

EVALUATION OF AUTOPSY DATA FOR OCCUPATIONAL LUNG DISEASE SURVEILLANCE

*“This is the place where death delights to help the living”**

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A thesis submitted to the Faculty of Health Sciences,
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*“*This is the place where death delights to help the living*” translated from the Latin “*Hic locus est ubi mors gaudet succurrere vitae*” appears on the walls of many anatomy theatres around the world and is thought to date back to the 16th century (Lillie, 2014).



Photograph of the room where organs are examined at the National Institute for Occupational Health (N Kgokong)

DECLARATION

I, Ntombizodwa Ndlovu, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Date: 13 September 2019

DEDICATION

This thesis is dedicated to my parents,

Enoch Peni Dube

and

the late, Sannah Agnes Dube (nee Mbete)

PUBLICATIONS AND PRESENTATIONS ARISING FROM THE THESIS

Original papers

Ndlovu N, Nelson G, Vorajee N, Murray J. 38 years of autopsy findings in South African mine workers, *American Journal of Industrial Medicine*, 2016; 59: 307-314

Ndlovu N, Rees D, Murray J, Vorajee N, Richards G, teWaterNaude J. Asbestos-related diseases in mineworkers: a clinicopathological study, *ERJ Open Res*, 2017: 3: DOI: 10.1183/23120541.00022-2017

Ndlovu N, Musenge E, Park SK, Girdler-Brown B, Richards G, Murray J. Four decades of pulmonary tuberculosis in deceased South African miners: trends and determinants. *Occupational and Environmental Medicine*, 2018: 75(11):767-75.

Ndlovu N, Richards G, Vorajee N, Murray J. Silicosis and pulmonary tuberculosis in female South African miners. *Occupational Medicine, (Lond)*, 69, 272-278.

N Ndlovu conceptualised the study designs, acquired the data, conducted data management and statistical analyses, interpreted the findings, wrote the first drafts and critically revised the manuscripts for intellectual content, submitted the manuscripts to journals for publication, and revised and approved the final versions of each of manuscript before publication, with support from co-authors.

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Published abstracts

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Ndlovu N, Park S, Murray J. 2013. 409 The use of an autopsy compensation database for surveillance of pulmonary tuberculosis in the South African mining industry: 1975-2011, *Occupational and Environmental Medicine* 70 (Suppl 1) A140; DOI: 10.1136/oemed-2013-101717.409

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ABSTRACT

Background

There is little systematic occupational health surveillance in South Africa, and past attempts have been unsuccessful. Routine administrative databases, such as compensation databases, are attractive for occupational disease surveillance. South African law allows for examination of the cardio-respiratory organs of current and former miners for occupational lung disease (OLD) compensation at the National Institute for Occupational Health and the findings are captured into the Pathology Automation (PATHAUT) database. The data are generated primarily for compensation but have also been used extensively for research such that the PATHAUT database is recognised as a unique resource for OLD research worldwide.

Aim

This thesis evaluated the attributes and usefulness of the administrative, PATHAUT autopsy database for its use as a tool for OLD surveillance in the South African mining industry.

Methods

Data were analysed by population group because of differences in employment and access to autopsy services. Paper 1 described demographic and occupational information, and OLDs in black and white miners from 1975 to 2013. Paper 2, used autopsy diagnoses of asbestos-related diseases (ARDs) as the gold standard to determine sensitivity, specificity and predictive values for clinical diagnoses of Asbestos Relief Trust claimants who had autopsies at the NIOH in 2010 and 2011. Factors associated with false-negative diagnoses of asbestosis were investigated using binary logistic regression modelling. Paper 3 investigated pulmonary tuberculosis (PTB) trends (1975-2014) in black and white miners. The analyses were segmented to represent the pre-HIV, rapid HIV spread and ART periods. Factors associated with PTB (year of autopsy, age, gold employment duration, silicosis and HIV) were determined using binary logistic regression modelling. The fourth paper (Paper 4) compared silicosis and PTB proportions female and male gold miners who had autopsies from 2005 (when sex was introduced in the PATHAUT database) to 2015 and who had started gold mining after the introduction of an intervention to increase the participation of women in underground mining in 2002.

The evaluation used findings from the four epidemiological studies and was guided by the CDC Guidelines for Evaluating Public Health Surveillance Systems.

Results

Paper 1 analysed 109,101 records in the PATHAUT database (1975-2013): 72,348 (66.3%) of black and 34,794 (31.9%) of white miners. The annual numbers of autopsies declined from above 3,000 from 1975 to 1998, to 1,118 in 2013. The mean ages of black and white miners were 39.7 ± 11.4 and 60.9 ± 14.6 years, respectively. Fields for sex, employment status and place of origin of the organs were added to the database in 2005, 2007 and 2010, respectively. There were 320 (0.3%) women. At the time of death, 78.6% (n=5,077) black and 13.2% (n=428) white miners were in employment. Most organs were submitted from the North West (n=1,774; 34.8%), Free State (n=1,150; 22.6%) and Gauteng (n=1,139; 22.3%) provinces. Many miners had worked in more than one mining commodity (n=14,444; 13.2%) and, of the 34 commodities worked, most were gold (n=70,296; 72.7%), platinum (n=9,586; 8.8%), coal (n=7,741; 7.1%) or asbestos (n=2,560; 2.3%) miners. Over the study period, the major diseases diagnosed at autopsy were emphysema (15.5% in black and 49.5% in white miners), silicosis (12.0% and 20.5%) and PTB (13% and 2.4%). The proportions of silicosis and PTB increased over time.

One hundred and forty nine ARD cases were identified (Paper 2). More ARDs were diagnosed at autopsy (77 asbestosis, 27 mesothelioma and 22 lung cancer) than clinically (52 asbestosis, 14 mesothelioma and 3 lung cancer). The sensitivity values for the clinical diagnoses for asbestosis, mesothelioma and lung cancer were 50.6%, 40.7% and 13.6%, and the specificity values were 81.9%, 97.5% and 100.0%, respectively. False-negative diagnoses of asbestosis were more likely if chest radiographs were of acceptable compared to good quality, and in cases with autopsy-diagnosed PTB.

The proportions of male miners with PTB increased from 4.62% in 1975 to 43.1% in 2007 and decreased to 27.18% in 2014. For white miners, PTB increased from 2.07% in 1975 to 9.51% in 2007 and declined to 5.19% in 2014. The adjusted odds ratios (AORs) for PTB differed in magnitude and significance by population group and calendar period. PTB was positively associated with silicosis in both population groups and in all calendar periods. The AORs for year of autopsy (a surrogate for unmeasured confounding, e.g. unknown HIV status

and tuberculosis transmission) increased over time. PTB was also associated with increasing gold employment duration (a proxy for cumulative dust exposure) and HIV.

Paper 4 included 847 gold miners: 68 (8.0%) women and 779 (92.0%) men. There were no statistical sex differences in autopsy-diagnosed pulmonary silicosis [$n=3$ (4.4%) in women and $n=54$ (6.9%) in men; $p=0.61$], lymph gland silicosis [$n=11$ (16.2%) and $n=171$ (22.0%); $p=0.27$] or PTB [$n=29$ (42.6%) and $n=254$ (32.6%); $p=0.09$]. All three women with silicosis had slight disease. Two had worked for 3.3 and 3.8 years and were 26 and 35 years old, respectively. The third woman had 10.9 years of employment and was 47 years old.

Information in the four papers was used to evaluate seven system attributes (simplicity, flexibility, data quality, representativeness, sensitivity, stability and timelines) of the autopsy process and data. Acceptability and some aspects of other attributes were not assessed because stakeholder engagement was not included in this thesis. Predictive values were not assessed due to the lack of suitable external data. The usefulness of the autopsy data for use in surveillance was assessed by its abilities to detect OLDs, provide disease estimates, detect trends, determine factors associated with disease occurrence, identify sentinel cases and assess the effectiveness of prevention and control interventions.

Conclusion

The high levels of OLDs in miners are indicative of ineffective silica dust control programmes. The autopsy data provide the only source of long-term information to monitor OLDs and the effectiveness of prevention and control interventions in the South African mining industry. The evaluation findings indicate that the autopsy processes and data cover the core elements of surveillance, that is, ongoing and systematic reporting, data collection, analysis, interpretation and dissemination of information. Hence, the use of the PATHAUT database could be extended to include a surveillance function in addition to its use for compensation and research. The development of a surveillance programme using these data is relevant because of the scarcity of successful OLD surveillance systems globally.

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“To God be the glory”

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DEFINITIONS

Acceptability	Willingness of persons or organisations to participate in the surveillance system (CDC, 2001)
Asbestosis	A pneumoconiosis caused by inhalation of asbestos fibres, characterised by interstitial fibrosis of the lung parenchyma, predominantly in the upper lobes of the lung (American Thoracic Society, 2004)
Asbestos-related diseases	Include asbestosis, lung cancer and mesothelioma
Asbestos-related lung cancer	Cancer that occurs in the parenchyma, and is pathologically and clinically indistinguishable from lung cancers caused by other factors (Tossavainen, 1997)
Autopsy	In this thesis, refers to the pathological examination of the cardio-respiratory organs post-mortem
Data quality	The completeness and validity of the data recorded in the surveillance system (CDC, 2001)
Flexibility	The ability of a surveillance system to adapt to changing information needs with little additional time, personnel or allocation of funds (CDC, 2001)
Medical surveillance	Also known as medical screening, refers to the testing of individual workers for early disease detection and prevention at the individual level (Koh and Aw, 2003)
Mesothelioma	Cancer of the pleural membrane caused almost exclusively by asbestos exposure
Occupational disease	Any disease contracted primarily as a result of exposure to risk factors arising from work activity (WHO, undated)
Pneumoconiosis	A lung disease caused by inhalation of dust and characterised by inflammation, coughing, and fibrosis
Predictive value positive	The proportion of reported cases that actually have the health-related event under surveillance (CDC, 2001)
Public health surveillance	The ongoing, systematic collection, analysis, interpretation, and dissemination of data for use in public health to reduce morbidity and mortality and to improve health (CDC, 2001)
Pulmonary tuberculosis	Tuberculosis of the lung
Phthisis	An old term that refers to silicosis, pulmonary tuberculosis or both
Representativeness	The ability to accurately describe the occurrence of the health-related event over time and its distribution in the population by place and person (CDC, 2001)
Sensitivity	The ability to monitor changes in the number of cases over time or the proportion of cases of a disease detected by the surveillance system (CDC, 2001)

Silicosis	Pneumoconiosis caused by the inhalation of dust containing crystalline silica characterised by irreversible nodules of fibrotic scarring of the lung, predominantly in the upper lobes
Simplicity	The structural complexity of the surveillance system and its ease of operation. (CDC, 2001)
Stability	The ability of the surveillance system to collect, manage and provide data properly and without failure (reliability) and to be operational when it is needed (availability) (CDC, 2001)
System attributes	The inherent characteristics of the surveillance system
Timeliness	The time between any two steps in a surveillance system (CDC, 2001)
Tuberculosis	An infectious disease caused by <i>Mycobacterium tuberculosis</i>
Usefulness	The ability of a surveillance system to contribute to the prevention and control of adverse health events, improved knowledge of public health implications; to determine emerging adverse-health related events; and to contribute to performance measures including health indicators that are used in needs assessments and accountability systems (CDC, 2001)
Work-related diseases	Diseases with multiple causes, where factors in the work environment together with other risk factors play a role in disease development (WHO, undated)
Works	Places that are not mines or parts of mines where operations, such as the moving and handling of stone, rock and minerals; crushing and processing of rocks occur, including those obtained from mining operations (RSA, 1973)

ABBREVIATIONS AND ACRONYMS

ARD	Asbestos-related disease
CCOD	Compensation Commissioner for Occupational Diseases
CDC	Centers for Disease Control and Prevention
COIDA	Compensation for Occupational Injuries and Diseases Act of 1993
COPD	Chronic obstructive pulmonary disease
DMR	Department of Mineral Resources (former Department of Minerals & Energy)
DOL	Department of Labour
FEMA	Federated Employers Mutual Assurance
HIV	Human immunodeficiency virus
HSCC	Health Surveillance Coordinating Committee
ILO	International Labour Organization
MBOD	Medical Bureau for Occupational Diseases
MCSA	Minerals Council of South Africa
MHSA	Mine Health and Safety Act No 29 of 1996
MHSC	Mine Health and Safety Council
MHSI	Mine Health and Safety Inspectorate
MWCS	Mine Workers Compensation System
NDOH	National Department of Health
NIOH	National Institute for Occupational Health
ODMWA	Occupational Disease in Mines and Works Act
OEL	Occupational exposure limit
OHSA	Occupational Health and Safety Act of 1993
OLD	Occupational lung disease
PATHAUT	Pathology Automation System
PTB	Pulmonary Tuberculosis
RMA	Rand Mutual Assurance
SAMOSA	Surveillance of Upper Limb Musculoskeletal Disorders in South Africa
SORDSA	Surveillance of Occupational Respiratory Disease in South Africa
TB	Tuberculosis
TEBA	The Employment Bureau of Africa
WHO	World Health Organization
WNLA	Witwatersrand Native Labour Organisation

PREFACE

I worked as a medical scientist in the Pathology Division at the National Institute for Occupational Health (NIOH) for ten years (2004-2013). The Division performs autopsies on deceased South African miners for statutory compensation purposes. My core function was the management of all administrative processes in the autopsy process, supervision of the clerical staff and management of the PATHAUT database. I was also involved in a number of research projects.

When the laboratory was accredited, I wrote the Clerical Section's standard operating procedures (SOPs) detailing data collection and capture steps at different stages of the autopsy process. I also wrote and am still involved in data analysis and writing of the annual Pathology Division Surveillance Reports, which provide summaries of the occupational lung diseases (OLDs) diagnosed at autopsy.

I worked in a team that was passionate about increasing the awareness of miners and communities about OLDs autopsy compensation among miners, communities and other stakeholders in the mining industry. We attended meetings and travelled all over South Africa, and also to Lesotho, engaging with various stakeholders. I also led the process of developing posters, fliers and a booklet which have been distributed widely.

The use of autopsy data to improve the health of current and future workers is a fitting tribute to men and women who have lost their health and lives working in the South African mines. Indeed, *“this is the place where death delights to help the living”*.

Table 1 Overview of thesis and main contribution of individual papers to themes

Theme	Paper 1 Description of autopsy findings, 1975-2013	Paper 2 Clinico-pathological study of asbestos-related diseases	Paper 3 PTB trends in miners, 1975-2014	Paper 4 Silicosis and PTB in female gold miners, 2005-2015	Integrating narrative
Attributes of PATHAUT as a tool for surveillance	The attributes of simplicity, stability, flexibility, data quality, sensitivity (changes in disease proportions over time) and representativeness (distribution of OLDs in miners) were assessed. The underrepresentation of former black miners is due to poor awareness and inadequate provision of facilities for organ removal in labour sending areas.		This attributes of stability, flexibility, data quality and sensitivity were assessed.		The autopsy process and data have several attributes which make these administrative data suitable for OLD surveillance in South African miners.
Usefulness of PATHAUT as a tool for surveillance	Ability to detect disease detection and its magnitude: The data provide four decades of estimates of many OLDs (e.g. emphysema, silicosis, pulmonary tuberculosis (PTB), lung cancer, asbestosis mesothelioma, etc.) and commodities (e.g. gold, platinum and asbestos mining etc.). Disease magnitude and trends: Proportions of most OLDs increased over time.	Ability to detect disease: Autopsy diagnoses are the gold standard and detect disease that has been missed or misdiagnosed in life.	Ability to estimate disease magnitude and trends: PTB was five times higher in black compared to white miners. In both population groups, PTB increased from 1975, peaked in 2007 and decreased thereafter. The trends are similar to those in the general population. Ability to determine risk factors: Silicosis, year of autopsy, gold mining employment duration and HIV are important PTB determinants, and their effects differed by population group and calendar period. Ability to monitor prevention and control programmes: the data provided information to monitor interventions to control silica dust and prevent silicosis and PTB.	Identification of sentinel cases: Silicosis was diagnosed in three female gold miners who were relatively young and after short mine employment. Ability to monitor prevention and control programmes: The development of silicosis in women and men who entered the industry after introduction of the silicosis elimination campaign indicates failure to control dust.	The autopsy data provide estimates of the magnitude of OLDs over time and this information is useful for monitoring interventions to control dust and prevent OLDs in miners.

CHAPTER 1: INTRODUCTION

This introductory chapter begins with a brief background which provides the socio-political context of the South African mining industry. It is followed by descriptions of the diseases that are the subjects of the thesis papers: silicosis, tuberculosis, asbestosis, mesothelioma and lung cancer. Occupational lung disease compensation for miners is introduced, and the process for autopsy compensation is described. The history of the PATHAUT database is followed by a description of how surveillance-related activities using these data have evolved. The chapter ends with the aims of and objectives of the PhD.

Occupational diseases contribute to the global burden of disease and account for 82% of the 2.3 million occupation-related deaths that are reported across the world annually (Takala et al., 2014). These diseases not only cause suffering to affected workers and their families but also have a broad societal impact due to lost productivity and increased medical costs. The hazardous occupational exposures and risk factors that give rise to many occupational diseases are known, and the diseases are preventable through the enforcement of preventative policies and workplace interventions. Occupational disease surveillance plays a vital role in identifying groups of workers at risk of developing disease, producing information to inform the development of intervention programmes for disease prevention and control, and to monitor the effectiveness of intervention programmes. The main distinguishing feature between surveillance and research is that the primary purpose of surveillance is to produce information for action while that of research is to generate knowledge.

1.1 THE SOUTH AFRICAN MINING INDUSTRY

South Africa has a long history of racial and gender segregation which has had far-reaching effects, including population health. In 1948, the introduction of apartheid laws consolidated three centuries of racially motivated political exclusion, social separation and economic marginalization (SAHO, undated). White South Africans were classified as Europeans and were placed at the top of the hierarchy with Asians (Indian), coloured (mixed race) and

Bantus (black) below them (Coovadia et al., 2009). A combination of legislation, taxes and restrictions to land access created conditions that forced black men to leave their rural homes to find work in the towns and mines, thereby entrenching the migrancy of black men. Cheap migrant labour became the backbone of the economy, shaped social development and became a major determinant of disease patterns (Coovadia et al., 2009). Apartheid was dismantled in the early the 1990s, and the first democratic elections were held in 1994. However, the injustices of apartheid continue to contribute to the occurrence of occupational diseases in miners, and the mining industry accounts for 90% of the occupational lung diseases (OLDs) in South African workers (DOH, 2007).

1.1.1 Commodities

Mining has been a significant contributor to the economy since the discovery of diamonds in the Northern Cape Province in 1867 and gold in the Transvaal Province (now Gauteng) in 1886. Although its dominance has declined, in 2017, mining contributed 6.8% (R335 billion) to the national Gross Domestic Product (Nelson and Murray, 2013a, MCSA, 2018).

South Africa has vast mineral wealth, and over 50 commodities have been mined commercially. Before 2007, the country was the leading gold producer but fell to eighth place in world rankings in 2017 (Staff Writer, 2018). It is the leading producer of platinum and holds 70% of the world's platinum reserves. Platinum production has more than doubled since the 1980s and currently exceeds that of gold (Nelson, 2012). Other commodities of current economic significance include coal, iron, manganese, chrome and diamonds (MCSA, 2018).

Asbestos was the "magic mineral" of the 20th century because of its versatility, high tensile strength and fire-resistant properties which made it suitable for widespread usage in thousands of engineering and building materials (McCulloch and Tweedale, 2004). South Africa started mining asbestos in the early 1890s and, at the peak of production, was the third largest producer of amphibole asbestos (McCulloch, 2003). The country was unique in that three types of asbestos were mined producing most of the world's crocidolite (blue asbestos) and amosite (brown asbestos), and smaller quantities of chrysotile (white asbestos). Growing evidence of the adverse health effects of asbestos eventually resulted in decreased demand and closure of many asbestos mining operations. By 2003, all asbestos mines had been closed

and in March 2008, South Africa joined over 50 countries when it effectively banned the mining and use of asbestos (teWaterNaude, 2014a, Kazan-Allen, 2018). However, widespread contamination of the environment persists in areas where asbestos mines operated.

1.1.2. Labour

The South African mining industry continues to be a significant employer even though the number of miners almost halved from 806,876 in 1985 (Nelson, 2012) to 464,667 in 2017. Currently, most miners are employed in platinum and gold mines (MCSA, 2018). Declining gold production and downsizing of gold mines accompanied by the retrenchment of workers and expanding platinum production has changed the pattern of employment. From 1985 to 2017, the annual numbers of gold miners decreased almost five-fold from 527,947 to 112,200, while those of platinum miners more than doubled from 73,880 to 172,171 (MCSA, 2018, Nelson, 2012).

Compared to other commodities, fewer people worked in South African asbestos mines and mills. The labour force consisted mainly of family units that lived close to asbestos operations. Men worked in the mines while women and children, who were mostly undocumented in the employment records of mining companies, cobbled, sorted, and packed fibres (Braun and Kisting, 2006). A small number of asbestos workers were recruited from Mozambique, Swaziland, and Malawi to work in asbestos mines (McCulloch and Tweedale, 2004). The waste (tailings) were dumped near villages or used in construction or surfacing of roads giving rise to a legacy of extensive environmental contamination of former asbestos mining areas (McCulloch, 2003, Felix, 1997).

The mining industry has relied heavily on its migrant workforce. In the early days of gold mining, skilled miners came from Britain, Germany, the United States and Australia and unskilled labour was recruited from rural South Africa and neighbouring countries. As mining methods changed from open cast to underground extraction, a plentiful and cheap labour supply was required. In 1900, the Witwatersrand Native Labour Association (WNLA, popularly known as Wenela), now called The Employment Bureau of Africa (TEBA), was formed (Harington et al., 2004). It recruited workers mainly from Mozambique and countries to the north of South Africa, and for a brief period (1904-1910) from as far afield as China

(Ndlovu et al., 2006, Mansell Prothero, 1974). The WNLA recruited largely for the gold mines and, to a lesser extent, platinum and coal mines. Other labour organisations recruited from within South Africa and from Lesotho, Swaziland and Botswana (Mansell Prothero, 1974). Following industry initiatives to reduce reliance on foreign migrant workers, the proportions of miners recruited from Lesotho, Mozambique and other neighbouring countries drastically declined from 53.66% in 1973-1977 to 24.52% in 2008-2012 (Ehrlich et al., 2017).

Oscillating or circular migration was a key feature of the South African migrant labour system. It was characterised by miners working short-term contracts of three to nine months, going back to their families and then returning to the mines to work new contracts (Rees et al., 1999). In the mid-1970s, several external factors e.g. the rise in gold prices and internal pressures and drought in the rural homelands, led to black miners being permitted to work long term contracts and to return to work in the same mine: a phenomenon known as stabilisation of the mining workforce (Leger, 1992, Smith and Blom, 2019). Stabilisation resulted in increasing age and cumulative dust exposure of the black workforce over time.

Historically, miners lived in overcrowded and poorly ventilated single-sex hostels on the mines where it was not unusual for six to 10 men to share a room (Hanifa et al., 2009). These living conditions resulted in increased risks of TB transmission and infection, and HIV infection due to high-risk sexual behaviours driven by family separation (Smith and Blom, 2019). Since the end of apartheid in 1994, significant improvements have been made in housing. The Minerals Council of South Africa (MCSA, formerly Chamber of Mines) reported 73% and 63% success rates in the attainment of targets to achieve single room occupancy and conversion of hostels into family units in its member mines, and continues to promote rental, home ownership and the integration of miners into local communities (MCSA, undated).

The exact number of former miners who have left the industry is not known. In 2014, the World Bank estimated that more than 4 million people have worked in the South African mining industry, of which 2 million were still alive (World Bank, 2014). Using TEBA records, it was estimated that, in the period 1973 to 2012, approximately 1.6 million migrant workers were recruited (Ehrlich et al., 2017). Migrant miners might develop diseases after returning to labour sending areas, thereby contributing to poverty in their communities and

externalisation of medical care costs from the mines to the public health system (Roberts, 2009). The inadequacy of occupational health services in labour sending areas gives rise to poor disease detection and underestimation of OLDs in former miners (Rees et al., 2010). This is particularly so for diseases with long latency periods, that is, the time from first exposure to onset of disease.

1.2 OCCUPATIONAL LUNG DISEASES IN SOUTH AFRICAN MINERS

Occupational lung diseases in the South African mining industry are a public health concern because (i) there are large numbers of current and former miners; (ii) certain exposures increase the life-long risk of developing disease; (iii) some occupational diseases, e.g. the pneumoconioses and malignant diseases, have long latency periods, and develop long after leaving employment and occupational exposures have ceased; (iv) some diseases are progressive with severity increasing over time; and (v) in the case of infectious diseases, the risk goes beyond the individual to communities.

1.2.1 Diseases associated with silica exposure

Workers in industries (e.g. mining, construction, foundries and sandblasting) where rocks, sand or concrete are broken are exposed to fine dust particles and are at risk of developing OLDs. The rock from which gold, and to a lesser extent, platinum and coal are mined contains crystalline silica or quartz dust (silica dust). The inhalation of crystalline silica causes many diseases including silicosis, pulmonary tuberculosis (PTB), lung cancer, chronic obstructive pulmonary disease (COPD), emphysema, autoimmune diseases and renal disease (Ross and Murray, 2004). The discussion below is limited to silicosis and tuberculosis, which are the two most important OLDs in the South African gold mining industry and the subject of three of the papers in this thesis.

Silicosis

Silicosis is a pneumoconiosis characterised by irreversible nodules of fibrotic scarring mainly in the upper lobes of the lung parenchyma (Rees and Murray, 2017). Silicotic nodules in the lymph glands are precursors of pulmonary silicosis (Cox-Ganser et al., 2009, Murray et al., 1991). The three forms of silicosis (chronic, accelerated and acute) differ according to

intensity of silica dust exposures, latency periods and natural histories. Chronic silicosis, the most common form, manifests 10 to 20 years after first exposure and may progress to progressive massive fibrosis. Less common are accelerated silicosis, which develops five to 10 years, and acute silicosis, which develops months to five years after intense, excessive silica exposures (Rees and Murray, 2017). Silicosis is progressive and might first manifest or increase in severity after mining exposure has ceased. The diagnosis and classification of silicosis is usually based on chest radiography using the standardised International Labour Organization (ILO) classification (International Labour Office, 2011).

In cross-sectional studies, silicosis prevalence in employed black gold miners ranged from 1.4% in the mid-1980s (Cowie and van Schalkwyk, 1987) to 18.3-19.9% in miners with over 20 years employment in 2000-2001 (Churchyard et al., 2004). The earlier study highlighted the difficulty of conducting prevalence studies among employed miners because of migrancy: on any given day some miners were returning from home while others were leaving to go home (Cowie and van Schalkwyk, 1987). In a recent large multi-company survey of employed miners from 2004 to 2009, Knight et al. (Knight et al., 2015) found an unexpectedly low silicosis prevalence of 6% which was probably due to a healthy worker effect caused by miners leaving employment due to ill-health, as suggested by the 50% higher risk of leaving the workforce in those who had silicosis or TB (Knight et al., 2015).

Cross-sectional studies of former black miners living in Botswana, the Eastern Cape and Lesotho, reported higher silicosis prevalence in the range of 22.0 to 36.0% (Steen et al., 1997, Trapido et al., 1998, Girdler-Brown et al., 2008, Park et al., 2009, Meel, 2002) compared to 1.4% to 19.9% in employed miners (Cowie and van Schalkwyk, 1987, Churchyard et al., 2004, Knight et al., 2015). The well-cited cohort study of Hnizdo and Sluis-Cremer (Hnizdo and Sluis-Cremer, 1993) followed up white gold miners from 1968-1971 to 1991. The study reported a cumulative incidence of 14% for radiologically detected silicosis, and in most cases (57%), silicosis was first detected 7.4 years after employment ceased (Hnizdo and Sluis-Cremer, 1993). In the 2003 follow-up of the same cohort using radiographic and autopsy diagnoses, the incidence of silicosis had increased to 51.6% (Murray and Hnizdo, 2005).

A trend analysis using autopsy data from the National Institute for Occupational Health () showed a 10-fold, increase in silicosis in black gold miners from 3.0% in 1975 to 32.0% in

2007, and from 18.0% to 22.0% in white gold miners (Nelson et al., 2010). Most black miners with silicosis were younger (91.3% were under 60 years) and had worked for shorter periods (average of 7.7 years) compared to white miners with silicosis (59.6% were under 60 years and average employment duration, 17.1 years) (Nelson et al., 2010). The ages and duration of employment of miners increased over the study period and explained the increases in silicosis over time observed in both population groups. In black miners, increasing year of autopsy (a proxy for other factors that were not measured) was also an important factor (Nelson et al., 2010).

The mineralogy of the rock from which platinum is mined, suggests that platinum miners may be exposed to crystalline silica dust. Studies have reported silica dust levels that were below the South African occupational exposure limit (OEL) of 0.1 mg/m³ but above the 0.025 mg/m³ limit of the American Conference of Governmental Industrial Hygienists (ACGIH) (Nelson, 2013). Pulmonary silicosis was diagnosed in 85 (2.2%) and lymph gland silicosis in 490 (12.7%) of the platinum miners who had autopsies at the NIOH (Nelson and Murray, 2013b). Most of these miners had previously been employed in gold mines. Among men who had worked in platinum mines only, five had pulmonary silicosis and 25 had lymph gland silicosis (Nelson and Murray, 2013b). Phillips et al. (Phillips et al., 2014) found that of the 34 platinum miners who were shot and died during wage-related unrest in Marikana in 2012, three had pulmonary silicosis and four had lymph gland silicosis. Of these, two cases with pulmonary silicosis and one with lymph gland silicosis had no previous gold mining experience (Phillips et al., 2014). These findings support the suggestion that platinum miners are at risk of developing silicosis.

Tuberculosis

Tuberculosis is a chronic, infectious disease caused by inhalation of *Mycobacterium tuberculosis*. By definition, TB is a work-related disease because, although it affects the whole population, there are factors in the workplace (e.g. dust) that play a role in its development. For simplicity, TB is referred to as an occupational disease in this thesis.

Tuberculosis is a public health concern globally. Risk factors for TB infection include high background levels of TB in the community, increased age, overcrowding, poor ventilation, migration, poor nutrition and poverty (Hargreaves et al., 2011). In occupational settings, such as mining, silica dust exposure, with or without the development of silicosis, increases the

lifelong risk of tuberculosis, with risk continuing even after exposure has ceased (Rees and Murray, 2007, Hnizdo and Murray, 1998). The risk is three-fold higher in miners with silicosis compared to those without silicosis and increases with increasing silicosis severity (Hnizdo and Murray, 1998). HIV infection increases TB risk five-fold in gold miners and interacts multiplicatively with silicosis to increase the risk 15-fold in miners with both silicosis and HIV (Churchyard et al., 1999, Corbett et al., 2000).

South Africa is among 30 countries with the highest TB burden (WHO, 2017). The increase in TB incidence from 250 per 100,000 in 1996 (WHO, 1998) to 781 per 100,000 in 2016 (WHO, 2017) is mostly associated with the HIV epidemic which emerged in the 1980s and spread rapidly to approximately 30% in miners (Ras et al., 1983, Nanoo et al., 2015, DOH, 2011, Corbett et al., 2000). The South African gold mining industry probably has the highest incidence of TB in any occupational setting in the world (DOH, 2007).

A detailed trend analysis of PTB using the PATHAUT autopsy data showed an increase in PTB from 0.9% in 1975 to 3.9% in 1991 in black South African gold miners (Murray et al., 1996). In studies conducted between 1991 and 2001, the prevalence of current or inactive TB in gold miners was 19.4% and increased to 35.2% (Park et al., 2009, Steen et al., 1997, teWaternaude et al., 2006, Trapido, 2000). Cohort studies in gold miners conducted from 1990 to 2004 reported annual incidence rates ranging from 806 to 3,820 cases per 100,000 person years, which were much higher than national incidence (Park et al., 2009, Churchyard et al., 1999, Glynn et al., 2008).

Oscillating migration created unique social conditions that fuel TB transmission and treatment failure, and the spread of disease in the Southern African region. Poor ventilation in overcrowded mine hostels and underground in the mines increases the risk of TB infection. Family separation increased the likelihood of higher-risk sexual practices, thereby increasing the risk of HIV infection (Rees et al., 1999). It is estimated that each migrant miner with TB, who returns home can infect 10 to 15 community members (Baleta, 2012).

Silicosis elimination

Silica dust control is key to the prevention of silicosis and other silica-related diseases, including TB. In 2003, South Africa established a national silica elimination programme as part of the International Labour Organization (ILO) and World Health Organization's (WHO)

Global Program for the Elimination of Silicosis (DOL, undated). As part of this programme, the Mine Health and Safety Council (MHSC) (a tripartite structure that represents the State, employers, and labour) developed the 2003 industry milestones, summarised in Table 2.

When the milestones were set, it was already known the occupational exposure limit (OEL) of 0.1 mg/m³ for respirable silica dust was not protective against silicosis (Greaves, 2000) but it was thought that this limit was a good start towards lowering silica exposures. The 2008 target for dust reduction was not met, but compliance improved from about 80% in 2005 to 94.6% in 2013 (MHSI, undated-a). The 2014 updated milestones (Table 2), reduced the OEL for respirable silica to 0.05 mg/m³ and extended the targets to include other industries (platinum and coal) and diseases (coal workers' pneumoconiosis, TB and HIV) (Msiza, 2014). The 2016/2017 Mine Health and Safety Inspectorate report noted that although occupational diseases were still high, most were in miners who entered the industry before 2008 (MHSI, 2018).

Table 2 Summary of MHSC milestones set for the South African mining industry

DATE	TARGET
2003 Silicosis Milestones (MHSI, undated-a)	
Dec 2008	95% of individual respirable crystalline silica measurements below OEL of 0.1 mg/m ³
Dec 2013	No new cases of silicosis in workers who enter the industry after 2007
2014 OLD Milestones (Msiza, 2014)	
Dec 2024	95% of individual respirable crystalline silica measurements below OEL of 0.05 mg/m ³
Dec 2024	95% of individual respirable platinum dust particulates <1.5 mg/m ³ (<5% crystalline silica)
Dec 2024	95% of individual respirable coal dust particulates <1.5 mg/m ³ (<5% crystalline silica)
Dec 2024	No new cases of silicosis or coal workers' pneumoconiosis among workers who enter the industry after 2008
2014 HIV and TB Milestones (Msiza, 2014)	
Dec 2024	TB incidence rate at or below the national TB incidence rate
Dec 2024	100% of miners offered HCT annually and eligible miners linked to ART programmes as per the National Strategic Plan for HIV, TB and STI's: 2017-2020

1.2.2 Diseases associated with asbestos exposure

South Africa has a high but largely unknown burden of asbestos-related diseases (ARDs) affecting former asbestos miners; workers employed in industries that used asbestos products

(e.g. in replacement of motor vehicle brake linings, construction and fireproofing in foundries and power stations) or where asbestos is incidental to work activities (e.g. building maintenance and demolition) (Kgalamono et al., 2005); and residents in former asbestos mining areas (Braun and Kisting, 2006, Ndlovu et al., 2013). Dry milling made asbestos production a particularly dusty occupation. Diseases associated with the inhalation of asbestos fibres include non-malignant conditions, such as asbestosis, pleural plaques and effusions, and the malignant diseases mesothelioma and lung cancer. Generally, asbestosis and lung cancer are associated with high levels of exposure as occurs in occupational settings while pleural plaques, pleural thickening and malignant mesothelioma are the consequence of lower levels of exposure, for example, environmental exposures.

Asbestosis is a pneumoconiosis characterised by fibrosis of the lower lobes of the lung parenchyma (American Thoracic Society, 2004). The latency period (about 20 years) and progression are influenced by the duration and intensity of asbestos exposure (American Thoracic Society, 2004). The clinical diagnosis of asbestosis relies on imaging or histology and an occupational or environmental history of asbestos exposure or the presence of markers in the lung, after exclusion of other plausible findings (American Thoracic Society, 2004). Pleural plaques are benign areas of fibrous thickening on the parietal pleura of the lung or diaphragm, which are the most common indicator of asbestos exposure. However, they are not included in this thesis because the parietal pleura is seldom submitted with the lungs for examination at the NIOH. Mesothelioma is a tumour of the pleural membrane of the lung caused almost exclusively by asbestos exposure (Rudd, 2010). Asbestos-related lung cancers occur in the lung parenchyma and are indistinguishable from lung cancers caused by other factors (Tossavainen, 1997).

High levels of asbestosis have been detected in South African miners. In a study of employed miners using chest radiographs for diagnosis, the overall prevalence of asbestosis was 7.3% and was found to increase with increasing employment duration and age (Irwig et al., 1979). In the early 1960s, Sluis-Cremer reported that asbestosis was detected in 80% and 72% of black miners from Penge and the Cape, respectively, who had statutory autopsies (Sluis-Cremer, 1965). Davies et al. (Davies et al., 2001) detected pleural or parenchymal asbestosis in 96.2% of 770 female asbestos miners in the Northern Province (now, Limpopo province). The high prevalence of asbestosis was attributed to high exposures to amphibole asbestos

(amosite or crocidolite) and long residence time of asbestos-containing dust in the lungs (Irwig et al., 1979, Davies et al., 2001).

The autopsy case series of Wagner and co-workers established the association between pleural mesothelioma and asbestos exposures and is the most cited occupational health paper (Wagner et al., 1960). Many of the cases had no occupational exposures to asbestos but had been exposed while living with a person was employed in an asbestos operation (domestic exposure) or lived in the vicinity of such an operation (neighbourhood exposure). In a case-control study, Rees and coworkers (Rees et al., 1999) confirmed the importance of environmental exposures in the development of mesothelioma and showed the “*mesotheliomagenic potential*” of asbestos to be crocidolite > amosite > chrysotile, confirming that amphiboles are more potent than chrysotile.

Mesothelioma is of importance globally, and cases are sentinel events signaling asbestos exposure (Bianchi and Bianchi, 2007). There is no threshold of exposure and mesothelioma can occur after trivial exposure to asbestos. The latency period is usually around 40 years, and the prognosis is poor, with death occurring about a year after diagnosis (Rudd, 1989). South Africa was cited as being among ten countries with the highest number of mesothelioma deaths, with an age-adjusted mortality rate of 6.7 per million in the period 1994 to 2008 (Delgermaa et al., 2011). Table 3 summarises three South African studies which showed that incidence and mortality rates of mesothelioma differ by race and are two- to three-fold higher in men compared to women.

Table 3 Summary of population-based studies on mesothelioma in South Africa

Authors	Data source	Study period	Measure	Rate per million
Zwi et al., 1989 (Zwi et al., 1989)	Multicentre data	1976-1984	Age-standardised incidence rate	White men 32.9 White women 8.9 Black men 7.6 Black women 3.0 Coloured men 24.8 Coloured women 13.9
Janse van Rensburg et al. (Janse van Rensburg, 1987)	Department of National Health and Population Development and Central Statistical Services	1979-1983	Mortality rate	White men 15.8 White women 6.3 Black men 1.7 Black women 0.6 Coloured men 8.6 Coloured women 5.7
Kielkowski et al. 2011 (Kielkowski et al., 2011)	Statistics South Africa	1995-2007	Age-adjusted mortality rate	Men 13.0 Women 4.0

There is a synergistic interaction between asbestos and cigarette smoking: the risk of developing lung cancer in smokers who are exposed to asbestos is higher than in asbestos-exposed non-smokers (Uguen et al., 2017). Hence, smoking should be considered in epidemiological risk factor studies of asbestos-related lung cancer.

Few studies have reported on asbestos-related lung cancer in South Africa. Botha et al., (Botha et al., 1986) demonstrated that higher mortality rates for asbestosis and mesothelioma, and cancers of the lung and stomach in crocidolite compared to non-crocidolite mining districts and mortality rates for lung cancer were several-fold lower than those for asbestos or mesothelioma. There were no smoking data available, but it was concluded that the excess lung cancer mortality observed was probably not related to smoking only (Botha et al., 1986). Another mortality study showed that crocidolite was more potent than amosite for lung cancer and mesothelioma (Sluis-Cremer et al., 1992).

Although asbestos mining and usage were banned in South Africa over a decade ago, asbestos-related diseases remain important. The long latency of mesothelioma suggests that cases in workers who previously mined or used asbestos will be seen well into the middle of the 21st century. However, exposures continue to occur due to incidental and neighbourhood exposures. Therefore, the ARDs are set to continue indefinitely.

1.3 OCCUPATIONAL DISEASE COMPENSATION

South Africa has four occupational health laws (Table 4). The Occupational Health and Safety Act of 1993 (OHSA) (RSA, 1993b) and the Mine Health and Safety Act, No 29 of 1996 (MHSA) (RSA, 1996), provide for the protection of the health and safety of workers and contain procedures to prevent hazardous workplace exposures and enforcement of the law. The laws also outline the duties of employers, workers, and health and safety representatives. The Compensation for Occupational Injuries and Diseases Act of 1993 (COIDA) (RSA, 1993) provides for the compensation of all workers, except miners who develop OLDs who are covered by the Occupational Disease in Mines and Works Act, 1973 (ODMWA) (RSA, 1973).

The separation of compensation legislation for OLDs in miners from that of other workers is not unique to South Africa and is done in many countries (Ehrlich, 2012a). However, in South Africa, there are differences in disease thresholds and benefits, which often result in miners getting poorer benefits. For many years there have been discussions on the integration or harmonisation of the ODMWA and COIDA. One of the obstacles is the sizeable unfunded liability arising from the ODMWA's failure to acknowledge and cater for compensation of diseases of long latency in former miners (Ehrlich, 2012b). Under COIDA, the families of miners would also lose the benefit of statutory autopsy compensation.

Due to deficiencies and inefficiency of the ODMWA compensation, miners have resorted to legal recourse for OLD compensation. The Asbestos Relief Trust (ART) and Kgalagadi Relief Trust (KRT) were created as the result of voluntary court settlements between former workers and asbestos companies in 2003 and 2006, respectively (teWaterNaude, 2014a). The Trusts provide compensation for ARDs for qualifying former asbestos miners and individuals who worked on or lived near specific asbestos mines or processing operations (teWaterNaude, 2014b). The Trusts have similar structures and compensation provisions, and are jointly administered by the ART (teWaterNaude, 2014a). The Trusts also compensate dependents of deceased qualifying mineworkers and therefore encourage statutory ODMWA autopsies for the detection of previously undiagnosed ARDS or disease that may have progressed. Since 2006, the cardio-respiratory organs of deceased claimants have been submitted to the NIOH for examination.

Table 4 Occupational health legislation in South Africa

	OHSA, 1993	MHSA, 1996	ODMWA, 1973	COIDA, 1993
Objective	To safeguard the health and safety of workers through prevention and enforcement	To safeguard the health and safety of miners through prevention and enforcement	To compensate persons employed in mines and works who develop specified occupational lung and heart diseases	To compensate all workers for occupational injuries or diseases, and work-related death, except for occupational lung diseases in miners
Administration	Department of Labour (DOL)	Department of Mineral Resources (DMR)	National Department of Health (NDOH)	Department of Labour; Rand Mutual Assurance (RMA) & Federated Employers Mutual (FEMA)
Organisation	Pretoria and DOL regional offices	Pretoria and DMR regional offices	Compensation Commissioner for Occupational Diseases (CCOD), Medical Bureau for Occupational Diseases (MBOD) and NIOH in Johannesburg	Pretoria and DOL regional offices, RMA and FEMA offices in Johannesburg and in the regions
Coverage	All workers except those covered under the MHSA	All workers in mines	Miners for lung and heart diseases only	All workers in the formal economy for injuries and diseases, excluding OLDs in mine workers covered under the ODMWA
Funding	DOL	DMR	Levies on employers of 252 controlled mines and works (risk is rated by the Risk Committee)	Levies on approx. 337 000 employers, (risk is rated on claims record)

In March 2011, the Constitutional Court of South Africa made a landmark judgment which confirmed the right of miners to civil action for redress for OLDs from their employers (Constitutional Court of South Africa, 2011). In May 2018, a historic class action on behalf of miners who developed silicosis ended with seven mining firms agreeing to settle (Silicosis Settlement, 2019). The settlement covers qualifying miners who contracted silicosis or tuberculosis in qualifying mines from 12 March 1965 to date. The total estimated cost of the settlement is R5 billion with compensation pay-outs that are much higher than those under the ODMWA (See Section 1.3.2) ranging from R70 000 to R500 000 for silicosis and R10 000 to R100 000 for tuberculosis (Silicosis Settlement, 2019).

1.3.1 The ODMWA

South Africa has had statutory compensation for OLDs arising from mining for over a century. The first Act was introduced in 1911 and has been succeeded by 18 Acts (Ehrlich, 2012a). The current Act, the ODMWA (RSA, 1973) was introduced in 1973 and was amended to remove racially and gender-biased provisions in 1993 (RSA, 1993a). The ODMWA governs the lifelong medical surveillance of current and former mineworkers who performed risk work, that is, have been exposed to harmful dust in mines and works. Works are places that are not mines or parts of mines where operations, such as the moving and processing of stone, rock and minerals occur (RSA, 1973). In this thesis, the word “miner” includes workers in mines and works, as the vast majority of autopsied cases were miners. For example, in 2016, only 2.1% of those who were autopsied had been employed in works (industry, railways, silicon smelters, shaft sinkers, and iron and steel works) (Kgokong et al., 2017).

Employed miners, particularly those working on large mines, undergo regular medical surveillance for silicosis and tuberculosis. Former miners are entitled to biennial screening, but the vast majority do not have access to facilities for examination (Ehrlich et al., 2017). Initiatives are underway to improve access through the establishment of “One Stop” centres in labour sending areas in South Africa and neighbouring countries (Kistnasamy et al., 2018).

A feature of the ODMWA is the provision for autopsies on miners. Autopsies were a common practice as part of the standard of care from the early days of mining in the Witwatersrand (Ndlovu et al., 2008). Therefore, it is not surprising that autopsies were incorporated into compensation legislation from as early as the Miners’ Phthisis Act of 1916 (Donsky, 1993). Initially, this provision covered gold mineworkers who died of silicosis or TB (Donsky, 1993) but was later extended to include other diseases and mining sectors.

The ODMWA provides lump sum awards for the following diseases:

- pneumoconiosis (silicosis, asbestosis, coal workers’ pneumoconiosis and progressive massive fibrosis)
- pulmonary tuberculosis (PTB) in miners who have performed at least 200 risk shifts or are diagnosed within 12 months of leaving the industry, and PTB in the presence of silicosis with no time restriction

- joint pneumoconiosis and PTB
- permanent obstructive airways disease/emphysema
- platinum sensitivity
- progressive systemic sclerosis or scleroderma in silica-exposed miners
- malignant mesothelioma and lung cancer in asbestos-exposed miners

The ODMWA recognises that not all disease is detected in life and makes provision for detection using autopsies, which are the gold standard for diagnosis. However, some OLDs cannot be detected using autopsies and are only diagnosed in life using clinical assessment, e.g. occupational asthma.

Compensation is awarded at two levels: first degree for non-malignant conditions with a maximum award currently set at R63,000 and second degree for pneumoconiosis plus PTB or malignant conditions with a maximum award of R140,506 (RSA, 1973, Silicosis Settlement, 2019). Miners who receive second degree compensation while alive, are not eligible for further compensation and, therefore, it is less likely that their organs will be submitted for autopsy.

1.3.2 Autopsy compensation process

The ODMWA (Section 34.2) requires the last attending medical practitioner should arrange for organ removal if she/he “*knows or has reason to believe that such person worked at the mine or works*” (RSA, 1973). Autopsies are performed regardless of the clinical cause of death provided that there is written consent signed by the miner before death or by a near relative.

“... a medical practitioner shall not perform a post-mortem examination on any deceased person or remove his or her cardio-respiratory organs or any other organs or parts of his or her body, without the consent of his widow (if any) or an adult near relative of the deceased, if the widow or such a relative can readily be consulted.” (Section 34.3) (RSA, 1973).

The ODMWA is unique in that the only access to autopsy compensation is through submission of cardio-respiratory organs for examination at a “*prescribed place*” (Section 34.2 of the ODMWA) which has been the NIOH in Johannesburg since 1954. The costs for the removal, transportation and examination of the organs are borne by the mines for

workers who die while in employment and the State for former miners (Section 36.1) (RSA, 1973).

Figure 1 summarises the autopsy compensation process. Pathologists at the NIOH examine the cardio-respiratory organs using standardised procedures and disease definitions. The pathology findings, and demographic and limited occupational histories are captured into the PATHAUT database. Electronic pathology reports are uploaded to Mine Workers Compensation System (MWCS) at the Medical Bureau for Occupational Diseases (MBOD). The Certification Committee of the MBOD considers autopsy findings in conjunction with the commodities worked, intensity and duration of employment, where available, and in light of previous compensation. A certification certificate is issued stating if the OLD is present in the first or second degree, or if disease is present but non-compensable. Payments for compensable disease are made to dependents by the mines' Compensation Commission for Occupational Diseases (CCOD).

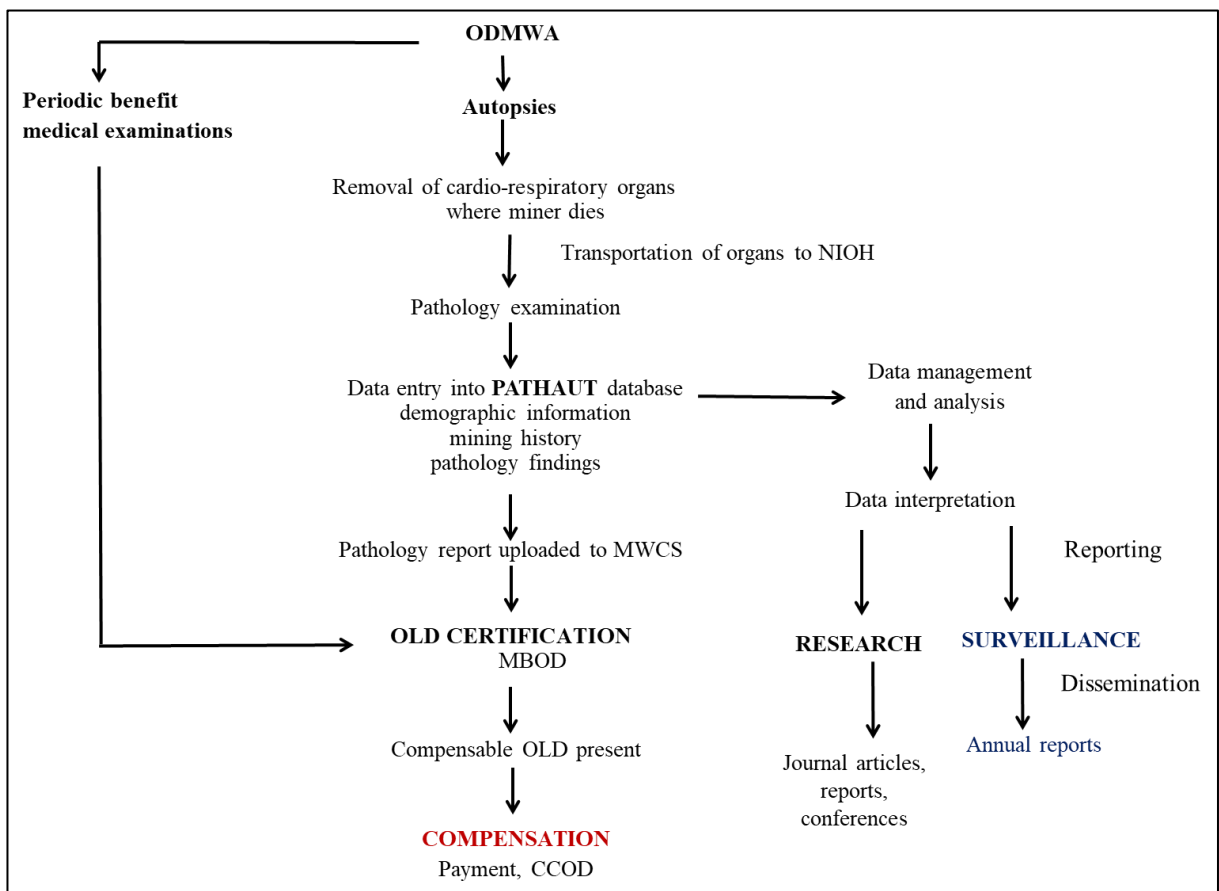


Figure 1 Overview of the ODMWA compensation processes

1.3.3 The PATHAUT database

The increasing use of computer technology in pathology laboratories resulted in the creation of the PATHAUT database, which came into use in 1975 (Soskolne et al., 1976). Prior to this (1959 to 1974), information was transferred from pathology examination reports to edge-punch cards for statistical analysis. This was a laborious task which required considerable human resources to clip and check about 3,000 cards annually (Soskolne et al., 1976).

The PATHAUT database was developed to improve efficiency and reduce costs associated with the data capture process, to enable data updates and enquiry, and the generation of typewritten reports for compensation. It was also developed to make the processes of case selection and data extraction less cumbersome and to produce data in formats suitable for statistical analysis using contemporary software packages. The PATHAUT database currently contains over 112,702 records (NIOH, 2018) and 450 variables, and is a rich resource of data for research. Since 1976, well over 100 journal publications have been produced using these data.

When the PATHAUT database was developed, no explicit surveillance function was envisaged. By 1987 when Hessel published twin papers describing the first ten years of PATHAUT data, there were 33,000 autopsy records on the database, but no surveillance reports had been produced (Hessel et al., 1987a, Hessel et al., 1987b). The first annual report that provided information on PTB and silicosis was produced in 1991 (Murray and Kielkowski, 1991). The NIOH obtained funding from the Mine Health and Safety Council to develop software programmes for the generation of annual pathology surveillance reports which were compiled to produce a comprehensive procedures manual (Murray et al., 1998). The software procedures and reporting format were piloted using the 1997 autopsy data. The same format is still in use. The reports describe disease proportions (emphysema, silicosis, PTB, lung cancer, asbestosis, mesothelioma, massive fibrosis, coal workers pneumoconiosis and mixed dust pneumoconiosis) by age, commodity worked and cumulative duration of employment,

In 2011, annual reports from 1975 to 1995 were written retrospectively. The full set of reports (1975-2017), excluding 1996 for which the pathology data are incomplete, are available on the NIOH website (www.nioh.ac.za/publications/pathology-disease-surveillance-

[reports/](#)). The reports are shared with mine medical doctors, the MBOD and CCOD, Department of Mineral Resources and academics and periodic summaries have been published in a local journal (Ndlovu, 2006, Ndlovu, 2012, Ndlovu et al., 2014, Ndlovu et al., 2012, Kgokong et al., 2018).

A timeline showing key dates with regard to autopsy compensation for OLDS and surveillance-related activities using the PATHAUT data is presented in Figure 2.

1911	Miners' Phthisis Allowance Act (No. 34 of 1911) First workers compensation law in South Africa
1916	Miners' Phthisis Act (No. 44 of 1916) Autopsy compensation for silicosis is added to the legislation
1956	Pneumoconiosis Act (No. 57 of 1956) Requirement for standardised methods for the examination of the cardio-respiratory organs
1973	Occupational Disease in Mines and Works Act of 1973 (No. 78 of 1973)
1975	Introduction of PATHAUT database
1976	First paper describing the PATHAUT database (Soskolne et al., 1976)
1987	Two papers describing the first ten years of PATHAUT data (Hessel et al., 1987a, Hessel et al., 1987b)
1993	ODMWA Amendment Act of 1993 (No 208 of 1993)
1996	PATHAUT database moved to a new platform
1999	First annual report using 1997 data, followed by annual reporting
2011	1975 to 1995 annual pathology reports written retrospectively
2019	Evaluation of PATHAUT for OLD surveillance

Figure 2 Important dates with regard to autopsy compensation and the PATHAUT database

1.5 PROBLEM STATEMENT

The century-old epidemics of silicosis, tuberculosis and asbestos-related diseases in the South African mining industry have placed the country at the centre of research on OLDs. The country was ranked fourth in terms of numbers and impact of publications on silicosis produced from 1920 to 2012 (Gerber et al., 2014). Despite excellence in research, there is little systematic occupational disease surveillance in South Africa.

Compensation data are a useful source of occupational surveillance data as they provide both disease and employment (e.g. commodity and employment duration) information. South African law (Section 25 of COIDA) requires the reporting of all cases of occupational disease, except OLDs in miners, to the COIDA Compensation Commissioner (RSA., 1993). However, no reports have been produced. The unavailability of national occupational disease

information led to the development of two national occupational disease surveillance systems by the NIOH. Both systems relied on voluntary reporting of new cases by physicians.

Surveillance of Occupational Respiratory Disease in South Africa (SORDSA) was introduced in 1996 (Esterhuizen, 2001). The system was used to identify industries where cases were occurring, create awareness of OLDs among medical practitioners, generate research questions and led to the initiation of research projects and had the potential to provide information on OLDs in former miners (Rees et al., 2001). Surveillance of Upper Limb Musculoskeletal Disorders in South Africa (SAMOSA) was introduced in the early 2000s to identify industries with high risk. The information generated was used to advise industry on the control of ergonomic hazards and led to formation of the SAMOSA referral clinic for the diagnosis of upper limb musculoskeletal disorders (NIOH., undated).

A limitation of SORDSA was poor reporting coverage, as most reports were submitted from three of the nine provinces of South Africa (Keilkowski, 2006). Both SORDSA and SAMOSA were terminated after a few years due to reporter fatigue and competing demands which caused physicians to stop reporting, and inadequate provision of human resources to maintain the systems at the NIOH (Sawry et al., 2006).

For the mining industry, the MHSA requires the reporting of all occupational diseases in miners to the Department of Mineral Resources (DMR). In an effort to improve the tracking of occupational diseases in miners, the DMR launched the South African Mines Occupational Diseases Database (SAMODD) in 2000. A single publication reporting occupational diseases in miners from 2000 to 2003 years was produced (Worku and Ohaju, 2004).

A potential source of occupational diseases surveillance data are the annual reports from mines on various medical conditions which are submitted to the Mine Health and Safety Inspectorate (MHSI) in the DMR in accordance with the MHSA (MHSA, 1996). Starting in 2007/2008, the MHSI has produced biennial reports reporting the numbers of cases of silicosis, silico-tuberculosis, PTB, noise-induced hearing loss, coal workers pneumoconioses, asbestosis and other diseases by commodity and year (MHSI, undated-b). It is difficult to interpret these data as they do not take the size of the population into consideration and are presented as numbers and not as rates or proportions.

The ODMWA requires the MBOD and CCOD to produce annual reports, but this requirement has not been met since the early 2000s. From the mid-1960s, the MBOD annual reports provided information on compensable OLD certifications in living and deceased miners (Leger, 1992). The frequency of reporting declined in the 1980s and the last available report was published in 2001.

The PATHAUT database provides the only source of comprehensive, long-term surveillance information on OLDs in the South African mining industry. Regular annual surveillance reports have been produced since 1997, but the use of the data for surveillance has not been evaluated.

1.6 JUSTIFICATION

The evaluation of surveillance systems should be done periodically, at any time, to document surveillance activities, identify strengths and weaknesses and to recommend improvements. This is done by assessing its attributes (structure and processes) and usefulness in the provision of information disease prevention and control. Assessment of the quality and representativeness of the information generated by the surveillance system is essential as under detection of disease and selection bias arising from reporting practices might result in biased findings. This can give rise to misleading conclusions and insufficient allocation of resources to the monitoring, management and prevention of significant health problems or allocation of large resources to health problems that are no longer significant (CDC, 2001).

There has hitherto been no formal assessment to determine if the administrative, PATHAUT autopsy data fulfil the requirements of surveillance and, if further development of a surveillance function is warranted. The findings from this evaluation will be used to inform the use of PATHAUT as a tool for surveillance, as well as to inform the use of routine, administrative databases for surveillance and to assess the suitability of the guideline for the evaluation for occupational disease surveillance systems.

1.7 AIM AND OBJECTIVES

This thesis aims to evaluate the attributes and usefulness of an administrative database, the PATHAUT autopsy compensation database, for the provision of information for OLD surveillance in the South African mining industry.

Objectives

The first two objectives specifically address the evaluation of PATHAUT as a tool for surveillance, and the remaining four objectives address the four epidemiological studies which provide information for the evaluation.

1. To determine the attributes of simplicity, stability, flexibility, data quality, sensitivity, representativeness and timeliness of PATHAUT as a tool for surveillance.
2. To determine the usefulness of PATHAUT as a tool for surveillance for detecting disease, providing estimates of disease magnitude, detecting disease trends, determining factors associated with the disease occurrence, identifying sentinel cases of disease and monitoring the effectiveness of prevention and control programmes.
3. To describe the PATHAUT database, and trends of key demographic characteristics, occupational exposures and autopsy-diagnosed OLDs in deceased South African miners from 1975 to 2013.
4. To compare the clinical and pathological diagnoses of asbestosis, mesothelioma, and lung cancer in asbestos miners who had autopsies at the NIOH in 2010 and 2011.
5. To determine long-term temporal trends and factors associated with autopsy-diagnosed PTB in deceased black and white miners from 1975 to 2014.
6. To compare autopsy-diagnosed pulmonary silicosis, lymph gland silicosis and PTB in female and male gold miners whose organs were examined at the NIOH from 2005 to 2015.

CHAPTER 2: LITERATURE REVIEW

This chapter focuses on public and occupational health surveillance. Key surveillance concepts which are relevant for the understanding of the types and scope of disease surveillance are introduced. A brief overview of occupational disease surveillance systems and the use of administrative data sources for surveillance is provided. The section on surveillance system evaluation frameworks includes information to support the selection of the CDC framework for evaluation of PATHAUT surveillance. The chapter also provides the conceptual framework of the thesis which was developed to guide the evaluation of PATHAUT as a tool for surveillance. The chapter ends with a brief description of the methodological approach used in this thesis.

2.1 PUBLIC HEALTH SURVEILLANCE

The concept and definitions of surveillance evolved over centuries and, in the early years, focused on infectious diseases in populations. The Centre for Disease Control (CDC) defines public health surveillance as the “*ongoing, systematic collection, analysis, interpretation, and dissemination of data for use in public health to reduce morbidity and mortality and to improve health*” (CDC, 2001). Figure 3 outlines the steps in public health surveillance. The CDC definition, like most contemporary definitions, encompasses the three main surveillance activities, which are:

- (i) continuous and orderly data collection and reporting of data to the surveillance system;
- (ii) data collation, analysis and interpretation, and
- (iii) timeous dissemination of information to those who can use it for public health action.

The definition proceeds to link surveillance activities to disease control and prevention.

However, it is not a function of surveillance to carry out control and prevention activities (Choi, 2012).

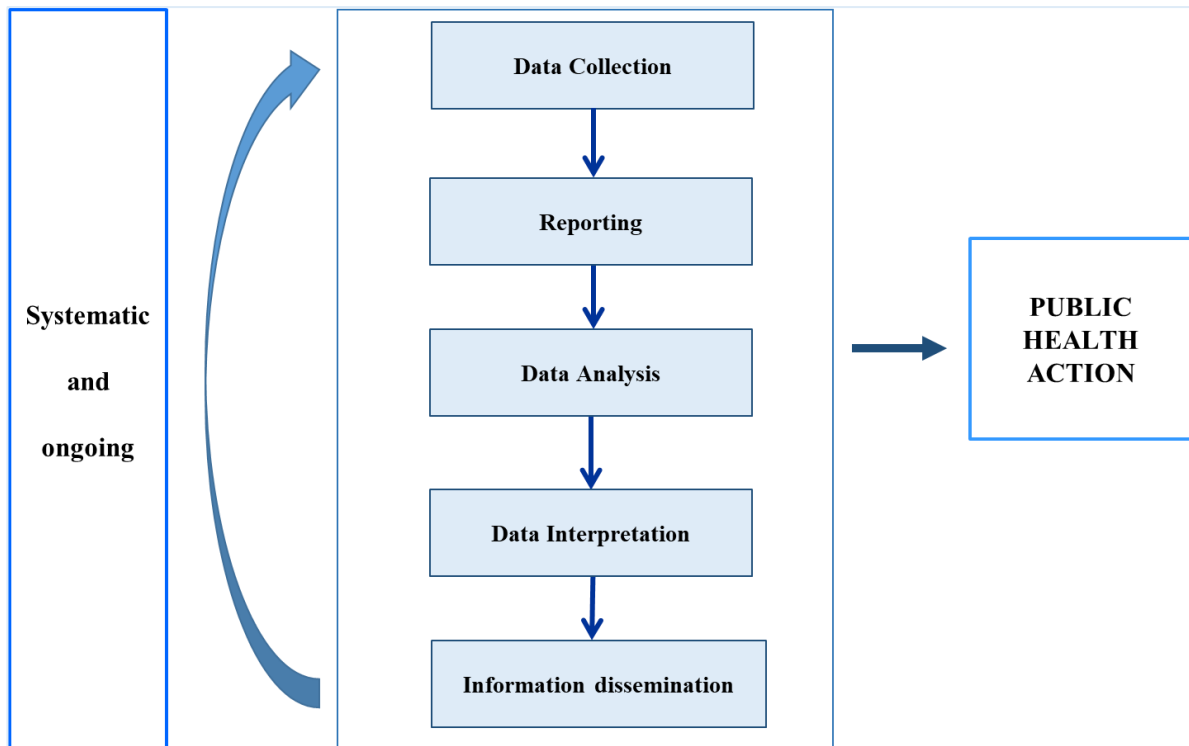


Figure 3 Components of public health surveillance (source not known)

Surveillance plays a role within the public health approach to disease prevention which aims to improve the health of all individuals by addressing factors that increase the risk of developing disease. In this approach surveillance is used to detect and define health-related problems through disease detection; measuring changing patterns of disease occurrence over time; identifying populations at high risk; identifying new or emerging health concerns and using this information to formulate research hypotheses (Checkoway, 2004). Research is used to identify modifiable risk factors and the findings are used to design, develop and implement interventions to reduce disease through risk factor modification. Surveillance activities are then used to monitor the effectiveness of interventions on disease prevention.

Generation of data for research is an accepted goal of surveillance, but there is a fine line between surveillance and research. The main differences are

- (i) that the primary role of surveillance is to provide information for action while research generates new knowledge;
- (ii) surveillance uses descriptive methods while research is hypotheses driven, usually involving the use of analytical, statistical methods, and
- (iii) surveillance data are usually limited in detail, whereas research requires detailed individual data.

The tradition has been to separate surveillance from research activities because of the concern that combining them could lead to a costly collection of large amounts of detailed data which could result in failure of surveillance systems (Choi, 2012).

Surveillance systems vary in type and complexity from simple systems that collect data from a single source to electronic systems that gather information from multiple sources. They also range from local, single-institution programmes to national and global initiatives.

Depending on the method of reporting, surveillance systems are classified as active or passive. Active surveillance involves regular outreach to potential reporters to stimulate reporting of specific events. Reporting tends to be more accurate and complete but is costly as it requires more resources (Teutsch and Churchill, 2000). In passive systems, such as notifiable disease surveillance systems, health care providers report events to the appropriate authority as they come to their attention. The advantages of passive surveillance are that it is simple, relatively inexpensive in terms of human and financial resources, and allows for coverage of large geographical areas (Teutsch and Churchill, 2000). Its main disadvantages are that the data provided may be of variable and poor quality, and reporting may be delayed and untimely.

Sentinel surveillance may be used when high-quality data are required. In this type of surveillance, a few sites that are likely to see cases of the disease of interest, have good laboratory facilities and qualified staff are selected to identify and notify cases. Unlike passive surveillance which collects data from any site, in this type of surveillance, data is deliberately collected from a few carefully selected reporting sites.

2.2 OCCUPATIONAL DISEASE SURVEILLANCE

In the last century the concept of surveillance has spread to include chronic diseases and other disciplines, such as environmental and occupational health (Choi, 2012). Hazard surveillance and health surveillance are two broad categories of surveillance. Hazard surveillance has received little attention. It identifies workers or work areas with excessive exposures who therefore have the potential to develop disease (leading indicators).

Interventions can then be put in place to reduce hazardous workplace exposures and thereby reduces disease risk (National Academies of Sciences and Medicine, 2018).

Occupational health surveillance is the “*systematic investigation of the occurrence of health outcomes in relation to work conditions*” in worker populations and differs from medical surveillance (also known as medical screening) which refers to the testing of individual workers for early disease detection and prevention at the individual level (Koh and Aw, 2003). It uses concepts and methods of public health surveillance to protect and promote the health of workers through the prevention and control of occupational diseases by reducing hazardous occupational exposures and seeks to discover new associations between occupational exposures and disease (Checkoway et al., 2004, Koh and Aw, 2003).

Most occupational health surveillance systems report disease or health outcomes (lagging indicators). This type of surveillance requires information on the work-related health outcomes (injuries, disease or fatalities) of interest and exposures that are hazardous to health in order to establish the link between the event and the work-place. In the absence of objective measures of exposure, information on occupation, job and length of time in a particular job are used as proxies for exposure.

In public health, a sentinel health event (SHE) is defined as “*a preventable disease, disability, or untimely death whose occurrence serves as a warning signal that the quality of preventive or therapeutic medical care may need to be improved*” (Rutstein et al., 1983). In the early 1980s, Rutstein (Rutstein et al., 1983) introduced the concept of occupational SHE (Occupational) as occupationally-related health events whose occurrence may stimulate epidemiologic or occupational hygiene research or provide warning signals for the need for the implementation of control and prevention measures to reduce exposures through improved equipment design or work practices, use of personal protection equipment (PPE) or medical treatment (Markowitz, 2007). Hence, the diagnosis of an occupational disease in a worker signifies failure to control an occupational hazard and allows for investigation and identification of populations of workers who are at risk of developing the same disease (Markowitz, 2007). The pneumoconioses (coal workers' pneumoconiosis, asbestosis and silicosis), pulmonary tuberculosis and mesothelioma are listed as occupational sentinel health events (Rutstein et al., 1983).

2.2.1 Occupational disease surveillance systems

Occupational health surveillance may either be industry-based through periodic exposure and health assessments of workers in specific industries or population-based, relying on information from periodic surveys of occupational illnesses and injuries in the general population (Checkoway et al., 2004). Most occupational disease surveillance systems are passive depending on reporting from physicians who report voluntarily or are obliged to do so by law or use existing data sources (Bakusic et al., 2017).

A recent comprehensive systematic literature review identified 75 occupational disease surveillance systems in Europe, the USA, Asia, Australia, New Zealand and Africa (Bakusic et al., 2017). SORDSA, which had already been terminated, was the only African system identified. Most (n=68) of the systems were worker-based while seven systems were population-based, covering the general public and workers. Sixty one of the 68 worker-based surveillance systems were passive and 12 were sentinel surveillance systems.

Almost all countries in the European Union (EU) have national occupational disease surveillance systems, most of which are compensation-based and are part of social security or independent systems (European Commission, 2012). The registries differ among countries with respect to case definitions, notification guidelines and legal and social security contexts, making it difficult for comparisons to be made between countries. Some countries also have reporting systems based on voluntary or statutory reporting from doctors or employers (European Commission, 2012, Carder et al., 2015).

In the USA, the National Institute for Occupational Safety and Health (NIOSH) plays a central role by conducting and coordinating occupational disease surveillance. It conducts risk assessments and occupational health studies in workers across all industries. It also oversees the use of existing administrative data sources from various organisations and uses the information to develop national and state-based systems(<https://www.cdc.gov/niosh/about/>).

Despite high-income countries having surveillance systems, many challenges are experienced. An evaluation of occupational disease surveillance in six EU countries found variable data quality among the countries due to poor notification criteria and poor physician

reporting leading to inadequate disease monitoring and detection of emerging diseases (Spreeuwiers et al., 2010).

Occupational disease surveillance is lacking in most developing countries (Loewenson, 1999, SafeWork, 2013). In these settings, implementation of surveillance activities can be particularly challenging because of the inadequacy of health services, shortages of medical practitioners of whom few have training in occupational medicine resulting in poor occupational disease detection and underreporting; inadequate provision of suitable diagnostic equipment, particularly in rural areas where many migrant workers return after employment; and workers who are unaware of occupational causes of disease and who may not seek treatment (Loewenson, 1999, Antao and Pinheiro, 2015).

Particularly in resource-scarce settings, simple strategies involving the use of existing resources and technology are the best and most sustainable approach to occupational disease surveillance (Antao and Pinheiro, 2015). Advances in technology over the last three decades have made the use of administrative data particularly attractive for the provision of health information. These are data that are routinely collected for other purposes, e.g. electronic death and mortality data, cancer registries, workers compensation records, hospital discharge records and household surveys (Grosse et al., 2010, Hux et al., 2002, Powell et al., 2003). The advantages of using administrative data are that the data are readily available; provide cheap and easy to access to large numbers of individuals over large geographical areas; are often population-based and therefore representative of important population subgroups; allow comparisons to be made between cases with and without disease, and can provide both cross-sectional and longitudinal information about disease prevalence and incidence (Hashimoto et al., 2014).

Table 5 summarises data sources for occupational disease surveillance and their advantages and limitations. Insurance and compensation data are usually the most comprehensive data sources as they provide both disease and employment (exposure) information (Loewenson, 1999).

Table 5 Summary of types of routine occupational disease surveillance data

Data source	Uses	Advantages	Disadvantages
Death certificates for occupational mortality	Identification of unusual associations between occupation and cause-specific mortality	Legal requirement of death certification in most countries Identification of occupational groups with increased cause-specific mortality	Variation in accuracy of death certificate completion Unable to ascertain accuracy of occupational information on death certificates Broad occupational or industry categories may obscure mortality due to specific exposures in narrowly defined industrial sectors
Cancer registries	Detection of occupational cancers	Contain detailed information on patient demographics, cancer morphology and histology	Lack of information on employment and cancer risk factors
Workers compensation systems	Provide provincial and national statistics	Records contain demographic and employment information, name of workplace where illness occurred and occupational exposures. Provide opportunities for immediate follow-up and control of diseases	Differential reporting between provinces and countries Variations in physician reporting practices due to under-recognition of health condition Long latency diseases may not be reported
Hospital discharge records	Useful for the identification of potential occupational health problems, unusual patterns of disease, occurrence of sentinel events (e.g. pneumoconiosis)	Permits follow-up of cases for detailed investigations	Captures cases with severe disease requiring hospitalisation Lack of information on non-hospitalised individuals Might lack risk factor information Data may be incomplete
Household surveys	Identification of unusual occupational disease patterns for selected industries	Provide high-quality data Provide detailed personal, demographic, health-related and occupational information	Due to high costs, reporting may be irregular.

Information source: Melius et al. (Melius et al., 1989)

2.3 EVALUATION OF SURVEILLANCE SYSTEMS

As shown above, surveillance systems vary in complexity, scope, purpose and objectives depending on the epidemiological, economic and social contexts in which they operate. The evaluation of surveillance systems is critical for ensuring the quality and representativeness of the data generated. Evaluation is defined as a “*process that attempts to determine, as systematically and objectively as possible, the relevance, effectiveness and impact of activities in light of their objectives*” (Last, 2001). The periodic evaluation of surveillance

systems enables efficient and effective monitoring of important public health problems, and, provides opportunities to adjust the focus and resources according to information needs (CDC, 2001).

Several frameworks and guidelines have been developed for surveillance system evaluation. Calba et al (Calba et al., 2015b) reviewed 15 frameworks and guidelines for public, animal and environmental health surveillance. Most of the approaches were designed to evaluate communicable disease surveillance systems, but three guidelines were considered to be versatile, enabling evaluation of non-communicable surveillance systems as well. These are the 1997 WHO (WHO, 1997), 2004 Canadian Health Surveillance Coordinating Committee (HSCC) (HSCC, 2004) and the 1988 CDC guidelines (CDC, 1988). The CDC guidelines were updated in 2001 to accommodate technological advances, such as, surveillance and health information system integration, exchange of health data, and to facilitate the detection of emerging diseases (CDC, 2001).

The guidelines focus on three broad categories: the process or steps to be followed in the evaluation, assessment of attributes and usefulness of surveillance systems (Table 6). The process begins with preparation which includes developing evaluation questions and engagement of stakeholders, description of the surveillance system to be evaluated, followed by data collection and analysis, and conclusion and recommendations. The CDC and HSCC guidelines also include dissemination or sharing of findings and follow-up to support the use of the results.

The attributes of a surveillance system are defined as inherent, characteristics of a surveillance system and are used to assess capacity to monitor health events. Thirty five attributes have been identified in the literature (Calba, 2013). The CDC, HSCC and WHO frameworks have seven system attributes in common viz acceptability, data quality/completeness, flexibility, representativeness, sensitivity, simplicity, and timeliness (CDC, 2001, HSCC, 2004, WHO, 1997). Also, the HSCC also assesses compliance with laws or policies and measures to safeguard confidentiality (HSCC, 2004). The CDC and HSCC guidelines evaluate positive predictive value (PPV). The WHO guideline does not assess stability (Table 6).

The attributes are closely linked and may influence each other. Multiple attributes are assessed when evaluating surveillance systems, and the choice of attributes depends on the context and objectives of the evaluation. As surveillance systems are different, attributes that are of importance to one system may be less relevant to another. Hence, the approach to an evaluation is flexible and emphasising only those attributes that are most relevant and important to the system under consideration (CDC, 2001).

Table 6 Overview of components of the WHO, CDC and HSCC surveillance evaluation guidelines

Category	WHO (1997)	CDC (2001)	HSCC (2004)
Process	Preparation	Engage stakeholders	Establishing context
	Documentation & evaluation	Describe the system	Identifying evaluation questions
	Evaluation of capacity	Focus the design	Data collection/management
	Outcome	Gather evidence	Findings
	Recommendations	Conclusions and recommendations	Reviewing report
		Ensure use of findings	Follow-up
System attributes	Acceptability	Acceptability	Acceptability
	Completeness	Data quality (completeness)	Data quality (completeness)
			Compliance
	Flexibility	Flexibility	Flexibility
		PPV	PPV
	Representativeness	Representativeness	Representativeness
	Sensitivity	Sensitivity	Sensitivity
	Simplicity	Simplicity	Simplicity
	Specificity		Specificity
		Stability	Stability
	Timeliness	Timeliness	Timeliness
System performance	Usefulness	Usefulness	Usefulness
			Effectiveness
			Efficiency

The three guidelines evaluate system performance of surveillance systems in terms of usefulness which is defined as the ability to contribute to prevention and control, and understanding of the disease (CDC, 2001). Usefulness is assessed with respect to the key functions of surveillance:

- disease detection;

- provision of estimates of disease magnitude;
- detection of disease trends,
- identification of risk factors,
- identification of new or emerging health concerns (sentinel case detection),
- stimulation of research leading to prevention and control and provision of evidence to inform planning and policy,
- monitoring of disease prevention and control programmes and
- lead to improved clinical, behavioural, policy or environmental practices

(Checkoway, 2004, Spreeuwers et al., 2010, CDC, 2001).

Only one evaluation guideline specific for the evaluation of occupational disease surveillance systems was identified. The ODIT audit tool was developed to assess the quality of passive, national occupational health registries based on physician reporting in the European Union (Spreeuwers et al., 2009). It consists of nine categories of indicators and is designed to assess the ability of national registries to monitor the magnitude and distribution of known occupational diseases over time (the monitor function) and to discover new associations between existing or new exposures and diseases (the alert function). Unlike the three public health evaluation frameworks described above, this tool provides cut-off values for acceptable results (e.g. for coverage of registration, notifying physicians must cover at least 75% of the working population). In addition, the ODIT tool includes specific indicators for occupational exposure, occupation, and economic sector which enable incidence rates to be expressed by working population, occupation or sector (Spreeuwers et al., 2009).

2.4 CONCEPTUAL FRAMEWORK, METHODOLOGICAL APPROACH AND THESIS STRUCTURE

The ODIT tool, described above, focuses on data quality only and was considered to be too narrow for the current evaluation. The updated CDC evaluation framework has been used widely to evaluate different types of public health, animal health and environmental surveillance systems and both communicable and non-communicable disease surveillance systems (Calba et al., 2015b). It is versatile and therefore, was selected for use in this thesis.

The conceptual framework developed for this thesis combines the key steps in the autopsy compensation process culminating in disease prevention and control, and components of the CDC evaluation guideline (Figure 4). It also incorporates the influence of stakeholders (individual/family factors and institutional/service provider factors) on autopsy uptake and illustrates how attributes of the autopsy process and PATHAUT database could provide information for OLD prevention and control.

The approach adopted for this thesis is based on the premises that the scope is specific to this evaluation, uses only those components of the framework that are pertinent to the purpose of the evaluation and that different methods of scientific study are acceptable (CDC, 2001, HSCC, 2004). This thesis is based on an approach which primarily draws from four epidemiological studies (Appendices 1 to 4) which provide information to address the aim and objectives of the evaluation. Each study contributed to improved understanding of the epidemiology of OLDs in South African miners. Additional information for the evaluation was obtained from the Pathology Division's standard operation procedures (SOPs).

Attributes can be assessed using quantitative, qualitative or mixed-methods. Qualitative methods enable the assessment of the experiences and perceptions of the implementers and stakeholders of surveillance systems. The thesis papers provided quantitative information only and existing literature used to explain some of the observations.

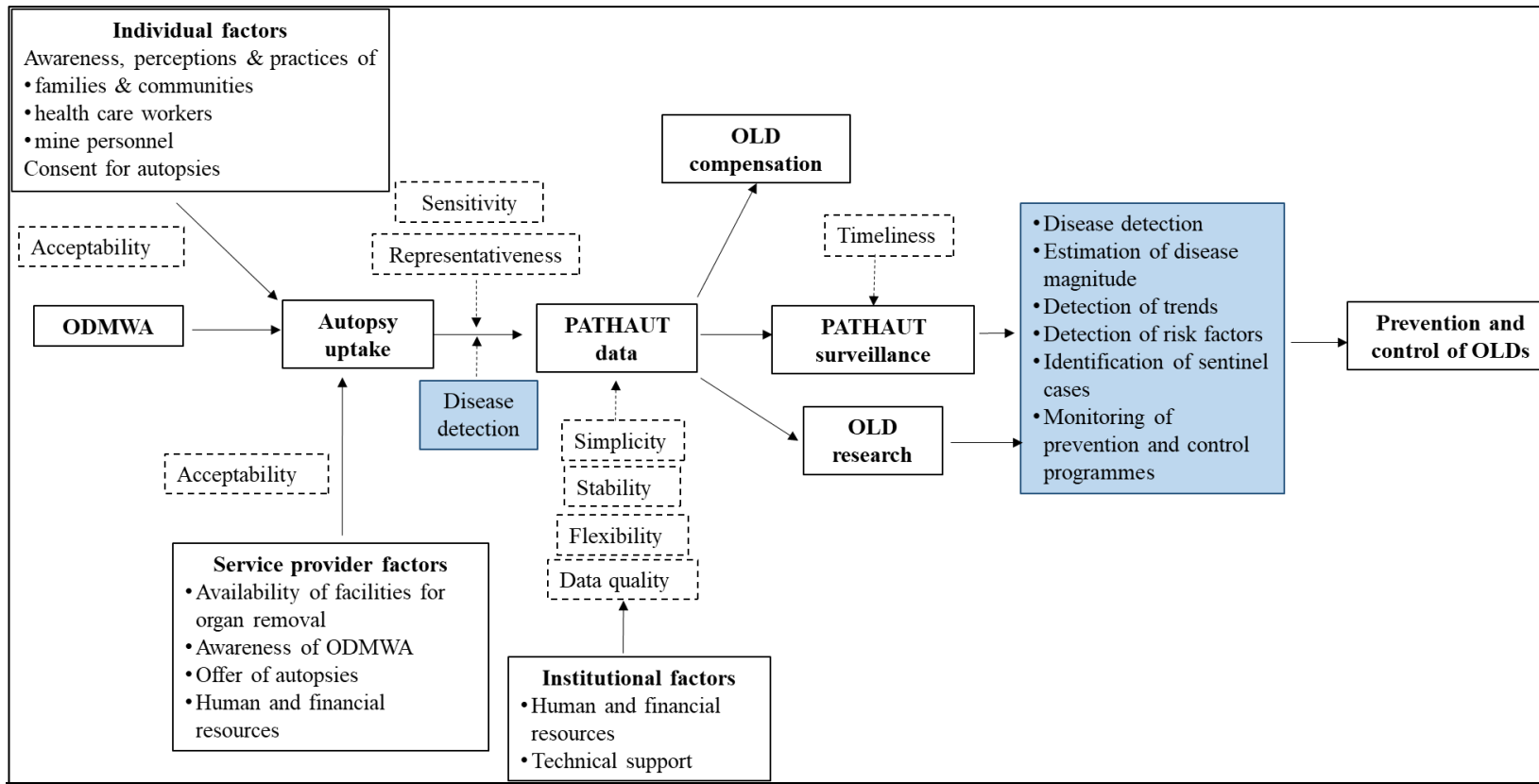


Figure 4 Conceptual framework for this thesis

Text boxes with dotted indicate attributes and shaded boxes indicate usefulness

NB: acceptability, though included in the conceptual framework, was not assessed in this thesis

The CDC evaluation guideline recommends a series of tasks which were performed in this PhD as summarised below.

Task A: *Engagement with stakeholders to ensure that the evaluation addresses relevant and appropriate questions; assesses pertinent attributes and that its findings will be acceptable and useful* (CDC, 2001).

Stakeholders are individuals and organisations who contribute to, use, and benefit from surveillance. For surveillance using PATHAUT, these include current and former miners, families of deceased miners, members of affected communities living near mines or in labour sending areas, unions such as the National Union of Mineworkers and Solidarity, occupational and public health practitioners, policymakers in the NDOH and DMR, academics, mining companies, and professional associations such as the Mine Medical Professionals Association (MMPA) and the South African Society for Occupational Health Nurses (SASOHN). There was no formal engagement with stakeholders during the evaluation. However, the evaluation had buy-in from the NIOH. The results of the individual studies were presented at various fora where input was obtained from stakeholders.

Task B: *Description of the surveillance system to be evaluated including descriptions of the public health importance of the disease under surveillance, the purpose and operation of the system, and resources required to operate the system* (CDC, 2001).

Information on the public health importance of the OLDs under surveillance, purpose and operation, and resources required for the operation of PATHAUT as a surveillance programme is provided in **Chapter 1** (Introduction). In **Chapter 2** (Literature Review), background information on occupational disease surveillance and evaluation guidelines for surveillance is provided.

Task C: *Focus of the evaluation design to determine the purpose and intended use of the findings of the evaluation, and standards for assessing the performance of the system* (CDC, 2001).

The methods used in the four thesis papers and for the evaluation of the suitability of the use of PATHAUT as a surveillance programme are provided in the **Chapter 3** (Methods).

Task D *Gathering of credible evidence regarding the performance of the surveillance system* (CDC, 2001).

D.1. Assessment of the usefulness of the system, that is, its ability to detect disease, estimate the magnitude of the problem, detect trends, assess the effectiveness of preventive and control programmes, lead to improved practices or stimulate research.

D.2. Description of system attributes – simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, timeliness and stability.

Selected findings from the four thesis papers which apply to the evaluation are presented in **Chapter 4** (Results).

Task E: *Justify and state conclusions, and make recommendations* (CDC, 2001).

The thesis findings are discussed in **Chapter 5** (Discussion). The final thesis chapter, **Chapter 6**, presents the recommendations and conclusions of the evaluation.

Task F *Utilisation of evaluation findings and sharing of lessons learnt* (CDC, 2001).

This task is beyond the scope of this thesis. However, the thesis findings and recommendations will be presented to the NIOH for further action.

CHAPTER 3: METHODS

This chapter presents summaries of the methods used in the four thesis papers and evaluation of PATHAUT as a tool for surveillance. The methods are presented in the order in which the papers were written and published. Each summary includes a brief section providing a background to the study, study design, study population, data sources, data management and statistical analysis. This is followed by descriptions of methods used in the evaluation according to the two thesis themes, namely system attributes and usefulness, using the information contained in the four thesis papers. The chapter ends with ethical considerations.

3.1 DESCRIPTION OF THE PATHAUT DATABASE

Background: The last comprehensive description of the PATHAUT database was provided by Hessel and coworkers in two papers which described the types and quality of data in the first ten years (1975-1984) of operation of the database (Hessel et al., 1987a, Hessel et al., 1987b). These papers aimed to encourage the use of the data for research. This study extended the description of the demographic characteristics, occupational exposures and compensable autopsy-diagnosed OLDs data to the current period and introduced the use of PATHAUT for surveillance.

Study design: descriptive cross-sectional study

Study population: All black and white miners whose cardio-respiratory organs were examined at the NIOH from 1975 to 2013.

Data source: PATHAUT database

Data management and analysis: The data were exported from the PATHAUT database to SAS (version 9.3) for analysis. Due to racial differences in socioeconomic status, employment patterns and access to facilities for autopsies, the analyses were stratified by population group. The Student t-test and the chi-square test were used to determine significant differences between means and frequencies, respectively. Linear trends in

proportions were determined using the Cochran-Armitage test. Statistical significance was defined at $p < 0.05$.

3.2 CLINICO-PATHOLOGICAL STUDY OF ARDS

Background: Autopsies provide unique opportunities to validate and correlate clinical and laboratory findings with pathological changes. The clinical diagnoses of asbestos-related diseases are difficult, and many cases may be missed or misdiagnosed. For a diagnosis to be made, a history showing asbestos exposure, clinical signs, radiology or the more sensitive CT imaging, and histology are required (Wolff et al., 2014). Few studies have compared the clinical and pathological diagnoses of ARDs using autopsies as the gold standard and many of these studies were published two decades ago. This study provided recent clinico-pathological information on ARD diagnosis.

Study design: Descriptive case series

Study population: All deceased ART claimants whose cardio-respiratory organs were examined at the NIOH in 2010 and 2011. Data from this period were used, as these were the most recent and complete data available when data was collected from the ART.

Data sources: PATHAUT and ARTmis (Asbestos Relief Trust Management Information System) and paper records of the ART.

Data management and analysis: deceased claimants were identified on ARTmis and demographic information, occupational histories, clinical and radiographic findings were obtained from the paper records stored at the ART offices in Cape Town. Autopsy diagnoses were obtained from the PATHAUT database. The ART and PATHAUT data were exported from Excel and SAS, respectively, to Stata and merged using the unique pathology autopsy number, bureau number (a unique number assigned by the MBOD) and year of death.

The pathology findings were used as the gold standard to calculate sensitivity, specificity, positive and negative predictive values for the clinical diagnoses of asbestosis, mesothelioma and lung cancer.

For asbestosis, binary logistic regression was used to evaluate factors associated with false-positive diagnoses and the κ -statistic was used to test the correlation between the severity of asbestosis diagnosed clinically and pathologically.

3.3 PTB TREND ANALYSIS

Background: A previous study, using the PATHAUT data, assessed the trends of autopsy-diagnosed PTB and silicosis in black gold miners who died of external (unnatural) causes in the pre- and early-HIV period (1975 to 1991) (Murray et al., 1996). PTB increased from 0.9% to 3.9% and was associated with silicosis, increasing age at death and duration of employment. The current study extended the analyses to include the periods of rapid HIV spread and antiretroviral therapy and provides the first long-term trend analysis of PTB in not only black but white South African miners as well.

Study design: Time-trend analysis

Study population: All black and white miners whose cardio-respiratory organs were examined at the NIOH from 1975 to 2014

Data source: PATHAUT database

Data management and analysis: Data management and analyses were performed using SAS version 9.3 and Stata version 14.

Since miners might not have had an HIV test in life and deaths related to HIV-infection or AIDS may not have been recorded as such, several pathological and clinical cause of death codes for AIDS-related diseases were used to supplement the information in the PATHAUT database. These included Kaposi sarcoma, cryptococcal pneumonitis, *Pneumocystis jiroveci* pneumonia, cytomegalovirus pneumonitis and cryptococcal meningitis.

Student's t-test and the chi-square test were used to determine differences between means and frequencies, respectively. Linear trends were determined using the Cochran-Armitage test for proportions and linear regression for continuous variables. Significance was defined at $p < 0.05$.

Analyses were stratified by race because of effect modification and were segmented to represent phases of the HIV epidemic, that is, the pre-HIV (1975–1989), rapid HIV spread (1990–2004) and antiretroviral therapy (2005–2014) eras. Binary logistic regression modelling was used to evaluate the determinants (year of autopsy, age at death, duration of gold mining employment, silicosis and HIV) of autopsy-diagnosed PTB. Interaction terms for year and age, year and duration, age and duration, and silicosis and HIV were tested, but none were included in the final models. Post-regression analyses were performed using the Hosmer-Lemeshow goodness-of-fit test.

Sensitivity analyses were conducted to further explore the effect of employment duration on PTB in models which silicosis was excluded. The effect of the exclusion of large numbers of cases with missing data from the study was explored by using multiple iterative chained equations (MICE) to create a dataset containing ten imputations of missing values for age and employment duration for black miners. The mechanism of missingness was defined as missing at random (MAR) because the outcome variable (PTB) was complete, and missing age and employment duration were likely to be related to population group as more black miners had missing demographic and employment information than white mines.

The final logistic models were run using the dataset containing imputed values. Imputation diagnostics included the examination of the relative increase in variance (RVI), the fraction of missing information (FMI), degrees of freedom (DF), relative efficiency (RE) and, between and within imputation variance estimates. Convergence of each imputed variable was assessed using trace plots. The resulting coefficients were converted to odds ratios by calculating exponents because Stata does not report odds ratios for the *mi estimate* command. The estimates and standard error values from the logistic models using complete data only and imputed values were compared.

3.4 SILICOSIS AND PTB IN FEMALE MINERS

Background: Women were legally prohibited from working underground in South African mines until this restriction was removed in the ODMWA (RSA, 1973). The 2002 Mining Charter was introduced to increase the participation of women in core mining activities, including underground mining [5].

As the participation of women in mining has increased, research has focused on gendered labour-relations, social interactions, ergonomics and reproductive effects of mining (Zungu, 2012, Badenhorst, 2009, Botha, 2016, Benya, 2016). No studies have investigated OLDs in female South African gold miners. This study is the first to investigate silicosis and PTB in female miners and contributes to the sparse literature that is available on silica-related OLDs in women.

Study design: descriptive cross-sectional study.

Study population: Gold miners whose organs were examined at the NIOH from 2005 (when the recording of gender in the PATHAUT database was initiated) to 2015 and had started employment in the gold mining industry from 2002, after the introduction of the Mining Charter.

Data sources: PATHAUT database and documents submitted with the organs which are archived at the NIOH (e.g. death certificates and employment histories)

Data management and analysis: The sex of female miners was verified using documents submitted with the organs. Of the 394 cases which were captured as women, 365 were confirmed to be women. Some of the misclassification arose in cases where men were given names of women. Nine cases could not be classified due to missing or incorrectly captured South African identity ID numbers which contain information on sex and 10 were migrant workers who had foreign passport numbers only. The sex of male miners in the study population was not verified due to the relatively large numbers.

Records with missing sex, age or duration of employment were excluded from the study. Cases diagnosed with pulmonary silicosis, lymph gland silicosis or PTB were identified. Differences in characteristics and proportions of disease of women and men were determined using the Mann-Whitney and chi-square tests for medians and proportions, respectively. P-values of <0.05 were considered statistically significant.

3.5 EVALUATION OF PATHAUT AS A TOOL FOR SURVEILLANCE

Background: The primary function of the PATHAUT autopsy database is to provide pathology reports for OLD compensation. However, it is well recognised as a national resource for research and has made a significant contribution to knowledge on OLDs (Naidoo, 2013). Although the NIOH has had the intention to use the autopsy data for surveillance for many years, a surveillance programme has not been developed. This evaluation sought to assess the usefulness and attributes of the autopsy compensation process and data for surveillance.

Data sources: The four thesis papers and the NIOH Pathology Division SOPs.

Data management and analysis

The evaluation was conducted according to the CDC Updated Guidelines for Evaluating Public Health Surveillance Systems (CDC, 2001)

Evaluation of the attributes of PATHAUT as a tool for surveillance: Seven of the nine system attributes recommended in the CDC guidelines were assessed. Predictive values could not be evaluated because there were no suitable external data to use as denominators in calculations. Acceptability was not evaluated as it requires stakeholder engagement which was excluded from this thesis. Table 7 shows the measures which were used to assess attributes.

Table 7 Measures used to evaluate system attributes of PATHAUT as a tool for surveillance

Attribute	Definition	Measure	Information source
<i>Simplicity</i>	Description of the autopsy and data capture processes	Description of the autopsy process, data flow and information dissemination processes at the NIOH	Pathology Division SOPs, Paper 3
<i>Stability</i>	Availability of the autopsy data	Major downtimes of the PATHAUT database	Papers 1 and 3
<i>Flexibility</i>	Ability to adapt to changing information needs	Addition of new fields to the PATHAUT database	Papers 1 and 3
<i>Data quality</i>	Validity Completeness of data	Data checks Numbers and proportions of missing values for population group, commodity, age and gold employment duration	Pathology Division SOPs Paper 3
<i>Sensitivity</i>	Changes in numbers of cases over time	Influence of industry practices on PTB trends (1975-2014)	Paper 3
<i>Representativeness</i>	Characteristics of the population	Distribution of autopsies by sex, age, employment duration and status, and commodity	Paper 1
<i>Timeliness</i>	Time between any two steps in the surveillance system	Time between organ submission and availability of annual reports	SOPs

Evaluation of the usefulness of PATHAUT as a tool for surveillance: The measures used to assess usefulness are summarised in Table 8.

Table 8 Measures used to evaluate the usefulness of PATHAUT as a tool for surveillance

Characteristic	Measure	Information source
Ability to detect disease	Sensitivity, specificity, positive and negative predictive values for clinical diagnoses of ARDs using autopsies as the gold standard. Determination of factors that contributed to clinical misdiagnosis of asbestosis.	Paper 1 and 2
Ability to provide estimates of disease magnitude	Proportions of OLDs in deceased miners	Paper 1
Ability to detect trends	PTB trends (1975-2014) and factors associated with these trends	Paper 1 and 3
Ability to determine risk factors	PTB trends (1975-2014) and factors associated with these trends	Paper 3
Ability to identify sentinel cases	Description of pulmonary and lymph node silicosis, and PTB in female miners	Paper 4
Ability to monitor prevention and control programmes	Based on findings from the thesis papers.	Papers 1, 3 and 4

3.6 ETHICAL CONSIDERATIONS

Ethical approval for the PhD protocol was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa (Ethics Certificate number: M230236 – Appendix 5). Ethical clearance was also obtained from the University of Michigan Health Sciences and Behavioural Sciences Institutional Review Board. A Determination of “Not Regulated” Status was given as the study involved deceased individuals only (Study eResearch ID: HUM00069012 – Appendix 6).

Permission to use the PATHAUT database for this PhD was obtained from the National Institute for Occupational Health. Permission to access the ARTmis data and to review paper records for the ARD clinic-pathological study was obtained from the Asbestos Relief Trust.

CHAPTER 4: RESULTS

The findings of the four studies in this PhD are comprehensively described in each of the four thesis papers. This chapter presents results from the papers and descriptions of the autopsy process outlined in the Pathology Division's SOP that are pertinent to the evaluation. The evaluation findings are presented according to the two thesis themes: attributes and usefulness.

4.1 ATTRIBUTES OF PATHAUT AS A TOOL FOR SURVEILLANCE

Findings on the eight system attributes that were evaluated are presented in this section.

Simplicity

An overview of workflow, staff roles and the processes at the NIOH is presented in Appendix 7. The process begins locally, where the miner dies. For miners who die while in employment, families are offered autopsies by mine administrative or hospital staff. For former miners, the onus usually lies with the family to ask the last attending doctor or the NIOH to arrange for organ removal. In labour-sending areas, organ removal is performed by health care practitioners and pathologists in the private sector or state-owned academic hospitals and forensic pathology mortuaries. Families tend to use the services of private health care practitioners. Although the MBOD has provisions to pay private practitioners for organ removal, the amount is meagre, and the system for reimbursement is cumbersome. Hence, private practitioners require upfront payments for their services and the amounts may be beyond the means of families.

After obtaining written consent, the organs are removed in government mortuaries or private funeral homes, under the supervision of a medical doctor. The organs are placed in formalin, and together with the required documents are put in containers (Figure 5) and are transported to the NIOH by courier or mine vehicles. This process is followed for about 95% of cases submitted to the NIOH. For the remaining 5% who die in or near Johannesburg, the bodies are transported to the NIOH for organ removal (NIOH, 2018).



Figure 5 Photograph showing containers used to transport organs to the NIOH
(N Kgokong)

At the NIOH, each set of organs is allocated a unique identifying number. Prosecutors prepare the organs for examination and store the organs after examination. During macroscopic examinations, pathologists take specimens for microscopic examination. Medical technologists process the tissue sections for microscopic examination by the pathologists. All procedures are performed according to standard protocols which have remained unchanged for many years. Case definitions for asbestosis, mesothelioma and lung cancer are given in Paper 2, definitions for PTB and silicosis are provided in Papers 3 and 4. Clerical staff collect and capture the information into the PATHAUT database and MWCS at various stages of the process. They also contact mines and families to obtain missing information. Scientists perform data management and analysis.

The PATHAUT database is housed in the Pathology Division at the NIOH and is maintained by NDOH and NIOH information technology staff. The database is server-based and runs on the NIOH network. It consists of a series of windows (Figure 6) and its data entry fields align with the hard copy booklet (data capture sheet) on which information is written by hand before it is entered into the database (Appendix 8). There are multiple drop-down fields which contain numerically pre-coded option statements, as well as, provisions to add information that cannot be captured in the drop-downs as free text. The data collected includes administrative, process (pertaining to the stages of the autopsy process), personal

and occupational information. Additionally, macroscopic and microscopic pathological findings on the regional glands, heart, pleura, bronchi, lungs and oesophagus are collected.

The PATHAUT database is independent and is not integrated into any other database. It generates individual pathology reports which are uploaded to the MWCS for compensation. Before the pathology reports are uploaded, pathologists check the pathology findings and content of the pathology report to ensure that information has been captured correctly. For analysis, the data are exported from PATHAUT to text files which are read into spreadsheet format in SAS. A data dictionary, in the form of an annotated booklet, containing variable names and code descriptions is available. Data cleaning (validation) of key variables is performed periodically by scientists and includes checks for outliers, incorrect entries, inconsistencies between macroscopic and microscopic findings and missing information. This also involves follow-up with mines and families for missing information, and searches on the MWCS for information, e.g. occupational histories that might have been captured by the MBOD after pathology reports have been uploaded. After cleaning, the data are appended to the master PATHAUT spreadsheet that contains data from 1975.

Stability

The original platform on which the PATHAUT database ran was replaced in 1996 as it was rapidly becoming obsolete. This created an opportunity to review and redesign the booklet that had been in use since 1975. The original booklet was designed to capture all data in the files of white miners who had annual medical examinations at the MBOD. At the time black miners had less frequent medical examinations on the mines and had much thinner files. The files of white miners contained large amounts of information (e.g. electrocardiogram data) and summarising this information and data entry had become a cumbersome process. The new, simplified booklet captured less detailed occupational and clinical information, but the pathology information remained virtually unchanged. These changes necessitated the redesign of the PATHAUT database. During this process, the PATHAUT database was unavailable. Thus, pathology information in the database for 1996 is incomplete and is reflected by lower than expected silicosis and PTB proportions in this year, as demonstrated in Papers 1 and 3.

Flexibility

Information on sex, employment status (current or former miners) and province or country from which organs were submitted has been captured from 2005, 2007 and 2010 (Paper 1).

In the process of creating the HIV variable for Paper 3, it was noticed that some cause of death codes had changed between 1976 and 1998. For example, the code for broncho-alveolar carcinoma/peripheral – small cell had changed to Kaposi sarcoma of lungs (5). An extensive exercise was undertaken to identify such cause of death codes and to replace them with codes currently in use. It was also noted that several death codes e.g. TB pericarditis and extra-pulmonary TB, were added between 1976 and 1998 (Appendix 9).

Data quality

As stated above under Simplicity, validity checks are built into processes at the NIOH. In addition, for Papers 2 and 4, the diagnoses of the ARDs and silicosis were reviewed by two pathologists.

In the PTB trend analysis (Paper 3), cases with variables with missing information were excluded sequentially from the study. Of the 110,167 cases on PATHAUT (1975-2014), 369

cases belonging to groups with small numbers (females and other population groups, n=369) and 23,890 (21.8%) cases with missing employment duration, age and commodity (n=17,447, n=3,937 and n=2,506, respectively) were excluded.

Sensitivity

The findings used to assess sensitivity are described in Section 4.2 under the heading “Ability to detect trends and determine risk factors”.

Representativeness

A total of 109,101 autopsies were performed from 1975 to 2013. The annual number of autopsies exceeded 3,000 from 1975 to 1998 but declined thereafter to 1,188 in 2013. Most of the cases in the PATHAUT database are men (n=108,781, 99.7%). Most miners (1975-2013) were black (n=72,348, 66.3%), 34,794 (31.9%) were white, 1 612 (1.5%) were coloured and three (0.0%) were Indians. There were 320 (0.3%) women on the database. Most black miners (n=5,077; 78.6%) and few white miners (n=428; 13.2%) died while in employment. The organs of most black miners originated from the North West (39.6%), Free State (28.6%), Northern Cape (12.2%) and Gauteng (9.9%) provinces whereas most of those of white men were from Gauteng (44.3%), North West (26.3%), Free State (11.9%) and Mpumalanga (9.2%). Few organs were submitted from the neighbouring countries of Lesotho (n=76, 1.9%) and Botswana (n=2, 0.1%).

On average, black miners were significantly younger (39.7 ± 11.4 years) than white miners (60.9 ± 14.6 years) ($p < 0.0001$) and had worked for shorter periods (10.0 ± 8.0 years) than white miners (23.4 ± 11.9 years). Employment duration for black miners increased from 5.5 ± 5.7 years in 1975 to 15.8 ± 9.7 years in 2013 but decreased from 24.9 ± 11.7 to 22.6 ± 11.0 years for white miners.

Commodity is defined as the mining industry in which miners worked for the longest period because most miners work in more than one commodity during their mining careers. Many miners had worked in more than one mining commodity (n=14,444; 13.2%) and, of the 34 commodities worked, most were gold (n=70,296; 72.7%), platinum (n=9,586; 8.8%), coal (n=7,741; 7.1%) or asbestos (n=2,560; 2.3%) miners. Gold mining was the predominant commodity with 73.8% black and 74.4% white miners. The proportions of black gold miners

increased from 68.8% in 1975 to 81.7% in 1995 then decreased to 55.9% in 2013, whereas those of black platinum miners increased from 5.5% to 25.7%. Over the study period, the proportions of white gold miners decreased from 80.8% to 67.9% while those of white platinum miners increased from 1.8% to 7.8%.

Timeliness

According to the SOP, the turnaround time for examination of organs is three months, that is, from the date of receiving organs at the NIOH to the finalisation of the pathology report. Annual reports are written after all cases received in the previous year have been examined. Before this done, data check are performed on the variables required for the report. The reports are written according to a standard template and format, and are finalised in the second half of each year. Electronic copies are posted on the NIOH website and sent by email to stakeholders, and a limited number of hard copies are also produced for dissemination. The findings are also presented at workshops and conferences, and are published in journal articles.

4.2 USEFULNESS OF PATHAUT AS A TOOL FOR SURVEILLANCE

Ability to detect disease and estimate disease magnitude

The major compensable diseases on the database were emphysema, silicosis and PTB and the proportions differed by population group Figure 7. The proportions of silicosis and PTB were lower in platinum compared to gold miners and increased over time in both black and white miners.

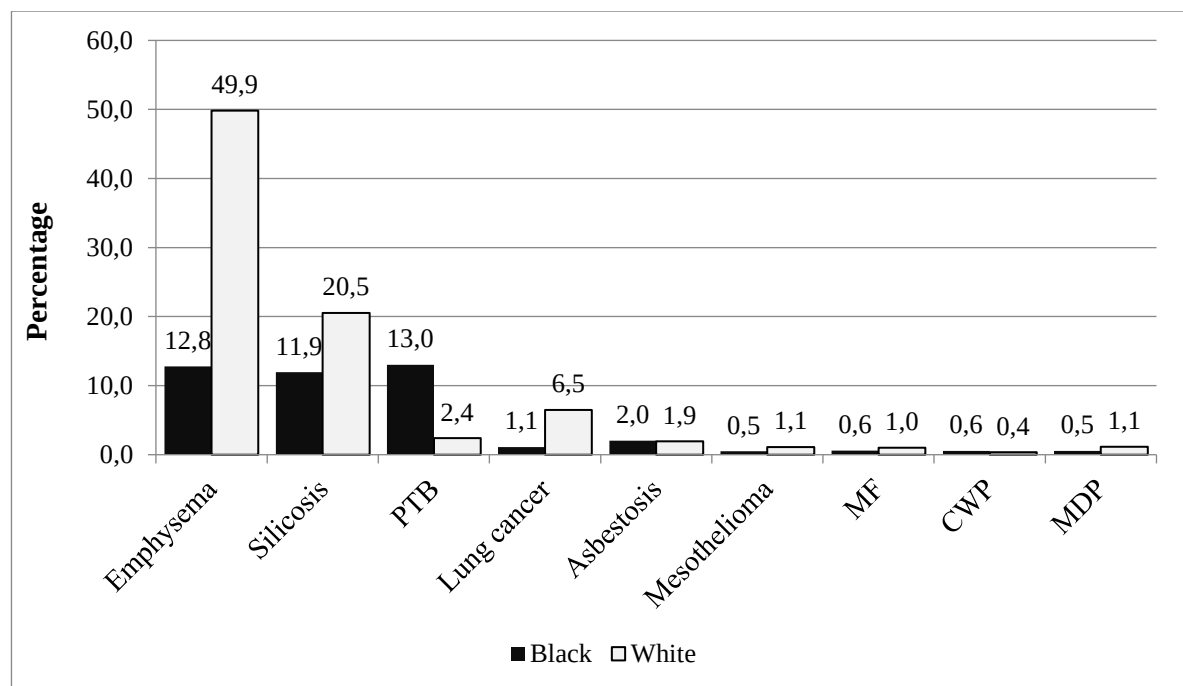


Figure 7 Overall proportions of autopsy-diagnosed OLDs in black and white miners, 1975-2013. MF: progressive massive fibrosis; CWP: coal workers' pneumoconiosis; MDP; mixed dust pneumoconiosis

The clinico-pathological study showed that more ARDs were diagnosed at autopsy than clinically (Table 9). The sensitivity values indicate that 49.4% of asbestosis, 59.3% of mesothelioma and 96.4% of lung cancer cases that were diagnosed at autopsy had been missed clinically. The specificity values indicate that there were few clinical misdiagnoses of asbestosis and mesothelioma (18.1% and 2.5%, respectively) and none of lung cancer.

Table 9 Sensitivity, specificity and predictive values for ARDs

Disease	Clinically diagnosed (n)	Autopsy diagnosed (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Asbestosis	52	77	50.6	81.9	75.0	60.8
Mesothelioma	14	27	40.7	97.5	78.6	88.1
Lung cancer	3	22	13.6	100.0	100.0	87.0

Three independent readers re-read the chest radiographs of cases that had been missed clinically (false-negative diagnoses) and found good agreement (83.3%) with the original

readings. The logistic regression model showed that, compared to true positive diagnoses, the clinical diagnosis of asbestosis was more likely to be missed if the miner had autopsy-diagnosed PTB (AOR=8.45, CI 1.16-61.69) or if radiographs were lower quality (acceptable versus good quality) (AOR=12.33; 2.54-59.72).

For most (47 of 49) of the cases with autopsy-diagnosed malignancies, the clinical diagnosis had been made using histology and immunochemistry. Most of the 35 diagnoses that had been missed clinically (false-negative) had advanced tumours at autopsy. Sixteen mesothelioma and 19 lung cancer cases had clinical examinations 4.8 years (range 0.3-6.3 years) and 4.4 years (range 0.7-7.0 years) before death, respectively.

Ability to detect trends and determine risk factors

Paper 1 showed crude trends of silicosis and PTB from 1975 to 2013 in black and white, gold and platinum miners. Table 10 shows increases in silicosis and PTB over the study period. Apart from silicosis in the early years, disease proportions are higher for black compared to white miners, and gold compared to platinum miners.

Table 10 Proportions of autopsy-diagnosed silicosis and PTB in gold and platinum miners, 1975-2013

Year	Silicosis (%)				PTB (%)			
	Gold		Platinum		Gold		Platinum	
	Black	White	Black	White	Black	White	Black	White
1975	3.9	27.2	0.0	0.0	2.6	1.2	2.8	0.0
1997		18.3						
2002							38.3	
2004								12.0
2007						9.8		
2008					43.8			
2013	38.0	30.8	11.7	6.1	32.2	2.6	19.9	3.0

In the PTB trend analysis (1975-2014), the overall proportion of PTB was five-fold higher in black miners (n=8,977, 16.80%) compared to white miners (n=1,003, 3.26%). PTB increased in both black and white miners with peaks observed in 2007 (Figure 8). Silicosis increased in black miners from 3.03% to 23.62% while silicosis in white miners decreased from 24.88% to 19.51%. In black miners, HIV increased rapidly from 1987 to a peak in 2002 (47.20%). In

white miners, HIV proportions were low (range: 0.12% to 1.49%) and increased over the study period.

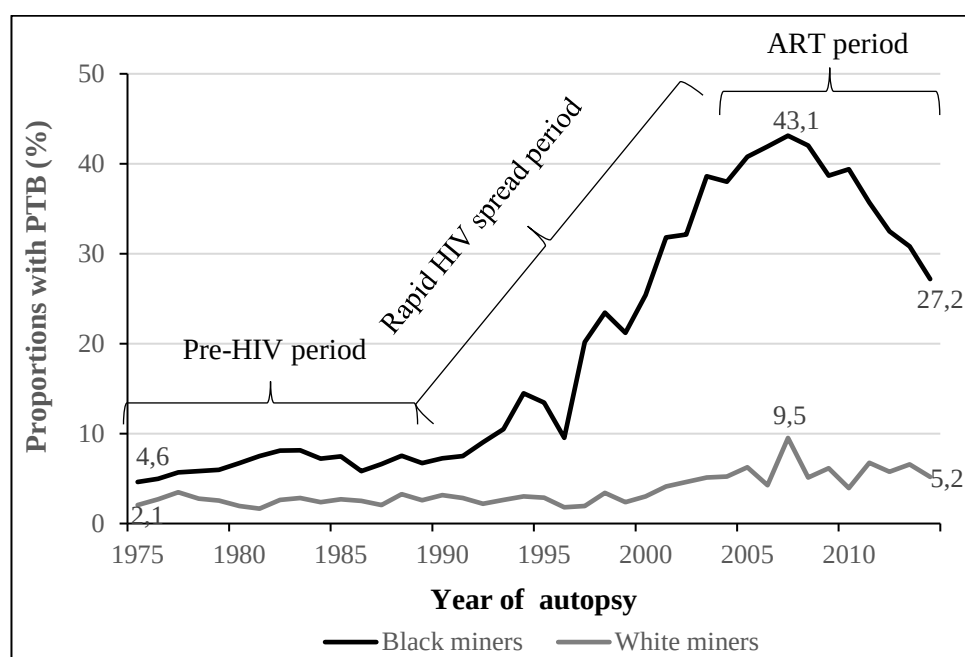


Figure 8 Crude proportions of autopsy-diagnosed PTB in black and white miners, 1975-2014

In the models, the magnitude of AORs varied by population group and calendar period (Table 11). Silicosis and year of autopsy were significant predictors of PTB in both population groups in the three calendar periods. Except in the pre-HIV calendar period (1975-1989), age was a significant predictor of PTB in black miners and its AORs were significantly reduced in white miners in the ART period (2005-2014). The AORs for gold employment duration were significantly elevated in the pre-HIV period for white miners and ART period for black miners. Employment duration was a significant predictor for PTB in black miners in models that were run without silicosis. The AORs for HIV were significantly elevated for black miners in 1990-2004 and both population groups in 2005-2014.

The AORs for PTB in models using the dataset with missing values and a dataset with complete values in which missing values were imputed, were similar (Paper 3, Supplementary Table S4).

Table 11 Summary of adjusted odds ratios (AORs) for PTB in black and white miners at autopsy, by calendar period

BLACK							WHITE						
Variable	1975-1989		1990-2004		2005-2014		Variable	1975-1989		1990-2004		2005-2014	
	n	AOR	n	AOR	n	AOR		n	AOR	n	AOR	n	AOR
Year of autopsy							Year of autopsy						
1975-1979	440	Ref	440	Ref	440	Ref	1975-79	128	Ref	128	Ref	128	Ref
1980-1984	601	1.31					1980-84	119	0.84				
1985-1989	580	1.09					1985-89	132	1.02				
1990-1994			673	1.62			1990-94			123	1.12		
1995-1999			1010	2.71			1995-99			91	1.03		
2000-2004			2163	5.95			2000-04			132	1.87		
2005-2009					2,303	9.79	2005-09					157	2.74
2010-2014					1,207	7.78	2010-14					121	2.46
Age (years)							Age (years)						
<30	367	Ref	196	Ref	117	Ref	<50	55	Ref	59	Ref	45	Ref
30-39	425	1.33	1,193	1.40	761	1.33	50-59	66	1.02	85	1.26	67	0.98
40-49	441	1.81	1,689	1.58	1,557	1.30	60-69	135	1.30	93	0.69	82	0.76
50-59	293	2.24	685	1.44	927	1.00	≥70	123	1.40	109	0.85	84	0.53
≥60	95	2.47	83	1.39	148	0.65							
Gold employment duration (years)							Gold employment duration (years)						
0	250	Ref	567	Ref	826	Ref	0	27	Ref	42	Ref	35	Ref
<10	936	1.05	1,113	0.97	718	1.13	<10	35	1.22	61	1.30	34	1.03
10-19	340	1.10	1,634	1.00	970	1.46	10-19	59	1.67	74	1.10	70	1.18
≥20	95	1.05	532	0.99	996	1.43	20-29	105	1.88	88	1.18	82	1.22
							≥30	153	1.39	81	0.89	57	0.96
Silicosis							Silicosis						
Absent	1,311	Ref	2,960	Ref	2,473	Ref	Absent	210	Ref	212	Ref	142	Ref
Present	310	3.08	886	1.54	1,037	1.34	Present	169	2.21	134	3.15	136	3.59
HIV							HIV						
Absent	1,621		2,477	Ref	2,473	Ref	Absent	379		343	Ref	272	Ref
Present	-		1,369	1.37	1,037	1.17	Present	-		3	1.83	6	2.53

AORs in bold are significant at p<0.05

Ability to identify sentinel cases

The study population comprised 68 (8%) female and 779 (92%) male gold miners. The proportions of autopsy-diagnosed pulmonary and lymph node silicosis, and PTB were similar in women and men (Table 12). Three women had slight pulmonary silicosis, two of whom were young (26 and 35 years) and had worked for short periods (3.3 and 3.8 years, respectively). The third woman was older (47 years) and had worked for longer (10.9 years). All three women had lymph gland silicosis, and one had PTB.

Fifty-four (7%) men had pulmonary silicosis, of which most (n=43, 80%) was slight. Most of the men with pulmonary silicosis were under 50 years (n=38, 70%) and had been employed for ten or fewer years (n=51, 94%).

Table 12 Pulmonary and lymph gland silicosis, and PTB in male and female gold miners at autopsy, 2005-2015

Characteristic	Pulmonary silicosis			Lymph node silicosis			PTB		
	Women	Men	p-value	Women	Men	p-value	Women	Men	p-value
Number (%)	3 (4)	54 (7)	0.613	11 (16)	171 (22)	0.266	29 (43)	254 (33)	0.089
Pulmonary silicosis severity									
Occasional/few	3 (100)	43 (80)	0.747	-	-		-	-	
Moderate	0 (0)	10 (18)							
Large no	0 (0)	1 (2)							

Ability to monitor prevention and control programmes

Results presented in this chapter will be used assess this attribute.

CHAPTER 5: DISCUSSION

The chapter begins with an overview of the scholarly contribution to knowledge on OLDs of the four thesis papers. The following section highlights methodological issues related to the use of administrative databases for surveillance and research. The evaluation findings are discussed according to the themes of system attributes and usefulness. The chapter ends with the strengths and limitations of the use of PATHAUT data for surveillance.

5.1 SCHOLARLY CONTRIBUTION OF THESIS PAPERS

The scholarly contribution and recommendations from each of the four thesis papers are highlighted in Table 13.

Table 13 Scholarly contribution of the thesis to knowledge on OLDs

Thesis paper	Scholarly contributions and recommendations
Paper 1: Description of the PATHAUT database	• The burden of OLDs in South African miners is high and, for most OLDs, has increased over time in spite of good occupational disease policies. • Silicosis in platinum miners increased over time, probably reflecting the movement of miners from gold to platinum mining. • Despite the removal of racial discrimination, former black miners still have limited access to autopsies and compensation. There is a need to provide adequate facilities for organ removal in labour sending areas.
Paper 2: Clinico-pathological study of ARDs	• Many former asbestos miners are developing ARDs. • The clinical diagnosis of ARDs missed almost 60% of autopsy-diagnosed disease, much of which was advanced disease. Correct clinical ARD diagnoses are essential to ensure that individuals with these diseases are managed appropriately and claim compensation. • Clinical detection of ARDs can be improved by the use of more sophisticated tests in people who have ARD symptoms but have normal chest radiographs. Health care providers should be trained to increase their diagnostic awareness.
Paper 3: PTB trend analysis	• There are limited data available to monitor the triple epidemic of tuberculosis, silicosis and HIV in South African miners. • The PATHAUT database provides the longest, long-term data on PTB in miners across all commodities and spanning over 40 years which cover the pre-HIV, HIV spread and ART roll-out periods. • Even in the era of HIV, silica dust exposure and silicosis remain important determinants of PTB. Therefore, silica dust control continues to be an essential component of tuberculosis control in the mining industry. Improved tuberculosis and HIV treatment and management are also important.
Paper 4: Silicosis and PTB in female miners	• This is the first study of silicosis and PTB in female South African miners and contributes to the scarce knowledge of OLDs in women. • The numbers of female miners in this study are too few to draw definitive conclusions from the comparison of rates between men and women. However, the findings highlight the need to increase the focus on prevention of silica-related OLDs in women. • The detection of silicosis in women after short employment in the gold mines, most of whom entered the industry after the introduction of interventions to control silica dust, indicates inadequate dust control. Dust reduction remains key to the prevention of silica-related diseases. • Sex and gender should be considered when assessing occupational health risks and exposures, and designing prevention strategies, e.g. personal protective equipment. • Research and surveillance findings should be reported separately by sex, even if the numbers of women are small.

5.2 METHODOLOGICAL ISSUES

This section discusses methodological issues that are related to the use of administrative data for research and surveillance.

It is necessary to understand the social, economic and political context when using and interpreting administrative data. In South Africa, race should be considered because of the country's sociopolitical history. Findings in this thesis are reported by race because it serves as a proxy measure for differences in occupational exposures, environmental factors and access to health services, including medical surveillance and autopsies. Combining black and white miners in analyses could obscure disease patterns as risk factors might be different.

An advantage of using administrative data is the availability of data collected over a long time. However, changes in the coding of information that is, temporal consistency of the data, might occur over time (Mazzali and Duca, 2015). The change in some of the cause of death codes in the PATHAUT database between 1976 and 1998 highlights the need for thorough data checks and a good understanding of the data. Hence, all surveillance-related information, such as case definitions, disease codes and changes to the database should be documented.

Administrative databases might lack key variables required for analyses. The PATHAUT database does not contain comprehensive information on HIV status, probably because it is not required for the determination of compensation. However, a variable for HIV was generated using AIDS-related causes of death for cases where HIV/AIDS was not stated on the death certificate. Also, cumulative duration of employment is used as a proxy measure for cumulative dust since individual dust measurements are not available. These examples demonstrate how variables can be generated and proxy measures can be used in analyses using administrative data. However, the limitations of these variables should be taken into account when interpreting the results.

An advantage of using an administrative dataset, such as PATHAUT, is the very large sample size that it provides. However, in statistical analyses, the large numbers can result in small p-values for minute differences between groups. Hence, statistical significance in these analyses

must be interpreted with caution and conclusions should be based on the clinical or biological significance of findings rather than confidence intervals or p-values alone (Lin et al., 2013, van Walraven and Austin, 2012).

Although not related to the use of administrative databases only, the reporting of women in studies is an important methodological issue. In recent studies using the PATHAUT data, women have been handled differently. In Paper 1 and the silica trend analysis (Nelson et al., 2010), cases were not reported by sex and women were included in the term “men”. In the PTB trend analysis (Paper 3) and in the emphysema study (Mabila et al., 2018), women were excluded. Such practices are not unusual in studies in male-dominated occupational settings where the numbers of women are small (Greenberg and Dement, 1994, Betansedi et al., 2018). In future studies, women should be reported separately to build a body of knowledge on OLDS in women and to capture differences in exposures to hazards arising from gender-related differences in performance of tasks (Locke et al., 2014).

5.3 EVALUATION OF PATHAUT AS A TOOL FOR SURVEILLANCE

The PATHAUT autopsy data are a national resource which serves three functions: compensation, research and surveillance. This thesis provides the first surveillance evaluation of PATHAUT and demonstrates its potential usefulness as a surveillance tool. However, due to the exclusion of stakeholder engagement and interviews with database users, this evaluation could not assess attributes comprehensively.

Occupational lung diseases in current and former miners are of public health importance because their heavy burden has an impact on the communities in which they live. The autopsy data can be used for passive, pathology, compensation-based OLD surveillance based on the voluntary submissions of cardio-respiratory organs of miners to the NIOH as outlined in the ODMWA. The surveillance programme would be industry-based, providing information for stakeholders in the South African mining industry.

5.3.1 Attributes of PATHAUT as a tool for surveillance

The attributes of a surveillance system influence its performance, contribute directly to its ability to meet its purpose and objectives, and determine its strengths and weaknesses (Groseclose and Buckeridge, 2017, Teutsch and Churchill, 2000). The discussion below includes elements of the attributes that could be assessed using information derived from the thesis papers.

Simplicity

The findings suggest that the use of the autopsy data for surveillance would involve the same human, infrastructural, technical and financial resources used for the compensation process, and thus maximise the use of existing resources. The autopsy compensation process comprises many steps some of which requires external players, e.g. mine personnel who seek consent, arrange for organ removal and transportation to NIOH and family members who provide consent and information. The process involves a range of skills, including skilled personnel to diagnose OLDs and to manage and analyse data, and write reports.

Stability

In the 40 years of its existence, the PATHAUT database has been available and has continuously produced pathology reports except for one year. This suggests general stability of the database. When the database was unavailable, autopsy examinations continued as usual, and the information is available in original pathology booklets and needs to be transcribed to new pathology booklets for capture into the PATHAUT database.

Flexibility

The flexibility of the PATHAUT database enables the addition of data fields according to changing information needs. Data fields for demographic (sex and province), work-related (employment status) and disease variables have been added to the PATHAUT database when required. For example, as the HIV epidemic spread and the numbers of cases with HIV-related diseases increased, new cause of death codes were added to the database. These included codes for the non-compensable diseases that were used to create the HIV variable in the PTB trend analysis, such as, Kaposi sarcoma and cryptococcal pneumonitis.

Although the ODMWA compensates specific OLDs on a fixed and predefined ‘closed list’, the ability to add diseases to the database suggests that PATHAUT surveillance would be an ‘open list’ programme (Bakusic et al., 2017). As such, it would have the potential to detect new compensable and non-compensable OLDs, in line with the current focus of occupational disease surveillance on the detection emerging diseases (Bakusic et al., 2017).

Data quality

Validity checks of pathology diagnoses and data entry of key variables are built into the autopsy process to ensure that data has been captured correctly in the database. The review of the diagnoses for research purposes confirmed the diagnoses.

Completeness was assessed from the results of the PTB trend analysis which indicated that over the 40 year period, a fifth (21.8%) of the records had missing employment (employment duration or commodity) or demographic information (age). In 1975, 242 (7.9%) cases had missing age, 105 (3.4%) had missing commodity and 603 (19.6%) had missing employment (Ndlovu et al., 2011). By 2017, there were 6 (1.0%) cases with missing age, 16 (2.0%) with missing commodity and 27 (3.4%) with missing employment duration (Kgokong et al., 2019). This improvement in the completeness of key variables is attributed to active follow-up with families and mines to obtain missing information.

Sensitivity

In this thesis, sensitivity is defined as “the ability to monitor changes in the number cases over time” and was illustrated by the influence of changes in work practices and magnitude of risk factors on PTB trends over the study period. Changes in policies allowing black miners to work long term contracts and to return to work after completing TB treatment (Rees et al., 2010), resulted in increasing age and employment duration of black miners, which resulted in increasing proportions of silicosis and PTB. The recent increase of silicosis in black platinum miners reflects the move of miners from gold to platinum mining and silica dust exposures in the platinum mining industry (Nelson and Murray, 2013b). Sensitivity was demonstrated further by the rise in PTB proportions parallel to the steep increase of HIV from the early 1990s and the decrease in PTB following the roll-out of ART. The observed PTB trend was similar to TB

mortality trends in platinum miners (Lim et al., 2012) and the general South African population (Pillay-van Wyk et al., 2016) and population incidence (Nanoo et al., 2015).

Representativeness

The CDC guideline acknowledges that it is often difficult to find suitable denominators to quantify the extent of reporting of health events. Hence, representativeness can be evaluated by assessing the characteristics of the population, clinical course of disease, medical practices and by making comparisons with other data sources (CDC, 2001). In this thesis, representativeness was assessed by identifying subpopulations that are systematically excluded from the autopsy compensation system.

The vast majority (99.7%) of miners in the PATHAUT database are men but the numbers of women have increased in recent years. Most black miners (78.6%) died while in employment while most (86.8%) white miners had left the mines. These proportions are similar to those from cohort studies which showed high autopsy uptake rates for black employed miners (70%) (Murray et al., 2007) and former white miners (85%) (Hnizdo and Sluis-Cremer, 1993). These differences are also reflected in the age profile, black miners being younger than white miners. Generally, former black miners would have worked in high dust occupations and are more likely to have dust-related OLDs with long latency periods (e.g. the pneumoconioses and cancers) which might manifest or progress after leaving employment. They also have a life-long risk of developing TB. Therefore, their exclusion leads to undercounting of OLDs and low detection of severe disease.

Despite the removal of racial provisions from the ODMWA in 1993, racial disparities continue to prevent access to medical surveillance and autopsies by former black miners (Ehrlich, 2012a). This, together with lack of knowledge of the ODMWA by mine workers, communities and healthcare professionals, perpetuates the “*hidden epidemic*” of OLDs in former black miners (Roberts, 2009). These systematic barriers to autopsy access reduce the representativeness and generalizability of the autopsy data.

Consent is a recognised barrier to autopsy uptake in this and other settings (Mthombeni, 2017, Banyini et al., 2013, Burton et al., 2004). A study in three mine hospitals, showed high uptake (86%) in one hospital and low uptake (34% and 12%) in the others (Mthombeni, 2017). Barriers to consent, and therefore autopsy uptake, include family/community factors, such as gender power relations, mistrust of the mining industry and, cultural and religious beliefs. Institutional or service provider-related barriers include the inefficient compensation system, overworked or unwilling service providers and poor knowledge of the ODMWA (Mthombeni, 2017, Banyini et al., 2013). Uptake was high where mine personnel had good communication strategies, were motivated and had good knowledge of the ODMWA (Mthombeni, 2017).

The challenges of representativeness and underreporting of cases are not unique to PATHAUT and occur in other occupational health surveillance systems due to the exclusion of certain groups from the system. For example, evaluation of national survey-based non-fatal injury surveillance in the U.S.A showed that farmworkers who were self-employed and those who worked in farms with fewer than 11 workers were not represented and that as many as 77.5% of injuries could have been missed (Patel et al., 2017). On the other hand, the Census of Fatal and Occupational Injuries (CFOI) was found to have good representativeness for fatal occupational injuries because it uses multiple data sources to improve case detection and representativeness (Austin, 1995). In South Africa, improved surveillance of, for example, mesothelioma could be achieved by combining data from the PATHAUT, Asbestos Relief Trust, Statistics South Africa (mortality data) and the National Cancer Registry databases.

Timeliness

The timely reporting surveillance results is a crucial attribute in communicable disease surveillance systems as it affects the speed of responses and, the control and prevention of the further spread of disease and outbreaks. There is a lag period of about 18 months between disease diagnoses and dissemination of annual pathology surveillance reports. For autopsy diagnosed communicable diseases, such as PTB, while reporting has no benefit for individual miners, timely reporting to mine doctors is important as the information can be used to review and improve TB case management of current patients. For the pneumoconioses, malignancies and emphysema, which are non-communicable, chronic diseases with long latency periods of 10

to 30 years, rapid identification and reporting are not required. The diagnoses serve as lag indicators of past hazardous occupational exposures and provide a means of monitoring dust exposures and the effectiveness of interventions.

5.3.2 Usefulness of PATHAUT as a tool for surveillance

Ability to detect disease and estimate disease magnitude

In spite of recent advances in technology, discrepancies of 20% to 40% between clinical and autopsy diagnoses are still observed and autopsies are valuable for disease detection (du Toit-Prinsloo and Saayman, 2012). The finding that almost 60% of the ARDs diagnosed at autopsy had not been diagnosed clinically shows that a surveillance programme reporting autopsy findings would report disease had been missed in life. Similar findings have been made for other OLDs. Using autopsies as the gold standard, the chest radiograph was shown to have missed two-thirds of silicosis and the sensitivity improved with increasing silicosis severity (Hnizdo et al., 1993). In another study, the clinical diagnosis of TB was demonstrated to have missed 52% of cases which were found to have had extensive TB at autopsy (Field et al., 2011).

A study of gold, platinum and coal miners observed that of the cases of PTB diagnosed at autopsy, 27% had been diagnosed clinically, 44% had been missed clinically and 29% had incorrect PTB diagnoses (Murray, 2000). The medical records of these cases were reviewed to assess clinical practice and the findings led to the recommendation of process-based performance review (PBPR) by clinicians. This is an effective way to improve clinical practice and TB management through the review of patient and NIOH autopsy reports, to identify and correct “*missed windows of opportunity to have made a timely and correct diagnosis*” (Murray et al., 2004). This programme has been rolled out in the mining industry.

Since the 1980s, there have been discussions about merging the ODMWA with COIDA which has no provision for autopsies (Ehrlich, 2012a). The clinico-pathological studies show that a substantial proportion of compensable OLDs will be missed if autopsies are withdrawn from the

legislation and provide evidence to argue for the retention of autopsies for miners in new legislation that might be introduced.

Ability to detect trends and determine risk factors

The autopsy data provide information to detect disease trends and determinants. In the PTB trend analysis, PTB in black miners increased almost 10-fold from 1975 to its peak in 2007 (4.62% to 43.12%) and increased four-fold (2.07% to 9.51%) in the same period in white miners. Silicosis increased ten-fold (3% to 32%) in black gold miners and by 22% (18% to 22%) in white gold miners from 1975 to 2007 (Nelson et al., 2010). Emphysema was almost five-fold higher in white (51.6%) compared to black miners (11.5%) in the period 1975 to 2014. With some variations, age, duration of employment and increasing year of autopsy were important determinants in the three studies (Mabila et al., 2018, Nelson et al., 2010). Smoking was an important determinant of emphysema in white miners in the period 1975 to 1995, when reliable smoking data were available for white miners (Mabila et al., 2018) and HIV was found to be a determinant for PTB.

These studies identified risk factors for OLDs which can be targeted for intervention. Although silica dust control is key to the prevention of these OLDs, other factors need to be considered. The silicosis elimination campaign discussed in Chapter 1, is underway to reduce dust exposures in mining and to improve the management of HIV and TB. Year of autopsy is a measure of confounders that were not measured in the analyses. These include factors such as overcrowding, poor ventilation and TB transmission, which are determinants of OLDs. Smoking can enhance the effect of silica dust and increase the risk of developing chronic obstructive pulmonary disease, including emphysema, and TB (Ross et al., 2005). Anti-smoking campaigns will contribute to the protection of ensure from the development of OLDS. Ongoing trend analyses provide information to monitor the effectiveness of interventions to control and prevent OLDs.

Ability to identify sentinel cases

As stated previously (Section 2.2), silicosis is considered an occupational health sentinel event. Therefore, silicosis cases serve as alerts of previous exposures to high levels of silica dust.

Differences between women and men with respect to their biology, job assignments and performance may influence their susceptibility to dust (Becklake and Kauffmann, 1999, Camp et al., 2004, Benya, 2016, Messing et al., 1994). In this thesis, the three women and most of the men with silicosis had slight disease that might not have been radiologically detectable. Although usually asymptomatic, individuals with subradiological silicosis have a persistent, increased risk for silicosis progression and the development of TB (Ehrlich et al., 2018).

The lack of statistical differences in the proportions silicosis and PTB between female and male gold miners suggests OLD susceptibility is comparable between the sexes but the number of women with silicosis is too small to make a definitive conclusion. In a study of Indian agate workers which had a larger sample size (102 women and 242 men) (Rastogi et al., 1991) found that pneumoconiosis prevalence was similar in women and men (19.61% vs 17.92%). However, TB prevalence was almost double in women compared to men (21.57% vs 12.92%) (Rastogi et al., 1991).

Ability to monitor prevention and control programmes

Currently, the PATHAUT data provide the only health data that can be used to monitor the effectiveness of prevention and control programmes in the South African mining industry. The high levels of silicosis and PTB over 40 years suggest persistent and inadequate dust control. The diagnosis of silicosis in gold miners who entered the gold mining industry after the introduction of the national silica elimination programme in 2003, indicates that the milestone target to reduce silica dust exposures to below the OEL 0.1 mg/m^3 was not attained, as has been confirmed in MHSI reports (MHSI, undated-a). This provides evidence to support the lowering of the OEL to 0.05 mg/m^3 (Msiza, 2014). Also, the PTB data will provide information to monitor the effectiveness of regional efforts to reduce mining-related TB (Reiprich, 2017).

5.4 STRENGTHS AND LIMITATIONS OF PATHAUT AS A TOOL SURVEILLANCE

This evaluation demonstrated that the autopsy compensation data can be used for the surveillance of OLDs in South African miners. A limitation of this evaluation is the exclusion of stakeholder engagement. The experiences and perceptions of users of the system are required to fully assess attributes, in particular, acceptability, simplicity and timeliness and some aspects of usefulness, such as timeousness of reporting and usefulness of the data for disease prevention and control.

The autopsy process and data have several strengths but also has limitations which need to be considered when interpreting the information provided.

Strengths

This evaluation demonstrated that the autopsy data have attributes of which make it reliable to detect and monitor the magnitude of OLDs in South African miners. Despite the large proportion of missing data and declining annual numbers of autopsies in recent years, the dataset is large enough to enable robust statistical analyses and determination of risk factors.

The strengths of using PATHAUT for OLD surveillance are listed below.

1. The major strength of using the PATHAUT data for surveillance is that the autopsy compensation system is underpinned by legislation. The link with compensation creates an incentive to submit organs for autopsy thus making it more attractive than surveillance based on physician reporting which has been unsuccessful, e.g. SORDSA which failed due to underreporting and neglect. In addition, the use of the autopsies for surveillance would use the same resources used in the autopsy compensation process including a multidisciplinary team with specific roles to collate and capture data (clerical staff), interpret clinical and pathology findings (pathologists) and to analyse and interpret data, and write annual surveillance reports (scientists).

2. The “centralisation” of ODMWA autopsy examinations at the NIOH, with diagnoses made by pathologists using standardised disease definitions, ensures consistent use of case definitions which allows for comparisons of disease occurrence across time.
3. The reporting of autopsy-diagnosed OLDs is another strength. Many of the OLDs have distinct pathologic features such that the autopsy is the gold standard for diagnosis and detects disease that is missed or misdiagnosed in-life due to limitations of current clinical diagnostic methods. Hence autopsies contribute to the delivery of compensation to dependents. A study showed that compared to in-life certifications of miners with compensable OLDs (9.5%), twice as many new certifications (19%) were made using autopsy findings (Murray et al., 2002).
4. The autopsy data provide information on several OLDs across the mining industry, in many mining commodities.
5. The detection of mild disease, which may not be apparent clinically, enables the reporting of disease that had the potential to progress and develop into severe disease. Therefore, autopsy data have an advantage over clinical diagnoses by providing a more comprehensive picture of the magnitude of compensable OLDs in South African miners.
6. The ability to detect of occupational sentinel health events provides an alert function. The ability to collect and capture information on new diseases and exposures suggests the potential to detect emerging occupational health concerns.

Limitations

1. As is common to other surveillance systems, a limitation of the use of these autopsy data is the lack of suitable denominators to calculate prevalence rates as the size of the population at risk (total numbers of deaths in employed and former miners) is not known. Hence, diseases are reported as proportions, using the annual numbers of cases submitted for autopsy as the denominator. A disadvantage of using proportions is that they do not capture changes in the numbers of cases submitted for autopsy at any given time.

2. The use of autopsy data for surveillance has limitations that are inherent of passive surveillance systems. The exclusion of former black miners from the PATHAUT database indicates poor representativeness of this subpopulation, selection bias and limits the generalizability of findings. These factors need to be considered when interpreting information generated using these data.
3. Although there have been improvements, the incomplete personal and employment information on the database is another limitation.
4. The database does not contain exposure measurements or comprehensive employment histories, e.g. job types, type of mining (surface or underground), or other non-mining jobs where exposures might have occurred. Hence, imprecise proxy measures for cumulative dust exposure (age, employment duration and commodity) are used.

CHAPTER 6: RECOMMENDATIONS AND CONCLUSION

6.1 RECOMMENDATIONS

Several recommendations arise from this evaluation. While some of the recommendations are specific to the use of PATHAUT for surveillance, many are generalisable to occupational disease surveillance. The recommendations are presented under three categories: policy, surveillance and research recommendations.

6.1.1 Policy recommendations

Promote the use of routine, administrative data for occupational disease surveillance

This evaluation provides a case study of how, in spite of its limitations, a routine, administrative database can be used for surveillance. In developing countries where resources to build and maintain stand-alone surveillance systems may be scarce, simple strategies using existing resources can be implemented. In countries that provide workers compensation, these data are particularly attractive for occupational disease surveillance as they contain information on employment. Hospital and mortality records can also be used if they contain employment information. However, hospital records tend to report cases with severe disease and mortality data are prone to under-recognition and underreporting of disease. It has also been suggested that occupational disease reporting could be included in national notifiable disease surveillance programmes (Antao and Pinheiro, 2015). For example, silicosis reporting could be integrated into tuberculosis notification in settings where both diseases are highly prevalent. Specifically for the South African mining industry, the use of MBOD and DMR records for occupational health and hazard surveillance, respectively, should be encouraged. The success of such systems would require the engagement of suitably qualified individuals to perform the surveillance activities (Mazzali and Duca, 2015).

6.1.2 Surveillance recommendations

Addition of surveillance functionality to PATHAUT

Currently, the use of PATHAUT as a surveillance tool is not formalised or documented. It was not recognised as a surveillance programme in the European Agency for Safety and Health at Work's global search for occupational disease surveillance systems, while SORDSA which no longer exists was identified (Bakusic et al., 2017). However, Antao et al. (Antao and Pinheiro, 2015) listed the PATHAUT database when illustrating the experience of selected developing countries with OLD surveillance.

The following actions are recommended.

1. Stakeholder engagement

Lessons learned from this evaluation should be shared with relevant stakeholders and be used to inform decisions on the use of the database for OLD surveillance. Stakeholders should also be involved in the design of the PATHAUT surveillance programme to increase autopsy uptake and use of the information generated. The mines have a significant role to play in such a process to ensure that the information generated is used for the prevention and control of OLDs. In addition, interviews with users of the system should be included to assess qualitative aspects of the attributes and usefulness.

2. Naming and development of objectives

The autopsy compensation-based surveillance programme should be given a name to ensure its visibility. The findings on usefulness reported in this thesis could be used to develop objectives which are linked to the prevention and control of OLDs.

3. Dissemination of information

Although most of the diseases reported are occupational sentinel health events with no direct benefit for the diseased individuals (as previously discussed in Section 5.3), the timeliness of dissemination of information should be considered. For PTB, more frequent reporting, e.g. quarterly reports to mine doctors would enable the timely review and improved TB case

management which would contribute to the attainment of targets to reduce the TB incidence and transmission (Msiza, 2014). For non-communicable, chronic diseases, individual cases of silicosis in relatively young (under 40 year old) miners with short mine employment (<10 years) could be reported to mine doctors where the miner worked to initiate the review of silica dust control practices in the mine.

4. Development of SOPs for PATHAUT surveillance

It is recommended that after establishment of the PATHAUT surveillance programme, SOPs should be developed. These should include steps for data management, including processes for data cleaning and storage, annotated SAS programs for data analysis, templates for creation of tables and figures for annual reports, dissemination of the reports and stakeholder engagement. The availability of SOPs will ensure the sustainability of the surveillance programme.

5. Future evaluation of the PATHAUT surveillance programme

The programme should be evaluated to assess its performance according to its objectives. Stakeholders should be involved in the planning and development of objectives for the evaluation. In addition to quantitative measures of attributes, the evaluation should include interviews to assess the experiences and perceptions of all involved in the autopsy and surveillance processes.

Improve autopsy uptake

Provision of facilities for organ removal for former miners

While mines bear the cost and organize organ removal for employed miners, the situation is more complicated for miners who die after leaving employment due to lack of facilities for organ removal and poor awareness of autopsy compensation by families and health care practitioners. In order to improve access to state-owned facilities for organ removal, it is recommended that the NIOH Pathology Division should continue engagements with the NDOH to make provisions for the forensic services to assist with organ removal. Provisions for autopsies for miners who have worked in South African mines, should also be included in current initiatives to deliver benefit medical examinations to former miners (Kistnasamy et al., 2018).

Increase awareness

Improved awareness of autopsy compensation by stakeholders is required to increase autopsy uptake. In the past (2006 to 2012), the NIOH Pathology Division ran an outreach programme through regular engagements stakeholders to raise OLD and autopsy compensation awareness, and support external health practitioners involved in the autopsy process. Posters and pamphlets in seven local languages and a booklet on autopsy compensation were produced for dissemination (<http://www.nioh.ac.za/services/lung-autopsy-examination-services/>). Although the Division has continued with outreach activities, the activities have been sporadic. It is recommended that a formal outreach programme should be reintroduced. Mines and mine unions should be encouraged to include OLD prevention and autopsy compensation in their awareness programmes. The TEBA data could be used to identify areas where migrant miners live to target awareness-raising activities about autopsy compensation.

Increase the efficiency of the compensation process

The CCOD's inefficiencies in making pay-outs to families of deceased claimants is a barrier to autopsy uptake (Banyini et al., 2013, Mthombeni, 2017). While there have been significant improvements in the numbers of payments made by the CCOD, there is still a backlog of unpaid compensation claims (Kistnasamy et al., 2018). Although the recent Silicosis Settlement includes autopsy compensation, it is limited to miners who worked for specified mining houses (Silicosis Settlement, 2019). Hence, the efficiency of the CCOD still needs to be improved to raise confidence and uptake of autopsy compensation.

Develop guidelines for occupational disease surveillance design and evaluation

The advantage of the ODIT tool is that it provides detailed methods including cut-off values for assessment but only for a single attribute (data quality) (Spreeuwiers et al., 2009) while the CDC guideline provides guidance for the assessment nine attributes and several measures of usefulness. A new guideline for occupational health surveillance evaluation that includes attributes in the CDC guideline but with better guidance on the selection of appropriate attributes, practical methods for attribute assessment as has been done for animal health surveillance (Drewe et al., 2015), and cut-off values for the quantitative assessment of attributes (Spreeuwiers et al., 2009) should be developed. The tool could also include other attributes which

are relevant to occupational health, e.g. economic attributes which are central to resource allocation; social attributes, e.g. communication and stakeholder perceptions, needs and expectations, and compliance to assess ethical issues associated with surveillance (Calba et al., 2015a).

It is envisaged that stakeholders would play a crucial role and provide input in the development and piloting of such a tool. The performance of the new tool could be assessed and used to evaluate the proposed PATHAUT surveillance programme.

6.1.3 Research recommendations

Estimation of underrepresentation

There have been no studies to address the underrepresentation of cases in the PATHAUT database by sub-group, for example, by race, age and sex. Representativeness is important as it affects the validity of inferences drawn using these data and the use of the information generated for policy decision making. Therefore, a study to investigate the magnitude of underrepresentation in the PATHAUT database is recommended. This can be done by estimating autopsy uptake by both current and former miners.

OLDs in female miners

Information on silicosis in female workers is sparse. Currently, there are too few female miners in the PATHAUT database to perform robust analytical studies. This thesis focused on female gold miners: similar studies should be done for other commodities.

The establishment of a cohort of women for a follow-up study on OLDs would enable the study of the incidence of OLDs in women and in-depth study of risk factors which are unique to women, e.g. work practices. However, in designing such a study, the challenges of follow-up studies in miners due to movement of miners from one mine to another, migrancy and poor access to benefit medical examinations and autopsy examinations after leaving the industry should be taken into account.

6.2 CONCLUSION

This thesis used four epidemiological studies to assess properties of an administrative, autopsy database for OLD surveillance. The findings indicate that the processes for organ examinations, data capture and information dissemination cover the core elements of a surveillance programme, namely, ongoing and systematic reporting, data collection, analysis, interpretation and dissemination of information. The autopsy data also fulfil several of the criteria for usefulness: OLD detection, estimation of disease magnitude, monitoring of trends, determination of risk factors, identification of occupational sentinel cases and assessment of the effectiveness of interventions. Some attributes of successful systems were also assessed: simplicity, flexibility, stability, data quality, sensitivity, representativeness, and timeliness. Given the long-recognised value of the autopsy system for OLD compensation and research, this thesis provides a basis to extend the use of the PATHAUT database to include a surveillance function. The development of a surveillance programme using these administrative data is relevant because of the scarcity of successful OLD surveillance systems not just in South Africa, but worldwide.

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APPENDICES

APPENDIX 1

Ndlovu N, Nelson G, Vorajee N, Murray J. 38 years of autopsy findings in South African mine workers, *American Journal of Industrial Medicine*, 2016; 59: 307-314.

38 Years of Autopsy Findings in South African Mine Workers

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Background South African miners have a statutory right to autopsies for occupational lung disease compensation. These autopsies also provide information for research and surveillance.

Methods Cardio-respiratory organs are removed where miners die and are examined at the National Institute for Occupational Health. We extracted data from the PATHAUT database and described key demographic, exposure and disease trends (1975–2013).

Results Of 109,101 autopsies, 72,348 (66.3%) were black, and 34,794 (31.9%) were white miners. Autopsies declined from over 3,000 (1975–1998) to 1,118 in 2013. Most were gold miners (74.0%). 78.6% black and 13.2% white miners died while in employment. Overall proportions of silicosis and pulmonary tuberculosis were 12.0% and 13.0% in black, and 20.5% and 2.4% in white miners, respectively. Disease increased over time.

Conclusions High levels of disease persist. Black ex-miners are underrepresented, indicating a need for strategies to improve awareness and provision of autopsy facilities in labor-sending areas. Am. J. Ind. Med. 59:307–314, 2016. © 2016 Wiley Periodicals, Inc.

KEY WORDS: occupational lung disease; silicosis; tuberculosis; PATHAUT; administrative database

INTRODUCTION

The mining industry played a dominant role in the development of South Africa. Although the industry has sunk considerably in the last two decades, it continues to contribute significantly to the economy and employed 10,099 miners in 2013 [DMR, 2014]. However, from the inception of mining over a century ago, there have been high

levels of occupational lung diseases (OLDs) [Ndlovu et al., 2008]. To this day, the health, or more appropriately ill-health, of miners remains a concern, influencing the health, and socio-economic fabric of the communities in which miners live.

Statutory compensation for OLDs was introduced in 1911 [Ehrlich, 2012] and, from the earliest Acts, made provisions for autopsies. Under the current Occupational Diseases in Mines and Works Act of 1973 (ODMWA) [RSA, 1973], the cardio-respiratory organs of deceased active (employed) and ex-miners are examined at the National Institute for Occupational Health (NIOH). From the mid-1950s, autopsy findings were recorded on edge-punched cards [Soskolne et al., 1976]. In 1975, the computerised Pathology Automation System (PATHAUT) was introduced to improve data management and efficiency of the autopsy compensation process. PATHAUT automatically generates standardized pathology reports which are uploaded to the Medical Bureau for Occupational Diseases (MBOD) for certification of compensable OLDs. These include the pneumoconioses (e.g. silicosis, coal workers' pneumoconiosis [CWP], mixed

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dust pneumoconiosis [MDP], and massive fibrosis), active pulmonary tuberculosis (PTB), asbestos-related diseases (pleural plaques, asbestosis, mesothelioma, and lung cancer), and emphysema.

Electronic reporting and advances in technology have enabled improved management and analysis of routinely collected administrative data, for example, death, hospital, insurance, and compensation registries. The advantages of using such data are reductions in time and costs associated with data collection and provision of uniform, long-term information. However, because administrative data are collected for operational purposes, they are sometimes viewed with suspicion and validity is often questioned [Virnig and McBean, 2001]. A review of NIOH autopsy diagnoses by external pathologists showed good to excellent agreement for silicosis, PTB and CWP, and fair agreement for emphysema [Naidoo et al., 2005b].

To stimulate interest and collaborative use of the PATHAUT data for research, Hessel and coworkers published two papers describing the first 10 years of data [Hessel et al., 1987a,b]. This paper extends the description by an additional 28 years, presents trends of key demographic characteristics, occupational exposures and OLDs, and reflects on the usefulness of the autopsy data.

METHODS

We use the word “miner” to include all categories of mine workers. Statutory autopsies on miners are performed regardless of the clinical cause of death and with written consent from the next of kin [RSA, 1973]. The organs are removed locally where the miners die and are examined by pathologists at the NIOH, using standardized criteria for the diagnosis and determination of the severity of compensable OLDs. The organs are examined macroscopically and sections are taken from all zones of the lungs for routine histological examination. Personal details, causes of death, occupational disease histories, summaries of labor histories, and pathological findings are entered into the PATHAUT database.

All records (1975–2013) were exported from PATHAUT to SAS (version 9.3) for analysis. Results are expressed as means and standard deviations for continuous variables, and as frequencies and proportions for categorical variables. The data were analyzed by population group because of racial differences in patterns of employment, levels of dust exposure, and access to autopsy services [Nelson et al., 2010]. Differences between means and frequencies were determined using Student's *t*-test and the chi-square test, respectively. The Cochran–Armitage test was used to determine linear trends in disease proportions. Statistical significance was defined at $P < 0.05$.

Ethical approval for this study was granted by the University of the Witwatersrand Human Research Ethics Committee (clearance certificate number M120236); and the

University of Michigan, Health Sciences and Behavioral Sciences Institutional Review Board (HUM00069012).

RESULTS

There were 109,101 autopsy records on the database. More than 3,000 autopsies were performed annually up to 1998 and declined thereafter to 1,188 in 2013 (Fig. 1). Most miners were black ($n = 72,348$; 66.3%) followed by white ($n = 34,794$; 31.9%), mixed race ($n = 1,612$; 1.5%), and Indian ($n = 3$; 0.0%) miners. Population group was not stated for 344 (0.3%) miners. This paper focuses on black and white miners because they constituted the majority of cases.

The sex of miners has been captured from 2005 and there were 320 (0.3%) records of women on the database. Due to the small numbers, findings in women are not reported separately and the word “men” encompasses both sexes.

On average, white miners were older than black miners (Table I). More black miners (90.9%) were aged below 60 years compared to white miners (40.2%). The mean age of black miners increased from 35.3 ± 11.7 years in 1975 to 49.5 ± 11.4 years in 2013 and that of white miners from 57.8 ± 13.8 years to 68.1 ± 12.1 years.

Employment status and the provinces or countries from which organs were submitted were captured from 2007 to 2010, respectively. The majority of black miners (78.6%) were employed, whereas most (86.8%) white miners had left employment at the time of death (Table I). Most organs (86.2%) originated from the North West, Free State, Gauteng, and Mpumalanga provinces (Table II).

Many miners are employed in more than one mining commodity in their working lives. We define “commodity” as the mining industry in which the longest period of employment occurred. Most autopsies were performed in gold miners, followed by platinum, coal, and asbestos miners (Table I). Many ($n = 14,444$; 13.2%) had worked in two or more commodities. The proportions of autopsies on black gold miners increased from 68.8% in 1975 to 81.7% in 1995 and then declined to 55.9% in 2013, and increased from 6.5%

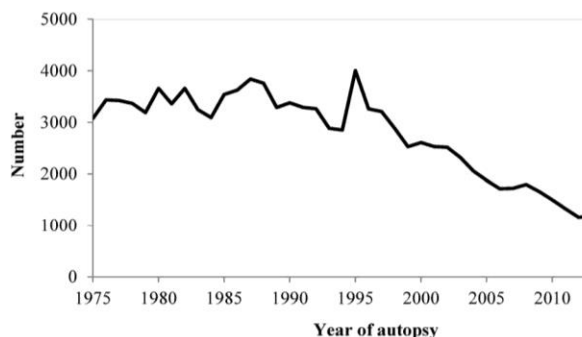


FIGURE 1. Annual numbers of cases submitted to the NIOH, 1975–2013.

TABLE I. Characteristics of Deceased Miners Whose Cardio-Respiratory Organs Were Examined at the NIOH, 1975–2013

Characteristics	Black	White	P-value
Number (%)	72,348 (66.3)	34,794 (31.9)	
Age (years), mean $\pm$ SD	39.7 $\pm$ 11.4	60.9 $\pm$ 14.6	<0.0001
Age groups (years), n (%)			
<20	644 (0.9)	56 (0.2)	<0.0001
20–29	13,944 (19.3)	1,264 (3.6)	
30–39	20,337 (28.1)	1,988 (5.7)	
40–49	19,746 (27.3)	3,759 (10.8)	
50–59	11,071 (15.3)	6,913 (19.9)	
60–69	2,288 (3.2)	10,066 (28.9)	
>70	637 (0.9)	10,495 (30.2)	
Missing	3,681 (5.1)	253 (0.7)	
Employment status, n (%)			
Former miner	1,383 (21.4)	2,818 (86.8)	<0.0001
Active miner	5,077 (78.6)	428 (13.2)	
Not stated	265 (3.9)	189 (5.5)	
Commodity, n (%)			
Gold	53,423 (73.8)	25,873 (74.4)	<0.0001
Platinum	8,365 (11.6)	1,221 (3.5)	
Coal	5,544 (7.7)	2,197 (6.3)	
Asbestos	1,661 (2.3)	899 (2.6)	
Copper	330 (0.5)	656 (1.9)	
Diamond	471 (0.7)	416 (1.2)	
Iron	197 (0.3)	192 (0.6)	
Iskor	254 (0.4)	1,719 (4.9)	
Manganese	144 (0.2)	51 (0.1)	
Other**	215 (0.3)	330 (0.9)	
Not stated	1,744 (2.4)	1,240 (3.6)	
Employment duration (years), mean $\pm$ SD	10.0 $\pm$ 8.0	23.4 $\pm$ 11.9	<0.0001
Employment duration groups (years), n (%)			
<10	29,458 (40.7)	4,749 (13.6)	<0.0001
10–19	16,012 (22.1)	6,466 (18.6)	
20–29	5,929 (8.2)	7,796 (22.4)	
30–39	1,004 (1.4)	7,807 (22.4)	
>40	83 (0.1)	2,386 (6.9)	
Missing	19,862 (27.5)	5,590 (16.1)	
Silicosis, n (%)	8,669 (12.0)	7,147 (20.5)	<0.0001
Pulmonary tuberculosis, n (%)	9,406 (13.0)	832 (2.4)	<0.0001

*Data available from 2007.

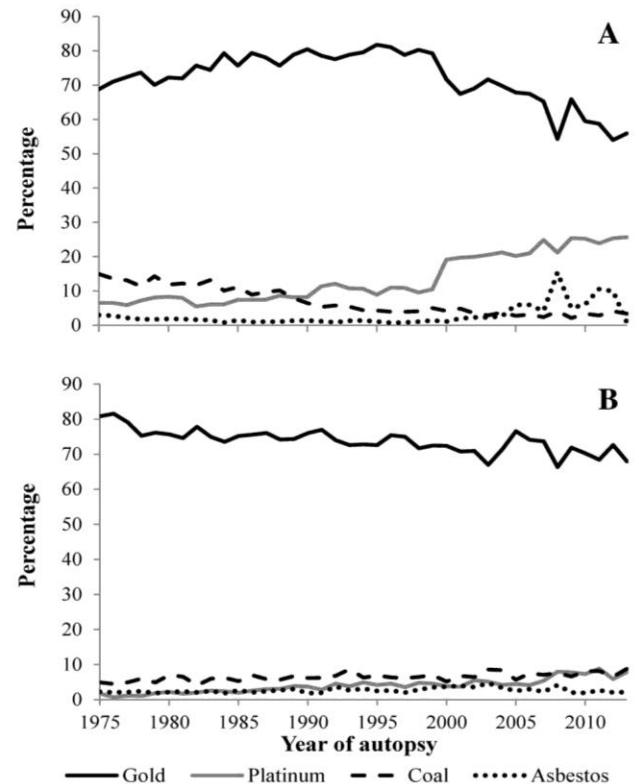
**Includes aluminium, antimony, cement, chrome, construction, environmental asbestos, Eskom, fluorspar, phosphate, industry, lead, lime, mica, minerals, nickel, quarry, refinery, railways, silica, steel, tin, uranium, vanadium, works, zinc.

in 1975 to 25.7% in black platinum miners (Fig. 2A). Over the study period, the proportions of white gold miners decreased from 80.8% to 67.9% and white platinum miners increased from 1.8% to 7.8% (Fig. 2B). One fifth of the platinum miners (n = 2,010, 21.0%) had previously worked in gold mines.

TABLE II. Origins of Cardio-Respiratory Organs, by Population Group, 2010–2013

Place of origin	Black n (%)	White n (%)	Total N (%)
South African province			
North West	1,290 (39.6)	484 (26.3)	1,774 (45.1)
Free State	931 (28.6)	219 (11.9)	1,150 (29.2)
Gauteng	323 (9.9)	816 (44.3)	1,139 (29.0)
Mpumalanga	164 (5.0)	169 (9.2)	333 (8.5)
Northern Cape	396 (12.2)	44 (2.4)	440 (11.2)
Limpopo	45 (1.4)	19 (1.0)	64 (1.6)
KwaZulu-Natal	7 (0.2)	45 (2.4)	52 (1.3)
Western Cape	6 (0.2)	30 (1.6)	36 (0.9)
Eastern Cape	17 (0.5)	14 (0.8)	31 (0.8)
Neighbouring country			
Lesotho	76 (2.3)	0	76 (1.9)
Botswana	2 (0.1)	0	2 (0.1)
Total	3,257	1,840	5,095

White miners worked for longer periods than black miners (Table I). Duration of employment decreased from 24.9 ± 11.7 years in 1975 to 22.6 ± 11.0 years in 2013 for white miners, but increased from 5.5 ± 5.7 years to

**FIGURE 2.** Proportions of autopsies of black (A) and white (B) miners, by year and commodity, 1975–2013.

15.8 ± 9.7 years for black miners. The duration of employment was not stated for 23.7% ($n = 25,451$) cases. There were more records with missing duration of employment in the period 1975–2003 (range: 15.3–44.4%) than after 2003 (2.0–6.9%).

Figure 3 shows the OLDs at ~20 year intervals. The major diseases diagnosed were emphysema, silicosis and PTB. The proportions of most diseases increased over time. From 1995 to 2013, the proportions of asbestosis and mesothelioma increased several-fold in both population groups (Fig. 3). There was more asbestosis and silicosis in white miners in 1975 and 1995, but in 2013 proportions were higher in black miners.

Silicosis and PTB trends in gold and platinum miners are shown in Figures 4 and 5. The proportions of disease dropped sharply in 1996 due to incomplete data entry. One-sided P -values for all trends were significant ($P < 0.0001$) except where stated.

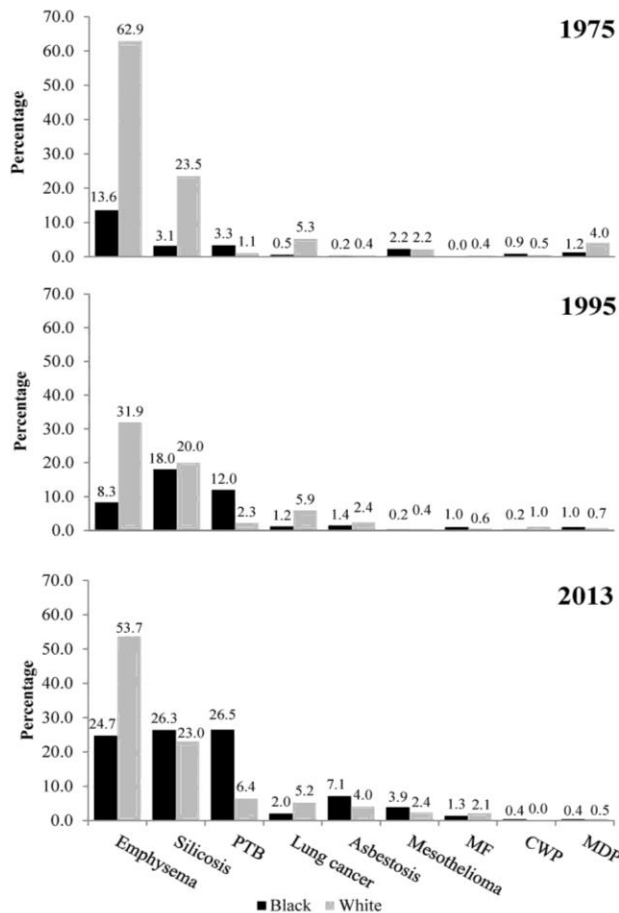


FIGURE 3. Occupational lung diseases diagnosed in black and white miners at autopsy in 1975, 1995, and 2013.

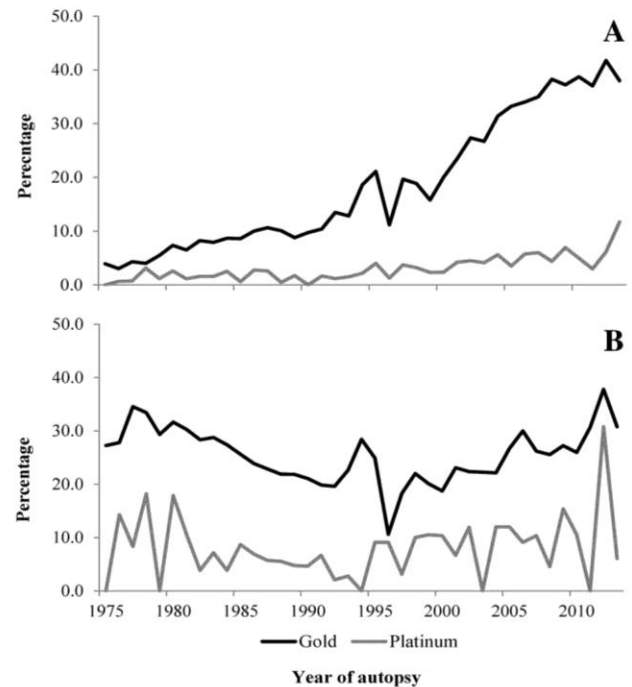


FIGURE 4. Silicosis diagnosed in black (A) and white (B) platinum and gold miners at autopsy, 1975–2013.

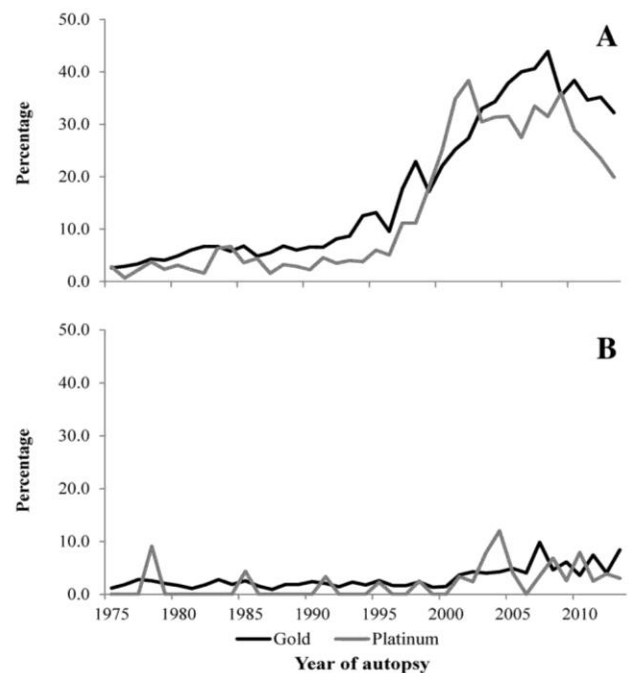


FIGURE 5. Pulmonary tuberculosis diagnosed in black (A) and white (B) platinum and gold miners at autopsy, 1975–2013.

From 1975 to 2013, silicosis increased nine- and five-fold in black gold and platinum miners, respectively (Fig. 4A). In white gold miners, silicosis decreased from 27.2% in 1975 to 18.3% in 1997 and then increased to 30.8% in 2013 (Fig. 4B). Although proportions were lower, the trend was similar in white platinum miners ($P = 0.03$).

Pulmonary tuberculosis was five times higher in black than white miners (Table I) and increased over time in both population groups (Fig. 5). Peaks were observed in 2002 and 2008 for platinum and gold miners, respectively (Fig. 5A). Over the study period, PTB increased seven- and three-fold in white gold and platinum miners, respectively (Fig. 5B). The small numbers of white platinum miners (7–50 per year) may explain the fluctuations in silicosis and PTB trends (Figs. 4 and 5B).

DISCUSSION

The collection of more than 109,000 autopsy records over a 38-year period attests to sustained institutional commitment and meticulous data collection. The inclusion of many commodities and pathologies in the database has resulted in the study of common and rare occupational exposures and diseases. The public availability of an almost complete set of annual reports (excluding 1996), numerous research reports, and more than 100 peer-reviewed scientific papers provides information for the generation of research questions and has fostered much international collaboration. This has given PATHAUT world-wide recognition as a leading autopsy database [Naidoo, 2013]. Locally, this body of knowledge provides evidence for the development of occupational health policies, research agendas, and monitoring of interventions, such as the current National Programme for the Elimination of Silicosis [DOL, 2015].

Autopsies provide accurate diagnoses for use in mortality statistics and are important in public health. They can also be used to evaluate clinical diagnoses [Roulson et al., 2005]. Clinico-pathological correlation studies at the NIOH showed that 60–80% of autopsy-diagnosed silicosis and 62% of PTB had not been diagnosed clinically [Hnizdo et al., 1993; Murray et al., 2000]. Hence, autopsies afford a final opportunity to access financial compensation.

The decreasing numbers of autopsies on miners in the last two decades are worrying. Globally, autopsies have declined since the 1960s [Burton and Underwood, 2007]. Reasons include improvements in imaging techniques, which have reduced the perceived value of the autopsy, and the increasingly onerous task of obtaining consent [Burton and Underwood, 2007]. In developing countries, lack of human and financial resources are also important [Mudenda et al., 2012]. For South African miners, the shrinkage of the mining labor force by ~40% in the last few decades [Nelson and Murray, 2013a] has contributed to the decline.

The addition of place of origin and employment status on the PATHUAT database enables assessment of utilisation of autopsy services. Most organs originated from provinces where mining activity is high and few were submitted from labor-sending areas. The majority of black miners died while in employment whereas most whites were ex-miners. These findings indicate racial differences in utilisation of autopsy services and are similar to findings from two cohort studies, which showed high autopsy rates of 70% for black active miners [Murray et al., 2007] and 85% for white ex-miners [Hnizdo et al., 1993]. Considering that hundreds of thousands of men have worked in the mines, it is apparent that the families of black ex-miners are not accessing or utilising autopsy services [Roberts, 2009].

Disparities in access to compensation are explained by social, economic, and political circumstances peculiar to South Africa [van Niekerk, 2013]. The South African migrant labor system, in existence since the inception of mining, is characterized by “oscillation” of miners between the mines and the homes to which they return when employment ceases [Rees et al., 2010]. However, despite deracialization of the ODMWA in 1993 [RSA, 1993], there are still virtually no state facilities offering autopsies in labor-sending areas. With few exceptions, forensic pathology mortuaries are the only state-owned services providing this service for miners; mostly for men who die from non-natural causes. Consequently, outside the major mining regions, organs are removed primarily by pathologists in academic hospitals.

According to the ODMWA, it is the responsibility of the last attending doctor to arrange for the removal of the cardio-respiratory organs of a miner [RSA, 1973]. Due to greater awareness of autopsy compensation among the families of white miners, they are more likely to request for autopsies than the families of black miners [Roberts, 2009]. Hence, the families of the majority of black miners are precluded from autopsy compensation.

It has been suggested that socio-cultural beliefs prevent the families of black miners from consenting to autopsies [Banyini et al., 2013]. In recent years, the NIOH has received increased numbers of organs of black ex-miners from the Northern Cape Province, a former asbestos mining area. This is attributed to the awareness-raising activities of the Asbestos and Kgalagadi Relief Trusts [ART, 2013]. In a neuropathology study of South African manganese miners, a 75% consent rate for brain removal was achieved [Nelson et al., 2012]. These observations support the findings that careful and sympathetic explanation of the processes and benefits of autopsies improves their acceptability [Burton and Underwood, 2007; Roberts, 2009] and that cultural beliefs are not insurmountable barriers to autopsy uptake.

The autopsy data show persistently high and increasing OLDs in miners: the highest being emphysema, silicosis and PTB. Studies on emphysema have been hampered by the

unavailability of information on smoking (an important confounder for emphysema) on the PATHAUT database. However, a few studies have been possible, utilizing information contained in the MBOD's paper files [Hnizdo et al., 1991; Naidoo et al., 2005a].

The high levels of silicosis indicate failures to control and prevent silica dust exposures in the gold mining industry [Hermanus, 2007]. In black miners, the increasing silicosis trends are explained by increasing employment duration (a surrogate for cumulative dust exposure) and age at death [Nelson et al., 2010]. These are consequences of regulatory changes in the 1980s, which allowed black miners to work long-term contracts. Silicosis in platinum miners is explained largely by previous silica dust exposures in the gold mining industry. However, the autopsy diagnosis of silicosis in five platinum miners with no history of gold mining suggests that silica dust exposures might occur in the platinum mining industry [Nelson and Murray, 2013b].

South African gold miners have the highest rates of PTB in the world [DOH, 2007]. Risk factors for PTB include its prevalence in the general population, age, exposure to silica dust, general health, and HIV infection [Ross and Murray, 2004]. Even in 1975, well before the HIV pandemic, autopsy diagnosed PTB was at epidemic levels by international standards and was associated with silica dust exposure in gold miners [Murray et al., 1996]. The steep increase in PTB in black gold and platinum miners from the mid-1990s is associated with the rapid spread of HIV and the multiplicative effect of HIV and silicosis on PTB risk [Rees and Murray, 2007]. The decreases observed from the early 2000s are attributed to the roll-out of anti-retroviral therapy for HIV [Lim et al., 2012]. Given the low prevalence of HIV in the white population, estimated at 0.3% [Shisana et al., 2014], the increasing prevalence of PTB in this population group is probably associated with the high prevalence of tuberculosis in the general population, and increasing age and employment duration [Ross and Murray, 2004].

Limitations of the PATHAUT data that need to be considered when interpreting findings include: (i) the underrepresentation of black ex-miners which results in underestimation of diseases, especially those with long latency, such as the pneumoconioses and malignancies; (ii) the unavailability of suitable denominators (annual numbers of deaths of active and ex-miners) which prevents calculations of prevalence; hence, diseases can only be presented as proportions; (iii) the large size of the database, which results in small *P*-values for even minute differences; therefore, *P*-values need to be interpreted with caution, and conclusions based on the practical or biological significance of the findings [Lin et al., 2013]; and (iv) the large proportion of cases with incomplete information in earlier years; however, active follow-up with mines and families to obtain missing personal and exposure information has resulted in improvements in the completeness of the data.

The continuing high levels of OLDs among miners in a well-resourced and technically-advanced industry are of great concern. Improvements in the health of miners require stronger commitments by key stakeholders, both in government and industry, to implement preventive strategies [van Niekerk, 2013]. The PATHAUT database is a rich resource, currently providing the only long-term information on OLDs in the South African mining industry. However, its future and sustainability depend largely on the provision of state facilities for autopsies in labor-sending areas, and improved awareness and autopsy uptake by ex-miners.

AUTHORS' CONTRIBUTIONS

NN: Had full access to the study data and was responsible for data integrity and analysis. She substantially contributed to conception, design, acquisition of the data, statistical analysis, data interpretation, drafting of the manuscript, and critical revision of the manuscript for intellectual content, and revised and approved the final version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GN: Substantially contributed to the interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and revised and approved the final version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. VN: Substantially contributed to acquisition of the data, data interpretation and critical revision of the manuscript for intellectual content, and revised and approved the final version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JM: Substantially contributed to acquisition of the data, conception, design, interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and revised and approved the final version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

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APPENDIX 2

Ndlovu N, Rees D, Murray J, Vorajee N, Richards G, teWaterNaude J. Asbestos-related diseases in mineworkers: a clinicopathological study, ERJ Open Res, 2017: 3: DOI: 10.1183/23120541.00022-2017



Asbestos-related diseases in mineworkers: a clinicopathological study

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ABSTRACT The accurate diagnosis of asbestos-related diseases is important because of past and current asbestos exposures. This study evaluated the reliability of clinical diagnoses of asbestos-related diseases in former mineworkers using autopsies as the reference standard.

Sensitivity, specificity, positive predictive value and negative predictive value were calculated.

The 149 cases identified had clinical examinations 0.3–7.4 years before death. More asbestos-related diseases were diagnosed at autopsy rather than clinically: 77 *versus* 52 for asbestosis, 27 *versus* 14 for mesothelioma and 22 *versus* 3 for lung cancer. Sensitivity and specificity values for clinical diagnoses were 50.6% and 81.9% for asbestosis, 40.7% and 97.5% for mesothelioma, and 13.6% and 100.0% for lung cancer. False-negative diagnoses of asbestosis were more likely using radiographs of acceptable (*versus* good) quality and in cases with pulmonary tuberculosis at autopsy.

The low sensitivity values are indicative of the high proportion of false-negative diagnoses. It is unlikely that these were the result of disease manifestation between the last clinical assessment and autopsy. Where clinical features suggest asbestos-related diseases but the chest radiograph is negative, more sophisticated imaging techniques or immunohistochemistry for asbestos-related cancers should be used. Autopsies are useful for the detection of previously undiagnosed and misdiagnosed asbestos-related diseases, and for monitoring clinical practice and delivery of compensation.



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Asbestos-related diseases are difficult to diagnose; 58% diagnosed at autopsy had been missed clinically <http://ow.ly/L9u230dr0bv>

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Introduction

This study compared clinical and autopsy findings for three asbestos-related diseases (asbestosis, mesothelioma and lung cancer) in former asbestos mineworkers, and explored factors that influenced agreement between clinical and autopsy findings using data from two compensation systems. In South Africa, statutory compensation for occupational lung diseases in mineworkers makes provisions for autopsy examinations of the cardio-respiratory organs at the National Institute for Occupational Health (NIOH) in Johannesburg [1]. In addition, the Johannesburg-based Asbestos Relief Trust and Kgalagadi Relief Trust (the “Trusts”) compensate individuals with defined asbestos-related diseases who worked in or lived near qualifying asbestos mining or processing operations [2]. The Trusts also compensate dependents of deceased qualifying mineworkers and therefore encourage statutory autopsies for the detection of previously undiagnosed asbestos-related disease or disease that may have progressed to higher compensation grades.

South Africa was the third largest producer of asbestos and cumulatively produced 97% of the world’s crocidolite [3]. It is among 57 countries that have banned the mining and/or use of all types of asbestos [4]. However, past and current occupational exposures, and nonoccupational domestic and neighbourhood exposures in communities living near asbestos operations, have resulted in a global asbestos-related disease pandemic [5, 6].

The reliability of the clinical diagnosis of asbestos-related diseases continues to be important given the large numbers of affected individuals, projections that the asbestos-related disease epidemic is yet to reach its peak and the significant underreporting of asbestos-related diseases [5, 7, 8]. In many parts of the world, benign asbestos-related diseases are often diagnosed based on history, clinical features and chest radiology alone, despite evidence showing that the chest radiograph is inadequate for diagnosis [9, 10]. Similarities between the presenting features of asbestosis and those of other types of diffuse interstitial fibrosis contribute to this unreliability [9, 11]. The malignant diseases, mainly mesothelioma and lung cancer, require histological and immunohistochemical confirmation as their radiological appearance may be misleading [9, 12–14]. In addition, metastases and infections, such as tuberculosis, may mimic the appearance of mesothelioma and result in misdiagnosis.

Few recent studies have validated chest imaging findings for asbestos-related diseases using the autopsy as the reference standard (table 1). The chest radiograph was shown to underestimate asbestosis and, conversely, to overestimate it when readers were aware of previous asbestos exposure [15, 16]. AKIRA *et al.* [17] found good correlation between high-resolution computed tomography (HRCT) and autopsy-diagnosed asbestosis. Two other studies showed variability in the proportions of mesothelioma cases confirmed at autopsy [18, 19]. No similar clinicopathological studies were identified for

TABLE 1 Summary of asbestos-related disease clinicopathological studies that compared imaging and autopsy findings

First author [ref.]	Study population	Methods compared	Findings
Asbestosis			
KIPEN [15]	138 deceased insulation workers with primary lung carcinoma	Radiology, biopsy and autopsy	False-negative: 18.1%
SLUIS-CREMER [20]	172 deceased asbestos mineworkers	Radiological findings of three readers and autopsy	67 (39.0%) autopsy-diagnosed asbestosis cases; for readers 1, 2 and 3, respectively: # true-positive: 38, 18 and 30; false-positive: 25, 5 and 21; false-negative: 29, 49 and 36; true-negative: 80, 100 and 84; sensitivity: 56.7%, 26.9% and 45.5%; specificity: 76.2%, 95.2% and 80.0%
AKIRA [17]	7 deceased asbestos workers with radiologically diagnosed asbestosis	HRCT, biopsy and autopsy	Good correlation between HRCT and autopsy findings
MIZELL [16]	273 deceased asbestos workers with radiologically diagnosed asbestosis	Radiology and autopsy	True-positive: 36.8% (89 out of 242 in study group); false-positive: 63.2% (153 out of 242 in study group)
Mesothelioma			
YATES [19]	272 deceased cases with suspected or confirmed mesothelioma	Clinical features, radiology and autopsy	True-positive: 99.2% (265 out of 267 autopsies)
TAKESHIMA [18]	382 deceased cases with clinically diagnosed mesothelioma	Clinical features, radiology, pathology and autopsy	True-positive: 74.3% for males and 59.2% for females
HRCT: high-resolution computed tomography. #: values derived from SLUIS-CREMER <i>et al.</i> [20].			

asbestos-related lung cancer. However, one study showed that radiology alone detected fewer cases of lung cancer than when used in conjunction with HRCT and cytology [14].

Materials and methods

Study subjects

This retrospective, consecutive case series included the records of all former asbestos mineworkers who were clinically examined by the Trusts and had autopsy examinations at the NIOH in 2010 and 2011. No mineworker had occupational asbestos exposure after the clinical evaluation for asbestos-related diseases.

Ethical approval for the study was obtained from the University of the Witwatersrand, Human Research Ethics Committee (M120236) and the University of Michigan Health Sciences and Behavioural Sciences Institutional Review Board (HUM00069012).

Clinical assessment of asbestos-related diseases

Clinical diagnoses were made by the Trusts' Specialist Occupational Medical Panel (SOMP) that consisted of two radiologists and four occupational medical specialists, three of whom were current or former University of Cape Town medical professors. The SOMP was experienced with occupational lung diseases, and the reading and interpretation of computed tomography images and chest radiographs using the International Labour Office (ILO) classification of chest radiographs [21]. At each session, cases were evaluated by two members of the SOMP (a radiologist and an occupational medical specialist). If the SOMP could not reach a diagnosis, further clinical testing was requested and where there was uncertainty the case was referred to the SOMP Forum, which consisted of all six panellists, for certification.

Posterior–anterior chest radiographs were read according to the ILO methodology, and radiograph quality and any significant radiological changes or abnormalities were recorded [21]. Asbestosis was considered in individuals with small, bilateral irregular linear parenchymal opacities classified as s, t or u of profusion $\geq 1/0$ in the lower zones of the lungs (with or without extension into the middle and upper zones) [21]. The cut-point of 1/0 was used to distinguish radiographs that were positive for asbestosis from those that were negative [22]. Individuals with radiological features were diagnosed with asbestosis if they had an appropriate occupational history and latency period, clinical findings consistent with asbestosis, and the absence of competing explanations for the observed radiological changes, in accordance with the guidelines of the American Thoracic Society [22]. Chest radiograph quality was categorised according to the ILO criteria for the classification of pneumoconiosis as good, where all criteria were met; acceptable, with few technical defects; acceptable, with defects but still adequate; or unreadable [21]. Only clinical asbestosis cases with good or acceptable radiographs were included in the analyses.

Malignant pleural mesothelioma and lung cancer were diagnosed in individuals with suggestive clinical and radiological findings, usually followed by biopsy of the lesion and confirmation by histology, including immunohistochemistry where available.

Pathological assessment of asbestos-related diseases

The cardio-respiratory organs were removed with consent at the site where mineworkers died, placed in formalin and sent to the NIOH for examination by specialist anatomical pathologists. The nature and extent of occupational lung diseases, including asbestos-related diseases, were recorded and captured on the Pathology Automation (PATHAUT) database [23].

The presence of asbestos-related diseases was determined by pathological examination of the lungs according to a standard protocol. Slices of lung tissue (1 cm thick) were examined macroscopically. Thereafter, a section of the main bronchus with the hilar lymph nodes and a minimum of three sections from each zone of both lungs were taken for microscopic examination. Depending on the pathology identified, additional sections were taken, as appropriate, from areas of the lung with fibrosis or affected by malignancy.

Routine special stains used to assess the degree of fibrosis and detect ferruginous bodies were Gordon and Sweets' reticulin silver and Perl's Prussian blue iron stains, respectively.

The extent of asbestosis was graded using a modification of the grading scheme of CRAIGHEAD *et al.* [24]. Asbestosis was considered absent if there was no fibrosis; mild where fibrosis was confined to the area around the respiratory bronchioles and the immediately adjacent alveoli; moderate if there was coalescence of fibrosis involving all alveoli between two adjacent bronchioles; and severe if there was widespread fibrosis with the formation of abnormal airspaces or honeycombing.

Pleural malignant mesothelioma and lung cancer were diagnosed based on morphology supported by immunohistochemistry. Calretinin, WT1 (Wilms tumour 1) and CK5/6 (cytokeratin 5/6) were routinely used to confirm mesothelioma. Tumour protein p63 and TTF-1 (thyroid transcription factor-1) were used

to confirm squamous carcinomas and adenocarcinomas, respectively. The World Health Organization TNM classification was used to determine the pathological stages of mesothelioma and lung tumours that had not been diagnosed in life [25]. For this study, all histology slides and pathology reports were reviewed and confirmed by two pathologists experienced in asbestos-related diseases.

Data collection

Personal/occupational information, radiology and other clinical findings were obtained from the Trusts' records; pathology findings were obtained from the PATHAUT database. The study did not assess nonmalignant pleural diseases because for many cases the parietal pleurae were not submitted for autopsy. Both clinicians and pathologists were aware of asbestos exposures at the time of examination.

Statistical analysis

Summary measures are presented as frequencies and percentages or medians and ranges. The Mann–Whitney, Chi-squared and Kruskal–Wallis tests were used to determine statistical differences between and among groups, as appropriate. Statistical significance was defined at $p \leq 0.05$. Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with autopsy findings as the reference standard.

Radiological profusion scores for asbestosis were grouped as none (0/0 and 0/1), mild (1/0, 1/1 and 1/2), moderate (2/1, 2/2 and 2/3) and severe (3/2 and 3/3). The κ statistic was used to test agreement between the clinical and pathological diagnoses. Factors associated with false-negative asbestosis diagnoses were determined using binary logistic regression, with true-positive asbestosis cases as the reference group. Variables with p -values ≤ 0.2 in the univariate analyses were included in the multivariable model. Post-regression analysis was done using the Hosmer–Lemeshow goodness-of-fit test. All analyses were performed using Stata version 13 (StataCorp, College Station, TX, USA).

Results

There were 149 former asbestos mineworkers, of which 131 (87.9%) were male. The overall median (range) age at death was 66.1 (41.8–95.2) years. Most ($n=131$ (87.9%)) were from the Northern Cape Province, a former crocidolite mining area. First occupational asbestos exposures occurred between 1952 and 1990 (median 1976) and the median (range) latency period (first asbestos exposure to asbestos-related disease diagnosis) was 31.0 (15.0–56.0) years. Approximately one-third had worked in other mining industries, *e.g.* gold, manganese, platinum and iron.

Based on clinical evaluation, the SOMP diagnosed 52 (34.9% of the study population) asbestosis cases, 14 (9.4%) mesothelioma cases and three (2.0%) lung cancer cases. At autopsy, 77 (51.7%) cases of asbestosis, 27 (18.1%) cases of mesothelioma and 22 (14.8%) cases of lung cancer were diagnosed (table 2). Asbestosis was also diagnosed in 10 lung cancer cases and seven mesothelioma cases. The asbestosis cases were older, and had longer employment duration and intervals from first asbestos exposure to death, than those with malignancies. The interval from last clinical assessment to death was shorter compared with lung cancer cases.

Of the 126 asbestos-related diseases diagnosed at autopsy, 73 (57.9%) were not diagnosed clinically. The low sensitivity values (table 3) indicate that most autopsy-diagnosed asbestos-related diseases had not been diagnosed clinically. The specificity, PPV and NPV for asbestosis were lower than those for malignancies (table 3).

TABLE 2 Characteristics of former asbestos mineworkers with asbestos-related diseases diagnosed at autopsy

	Asbestosis	Mesothelioma	Lung cancer
Subjects	77	27	22
Age at death years	67.8 [#] [48.1–93.0]	62.0 [44.2–82.7]	65.4 [46.8–91.5]
Interval from clinical assessment to death years	5.4 [¶] [0.4–7.4]	4.5 [0.3–6.3]	4.3 [0.7–7.0]
Employment duration in asbestos mines years	4.3 [¶] [0.3–31.0]	3.0 [0.3–18.0]	2.0 [0.3–20.5]
Latency years	36.0 [16.0–53.0]	29.0 [16.0–56.0]	30.0 [15.0–53.0]
Interval from first asbestos exposure to death years	41.0 ^{#,¶} [21.0–58.0]	34.0 [21.0–57.0]	35.0 [20.0–57.0]

Data are presented as n or median [range]. [#]: significant difference between asbestosis and mesothelioma cases (Kruskal–Wallis test; $p \leq 0.05$);

[¶]: significant difference between asbestosis and lung cancer cases (Kruskal–Wallis test; $p \leq 0.05$).

significantly different. Using tertiles of this interval, we found that although the sensitivity values for asbestosis increased with increasing interval, the differences were not significant.

Compared with true-positive asbestosis cases, the likelihood of false-negative diagnoses was significantly higher in cases with acceptable radiographs (*versus* good) and in those with autopsy-diagnosed PTB (table 5).

There was poor agreement (47.0%; $\kappa=0.15$) between the severity of radiological and autopsy-diagnosed asbestosis. Of the 72 individuals who did not have asbestosis at autopsy, 12 had mild asbestosis (1/0, 1/1 and 1/2) and one had severe asbestosis (3/3) (table 6). Of the 39 true-positive cases, 27 had more severe disease at autopsy. Nine cases had severe asbestosis at autopsy and profusion scores of $\leq 1/0$. Of these, two had normal spirometry, and restrictive patterns in the remaining cases were mild ($n=1$), moderate ($n=3$) and severe ($n=3$).

Asbestos-related cancer

27 cases of mesothelioma and 22 cases of lung cancer were diagnosed at autopsy. 14 (28.6%) malignancies had been correctly diagnosed clinically, resulting in low sensitivity values (table 3). Specificity values were high with no false-positive diagnoses of lung cancer. The three false-positive cases of mesothelioma were diagnosed as large ($n=1$) and squamous cell ($n=2$) carcinomas at autopsy. All clinical diagnoses were confirmed using histology and immunochemistry, except for two mesothelioma cases: one refused biopsy and another died while undergoing investigation. HRCT was used to diagnose two of the true-positive malignancies.

There were 35 false-negative diagnoses of malignant disease. The 16 mesothelioma cases and 19 lung cancer cases had last been examined 4.8 years (range 0.3–6.3 years) and 4.4 years (range 0.7–7.0 years) before death, respectively. 24 of the cases had benign asbestos-related diseases (11 had asbestosis, four had pleural disease, and nine had both asbestosis and pleural disease). Seven false-negative cases (five mesotheliomas and two lung cancers) died while undergoing investigation.

Three of the 16 false-negative mesotheliomas were from lungs that were received piecemeal. The pathological classification of four of the mesotheliomas was T2 (with confluent visceral pleural tumours), one of which also had invasion of the lung parenchyma. 12 were T4 with direct extension to the contralateral pleura and/or invasion of the myocardium. The thickness of the mesotheliomas was <10 ($n=1$), 10–20 ($n=7$) and ≥ 30 mm ($n=8$). Four of the 19 false-negative primary lung cancers were from lungs that were received piecemeal and could not be classified. The lung cancers were classified as T1b ($n=1$), T2 ($n=4$), T3 ($n=8$) and T4 ($n=2$). One lung cancer was >30 mm in diameter and the remainder were >70 mm.

Discussion

This study provides recent clinicopathological findings on three asbestos-related diseases in former asbestos mineworkers using autopsies as the reference standard for comparison. The major finding was that many diagnoses had been missed clinically.

One limitation of this study is the interval (0.3–7.4 years) between the last clinical assessment and death. This might explain the large proportion of false-negative cancer diagnoses, as tumours may have developed and progressed rapidly during this interval and/or manifested clinical symptoms late [26]. This

TABLE 5 Factors associated with false-negative diagnoses of asbestosis

	Odds ratio (95% CI)	p-value
Age at death years	0.95 (0.87–1.03)	0.24
Employment duration years	0.93 (0.86–1.02)	0.14
Latency years	1.01 (0.93–1.10)	0.78
Smoking	2.08 (0.48–9.08)	0.33
Chest radiograph quality		
Acceptable <i>versus</i> good	12.33 (2.54–59.72)	0.00
Severity of asbestosis		
Moderate <i>versus</i> mild	1.18 (0.24–5.71)	0.84
Severe <i>versus</i> mild	0.26 (0.04–1.73)	0.16
Lung cancer at autopsy	3.17 (0.39–25.80)	0.28
PTB at autopsy	8.45 (1.16–61.69)	0.04

PTB: pulmonary tuberculosis.

TABLE 6 Agreement between the severity of radiological and autopsy diagnoses of asbestosis

Radiological asbestosis	Pathological asbestosis				Total
	None	Mild	Moderate	Severe	
None					
0/0	43	11	11	4	69
0/1	16	6	5	1	28
Mild					
1/0	10	7	3	4	24
1/1	1	1	8	4	14
1/2	1	1	2	2	6
Moderate					
2/1	0	1	0	1	2
2/2	0	0	2	2	4
2/3	0	0	0	1	1
Severe					
3/3	1	0	0	0	1
Total	72	27	31	19	149

could also explain the poor agreement between the clinical and autopsy grading of asbestosis but this is unlikely, as discussed later.

The proportion (49.4%) of false-negative asbestosis diagnoses is higher than that reported for interstitial fibrotic lung diseases (10–20%) [22, 27–29]. The sensitivity value for asbestosis is within the range of 26.9–56.7% reported for deceased South African asbestos mineworkers [20]. False-negative asbestosis diagnoses may have occurred because the Trusts used radiological detection of opacities as the entry point for investigation of asbestosis and, as such, a negative reading would preclude further investigation. The missed diagnoses were not due to poor interpretation of films by the SOMP as its findings were confirmed by three independent readers.

The false-negative cases may have arisen from progression in the interval between the clinical and autopsy examinations. Progression from normal to radiologically detectable asbestosis, even long after exposure cessation, is well established and occurs in a minority of amphibole exposed workers [30–32]. The determinants of progression include cumulative asbestos exposure, intensity of exposure, duration of follow-up and age, but vary among study cohorts [30–33]. Asbestosis developed in 10.6% of former South African mineworkers 5.7 years after exposure cessation and in 4–10% of former US amosite factory workers after ≥10 years [31–33]. As in our study, the workers had been exposed to amphibole asbestos (amosite and/or crocidolite), but decades earlier and after shorter asbestos exposures [31–33]. Hence, progression rates reported elsewhere may not be directly applicable to our setting.

Diagnostic accuracy may be improved by having serial chest radiographs, but we did not have the data to examine this. HRCT, a more sensitive tool for asbestosis diagnosis, is particularly useful where there are no or indeterminate radiological findings (0/0 or 0/1) in symptomatic, exposed individuals with abnormal lung function [22, 26]. It reduces false-positive diagnoses through identification of other pleural and parenchymal conditions, *e.g.* emphysema and bronchiectasis, which may explain radiological changes thought to be asbestosis [22, 34]. Nonetheless, HRCT may miss disease, detect nonspecific changes unrelated to asbestosis and is prone to inter-reader variability [10, 35]. In settings with limited access to HRCT, patients with asbestos exposure and clinical features of asbestosis, including exertional dyspnoea, crackles on auscultation of the chest and abnormal lung function tests, particularly chest restriction or reduced transfer factor of the lung for carbon monoxide, should be prioritised for imaging [22].

The second limitation is the small number of cases available to determine factors associated with false-negative asbestosis diagnoses. Hence, some explanatory variables may not have been identified. Nonetheless, our findings suggest that asbestosis is more likely to be diagnosed using radiographs of good quality and less likely in cases with PTB.

There were few false-positive diagnoses of asbestosis and mesothelioma, and none of lung cancer. The specificity of asbestosis (81.6%) is similar to that observed in a previous study (76.2–80.0%) [20]. Factors associated with false-positive asbestosis readings include radiographic technique, aging, obesity, smoking, presence of chronic obstructive pulmonary disease and dust exposures [10, 20]. We found that the false-positive cases had other pathologies (PTB, emphysema or lung cancer) that could have been misread as asbestosis.

Most of the 35 cases with false-negative malignancies had advanced tumours at autopsy. Although seven malignancies were suspected in life, the cases died before a definitive diagnosis was made. The predominantly advanced pathological stage of the tumours suggests that there could have been more true-positive clinical diagnoses if clinicians had a higher index of suspicion and had been more aggressive in investigating these tumours. Accuracy could be improved by the introduction of standardised protocols for immunohistochemistry panels for mesothelioma and lung cancer in peripheral pathology laboratories.

Conclusions

This study confirms that chest radiography, as the sole imaging tool in asbestos-exposed individuals, substantially underdiagnoses asbestos-related diseases but has good specificity, producing few false-positive results. Accurate clinical diagnoses ensure timely management and treatment of diseases that present similarly to asbestos-related diseases, and provide more reliable incidence and prevalence estimates to inform prevention strategies [8]. Increased diagnostic awareness among healthcare providers is necessary for asbestos-related disease diagnosis, particularly in the poorly resourced public healthcare facilities to which many South Africans present [36]. This study highlights the valuable role of autopsies in the detection of undiagnosed disease, monitoring of clinical practice and delivery of compensation.

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APPENDIX 3

Ndlovu N, Musenge E, Park SK, Girdler-Brown B, Richards G, Murray J. Four decades of pulmonary tuberculosis in deceased South African miners: trends and determinants. *Occupational and Environmental Medicine*, 2018; 75(11):767-75.

ORIGINAL ARTICLE

Four decades of pulmonary tuberculosis in deceased South African miners: trends and determinants

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ABSTRACT

Objective We investigated trends and determinants of pulmonary tuberculosis (PTB) in deceased South African miners.

Methods Statutory autopsies are performed on miners for occupational lung disease compensation, irrespective of cause of death. Data were extracted from the PATHAUT (Pathology Automation System) autopsy database. PTB trends were analysed and explanatory variables (year of autopsy, age at death, gold employment duration, silicosis and HIV) were evaluated using binary logistic regression modelling. Analyses were stratified by population group because of racial differences in socioeconomic status, employment patterns and access to facilities for autopsies. The analyses were segmented to represent the pre-HIV (1975–1989), rapid HIV spread (1990–2004) and antiretroviral therapy (2005–2014) periods.

Results The proportions of men with PTB at autopsy increased from 4.62% in 1975 to 27.18% in 2014 in black miners, and from 2.07% to 5.19% in white miners, with peaks in 2007 (43.12% and 9.51%, respectively). The magnitude and significance of adjusted ORs of determinants differed by population group and calendar period. PTB was largely associated with silicosis, increasing gold employment duration and year of autopsy (a surrogate for unmeasured confounders, such as unknown HIV status and tuberculosis transmission).

Conclusions Changes in PTB time trends and determinants reflect the complex social and political environment in which mining occurs. Silica dust reduction remains a key intervention for tuberculosis reduction, together with tuberculosis and HIV treatment and management. The autopsy data provide reliable information to monitor progress towards the achievement of industry and national targets to reduce tuberculosis.

INTRODUCTION

Mining activity is associated with increased tuberculosis (TB) incidence, prevalence and mortality in sub-Saharan Africa.¹ In studies of active and former South African miners conducted in the period 1991–2001, the prevalence of active and inactive TB based on self-reported history, chest radiography or bacteriology (sputum smear and culture) was between 19.4% and 35.2%.^{2–5} None of these studies used autopsy diagnosis or reported time trends. Using similar modalities of diagnosis in cohorts of gold miners studied from 1990 to 2004, the observed annual incidence rates ranged from

Key messages

What is already known about this subject?

- There is a triple epidemic of tuberculosis, silicosis and, in more recent decades, HIV infection in South African miners, but data to monitor tuberculosis trends are limited.

What are the new findings?

- This is the first study to show autopsy-diagnosed pulmonary tuberculosis (PTB) trends in both black and white South African miners spanning the pre-HIV (1975–1989), rapid HIV spread (1990–2004) and antiretroviral therapy roll-out (2005–2014) periods.
- Overall, PTB was five times higher in black compared with white miners and increased rapidly in the era of HIV to peak in 2007 in both population groups.
- Silicosis and duration of employment were important determinants of PTB, even in the era of HIV.

How might this impact on policy or clinical practice in the foreseeable future?

- Silica dust control remains key to tuberculosis control in the mining industry.
- Interventions to improve tuberculosis and HIV treatment and management are also important.

806 to 3821 cases per 100 000 person years,^{2,6,7} and were much higher than national estimates, which increased from 250 per 100 000 in 1996⁸ to 781 per 100 000 in 2004.⁹

The South African mining industry continues to rely heavily on migrant workers from rural areas and neighbouring countries. Oscillating migration of mine workers has created a unique social context which contributes to the disruption of TB detection and care, treatment failure, poor treatment outcomes, development of drug-resistant strains and transmission throughout the southern African region.^{10–11} This is exacerbated by overcrowded living conditions and work in dusty, poorly ventilated mine shafts. The Southern African Development Community committed itself to address TB and associated risk factors in miners and affected communities,¹² and The Global Fund to Fight AIDS, Tuberculosis and Malaria is supporting a coordinated regional response to reduce mining-related TB.¹³

Occupational exposures to crystalline silica have resulted in high silicosis prevalence among current (8.3%–19.9%)¹⁴ and former (22.0%–36.0%)^{15 16} South African gold miners. Both silica dust and silicosis are risk factors for pulmonary tuberculosis (PTB). The risk is three times higher in miners with silicosis compared with those without, increases with silicosis severity and is lifelong, continuing after dust exposure cessation.^{16 17}

Family separation, another consequence of migrancy, is associated with higher risk sexual practices and increased HIV incidence.¹¹ Since its advent in the 1980s, HIV prevalence in miners has increased to about 30%.¹⁸ In gold miners, HIV infection has been shown to increase the risk of TB fivefold.⁶ One study has demonstrated a multiplicative, 15-fold increase in PTB risk in silicotic, HIV-positive miners, compared with non-silicotic, HIV-negative miners.¹⁹

Under the apartheid regime, health services were fragmented along racial lines, with inferior services offered to the black population. Since 1994, the postapartheid government has aligned South Africa's TB control policies with those of the WHO.²⁰ Initiatives have included implementation of the Directly Observed Treatment, Short-course (DOTS) strategy from 1995, standardised reporting and improvements in TB control.²⁰ Interventions to reduce silica dust exposures and eliminate silicosis,²¹ and to improve the prevention, detection and treatment of HIV and TB,²² are in progress. Currently, many mines provide TB services for miners and have TB cure rates that meet or exceed the WHO target of 85%.²³ Even so, the TB epidemic continues.

Strengthening the reporting and surveillance of HIV, TB and silicosis is an essential component of TB control. The main sources of national TB statistics are the National Department of Health's Electronic TB Register, the National Health Laboratory Service's laboratory-based Corporate Data Warehouse, and Statistics South Africa's mortality statistics. Most of these sources provide recent data (from the 1900s onwards) and do not provide industry-specific TB data.

South African law recognises TB in miners as a compensable occupational lung disease, irrespective of HIV status. The law allows for examinations of the cardiorespiratory organs of deceased miners, regardless of the clinical cause of death and with consent from a near relative.²⁴ Cardiorespiratory organs are removed locally where the miner dies and preserved in formalin. The organs are submitted to the National Institute for Occupational Health (NIOH) in Johannesburg, where detailed autopsy examinations are performed. Since 1975, the pathological findings, demographic information and work histories have been captured on the PATHAUT (Pathology Automation System) database, which was developed primarily for compensation purposes but is also used extensively for research and surveillance.

From 1975 to 1991, the proportions of black gold miners with autopsy-diagnosed PTB and silicosis increased from 0.9% to 3.9% and from 9.3% to 12.8%, respectively.²⁵ These changes were explained by increasing age at death and duration of employment over time. Silicosis and year of autopsy were also significant determinants of PTB. A more recent study demonstrated that the proportion of silicosis which was six times lower in black miners (0.03) than white miners (0.18) in 1975 was 1.5 times higher (0.32 vs 0.22, respectively) by 2007.²⁶ The main determinants of silicosis were increasing age and duration of employment in both population groups, and year of autopsy in black miners. These silicosis trend analyses^{25 26} were restricted to men who died of external (unnatural) causes to reduce potential bias arising from increased TB-associated mortality in miners with silicosis.

Our study investigated autopsy-diagnosed PTB trends and determinants in black and white South African miners over a 40-year period (1975–2014). Unlike the previous trend analyses,^{25 26} we included all autopsies regardless of the cause of death, that is, both external and non-external (natural) causes, and all commodity groups, not only gold. The data were analysed by population group because of racial differences in the types and duration of mining employment, intensity of dust exposure, living conditions and access to autopsy examination. Generally, black miners are employed in occupations such as stoping and drilling, which have higher silica dust exposures than the supervisory and maintenance positions held by white miners. Historically, black miners worked short-term contracts, while white miners worked as career miners. Policy changes in the last three decades have allowed black miners to work long-term contracts. This has resulted in increased ages, lengths of employment, cumulative silica exposures and silicosis prevalence.²⁶ These factors, together with overcrowded living conditions in hostels or shacks and high HIV prevalence, have increased TB risk in black miners. Furthermore, there is inadequate provision of autopsy services in the rural areas to which many black miners return after leaving the industry.²⁷

METHODS

Study population

The study population comprised male black and white miners whose cardiorespiratory organs were examined at the NIOH from 1975 to 2014.

Exposure characteristics

In the absence of dust measurements, cumulative years of service in the gold mining industry (gold employment duration) were used as proxy measures for cumulative silica dust exposure.

Except where stated otherwise, miners were categorised according to the mining commodity in which they worked for the longest time. Commodity refers to the type of mineral mined.

Disease diagnosis and definitions

Examinations of the cardiorespiratory organs are performed by experienced pathologists using macroscopic and microscopic procedures, which did not change over the study period.

The pathological diagnosis of PTB was based on the presence of microscopic epithelioid granulomas associated with caseous necrosis in the lungs or regional glands, after exclusion of other causes. Silicosis was defined as the presence of palpable silicotic nodules on macroscopic examination of the lung, confirmed by the presence of microscopic silicotic islets histologically.

Clinical causes of death were obtained from death certificates and other documents submitted to the NIOH. We defined HIV in cases where clinicians and/or NIOH pathologists stated HIV or any of the following AIDS-related diseases as a cause of death: Kaposi sarcoma, cryptococcal pneumonitis, *Pneumocystis jirovecii* pneumonia, cytomegalovirus pneumonitis or cryptococcal meningitis. Despite TB being an AIDS-related disease, it was excluded from the definition of HIV because it was the outcome of interest.

Statistical analyses

Data management and analyses were performed using SAS V.9.3 and Stata V.14 software. Disease proportions are expressed as percentages. Student's t-test and the χ^2 test were used to determine differences between means and frequencies, respectively. Linear trends were determined using the Cochran-Armitage

trend test for proportions and linear regression for continuous variables. Statistical significance was defined at $p < 0.05$.

The analyses were segmented according to phases of the HIV epidemic. Following the first reported cases of HIV/AIDS in South Africa in 1982,²⁸ antenatal surveys showed an explosive spread of HIV from 0.8% in 1990 to approximately 29.0% in 2007.²⁹ In 2004, the national roll-out of antiretroviral therapy (ART) was initiated.³⁰ Our analyses reflect the pre-HIV and early HIV (1975–1989), rapid HIV spread (1990–2004), and ART (2005–2014) periods.

Binary logistic regression models were used to estimate the association of PTB (0=absent, 1=present) with explanatory variables. The initial selection of explanatory variables was based on a priori knowledge. Variables with crude ORs of $p < 0.25$ in the univariable logistic analysis were included in the full models for black miners. The same variables were included in the models for white miners to allow for comparison and because the distribution of significant variables and categories within variables differed across calendar periods. In the initial models, we included silicosis severity categorised as none, occasional, few, moderate and large numbers of nodules. In both population groups, the adjusted ORs (AORs) were significant and were highest in the group with moderate silicosis and lowest in those with marked silicosis. In the absence of a clear trend between PTB and silicosis severity, silicosis was included as a binary variable in the final models. The explanatory variables in the initial multivariable models were population group (black or white), year of autopsy, age at death, gold mining duration, silicosis (0=absent, 1=present) and HIV (0=absent, 1=present). The final models were stratified by population group because of effect modification and were segmented as explained above. HIV was excluded from the 1975–1989 models because the first case of HIV in our study population was recorded in 1987 and there were few cases of HIV ($n=4$) before 1990.

Interaction terms for year and age, year and duration, age and duration, and silicosis and HIV were included in the initial models. Although some of the interaction terms were statistically significant, none were included in the final models because little interaction was demonstrated in interaction plots and their inclusion made little difference to the AORs. In the interests of parsimony, these interaction terms were omitted from the models.

Postregression analyses were performed using the Hosmer-Lemeshow goodness-of-fit test. This test was selected rather than Pearson's goodness-of-fit test because more than 25% of the expected cells contained fewer than five cases. In this test, p values of < 0.05 indicate poor fit, that is, that the observed and expected numbers of PTB cases and non-cases differ more than expected by chance.

To determine if excluded cases biased our findings, we used multiple iterative chained equations to create a data set containing 10 imputations of missing values for age and employment duration for black miners. The mechanism of missingness was defined as missing at random. The final logistic regression models were applied to the imputed data set.

RESULTS

Study population

The study population consisted of 83 972 deceased miners after exclusion of groups with few cases (female miners and population groups other than black or white) and cases with missing age or employment information (table 1).

Table 1 Numbers of cases on the PATHAUT (Pathology Automation System) database and reasons for exclusions

Exclusion criteria	Excluded	Remaining
All cases (1975–2014)		101 167
Female*	369	109 798
Race not black or white	1936	107 862
No age at death or invalid age (<16 or >100 years)	3937	103 925
Commodity not stated	2506	101 419
Employment duration, 0 or missing	17 447	83 972
Total	26 195	

*Data available from 2005.

There were 53 248 (63.41%) autopsies in black and 30 724 (36.59%) in white miners (table 2). Black miners were younger and had significantly shorter periods of employment. Most blacks were active miners (79.20%), whereas most whites were former (86.93%) miners. The majority were gold miners (77.98%). The crude proportion of silicosis in black miners was 0.62 that of white miners, and the crude proportion of HIV was 48.96 times higher in black miners.

There were 7389 cases of HIV. Of these, 4705 were defined using clinical causes of death and 2684 cases using a pathological cause of death. Of the HIV-negative cases, 5837 had neither a clinical nor a pathological cause of death stated.

Pulmonary tuberculosis

Autopsy-diagnosed PTB was detected in 9980 (11.88%) miners and was five times higher in black miners compared with white miners (table 2). The proportions of PTB by calendar period and population group are provided in online supplementary table S1. The proportions of PTB in black and white miners with autopsy-diagnosed silicosis were 31.34% ($n=2233$) and 6.44%

Table 2 Characteristics of the study population, by population group (1975–2014)

Characteristics	Black n=53 248	White n=30 724	P values
Age (years), mean±SD	39.73±11.27	61.70±13.98	<0.0001
Employment duration (year), mean±SD	10.51±8.11	24.95±8.90	<0.0001
Employment status*, n (%)			
Current miner	5385 (79.20)	473 (13.07)	<0.0001
Former miner	1414 (20.80)	3147 (86.93)	
Commodity†, n (%)			
Gold	41 308 (77.58)	24 170 (78.67)	<0.0001
Platinum	6369 (11.96)	1087 (3.54)	
Coal	3414 (6.41)	1945 (6.33)	
Asbestos	1178 (2.21)	741 (2.41)	
Other‡	979 (1.84)	2781 (9.05)	
Any gold service§	43 506 (81.70)	26 203 (85.29)	
Silicosis, n (%)	7125 (13.38)	6817 (22.19)	<0.0001
HIV, n (%)	7302 (13.71)	87 (0.28)	<0.0001
Pulmonary tuberculosis, n (%)	8977 (16.8)	1003 (3.26)	<0.0001

*Data available from 2007.

†Commodity is defined as the mining industry in which miners worked the longest.

‡Includes aluminium, antimony, cement, chrome, construction, environmental asbestos, Eskom, fluorspar, phosphate, industry, lead, lime, mica, minerals, nickel, quarry, refinery, railways, silica, steel, tin, uranium, vanadium, works and zinc.

§Any gold service is defined as employment for at least 0.1 years in the gold mining industry.

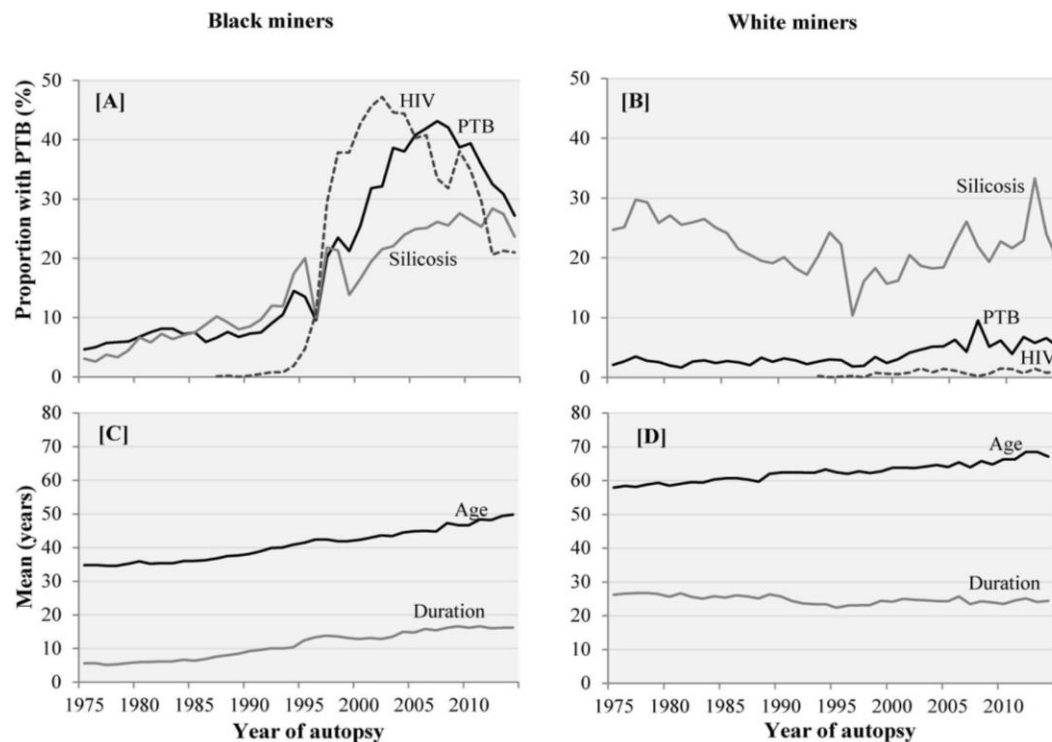


Figure 1 Crude proportions of pulmonary tuberculosis (PTB), silicosis and HIV (A and B), and mean ages and mean employment duration (C and D) in black and white miners from 1975 to 2014.

($n=439$), respectively. Silicosis severity was similar in both population groups and was mild in 1816 (67.96%), moderate in 649 (24.29%) and marked in 153 (5.73%) cases.

In black and white miners with HIV, 35.89% ($n=2621$) and 10.34% ($n=9$) had PTB, respectively. Among those who were HIV-negative, PTB was present in 13.83% ($n=6356$) of black and 3.24% ($n=994$) of white men.

The proportions of PTB increased across the three calendar periods and the distribution of PTB within each variable differed by population group (see online supplementary table S1).

Trends

All linear time trends were significant ($p<0.001$). Disease trends are shown in figure 1A,B. The lower than expected proportions of PTB and silicosis in 1996 were due to incomplete data entry on the PATHAUT database. In black autopsied miners, PTB increased from 4.62% in 1975, peaked at 43.12% in 2007 and decreased to 27.18% in 2014; silicosis increased from 3.03% to 23.62% over the study period; and HIV increased rapidly from below 1.00% from 1987 to 1993, to a peak in 2002 (47.20%), and then decreased to 20.96% in 2014.

In white autopsied miners, the proportions of PTB fluctuated between 2.00% and 3.00% from 1975 to 2000, increased to 9.51% in 2007 and decreased to 5.19% in 2014. The proportions of silicosis declined from 24.88% in 1975 to 19.51% in 2014. The proportions of HIV were low (range: 0.12%–1.49%) and increased over the study period.

Figure 1C,D illustrates increases in the mean ages of deceased miners from 34.71 ± 11.21 years in 1975 to 49.75 ± 11.27 years in 2014 in black men, and from 57.89 ± 13.52 years to 67.05 ± 12.21 years in white men. The mean duration of employment (all mining commodities) increased from 5.66 ± 5.73 years

to 17.17 ± 9.72 years in black miners, and decreased from 26.16 ± 11.35 years to 24.38 ± 10.77 years in white miners.

Determinants of PTB trends

The goodness-of-fit test p values were $p<0.0001$ for the 1990–2004 and 2005–2014 models for black miners, and $p=0.042$ for the 1990–2004 model for white miners. The modelling process was repeated in a 25% random sample of the study population, and good fit ($p>0.05$) was obtained for the models in each calendar period.

Tables 3 and 4 present the unadjusted and adjusted ORs for PTB by calendar period in black and white miners, respectively.

1975–1989

In black miners, silicosis, increasing age and year of autopsy group were significant predictors of PTB in the 1975–1989 calendar period. The results for duration of employment are discussed ahead. The odds of PTB in miners with silicosis were three times higher (AOR=3.08, 95% CI 2.65 to 3.57) than in non-silicotic miners. Compared with miners younger than 30 years of age, the odds of PTB increased with increasing age, from AOR=1.33 (95% CI 1.15 to 1.54) in the age group 30–39 years to AOR=2.47 (95% CI 1.92 to 3.18) in those aged 60 years and older. In this calendar period, the AORs of PTB were only significantly elevated for miners who died in 1980–1984 (AOR=1.31, 95% CI 1.15 to 1.49) using 1975–1979 as the reference group.

In white miners, silicosis (AOR=2.21, 95% CI 1.72 to 2.76) was a significant determinant of PTB. Compared with miners with no gold mining service, the odds of PTB were also significantly elevated in miners with 10–19 and 20–29 years of

Table 3 Unadjusted OR and adjusted ORs (AORs) for pulmonary tuberculosis in black miners at autopsy, by calendar period

Variable	1975–1989				1990–2004				2005–2014				P values*	
	n	OR (95% CI)	P values*	AOR (95% CI)	P values*	n	OR (95% CI)	P values*	AOR (95% CI)	P values*	n	OR (95% CI)		P values*
Year of autopsy														
1975–1979	440	Reference		Reference		440	Reference	128	Reference		440	Reference		Reference
1980–1984	601	1.42 (1.25 to 1.61)	<0.001	1.31 (1.15 to 1.49)	<0.001									
1985–1989	580	4.28 (1.12 to 1.45)	<0.001	1.09 (0.96 to 1.25)	0.182									
1990–1994						673	1.84 (1.62 to 2.08)	<0.001	1.62 (1.42 to 1.84)	<0.001				
1995–1999						1010	3.56 (3.16 to 4.00)	<0.001	2.71 (2.39 to 3.08)	<0.001				
2000–2004						2163	8.60 (7.71 to 9.59)	<0.001	5.95 (5.25 to 6.73)	<0.001				
2005–2009											2303	12.24 (10.96 to 13.66)	<0.001	9.79 (8.58 to 11.16)
2010–2014											1207	8.88 (7.89 to 10.00)	<0.001	7.78 (6.78 to 8.93)
Age (years)														
<30	367	Reference		Reference		196	Reference		Reference		117	Reference		Reference
30–39	425	1.46 (1.26 to 1.68)	<0.001	1.33 (1.15 to 1.54)	<0.001	1193	2.54 (2.24 to 2.88)	<0.001	1.40 (1.22 to 1.61)	<0.001	761	3.59 (3.09 to 4.16)	<0.001	1.33 (1.13 to 1.58)
40–49	441	2.30 (1.99 to 2.65)	<0.001	1.81 (1.55 to 2.11)	<0.001	1689	3.83 (3.39 to 4.34)	<0.001	1.58 (1.38 to 1.82)	<0.001	1557	6.22 (5.40 to 7.16)	<0.001	1.30 (1.09 to 1.54)
50–59	293	2.88 (2.46 to 3.39)	<0.001	2.24 (1.88 to 2.66)	<0.001	685	3.25 (2.84 to 3.73)	<0.001	1.44 (1.23 to 1.68)	<0.001	927	5.37 (4.63 to 6.23)	<0.001	1.00 (0.83 to 1.20)
≥60	95	3.16 (2.49 to 4.01)	<0.001	2.47 (1.92 to 3.18)	<0.001	83	2.46 (1.96 to 3.10)	<0.001	1.39 (1.09 to 1.78)	<0.001	148	2.99 (2.43 to 3.68)	<0.001	0.65 (0.51 to 0.82)
Gold employment duration (years)														
0	250	Reference		Reference		567	Reference		Reference		826	Reference		Reference
<10	936	0.98 (0.85 to 1.13)	0.806	1.05 (0.88 to 1.18)	0.832	1113	0.70 (0.63 to 0.77)	<0.001	0.97 (0.87 to 1.09)	0.637	718	0.55 (0.50 to 0.61)	<0.001	1.13 (1.01 to 1.27)
10–19	340	1.72 (1.45 to 2.04)	<0.001	1.10 (0.92 to 1.32)	0.300	1634	1.34 (1.21 to 1.47)	<0.001	1.00 (0.89 to 1.11)	0.934	970	1.84 (1.66 to 2.04)	<0.001	1.46 (1.29 to 1.64)
≥20	95	2.08 (1.62 to 2.67)	<0.001	1.05 (0.80 to 1.36)	0.733	532	1.64 (1.45 to 1.86)	<0.001	0.99 (0.86 to 1.14)	0.921	996	2.41 (2.17 to 2.69)	<0.001	1.43 (1.26 to 1.63)
Silicosis														
Absent	1311	Reference		Reference		2960	Reference		Reference		2473	Reference		Reference
Present	310	4.15 (3.62 to 4.76)	<0.001	3.08 (2.65 to 3.57)	<0.001	886	2.32 (2.13 to 2.52)	<0.001	1.54 (1.4 to 1.69)	<0.001	1037	2.89 (2.65 to 3.15)	<0.001	1.34 (1.20 to 1.49)
HIV														
Absent	1621					2477	Reference		Reference		2258	Reference		Reference
Present	–					1369	3.28 (3.04 to 3.53)	<0.001	1.37 (1.25 to 1.49)	<0.001	1252	3.06 (2.81 to 3.32)	<0.001	1.17 (1.07 to 1.28)

χ^2 tests for trend were significant ($p < 0.001$) for year, age and gold employment duration groups in each calendar period.

*Wald test p values.

Table 4 Unadjusted (OR) and adjusted ORs (AORs) for pulmonary tuberculosis in white miners at autopsy, by calendar period

Variable	1975–1989				1990–2004				2005–2014			
	n	OR (95% CI)	P values*	AOR (95% CI)	n	OR (95% CI)	P values*	AOR (95% CI)	n	OR (95% CI)	P values*	AOR (95% CI)
Year of autopsy												
1975–1979	128	Reference		Reference	128	Reference		Reference	128	Reference		Reference
1980–1984	119	0.83 (0.64 to 1.07)	0.149	0.84 (0.65 to 1.08)	0.173							
1985–1989	132	0.96 (0.75 to 1.23)	0.742	1.02 (0.80 to 1.31)	0.856							
1990–1994					123	1.02 (0.79 to 1.30)	0.907	1.12 (0.87 to 1.45)	0.370			
1995–1999					91	0.90 (0.69 to 1.18)	0.447	1.03 (0.78 to 1.36)	0.855			
2000–2004					132	1.64 (1.28 to 2.10)	<0.001	1.87 (1.45 to 2.42)	<0.001			
2005–2009									157	2.38 (1.87 to 3.02)	<0.001	2.74 (2.14 to 3.52)
2010–2014									121	2.10 (1.63 to 2.70)	<0.001	2.46 (1.87 to 3.22)
Age (years)												
<50	55	Reference		Reference	59	Reference		Reference	45	Reference		Reference
50–59	66	1.23 (0.86 to 1.76)	0.265	1.02 (0.70 to 1.49)	0.921	1.41 (1.06 to 1.89)	0.020	1.26 (0.93 to 1.71)	0.136	1.32 (0.96 to 1.82)	0.089	0.98 (0.70 to 1.38)
60–69	135	1.71 (1.24 to 2.34)	0.001	1.30 (0.92 to 1.84)	0.138	1.13 (0.85 to 1.50)	0.389	0.69 (0.50 to 1.27)	0.677	1.13 (0.83 to 1.54)	0.434	0.76 (0.54 to 1.05)
≥70	123	1.99 (1.44 to 2.74)	<0.001	1.40 (0.97 to 2.00)	0.071	1.13 (0.85 to 1.50)	0.395	0.85 (0.62 to 1.16)	0.304	1.02 (0.75 to 1.40)	0.888	0.53 (0.37 to 0.76)
Gold employment duration (years)												
0	27	Reference		Reference	42	Reference		Reference	35	Reference		Reference
<10	35	1.17 (0.71 to 1.94)	0.541	1.22 (0.73 to 2.03)	0.447	1.34 (0.94 to 1.91)	0.110	1.30 (0.90 to 1.87)	0.156	1.10 (0.73 to 1.67)	0.654	1.03 (0.68 to 1.57)
10–19	59	1.94 (1.23 to 3.07)	0.005	1.67 (1.05 to 2.65)	0.030	1.33 (0.94 to 1.87)	0.108	1.10 (0.77 to 1.56)	0.601	1.44 (1.00 to 2.07)	0.052	1.18 (0.81 to 1.71)
20–29	105	2.52 (1.64 to 3.86)	<0.001	1.88 (1.22 to 2.91)	0.004	1.65 (1.19 to 2.27)	0.002	1.18 (0.84 to 1.65)	0.338	1.67 (1.18 to 2.35)	0.003	1.22 (0.85 to 1.75)
≥30	153	2.14 (1.41 to 3.23)	<0.001	1.39 (0.90 to 2.14)	0.137	1.24 (0.90 to 1.70)	0.194	0.89 (0.63 to 1.25)	0.489	1.13 (0.80 to 1.60)	0.498	0.96 (0.66 to 1.40)
Silicosis												
Absent	210	Reference		Reference	212	Reference		Reference	142	Reference		Reference
Present	169	2.53 (2.06 to 3.11)	<0.001	2.21 (1.77 to 2.76)	<0.001	2.78 (2.31 to 3.36)	<0.001	3.15 (2.56 to 3.86)	<0.001	3.04 (2.48 to 3.71)	<0.001	3.59 (2.89 to 4.48)
HIV												
Absent	379	Reference		Reference	343	Reference		Reference	272	Reference		Reference
Present	–				3	2.37 (0.73 to 7.70)	0.149	1.83 (0.55 to 6.03)	0.323	3.62 (1.52 to 8.62)	0.004	2.53 (1.03 to 6.22)

χ^2 tests for trend were significant ($p<0.01$) for year of autopsy, age and gold duration groups with the exception of year in 1975–1989 ($p=0.320$) and 2005–2014 ($p=0.316$); age in 1990–2004 ($p=0.122$); and gold employment duration in 1990–2004 ($p=0.059$).

*Wald test p values.

employment in gold mines (AOR=1.67, 95%CI 1.05 to 2.65, and AOR=1.88, 95%CI 1.22 to 2.91, respectively).

1990–2004

In 1990–2004, increasing year of autopsy was the most significant determinant of PTB in black miners. The AORs for silicosis and age were significant but lower than in 1975–1984. The pattern of increasing AORs with increasing age observed in the previous calendar period (1975–1989) was not observed. The AOR for HIV was also significant (AOR=1.37, 95%CI 1.25 to 1.49).

In white miners, the AORs for PTB in miners with silicosis were significant and higher than in the previous calendar period. Year of autopsy was significant in 2000–2004.

2005–2014

For black miners, the AORs for PTB continued to increase with increasing year of autopsy and were highest in 2005–2009 (AOR=9.79, 95%CI 8.58 to 11.16). The AORs were significantly elevated and increased with increasing gold employment duration. The AORs for PTB were significantly elevated in black miners aged 30–49 years, were not significant in the age group 50–59 years and were significantly reduced in those aged 60 years and older (AOR=0.65, 95%CI 0.51 to 0.82). The AORs for PTB in miners with silicosis and HIV were significantly elevated but were lower than in the previous calendar period.

In white miners, the AORs for PTB were significantly elevated in miners with silicosis and in each year category, and were higher than in the previous calendar period. The AOR for PTB in the HIV-positive was significantly higher than that in the HIV-negative (2.53, 95%CI 1.03 to 6.22) and was higher than in black miners (AOR=1.17, 95%CI 1.07 to 1.28). However, the overlap in CIs indicates that the difference by population group was not statistically significant.

Duration of employment

To further explore the association between PTB and duration of employment, logistic regression modelling was repeated excluding the silicosis variable (model 2). In these models, the AORs for PTB increased with increasing duration (see online supplementary tables S2 and S3) and were significantly elevated in miners with at least 10 years of gold mining employment in 1975–1989 and 2005–2014, but not in 1990–2004.

Missing data

Of the 26 195 excluded cases (table 1), 24 229 had missing values: 19 727 (75.31%) were black and 4502 (17.19%) were white miners. There were 4267 (16.29%) cases with missing age, 3309 (12.63%) with missing commodity and 21 898 (83.60%) with missing employment duration. Among the excluded cases, 3008 (13.77%) miners had PTB. The AORs and standard errors (SEs) were similar in models using complete cases or imputed data for black miners (see online supplementary table S4).

DISCUSSION

This study investigated PTB diagnosed pathologically at autopsy in South African miners over four decades of major political, legislative and policy reforms and economic changes in the industry. During this period neither the statutory criteria for access to autopsy compensation nor the pathological criteria for the diagnosis of PTB and silicosis changed. Our main findings were that even before the advent of HIV, the proportions of miners with PTB were high; were five times higher in black

compared with white miners; increased over time in both black and white miners; and the magnitude and distribution of determinants of the disease differed by population group and calendar period.

Black miners

Pre-HIV period

In 1975–1989, the proportions of PTB in black miners were low but increased over time. During this period, mine dust levels did not change,³¹ silicosis rates in black miners increased²⁶ and two important work practice changes were implemented. In 1975, workforce stabilisation, which allowed experienced black miners to work long-term contracts, was introduced, and from 1983 miners who completed TB treatment successfully were permitted to resume underground work.¹¹ Prior to this, miners with TB were permanently excluded from working in mines or in dusty surface work. Hence, TB cases in the PATHAUT database prior to 1983 were largely men who had either not been clinically diagnosed or who were awaiting discharge from employment. These policies resulted in an older workforce and increased cumulative dust exposures, which in turn increased silicosis and PTB risks.

In this early period, we could not compare observed PTB trends with those in other South African populations as there are no reliable mortality data.³² Silicosis, increasing age and increasing gold mining employment duration were the main PTB determinants in black miners and reflect industry changes at this time.

Rapid HIV spread period

In 1990–2004, the steep increase in the proportions of black miners with PTB at autopsy coincided with the initiation and rapid spread of HIV²⁹ and HIV-related mortality.³³ Increasingly, the year of autopsy was the most significant predictor of PTB in black miners. Although statistically significant, the AOR (AOR=1.37) for HIV was much lower than expected. The definition of HIV that was used is problematic and is discussed ahead. Year of autopsy possibly subsumed the effects of HIV as it is a surrogate for unmeasured confounders. These include the unknown HIV status of many autopsied miners and thus possible misclassification of HIV-negative cases and ongoing and onward transmission of *Mycobacterium tuberculosis* to both HIV-negative and HIV-positive miners because of high TB prevalence.³⁴

ART period

The peaks in PTB proportions that we observed in 2007 for both population groups occurred around the same time as peak national TB mortality. Pillay-van Wyk *et al*³² reported combined HIV/AIDS and TB mortality trends based on death notifications from 1997 to 2012. Both the crude and age-adjusted trends increased rapidly from 1997 to peaks in 2006 and declined thereafter. Lim *et al*,³⁵ using data from various sources and autopsies, observed a similar pattern of mortality in platinum miners from 1992 to 2012, with a peak in 2003. The declines in mortality observed after the peaks are associated with the roll-out of ART.

In black miners, year of autopsy continued to be the most significant predictor of PTB in 2005–2014. Age increased the likelihood of PTB in miners aged 30–49 years. However, no association was observed among those aged 50–59 years probably because of a healthy worker effect caused by older miners leaving the industry due to ill-health. The reduced odds of PTB among black miners older than 60 years are explained by selection bias due to poor autopsy uptake by former black miners.²⁷

Gold mining employment duration was a significant determinant of PTB in black miners in 2005–2014. A dose-related association between increasing cumulative silica dust exposure and PTB risk has been described.¹⁷ However, in a recent study of copper miners, the association was only significant in the highest exposure group.³⁶

White miners

Few studies have investigated PTB in white South African miners. In a cohort of white gold miners, no PTB deaths were recorded in men who died in the 1970s.³⁷ In another cohort, 115 of 2255 (5.1%) miners developed PTB over a 25-year period (1968–1971 to 1995).¹⁷ We observed that the proportions of PTB in white miners remained low well into the period of rapid HIV spread but doubled from 2000 to 2007.

Silicosis was the most important determinant of PTB in white miners throughout the study. The significantly elevated odds of PTB by year group from 2000 to 2004 onwards suggest undisclosed HIV infection in white miners as well as onward transmission of TB to HIV-negative miners.³⁴ However, the higher than expected AORs for PTB and HIV in white miners in 2005–2014 (AOR=2.53 vs AOR=1.37 in black miners) may be an anomaly arising from the small numbers of HIV-positive white miners with PTB.

In 2003, voluntary industry milestones were set to reduce 95% of all respirable crystalline silica dust measurements to below the occupational exposure limit (OEL) of 0.1 mg/m³ and to ensure no new cases of silicosis in novice miners who entered the industry after 2008.²¹ Updated milestones have reduced the OEL to 0.05 mg/m³ and, in line with the latest national TB guidelines,²² aim to reduce TB incidence to the national rate or below, and improve access to HIV counselling, testing and ART, and health education and communication by 2024.³⁸

Strengths and limitations

A major limitation of this study is that the autopsy data do not represent all deceased South African miners due to inadequate provision of autopsy services for former black miners in labour sending areas.²⁷ This was exacerbated by the overall decline in mine employment, which may partially explain the annual decreases in autopsy numbers from the late 1980s. Furthermore, in the era of HIV, increasing numbers of sick miners, many of whom would have had TB, left the mines and had limited access to autopsy services.¹⁸ Hence, PTB was probably underestimated.

Other limitations are related to the use of routine, administrative data. The PATHAUT database provides information for compensation, which requires limited demographic and exposure information. The unavailability of dust measurements in the database necessitated the use of an imprecise proxy measure, duration of employment, in our analyses. Increasing gold employment duration was an important determinant of PTB. Our models show that silicosis diluted the effect of duration. This highlights the complexity of disentangling the biological effects of these risk factors. The insignificant AORs for PTB and duration in 1990–2004 might be explained by the dramatic spread of the HIV epidemic in this period.

The definition of HIV is an important limitation of this study. Therefore, the AORs for PTB and HIV should be interpreted with caution. HIV status is not required for the determination of compensation for PTB and is often not stated on the death certificate. The exclusion of TB deaths from the definition of HIV and the 5837 cases which were classified as HIV-negative because no cause of death was stated may have resulted in

the underestimation of HIV. Although the proportions of HIV in our study were comparable with the 30% prevalence rates reported in living miners,^{2,18} we expected a higher proportion of HIV in deceased miners. Misclassification of some HIV negative cases might have also biased the estimates in our models.

A potential limitation was the large number of cases with missing information which were excluded in our analyses. However, the excluded cases did not bias our findings as similar estimates were obtained in models using complete cases or imputed data. Ideally, standardisation of PTB by, for example, age, population group and social class, would have been appropriate. However, there were no appropriate external population data available for standardisation, but we have demonstrated that in more recent years the trends of PTB in this study were comparable with TB trends in the general South African population.³²

A strength of the study was the diagnosis of PTB based on pathological findings at autopsy, which have higher specificity and sensitivity than clinical diagnoses.³⁹ Furthermore, the pathological diagnostic criteria were constant throughout the study period and thereby enabled comparisons over time. In contrast to other South African studies that reported TB trends from the 1990s onwards, the availability of long-term data enabled us to analyse trends beginning well before the era of HIV.

CONCLUSIONS

Despite its limitations, the PATHAUT database provides the longest standing source of surveillance information for PTB in the South African mining industry and general population. Although PTB in miners has declined since the initiation of ART, the proportions are still high and indicate continued disease transmission. In our analyses, the major determinants of PTB in the most recent calendar period were year of autopsy, long duration of employment in gold mining, silicosis and HIV. Our findings underscore the complexity of the mining environment and provide clear indications of areas of intervention required to achieve current targets to reduce TB and to address its determinants. Silicosis and gold mining duration are important determinants of PTB, even in the era of HIV; therefore silica dust control remains key to TB control in the mining industry. Interventions to improve TB and HIV treatment and management are also important. The autopsy data provide reliable information for monitoring the outcomes of interventions to reduce TB in the mining industry.

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Competing interests None declared.

Patient consent Next of kin consent obtained.

Ethics approval This study was approved by the University of the Witwatersrand Human Research Ethics Committee (clearance certificate number, M120236) and the University of Michigan Health Sciences and Behavioural Sciences Institutional Review Board (HUM00069012).

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SUPPLEMENTARY MATERIAL

FOUR DECADES OF PULMONARY TUBERCULOSIS IN DECEASED SOUTH AFRICAN MINERS: TRENDS AND DETERMINANTS

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Table S1 Crude group-specific proportions of PTB in miners at autopsy, by calendar period and population group (1975-2014)

Characteristic	Black miners						Characteristic	White miners					
	1975-1989 N=24,570		1990-2004 N=19,529		2005-2014 N=9,149			1975-1989) N=14,927		1990-2004 N=11,117		2005-2014 N=4,680	
	n	PTB (n, %)	n	PTB (n, %)	n	PTB (n, %)		n	PTB (n, %)	n	PTB (n, %)	n	PTB (n, %)
Year of autopsy							Year of autopsy						
1975-1979	8,096	440 (5.43)					1975-1979	4,682	128 (2.73)				
1980-1984	7,979	601 (7.53)					1980-1984	5,218	119 (2.28)				
1985-1989	8,495	580 (6.83)					1985-1989	5,027	132 (2.63)				
1990-1994			7,041	673 (9.56)			1990-1994			4,434	123 (2.77)		
1995-1999			5,948	1,010 (16.98)			1995-1999			3,689	91 (2.47)		
2000-2004			6,540	2,163 (33.07)			2000-2004			2,994	132 (4.41)		
2005-2009					5,578	2,303 (41.29)	2005-2009					2,507	157 (6.26)
2010-2014					3,571	1,207 (33.80)	2010-2014					2,173	121 (5.57)
Age (years)							Age (years)						
<30	8,945	367 (4.10)	1,941	196 (10.10)	330	117 (35.45)	<50	3,258	55 (1.69)	1,889	59 (3.12)	526	45 (8.56)
30-39	7,238	425 (5.87)	6,533	1,193 (18.26)	1,787	761 (42.59)	50-59	3,196	66 (2.07)	2,170	85 (3.92)	877	67 (7.64)
40-49	4,922	441 (8.96)	7,134	1,689 (23.68)	3,643	1,557 (42.74)	60-69	4,742	135 (2.85)	3,135	93 (2.97)	1,297	82 (6.32)
50-59	2,667	293 (10.99)	3,368	685 (20.34)	2,654	927 (34.93)	≥70	3,731	123 (3.30)	3,923	109 (2.78)	1,980	84 (4.24)
≥60	798	95 (11.90)	553	83 (15.01)	735	148 (20.14)							
Commodity							Commodity						
Gold	19,387	1,317 (6.79)	16,128	3,150 (19.53)	5,793	2,491 (43.00)	Gold	12,123	336 (2.77)	8,579	282 (3.29)	3,468	232 (6.69)
Platinum	2,465	174 (7.06)	664	89 (13.40)	285	63 (22.11)	Platinum	859	9 (1.05)	741	11 (1.48)	345	7 (2.03)
Asbestos	346	32 (9.25)	243	42 (17.28)	589	140 (23.77)	Asbestos	321	13 (4.05)	316	15 (4.75)	104	6 (5.77)
Coal	1,928	71 (3.68)	2,207	528 (23.92)	2,234	768 (34.38)	Coal	327	3 (0.92)	450	13 (2.89)	310	15 (4.84)
Other	444	27 (6.08)	287	37 (12.89)	248	48 (19.35)	Other	1,297	18 (1.39)	1,031	25 (2.42)	453	18 (3.97)
Gold employment duration (years)							Gold employment duration (years)						
0	4,216	250 (5.93)	2,819	567 (20.11)	2,747	826 (30.07)	0	1,985	27 (1.36)	1,820	42 (2.31)	840	35 (4.17)
<10	16,055	936 (5.83)	6,733	1,113 (16.53)	1,917	718 (37.45)	<10	2,203	35 (1.59)	1,810	61 (3.37)	646	26 (5.26)
10-19	3,481	340 (9.77)	7,772	1,634 (21.02)	2,141	970 (45.31)	10-19	2,262	59 (2.61)	2,086	74 (3.55)	933	70 (7.50)
≥20	818	95 (11.61)	2,205	532 (24.13)	2,344	996 (42.49)	20-29	3,128	105 (3.36)	2,434	88 (3.62)	1,162	82 (7.06)
							≥30	5,349	153 (2.86)	2,967	81 (2.73)	1,099	57 (5.19)
Silicosis absent	23,024	1,311 (5.69)	14,966	2,871 (19.18)	5,858	2,108 (35.98)	Silicosis absent	11,249	210 (1.87)	8,311	191 (2.30)	3,171	121 (3.82)
Silicosis present	1,546	310 (20.05)	3,201	886 (27.68)	2,378	1,037 (43.61)	Silicosis present	3,678	169 (4.59)	2,051	134 (6.53)	1,088	136 (12.5)
HIV absent	24,566	1,621 (6.60)	13,750	2,379 (17.24)	5,419	1,972 (36.39)	HIV absent	14,927	379 (2.54)	10,128	313 (3.09)	4,110	239 (5.83)
HIV present	4	-	4,294	1,369 (31.88)	3,004	1,252 (41.68)	HIV present	0	-	44	3 (6.82)	43	6 (13.95)
PTB present	24,570	1,621 (6.60)	19,529	3,846 (19.69)	9,149	3,510 (38.36)	PTB present	14,927	379 (2.54)	11,117	346 (3.11)	4,680	278 (5.94)

Trends for PTB by age group and gold employment duration were significant ($p < 0.001$) for black miners in the three calendar periods and for white miners except for age group in 1990-2004 ($p = 0.122$) and gold employment duration in 1990-2004 ($p = 0.588$) and 2005-2014 ($p = 0.181$).

Table S2 Adjusted odds ratios (AORs) for PTB in models with and without silicosis in black miners, by calendar period

Variable	1975-1989					1990-2004					2005-2014				
	Model 1 Model with silicosis			Model 2 Model without silicosis		Model 1 Model with silicosis			Model 2 Model without silicosis		Model 1 Model with silicosis			Model 2 Model without silicosis	
	n	AOR (95%CI)	p-value	AOR (95%CI)	p-value	n	AOR (95%CI)	p-value	AOR (95%CI)	p-value	n	OR (95%CI)	p-value	AOR (95%CI)	p-value
Year of autopsy															
1975-1979	440	Reference		Reference		440	Reference	128	Reference		440	Reference	128	Reference	
1980-1984	601	1.31 (1.15, 1.49)	<0.001	1.38 (1.22, 1.57)	<0.001										
1985-1989	580	1.09 (0.96, 1.25)	0.182	1.18 (1.04, 1.35)	0.010										
1990-1994						673	1.62 (1.42, 1.84)	<0.001	1.65 (1.45, 1.87)	<0.001					
1995-1999						1,010	2.71 (2.39, 3.08)	<0.001	2.77 (2.44, 3.14)	<0.001					
2000-2004						2,163	5.95 (5.25, 6.73)	<0.001	6.14 (5.42, 6.95)	<0.001					
2005-2009											2,303	9.79 (8.58, 11.16)	<0.001	10.07 (8.83, 11.48)	<0.001
2010-2014											1,207	7.78 (6.78, 8.93)	<0.001	8.00 (6.97, 9.18)	<0.001
Age (years)															
<30	367	Reference		Reference		196	Reference		Reference		117	Reference		Reference	
30-39	425	1.33 (1.15, 1.54)	<0.001	1.39 (1.20, 1.61)	<0.001	1,193	1.40 (1.22, 1.61)	<0.001	1.40 (1.22, 1.60)	<0.001	761	1.33 (1.13, 1.58)	0.001	1.32 (1.12, 1.57)	0.001
40-49	441	1.81 (1.55, 2.11)	<0.001	2.12 (1.87, 2.47)	<0.001	1,689	1.58 (1.38, 1.82)	<0.001	1.66 (1.45, 1.91)	<0.001	1,557	1.30 (1.09, 1.54)	0.003	1.32 (1.12, 1.57)	0.001
50-59	293	2.24 (1.88, 2.66)	<0.001	1.63 (2.21, 2.11)	<0.001	685	1.44 (1.23, 1.68)	<0.001	1.55 (1.33, 1.81)	<0.001	927	1.00 (0.83, 1.20)	0.990	1.04 (0.87, 1.24)	0.681
≥60	95	2.47 (1.92, 3.18)	<0.001	2.83 (2.21, 3.64)	<0.001	83	1.39 (1.09, 1.78)	<0.001	1.48 (1.16, 1.89)	0.002	148	0.65 (0.51, 0.82)	0.000	0.67 (0.53, 0.85)	0.001
Gold employment duration (years)															
0	250	Reference		Reference		567	Reference		Reference		826	Reference		Reference	
<10	936	1.05 (0.88, 1.18)	0.832	1.09 (0.95, 1.27)	0.215	1,113	0.97 (0.87, 1.09)	0.637	1.02 (0.92, 1.14)	0.696	718	1.13 (1.01, 1.27)	0.030	1.16 (1.04, 1.30)	0.010
10-19	340	1.10 (0.92, 1.32)	0.300	1.38 (1.16, 1.65)	<0.001	1,634	1.00 (0.89, 1.11)	0.934	1.09 (0.98, 1.22)	0.098	970	1.46 (1.29, 1.64)	<0.001	1.57 (1.40, 1.76)	<0.001
≥20	95	1.05 (0.80, 1.36)	0.733	1.35 (1.04, 1.70)	0.022	532	0.99 (0.86, 1.14)	0.921	1.14 (0.99, 1.30)	0.062	996	1.43 (1.26, 1.63)	<0.001	1.63 (1.45, 1.84)	<0.001
HIV															
Absent	1,621					2,477	Reference		Reference		2,258	Reference		Reference	
Present	-					1,369	1.37 (1.25, 1.49)	<0.001	1.38 (1.26, 1.50)	<0.001	1,252	1.17 (1.07, 1.28)	<0.001	1.16 (1.06, 1.27)	0.001

Table S3 Adjusted odds ratios (AORs) for PTB in models with and without silicosis in white miners, by calendar period

Variable	1975-1989					1990-2004					2005-2014				
	Model 1 Model with silicosis			Model 2 Model without silicosis		Model 1 Model with silicosis			Model 2 Model without silicosis		Model 1 Model with silicosis			Model 2 Model without silicosis	
	n	AOR (95%CI)	p-value	AOR (95%CI)	p-value	n	AOR (95%CI)	p-value	AOR (95%CI)	p-value	n	OR (95%CI)	p-value	AOR (95%CI)	p-value
Year of autopsy															
1975-1979	128	Reference		Reference		128	Reference		Reference		128	Reference		Reference	
1980-1984	119	0.84 (0.65, 1.08)	0.173	0.84 (0.65, 1.08)	0.172										
1985-1989	132	1.02 (0.80, 1.31)	0.856	0.96 (.075, 1.24)	0.773										
1990-1994						123	1.12 (0.87, 1.45)	0.370	1.02 (0.79, 1.32)	0.864					
1995-1999						91	1.03 (0.78, 1.36)	0.855	0.91 (0.69, 1.20)	0.489					
2000-2004						132	1.87 (1.45, 2.42)	<0.001	1.66 (1.29, 2.14)	<0.001					
2005-2009											157	2.74 (2.14, 3.52)	<0.001	2.53 (1.98, 3.24)	<0.001
2010-2014											121	2.46 (1.87, 3.22)	<0.001	2.33 (1.78, 3.04)	<0.001
Age (years)															
<50	55	Reference		Reference		59	Reference		Reference		45	Reference		Reference	
50-59	66	1.02 (0.70, 1.49)	0.921	1.11 (0.76, 1.61)	0.591	85	1.26 (0.93, 1.71)	0.136	1.38 (1.02, 1.86)	0.038	67	0.98 (0.70, 1.38)	0.917	1.10 (0.79, 1.54)	0.580
60-69	135	1.30 (0.92, 1.84)	0.138	1.51 (1.07, 2.12)	0.019	93	0.69 (0.50, 1.27)	0.677	1.10 (0.82, 1.49)	0.510	82	0.76 (0.54, 1.05)	0.104	0.93 (0.67, 1.29)	0.653
≥70	123	1.40 (0.97, 2.00)	0.071	1.72 (1.21, 2.46)	0.003	109	0.85 (0.62, 1.16)	0.304	1.08 (0.79, 1.47)	0.628	84	0.53 (0.37, 0.76)	<0.001	0.71 (0.50, 1.00)	0.051
Gold employment duration (years)															
0	27	Reference		Reference		42	Reference		Reference		35	Reference		Reference	
<10	35	1.22 (0.73, 2.03)	0.447	1.27 (0.76, 2.12)	0.354	61	1.30 (0.90, 1.87)	0.156	1.41 (0.98, 2.01)	0.066	34	1.03 (0.68, 1.57)	0.892	1.13 (0.74, 1.72)	0.575
10-19	59	1.67 (1.05, 2.65)	0.030	1.90 (1.20, 3.01)	0.006	74	1.10 (0.77, 1.56)	0.601	1.34 (0.95, 1.90)	0.940	70	1.18 (0.81, 1.71)	0.380	1.50 (1.04, 2.17)	0.030
20-29	105	1.88 (1.22, 2.91)	0.004	2.36 (1.54, 3.63)	<0.001	88	1.18 (0.84, 1.65)	0.338	1.67 (1.21, 2.31)	0.002	82	1.22 (0.85, 1.75)	0.278	1.80 (1.28, 2.55)	0.001
≥30	153	1.39 (0.90, 2.14)	0.137	1.79 (1.17, 2.73)	0.007	81	0.89 (0.63, 1.25)	0.489	1.28 (0.92, 1.78)	0.149	57	0.96 (0.66, 1.40)	0.843	1.49 (1.04, 2.15)	0.031
HIV															
Absent	397					343	Reference		Reference		272	Reference		Reference	
Present	-					3	1.83 (0.55, 6.03)	0.323	1.93 (0.90, 6.32)	0.277	6	2.53 (1.03,6.22)	0.043	2.50 (1.04, 6.02)	0.040

Table S4 Adjusted odds ratios (AORs) for complete case analysis and multiple imputation in black miners at autopsy, by calendar period

Variable	1975-1989				1990-2004				2005-2014			
	Complete case analysis		Iterative chained equations		Complete case analysis		Iterative chained equations		Complete case analysis		Iterative chained equations	
	AOR	SE*	AOR	SE*	AOR	SE*	AOR	SE*	AOR	SE*	AOR	SE*
Year of autopsy												
1975-79	Reference		Reference		Reference		Reference		Reference		Reference	
1980-84	1.31 (1.15, 1.49)	0.086	1.32 (1.17, 1.50)	0.064								
1985-89	1.09 (0.96, 1.25)	0.073	1.10 (0.97, 1.25)	0.065								
1990-94					1.62 (1.42, 1.84)	0.106	1.62 (1.43, 1.83)	0.064				
1995-99					2.71 (2.39, 3.08)	0.176	2.72 (2.40, 3.07)	0.063				
2000-04					5.95 (5.25, 6.73)	0.378	5.92 (5.24, 6.69)	0.062				
2005-09									9.79 (8.58, 11.16)	0.657	9.95 (2.17, 2.42)	0.065
2005-14									7.78 (6.78, 8.93)	0.548	7.68 (1.89, 2.19)	0.075
Age (years)												
<30	Reference		Reference		Reference		Reference		Reference		Reference	
30-39	1.33 (1.15, 1.54)	0.099	1.30 (1.12, 1.50)	0.074	1.40 (1.22, 1.61)	0.098	1.36 (1.19, 1.56)	0.069	1.33 (1.13, 1.58)	0.114	1.30 (0.09, 0.43)	0.085
40-49	1.81 (1.55, 2.11)	0.142	1.73 (1.48, 2.01)	0.078	1.58 (1.38, 1.82)	0.113	1.52 (1.32, 1.74)	0.070	1.30 (1.09, 1.54)	0.113	1.26 (1.06, 1.49)	0.087
50-59	2.24 (1.88, 2.66)	0.199	2.11 (1.75, 2.89)	0.088	1.44 (1.23, 1.68)	0.113	1.38 (1.19, 1.61)	0.078	1.00 (0.83, 1.20)	0.092	0.96 (0.80, 1.15)	0.092
≥60	2.47 (1.92, 3.18)	0.319	2.25 (1.75, 2.89)	0.128	1.39 (1.09, 1.78)	0.173	1.27 (1.01, 1.61)	0.120	0.65 (0.51, 0.82)	0.077	0.64 (0.51, 0.81)	0.119
Gold employment duration (years)												
0	Reference		Reference		Reference		Reference		Reference		Reference	
<10	1.05 (0.88, 1.18)	0.076	1.01 (0.87, 1.17)	0.074	0.97 (0.87, 1.09)	0.054	0.97 (0.87, 1.08)	0.055	1.13 (1.01, 1.27)	0.066	1.17 (1.04, 1.31)	0.059
10-19	1.10 (0.92, 1.32)	0.101	1.11 (0.93, 1.32)	0.090	1.00 (0.89, 1.11)	0.055	1.00 (0.87, 1.11)	0.055	1.46 (1.29, 1.64)	0.088	1.49 (1.32, 1.68)	0.061
≥20	1.05 (0.80, 1.36)	0.141	1.08 (0.83, 1.40)	0.131	0.99 (0.86, 1.14)	0.070	1.00 (0.87, 1.15)	0.070	1.43 (1.26, 1.63)	0.093	1.46 (1.28, 1.66)	0.066
Silicosis												
Absent	Reference		Reference		Reference		Reference		Reference		Reference	
Present	3.08 (2.65, 3.57)	0.233	3.08 (2.66, 3.56)	0.075	1.54 (1.4, 1.69)	0.073	1.57 (1.44, 1.73)	0.047	1.34 (1.20, 1.49)	0.072	1.33 (1.20, 1.48)	0.055
HIV												
Absent					Reference		Reference		Reference		Reference	
Present					1.37 (1.25, 1.49)	0.061	1.39 (1.28, 1.52)	0.044	1.17 (1.07, 1.28)	0.055	1.16 (1.06, 1.28)	0.048

*SE, standard error

APPENDIX 4

Ndlovu N, Richards G, Vorajee N, Murray J. Silicosis and pulmonary tuberculosis in deceased female South African miners. *Occupational Medicine*, (Lond), 69, 272-278.

Silicosis and pulmonary tuberculosis in deceased female South African miners

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Background	Implementation of South Africa's 2002 Mining Charter increased women's participation in underground mining. However, occupational lung diseases (OLDs) in female gold miners have not been studied.
Aims	To compare autopsy-diagnosed pulmonary silicosis, lymph gland silicosis (a precursor of pulmonary silicosis) and active pulmonary tuberculosis (PTB) in South African gold miners.
Methods	The law allows for autopsies on miners for OLD compensation. Information is stored on the Pathology Automation (PATHAUT) database. We selected records of deceased miners who had worked only in gold mines, started employment from 2002, and were autopsied between 2005 and 2015. Using descriptive statistics, we compared demographic and employment characteristics, and disease proportions by sex.
Results	The study comprised 847 gold miners: 68 women and 779 men. There were no statistically significant differences in proportions of autopsy-diagnosed pulmonary silicosis [3 (4%) in women and 54 (7%) in men], lymph gland silicosis [11 (16%) and 171 (22%)] or PTB [29 (43%) and 254 (33%)]. Age and employment duration in women and men with disease were similar. Most miners with pulmonary silicosis had started employment from 2003 [315 (77%)] and worked for under 10 years.
Conclusion	It is important to report research findings by sex. Proportions of silicosis and PTB were comparable in women and men, suggesting similar exposures. Silicosis detection after short employment indicates inadequate dust control, particularly as most entered the industry after implementation of interventions to control silica dust in 2003.
Key words	Autopsy; lymph gland fibrosis; occupational lung disease; PATHAUT; silicosis; tuberculosis.

Introduction

South African gold miners are experiencing epidemics of silicosis and pulmonary tuberculosis (PTB). Silicosis is associated with high occupational exposures to crystalline silica. Both silica and silicosis are risk factors for PTB [1]. In 2016, silicosis and PTB were diagnosed in 29 and 16% of gold miners who were autopsied at the National Institute for Occupational Health (NIOH) for compensation purposes [2]. Epidemiological studies in gold miners reported high silicosis prevalence (8–20% in active miners and 22–36% in former miners) and active PTB incidence (3000 per 100 000 persons) [1].

The mining industry is male-dominated. In South Africa, women were legally prohibited from working

underground in 1911. Women continued to work in surface activities, mostly in asbestos mines where they comprised about half of the labour force and performed tasks such as sweeping, cobbing (processing) the ore and packing asbestos fibres for shipment [3]. Despite the removal of restrictions on underground mining in 1973 [4], women in the gold mining industry continued to occupy surface jobs (e.g. administration or cleaning). The Mining Charter of 2002, implemented in 2004, set a target to increase the participation of women in core mining activities to 10% by 2009. Core mining activities are jobs that are equivalent to those of men and include underground occupations, such as winch driving and drilling [5]. The employment of women in mining increased from <1% before 2002 to just >10% in 2013 [6].

Key learning points

What is already known about this subject:

- Sex- and gender-related factors might influence lung development, responses to exposures to dust and susceptibility to lung diseases.
- Globally, there are few studies on silicosis and tuberculosis in women.
- Most existing studies were on women in the ceramic industry but the findings were inconsistent with some finding higher silicosis incidence and mortality in women compared to men, others finding lower rates and another showing no difference.

What this study adds:

- Similar proportions of autopsy-diagnosed silicosis and active PTB in female and male South African gold miners suggests comparable exposures to dust and other risk factors.
- Detection of pulmonary silicosis in gold miners after short employment and after introduction of silica dust control interventions indicates inadequate dust control.

What impact this may have on practice or policy:

- Dust reduction remains key to silica-related disease prevention.
- Sex and gender should be considered when assessing occupational health risks and exposures, and designing prevention strategies.
- To gain insight into the effect of occupational dust exposures on women, findings should be reported separately by sex, even if the numbers are small.

However, the report did not include the proportion of women involved in underground mining *per se*.

The literature on South African women in mining addresses gender-based discrimination and violence, work-related skin rashes and musculoskeletal and reproductive disorders [7,8]. Recognizing the anatomical and physiological differences between women and men, the Mine Health and Safety Council (a tripartite institution representing government, employers and labour) commissioned research to assess the physical abilities and ergonomic requirements of female underground miners. The findings informed the development of guidelines for personal protective equipment (PPE) for women [9].

Factors related to sex (anatomical, physiological, immunological and hormonal characteristics) and gender (environmental and sociocultural issues) might influence lung development, exposures and responses to inhaled dusts, and susceptibility to lung diseases [10]. It has been noted that women have smaller lungs than men of the same height, lower lung capacities and greater forced expiratory flow rates, which affects the degree to which particles are inhaled [11]. In addition, dissimilarities in body segments and limb lengths often results in women handling equipment and donning ill-fitting PPE that was designed for men [12]. Furthermore, intra-job variability, where women and men with the same job title may be assigned different tasks or perform tasks differently, results in differential exposures [12]. Benya [13] observed that male South African gold miners often volunteered to perform more strenuous tasks, while female miners assisted by fetching drinking water, passing equipment to the men or cleaning the work area.

In occupational settings where there are few women, they are often excluded from studies or findings are reported without distinguishing between the sexes [14,15]. As such, we are not aware of any previous studies on silica-related diseases in female South African miners. Globally, there are few published studies on silicosis in women. Most research was conducted in the ceramic industry which has a long history of employing women, but the findings were inconsistent. Two studies found higher silicosis incidence [16] and mortality rates [17] in women, three showed lower silicosis incidence rates in women [18–20] and one reported no sex differences in pneumoconiosis prevalence [21]. One study reported shorter latency periods and faster silicosis progression in women [16], but another reported the opposite [20]. Two of the studies reported higher tuberculosis prevalence [21] and mortality [17] rates in women.

South African women have worked as underground miners for a shorter period than men. As they work for longer periods and accumulate dust in their lungs, their risk for developing silicosis and other silica-related diseases will increase. Since 2005, the annual pathology surveillance reports of the NIOH have provided the only source of information on occupational lung diseases (OLDs) in female miners [2]. Examinations of the cardiorespiratory organs of miners for OLD compensation are performed regardless of the clinical causes of death and with consent from the next of kin [4]. Organs are removed locally where death occurs, preserved in formalin, and sent to the NIOH in Johannesburg for examination. From 1975, limited demographic and employment information, and pathology findings have been entered in

the Pathology Automation (PATHAUT) database [22]. Miners' sex has been recorded since 2005.

We used PATHAUT data to describe and compare autopsy-diagnosed pulmonary silicosis, lymph gland silicosis and active PTB in female and male gold miners from 2005 to 2015. We included lymph gland silicosis because it is an early response to silica dust exposure, preceding the development of silicosis in the lungs [23,24]. Fibrosis in the lymph glands may impair elimination of silica dust from the lungs resulting in its accumulation and increasing the risk of pulmonary silicosis development [23].

Methods

We defined gold miners as those who had worked exclusively in gold mines, with no employment in any other mining industry. The study population comprised deceased gold miners whose organs were examined at the NIOH from 2005 (the year from which sex was recorded on the database) to 2015. To restrict the study to women who entered the industry after introduction of the Mining Charter, we selected miners who started work in the mines from 2002.

Organs submitted to the NIOH are examined by experienced pathologists, using standardized diagnostic criteria. This remained unchanged over the study period. At autopsy, pathological diagnosis of pulmonary silicosis is based on the detection of palpable silicotic nodules on macroscopic examination of the lungs, confirmed by the presence of microscopic silicotic nodules on histological examination. Silicosis severity is determined by the numbers of macroscopic nodules categorized as occasional (1–4), few (5–14), moderate (15–30) and large (>30). Cases with occasional or few nodules are categorized as having slight silicosis. Histology is used to detect the presence of silicosis in the hilar lymph glands of both lungs. Autopsy-diagnosed active PTB is defined as the presence of microscopic epithelioid granulomas associated with caseous necrosis, after the exclusion of other causes.

For case selection and analysis, we exported records from the PATHAUT database to Stata version 14 (StataCorp, College Station, TX, USA). We excluded records with missing sex, age or employment duration. To minimize misclassification of sex, we reviewed documents submitted to the NIOH (e.g. birth and death certificates, employment records etc.) to verify the sex of female miners in the study population. Due to the large number, we did not verify the sex of male miners.

We used Mann–Whitney and chi-square tests to determine differences between medians and proportions, respectively. We considered a P value of <0.05 to be statistically significant.

The miners' next-of-kin consented for autopsy examination in accordance with the Occupational Disease in

Mines and Works Act of 1973 [4]. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (clearance certificate number M120236) and the University of Michigan Health Sciences and Behavioural Sciences Institutional Review Board (HUM00069012).

Results

There were 15 941 autopsy records on the PATHAUT database from 2005 to 2015: 385 women, 15 385 men and 171 for whom sex was not stated. We excluded miners with mining experience in industries other than gold, who started employment before 2002 and/or had missing sex, age or employment duration. The study population comprised 847 gold miners (Table 1).

The characteristics of study participants are summarized in Table 2. There were 68 (8%) women and 779 (92%) men. All the women and 94% of the men were black. Most miners died while in mine employment: 93% of the women and 75% of the men. The overall median age was 35 years (range: 19–65 years) and women were significantly older than men ($P < 0.05$). Most women (76%) started employment in 2006–10, whereas most men (57%) started in 2002–05. The PATHAUT database does not record miners' occupations.

Respiratory diseases were the most common clinical cause of death [305 (36%): 33 (49%) women and 272 (35%) men]. PTB and pneumonia accounted for 14 (21%) and 13 (19%) deaths in women, and 122 (16%) and 116 (15%) deaths in men, respectively. Silicosis was not stated as a clinical cause of death for any miner. Unnatural (external) causes accounted for the second largest number of deaths [116 (14%): 3 (4%) women and 113 (15%) men]. Other deaths [352 (42%)] arose from many diseases, e.g. cardiovascular, central nervous and gastrointestinal disorders etc. Cause of death was not stated for 4 (6%) women and 70 (9%) men.

There were 407 miners with autopsy-diagnosed pulmonary or lymph node silicosis and/or PTB. Most [315 (77%)] started gold mining from 2003. Despite known racial differences in job types, employment duration, dust exposure, living conditions and access to autopsy examination [22], we did not analyse the data by

Table 1. Selection of the study population

Exclusion criteria	Excluded	Remaining
All cases (2005–15)		15 941
Worked in sectors other than gold	7161	8780
Started work in gold mines before 2002	7756	1024
Sex not stated	171	853
Age or duration of employment not stated	6	847
Total	15 094	

Table 2. Characteristics of deceased gold miners whose organs were examined at the NIOH by sex, 2005–15

Characteristic	Women	Men	Total	P value
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Number (%)	68 (8)	779 (92)	847	
Race				
Black	68 (100)	735 (94)	803 (95)	NS
White	0 (0)	43 (6)	43 (5)	
Mixed race	0 (0)	1 (0)	1 (0)	
Employment status ^a				
Active miner	63 (93)	586 (75)	649 (77)	<0.01
Ex-miner	3 (4)	89 (11)	92 (11)	
Not stated	2 (3)	104 (14)	106 (12)	
Median age at death in years (range)	37.5 (26.0–54.0)	35.0 (19.0–65.0)	35.0 (19.0–65.0)	<0.05
Age group (years)				
<30	12 (18)	173 (22)	185 (22)	<0.05
30–39	29 (43)	403 (52)	432 (51)	
40–49	25 (37)	152 (19)	177 (21)	
50–59	2 (3)	44 (6)	46 (5)	
60–65	0	7 (1)	7 (1)	
Median year employment started (range)	2006 (2002–13)	2005 (2002–15)	2005 (2002–15)	<0.001
Year employment started group				
2002–05	14 (21)	442 (57)	456 (54)	<0.001
2006–10	52 (76)	308 (39)	360 (42)	
2011–15	2 (3)	29 (4)	31 (4)	
Median employment duration in years (range)	4.6 (1.0–10.9)	4.3 (0.1–18.9)	4.3 (0.1–18.9)	NS
Employment duration group (years)				
0.1–4.9	37 (54)	455 (58)	492 (58)	NS
5.0–9.9	29 (43)	282 (36)	311 (37)	
10.0–14.9	2 (3)	39 (5)	41 (5)	
15.0–19.9	0 (0)	3 (0)	3 (0)	

NS, not significant.

^aData captured on PATHUAT database from 2007.

race because all the women and most men with disease were black viz. pulmonary silicosis [52 (96%)], lymph gland silicosis [156 (91%)] and PTB [253 (99.6%)]. The proportions of pulmonary silicosis, lymph gland silicosis and PTB were similar between women and men (Table 3). With the exception of year of employment in miners with PTB, the characteristics of women and men with disease were similar. Most miners with disease were aged 30–49 years [301 (4%)] and had been employed for under 10 years [53 (94%)].

Pulmonary silicosis was diagnosed in three women, all of whom had occasional or few nodules, that is, slight silicosis (Table 3). Two of the women were 26 and 35 years old, had started mining in 2006 and worked for 3.3 and 3.8 years, respectively. The third woman was older (47 years), started employment in 2003 and worked for 10.9 years. All three women with pulmonary silicosis had lymph gland silicosis and one had PTB.

Fifty-four (7%) men were diagnosed with pulmonary silicosis, most of which [43 (80%)] was categorized as

slight (Table 3). Most [38 (70%)] men were <50 years and six (11%) were <30 years (range 26–29 years). Most men with silicosis [36 (65%)] started employment in 2002–05 and had been employed for <10 years [51 (94%)].

More women and men had lymph gland silicosis [11 (16%) and 171 (22%), respectively] than pulmonary silicosis [3 (4%) and 54 (7%), respectively]. Of those with lymph gland silicosis, 3 (27%) women and 43 (24%) men also had pulmonary silicosis, categorized as slight in all the women and 32 (74%) men.

PTB was diagnosed in 29 (43%) women of whom 1 (3%) had silicosis, 7 (24%) had lymph gland silicosis and 22 (76%) had neither pulmonary nor lymph gland silicosis. Of the 254 (33%) men diagnosed with PTB, 22 (9%) had pulmonary silicosis, 58 (23%) had lymph gland silicosis and 192 (76%) had neither pulmonary nor lymph gland silicosis.

In women and men, respectively, PTB was stated as a cause of death for 1 (33%) and 16 (20%) cases with

Table 3. Comparison of characteristics of deceased gold miners diagnosed with OLDs, by sex (2005–15)

Characteristic	Pulmonary silicosis			Lymph gland silicosis			PTB		
	Women	Men	<i>P</i> value	Women	Men	<i>P</i> value	Women	Men	<i>P</i> value
Number (%)	3 (4)	54 (7)	NS	11 (16)	171 (22)	NS	29 (43)	254 (33)	NS
Pulmonary silicosis severity (number of silicotic nodules)									
Occasional/few ^a	3 (100)	43 (80)	NS	N/A			N/A		
Moderate	0 (0)	10 (18)							
Large number	0 (0)	1 (2)							
Median age in years (range)	35.0 (26.0–47.0)	43.0 (26.0–60.0)	NS	42.0 (26.0–54.0)	40.0 (25.0–63.0)	NS	37.0 (26.0–54.0)	35.0 (21.0–56.0)	NS
Age groups (years)									
<30	1 (33)	6 (11)	NS	1 (9)	16 (9)	NS	5 (17)	52 (20)	NS
30–39	1 (33)	15 (28)		2 (18)	66 (39)		13 (45)	147 (58)	
40–49	1 (33)	17 (31)		7 (64)	55 (32)		10 (34)	45 (18)	
50–59		14 (26)		1 (9)	30 (18)		1 (3)	10 (4)	
60–65		2 (4)		0 (0)	4 (2)				
Median employment duration in years (range)	3.8 (3.3–10.9)	5.0 (0.5–11.9)	NS	5.8 (3.1–10.9)	4.8 (0.1–15.6)	NS	4.7 (1.0–9.7)	4.7 (0.2–11.9)	NS
Employment duration group (years)									
0.1–4.9	2 (67)	26 (48)	NS	5 (45)	89 (52)	NS	16 (55)	135 (53)	NS
5.0–9.9	0 (0)	25 (46)		5 (45)	68 (40)		13 (45)	105 (41)	
10.0–14.9	1 (33)	3 (6)		1 (9)	13 (8)		0 (0)	14 (6)	
15.0–19.9	0 (0)	0 (0)		0 (0)	1 (1)		0 (0)	0 (0)	
Median year employment started (range)	2006 (2003–06)	2004 (2002–09)	NS	2006 (2002–09)	2005 (2002–13)	NS	2006 (2002–13)	2004 (2002–13)	<0.001
Year employment started groups									
2002–05	1 (33)	35 (65)	NS	3 (27)	104 (61)	NS	8 (28)	169 (67)	<0.001
2006–10	2 (67)	19 (35)		8 (73)	64 (37)		20 (69)	80 (31)	
2011–15	0 (0)	0 (0)		0 (0)	3 (2)		1 (3)	5 (2)	

NS, not significant.

^aSlight silicosis.

autopsy-diagnosed silicosis, 5 (45%) and 44 (27%) with lymph gland silicosis and 11 (39%) and 102 (40%) cases with PTB.

Discussion

This study contributes recent findings to the sparse literature on OLDs in women in the mining industry. The findings are pertinent to other occupational settings where workers are exposed to silica dust. Despite the small numbers of women, we observed similar proportions of autopsy-diagnosed pulmonary silicosis, lymph gland silicosis and PTB in women and men. This suggests that women's exposures to dust and other risk factors were comparable to those of men. This study also demonstrated the value of autopsies in the provision of early, sensitive indicators for silicosis much of which had been missed clinically. The findings of silicosis after a short employment support current interventions to lower dust exposures in mines.

The use of autopsy data is a major strength of this study as autopsies are the gold standard for diagnosis. Of the 57 cases with autopsy-diagnosed pulmonary silicosis (11 of which had moderate or large numbers of nodules), none had a diagnosis of silicosis stated as the clinical cause of death. Similarly, fewer cases of PTB were diagnosed clinically (14 in women and 122 in men) than at autopsy (29 in women and 254 in men). These findings

are in agreement with studies that have shown autopsies to have higher sensitivity and specificity than clinical diagnoses of silicosis and TB [25–27].

The small number of women is a limitation of this study. Further research with larger numbers of women is required to investigate the association of sex and gender on the occurrence of OLDs. Another limitation is the lack of information on occupations of miners and employment in other industries where silica exposure might have occurred (e.g. ceramic manufacturing and construction) in the PATHAUT database. Also, the available employment data might be incomplete as there are gaps in many occupational histories due to undisclosed mining employment information. Furthermore, the proxies of dust exposure (age and duration of employment) that we used may not be appropriate when comparing women and men, due to intra-job variability.

We found no differences in silicosis and PTB prevalence in women and men although previous studies reported significant differences [16–18,20,21]. Our findings suggest that the risk factors for silicosis and PTB in women and men may be similar, but the numbers of women were too small to explore this further. Trend analyses using the PATHAUT data showed that year of autopsy (a surrogate for unmeasured confounding factors), increasing age and employment duration explained the increasing proportions of silicosis and PTB in male black

miners over time. Silicosis and HIV were also significant determinants of PTB [28].

Lymph node silicosis, the ‘canary in the miner’, precedes the development of pulmonary silicosis [24]. We found that all three women and 80% of men with pulmonary silicosis had lymph gland silicosis and, that the proportions of miners with lymph gland silicosis were greater (16% in women and 22% in men) than those with pulmonary silicosis (4% and 7%, respectively). Our findings agree with other studies that showed that pulmonary silicosis was less prevalent than lymph node silicosis and that most (~90%) cases with pulmonary silicosis had lymph gland silicosis [23,24].

Most of the pulmonary silicosis reported in this study (100% in women and 80% in men) was categorized as slight disease, which is probably not radiologically detectable. A study of South African gold miners demonstrated that only about 20% of slight, autopsy-diagnosed silicosis had been detected radiologically [26]. While individuals with slight silicosis are usually asymptomatic, the presence of slight silicosis is important as the disease is progressive and many could develop more severe symptomatic silicosis. Additionally, the risk of developing TB and other silica-related diseases, such as lung cancer and chronic obstructive pulmonary disease, is elevated in those with slight silicosis [25].

The detection of silicosis in miners who had worked for short periods (<10 years) indicates recent high exposures to silica dust and that the gold mining industry has failed to control dust adequately. Additionally, most miners entered the industry after the 2003 tripartite Mine Health Safety Council’s voluntary programme to control silica dust exposures and eliminate silicosis in the South African mining industry by 2030 [25]. The milestone of 95% compliance to the occupational exposure limit (OEL) of 0.1 mg/m³ by 2008 was not achieved. By 2013, compliance had reached 95% [29]. The OEL of 0.1 mg/m³ is known to be inadequate for the prevention of silicosis, therefore the more recent 2014 milestone has lowered the OEL to 0.05 mg/m³ [30] which will be more protective of the health of miners, regardless of sex and gender.

This study demonstrates the importance of the inclusion and separate reporting of women when studying OLDs, even if the numbers of women are small. Further studies are required to ascertain the roles of sex and gender (e.g. intra-job variability) in defining occupational health risks and prevention strategies. Although the South African mining industry has developed a guideline for ergonomically suitable PPE for women [9], our findings highlight the importance of dust reduction in the prevention of OLDs.

In addition to its usefulness in monitoring the effectiveness of dust reduction interventions, autopsy data have an important alert function in identifying OLDs in occupational subpopulations that were previously not

recognized and in individuals whose disease might not have been detected in life.

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Competing interests

None declared.

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APPENDIX 5

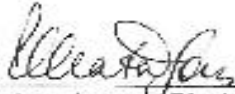
University of the Witwatersrand Human Research Ethics Certificate



R14/49 Mrs Ntombizodwa Ndlovu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170287

NAME: Mrs Ntombizodwa Ndlovu
(Principal Investigator)
DEPARTMENT: School of Public Health
PROJECT TITLE: Evaluation of Autopsy Data for Occupational Lung Disease Surveillance
DATE CONSIDERED: 24/02/2012 (Initial Approval)
DECISION: Approved unconditionally
CONDITIONS: Renewal for 5 Years
Valid for the Period 01 February 2017 - 28 February 2022
Previously M120236
SUPERVISOR: Prof Jill Murray
APPROVED BY: 
Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL: 24/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princes of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____

Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 6

University of Michigan Institutional Review Board Certificate

To: Ntombizodwa Ndlovu

From:

There are no items to display

Cc:

Ntombizodwa Ndlovu

Subject: Notice of Determination of "Not Regulated" Status for [HUM00069012]

SUBMISSION INFORMATION:

Title: Evaluation of autopsy data for occupational lung disease surveillance

Full Study Title (if applicable): Evaluation of autopsy data for occupational lung disease surveillance

Study eResearch ID: [HUM00069012](#)

Date of this Notification from IRB: 11/15/2012

Date of IRB Not Regulated Determination : 11/15/2012

IRB NOT REGULATED STATUS:

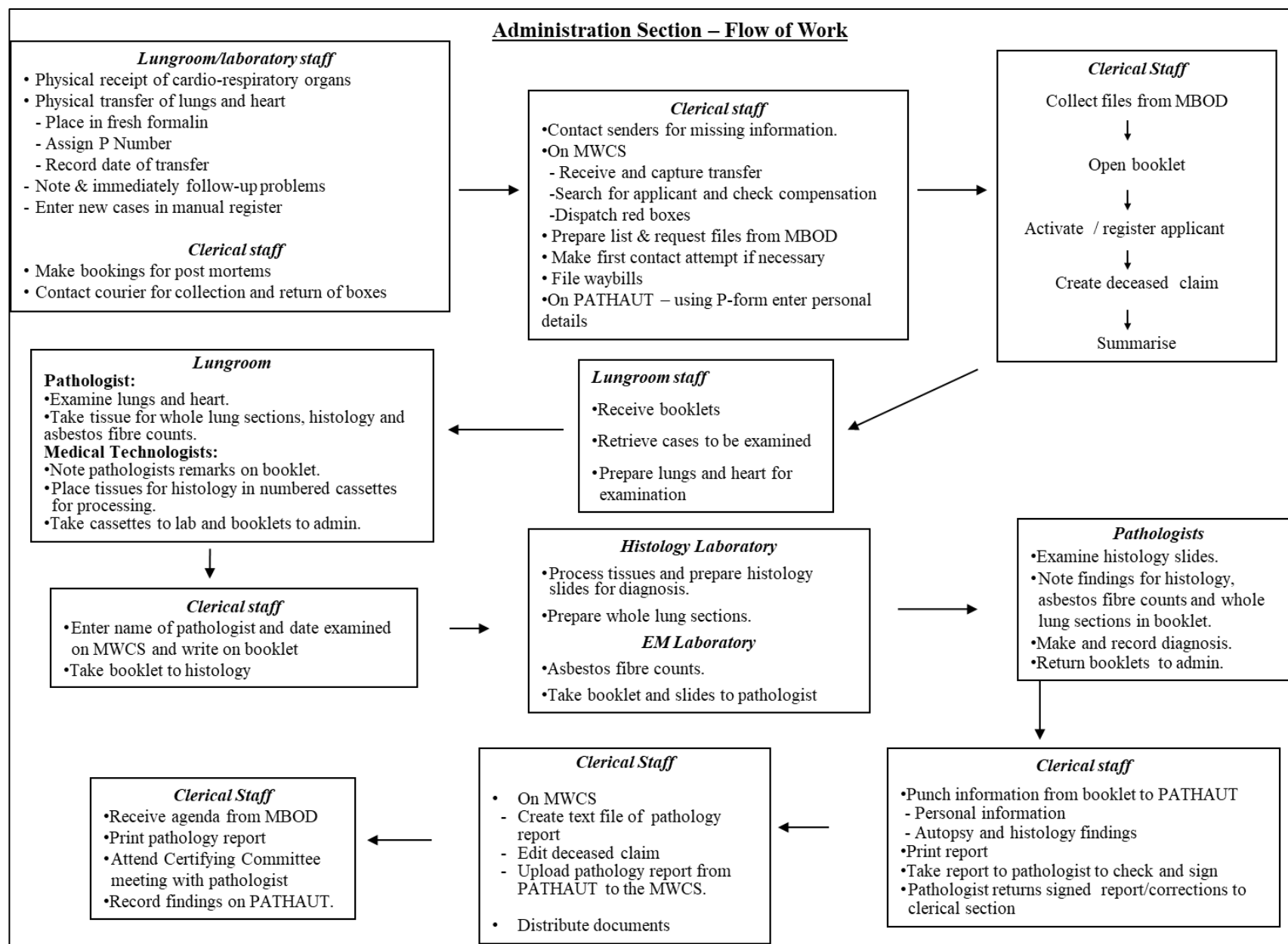
Category	Outcome Letter Text
Research Involving Only Decedents (Deceased Individuals)	Based on the information provided, the proposed study does not involve a living individual. In accordance with federal regulations for human subjects research (45 CFR Part 46) deceased individuals are not considered human subjects.



Richard Redman
Chair, IRB HSBS

APPENDIX 7

Workflow of autopsy process at the NIOH



APPENDIX 8

NIOH pathology examination booklet

NIOH: Pathology Examination Booklet

Ex-miner: Yes ☐ No ☐

Examination Report Status Code

P number

cardio-respiratory organs only ☐

Bureau no

cardio-respiratory organs with limited autopsy see appended report ☐

Pathologist

cardio-respiratory organs with full autopsy see appended report ☐

Applic ID

Red Box No

Cause of death: death certificate

Cause of death: NIOH Pathologist

Surname
First name plus initials
Industry no
National ID no

Population group ☐

Gender ☐

Exposure:	Type	Year
most		
2 nd most		
3 rd most		
4 th most		
Other		

	dd	mm	year
received			
examined			
report			
birth			
death			
age			

Calender period: year started
year ended

Last mine worked

block no.	no.	tissue	remarks

Slight case ☐

Additional comments

Macroscopic report

Regional glands

1		could not be examined
2		show no gross change
3		are autolysed
4		are pigmented
5		are enlarged
6		are fibrosed
7		are calcified
8		are tuberculous
9		are tumour infiltrated
10		additional comments _____

Pulmonary vessels

1		could not be examined
2		show no gross change
3		thrombo embolism is present
	1	on left
	2	on right
4		additional comments _____

Pleura

1		plaques are absent
2		occasional
3		few
4		moderate
5		numerous
6		a chronic non-specific plurisy present
	1	on left
	2	on right
7		an acute pleurisy is present
	1	on left
	2	on right
8		asbestotic plaque formation
	1	on left
	2	on right
9		this involves the
	1	parietal pleura
	2	visceral pleura
	3	diaphragm
10		pleural shows malignant infiltration
	1	on left
	2	on right
11		additional comments _____

Bronchi

1		could not be examined
2		show no gross change
3		bronchiectasis is present
	1	on left
	2	on right
4		additional comments _____

Heart

1		not submitted
2		poorly preserved
3		shows no gross change
4		total weight
5		ventricular mass (N<250)
6		mass of L V + septum (N190)
7		mass of R V (N<65)
8		L V + septum: R V
9		is enlarged due to
	1	left ventricular hypertrophy
	2	right ventricular hypertrophy
10		atherosclerosis is
	1	absent
	2	slight
	3	moderate
	4	marked
11		disease is present in the
	1	mitral valve
	2	aortic valve
	3	tricuspid valve
	4	pulmonary valve
12		the pericardium shows a
	1	chronic non-specific pericarditis
	2	fibrinous pericarditis
	3	tuberculous pericarditis
13		ante mortem thrombus is present
14		bypass grafts are present
15		there is ischaemic fibrosis
16		a valve replacement is present
17		there is a wound
18		additional comments _____

Lungs

1		inflated: not weighted	
2		poorly preserved	
3		a whole lung section was taken	
4			
	1	left lung	g
	2	incomplete not weighed	
5			
	1	right lung	g
	2	incomplete not weighed	
6		show(s) an increase in pigment	
7		there is no evidence of a pneumoconiosis	
8		the pigment is aggregated in	
	1	occasional	
	2	a few	
	3	a moderate number	
	4	a large number	islets
9		the pigment is aggregated in	
	1	occasional	
	2	a few	
	3	a moderate number	
	4	a large number	nodules
10		the pigment is aggregated in	
	1	occasional	
	2	a few	
	3	a moderate number	
	4	a large number	macules
11		emphysema is	
	1	absent	
	2	insignificant	
	3	moderate	
	4	marked	
12		the type of emphysema is	
	1	panacinar	
	2	centrilobular	
	3	focal	
	4	irregular	
13		emphysema score on the W.L.S.	
14		the W.L.S. is not suitable	
15		marginal bullae are present	

16		there is a primary neoplasm in
	1	the left lung
	2	the right lung
17		the tumour is
	1	central
	2	peripheral
18		the tumour measures mm
19		metastatic neoplastic deposits are
	1	present in the left lung
	2	present in the right lung
20		consolidation is
	1	absent
	2	present in the left lung
	3	present in the right lung
21		the parenchyma shows
	1	necrosis
	2	fibrosis
	3	encapsulated necrosis
	4	cavitation
	5	milliary TB
22		tuberculosis is
	1	absent
	2	insignificant
	3	moderate
	4	marked
23		there is a lacerated wound
24		haemorrhage is present
25		palpable foci are present
26		additional comments _____ _____ _____ _____ _____ _____ _____ _____

Oesophagus

1		there is a neoplasm	
2		the tumour measures	mm
3		additional comments	

Microscopic report

Regional glands

1		too poorly preserved for assessment
2		dust deposition but no fibrosis
3		diffuse non-specific fibrosis
4		foci of concentric fibrosis
5		foci of calcification

6		encapsulated necrosis consistent with with inactive TB
---	--	--

7		granulomatous inflammation consistent with active TB
8		sarcoidosis cannot be excluded
9		foci of malignancy
10		additional comments

Lungs

1		show	
	1	slight	dust deposition but
	2	moderate	no pneumoconiosis
	3	marked	
2		foci of dust reticulation	
	1	with insignificant collagenisation	
	2	with significant collagenisation	
3		silicotic islets	
4		silicotic pleural plaques	
5		ferruginous bodies	
	1	are not present	
	2	are present but no associated fibrosis	
	3	with slight interstitial fibrosis	
	4	with moderate interstitial fibrosis	
	5	with marked interstitial fibrosis	

6		the macules show
	1	insignificant collagenisation and focal emphysema

2		significant collagenisation and focal emphysema
---	--	---

3		significant collagenisation without focal emphysema
---	--	---

7		nodules - mixed dust pneumoconiosis
8		show massive fibrosis
9		the necrosis shows granulomas consistent with an active

1		fibrocaseous tuberculosis
2		tuberculoma
3		tuberculous bronchopneumonia
4		milliary tuberculosis
5		tuberculous cavity

10		stains for acid fast bacilli were
	1	positive
	2	negative

11		necrosis is encapsulated in keeping with inactive TB
----	--	--

12		the consolidation shows
	1	an acute broncho-pneumonia
	2	an acute lobar pneumonia
	3	an organising pneumonia
	4	a suppurative pneumonia
	5	a viral pneumonia
	6	diffuse alveolar damage (shock lung)
	7	a fungal infection
	8	an aspiration pneumonia
	9	other (specify)

13		foci of broncho-pneumonia are present in some sections
----	--	--

14		the neoplasm is a:
	1	small lung carcinoma
	2	large cell lung carcinoma
	3	squamous lung carcinoma
	4	lung adenocarcinoma
	5	broncho-alveolar carcinoma
	6	metastatic neoplasm
	7	chondroid hamartoma
	8	other lung tumour

15		the pleura shows a mesothelioma
	1	epithelial
	2	sarcomatous
16		the cavity is:
	1	an inactive tuberculous cavity
	2	a bronchiectatic cavity
	3	an abscess cavity
	4	other (specify) _____

17		the palpable foci shows:
	1	non-specific fibrosis
	2	non-specific fibrosis with elastosis
	3	nodular muscular hyperplasia
	4	parenchymal lymph nodes
18		the pleura shows:
	1	an active tuberculous pleurisy
	2	a chronic non-specific pleurisy
	3	a fibrinous pleurisy
	4	an empyema
	5	a fibrino-haemorrhagic pleurisy
	6	fibrosis with elastosis consistent with a Medlar's cap

19		necrosis shows features of an infarct
20		bilharzia is present
21		there is intra-alveolar
	1	haemorrhage
	2	oedema
22		tissue has been taken for asb fibre count
23		additional comments _____

Heart

the sections show:

1		a tuberculous pericarditis
2		an acute myocardial infarct
3		additional comments _____

Bronchi and bronchioles

1		chronic bronchiolitis
	1	cannot be assessed due to poor preservation
	2	is absent
	3	insignificant
	4	moderate
	5	marked
2		bronchial gland hyperplasia
	1	cannot be assessed due to poor preservation
	2	cannot be determined, main bronchi are absent
	3	absent
	4	insignificant
	5	moderate
	6	marked
3		The Reid Index is ,
4		additional comments _____

Oesophagus

1		sections show a squamous carcinoma
2		additional comments _____

--	--	--	--	--	--	--	--

--	--	--	--	--	--

[illegible]

Dust exposure totals:

High dust	
Low dust	
Surface dust	
Non-dust	
Gaps	
Grand total	

Certification

[illegible]

Calendar period: 19__ to 19__/_/___ years ___ months

APPENDIX 9

PATHAUT cause of death codes: 1976, 1998 and 2003

Code	1976	1998	2013
000	Not stated		
001		Not stated	Not stated
002		Pulmonary tuberculosis was not present	Pulmonary tuberculosis was not present
1. DISEASES OF THE RESPIRATORY SYSTEM			
101	Bronchogenic carcinoma - squamous (epidermoid)	Malignancies of the respiratory system - Squamous	Malignancies of the respiratory system - Squamous
102	Bronchogenic carcinoma - large cell	- Large cell	- Large cell
103	Bronchogenic carcinoma - small cell	- Small cell	- Small cell
104	Bronchogenic carcinoma - adeno carcinoma	- Adeno carcinoma	- Adeno carcinoma
105	Broncho-alveolar carcinoma/peripheral – squamous	- Broncho-alveolar	- Broncho-alveolar
106	Broncho-alveolar carcinoma/peripheral – large cell	- Type not stated	- Type not stated
107	Broncho-alveolar carcinoma/peripheral – small cell	Kaposi sarcoma of lungs	Kaposi sarcoma of lungs
108	Broncho-alveolar carcinoma/peripheral – adeno carcinoma	Upper respiratory tract malignancies	Upper respiratory tract malignancies
109	Mesothelioma	Mesothelioma	Mesothelioma
110	Other malignancies of the respiratory tract: carcinoid tumours, melanomas, sarcomas, C.A. larynx, bronchial gland tumours, multiple malignancies, Leiomyosarcoma, upper respiratory malignancies	Other malignancies of the respiratory tract: bronchial gland, larynx, carcinoid, melanomas, sarcomas, etc.	Other malignancies of the respiratory tract: larynx, carcinoid, melanomas, sarcomas, etc.
111	Pneumonia - lobar	Lobar pneumonia	Lobar pneumonia
112	Pneumonia - broncho	Broncho pneumonia	Broncho pneumonia
113	Pneumonia -others (fulminating, consolidation, terminal, bilateral viral influenza, pneumonitis, abscess,	Pneumonia (unspecified)	Pneumonia (unspecified)

Code	1976	1998	2013
	inhalation, empyema, fungal, organism, suppurative)		
114	Emphysema, chronic bronchitis, chronic obstructive lung disease (COLD)	Cryptococcal pneumonitis (fungal)	Cryptococcal pneumonitis (fungus)
Code	1976	1998	2013
115	Pulmonary embolus/thrombosis (congestion, lung function)	Pneumocystis carinii pneumonia	Pneumocystis carinii pneumonia
116	Others (oedema, respiratory failure, oedema of glottis, congestion, status asthmaticus, fibrosis, insufficiency, pleurisy and pleural effusion, pneumothorax, pulmonary haemosiderosis, haemoptysis)	Other Fungal (i.e. not Cryptococcus/Pneumocystis)	Other Fungal (i.e. not Cryptococcus/Pneumocystis)
117	Bronchogenic carcinoma - multiple malignancy (more than one)	Organising pneumonia	Organising pneumonia
118		Suppurative pneumonia	Suppurative pneumonia
119	Pneumoconiosis, asbestosis, silicosis, CWP	Viral pneumonia (cytomegalovirus)	Viral pneumonia (e.g. cytomegalovirus)
120	Tuberculosis (TB)	Tuberculosis: Pulmonary TB, TB site not stated, miliary TB	Tuberculosis: Pulmonary TB, Miliary TB
121	Bronchogenic carcinoma – type not stated (neoplasm at Carina)	Aspiration pneumonia	Aspiration pneumonia
122		Inactive / old tuberculosis	Inactive / old tuberculosis
123		Interstitial pneumonitis	Interstitial pneumonitis
124		Shock lung (Diffuse alveolar damage)	Shock lung (Diffuse alveolar damage)
125		Other pneumonia: Abscess, Necrotising pneumonia, Empyema, Inhalation, Respiratory infection etc.	Other pneumonia: Abscess, Necrotising pneumonia, Empyema, Inhalation, Respiratory infection etc.

Code	1976	1998	2013
126		Chronic obstructive lung disease, Chronic bronchitis, emphysema (COLD)	Chronic obstructive lung disease, Chronic bronchitis, emphysema (COLD)
127		Asthma	Asthma
128		Pulmonary embolism/thrombosis	Pulmonary embolism/thrombosis
129		Pneumoconiosis, Coal workers pneumoconiosis, Silicosis, Asbestosis, etc.	Pneumoconiosis, Coal workers pneumoconiosis, Silicosis, Asbestosis, etc.
130		Respiratory failure, Cardiorespiratory failure/arrest, Respiratory arrest, Lung disease	Respiratory failure, Cardiorespiratory failure/arrest, Respiratory arrest, Lung disease
131		Other, specified: Oedema, Fibrosis, Pleural effusion, etc.	Other, specified: Oedema, Fibrosis, Pleural effusion, etc.
2. CARDIO VASCULAR			
201	Cor Pulmonale (Right ventricular failure)	Cor Pulmonale (Right ventricular failure)	Cor Pulmonale (Right ventricular failure)
202	Hypertensive cardiac failure (Left ventricular failure), malignant hypertension	Hypertensive cardiac failure (Left ventricular failure)	Hypertensive cardiac failure (Left ventricular failure)
203	Coronary heart disease: Acute myocardial infarction, arteriosclerotic heart disease, atheroma, ischaemic fibrosis, occlusion, coronary thrombosis	Coronary heart disease: Acute myocardial infarction, arteriosclerotic heart disease, atheroma, ischaemic fibrosis, occlusion, coronary thrombosis	Coronary heart disease: Acute myocardial infarction, arteriosclerotic heart disease, atheroma, ischaemic fibrosis, occlusion, coronary thrombosis
204	Aneurysms, retroperitoneal haemorrhage	Aneurysms	Aneurysms
205	Other specified cardiovascular diseases: arrhythmia, auricular/ventricular fibrillation, bantú myocardosis, cardiomegaly, cardiomyopathy, coarctation, myocarditis, pericarditis n.o.s., tachycardia, tamponade	Other specified cardiovascular diseases: arrhythmia, auricular/ventricular fibrillation, bantú myocardosis, cardiomegaly, cardiomyopathy,	Other specified cardiovascular diseases: arrhythmia, auricular/ventricular fibrillation, bantú myocardosis, cardiomegaly, cardiomyopathy,

Code	1976	1998	2013
		coarctation, myocarditis, pericarditis n.o.s., tachycardia, tamponade	coarctation, myocarditis, pericarditis n.o.s., tachycardia, tamponade
206	Cardiac failure (C.F.F.) – not stated	Congestive cardiac failure, Cardiac failure, cardiac arrest, etc.	Congestive cardiac failure, Cardiac failure, cardiac arrest, etc.
207	Valvular diseases: Aortic stenosis/incompetence, Rheumatic	Valvular diseases: Aortic stenosis/incompetence, Rheumatic	Valvular diseases: Aortic stenosis/incompetence, Rheumatic
208		TB pericarditis	TB pericarditis
3. CENTRAL NERVOUS SYSTEM			
301	Cerebral vascular accident: aneurysm, apoplexy, cerebral thrombosis, cerebral infarction, cerebral haemorrhage, embolism, stroke, subdural/subarachnoid haemorrhage	Cerebral vascular accident: aneurysm, apoplexy, cerebral thrombosis, cerebral infarction, cerebral haemorrhage, embolism, stroke, subdural/subarachnoid haemorrhage	Cerebral vascular accident: aneurysm, apoplexy, cerebral thrombosis, cerebral infarction, cerebral haemorrhage, embolism, stroke, subdural/subarachnoid haemorrhage
302	Tumours: Astrocytoma, Glioma, etc.	Tumours: Astrocytoma, Glioma, etc.	Tumours: Astrocytoma, Glioma, etc.
303	Meningitis, Encephalitis, Abscess, Waterhouse-Fredrieichsen, meningococcal/tuberculous,/pneumococcal meningitis, septicaemia, Guillain Barrè syndrome	Bacterial meningitis, Encephalitis, Abscess	Bacterial meningitis, Encephalitis, Abscess
Code	1976	1998	2013
304	Others: Parkinson's, oedema, syringomyelia, rabies, status epilepticus/epilepsy, polyneuritis, cystercercosis, lesion, spinal cord, ependymoma	Others: Guillain Barrè syndrome, convulsions, cystercercosis, epilepsy, oedema, polyneuritis, progressive neuromuscular paralysis, syringomyelia	Others: Guillain Barrè syndrome, convulsions, cystercercosis, epilepsy, oedema, polyneuritis, progressive neuromuscular paralysis, syringomyelia
305		Tuberculosis: TB of the nervous system, TB meningitis, Tuberculomas	Tuberculosis: TB of the nervous system, TB meningitis, Tuberculomas
306		Cryptococcal meningitis	Cryptococcal meningitis
4 GASTRO-INTESTINAL TRACT			

Code	1976	1998	2013
401	Peptic ulceration, (duodenal, gastric)	Diseases of the stomach & duodenum Peptic ulceration, (duodenal, gastric)	Diseases of the stomach & duodenum Peptic ulceration, (duodenal, gastric)
402	Carcinoma of the Stomach	Carcinoma of the Stomach	Carcinoma of the Stomach
403	Carcinoma of the Pancreas	Carcinoma of the Pancreas	Carcinoma of the Pancreas
404	Carcinoma of the Oesophagus	Carcinoma of the Oesophagus	Carcinoma of the Oesophagus
405	Carcinoma of the Liver (hepatoma)	Carcinoma of the Liver (hepatoma), gallbladder, bile duct, Hepatocellular carcinoma	Carcinoma of the Liver (hepatoma), gallbladder, bile duct, Hepatocellular carcinoma
407	Carcinoma Other: rectum, colon, parotic, bile duct, gall bladder, bowel, tongue, mouth	Carcinoma Other: Parotid, Tongue, Mouth, Gingiva etc.	Carcinoma Other: Parotid, Tongue, Mouth, Gingiva etc.
408		Carcinoma of the Rectum, Colon	Carcinoma of the Rectum, Colon
406	Other (cirrhosis, mesenteric haemorrhage/thrombosis, budd chiari, peritonitis, hepatic failure, hepatomegaly, necrosis, volvulus colon, atrophy, pancreatitis, toxic dilated bowels, entero- colitis, aneurysm, abscess, TIT, haem. Biliary obstruction, cholecystitis, oesophageal varices, ulcerative colitis, hernia, haematemesis, liver failure, beriberi, subphrenic, intestinal obstruction, dysphagia and marasmus, hepatosplenomegaly, bowel fistula, fatty liver, gastritis, hepatitis, jaundice	Other diseases of the gastro-intestinal tract: Hepatic failure, Hepatomegaly, Fatty liver, Hepatitis, Jaundice, Cirrhosis, Budd Chiari, Biliary obstruction, Beriberi, Cholecystitis, Mesenteric haemorrhage, Mesenteric thrombosis, Peritonitis, Volvulus, Pancreatitis, Toxic dilated bowel, Entero-colitis, Abscess, Oesophageal varices, Ulcerative colitis, Hernia, Intestinal obstruction, Dysphagia & marasmus, Gastritis, Bowel fistula, Dysentery	Other diseases of the gastro-intestinal tract: Hepatic failure, Hepatomegaly, Fatty liver, Hepatitis, Jaundice, Cirrhosis, Budd Chiari, Biliary obstruction, Beriberi, Cholecystitis, Mesenteric haemorrhage, Mesenteric thrombosis, Peritonitis, Volvulus, Pancreatitis, Toxic dilated bowel, Entero-colitis, Abscess, Oesophageal varices, Ulcerative colitis, Hernia, Intestinal obstruction, Dysphagia & marasmus, Gastritis, Bowel fistula, Dysentery
409		Tuberculosis of the gastro-intestinal tract	Tuberculosis of the gastro-intestinal tract
5. GENITO URINARY TRACT			

Code	1976	1998	2013
501	Nephritis (glomerulonephritis, pyelonephritis)	Renal failure unspecified, Uraemia	Renal failure unspecified, Uraemia
502	Others: renal failure/calculus, CA ureter, kidney abscess, CA kidney, CA prostrate, necrosis, nephrosclerosis, polycystic	Unspecified acute renal failure	Unspecified acute renal failure
503	Carcinoma of the bladder	Chronic renal failure, End-stage renal disease	Chronic renal failure, End-stage renal disease
504		Carcinoma: Bladder, Prostate, Kidney, Ureter, etc.	Carcinoma: Bladder, Prostate, Kidney, Ureter, etc.
505		Other: Nephritis not specified, Glomerulonephritis, Pyelonephritis, Kidney abscess, Nephrosclerosis, Polycystic, Renovascular disease, Hydronephrosis	Other: Nephritis not specified, Glomerulonephritis, Pyelonephritis, Kidney abscess, Nephrosclerosis, Polycystic, Renovascular disease, Hydronephrosis
506		TB of genito urinary tract organs	TB of genito urinary tract organs
6. METABOLIC DISEASES			
601	Diabetes mellitus/coma	Diabetes mellitus	Diabetes mellitus
602	Other: Amyloidosis, Hyperaldosteronism, Hypoglycaemia	Other: Amyloidosis, Hyperaldosteronism, Hyperglycaemia, Hypoglycaemia	Other: Amyloidosis, Hyperaldosteronism, Hyperglycaemia, Hypoglycaemia
Code	1976	1998	2013
603	Uraemia		

Code	1976	1998	2013
7. ENDOCRINE SYSTEM			
701	Carcinoma - thyroid	Malignant neoplasm of the thyroid gland	Malignant neoplasm of the thyroid gland
702	Others: adenoma, pituitary, adeno cortex	Other tumours	Other tumours
8. HAEMATOLOGY AND R.E.S. (Reticulo Endothelial System)			
801	Leukaemia (monocytic, myeloid, lymphatic)	Leukaemia	Leukaemia
802	Lymphoma/reticulosis, , Hodgkin's disease, reticulum cell sarcoma	Other malignancies: Lymphoma, Hodgkin's disease, etc.	Other malignancies: Lymphoma, Hodgkin's disease, etc.
803	Other: anaemia, dyscrasia myelomatosis, haematemesis, idiopathic thrombocytopenic purpura, polycythaemia, splenomegaly, septicaemia,	Other: anaemia, dyscrasia myelomatosis, haematemesis, idiopathic thrombocytopenic purpura, polycythaemia, splenomegaly	Other: anaemia, dyscrasia myelomatosis, haematemesis, idiopathic thrombocytopenic purpura, polycythaemia, splenomegaly
9. MISCELLANEOUS			
900	Unnatural causes: Anoxia, Asphyxia, Brain damage, Contusion, Drowning, Exsanguination, General haemorrhages, Haemothorax, Motor vehicle accident (MVA, Car smash), Multiple injuries, Pneumothorax, Poisoning, Shock, Shot wounds, Stab wounds, Suffocation, Suicide	Unnatural causes: Anoxia, Asphyxia, Brain damage, Contusion, Drowning, Exsanguination, General haemorrhages, Haemothorax, Motor vehicle accident (MVA, Car smash), Multiple injuries, Pneumothorax, Poisoning, Shock, Shot wounds, Stab wounds, Suffocation, Suicide	Unnatural causes: Anoxia, Asphyxia, Brain damage, Contusion, Drowning, Exsanguination, General haemorrhages, Haemothorax, Motor vehicle accident (MVA, Car smash), Multiple injuries, Pneumothorax, Poisoning, Shock, Shot wounds, Stab wounds, Suffocation, Suicide

Code	1976	1998	2013
901		TB any other site (specified): T of the spine, etc. NB CLINICAL DISSEMINATED TB WITH NO PTB AT AUTOPSY CODE AS 901 29/10/03	TB any other site (specified): TB of the spine, etc. NB CLINICAL DISSEMINATED TB WITH NO PTB AT AUTOPSY CODE AS 901 29/10/03
991	Collagen diseases: Rheumatoid disease,	Collagen diseases: Rheumatoid disease, Scleroderma, Systemic lupus erythematosus	Collagen diseases: Rheumatoid disease, Scleroderma, Systemic lupus erythematosus
992	Collagen diseases: Scleroderma	 was not confirmed (clinical finding eg. Pulmonary TB was not confirmed)	 was not confirmed (clinical finding eg. Pulmonary TB was not confirmed)
993	Collagen diseases: others (Stevens Johnson syndrome) Systemic lupus erythematosus	Infections not specified: Septicaemia, Malaria, Bilharzia, Typhoid, Chickenpox, Septic shock, etc.	Infections not specified: Septicaemia, Malaria, Bilharzia, Typhoid, Chickenpox, Septic shock, etc.
994	Collagen diseases: disseminated systemic lupus erythematosus		
995	Malignancies (not defined and miscellaneous): Epithelial tumour, Maxillary antrum, Leiomyosarcoma in leg etc., Melanoma, Fibrosarcoma, Rhabdomyosarcoma, General carcinomatosis, Myosarcoma, Anaplastic neoplasm, Metastatic, Thymic	Malignancies (not defined and miscellaneous): Epithelial tumour, Maxillary antrum, Leiomyosarcoma in leg etc., Melanoma, Fibrosarcoma, Rhabdomyosarcoma, General carcinomatosis, Myosarcoma, Anaplastic neoplasm, Metastatic, Thymic, Kaposi sarcoma	Malignancies (not defined and miscellaneous): Epithelial tumour, Maxillary antrum, Leiomyosarcoma in leg etc., Melanoma, Fibrosarcoma, Rhabdomyosarcoma, General carcinomatosis, Myosarcoma, Anaplastic neoplasm, Metastatic, Thymic, Kaposi sarcoma

Code	1976	1998	2013
996	Other general: gangrene, mycosis fungoides, haemochromatosis, haemorrhage from anti-coagulants	Other general: Multi organ failure, Gangrene, Maycosis fungoides, Haemochromatosis, Haemorrhage from anti-coagulants, Toxaemia	Other general: Multi organ failure, Gangrene, Maycosis fungoides, Haemochromatosis, Haemorrhage from anti-coagulants, Toxaemia
997	Infections – malaria, bilharzia, septicaemia, typhoid, trypanosomiasis	HIV disease: HIV, Aids, Immune compromised, A.R.C, Poor immune response, etc.	HIV disease: HIV, Aids, Immune compromised, A.R.C, Poor immune response, etc.
998	(Undetermined) natural causes	(Undetermined) natural causes	(Undetermined) natural causes
999	Not confirmed – not found, not ascertained	Cause of death could not be ascertained	Cause of death could not be ascertained

128		Pulmonary embolism/thrombosis	Pulmonary embolism/thrombosis
129		Pneumoconiosis, Coal workers pneumoconiosis, Silicosis, Asbestosis, etc.	Pneumoconiosis, Coal workers pneumoconiosis, Silicosis, Asbestosis, etc.
130		Respiratory failure, Cardiorespiratory failure/arrest, Respiratory arrest, Lung disease	Respiratory failure, Cardiorespiratory failure/arrest, Respiratory arrest, Lung disease
131		Other, specified: Oedema, Fibrosis, Pleural effusion, etc.	Other, specified: Oedema, Fibrosis, Pleural effusion, etc.

2. CARDIO VASCULAR

201	Cor Pulmonale (Right ventricular failure)	Cor Pulmonale (Right ventricular failure)	Cor Pulmonale (Right ventricular failure)
202	Hypertensive cardiac failure (Left ventricular failure), malignant hypertension	Hypertensive cardiac failure (Left ventricular failure)	Hypertensive cardiac failure (Left ventricular failure)
203	Coronary heart disease: Acute myocardial infarction, arteriosclerotic heart disease,	Coronary heart disease: Acute myocardial infarction, arteriosclerotic	Coronary heart disease: Acute myocardial infarction, arteriosclerotic

	atheroma, ischaemic fibrosis, occlusion, coronary thrombosis	heart disease, atheroma, ischaemic fibrosis, occlusion, coronary thrombosis	heart disease, atheroma, ischaemic fibrosis, occlusion, coronary thrombosis
204	Aneurysms, retroperitoneal haemorrhage	Aneurysms	Aneurysms
205	Other specified cardiovascular diseases: arrhythmia, auricular/ventricular fibrillation, bantus myocardosis, cardiomegaly, cardiomyopathy, coarctation, myocarditis, pericarditis n.o.s., tachycardia, tamponade	Other specified cardiovascular diseases: arrhythmia, auricular/ventricular fibrillation, bantus myocardosis, cardiomegaly, cardiomyopathy, coarctation, myocarditis, pericarditis n.o.s., tachycardia, tamponade	Other specified cardiovascular diseases: arrhythmia, auricular/ventricular fibrillation, bantus myocardosis, cardiomegaly, cardiomyopathy, coarctation, myocarditis, pericarditis n.o.s., tachycardia, tamponade
206	Cardiac failure (C.F.F.) – not stated	Congestive cardiac failure, Cardiac failure, cardiac arrest, etc.	Congestive cardiac failure, Cardiac failure, cardiac arrest, etc.
207	Valvular diseases: Aortic stenosis/incompetence, Rheumatic	Valvular diseases: Aortic stenosis/incompetence, Rheumatic	Valvular diseases: Aortic stenosis/incompetence, Rheumatic
208		TB pericarditis	TB pericarditis
3. CENTRAL NERVOUS SYSTEM			
301	Cerebral vascular accident: aneurysm, apoplexy, cerebral thrombosis, cerebral infarction, cerebral haemorrhage, embolism, stroke, subdural/subarachnoid haemorrhage	Cerebral vascular accident: aneurysm, apoplexy, cerebral thrombosis, cerebral infarction, cerebral haemorrhage, embolism, stroke, subdural/subarachnoid haemorrhage	Cerebral vascular accident: aneurysm, apoplexy, cerebral thrombosis, cerebral infarction, cerebral haemorrhage, embolism, stroke, subdural/subarachnoid haemorrhage
302	Tumours: Astrocytoma, Glioma, etc.	Tumours: Astrocytoma, Glioma, etc.	Tumours: Astrocytoma, Glioma, etc.
303	Meningitis, Encephalitis, Abscess, Waterhouse-Friedrichsen, meningococcal/tuberculous, pneumococcal meningitis, septicaemia, Guillain Barré syndrome	Bacterial meningitis, Encephalitis, Abscess	Bacterial meningitis, Encephalitis, Abscess
Code	1976	1998	2013
304	Others: Parkinson's, oedema, syringomyelia, rabies, status	Others: Guillain Barré syndrome, convulsions, cystercercosis, epilepsy,	Others: Guillain Barré syndrome, convulsions, cystercercosis, epilepsy,

	epilepticus/epilepsy, polyneuritis, cystercercosis, lesion, spinal cord, ependymoma	oedema, polyneuritis, progressive neuromuscular paralysis, syringomyelia	oedema, polyneuritis, progressive neuromuscular paralysis, syringomyelia
305		Tuberculosis: TB of the nervous system, TB meningitis, Tuberculomas	Tuberculosis: TB of the nervous system, TB meningitis, Tuberculomas
306		Cryptococcal meningitis	Cryptococcal meningitis

4. GASTRO-INTESTINAL TRACT			
401	Peptic ulceration, (duodenal, gastric)	Diseases of the stomach & duodenum Peptic ulceration, (duodenal, gastric)	Diseases of the stomach & duodenum Peptic ulceration, (duodenal, gastric)
402	Carcinoma of the Stomach	Carcinoma of the Stomach	Carcinoma of the Stomach
403	Carcinoma of the Pancreas	Carcinoma of the Pancreas	Carcinoma of the Pancreas
404	Carcinoma of the Oesophagus	Carcinoma of the Oesophagus	Carcinoma of the Oesophagus
405	Carcinoma of the Liver (hepatoma)	Carcinoma of the Liver (hepatoma), gallbladder, bile duct, Hepatocellular carcinoma	Carcinoma of the Liver (hepatoma), gallbladder, bile duct, Hepatocellular carcinoma
407	Carcinoma Other: rectum, colon, parotid, bile duct, gall bladder, bowel, tongue, mouth	Carcinoma Other: Parotid, Tongue, Mouth, Gingiva etc.	Carcinoma Other: Parotid, Tongue, Mouth, Gingiva etc.
408		Carcinoma of the Rectum, Colon	Carcinoma of the Rectum, Colon
406	Other (cirrhosis, mesenteric haemorrhage/thrombosis, budd chiari, peritonitis, hepatic failure, hepatomegaly, necrosis, volvulus colon, atrophy, pancreatitis, toxic dilated bowels, entero- colitis, aneurysm, abscess, TIT, haem. Biliary obstruction, cholecystitis, oesophageal varices, ulcerative colitis, hernia, haematemesis, liver failure, beriberi, subphrenic, intestinal obstruction, dysphagia and marasmus, hepatosplenomegaly, bowel fistula, fatty liver, gastritis, hepatitis, jaundice	Other diseases of the gastro-intestinal tract: Hepatic failure, Hepatomegaly, Fatty liver, Hepatitis, Jaundice, Cirrhosis, Budd Chiari, Biliary obstruction, Beriberi, Cholecystitis, Mesenteric haemorrhage, Mesenteric thrombosis, Peritonitis, Volvulus, Pancreatitis, Toxic dilated bowel, Entero-colitis, Abscess, Oesophageal varices, Ulcerative colitis, Hernia, Intestinal obstruction, Dysphagia & marasmus, Gastritis, Bowel fistula, Dysentery	Other diseases of the gastro-intestinal tract: Hepatic failure, Hepatomegaly, Fatty liver, Hepatitis, Jaundice, Cirrhosis, Budd Chiari, Biliary obstruction, Beriberi, Cholecystitis, Mesenteric haemorrhage, Mesenteric thrombosis, Peritonitis, Volvulus, Pancreatitis, Toxic dilated bowel, Entero-colitis, Abscess, Oesophageal varices, Ulcerative colitis, Hernia, Intestinal obstruction, Dysphagia & marasmus, Gastritis, Bowel fistula, Dysentery
409		Tuberculosis of the gastro-intestinal tract	Tuberculosis of the gastro-intestinal tract
5. GENITO URINARY TRACT			

501	Nephritis (glomerulonephritis, pyelonephritis)	Renal failure unspecified, Uraemia	Renal failure unspecified, Uraemia
502	Others: renal failure/calculus, CA ureter, kidney abscess, CA kidney, CA prostate, necrosis, nephrosclerosis, polycystic	Unspecified acute renal failure	Unspecified acute renal failure
503	Carcinoma of the bladder	Chronic renal failure, End-stage renal disease	Chronic renal failure, End-stage renal disease
504		Carcinoma: Bladder, Prostate, Kidney, Ureter, etc.	Carcinoma: Bladder, Prostate, Kidney, Ureter, etc.
505		Other: Nephritis not specified, Glomerulonephritis, Pyelonephritis, Kidney abscess, Nephrosclerosis, Polycystic, Renovascular disease, Hydronephrosis	Other: Nephritis not specified, Glomerulonephritis, Pyelonephritis, Kidney abscess, Nephrosclerosis, Polycystic, Renovascular disease, Hydronephrosis
506		TB of genito urinary tract organs	TB of genito urinary tract organs
6. METABOLIC DISEASES			
601	Diabetes mellitus/coma	Diabetes mellitus	Diabetes mellitus
602	Other: Amyloidosis, Hyperaldosteronism, Hypoglycaemia	Other: Amyloidosis, Hyperaldosteronism, Hyperglycaemia, Hypoglycaemia	Other: Amyloidosis, Hyperaldosteronism, Hyperglycaemia, Hypoglycaemia
Code	1976	1998	2013
603	Uraemia		

7. ENDOCRINE SYSTEM			
701	Carcinoma - thyroid	Malignant neoplasm of the thyroid gland	Malignant neoplasm of the thyroid gland
702	Others: adenoma, pituitary, adeno cortex	Other tumours	Other tumours
8. HAEMATOLOGY AND R.E.S. (Reticulo Endothelial System)			
801	Leukaemia (monocytic, myeloid, lymphatic)	Leukaemia	Leukaemia
802	Lymphoma/reticulosis, , Hodgkin's disease, reticulum cell sarcoma	Other malignancies: Lymphoma, Hodgkin's disease, etc.	Other malignancies: Lymphoma, Hodgkin's disease, etc.
803	Other: anaemia, dyscrasia myelomatosis, haematemesis, idiopathic thrombocytopenic purpura, polycythaemia, splenomegaly, septicaemia,	Other: anaemia, dyscrasia myelomatosis, haematemesis, idiopathic thrombocytopenic purpura, polycythaemia, splenomegaly	Other: anaemia, dyscrasia myelomatosis, haematemesis, idiopathic thrombocytopenic purpura, polycythaemia, splenomegaly
9. MISCELLANEOUS			
900	Unnatural causes: Anoxia, Asphyxia, Brain damage, Contusion, Drowning, Exsanguination, General haemorrhages, Haemothorax, Motor vehicle accident (MVA, Car smash), Multiple injuries, Pneumothorax, Poisoning, Shock, Shot wounds, Stab wounds, Suffocation, Suicide	Unnatural causes: Anoxia, Asphyxia, Brain damage, Contusion, Drowning, Exsanguination, General haemorrhages, Haemothorax, Motor vehicle accident (MVA, Car smash), Multiple injuries, Pneumothorax, Poisoning, Shock, Shot wounds, Stab wounds, Suffocation, Suicide	Unnatural causes: Anoxia, Asphyxia, Brain damage, Contusion, Drowning, Exsanguination, General haemorrhages, Haemothorax, Motor vehicle accident (MVA, Car smash), Multiple injuries, Pneumothorax, Poisoning, Shock, Shot wounds, Stab wounds, Suffocation, Suicide

901		TB any other site (specified): T of the spine, etc. NB CLINICAL DISSEMINATED TB WITH NO PTB AT AUTOPSY CODE AS 901 29/10/03	TB any other site (specified): TB of the spine, etc. NB CLINICAL DISSEMINATED TB WITH NO PTB AT AUTOPSY CODE AS 901 29/10/03
991	Collagen diseases: Rheumatoid disease,	Collagen diseases: Rheumatoid disease, Scleroderma, Systemic lupus erythematosus	Collagen diseases: Rheumatoid disease, Scleroderma, Systemic lupus erythematosus
992	Collagen diseases: Scleroderma	 was not confirmed (clinical finding eg. Pulmonary TB was not confirmed)	 was not confirmed (clinical finding eg. Pulmonary TB was not confirmed)
993	Collagen diseases: others (Stevens Johnson syndrome) Systemic lupus erythematosus	Infections not specified: Septicaemia, Malaria, Bilharzia, Typhoid, Chickenpox, Septic shock, etc.	Infections not specified: Septicaemia, Malaria, Bilharzia, Typhoid, Chickenpox, Septic shock, etc.
994	Collagen diseases: disseminated systemic lupus erythematosus		
995	Malignancies (not defined and miscellaneous): Epithelial tumour, Maxillary antrum, Leiomyosarcoma in leg etc., Melanoma, Fibrosarcoma, Rhabdomyosarcoma, General carcinomatosis, Myosarcoma, Anaplastic neoplasm, Metastatic, Thymic	Malignancies (not defined and miscellaneous): Epithelial tumour, Maxillary antrum, Leiomyosarcoma in leg etc., Melanoma, Fibrosarcoma, Rhabdomyosarcoma, General carcinomatosis, Myosarcoma, Anaplastic neoplasm, Metastatic, Thymic, Kaposi sarcoma	Malignancies (not defined and miscellaneous): Epithelial tumour, Maxillary antrum, Leiomyosarcoma in leg etc., Melanoma, Fibrosarcoma, Rhabdomyosarcoma, General carcinomatosis, Myosarcoma, Anaplastic neoplasm, Metastatic, Thymic, Kaposi sarcoma

996	Other general: gangrene, mycosis fungoides, haemochromatosis, haemorrhage from anti-coagulants	Other general: Multi organ failure, Gangrene, Maycosis fungoides, Haemochromatosis, Haemorrhage from anti-coagulants, Toxaemia	Other general: Multi organ failure, Gangrene, Maycosis fungoides, Haemochromatosis, Haemorrhage from anti-coagulants, Toxaemia
997	Infections – malaria, bilharzia, septicaemia, typhoid, trypanosomiasis	HIV disease: HIV, Aids, Immune compromised, A.R.C, Poor immune response, etc.	HIV disease: HIV, Aids, Immune compromised, A.R.C, Poor immune response, etc.
998	(Undetermined) natural causes	(Undetermined) natural causes	(Undetermined) natural causes
999	Not confirmed – not found, not ascertained	Cause of death could not be ascertained	Cause of death could not be ascertained

