

10. Which of the following is/are TRUE about spontaneous reporting of ADRs?

A. It is one of the most useful ways of detecting rare adverse reactions to drugs.
B. It is an important source of information to regulatory agencies for changes in label requirements or removing drugs from distribution.
C. It is one of the cheapest means of collecting information on adverse reactions to drugs
D. All of the above are true about spontaneous reporting of ADRs

11. Which represents a logical flow of information about ADRs in a decentralised pharmacovigilance system?

A. From National Pharmacovigilance Center → provincial DOH → district hospitals → feeder clinics
B. From feeder hospitals → provincial DOH → provincial district clinics
C. From provincial district hospitals → National Pharmacovigilance Center → provincial DOH
D. From provincial clinics → provincial district hospitals → provincial DOH → National Pharmacovigilance Center

12. Which of the following does NOT determine the increased concern about drug safety?

A. The rapid scale-up of ARV treatment in this country
B. The high level of co-morbidities and co-infections in the HIV-infected population
C. The prevalence of the use of traditional medicines in place of/along with ARVs
D. The increased number of nurses managing the HIV-infected population

13. Which of the following does NOT support ethical pharmacovigilance?

A. Signed caregiver confidentiality agreements
B. Educating patients on pharmacovigilance and adverse drug reaction management.
C. Coding of clinic details and personal identifiers
D. Staff training on ethical health care practice

14. List three (3) topics a health professional should be trained on to practice pharmacovigilance effectively?

1.
2.
3.

15. Suggest four (4) objectives for a hospital pharmacovigilance programme.

1.
2.
3.
4.

16. What three (3) steps can be taken once a pharmacovigilance committee suspects an ADR?

1.
2.
3.

Document Linking Chapter 4/ Manuscript 3 to Chapter 5/ Manuscript 4

In Chapter 4 the participants were trained on the detection, assessment, understanding and management of ADRs and thereafter the importance of reporting. Consequently, the next phase of this research was to conduct an analysis of ADR reports. Chapter 5 presented herein is a "Descriptive Analysis of ADRs from the National Department of Health's Pharmacovigilance Centre for Public Health Programmes in South Africa" which has been submitted to Journal of the International AIDS Society.

This paper describes the analysis of data received from post-training data collected from the programme. It found areas where the PV programme needs to strengthened as well as the successes the programme achieved. It also detected the top causative agents causing safety issues in the HIV and TB programmes, the most common ADRs, as well as the difference in rate of ADRs experienced by males and females.

This pharmacovigilance programme may have the potential for extracting important data that can be used to inform HIV and TB programme treatment guidelines, identify trends and generate hypotheses to be further investigated.

CHAPTER 5

Evaluation of a Human Immunodeficiency Virus and Tuberculosis Pharmacovigilance Programme in the Public Health Sector of South Africa by Descriptive Analysis of the Adverse Drug Reactions Submitted by Healthcare Professional.

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Key words: Pharmacovigilance, Antiretroviral, Gender, Surveillance, adverse drug reactions, suspected medicine, training, low cost setting.

Key points: A decentralised approach to meet the pharmacovigilance challenges of rapidly expanding large scale public health programmes.

The most frequently reported ADRs: lipodystrophy, followed by renal failure.

The most commonly implicated medicines: stavudine, then tenofovir.

A disproportionately higher percentage of ADRs to zidovudine and nevirapine were reported for females

A disproportionately higher percentage of ADRs to efavirenz and abacavir were reported for males.

Abstract

Aim

Interrogation of adverse drug reaction reports submitted to provide a descriptive analysis of the data.

Introduction

Human immunodeficiency virus and tuberculosis pose major challenges for South Africa. In response, South Africa is rapidly scaling up its treatment programmes to end these epidemics. The Pharmacovigilance Centre for Public Health Programmes established an affordable decentralised pharmacovigilance programme as a national strategy to meet the safety challenges of these programmes.

Methods

We conducted a descriptive analysis of retrospectively collected anonymised suspected adverse drug reaction reports from the antiretroviral and tuberculosis programmes in South Africa submitted between 01 May 2013 and 31 March 2016.

Results

Healthcare professionals representing 704 of 4047 facilities (17.4%) were trained to report adverse drug reactions to support the pharmacovigilance programme. All 5063 reports submitted from the programme were reviewed, analysed and profiled. The most frequently implicated medicines were stavudine (30.7%) and tenofovir (19.9%) and the most frequently cited adverse drug reactions were lipodystrophy and renal failure. Females experienced a disproportionally higher percentage of adverse drug reactions from zidovudine and nevirapine, while males experience a disproportionally higher percentage of adverse drug reactions from efavirenz and abacavir.

Discussion

Reporting of adverse drug reactions began soon after training. Doctors and nurses did the bulk of the reporting, while pharmacists lagged behind even though a high percentage of pharmacists were trained to report. The implicated medicines were largely as expected. There were disproportionate percentages of adverse drug reactions reported in males and females to a number of medicines. The analysis raised questions, suggestions and hypotheses regarding a number of trends that require more specific and more detailed analysis of the adverse drug reactions.

Conclusion

The decentralised pharmacovigilance programme was effective in that it detected the top causative agents implicated in safety issues, the most common adverse drug reactions, as well

as gender difference in rate of adverse drug reactions experienced. This pharmacovigilance programme has the potential for extracting important data that may inform treatment guidelines as well as achieve health systems strengthening in South Africa. This approach is recommended for use in low-income settings.

INTRODUCTION

One of the most significant public health concerns South Africa (SA) continues to face is human immunodeficiency virus infection and subsequently acquired immunodeficiency syndrome (HIV/AIDS). An estimated 6.19 million people (16.6% of population) are HIV-positive. Approximately 3.4 million of these persons have been initiated on anti-retroviral therapy (ART)[1]. SA also has a high tuberculosis (TB) burden, with approximately 1% of the population developing active TB disease each year and 63% are co-infected with HIV[2]. In order to tackle these challenges, SA has been rapidly scaling up public health HIV and TB programmes for the past few years, and currently has the largest ART programme globally[3]. With SA's adoption of the ambitious United Nations Programme on HIV/AIDS's (UNAIDS) 90-90-90 treatment goals by 2020, the global plan to end the HIV epidemic as a public threat by the year 2030, as well as the Universal-Test-and-Treat approach, the number of people on ART in SA will grow significantly.

The morbidity experienced with medicines used to treat HIV and TB [hepatatoxicity with most TB medicines, lactic acidosis with stavudine (d4T), renal failure with tenofovir (TDF) and anaemia with zidovudine (AZT)], and its subsequent decrease in the quality of life, treatment discontinuation, loss of productivity, healthcare costs and medicine resistance[4] validate the need for an efficient monitoring and reporting system for Adverse Drug Reactions (ADRs) in all public health programmes, especially the HIV and TB programmes.

ADRs, which are associated with substantial morbidity and mortality, are leading causes of death even in developed countries[5]. In the latter, it has been estimated that 1 in 16 hospital admissions are due to ADRs, with the reported incidence of serious ADRs as high as 6.7% in some cases[6]. The percentage of hospital admissions due to ADRs in some countries such as Norway, France and the United Kingdom is more than 11%[7]. A recent cross-sectional survey conducted in four hospitals in SA found that 8.4% of admissions were ADR-related[8]. ADRs impose a high financial burden due to their high costs and some countries spend up to 15-20% of their hospital budget dealing with drug complications[9]. With the

largest HIV/AIDS ART programme globally, the financial burden of ADRs on SA's health budget is expected to be colossal.

The National Department of Health's Pharmacovigilance Centre for Public Health Programmes (NPC), as part of the National ART strategy, designed, piloted and implemented a decentralised PV programme in response to these safety challenges[10,11]. An approach where healthcare professionals (HCPs) are trained and capacitated to form and manage mini PV centres. These centres oversee all activities and management of ADRs emanating from their facilities. This participatory approach encourages multidisciplinary teams of healthcare professionals to work together to identify, report and manage any ADRs reported by patients.

HCPs were trained on why, what and how to report ADRs and encouraged to complete the ADR reporting form and email or fax the completed form back to the NPC. In the absence of fax and email facilities at the healthcare centre, a book containing triplicate carbonised ADR forms were used. A focal person collects these forms and submits them to the NPC in a manner that is most convenient to the cluster. Once received, data from these forms are then entered into a database at the NPC.

This PV system for public health programmes is easily implementable in resource-constrained settings, such as in SA. It uses existing infrastructure and resources to collect PV information that is converted into useful medicines safety information to manage ADRs effectively. This approach is dynamic and therefore easily adaptable to any low income setting with significant benefits. This manuscript aims to interrogate adverse drug reaction reports submitted to NPC to provide a descriptive analysis of the data.

METHODOLOGY

A retrospective review of anonymised suspected ADRs from the ART and TB programmes in South Africa was conducted. All 5063 reports submitted between 01May 2013 and 31 March 2016 were reviewed. All reports were capture into a database at NPC. The data were extracted into a Microsoft Access database and into an Excel spreadsheet. All reports were analysed. Reports with missing information were also analysed, e.g 800 (15.8%) reports that did not mention the cadre of HCPs or 763 (15.1%) reports that did not included an ADR or a medicine. The missing information was included in the various tables, categorised as "item not stated".

Data were interrogated as follows:

1. Number of facilities that participated in the training/roll-out.
2. Number of facilities that are documenting their PV activities as well as submitting reports to the NPC.
3. Number and cadre of the healthcare professionals that participated in the training.
4. Number of reports submitted as well as their descriptive statistics which were analysed for most common suspected drugs using STATA10® (StataCorp, 2007).

Ethical approval

Full ethical approval for the study was obtained from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (HSS/1328/016D), and permission to use the data was obtained from the South African National Department of Health.

RESULTS

The decentralised PV programme was rolled out in six of SA's nine provinces over the period under consideration (Table 1).

Table 1: Number of facilities reporting per province from 01May 2013 to 31 March 2016

Area/Province	**Total Facilities**[12]	**Trained Facilities**	**Facilities Reporting**
National	4047	704	587
Eastern Cape	877	73	85
Free State**	250	0	2
Gauteng	400	10	33
KwaZulu Natal	741	0	24
Limpopo**	512	231	215
Mpumalanga	340	195	137
North West	369	107	79
Northern Cape	241	82	7
Western Cape**	317	6	5

** provinces still to receive training in pharmacovigilance

Table 2: Type of facilities reporting

Type of Facility Reporting	Number of Reports	%
Provincial / District Hospital	3458	68.3
Community Healthcare Centre	499	9.9
Primary Healthcare Centre	1106	21.8
Total	5063	100.0

NPC trained 2150 healthcare professionals including doctors, nurses, pharmacists and other allied healthcare professionals (Table 3). Other workers include community healthcare workers and counsellors.

Table 3: Cadre of HCPs who participated in the training workshops

Healthcare Professional	Number	%
Nurse	876	40.7
Pharmacist	475	22.1
Doctor	170	7.9
Social Service	46	2.1
Laboratory Personnel	4	0.2
Other*	579	26.9
Total	**2150**	**100**

* Community healthcare workers and counsellors.

Table 4: Cadre of HCPs reporting ADRs

Healthcare Professional Reporting	Number	%
Nurse	2248	44.40
Pharmacist	554	10.94
Doctor	1461	28.86
Cadre not stated	800	15.80
Total	5063	100.00

Adverse Drug Reaction Reports

The cumulative total number of ADR reports received during the period was 5063. The average age of the patients that experienced ADRs was 40.7 years and 56.6% were females (Table 5). Among the female patients, 4.12% were pregnant. The most common allergy was to cotrimoxazole.

Table 5 : Descriptive Statistics of Adverse Drug Reaction Reports Received by NPC

Descriptive Statistics	
Characteristics	**Number of ADR reports (%) N=5063**
Age in years	
<10	128 (2.5)
10-20	226 (4.5)
21-30	425 (8.4)
31-40	1476 (29.2)
41-50	1316 (26.0)
>50	1090 (21.5)
Age not stated	402 (7.9)
Total	5063
Average Age	40.7
Sex	**Number (%)**
Males	1619 (32.0)
Females	2866 (56.6)
Pregnancy	118 (4.1% of females)
Sex not stated	578(11.4)
Total	5063
Allergies (Total)	**23**
Antibiotic:cotrimoxazole, penicillin	6,1
ARVs: NNRTIs, NVP, EFV, AZT	1,3,1,1
TB drugs:not specified TB drugs, INH, Terizidone	2,1,1
Food:pork, fish	1,1
Allergy to substance not stated	4

ADR adverse drug reaction, ARV antiretrovirals, AZT zidovudine, EFV efavirenz, INH isoniazid, NNRTI non nucleoside reverse transcriptase inhibitors, NVP nevirapine, TB tuberculosis,

1 **Table 6 : Profile of the most suspected ADR-causing medicines**

Suspected Medicine	Female Number (% of column 3)	Male Number (% of column 3)	Total Number of reports implicating suspected medicine	Total Percentage (% of column 3)	Sum of top 6 medicines and sum of rest of medicines
Column Number	1	2	3	4	5
Notes	a	b	c	d	
Stavudine	931 (59.9)	456 (29.4)	1552	30.7%	
Tenofovir	554 (54.9)	350 (34.7)	1010	19.9%	
Lamivudine	291 (60.5)	158 (32.9)	481	9.5%	
TDF/FTC/EFV	230 (53.2)	154 (35.7)	432	8.5%	83%
Zidovudine	235 (58.6)	72 (18.0)	401	7.9%	
Efavirenz	145 (45.0)	143 (44.4)	322	6.4%	
Nevirapine	114 (79.7)	18 (12.6)	143	2.8%	
Rifafour	57 (54.3)	41 (39.1)	105	2.1%	
Abacavir	41 (39.1)	53 (50.5)	105	2.1%	
Cotrimoxazole	40 (62.5)	17 (26.6)	64	1.3%	
Enalapril	21 (43.8)	18 (37.5)	48	0.9%	
Emticitabine	25 (53.2)	16 (34.0)	47	0.9%	
Aluvia	21 (60.0)	13 (37.1)	35	0.7%	
Pyrazinamide	11 (40.7)	12 (44.4)	27	0.5%	17%
Isoniazide	11 (52.4)	7 (33.3)	21	0.4%	
Hydrochlorthiazide	11 (57.9)	7 (36.4)	19	0.4%	
Kanamycin	7 (38.9)	8 (44.4)	18	0.4%	
Combivir	13 (86.7)	2 (13.3)	15	0.3%	
Medicine not stated	14 (36.8)	9 (23.7)	38	0.8%	
Other medicines	103 (57.2)	55 (30.5)	180	3.6%	
Total	2876(56.8)	1605(31.7)	**5063**	**100.0%**	100%

Notes

a. % of females that experience ADRs from the suspected medicine

b. % of males that experience ADRs from the suspected medicine

c. sum of male and females does not equal the total number of ADR reports due to missing gender values in the ADR reports

d. % of total reports

TDF/FTC/EFV tenofovir/emtricitabine/efavirenz

2

Generally, the most commonly suspected ADR causing medicine reported was stavudine, followed by tenofovir with 30.7 and 19.9% respectively. The rest of the suspect drugs were under 10%. Notably, the recently introduced fixed dose combination (FDC) containing tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) was attributed to 8.5% of the reported suspected ADRs.

Table 7: Profile of the top five ADRs and medicine suspected to have caused the ADRs

Name of ADR	Number of ADR reports	Females (%)*	Male (%)*	Drug suspected
Lipodystrophy	238	141 (59.2)	57 (24.0)	Stavudine
Renal Failure	134	69 (51.5)	39 (29.1)	Tenofovir
Lactic acidosis	131	65 (49.6)	29 (22.1)	Stavudine
Anaemia	94	56 (59.6)	17 (18.1)	Zidovudine
Renal impairment	88	43 (48.9)	38 (43.2)	Tenofovir

*sum of male and females does not equal the total number of ADR reports due to missing gender values in the ADR reports

DISCUSSION

The decentralised PV programme was implemented in six of SA's nine provinces as at 31 March 2016. Healthcare professionals from 704 of the 4047 public healthcare facilities in South Africa were trained. Of the 704 facilities, a large number of facilities (587) began reporting immediately after training (Table 1). It can also be seen that majority of the facilities trained were reporting ADRs. This is significant progress. However, if SA is to achieve its 90-90-90 objectives as well as successfully manage the anticipated universal test and treat programme, it still needs to increase its efforts to extend the programme to all the facilities country-wide.

Hospitals reported the bulk of the ADRs (68.3%, Table 2). Of the 5063 ADRs reported, close to 70% were from provincial or district hospitals, with Primary Healthcare Centres (PHCs)

accounting for a further 21.8% and the remainder from Community Healthcare Centres (CHCs). This maybe attributable to the current focus of PV training on hospitals with CHCs and PHCs serving as feeder facilities to the hospitals.

Cadres of Healthcare

The widespread introduction of multidisciplinary teams for ADR management through the formation of clusters and mini-PV centers country-wide presents clear advantages in light of the increasing complexity of ART treatment and medicines safety decision-making. Training of all cadres of healthcare workers help to bring together a range of backgrounds to discuss and agree on treatment recommendations and ongoing management for individual patients.

All categories of healthcare workers were encouraged to attend. Training was done in groups of multidisciplinary team. Emphasis was placed on nurses and pharmacists that are directly involved in the HIV/TB programmes. Nurses managing these programmes in clinics were actively recruited.

Only 10.9% of the ADR reports were completed by pharmacists (Table 4) even though 22% (Table 3) participated in the training workshops. This may be due to pharmacists having less frequent and regular interaction with the patient. Activities to engage pharmacists with patients and other cadres of HCPs need to be encouraged.

Nurses completed the bulk of the reports (44.4%) (Table 4). The NPC strategy to focus on the training of nurses worked successfully. This strategy was based on nurse dispensing ARVs and initiation of ART in SA[13]. While the percentage of doctors reporting was also high (28.9%), this maybe due to the doctors finalising ADRs reports that were initiated and identified by other members of the health team.

ADR REPORTS

Age

The age ranges with the highest number of ADR reports were 31–40 years, and 41–50 years as well as above 50 years with 29.15, 25.99 and 21.53% respectively. Of note is the low number of ADRs reported amongst children under ten years as well as teenagers (2.5% and 4.5% respectively). This maybe due to the smaller percentage of people living with HIV in these age groups [14] or a consequence of underreporting in these groups.

Sex

A higher percentage of ADRs were reported for females (56.6%) than males (32%). The percentage is in keeping with the SA national survey, where the prevalence rate of HIV for females is 55%[14] and 44% for males. A recent study[13] found similar results to this study where a lower rate of ADRs were reported for males (32%). It appears that females are more susceptible to adverse events related to antiretroviral treatment than males [15].

Suspected Medicines

Profiling the top causative agents causing safety issues is important for the treatment programmes. d4T was the top causative agent. The top six medicines causing ADRs were ARVs and they accounted for 83% of the ADRs reported (Table 6).

Females reported a disproportionally higher percentage of ADRs from zidovudine (AZT) and nevirapine (NVP) (Table 6). Males reported a disproportionally higher percentage of ADRs from efavirenz (EFV) and abacavir (ABC).

The higher percentage of females with ADRs to AZT (Table 6) was probably largely driven by anaemia, which is more prevalent in females and possibly more females received AZT, especially earlier in the reporting period as part of PMTCT programme[16]. It was also found that females maintain a significantly higher intracellular concentration of AZT[17]. Females were also placed on NVP from the PMTCT programme and many were switched to NVP from EFV when they fell pregnant, in the early years of the ART programme. This may also explain why women have a lower percentage of ADRs to EFV compared to men. Further, SA's ART programme started with the prevention of mother to child transmission (PMTCT) in the year 2002[18], with the use of AZT then NVP and later dual therapy (AZT and NVP). The Highly Active Anti-retroviral Therapy (HAART) programme only started in 2004 with the issuing of free ARVs in the public sector to the more sick patients[16]. The initial regimen was d4T/3TC/EFV.

Women reported a higher percentage of lipodystrophy from d4T. A prospective study in Uganda showed that d4T toxicity was almost twice as likely in women as in men[19]. Lactic acidosis, a common ADR of d4T, was also reported to be more frequent in women than men (Table7). This was particularly in the initial years of ART therapy, where the regimen was

d4T/3TC/EFV. In 2010, South Africa changed its ART guidelines; d4T was phased out and replaced with TDF[20].

The most commonly reported ADRs were lipodystrophy and renal failure with the top suspected agent for these ADRs being d4T and TDF respectively (Tables 6, 7). There have been changes to the HIV treatment guidelines that have removed d4T from first-line therapy. Earlier implementation of this decentralised PV programme may have resulted in the earlier removal of d4T from the first-line regimen.

As expected, TDF was the lead suspect drug for renal and urinary disorders. It was also implicated to be a suspect agent in skin and subcutaneous disorders. This maybe due to its co-formulation with EFV or concomitant treatment with cotrimoxazole. It is therefore suggested that the PV programme include more elaborate training in determining and pinpointing the medicine causing the ADR/s.

Other medicines on the ART programme reported to cause ADRs include 3TC (9.5%), FDC (TDF/FTC/EFV)(8.5%), AZT (7.9%) and EFV (6.4%,Table 6).The high percentage of ADRs suspected for 3TC maybe due to its frequent use in combination with other ARVs: AZT/3TC, TDF/3TC and d4T/3TC.

The relatively high percentage of ADRs to the FDC is most likely due to the TDF or EFV components of the FDC. Patients taking the FDC tablet are expected to experience the same ADR profile as patients taking the three individual drugs. However, upon switching from individual drugs to FDC, some patients have reported experiencing oedema as a new ADR. It is uncertain whether this is associated with the binding components within the co-formulation or alternatively it may be due to better compliance to treatment. It may be due to the FTC, although oedema is not a common side effect of FTC.

The above findings raised questions and hypotheses regarding a number of trends that require further investigation, more specific and more detailed analysis of the ADRs. These can be used to identify specific signals to minimise harm, serve as an early warning indicators of large-scale toxicity and morbidity and optimise treatment in all people infected with HIV and TB. There is also a strong need to conduct further research on the different responses to ART in males and females in order to optimise and individualise therapy.

Limitations

Firstly, all the reports were from passive surveillance and rely on reporting, therefore there may have been reporting biases. Additionally, we had to work with many incomplete records; a follow up was not always possible due to analysis being retrospective, and some reports were few years old. Finally, ADR reports were not interrogated before being sent to the NPC.

Conclusion

This paper has described a successful, low cost, affordable, PV programme for public health programmes that can be easily implemented in a resource constrained setting using existing infrastructure and resources.

Improving the quantity and quality of the reports may be augmented by the programme with further training in causality assessment, detection of ADRs and proper completion of ADR reports. More attention should be paid to the training of HCPs from CHCs and PHCs to get the benefit of further ADR reports from these facilities. Pharmacists, who were previously targeted for training, should be further engaged to play a stronger role in the reporting process.

The immediate and very important benefit of this programme is the increase in the number of HCPs reporting after being trained. Efforts to maintain this momentum as well as complete the training of the PV programme in the remaining provinces should be accelerated to realise the benefits of the all provinces reporting ADRs. The successes with the reporting rates from nurses and HCPs from hospitals reporting ADRs should be further encouraged.

The programme detected the top causative agents causing safety issues in the HIV and TB programmes, the most common ADRs, as well as the difference in rate of ADRs experienced by males and females.

This PV programme has the potential for extracting important data that may inform treatment guidelines as well as achieve health systems strengthening in SA. Information from this PV process may be used to identify trends and generate hypotheses to be further investigated and it also serves as a data source and signal for more specific studies.

Acknowledgements

The authors would like to acknowledge each healthcare professional that submitted an ADR report to the NPC. The staff at NPC for their assistance and support throughout the development of the decentralised PV programme. The National and Provincial Departments of Health for helping to pave the way, organisationally and administratively, to allow its HCPs to be part of this decentralised pharmacovigilance programme to improve quality of care in HIV/AIDS and TB patients.

Conflict of Interest

Dheda M and Kambafwile H are employed by the National PV Centre for Public Health Programmes (NPC) at the National Department of Health, WB Plummer and Mukudu H are independent technical assistants to the NPC. Moorhouse M and Oosthuizen F have no conflicts of interest that are directly relevant to this study.

References

1. UNAIDS. Global Aids Update [Internet]. 2016. Available from: http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf
2. The Global Fund. TB and HIV Concept Note: Investing for impact against HIV tuberculosis and HIV [Internet]. 2014. Available from: http://sanac.org.za/wp-content/uploads/2015/11/South-Africa-TB-HIV-Concept-Note-FINAL.pdf
3. Bekker LG, Venter F, Cohen K, Goemare E, Van Cutsem G, Boulle A, et al. Provision of antiretroviral therapy in south africa: The nuts and bolts. Antivir Ther [Internet]. 2014;19:105–16. Available from: https://www.intmedpress.com/journals/avt/abstract.cfm?id=2905&pid=88
4. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. [Internet]. Vol. 155, Archives Of Internal Medicine. 1995. p. 1949–56. Available from: https://pallas2.tcl.sc.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=7575048&site=ehost-live
5. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies [Internet]. Vol. 279, J Am Med Assoc. 1998. p. 1200–5. Available from: http://dx.doi.org/10.1001/jama.279.15.1200

6. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj [Internet]. 2004;329(7456):15–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15231615http://www.bmj.com/cgi/reprint/329/7456/15.pdf\nhttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC443443/pdf/bmj32900015.pdf
7. World Health Organisation. Safety of Medicines. 2002; Available from: http://apps.who.int/iris/bitstream/10665/67378/1/WHO_EDM_QSM_2002.2.pdf
8. Mouton JP, Njuguna C, Kramer N, Stewart A, Mehta U, Blockman M, et al. Adverse Drug Reactions Causing Admission to Medical Wards. A Cross-Sectional Survey at 4 Hospitals in South Africa. Medicine (Baltimore). 2016;95(19):1–10.
9. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. Vol. 15, PharmacoEconomics. 1999. p. 445–58.
10. Dheda M, Distefano K, Williams F, Kambafwile K. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga Success & Moving Forward. 2013;5(5). Available from: http://www.academicjournals.org/JAHR
11. Dheda M. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga as pilot province for national roll- out. J AIDS HIV Res. 2013;5(9):357–65.
12. HISP. South Africa District Health Information System [Internet]. Available from: access Nov 2015
13. Njuguna C, Stewart A, Mouton JP, Blockman M, Maartens G, Swart A, et al. Adverse Drug Reactions Reported to a National HIV & Tuberculosis Health Care Worker Hotline in South Africa: Description and Prospective Follow-Up of Reports. Drug Saf [Internet]. 2016;39(2):159–69. Available from: "http://dx.doi.org/10.1007/s40264-015-0359-8
14. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, Labadarios D OD et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town; 2014.
15. Floridia M, Giuliano M, Palmisano L, Vella S. Gender differences in the treatment of HIV infection. Pharmacol Res. 2008;58(3–4):173–82.
16. AVERT. HIV/Aids in South Africa timeline 1940s-2009 [Internet]. AVERT.org. 2014. Available from: http://www.avert.org/hiv-aids-south-africa.htm
17. Anderson PL, Kakuda TN, Kawle S, Fletcher C V. Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected

individuals. AIDS. 2003;17(15):2159–68.

18. Simelela NP, Venter WDF. A brief history of South Africa's response to AIDS. South African Med J. 2014;104(3):249–51.

19. Castelnuovo B, Kiragga A, Kamya MR, Manabe Y. Stavudine toxicity in women is the main reason for treatment change in a 3-year prospective cohort of adult patients started on first-line antiretroviral treatment in Uganda. J Acquir Immune Defic Syndr [Internet]. 2011;56(1):59–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20861741

20. South African National AIDS Council South Africa Department of Health. The South African Antiretroviral Treatment Guidelines. Johannesburg; 2010.

CHAPTER 6

6. General Conclusions

6.1 Conclusion

It is widely accepted that adverse drug reactions (ADRs) cause significant morbidity and mortality globally[1]. ADRs are reported to be the fourth to sixth leading cause of death in hospitalised patients [2,3]. Economic loss, including lost income, lost household production, disability, and healthcare costs, together with patients' treatment defaulting, poor adherence and/or loss of confidence in healthcare systems have severe implications for a country[4]. In South Africa (SA) this is exacerbated by the burden of the twin diseases of acquired immune deficiency syndrome (AIDS) and tuberculosis (TB)[5]. This makes it crucial for SA to have a comprehensive pharmacovigilance (PV) programme as an integral part of its treatment programmes. South Africa has several PV activities that have been ongoing since 1987, albeit fragmented. Among these is the decentralised PV programme by the National Department of Health (NDoH). This thesis evaluated PV in public health institutions and programmes from a national perspective, beginning with its history to its current state with the aim to meet the PV challenges in the face of rapidly increasing public health treatment programs, new drugs and increased drug resistance threats.

6.2 Aims and achievements

In order to achieve the above this thesis undertook four specific objectives:

Objective 1

To trace and reconstruct the history of PV activities to date in SA

Achievement

For the first time, a clear reconstruction of the evolution of PV in SA, from its beginning in January 1987 to 30th September 2015, was presented. A review of published articles, international and regional reports, health law and policy documents, as well as strategic plans and reports from within SA were gathered to inform the review. The review also showed how the public health PV system in SA was bolstered to meet the safety challenges of treatment programmes.

Objective 2

To benchmark PV activities through an appropriate baseline assessment

Achievement

A baseline assessment of PV activities among training-in-PV naïve healthcare professionals (HCPs) identified gaps in the knowledge, awareness and practice of PV among public HCPs. The identified gaps revealed areas that required appropriate training interventions for a successful implementation of a decentralised PV programme. Strategies were formulated to fill these gaps with an aim to roll out the decentralised PV programme more effectively.

Objective 3

To determine the impact of a PV training intervention

Achievement

This evaluation showed that the training intervention increased medicine safety awareness among the healthcare professionals. There was an increase in knowledge gained on every aspect tested, albeit to varying degrees. It highlighted aspects of the training programme that needed further strengthening. In the long term the knowledge gained could be translated into an increase in the quality and quantities of ADR reports, and if incorporated into every day clinical practice this could certainly improve patient outcomes.

Aim 4

To evaluate the effectiveness of a low cost SA-specific PV strategy implemented in response to the major public health challenges, namely HIV/AIDS and tuberculosis, through analysis of the data collected.

Achievement

Data collected from a low cost, affordable, PV programme/system were interrogated for information to improve safety in HIV/AIDS and TB treatment. The analysis was used to detect the top medicinal agents causing safety issues in the HIV and TB treatment, the most common ADRs, as well as the difference in rate of ADRs experienced by males and females.

This process can be implemented in resource constrained settings using existing infrastructure and resources.

This thesis extracted important data that may inform treatment guidelines as well as achieve health systems strengthening in SA. It showed how information from this PV process may be used to identify trends and generate hypotheses to be further investigated.

6.3 Strengths and limitations

6.3.1 Strengths

From a practical perspective, this study was effective in that suggestions made from its findings were implemented by NDoH. It also provided healthcare policy makers with useful data to explore the current ADR reporting status among the various cadres of healthcare professionals to enable them to discuss suitable methods to improve reporting. It is hoped that NDoH will:

1. continuously evaluate and reconstruct its PV systems and processes, if needed,
2. interrogate data received from ADR reports,
3. understand the importance of good quality reports, and
4. periodically evaluate its training in PV.

This thesis demonstrated that the PV programme in SA has the potential of detecting medicine related problems (MRPs) and ADRs. Decreasing and/or preventing these ADRs can positively impact on the country's economy by reduced hospitalisations, reduced expenditure on expensive regimen switches and/or other treatment programmes. It can reduce work opportunity cost losses directly through decreased morbidity and mortality as well as increased quality of life and economic productivity.

6.3.2 Limitations

Chapter 1 was an introductory chapter and consequently had not limitations. This was the same with Chapter 6, which was the conclusion chapter. The limitations described herein therefore refer to chapters 2, 3, 4 and 5.

With Chapter 2, a literature review, a limitation was that there is a paucity of published literature with regards to the history of PV in SA. Chapter 3 was a baseline study that had several limitations. The cadre and number of participants could not be obtained as envisaged on account of challenges encountered at district level as there were many vacancies and even when staff were available, they were unable to participate in the study due to other commitments. Furthermore, the sample size was small and thus not representative of all HCPs in the province. Additionally, the limited timeframe for the exercise to be completed meant that there was no alternative day to re-visit the field for additional interviews. However, the findings provided insights of what needed to be considered in planning and implementing a PV system in various provinces. Finally, the scope of this particular analysis was quantitative excluding qualitative data obtained using the tool as well as that obtained through informal conversations.

Chapter 4 also had several limitations. One limitation of the study is the mode of assessing impact, which depended on the respondent's ability to recall if they had prior knowledge of PV, which is subject to recall bias. Furthermore, a truly representative sample was not achieved since HCPs were not selected from each of the five districts or indeed provinces of SA. Thirdly, selection bias may occur as respondents who are more interested in PV may have been the only ones who attended the workshop, as it was not compulsory. Fourthly, the long term knowledge retention and PV knowledge improvement needs to be conducted. Furthermore, the pre- and post-training data collection tools were not coded to link individual and HCP cadre gain in knowledge. Finally, a before-after design is sometimes considered to be a weak design when evaluating effects of interventions.

In Chapter 5, firstly, all the reports were from passive surveillance and relied on HCPs reporting, therefore there may have been reporting biases. Additionally, incomplete records had to be used, some reports were old and since the analysis of ADR reporting was retrospective, follow up was not always possible. Finally, ADR reports were not interrogated before being sent to the NPC.

6.4 Further investigation/ follow-on studies.

A more in-depth review of the data with various cross tabulation should be conducted.

PV in the private healthcare sector should be investigated, especially private hospitals. Signals and questions generated, such as difference in safety profile of specific medicines to

gender, should be further investigated using active surveillance. It should also be ascertain if ARVs are more toxic to females.

6.5 References

1. Franklin B, Vincent C, Schachter M, Barber N. The Incidence of Prescribing Errors in Hospital Inpatients [Internet]. Vol. 28, Drug Safety. London; 2005. p. 891–900. Available from: http://dx.doi.org/10.2165/00002018-200528100-00005
2. Muehlberger N, Schneeweiss S, Hasford J. Adverse drug reaction monitoring—cost and benefit considerations. Part I: frequency of adverse drug reactions causing hospital admissions. Pharmacoepidemiol Drug Saf [Internet]. 1997;6(S3):S71–7. Available from: http://2-i
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies [Internet]. Vol. 279, J Am Med Assoc. 1998. p. 1200–5. Available from: http://dx.doi.org/10.1001/jama.279.15.1200
4. Zolezzi M, Parsotam N. Adverse drug reaction reporting in New Zealand: implications for pharmacists. Ther Clin Risk Manag [Internet]. 2005;1(3):181–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18360558\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1661625
5. Bradshaw D, Groenewald P, Laubscher R, Nannan N, Nojilana B, Norman R, et al. Initial burden of disease estimates for South Africa, 2000. South African Med J. 2003;93(9):682–8.

CHAPTER 7

7 APPENDICES

7.1 National Department of Health permission to use data

The User agrees that his/her signature indicates his/her agreement to comply with the above-stated requirements (Points 1-9)

Please complete this form

Data/Set/s for which Agreement is signed (Provide detail list):	Pharmacovigilance program ADR's database
Name (Print or Type):	Mukesh Dheda
Organisation/Department:	NDoH
Position:	Director & PhD student
Purpose for which the data will be used (List attachment)	The data will be used as part of a study in a qualitative and quantitative study of Health Care Practitioners knowledge, attitude, perception and barriers towards Pharmacovigilance and ADR reporting.
Anticipated timeframe for completing the analysis/study/project for which data are requested	March 2016
Anticipated timeframe for sharing the results of the analysis/study/project with the National Department of Health	April 2016-September 2016
Title (Mr/Mrs/Ms/Dr/Prof) :	Mr.
Address:	CIVITAS
City:	Pretoria
Province:	Gauteng
Country:	South Africa
Telephone:	0123958176
Fax:	n/a
E-mail:	DhedaM@health.gov.za mukesh.dheda@gmail.com
Signature:	
Date:	16/3/2015
Witness: Name	Franci Williams
Witness: Contact No	0123959506
Date:	16/3/2015

For Department of Health use only:

Approval by DOH Representative*:	
Date:	24/03/2015

- **The Data User's Agreement must be signed by the Chief Director for Health Information Management, Monitoring and Evaluation.**

7.2 Ethics Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

5 September 2016

Mr Mukesh Dheda 7711007
School of Health Sciences
Westville Campus

Dear Mr Dheda

Protocol reference number: HSS/1328/016D
Project Title: Meeting SA Pharmacovigilance challenges in the face of rapidly increasing Public Health Treatment Programmes

Full Approval – Expedited Application

In response to your application received 22 August 2016, the Humanities & Social Sciences Research Ethics Committee has considered the abovementioned application and the protocol has been granted **FULL APPROVAL.**

Any alteration/s to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form, Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through the amendment /modification prior to its implementation. In case you have further queries, please quote the above reference number.

PLEASE NOTE: Research data should be securely stored in the discipline/department for a period of 5 years.

The ethical clearance certificate is only valid for a period of 3 years from the date of issue. Thereafter Recertification must be applied for on an annual basis.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully

.....

Dr Shenuka Singh (Chair)
Humanities & Social Sciences Research Ethics Committee

/pm

Cc Supervisor: Dr F Oosthuizen
Cc Academic Leader Research: Professor Mershen Pillay
Cc School Administrator: Ms P Nene

Humanities & Social Sciences Research Ethics Committee
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7.3 Hi Resolution of Figure 4 (Chapter 2)

Information flow in the decentralised pharmacovigilance programme