THE INCIDENCE OF TUBERCULOSIS IN THE INFLAMMATORY BOWEL DISEASE REGISTRY IN CAPE TOWN, SOUTH AFRICA

By

Dr. Mitesh Kanthi Pema
PMXMIT002

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In partial fulfilment of the requirements for the degree

Master of Medicine (MMed) in Medicine

Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN

Date of Submission: 22/02/2020

Supervisors: **Professor Sandie Thomson – Division of Gastroenterology, Department of Medicine, Groote Schuur Hospital**
Dr David Epstein – Private Gastroenterologist, Life Vincent Pallotti Hospital

DECLARATION

I, Mitesh Kanthi Pema, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: …14/03/2021…….

TABLE OF CONTENTS

APPENDICES

ABBREVIATIONS

IBD	inflammatory bowel disease
CD	crohn's disease
UC	ulcerative colitis
IBDU	inflammatory bowel disease unclassified
IST	immunosuppressive therapy
TNF-α	tumour necrosis factor-alpha
IMM	immunomodulator
AZA	azathioprine
6-MP	6-mercaptopurine
MTX	methotrexate
IPT	isoniazid prophylaxis therapy
TB	tuberculosis
PTB	pulmonary tuberculosis
EPTB	extrapulmonary tuberculosis
TST	tuberculin skin test
IGRA	interferon gamma releasing assay
LTBI	latent tuberculosis infection
LMI	low and middle income
FDA	food and drug administration
SA	South Africa
CCT	City of Cape Town
IR	incidence rate
PY	person years
aOR	adjusted odds ratio
CI	confidence interval

ACKNOWLEDGEMENTS

I would like to thank:

Professor SR Thomson for his patience and guidance during this entire journey. His vast knowledge and experience were invaluable and this thesis would not have been possible without his unconditional support.

Dr D Epstein for always dedicating time outside his busy practice hours to assist me in all aspects of this project and for giving me permission to use the data from the national registry he founded and created.

Kathryn Manning for assistance with the statistical analyses.

All the hardworking nursing and administrative staff in the E23 gastroenterology unit at Groote Schuur Hospital.

My mother and late father for their sacrifices and support in getting me to this point in my career.

And finally, my wife to whom I am eternally grateful for all her love, understanding and support.

CHAPTER1: INTRODUCTION & LITERATURE REVIEW

Introduction

Inflammatory bowel disease (IBD) has become a global disease.[1] In the past it was a disorder mostly prevalent in North American and European populations, but according to recent epidemiological studies, IBD is diagnosed more frequently in traditionally low-incident regions such as Asia, the Middle East, Eastern Europe and Africa.[2-6] Aside from the epidemiological shift, changes in therapeutic strategies have resulted in immunosuppressive therapy (IST) being used earlier and more often as first-line medical treatment compared to past practices. Included in this armamentarium are tumour necrosis factor-alpha (TNF-α) blockers which have enhanced management further, especially in cases previously refractory to conventional immunomodulators (IMMs). However, the risk of developing tuberculosis (TB) is significantly higher in patients using IST, and in particular TNF-α blockers.[7] This is a concern in the South African and Western Cape population where active and latent TB (LTB) infection rates are amongst the highest in the world.[8] The increasing burden of IBD in this environment therefore makes the use of IST extremely challenging and warrants the development of local treatment guidelines.

Epidemiology of IBD

Ulcerative colitis (UC) and Crohn's disease (CD) are the most common types of IBD. IBD unclassified (IBDU) is another variant assigned to the remaining 10-15% of cases where there is initially difficulty in establishing a definitive diagnosis of UC or CD. A diagnosis is made based on a combination of clinical, radiological and endoscopic findings together with supporting histological features on biopsy specimens.

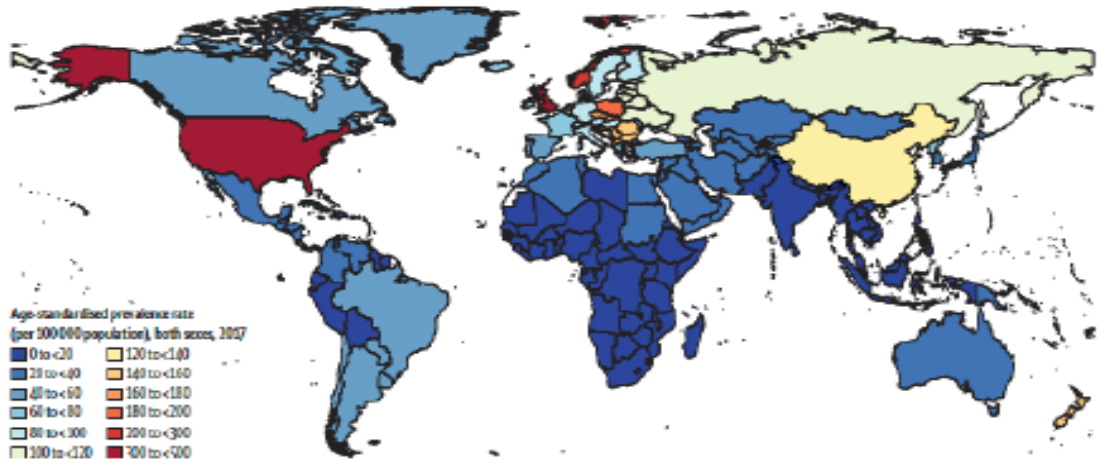
The exact aetiology of IBD is not known and its pathogenesis is still not completely understood despite extensive research in this area. Our current understanding suggests that proposed mechanisms involve a complex interplay between a subject's dysregulated immune system and their altered gut microbiome, which are activated by various environmental triggers in individuals with a genetic susceptibility

for the disease.[9] Several IBD classifications and severity assessment tools are used. Their rationale is to guide therapy, monitor progress and compare outcomes of therapeutic strategies. The Montreal classification is used to classify disease location in IBD patients (see Appendix A).[10] Disease activity and severity is determined using the Crohn's Disease Activity Index (CDAI) and Truelove & Witt's criteria for CD and UC respectively (see Appendices B & C).[11,12]

IBD is now a global disease. By 2017, there were over 6.8 million cases worldwide and the global prevalence rate has increased since 1990.[13] Traditionally the burden of disease was seen predominantly in developed countries where IBD today still affects 1.4 million Americans and more than 2.5 million people in Europe. This corresponds with peak incidence rates of 24.0 and 11.5 per 100 000 person years (PY) and a prevalence of 294 and 213 cases per 100 000 persons for UC & CD respectively in these regions.[14]

However, the turn of the 21st century has seen a distinct change in disease patterns as IBD has emerged in non-western countries where previously its occurrence was considered to be rare. In Japan, the prevalence of CD has increased from 2.9 in 1986 to 13.5 per 100 000 persons in 1998, whilst in Hong Kong the prevalence of UC has increased from 2.3 to 6.3 per 100 000 persons over a 9-year period.[15] Countries in the Middle East are also experiencing a similar trend and in Iran the incidence of IBD increased from 0.62 to 3.11 and the prevalence from 4.69 to 40.67 per 100 000 from 1990 to 2012.[16]

Figure 1 compares the 1990 to 2017 prevalence and shows there is an overall increase in the age-standardized prevalence rate of 5 and a reduction in the age-standardized death rate of 0.1 per 100 000. The graphic also shows that African nations' prevalence are a sixth of that seen in the UK and the United States (US) and are more comparable to data from South America and the Indian subcontinent. They show marked variation and highlight continental and national geographic differences in IBD.



The age-standardised prevalence rate increased:
79·5 (75·9–83·5) per 100 000 population in 1990
84·3 (79·2–89·9) per 100 000 population in 2017
The age-standardised death rate decreased:
0·61 (0·55–0·69) per 100 000 population in 1990
0·51 (0·42–0·54) per 100 000 population in 2017

Adapted from: The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017

Figure 1

In contrast, the rising incidence witnessed during the latter part of the 20th century in western countries has gradually stabilised and is evident from studies in these areas where rates of disease have shown a plateau.[17] The prevalence continues to escalate in high-burden areas. At present, IBD affects more than 0.3% of their respective populations and the projected burden of disease is likely to be substantially higher in the future based on this current trajectory.

Reasons for this epidemiological transition are likely multifactorial and include aspects such as vigilance by health staff, easier access to hospitals and clinics and improvement in diagnostic equipment and technology in the developing world. The contribution of progressive healthcare to this transformation is probably small and it is more likely that changes are linked to social and economic progress and the adoption of a modern and 'westernised lifestyle' by the population in developing countries.[18] IBD epidemiological patterns from the past have often demonstrated a parallel relationship between disease emergence and urbanisation and industrialisation of society.[19] The practices related to the hygiene hypothesis is believed to have accounted for this change in developing countries. Exposure to fewer childhood infections impairs development of the immune system and may later in life predispose individuals to autoimmune diseases like IBD.

Migration studies support this ideology, as subjects that immigrate from low-and-middle income countries (LMIC) to western countries are also at increased risk of developing IBD.[20,21] In the United Kingdom (UK), the incidence of UC in South Asians that have settled in Leicester has increased from 14.3/10^5 to 17.2/10^5 population/year over a period spanning more than two decades. In addition to quantity, disease behaviour has also progressively worsened as the extent of disease in the second-generation migrants appears to be comparable to the native population and is more severe than in first-generation and new migrants.[22]

Another geographic variant evident in IBD, both within and between countries, is its occurrence along a latitudinal north-south gradient relative to the equator. There were more hospitalisations for IBD in the northernmost states of the United States (US) as well as lower rates of disease in southern European countries in comparison to centres located at their respective opposite cardinal points.[23,24] An inverted relationship also exists in the southern hemisphere where high rates of IBD in Australia and New Zealand are comparable to those in North America and Europe.[25,26] It is speculated that changes in ultraviolet (UV) light exposure itself, or external environmental and lifestyle factors that influence exposure, in regions furthest from the equator forms the basis of the vitamin D positive feedback hypothesis and that the resulting deficiency may contribute to IBD pathogenesis and disease progression.[27,28]

IBD in Africa is still considered to be rare. There are no population-based epidemiological studies to accurately assess and quantify the burden of disease. In South Africa (SA), IBD data is limited to hospital-based cohort studies from the 1970s and ‘80s.[29-31] From 1970 -1984, there was a clear increase in the incidence of UC from 4.0 to 7.5, and CD from 1.5 to 4.7/100 000/year in the greater Cape Town area.[32] Many other African countries have also experienced socioeconomic improvement over recent decades and case series published during this same period indicate an increasing burden of disease.[33,34]

Impact of TB

TB is also a global problem and one of the leading infectious causes of mortality worldwide. In 2016 there were an estimated 10.4 million incident cases and more than 1.6 million deaths related to TB. South-East Asia, Africa and the Western Pacific regions are responsible for over 75% of all cases whilst Europe and the Americas together account for only 6% of the total, clearly highlighting the huge disparity in disease distribution between the developed and developing world. African countries contribute significantly to this burden (25%) with Nigeria and South Africa together accounting for 4% of the global total. An additional complicating factor in Africa is the high proportion of TB cases that are co-infected with human immunodeficiency virus (HIV), with rates in some areas in southern Africa exceeding 50%.[35] South Africa currently has one of the highest TB rates in the world.[36] In 2009 the City of Cape Town (CCT), which is a major metropolitan district of the Western Cape, had an incidence rate of 877/100 000.[37]

Pulmonary TB (PTB) is the main form of the disease, but extrapulmonary TB (EPTB), which affects all other organs, makes up about 15-20% of all diagnosed cases. Disseminated TB is another form of the disease used to describe spread of the primary lung infection to other parts of the body via the blood or lymph stream and occurs in 1-2% of immune competent individuals. The abdomen is the sixth most common site affected outside the lungs and contributes to 5-17% of extrapulmonary [38] and 2% of global TB cases. Abdominal infection can involve the peritoneum, solid or hollow organs and the lymphatic system. Gastrointestinal (GI) disease therefore makes up a smaller portion of cases from this system, but estimating its burden is not straightforward as many publications use the terms of abdominal & GI TB interchangeably. In 2015, GI TB was diagnosed in 5.9% of all cases in England and accounted for 10% of their EPTB total.[39] By comparison, a single South African tertiary hospital recorded higher rates of disease as 11.7% of all new cases involved the abdomen and contributed to 27.5% of extrapulmonary diagnoses.[40] There is no epidemiological data specifically for intestinal TB, but it is expected that the burden would follow the same pattern as for abdominal TB in that country.

EPTB has many additional challenges compared to regular TB. Their clinical presentations are non-specific and the difficulties with obtaining a suitable specimen

for testing, coupled with a poor microbiological yield from the sample, often lead to a delay in its diagnosis and treatment. An immunocompromised state is one of the main risk factors for developing EPTB and a high index of suspicion is warranted in this group. HIV co-infection rates were noted to be higher in patients with extrapulmonary and abdominal TB, particularly subjects from endemic countries but also in migrant populations currently living in low-burden settings.[40,41] EPTB can also mimic non-infectious conditions like IBD. Gastrointestinal involvement with either disease is sometimes indistinguishable based on their shared clinical, endoscopic, radiologic and histological findings and some instances require risky empiric treatment of one condition to exclude the other. This is worrying in high burden TB countries where IBD is also starting to emerge.

The influence of latent TB infection (LTBI) is also a significant factor due to the potential of such cases to later progress to active TB. LTBI refers to people infected with Mycobacterium TB (MTB) without clinical, radiologic or microbiologic evidence of active disease. It is believed to affect about a third of the world's population and contributes to the large reservoir of TB cases in high TB burden countries like South Africa.[42] About 5-10% of infected persons that are untreated will progress to TB disease during their lifetime, many within the first 2 years. People at high risk of acquiring infection include close contacts, children under 5 years, immigrants from high burden countries and those working or residing in high-risk institutions such as hospitals, shelters, prisons and nursing homes. Additionally, the risk of progression to TB disease is increased in infected people with weakened immune systems due to conditions such as HIV, diabetes, kidney disease, silicosis, substance abuse, organ transplants, malignancy as well as in people taking drugs that suppress immunity. In South Africa, the acquisition of TB by both these mechanisms contribute equally to the high TB incidence rate in the population.[35,43] Two screening methods are currently available to assist in establishing a diagnosis: the older tuberculin skin tests (TSTs) using the Mantoux technique and the modern interferon-gamma releasing assay (IGRA) blood tests e.g. the QuantiFERON-TB® Gold In-Tube (QFT-GIT) and T-SPOT.TB® tests. It is important to stress that there is no gold standard worldwide for the diagnosis of LTB and that both tests are used primarily to determine Mycobacterium TB (MTB) exposure and therefore cannot distinguish latent infection from active disease.

There are many operational and technical differences between these tests. Purified protein derivative (PPD) is the tuberculin material found in TSTs and consists of a mixture of antigens from MTB as well as *M. bovis*- Bacille Calmette-Guérin (BCG) and several other nontuberculous mycobacteria (NTM). Once injected under the skin, it causes a delayed-type hypersensitivity response driven by T-lymphocytes in infected individuals, that manifests 48-72 hours later as an area of induration around the injection site. In contrast, the QFT-GIT test uses an enzyme-linked immunosorbent assay (ELISA) technique to measure the concentration of interferon gamma (IFN-γ) produced within a whole blood sample tube lined with MTB-specific antigens (culture filtrate protein 10 (CFP-10), early secretory antigenic target protein 6 (ESAT-6), TB7.7). The T-SPOT.TB test works along similar principles, but uses an enzyme-linked immunospot (ELISPOT) assay to measure the number of IFN-γ producing mononuclear cells (spots) when stimulated by separate mixtures of CFP-10 and ESAT-6.

Interpretation of results also differ in accordance with their respective methodologies. TST outcomes are graded by the size of induration in millimetres (mm) measured on the forearm and the cut-off for positivity will vary depending on an individual's risk of infection and progression to TB. An induration of $\geq$5mm is considered positive in immunosuppressed patients, recent TB contacts or people with chest radiography consistent with old TB while people with no known risk factors are considered positive if induration is $\geq$15mm. A special consideration with TSTs though is the booster phenomenon which occurs mainly in older and previously infected adults and is based on the principle that one's immune response gradually wanes over time. Therefore, a positive change in result of a second TST performed 1-3 weeks later should be interpreted as a booster response in this vulnerable group as opposed to a new infection or test conversion. In contrast, IGRAs are analysed in the laboratory by specialised and expensive equipment and are reported according to the concentration of IFN-γ (QFT-GIT) or the number IFN-γ producing cells (T-SPOT.TB) in relation to controls and results can be either positive, negative or indeterminate.

Deciding which immunodiagnostic to use is often difficult as each test has its own limitations. A notable disadvantage of TSTs is their reduced capability to identify new LTB infections in BCG-vaccinated and NTM-infected individuals because of cross-reactivity of antigens present in the test. This frailty was later proven in a meta-analysis where the specificity between TSTs and IGRAs was noted to be similar among non-BCG-vaccinated individuals (97% versus 99% respectively), but markedly different in BCG-vaccinated individuals (59% versus 96% respectively).[44] TST sensitivity is also influenced negatively by multiple factors such as concurrent infections, recent TB infection (within 8 weeks), chronic renal failure, low protein states, immunosuppressive drugs, lymphoma, chronic leukaemia, extremes of age and stress.[45] IST use is a factor of particular concern in the IBD population being tested with TSTs as there is a higher rate of anergy in patients using them (steroids and IMMs) compared to no treatment (83% vs 43%, $p < 0,002$), resulting in higher rates of false-negative reactions.[46] TSTs also require a second visit back after exactly 48-72 hours for measuring skin reactions, which itself has the potential to be incorrectly interpreted by the health professional if not properly trained.

IGRAs are therefore more specific, but also have a better sensitivity than TSTs. In another meta-analysis comparing their performance in confirmed TB cases, TSTs had a sensitivity of 69.9% (95% CI, 67%-72%) compared to pooled sensitivities of 81% (95% CI, 78%-83%) and 87.5% (95% CI, 85%-90%) for QFT-GIT and T.SPOT.TB assays respectively.[47] The sensitivity of T-SPOT.TB is superior to QFT-GIT and may be explained by differences in their technical methodology.[48] The QFT-GIT assay is tested on whole blood which may not contain sufficient mononuclear cells in the sample from the start whereas the T-SPOT.TB assay first requires isolation of a standardised number of washed peripheral mononuclear cells before antigen exposure and analysis. Both IGRAs are also influenced by factors other than lymphopenia such as old age, hypoproteinaemia and immunosuppression.[49] Therefore like TSTs, IGRAs are also affected by immunosuppressive drugs as was demonstrated in a systematic review where their use in patients with autoimmune diseases was less likely to yield a positive result compared to no IST use (OR 0.66; 95% CI 0.53-0.83).[50] Indeterminate results in particular is the unfavourable outcome of this effect and often requires the test to be repeated.[51]

Although the reviews would tend to favour IGRAs over TSTs, it is important to note that many of these studies were conducted in developed countries with a low TB prevalence. Differences between tests are more heterogenous when evaluated in various high risk groups more commonly encountered in developing countries. TSTs were superior to IGRAs when conducted in children (sensitivity: 79% vs 67%; specificity: 94% vs 73%) and recent migrants from high TB burden countries (sensitivity: 90% vs 76%; specificity: 76% vs 65%). There were also mixed findings in immunocompromised individuals excluding HIV (transplant, dialysis, renal failure, autoimmune diseases) as IGRAs were more sensitive and TSTs more specific compared to the other. In the HIV population, QFT-GIT had a better sensitivity (59% vs 53%) and specificity (85% vs 82%) than TSTs [52]. In a South African study that compared the performances in health care workers (HCWs), TSTs were more sensitive, IGRAs more specific and the combination of both had a better negative predictive value than individual tests.[53] The WHO currently recommends that either test can be used to test for LTB and the choice is mainly dependent on its availability and affordability.[54]

Strategies to control TB and prevent resistance are directed mainly towards managing active disease, but an important secondary priority is also the identification and treatment of individuals at high risk of latent infection. All forms of TB are treated with combination therapies of 2 months of rifampicin (RMP), isoniazid (INH), pyrazinamide and ethambutol (initiation phase) followed by 4-7 months of RMP and INH (continuation phase). LTB chemoprophylaxis has more diverse regimens with RMP, rifapentine and INH used either alone or in combinations and given for varying durations ranging from 1-9 months.[55] Rifapentine and rifampicin-based regimens are attractive options as they require significantly shorter durations of therapy and are therefore more likely to be adhered to and completed.

Drug resistant TB is also a growing problem which threatens to affect TB control globally. In 2019 multidrug-resistant (MDR) TB, defined as resistance to RMP and INH, made up 3.3% of new cases and almost a fifth of previously treated cases.[56] South Africa has an MDR-TB incidence rate of 23 per 100 000 population and is more commonly diagnosed in their HIV-infected individuals.[57]. Drug-resistant TB is spread in the same way as drug-sensitive TB, but has an overall higher mortality rate

and additional challenges such as diagnostic difficulties as well as requiring expensive and less effective drugs for longer periods to treat it. Patients with MDR-TB also complicate the management of contacts exposed to such cases that may require LTB chemoprophylaxis. The CDC currently recommends 6 -12 months treatment with a fluoroquinolone, either alone or with a second drug based on the sensitivity testing of the source case. The addition of rifampicin to LTB regimens has also raised the concern that it may contribute to the growing MDR-TB burden in future. At present, the benefits of current LTB regimens outweigh this risk and there is insufficient evidence to prohibit the use of rifampicin in this manner.[58] In South Africa patients with IBD on immunosuppressive treatment and particularly anti-TNF-α therapy are exposed to these resistant variants, but to date there are no recorded cases of IBD on such therapy contracting these variants.

The decision whether to use preventive therapy is complex and must include a balanced approach for its implementation. Treatment will be most beneficial to groups at increased risk for infection and or disease progression and this must be weighed up against the potential harmful effects of therapy. Other factors that need to be considered include the results and reliability (true vs false-positive or negative) of screening tests, as well as the desired effects of treatment in high vs low TB burden settings. The target population at greatest risk for infection includes people with prior or current TB exposure as well as those with high risk comorbidities such as HIV, chronic kidney disease, stem cell/organ transplantation, silicosis and TNF-α inhibitor users.[59] The latest WHO guidelines currently recommend that this group should systematically be tested and treated for LTB, but makes a provision that treatment could also be considered if screening is unavailable.[55] For instance, in the HIV population living in a high-burden TB environment, preventive therapy for 36 months is advised for those with a positive or an unknown LTB status.

Medical therapy in IBD

IBD is an incurable disease. Therefore, the aims of management are to induce remission during acute attacks and to prevent further episodes of relapse. This can be achieved either through medical or surgical interventions or a combination of both and therapeutic options will largely depend on the location, severity and pattern of

disease present. The reliance on medical treatment in particular has expanded over the past few decades and plays an influential role in altering the natural course of IBD. A review article by Annese et al, to evaluate the impact that IST has had on IBD outcomes, concluded that surgery and colectomy rates have declined since their addition to the therapeutic armamentarium, irrespective of factors such as initial disease severity or the time of diagnosis.[60] In addition, a shift in treatment strategy from the traditional "step-up" to an aggressive "top-down" approach has contributed significantly to the earlier introduction and widespread use of IST.[61]

The launch especially of biologics towards the latter half of the 1990's has greatly improved IBD outcomes and represented a significant breakthrough in management. Severe cases, especially those resistant to conventional agents such as steroids, thiopurines (azathioprine (AZA) and 6-mercaptopurine (6MP)), and methotrexate (MTX) are now ideal candidates to start this therapy. Many international guidelines, including those in South Africa, recommend their use in IBD patients with moderate to severe luminal disease when conventional drugs fail to achieve remission. This is estimated to represent 10-15% and 5-10% of refractory CD and UC cases respectively.[62]

The benefits of IST though are counterbalanced by the increased risk of opportunistic infections associated with their use.[63] When TB bacilli first enter the lungs, they become engulfed by alveolar immune cells as part of the innate immune response. During early infection, bacilli in some macrophages are resistant to being killed through various inherent protective mechanisms and a small number of bacilli replicate and spread, both locally as well as systemically before adaptive immunity develops. However, the bacilli that are consumed by dendritic cells are presented to regional lymph nodes to prime T lymphocytes against mycobacterial antigens and is the initial step in the development of cellular immunity towards TB. $CD4^+$ T lymphocytes and the cytokines they produce, IFN-γ and TNF-α, play key roles in TB infection. TNF-α stimulates the migration of a number of immune cells to the infection site that are important for granuloma initiation and maintenance to contain the infection and to stop further replication of bacilli. It also acts synergistically with IFN-γ to enhance the antimicrobial capability of macrophages as well as by activating

cytotoxic CD8+ T cells to control bacillary growth and kill intracellular TB bacilli.[64,65] TNF-α deficiency therefore disrupts these defensive mechanisms and allows maturation and spread of previously dormant bacilli to the lungs as well as to draining lymph nodes and the bloodstream resulting in dissemination. EPTB occurs in the absence of PTB in about 15% of reactivated cases.[66]

In the IBD population, TNF-α antagonists in particular, as well as systemic steroids in the pre-biologics era, have been linked to reactivation of LTB and *de novo* TB infections.[67] Using data from the FDA's Adverse Event Reporting System, Keane et al reported an association between TB and the use of infliximab (a chimeric monoclonal antibody to TNF-α). Aside from the higher risk of infection, subjects in this study mainly developed EPTB and disseminated disease, both forms synonymous with diagnostic difficulties and higher rates of mortality compared to PTB.[68] The risk of TB increases significantly when TNF-α antagonists are combined with conventional IMMs. In a large systematic review to quantify this risk, patients on combined therapy had a 13-fold and 20-fold increased risk of TB compared to biologic monotherapy users and IMM + placebo users respectively. This same study also indicated that a synergistic effect likely exists with combined therapy that greatly elevates this risk compared to the intrinsic risk associated with each drug alone.[69]

The biologics approved for use in IBD are anti-TNF-α agents (infliximab (INF), adalimumab (ADA), golimumab (GOL), certolizumab pegol (CZP)), adhesion molecule antagonists which block leucocyte trafficking to inflamed tissues, (natalizumab, vedolizumab), an interleukin (IL)-12 and IL-23 inhibitor (ustekinumab) and a Janus kinase (JAK) inhibitor (tofacitinib). CZP & GOL are newer anti-TNF-α drugs that received FDA-approval in 2008 & 2013 respectively. CZP's structure differs from the other anti-TNF-α agents and is composed of only the humanised Fab' fragment of an anti-TNF monoclonal antibody, conjugated to polyethylene glycol and therefore lacks certain immunological functions such as apoptosis, antibody-dependent cellular cytotoxicity and complement activation. Vedolizumab is a monoclonal antibody that targets the $\alpha4\beta7$ integrin on T & B cells and blocks its binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) found specifically on GIT endothelial cells. Its safety profile is better than natalizumab

which only targets the α4 subunit of integrins and therefore also affects non-intestinal tissues like the central nervous system (CNS) where its use has been linked with cases of progressive multifocal leukoencephalopathy (PML).

Not all biologic agents carry the same degree of risk. Compared to the general population, the risk for developing TB is much higher in patients taking ADA and INF as opposed to etanercept, another anti-TNF-α agent used mainly in rheumatological conditions.[70] There was also no increased risk for TB in patients using CZP & GOL compared to placebo, but data from clinical trials suggested that the risk of reactivation was still higher in rheumatological patients using these agents compared to the newer non-anti-TNF-α biologics.[71,72] The Asia-Pacific Working Group on IBD has stated that vedolizumab and ustekinumab are considered to have a lower potential for TB reactivation based on current evidence.[73] Tofacitinib, in contrast to other newer biologic agents, appears to have a risk similar to TNF-α inhibitors.[74] It should be emphasised that TB data for newer biologic agents is extremely limited and more research is required in this area to accurately quantify this risk.

Before the advent of biologics, steroids and conventional IMMs were the cornerstone of medical IBD therapy for many decades. TB was also a major problem during this period and patients using steroids in particular had an increased risk compared to IMM users, and the general population too. In the United States (US), the incidence of TB was greater in patients with moderate-to-severe CD compared to the general population (rate ratio (RR), 2.79; 95% CI, 2.14-3.63). In this same study, the risk was higher in patients using steroids compared to conventional IMMs (RR, 6.44; 95% CI, 2.52-16.46 versus RR, 2.49; 95% CI, 1.00-6.21). The risk of infection was similar between those using conventional IMMs and those not on any treatment (RR, 2.45; 95% CI, 1.83-3.29), suggesting no additional risk with this therapy.[75] Thiopurines in this study were not specifically evaluated for their risk of TB, but formed part of the IMM group.

Patients using IMMs did have an increased risk of developing opportunistic infections (OIs). In a study that looked at the safety profile of therapy in IBD, there was a higher incidence of infections that occurred in UC patients receiving immunomodulators

(IMM) compared to the treatment-naïve group, although this did not reach statistical significance.[76] IBD patients using AZA/6MP did have a higher risk of OIs (odds ratio (OR) 3.8; 95% CI, 2.0-7.0; $p<0.001$) and the risk increased significantly when combined with corticosteroids (OR 17.5; 95% CI, 4.5-68; $p<0.001$). It should be noted that both these studies did not list MTB in their spectrum of OIs and AZA/6MP use was most commonly associated with opportunistic viral infections. In a study that did look specifically at the risk of TB in IBD patients before the era of biologics, no subjects diagnosed with used AZA/6MP or MTX within a 12-month exposure window before the end of follow up.[67]

In contrast to above, recent studies published from higher TB burden countries showed a significantly increased risk of TB in patients using thiopurine/azathioprine monotherapy and the risk escalated when combined with anti-TNF-α agents as was also demonstrated in the above studies.[77,78,79] More evidence is therefore needed in this area before any managerial changes can be implemented. At present, the European Crohn's and Colitis Organization (ECCO), the Asian Organization for Crohn's and Colitis (AOCC) and the Asia Pacific Association of Gastroenterology (APAGE) still suggest that thiopurines should be continued during anti-TB therapy, but note that current recommendations are based on very limited data.[80,81] Thiopurines form the bulk of medical immunosuppressant therapy for IBD patients in resource-poor countries due to the prohibitive cost of biologics and this data has the potential to significantly reduce the risk of TB in this environment. Table A below quantifies this risk and also compares it to other medications commonly used in IBD.

Table A: Tuberculosis risk in terms of medication

Publication & country	5-ASA	Thiopurines	Anti-TNF-α	Combination therapy
Choi *et al* (2020)[78] South Korea		I: 193,7 HR: 2,06	I: 195,8 HR: 1,70	I: 326,7 HR: 5,67
Fortes *et al* (2020)[79] Brazil		RR: 6,27	RR: 10,34	RR: 17,81
Weng *et al* (2018)[77] Taiwan	IR: 151,2 HR: 1,1	IR: 416,4 HR: 3,6	IR: 632,4 HR: 5,1	
Hong *et al* (2017)[82] South Korea	IR: 143,5 SIR: 1,69		IR: 554,1 SIR: 6,53	
Wu *et al* (2015)[83] Taiwan		HR: 2,27		
Lorenzetti *et al* (2014)[69]			OR: 4	OR: 54
Marehbian *et al* (2009)[75] USA			Rate ratio: 13,51	Rate ratio: 18,49

5-ASA: 5-Aminosalicylic acid. TNF-α: Tumour necrosis factor-alpha. I: Incidence. HR: Hazard ratio. IR: Incidence rate. SIR: Standardised incidence ratio. RR: Relative risk. OR: Odds ratio.

TB incidence in IBD

The threat of TB in IBD patients has become a growing topic of discussion worldwide following its link with the use of TNF-α blockers. Due to the high cost of this therapy though, there are very few studies in the literature that address this specific problem, particularly in LMI countries in Africa where TB is endemic. Alternatively, attempting to estimate TB risk accurately from randomised controlled trials (RCTs), where LTBI screening protocols are very strict, has many limitations on account of the small number of diagnosed incident TB cases as well as the absence of control groups for comparison.[84]

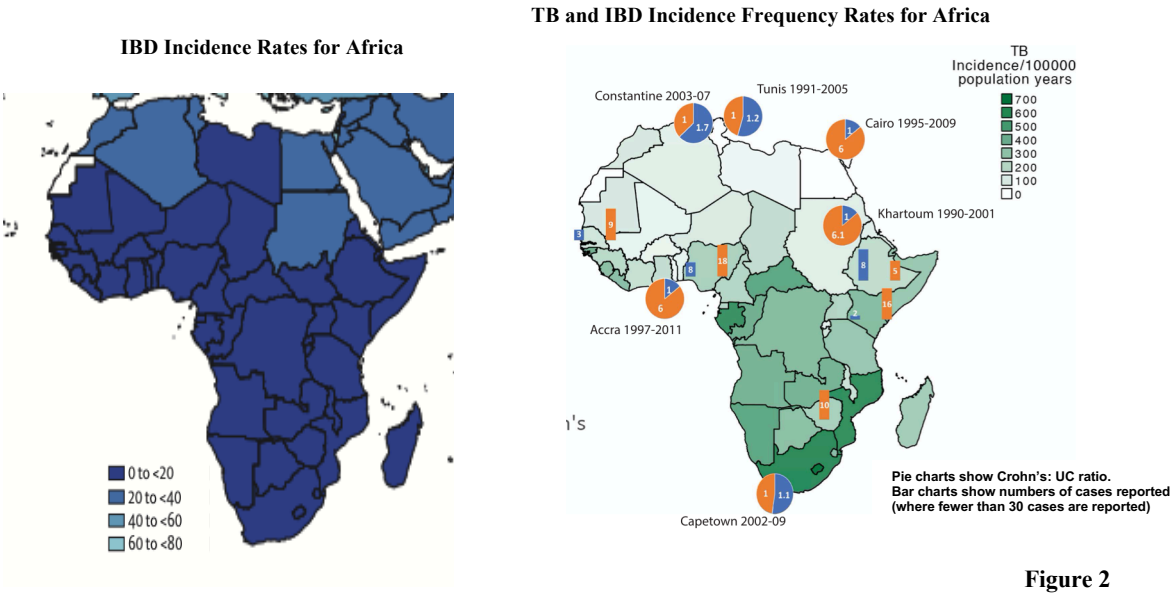


Figure 2

The incidence of IBD and TB in Africa is shown in Figure 2. There is currently only a single publication in Africa that addresses this growing problem. Deetlefs et al recorded the highest TB incidence of 12% in a general IBD cohort, although the bulk of cases (>55%) preceded the diagnosis of IBD. Using multivariate logistic regression models, extensive CD and ethnicity were the variables identified in this study as statistically significant risk factors for TB development. However, the author noted that the role of ethnicity in this instance was likely influenced by differences in socio- economic status and proposed that other causes for this finding required investigation.68 There are currently very few studies in TB endemic countries that quantify the burden of disease in IBD patients exposed to TNF-α antagonists,

highlighting the expensive nature and scarcity of this treatment in resource-poor countries.

Available data regarding the incidence of TB in the IBD population has mainly been evaluated in cohorts exposed to TNF-α antagonists, where much higher TB rates are reported compared to the general IBD population. In a single-centre retrospective IBD study that assessed the risk of TB in TNF-α blocker exposed versus naïve patients, the risk is significantly higher in the former group (adjusted OR (aOR), 11.7; 95% CI, 1.4-101.1; *P*=0.011).[85] In Korea, an intermediate TB-burden nation and one of the main contributors globally to this research topic, TB affects up to 4.2% of their IBD cohort that use biological therapy and has a peak IR of 3710 per 100 000 PY of follow up.[86,87] By comparison an American study, using data from their national cohort of military veterans with IBD, had a substantially lower TB incidence of 0.06% and an IR of 28 per 100 000 PY.[88]

Therefore, the risk of TB in IBD patients using TNF-α blockers is considerably lower in developed compared to developing countries, but altogether still much higher than the general IBD population not exposed to biologics. There are also differences in TB clinical features between cohorts which has an impact on future management. In a multicentre study from Spain there were higher rates of extrapulmonary and disseminated TB compared to PTB, and a third of all cases were diagnosed within 3 months of TNF-α blocker initiation.[89] Similar findings were noted in a Korean study where the median time to TB was also 3 months, but PTB was the dominant location.[90] In Hong Kong where the risk of TB was evaluated in patients with immune-mediated diseases using TNF-α blockers, the median time to TB was 14 months.[91] A shorter interval to TB suggests that diagnosed cases are likely as a result of reactivation of latent infection whereas longer intervals raise the concern of newly-acquired disease. This data has important implications for pre-biological LTB screening as well as the need for continued TB surveillance in patients already on therapy.

There is currently only a single publication in Africa that addresses this growing problem. Deetlefs et al recorded the highest TB incidence of 12% in a general IBD

cohort, although the bulk of cases (>55%) preceded the diagnosis of IBD. Using multivariate logistic regression models, extensive CD and race were the variables identified in this study as statistically significant risk factors for TB development. However, the author noted that the role of ethnicity in this instance was likely influenced by differences in socio-economic status and proposed that other causes for this finding required investigation.[92] There are currently very few studies in TB endemic countries that quantify the burden of disease in IBD patients exposed to TNF-α blockers, highlighting the expensive nature and scarcity of this treatment in resource-poor countries.

Guidelines have subsequently been introduced and are now available in many countries outside Africa to assist with risk stratification and management of TB in IBD patients using IST. A central component in all recommendations is to adequately screen for LTB, and active TB if indicated, prior to commencing anti-TNF-α therapy. Screening though has often been neglected or inadequately performed in this high-risk group. Vaughn et al determined that the level of adherence by gastroenterologists to follow screening guidelines for TB prior to starting TNF-α blockers only approached two-thirds of their cohort and less than one-fifth had adequate documentation of TB risk factors.[93] TB screening generally involves the combination of a thorough history, a complete physical examination, a chest radiograph and a LTB screening test. Screening methods vary, considerably in some instances, between countries as well as between different regulatory organisations within countries. Differences generally arise with regards to which screening test to adopt (TST or IGRA or both), but the British Thoracic Society (BTS) deviates further and only recommends a TST in suspected individuals with a normal chest X-ray who are not on IST or alternatively an individual risk assessment if already on IST.

In patients with confirmed LTBI, all guidelines advise starting chemoprophylaxis with various regimens in keeping with those recommended by the WHO. Some health authorities recommended 2 months of RMP and pyrazinamide or 4 months of RMP & INH in the past, but these regimens have now been discontinued.[94,95] Most guidelines also suggest treatment for 3-4 weeks before commencing anti-TNF-α therapy, although the BTS prefers that LTB therapy be completed before doing so. In

patients that develop active TB whilst on biologics, the European Crohn's and Colitis Organisation (ECCO), the Asian Organization for Crohn's and Colitis (AOCC) and the Asia Pacific Association of Gastroenterology (APAGE) all recommend stopping anti-TNF-α therapy immediately and suggest restarting only after 2 months of TB treatment has been completed. The BTS guidelines also recommend TB therapy but suggest that biologic therapy be continued uninterrupted if clinically indicated. As noted, there are many inconsistencies and conflicting recommendations between institutions from different countries.[71,96,97] Guidelines are also based predominantly on research from countries with a low TB prevalence which may not be applicable to LMIC's due to the diverse characteristics of TB infection in different regions of the world.[80,98,99]

Conclusion

IBD rates are increasing in TB endemic countries. The well-established benefits of IST are being counteracted by the high risk of infection associated with their use. There is limited evidence of this risk in IBD patients living in this environment and what strategies should be employed to protect them. The study of TB in IBD patients in South Africa is important and may later assist in formulating local guidelines, which can be used as a template for other TB endemic countries in the future.

Against this background this study aimed, in a large South African cohort of IBD patients with a high background prevalence of TB, to determine the incidence of TB since IBD diagnosis and to describe the clinical characteristics and potential risk factors of those who developed TB.

LITERATURE REVIEW REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012;142(1):46-54 e42; quiz e30.
2. Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology.* 2004;126(6):1504-1517.
3. Prideaux L, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. *J Gastroenterol Hepatol.* 2012;27(8):1266-1280.
4. Mansour-Ghanaei F, Haghkerdar M, Joukar F, et al. Epidemiologic Features of Inflammatory Bowel Disease in Guilan Province, North of Iran, During 2002-2012. *Middle East journal of digestive diseases.* 2015;7(2):69-74.
5. Lovasz BD, Golovics PA, Vegh Z, Lakatos PL. New trends in inflammatory bowel disease epidemiology and disease course in Eastern Europe. *Dig Liver Dis.* 2013;45(4):269-276.
6. Esmat S, El Nady M, Elfekki M, Elsherif Y, Naga M. Epidemiological and clinical characteristics of inflammatory bowel diseases in Cairo, Egypt. *World J Gastroenterol.* 2014;20(3):814-821.
7. Zhang Z, Fan W, Yang G, et al. Risk of tuberculosis in patients treated with TNF-alpha antagonists: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open.* 2017;7(3):e012567.
8. Western Cape Government Department of Health. Provincial Strategic Plan on HIV/AIDS, STIs and TB, 2012-2016. 2012.
9. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med.* 2009;361(21):2066-2078.
10. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol.* 2005;19 Suppl A:5A-36A.

11. Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology.* 1976;70(3):439-444.
12. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. *Br Med J.* 1954;2(4884):375-378.
13. Collaborators GBDIBD. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol.* 2020;5(1):17-30.
14. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. *Scand J Gastroenterol.* 2015;50(8):942-951.
15. Ng SC, Bernstein CN, Vatn MH, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. *Gut.* 2013;62(4):630-649.
16. Malekzadeh MM, Vahedi H, Gohari K, et al. Emerging Epidemic of Inflammatory Bowel Disease in a Middle Income Country: A Nation-wide Study from Iran. *Arch Iran Med.* 2016;19(1):2-15.
17. Loftus CG, Loftus EV, Jr., Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis.* 2007;13(3):254-261.
18. Soon IS, Molodecky NA, Rabi DM, Ghali WA, Barkema HW, Kaplan GG. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. *BMC gastroenterology.* 2012;12:51.
19. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet.* 2018;390(10114):2769-2778.
20. Li X, Sundquist J, Hemminki K, Sundquist K. Risk of inflammatory bowel disease in first- and second-generation immigrants in Sweden: a nationwide follow-up study. *Inflamm Bowel Dis.* 2011;17(8):1784-1791.
21. Probert CS, Jayanthi V, Hughes AO, Thompson JR, Wicks AC, Mayberry JF. Prevalence and family risk of ulcerative colitis and Crohn's disease: an epidemiological study among Europeans and south Asians in Leicestershire. *Gut.* 1993;34(11):1547-1551.

22. Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second- generation South Asians in Leicester (1991-1994). *Am J Gastroenterol.* 1999;94(10):2918-2922.
23. Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation of inflammatory bowel disease within the United States. *Gastroenterology.* 1991;100(1):143-149.
24. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996;39(5):690-697.
25. Wilson J, Hair C, Knight R, et al. High incidence of inflammatory bowel disease in Australia: a prospective population-based Australian incidence study. *Inflamm Bowel Dis.* 2010;16(9):1550-1556.
26. Gearry RB, Richardson A, Frampton CM, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis.* 2006;12(10):936-943.
27. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis.* 2015;21(11):2708-2717.
28. Linneman Z, Reis C, Balaji K, Moore J, Braude S. The vitamin D positive feedback hypothesis of inflammatory bowel diseases. *Med Hypotheses.* 2019;127:154-158.
29. Wright JP, Marks IN, Jameson C, Garisch JA, Burns DG, Kottler RE. Inflammatory bowel disease in Cape Town, 1975-1980. Part I. Ulcerative colitis. *S Afr Med J.* 1983;63(7):223-226.
30. Wright JP, Marks IN, Jameson C, Garisch JA, Burns DG, Kottler RE. Inflammatory bowel disease in Cape Town, 1975-1980. Part II. Crohn's disease. *S Afr Med J.* 1983;63(7):226-229.
31. Segal I. Ulcerative colitis in a developing country of Africa: the Baragwanath experience of the first 46 patients. *Int J Colorectal Dis.* 1988;3(4):222-225.
32. Wright JP, Froggatt J, O'Keefe EA, et al. The epidemiology of inflammatory bowel disease in Cape Town 1980-1984. *S Afr Med J.* 1986;70(1):10-15.
33. Archampong TN, Nkrumah KN. Inflammatory bowel disease in Accra: what new trends. *West African journal of medicine.* 2013;32(1):40-44.

34. Ouakaa-Kchaou A, Gargouri D, Bibani N, Elloumi H, Kochlef A, Kharrat J. Epidemiological evolution of epidemiology of the inflammatory bowel diseases in a hospital of Tunis. *Tunis Med.* 2013;91(1):70-73.
35. Mahtab S, Coetzee D. Influence of HIV and other risk factors on tuberculosis. *S Afr Med J.* 2017;107(5):428-434.
36. World Health Organization. Global tuberculosis report 2017 [Internet]. Geneva: World Health Organization; 2017.
37. Town CoC. State of Cape Town Report 2014. 2014:65-66.
38. Sheer TA, Coyle WJ. Gastrointestinal tuberculosis. *Curr Gastroenterol Rep.* 2003;5(4):273-278.
39. Public Health England. Tuberculosis in England: 2016 Report. In: Public Health England (ed.). 1.1 edn. Centre for Infectious Disease Surveillance and Control: London, 2016.
40. Gounden S, Perumal R, Magula NP. Extrapulmonary tuberculosis in the setting of HIV hyperendemicity at a tertiary hospital in Durban, South Africa. *Southern African Journal of Infectious Diseases.* 2017;33(3):57-64.
41. Nayagam JS, Mullender C, Cosgrove C, Poullis A. Abdominal tuberculosis: Diagnosis and demographics, a 10-year retrospective review from a single centre. *World J Clin Cases.* 2016;4(8):207-212.
42. World Health Organization. Global tuberculosis control: WHO report 2011 [Internet]. Geneva: World Health Organization; 2011.
43. Jordan AM, Podewils LJ, Castro KG, Zishiri V, Charalambous S. Prevalence and risk factors of tuberculosis disease in South African correctional facilities in 2015. *Int J Tuberc Lung Dis.* 2019;23(11):1198-1204.
44. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med.* 2008;149(3):177-184.
45. Centers for Disease Control and Prevention. Core Curriculum on Tuberculosis: What the Clinician Should Know, Chapter 3: Testing for Tuberculosis Infection and Disease.:57.
46. Mow WS, Abreu-Martin MT, Papadakis KA, Pitchon HE, Targan SR, Vasiliauskas EA. High incidence of anergy in inflammatory bowel disease patients limits the usefulness of PPD screening before infliximab therapy. *Clin Gastroenterol Hepatol.* 2004;2(4):309-313.

47. Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a metaanalysis. *Chest.* 2010;137(4):952-968.
48. Chee CB, Gan SH, Khinmar KW, et al. Comparison of sensitivities of two commercial gamma interferon release assays for pulmonary tuberculosis. *J Clin Microbiol.* 2008;46(6):1935-1940.
49. Bae W, Park KU, Song EY, et al. Comparison of the Sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB According to Patient Age. *PloS one.* 2016;11(6):e0156917.
50. Wong SH, Gao Q, Tsoi KK, et al. Effect of immunosuppressive therapy on interferon gamma release assay for latent tuberculosis screening in patients with autoimmune diseases: a systematic review and meta-analysis. *Thorax.* 2016;71(1):64-72.
51. Thi AA, Abbara A, Bouri S, et al. Challenges in screening for latent tuberculosis in inflammatory bowel disease prior to biologic treatment: a UK cohort study. *Frontline Gastroenterol.* 2018;9(3):234-240.
52. Auguste P, Madan J, Tsertsvadze A, et al. Identifying latent tuberculosis in high-risk populations: systematic review and meta-analysis of test accuracy. *Int J Tuberc Lung Dis.* 2019;23(11):1178-1190.
53. Adams S, Ehrlich R, Baatjies R, Dendukuri N, Wang Z, Dheda K. Evaluating Latent Tuberculosis Infection Test Performance Using Latent Class Analysis in a TB and HIV Endemic Setting. *Int J Environ Res Public Health.* 2019;16(16).
54. In: *Latent tuberculosis infection: updated and consolidated guidelines for programmatic management.* Geneva2018.
55. In: *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1: prevention.* Geneva2020.
56. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
57. Ismail NA, Mvusi L, Nanoo A, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. *Lancet Infect Dis.* 2018;18(7):779-787.
58. den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2016;20(8):1065-1071.

59. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection-the promise and the challenges. *Int J Infect Dis.* 2017;56:68-76.
60. Annese V, Duricova D, Gower-Rousseau C, Jess T, Langholz E. Impact of New Treatments on Hospitalisation, Surgery, Infection, and Mortality in IBD: a Focus Paper by the Epidemiology Committee of ECCO. *J Crohns Colitis.* 2016;10(2):216-225.
61. Amezaga AJ, Van Assche G. Practical Approaches to "Top-Down" Therapies for Crohn's Disease. *Curr Gastroenterol Rep.* 2016;18(7):35.
62. Rogler G, Bernstein CN, Sood A, et al. Role of biological therapy for inflammatory bowel disease in developing countries. *Gut.* 2012;61(5):706-712.
63. Toruner M, Loftus EV, Jr., Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology.* 2008;134(4):929-936.
64. Flynn JL, Goldstein MM, Chan J, et al. Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. *Immunity.* 1995;2(6):561-572.
65. Mohan VP, Scanga CA, Yu K, et al. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. *Infect Immun.* 2001;69(3):1847-1855.
66. Yang D, Kong Y. The bacterial and host factors associated with extrapulmonary dissemination of Mycobacterium tuberculosis. *Front Biol (Beijing).* 2015;10(3):252-261.
67. Aberra FN, Stettler N, Brensinger C, Lichtenstein GR, Lewis JD. Risk for active tuberculosis in inflammatory bowel disease patients. *Clin Gastroenterol Hepatol.* 2007;5(9):1070-1075.
68. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* 2001;345(15):1098-1104.
69. Lorenzetti R, Zullo A, Ridola L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. *Ann Med.* 2014;46(7):547-554.

70. Xie X, Li F, Chen JW, Wang J. Risk of tuberculosis infection in anti-TNF-alpha biological therapy: from bench to bedside. *J Microbiol Immunol Infect.* 2014;47(4):268-274.
71. Dobler CC. Biologic Agents and Tuberculosis. *Microbiol Spectr.* 2016;4(6).
72. Cantini F, Niccoli L, Goletti D. Tuberculosis risk in patients treated with non-anti-tumor necrosis factor-alpha (TNF-alpha) targeted biologics and recently licensed TNF-alpha inhibitors: data from clinical trials and national registries. *J Rheumatol Suppl.* 2014;91:56-64.
73. Ooi CJ, Hilmi I, Banerjee R, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. *Intestinal research.* 2019;17(3):285-310.
74. Evangelatos G, Koulouri V, Iliopoulos A, Fragoulis GE. Tuberculosis and targeted synthetic or biologic DMARDs, beyond tumor necrosis factor inhibitors. *Ther Adv Musculoskelet Dis.* 2020;12:1759720X20930116.
75. Marehbian J, Arrighi HM, Hass S, Tian H, Sandborn WJ. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J Gastroenterol.* 2009;104(10):2524-2533.
76. Lichtenstein GR, Rutgeerts P, Sandborn WJ, et al. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. *Am J Gastroenterol.* 2012;107(7):1051-1063.
77. Weng MT, Tung CC, Chang YT, et al. Trends of Medication Usage and Associated Outcomes for Taiwanese Patients with Inflammatory Bowel Disease from 2001 to 2015. *J Clin Med.* 2018;7(11).
78. Choi SJ, Kim MS, Kim ES, et al. Higher risk of tuberculosis in combination therapy for inflammatory bowel disease: A nationwide population-based cohort study in South Korea. *Medicine (Baltimore).* 2020;99(44):e22897.
79. Fortes FML, Sorte NB, Mariano VD, et al. Active tuberculosis in inflammatory bowel disease patients under treatment from an endemic area in Latin America. *World J Gastroenterol.* 2020;26(44):6993-7004.
80. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2014;8(6):443-468.

81. Park DI, Hisamatsu T, Chen M, et al. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: management. *Intestinal research.* 2018;16(1):17-25.
82. Hong SN, Kim HJ, Kim KH, Han SJ, Ahn IM, Ahn HS. Risk of incident Mycobacterium tuberculosis infection in patients with inflammatory bowel disease: a nationwide population-based study in South Korea. *Aliment Pharmacol Ther.* 2017;45(2):253-263.
83. Wu PH, Lin YT, Yang YH, Lin YC, Lin YC. The increased risk of active tuberculosis disease in patients with dermatomyositis - a nationwide retrospective cohort study. *Sci Rep.* 2015;5:16303.
84. Wang Q, Wen Z, Cao Q. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: A meta-analysis. *Exp Ther Med.* 2016;12(3):1693-1704.
85. Byun JM, Lee CK, Rhee SY, et al. The risk of tuberculosis in Korean patients with inflammatory bowel disease receiving tumor necrosis factor-alpha blockers. *J Korean Med Sci.* 2015;30(2):173-179.
86. Kim ES, Song GA, Cho KB, et al. Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. *World J Gastroenterol.* 2015;21(11):3308-3316.
87. Jung SM, Ju JH, Park MS, et al. Risk of tuberculosis in patients treated with anti-tumor necrosis factor therapy: a nationwide study in South Korea, a country with an intermediate tuberculosis burden. *Int J Rheum Dis.* 2015;18(3):323-330.
88. Hou JK, Kramer JR, Richardson P, Sansgiry S, El-Serag HB. Tuberculosis Screening and Reactivation Among a National Cohort of Patients with Inflammatory Bowel Disease Treated with Tumor Necrosis Factor Alpha Antagonists. *Inflamm Bowel Dis.* 2017;23(2):254-260.
89. Carpio D, Jauregui-Amezaga A, de Francisco R, et al. Tuberculosis in Anti-Tumour Necrosis Factor-treated Inflammatory Bowel Disease Patients After the Implementation of Preventive Measures: Compliance With Recommendations and Safety of Retreatment. *J Crohns Colitis.* 2016;10(10):1186-1193.
90. Lee JW, Choi CH, Park JH, et al. Clinical features of active tuberculosis that developed during anti-tumor necrosis factor therapy in patients with inflammatory bowel disease. *Intestinal research.* 2016;14(2):146-151.

91. Wang X, Wong SH, Wang XS, et al. Risk of tuberculosis in patients with immune-mediated diseases on biological therapies: a population-based study in a tuberculosis endemic region. *Rheumatology (Oxford).* 2018.
92. Deetlefs E, Epstein D, Watermeyer GA, Seggie RM, Thomson SR. Tuberculosis in an inflammatory bowel disease cohort from South Africa. *S Afr Med J.* 2012;102(10):802-804.
93. Vaughn BP, Doherty GA, Gautam S, Moss AC, Cheifetz AS. Screening for tuberculosis and hepatitis B prior to the initiation of anti-tumor necrosis therapy. *Inflamm Bowel Dis.* 2012;18(6):1057-1063.
94. Mariette X, Salmon D. French guidelines for diagnosis and treating latent and active tuberculosis in patients with RA treated with TNF blockers. *Ann Rheum Dis.* 2003;62(8):791.
95. Beglinger C, Dudler J, Mottet C, et al. Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. *Swiss Med Wkly.* 2007;137(43-44):620-622.
96. Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J.* 2010;36(5):1185-1206.
97. Banerjee R, Ali RAR, Wei SC, Adsul S. Biologics for the Management of Inflammatory Bowel Disease: A Review in Tuberculosis-Endemic Countries. *Gut Liver.* 2020;14(6):685-698.
98. Horsburgh CR, Jr., Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. *N Engl J Med.* 2011;364(15):1441-1448.
99. Shim TS. Diagnosis and Treatment of Latent Tuberculosis Infection due to Initiation of Anti-TNF Therapy. *Tuberculosis and respiratory diseases.* 2014;76(6):261-268.

CHAPTER 2: MANUSCRIPT

The Incidence of Tuberculosis in the Inflammatory Bowel Disease Registry in Cape Town, South Africa

AUTHORS

Mitesh Pema, MBChB[1]; Sandie Thomson, ChM, FRCS (Eng. & Ed), FRCP (Ed)[2]; David Epstein, MBChB, DCH, FCP (SA), Cert Gastroenterology (SA)[3]

1. Department of Medicine, University of Cape Town, Cape Town, South Africa. miteshpema@gmail.com

2. Division of Gastroenterology, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa. sandie.thomson@uct.ac.za

3. Private practice, Life Vincent Pallotti Hospital, Cape Town, South Africa. David@gastro-enterology.co.za

Correspondence:
Dr Mitesh K Pema
Department of Medicine
J Floor, Old Main Building
Groote Schuur Hospital
Observatory, Cape Town
7925
South Africa
Email: miteshpema@gmail.com

ABSTRACT

Background/Objectives: The risk of tuberculosis (TB) in inflammatory bowel disease (IBD) patients using immunosuppressive therapy (IST) is higher than the background population in developed countries. Corresponding data in areas of high endemicity like South Africa (SA) is limited. Our objectives were to calculate the incidence, identify predictors and determine clinical characteristics of TB common to IBD patients living in this environment.

Methods: In this retrospective study, patients that developed active TB after their IBD diagnosis between 1948 and 2017 were selected from the SA IBD Registry. Incidence rates were calculated for the study population and for cases prescribed TNF-α (tumour necrosis factor-alpha) blockers. A multivariable logistic regression model, using non-TB IBD patients as controls, was applied to determine risk factors for infection. We analysed IBD and TB clinical features as well as screening tests for latent TB (LTB).

Results: 42 TB cases (4%) out of 1041 consented IBD patients were identified. Incidence rates (IRs) for active infection per 100 000 person years (PY) of follow-up were 330 and 2749, for the cohort and TNF-α blocker users respectively. Patients with Crohn's disease (CD) (adjusted Odds Ratio (aOR) = 2.00, 95% confidence interval (CI): 0.92- 4.36), a smoking history (aOR = 1.44, 95% CI: 0.66-3.14), attendance at public hospitals (aOR = 1.81, 95% CI: 0.75-4.37) and a history of TNF-α blocker use (aOR = 2.45, 95% CI: 0.88-6.80) were at greater risk for infection, although none were statistically significant. The median time to TB diagnosis was 96.7 months (interquartile range (IQR): 42.2-164.8) for the cohort and 11.3 months (IQR: 8.1-29.2) for biologics users. Over half the TB cases occurred in patients that live in districts with predominantly low-income households. The lung was the most common site affected. Latent TB infection (LTBI) occurred in twenty-four patients that were prescribed IST. Ten received isoniazid prophylaxis therapy (IPT) and one later developed active TB.

Conclusion: TB is a significant problem in our IBD population. The establishment of local guidelines is recommended to assist clinicians with risk stratification and management of latent and active disease, especially in patients being considered for TNF-α blockers.

INTRODUCTION

According to the World Health Organization (WHO), SA ranks consistently amongst the top 5 countries with the highest rates of TB.[1-3] The City of Cape Town (CCT), a metropolitan district of the Western Cape and home to over 4 million people, contributes significantly to this national burden.[4] IBD has also become a global disease and is emerging in developing countries, where it was historically thought rare due to a lack of epidemiological data.[5] It is an incurable disease and management is aimed at inducing remission during acute episodes and preventing further relapses. IST has played a pivotal role in achieving these goals, particularly in the last two decades since the adoption of an aggressive approach to control disease was decided.[6,7] This strategy coincided with the introduction of TNF-α blockers, a potent therapy reserved mainly for patients previously refractory to steroids and immunomodulators (IMM), but now also as 1st line therapy in selected severe cases.

The use of biologics is associated with an increased risk of opportunistic infections, particularly severe forms of TB such as extrapulmonary and disseminated TB.[8] In low and intermediate TB prevalent countries, IBD subjects using this treatment have significantly higher rates of infection compared to the general population.[9,10] The subsequent introduction of guidelines by those countries, to assist clinicians with risk stratification and management, has proven to be an effective strategy to combat this problem.[11-14] However, current recommendations are inconsistent and are based predominately on research from developed countries where rates of infection are low. There is limited evidence on the risk in patients from countries where TB is endemic and what policies should be employed to protect them in this environment.

Therefore, our primary objectives in this study are to investigate the incidence of TB in a large cohort of IBD patients living in a high TB burden country, to identify potential risk factors associated with TB development and to determine the clinical characteristics of TB that are common to our local IBD population.

METHODS

Study design and population

We conducted a retrospective cohort study using data accrued in the SA IBD Registry between 1948 and 2017. This registry was launched in 2007 under the auspices of the South African Gastroenterology Society (SAGES). It initially evolved from the Groote Schuur Hospital (GSH) IBD clinic database in the 1990s and has expanded over the years to include IBD patients from five private practices located in the southern suburbs of Cape Town, as well as patients that self-register at local IBD meetings. The registry contains relevant information pertaining to patient demographics, name of hospital facility attended, clinic visit dates, co-morbid conditions, IBD surgical history, chest X-ray (CXR) findings and IBD treatment history. All patients who signed consent to be added to this registry were included in this study and only relevant data pertaining to the study objectives were evaluated.

We identified all subjects that developed active TB after their IBD diagnosis. The following data points were investigated in the registry as potential risk factors for TB development: age, smoking history, human immunodeficiency virus (HIV) status, previous TB prior to IBD diagnosis, LTBI, IST use, type of IBD, extent of IBD at diagnosis and hospital facility type attended.

Postal code data in the registry was used to determine each subject's area of residence based on the CCT's district and suburb boundaries map.[15] We were then able to approximate household income by overlapping this data with statistics from the city's Socio-economic Profile report.[16]

Case definitions

Patients entered in the registry were considered to have TB if diagnosed by any one of the following 4 methods: a microbiological diagnosis based on either smear microscopy, Mycobacterium TB culture or DNA detection using a polymerase chain reaction (PCR) assay from any clinical specimen; a histological diagnosis consistent with TB from any tissue specimen; a radiological diagnosis on CXR compatible with TB in accordance with the Centers for Disease Control and Prevention (CDC) guidelines[17] or a credible history-based diagnosis from subjects treated with anti-TB chemotherapy, but excluding patients given empiric treatment for suspected intestinal TB.

Patients were considered to have LTB if either one or both the tuberculin skin test (TST) (≥ 5mm) and interferon gamma releasing assay (IGRA) results were positive, in the absence of signs for clinically manifested previous TB and current active TB. The use of IST was defined as any exposure to azathioprine (AZA), 6-mercaptopurine (6MP), methotrexate (MTX) or anti-TNF-α therapy, but excluded steroid therapy due to lack of data.

Statistical analyses
Descriptive data was presented as medians for numerical data and as frequencies and percentages for categorical data. TB positive versus negative patients were compared using the t-test or Mann-Whitney U test for normally and non-normally distributed continuous variables respectively, and chi-squared test or Fishers exact test for comparison of categorical variables.

The IR of active TB for the cohort was calculated as the number of cases divided by disease-free person-time of observation from date of IBD diagnosis to either date of TB diagnosis, death or last known follow up. In patients exposed to TNF-α blockers, the IR was calculated from start date of therapy to either the discontinuation date or to the same end points as listed for the cohort. Incidence was expressed as the number of new cases per 100 000 PY of follow up.

A multivariable logistic regression model was used to analyse associations between incident TB and clinical risk factors. Variable selection was primarily based on clinical relevance, whilst variables were excluded if evidence of collinearity was present or if there was a large proportion of data missing or data sparsity. The Hosmer and Lemeshow's goodness-of-fit test was used to assess model fit. $p<0.05$ was considered statistically significant.

Ethics
Formal ethics approval was obtained from the Human Research Ethics Committee, Health Sciences Faculty, University of Cape Town.

RESULTS

Clinical characteristics of IBD patients

From over 3000 entries currently recorded in the SA IBD Registry, 1041 subjects were included in this study, with exclusions mainly on account of the absence of informed consent. Six hundred and thirty-three were females and the median age of diagnosis was 33.0 years (IQR, 24-45). Their baseline characteristics are described in Table 1. Five hundred and twenty-three patients had CD, 488 had UC and the remainder had IBD unclassified (IBDU). A history of smoking was present in over half the cohort and was more common amongst CD patients. An ileocolonic location and a penetrating/fistulising disease behaviour were the most typical CD features. Over one third of UC subjects had extensive forms of colitis at onset of their IBD diagnosis.

TB Incidence rates and clinical characteristics of TB patients

Forty-two subjects developed TB post IBD diagnosis during 12 714 PY of follow-up. The IR for our study population is 330 per 100 000 PY. In the sixty-eight patients using anti-TNF-α therapy, the rate is 2749 per 100 000 PY of follow-up. The median time from IBD diagnosis to TB occurrence was 96.7 months (IQR, 42.2 - 164.8) and the median age at TB diagnosis was 40.5 years (IQR, 29-54). Pulmonary TB (PTB) was more commonly diagnosed in comparison to extrapulmonary and disseminated TB. Eighteen subjects were prescribed IST, which included one third using TNF-α antagonist therapy. LTBI screening tests were positive in a single patient. The majority of TB cases reside in the Mitchell's Plain/Khayelitsha (MP/K) and Cape Flats districts combined. Additional clinical characteristics of index cases are summarised in Table 2.

Risk factors for TB

A univariate analysis was done to identify risk factors for infection (Table 3). TB was most likely to occur in patients with CD (70% vs 51%, p=0.023), current or ex-smokers (73% vs 55%, p=0.024), HIV positive patients (6.9% vs 0.7%, p=0.027) and those with a history of IBD surgery (71% vs 49%, p=0.009). There were no statistical differences between the two groups regarding gender, IST use, IBD severity and LTB screening results. No significant associations were observed in a multivariable logistic regression analysis (Table 4), however the results indicated a moderate increase in risk of incident TB in patients with CD (aOR = 2.00, 95% CI: 0.92- 4.36) those with a previous or current smoking history (aOR = 1.44, 95% CI: 0.66-3.14), patients who attended public institutes (aOR = 1.81, 95% CI: 0.75-4.37) and cases exposed to TNF-α blockers (aOR = 2.45, 95% CI: 0.88-6.80).

LTBI screening tests

One hundred and fifty-eight screening tests were performed in the cohort and one hundred and thirty-one tests were conducted in subjects using IST (Table 5). A positive test was found in 17 (18.7%) TSTs and 10 (25%) IGRAs. Using both immunoassays as screening measures, 24/118 (20.3%) had confirmed LTBI. Isoniazid (INH) prophylaxis and full TB treatment were prescribed to ten (41.7%) and one subject (4.2%) respectively. One patient with LTB developed active TB almost 3 years afterwards despite receiving adequate INH prophylaxis. Both immunoassays were performed in 13 patients. Seven cases had discordant results, including in 1 of the 2 patients that had tests done simultaneously. Indeterminate results were present in seven IGRAs, three of which occurred in patients tested whilst using IST. The majority of test results were negative (68.7%), and included 28 assays of patients (31.1%) also using IST at the time of screening.

DISCUSSION & CONCLUSION

This is the second study to evaluate the risk of TB in a large IBD cohort from SA, a WHO-listed high burden country. In 2015, Cape Town had a TB incidence of 596 per 100 000 population.[18] The IR of active TB in our registry is 330 per 100 000 PY of follow up and equates to 4% of the study population. In patients treated with TNF-α blockers, 7.4% developed TB and their IR is 2749 per 100 000 PY. The IR of TB in a general cohort of IBD patients living in Korea, a country with an intermediate TB burden, is 223.9 cases per 100 000 PY of follow-up. In Korean IBD patients using TNF-α blockers, the IR ranged from 489-3710 per 100 000 PY of follow-up.[19,20] Considerably lower rates were reported from North American and European studies where TB affected 1.65% (7/423) of Spanish IBD patients using TNF-α blockers whilst in American subjects, the TB IR was 28 per 100 000 PY of follow-up.[21,22]

Our findings confirm that TB IRs are much higher in IBD patients using TNF-α blockers compared to the general population.[23] Research in this specific field is growing worldwide, but studies from TB endemic countries are limited. A recent Indian publication had a higher TB incidence of 11.6% (8/69) in IBD subjects exposed to TNF-α blockers.[24] In a previous SA study, TB was diagnosed in 5.2% of subjects from a general IBD cohort.[25] There are currently no local studies for comparison in the IBD population using TNF-α blockers. In 2017, Pettipher et al conducted similar research in over four thousand rheumatological subjects using data from their SA Biologicals Registry and determined their TB IR to be 1387 cases per 100 000 PY.[26] A notable difference and limitation of our study is the relatively small number of patients using this expensive form of therapy in our registry. Further research with larger sample sizes from our IBD population is warranted in the future.

In this study, predictors for a moderately increased risk of TB, confirmed by our multivariate model, included patients with CD, a smoking history, public hospital attendance and TNF-α blocker use, although none reached statistical significance (Table 4). Biologics are already a well-known risk factor for opportunistic infections in patients with immune-mediated diseases, but both CD and smoking have also previously been identified as additional risks for active TB in the IBD population.[27,28] In our CD patients, more than two-thirds had a smoking history and IST was prescribed more frequently in them compared to UC (61% vs 22%), particularly in those with complicated Crohn's (85%). HIV positivity was identified as a significant risk factor in our univariate analysis but should be interpreted with caution given the very small sample size present.

The type of healthcare sought by our IBD patients also poses an additional risk for TB. Its relevance requires an understanding of SA's healthcare system, which is strongly reflective of the socio-economic divide between the poorer public and wealthier private sector.[29] In the CCT, Mitchell's Plain/Khayelitsha (MP/K) and the Cape Flats districts have the highest percentage of low-income households.[16] In this study, these 2 districts combined had the greatest number of incident TB cases and contributed to the largest ratio of our IBD patients that seek medical care in the state sector (>85%). TB burden is often aligned with socio-economic status, a factor which needs to be included in risk stratification for patients living in a high burden country.

PTB was more common than extrapulmonary and disseminated TB in our study, including in subjects exposed to biologics. Our rates are in keeping with the general SA TB population

where PTB accounts for around 80% of total cases. Current data is conflicted regarding the location of disease in IBD subjects using TNF-α blockers. EPTB is understood to occur more commonly in severely immunocompromised individuals, but this did not mirror our findings nor those in a Korean study where the lungs were the predominant site of infection.[19] EPTB and disseminated TB are potentially under-reported in our setting as subsequent investigations to determine the extent of spread usually do not take place once a diagnosis of PTB is established, mainly on account of limited resources.

In our cohort, there was a relatively long interval between IBD and active TB diagnoses. The interval became shorter in patients using conventional IMMs (median: 71.4 months) and was similar to those not using any IST (median: 75.5 months). In our biologic's patients, the time to TB was considerably quicker (median: 11.3 months) and fits within the range described in other IBD studies where time frames between three months and two years were reported after initiation of TNF-α blockers.[30,19] The shorter the time frame, the more likely the scenario that TB development is due to reactivation of latent infection and highlights the importance of screening, especially prior to starting biologics.

Screening for and treatment of LTB in this study was suboptimal. In patients that were started on TNF-α blockers, 50/68 patients (74%) were screened beforehand. Less than half of those with positive screening received prophylaxis. Our rates are understandably lower compared to countries with established guidelines as nonadherence to recommendations is a renowned risk factor for TB development in those countries.[31] TSTs were the most frequently performed test due to the fact that IGRAs are not routinely available in our public hospitals (Table 5). In many instances TST was likely done alone as the only form of LTB screening which is not ideal given its inferior sensitivity and specificity compared to IGRAs.[32,33] Nearly 45% of cases with negative immunoassays and 60% with indeterminate IGRAs were using IMMs at the time of screening before starting biologics. IMMs are known to influence the results of both tests and some experts recommend performing them prior to starting any form of medical treatment.[34,35]

In our 42 incident TB cases, only one patient was previously diagnosed with LTB. This occurred almost 3 years prior and despite receiving full INH prophylaxis. No patients treated with TNF-α blockers were diagnosed with LTB beforehand. Some cases may have been missed due to false-negative screening tests, but our findings indicate that the majority of active TB in our cohort were as a result of newly acquired infections from exposure to other TB-infected persons in the community as opposed to infections resulting from reactivation of LTB. In countries with high TB endemicity like SA, the vast majority of recurrent disease is accounted for by newly acquired infections compared to low-incident areas where relapse of previous infection is the more probable cause of recurrence.[36,37] Continuous TB monitoring is therefore strongly recommended in our IBD population using IST and should prompt immediate investigations if appropriate symptoms and common risk factors for disease are present.

An intervention which has been advocated by the Asian Organization for Crohn's and Colitis (AOCC), and by other similar institutions from industrialised countries, is to repeat immunodiagnostic tests (TST and/or IGRA) on an annual basis in patients at high risk for infection, such as those exposed to a close TB contact, if their initial LTB screening at baseline was negative.[38] Re-testing has the dual advantage of diagnosing new infections as well as identifying false-negative reactivated LTB cases that were missed during baseline screening. In SA, the benefits of performing serial tests were validated in a local study of

healthcare workers (HCWs) being screened for occupational TB, where a peak conversion rate of 38% was found, in TSTs, after 12 months of follow-up.[39] Similar research in IBD patients using biologics is either sparse or of limited use on account of the inefficiencies of currently available immunodiagnostics.[40]

In an effort to avoid this problem another solution, which has been proposed in Indian rheumatology patients using biologics, is to provide prophylaxis to all subjects at risk without screening for LTB beforehand.[41] In SA this concept of mass IPT has mainly been investigated in people living with HIV, in whom rates of TB are also much higher compared to the general population. Current findings from these studies as well as from a community-based randomised control trial (RCT) in SA gold miners suggest that this intervention alone is not sufficient to control TB at a population level.[42,43] One of the multiple reasons for its lack of efficacy, particularly in high burden TB countries, is the continuous risk of infection and transmission that recurs once IPT has been stopped. There are as yet no studies in patients with IBD or other immune-mediated diseases to support this strategy and further research in this area is needed.

Based on the findings from this study and when compared to established guidelines from other countries, many faults can be identified that need to be addressed. The burden of TB in Asia has the closest resemblance to that in Africa and South Africa and recommendations there should form the template by which local guidelines can be built. Screening practices to diagnose LTB in our IBD patients is an area that requires urgent attention and a simple recommendation universally accepted as a standard of care is for all patients to be screened prior to commencing biologics as opposed to only the 74% from this study. When screening patients with immunodiagnostics, it is preferable for both tests to be potentially performed if indicated in accordance with the 'either test positive strategy' to improve overall sensitivity and to identify the greatest number of eligible candidates for chemoprophylaxis. The lack of IGRA testing in the public sector is a major setback in this regard due to limited resources, but should be performed where available.[44] A TST performed alone, as was done in the majority of our screened patients, is not ideal, due to its inferior sensitivity and specificity compared to IGRAs, and a negative result should not be accepted in isolation.

Negative screening with either test does not entirely exclude the risk of subsequent infection due to the deficiencies of each test and these patients should still undergo further risk evaluation.[45] It is clear from this study that new TB infections pose a greater threat than reactivation cases. A detailed TB history, to identify traditional risk factors of infection, is critical and should be made mandatory at consultations both prior to treatment as well as at each follow-up visit whilst on biologic therapy and even for 6 months after therapy is completed. This information coupled with the risk factors identified in this study, specific to IBD patients, should be collectively taken into account when deciding on chemoprophylaxis. The AOCC & Asia Pacific Association of Gastroenterology (APAGE) guidelines suggest that the importance of a history of recent TB exposure should outweigh LTB screening in this decision and this same practice should be mirrored in our population until further evidence suggests otherwise.[46] Retesting for LTB whilst on biologics is an alternative screening option as mentioned previously, but requires further research to assess its effectiveness, especially in resource-limited settings.

Aspects that are within the control of the treating gastroenterologist should also be maximized and factored into this risk evaluation. The use of single therapy with a biologic is associated with a lower risk of TB compared to combinations with IMMs as was

demonstrated in a systematic review and also in this study where only 1 out of the six patients that developed TB using a biologic was on single therapy.[47] Patients using newer anti-TNF-α drugs, such as certolizumab pegol & golimumab, and non-anti-TNF-α biologics also have a lower TB risk and is an attractive alternative for high-risk individuals.[48,49] It is important to stress that this information is based on limited current evidence and more safety data from future research on these agents is still required. In South Africa, golimumab is available for use in UC patients and vedolizumab & ustekinumab are awaiting approval by the South African Health Products Regulatory Authority. Access to biologics in general, especially in the public sector where they are most needed, is extremely limited and approval will likely be even more challenging for these newer agents when available.

This study has highlighted some important clinical points and identified areas during the course of this discussion that still require more research. Two further areas not investigated by our study, due to a lack of data from our registry, that would be invaluable include research into the duration of LTB treatment, if required, before initiating biologics as well as the time period that biologics should be stopped for if active TB develops whilst on therapy. Many international guidelines have conflicting recommendations regarding these points and a comparison with data from an endemic TB country would be most beneficial.[50,51]

In conclusion, TB is a significant problem in SA's IBD population, particularly in patients using TNF-α blockers. Local guidelines are needed to assist clinicians with risk stratification and to manage TB in this environment. Although many of the recommendations from industrialised countries could also be applied to our IBD population, certain clinical aspects addressed by this study and that are unique to TB endemic countries, require more research and different interventions to combat this growing problem.

Conflict of Interest
None

Author Contributions
Mitesh Pema drafted the manuscript. Sandie Thomson and David Epstein supervised the study and were major contributors to the content, tables and outline of the final manuscript.

Funding Sources
None

REFERENCES

1. World Health Organization. Global tuberculosis control: WHO report 2011. Geneva: WHO, 2011. https://www.who.int/tb/publications/global_report/archive/en/ (accessed 17 August 2018).
2. World Health Organization. Global tuberculosis report 2017. Geneva: WHO, 2017. https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf (accessed 17 August 2018).
3. World Health Organization. Global tuberculosis report 2018. Geneva: WHO, 2018. https://www.who.int/tb/publications/global_report/archive/en/ (accessed 30 May 2019).
4. Wood R, Lawn SD, Caldwell J, Kaplan R, Middelkoop K, Bekker L-G. Burden of New and Recurrent Tuberculosis in a Major South African City Stratified by Age and HIV-Status. Public Library of Science ONE. 2011;6(10):e25098. https://doi.org/10.1371%2Fjournal.pone.0025098
5. Molodecky NA, Soon IS, Rabi DM, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. Gastroenterology. 2012;142(1):46-54 e42. https://doi.org/10.1053%2Fj.gastro.2011.10.001
6. Annese V, Duricova D, Gower-Rousseau C, Jess T, Langholz E. Impact of New Treatments on Hospitalisation, Surgery, Infection, and Mortality in IBD: a Focus Paper by the Epidemiology Committee of ECCO. Journal of Crohn's and Colitis. 2016;10(2):216-225. https://doi.org/10.1093%2Fecco-jcc%2Fjjv190
7. Amezaga AJ, Van Assche G. Practical Approaches to "Top-Down" Therapies for Crohn's Disease. Current Gastroenterology Reports. 2016;18(7):35. https://doi.org/10.1007%2Fs11894-016-0507-z
8. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor □-neutralizing agent. N Engl J Med. 2001;345(15):1098-1104. https://doi.org/10.1097%2F00019048-200112000-00012
9. Fidder H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. Gut. 2009;58(4):501-508. https://doi.org/10.1016%2Fs0739-5930%2809%2979314-6
10. Abreu C, Magro F, Santos-Antunes J, et al. Tuberculosis in anti-TNF-□ treated patients remains a problem in countries with an intermediate incidence: Analysis of 25 patients matched with a control population. Journal of Crohn's and Colitis. 2013;7(10):e486-e492. https://doi.org/10.1016%2Fj.crohns.2013.03.004
11. Horsburgh CR, Jr., Rubin EJ. Clinical practice. Latent Tuberculosis Infection in the United States. N Engl J Med. 2011;364(15):1441-1448. https://doi.org/10.1056%2Fnejmcp1005750
12. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis. 2014;8(6):443-468. https://doi.org/10.1016%2Fj.crohns.2013.12.013
13. Shim TS. Diagnosis and Treatment of Latent Tuberculosis Infection in Patients with Inflammatory Bowel Diseases due to Initiation of Anti-Tumor Necrosis Factor Therapy. Intestinal Research. 2014;12(1):12-19. https://doi.org/10.5217%2Fir.2014.12.1.12
14. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, et al. Effectiveness of Recommendations to Prevent Reactivation of Latent Tuberculosis Infection in Patients Treated With Tumor Necrosis Factor Antagonists. Arthritis Rheum. 2005;52(6):1766-1772. https://doi.org/10.1002%2Fart.21043

15. City of Cape Town. Find your District. City of Cape Town: Urban Planning & Design Department, 2019.
http://resource.capetown.gov.za/documentcentre/Documents/Maps%20and%20statistics/District%20and%20Suburb%20Boundaries%20Map.pdf (accessed 30 Apr. 2019).
16. Socio-economic Profile: City of Cape Town 2016. Cape Town: Western Cape Government, 2016;16-17.
https://www.westerncape.gov.za/assets/departments/treasury/Documents/Socio-economic-profiles/2016/City-of-Cape-Town/city_of_cape_town_2016_socio-economic_profile_sep-lg.pdf (accessed 30 Apr. 2019).
17. Centers for Disease Control and Prevention. Instructions to Panel Physicians for Completing Chest X-ray and classification worksheet (DS-3024). Atlanta: Centers for Disease Control and Prevention, 2007;2-7.
https://en.wikipedia.org/wiki/Tuberculosis_radiology (accessed 24 May 2017).
18. Kanabus A. TB Statistics South Africa - National, incidence, provincial. Global Health Education, 2018. https://tbfacts.org/tb-statistics-south-africa/ (accessed 30 May 2019).
19. Byun JM, Lee CK, Rhee SY, et al. The Risk of Tuberculosis in Korean Patients with Inflammatory Bowel Disease Receiving Tumor Necrosis Factor-α Blockers. J Korean Med Sci. 2015;30(2):173-179. https://doi.org/10.3346%2Fjkms.2015.30.2.173
20. Jung SM, Ju JH, Park M-S, et al. Risk of tuberculosis in patients treated with anti-tumor necrosis factor therapy: a nationwide study in South Korea, a country with an intermediate tuberculosis burden. International Journal of Rheumtic Diseases. 2015;18(3):323-330. https://doi.org/10.1111%2F1756-185x.12530
21. Jauregui-Amezaga A, Turon F, Ordás I, et al. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. Journal of Crohn's and Colitis. 2013;7(3):208-212. https://doi.org/10.1016%2Fj.crohns.2012.05.012
22. Hou JK, Kramer JR, Richardson P, Sansgiry S, El-Serag HB. Tuberculosis Screening and Reactivation Among a National Cohort of Patients with Inflammatory Bowel Disease Treated with Tumor Necrosis Factor Alpha Antagonists. Inflammatory Bowel Diseases. 2017;23(2):254-260. https://doi.org/10.1097%2Fmib.0000000000001003
23. Byun JM, Lee CK, Rhee SY, et al. Risks for opportunistic tuberculosis infection in a cohort of 873 patients with inflammatory bowel disease receiving a tumor necrosis factor-α inhibitor. Scand J Gastroenterol. 2015;50(3):312-320.
https://doi.org/10.3109%2F00365521.2014.1000960
24. Agarwal A, Kedia S, Jain S, et al. High risk of tuberculosis during infliximab therapy despite tuberculosis screening in inflammatory bowel disease patients in India. Intestinal Research. 2018;16(4):588-598. https://doi.org/10.5217%2Fir.2018.00023
25. Deetlefs E, Epstein D, Watermeyer GA, Seggie RM, Thomson SR. Tuberculosis in an inflammatory bowel disease cohort from South Africa. S Afr Med J. 2012;102(10):802-804. https://doi.org/10.7196%2Fsamj.5609
26. Pettipher C, Benitha R. Risk of Tuberculosis in Biologic Users for Rheumatic Diseases: Results from the South African Biologics Registry [abstract]. Arthritis Rheumatol. 2017; 69 (suppl 10). https://acrabstracts.org/abstract/risk-of-tuberculosis-in-biologic-users-forrheumatic-diseases-results-from-the-south-african-biologics-registry/
27. Hong SN, Kim HJ, Kim KH, Han S-J, Ahn IM, Ahn HS. Risk of incident Mycobacterium tuberculosis infection in patients with inflammatory bowel disease: a nationwide population-based study in South Korea. Aliment Pharmacol Ther. 2017;45(2):253-263.
https://doi.org/10.1111%2Fapt.13851
28. Aberra FN, Stettler N, Brensinger C, Lichtenstein GR, Lewis JD. Risk for Active Tuberculosis in Inflammatory Bowel Disease Patients. Clinical Gastroenterology and Hepatology. 2007;5(9):1070-1075. https://doi.org/10.1016%2Fj.cgh.2007.04.007

29. Burger R, Christian C. Access to health care in post-apartheid South Africa: availability, affordability, acceptability. Health Economics, Policy and Law. 2018;15(1):43-55. https://doi.org/10.1017%2Fs1744133118000300
30. Lee JW, Choi CH, Park JH, et al. Clinical features of active tuberculosis that developed during anti-tumor necrosis factor therapy in patients with inflammatory bowel disease. Intestinal Research. 2016;14(2):146-151. https://doi.org/10.5217%2Fir.2016.14.2.146
31. Gómez-Reino JJ, Carmona L, Ángel Descalzo M. Risk of Tuberculosis in Patients Treated With Tumor Necrosis Factor Antagonists Due to Incomplete Prevention of Reactivation of Latent Infection. Arthritis Rheum. 2007;57(5):756-761. https://doi.org/10.1002%2Fart.22768
32. Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a metaanalysis. *Chest.* 2010;137(4):952-968.
33. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med.* 2008;149(3):177-184.
34. Schoepfer AM, Flogerzi B, Fallegger S, et al. Comparison of Interferon-Gamma Release Assay Versus Tuberculin Skin Test for Tuberculosis Screening in Inflammatory Bowel Disease. Am J Gastroenterol. 2008;103(11):2799-2806. https://doi.org/10.1111%2Fj.1572-0241.2008.02050.x
35. Thi AA, Abbara A, Bouri S, et al. Challenges in screening for latent tuberculosis in inflammatory bowel disease prior to biologic treatment: a UK cohort study. Frontline Gastroenterology. 2018;9(3):234-240. https://doi.org/10.1136%2Fflgastro-2017-100951
36. van Rie A, Warren R, Richardson M, et al. Exogenous Reinfection as a Cause of Recurrent Tuberculosis after Curative Treatment. N Engl J Med. 1999;341(16):1174-1179. https://doi.org/10.1056%2Fnejm199910143411602
37. Bandera A, Gori A, Catozzi L, et al. Molecular Epidemiology Study of Exogenous Reinfection in an Area with a Low Incidence of Tuberculosis. J Clin Microbiol. 2001;39(6):2213-2218. https://doi.org/10.1128%2Fjcm.39.6.2213-2218.2001
38. Park DI, Hisamatsu T, Chen M, et al. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: management. Intestinal Research. 2018;16(1):17-25. https://doi.org/10.5217/ir.2018.16.1.17
39. Adams S, Ehrlich R, Baatjies R, et al. Incidence of occupational latent tuberculosis infection in South African healthcare workers. Eur Respir J. 2015;45(5):1364-1373. https://doi.org/10.1183%2F09031936.00138414
40. Papay P, Primas C, Eser A, Novacek G, Winkler S, Frantal S, et al. Retesting for latent tuberculosis in patients with inflammatory bowel disease treated with TNF-alpha inhibitors. Aliment Pharmacol Ther. 2012;36(9):858-65.
41. Handa R, Misra R, Chaturvedi VP, Pispati PK, Rao URK, Joshi VR. Guidelines for tuberculosis prophylaxis during anti-tumour necrosis factor-α treatment: Indian Rheumatology Association. APLAR Journal of Rheumatology, 9(2): 181-183. https://doi.org/10.1111%2Fj.1479-8077.2006.00181.x
42. Wood R, Bekker L-G. Isoniazid preventive therapy for tuberculosis in South Africa: An assessment of the local evidence base. S Afr Med J. 2014;104(3):174-177. https://doi.org/10.7196%2Fsamj.7968
43. Churchyard GJ, Fielding KL, Lewis JJ, et al. A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control. N Engl J Med. 2014;370(4):301-310. https://doi.org/10.1056%2Fnejmoa1214289

44. Jung YJ, Lee JY, Jo KW, Yoo B, Lee CK, Kim YG, et al. The 'either test positive' strategy for latent tuberculous infection before anti-tumour necrosis factor treatment. Int J Tuberc Lung Dis. 2014;18(4):428-434.
45. Abitbol Y, Laharie D, Cosnes J, Allez M, Nancey S, Amiot A, et al. Negative Screening Does Not Rule Out the Risk of Tuberculosis in Patients with Inflammatory Bowel Disease Undergoing Anti-TNF Treatment: A Descriptive Study on the GETAID Cohort. J Crohns Colitis. 2016;10(10):1179-1185.
46. Park DI, Hisamatsu T, Chen M, Ng SC, Ooi CJ, Wei SC, et al. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 1: risk assessment. Intestinal research. 2018;16(1):4-16.
47. Lorenzetti R, Zullo A, Ridola L, Diamanti AP, Lagana B, Gatta L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. Ann Med. 2014;46(7):547-554.
48. Cantini F, Niccoli L, Goletti D. Tuberculosis risk in patients treated with non-anti-tumor necrosis factor-alpha (TNF-alpha) targeted biologics and recently licensed TNF-alpha inhibitors: data from clinical trials and national registries. *J Rheumatol Suppl.* 2014;91:56-64.
49. Ooi CJ, Hilmi I, Banerjee R, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. *Intestinal research.* 2019;17(3):285-310.
50. Dobler CC. Biologic Agents and Tuberculosis. *Microbiol Spectr.* 2016;4(6).
51. Banerjee R, Ali RAR, Wei SC, Adsul S. Biologics for the Management of Inflammatory Bowel Disease: A Review in Tuberculosis-Endemic Countries. *Gut Liver.* 2020;14(6):685-698.

TABLES

TABLE 1. Baseline characteristics of the study population

	IBD* N = 1011		Crohn's Disease N = 523		Ulcerative Colitis N = 488	
	Years	**IQR**	**Years**	**IQR**	**Years**	**IQR**
Age	33.0	24.2-45.2	30.7	22.8-40.3	36.3	26.5-50.8
	N (%)†		**N (%)†**		**N (%)†**	
Sex: Female	633 (62.8)		333 (63.9)		300 (61.6)	
Smoking‡	532 (55.9)		332 (66.3)		200 (44.4)	
Family history§	109 (10.9)		71 (13.6)		38 (8.0)	
Location/Extent¶	783 (77.4)		414 (79.2)		369 (75.8)	
CD L1 Ileal			150 (28.7)			
CD L2 Colonic			97 (18.5)			
CD L3 Ileocolonic			167 (31.9)			
UC E1 Proctitis					62 (12.7)	
UC E2 Left Sided					139 (28.5)	
UC E3 Extensive					168 (34.4)	
Behaviour¶			347 (66.3)			
CD B1 Non S or P			125 (23.7)			
CD B2 Stricturing			87 (16.6)			
CD B3 Penetrating			135 (25.8)			
CD P Perianal			129 (24.7)			
Hospital type: Public	639 (63.2)		339 (64.8)		300 (61.5)	
Residential district	688 (68.1)		364 (69.6)		324 (66.4)	
Cape Flats	177 (17.4)		88 (16.7)		89 (18.3)	
MP/K	151 (14.9)		80 (15.2)		71 (14.6)	
Southern	146 (14.4)		77 (14.6)		69 (14.2)	
Table Bay	91 (9.0)		44 (8.3)		47 (9.7)	
Tygerberg	47 (4.6)		31 (5.9)		16 (3.9)	
Blaauwberg	38 (3.7)		22 (4.2)		16 (3.3)	
Northern	29 (2.9)		14 (2.7)		15 (3.1)	
Helderberg	9 (0.9)		8 (1.5)		1 (0.2)	

*Excludes subjects with unspecified colitis.
†Numbers vary due to missing data and clinical characteristic.
‡Current and ex-smokers. §First degree relative with IBD. ¶Montreal classification.
Non S or P: non-stricturing, non-penetrating disease. IBD: Inflammatory bowel disease.
CD: Crohn's Disease. UC: Ulcerative Colitis. MP/K: Mitchell's Plain/Khayelitsha.
IQR: interquartile range.

TABLE 2: Characteristics of patients with newly developed tuberculosis infections

Variable		N = 42	
		Median (years)	**IQR (years)**
Age at TB diagnosis		40.5	29.0 – 54.2
		Median (months)	**IQR (months)**
Time to TB diagnosis	All patients	96.7	42.2-164.8
	No IST	75.5	31.7-146.3
	On IMM	71.4	5.4-115.5
	On Anti-TNF-α only	11.3	8.1-29.2
		N (%)	
Residential district	Mitchells Plain and Khayelitsha	13 (31.0)	
	Cape Flats	9 (21.4)	
	Tygerberg	5 (11.9)	
	Southern	3 (7.1)	
	Table Bay	1 (2.4)	
	Blaauwberg	1 (2.4)	
Hospital facility	State/Public	32 (76.2	
Type of IBD	Crohn's Disease	28 (66.7)	
	Ulcerative Colitis	12 (28.6)	
	IBD unclassified	2 (4.8)	
Disease location*	L3	14 (33.3)	
	L1	9 (21.4)	
	E3	6 (14.3)	
	L2	5 (11.9)	
Immunosuppressive therapy	Azathioprine	9 (21.4)	
	IMM + TNF-α blocker	5 (11.9)	
	TNF-α blocker	1 (2.4)	
	Methotrexate	2 (4.8)	
	6-Mercaptopurine	1 (2.4)	
Past history of TB		6 (14.3)	
LTBI screening‡	Positive	1 (2.4)	
	Negative	8 (19.0)	
	Not available	8 (19.0)	
	Not done	25 (59.5)	
Location of TB	Pulmonary	33 (78.6)	
	Extra-pulmonary	7 (16.7)	
	Disseminated	1 (2.4)	
	Not available	1 (2.4)	
TB diagnosis	Microbiology	26 (62.0)	
	Histology	3 (7.1)	
	Chest Radiograph	9 (21.4)	
	History†	4 (9.5)	

*Montreal classification. †Based on TB symptoms and clinical improvement on treatment.
‡Results based on tuberculin skin test and/or Interferon-Gamma Releasing Assay.
IQR: Interquartile range. TB: Tuberculosis. IBD: Inflammatory bowel disease. IMM: Immunomodulator. TNF: Tumour necrosis factor. LTBI: Latent tuberculosis infection.

TABLE 3. Analysis of risk factors for active tuberculosis infection

Risk factor	Non-TB N = 999		TB N = 42		P-value
	Median (years)	IQR (years)	Median (years)	IQR (years)	
Age	33.5	24.6-46.1	28.2	21.4-42.5	0.103
	N (%)*		N (%)*		
Sex: Female	623/996 (62.6)		27 (64.3)		0.820
Smoking	520/940 (55.3)		30/41 (73.2)		0.024
State hospital	627/999 (62.8)		32 (76.2)		0.077
(+) LTBI screening	27/120 (22.5)		1/9 (11.1)		0.683
HIV positivity	4/604 (0.66)		2/29 (6.9)		0.027
IBD type: CD	495/971 (51.0)		28/40 (70.0)		0.023
Extensive disease					
CD (L2+3/L total)†	245/386 (63.5)		19/28 (67.9)		0.641
UC (E3/E total)†	168/377 (44.6)		6/13 (46.2)		0.910
Complicated CD					
(B2+3/B total) †	202/320 (63.1)		20/27 (74.1)		0.255
IBD surgery	343/695 (49.4)		27/38 (71.1)		0.009
IST‡	404/769 (52.5)		18/40 (45.0)		0.352
TNF-α blocker	62/769 (8.1)		6/40 (15.0)		0.123

*Numbers vary due to missing data and risk factor, denominators included where applicable.
†Montreal classification. ‡Excludes steroid therapy.
IQR: Interquartile range. LTBI: Latent tuberculosis infection. CD: Crohn's disease.
UC: Ulcerative colitis. IST: Immunosuppressive therapy. HIV: Human immunodeficiency virus.

Table 4: Multivariate analysis of risk factors for active tuberculosis infection

Risk Factor	Adjusted OR (95% CI)	*P*-value
Crohn's disease	2.00 (0.92- 4.36)	0.079
Smoking	1.44 (0.66-3.14)	0.360
Public hospital	1.81 (0.75-4.37)	0.186
TNF-α blockers	2.45 (0.88-6.80)	0.086

OR: Odds Ratio. CI: Confidence Interval.

TABLE 5. Latent tuberculosis infection screening tests in subjects using immunosuppressive therapy[*]

Total = 131	
Test	**N (%)**
Tuberculin Skin Test (TST)	
Positive[†]	13 (9.9)
Negative	63 (48.1)
NA	2 (1.5)
Interferon Gamma Releasing Assay (IGRA)	
Positive	7 (5.3)
Negative	12 (9.2)
Indeterminate	5 (3.8)
NA	3 (2.3)
TST/IGRA	
Positive/Positive	1 (0.8)
Negative/Negative	4 (3.1)
Positive/Negative	3 (2.3)
Negative/Positive[†]	2 (1.5)
Negative/Indeterminate	2 (1.5)
NA/NA	1 (0.8)

[*]Excludes steroid therapy. [†]One positive test at same time of active TB diagnosis.
NA: results not available.

APPENDICES

APPENDIX A: MONTREAL CLASSIFICATION

Montreal classification for Crohn's disease (CD)		
Age at diagnosis	A1	below 16 y
	A2	between 17 and 40 y
	A3	above 40 y
Location	L1	ileal
	L2	colonic
	L3	ileocolonic
	L4	isolated upper disease*
Behaviour	B1	non-stricturing, non-penetrating
	B2	stricturing
	B3	penetrating
	p	perianal disease modifier†

*L4 is a modifier that can be added to L1-L3 when concomitant upper gastrointestinal disease is present.
† "p" is added to B1-B3 when concomitant perianal disease is present.

Montreal classification of extent of ulcerative colitis (UC)	
Extent	**Anatomy**
E1 Ulcerative proctitis	Involvement limited to rectum
E2 Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3 Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

APPENDIX B: CROHN'S DISEASE ACTIVITY INDEX (CDAI)

	SUM OF 7 DAYS	FACTOR	SUBTOTAL
Number of liquid or soft stools	- - -	2	- - -
Abdominal pain[1]	- - -	5	- - -
General well-being[2]	- - -	7	- - -
Number of complications (presence or absence):			
Arthritis or arthralgia			
Iritis or uveitis			
Anal fissure, fistula or abscess	- - -[3]	20	- - -
Erythema nodosum, pyoderma gangrenosum, aphthous stomatitis			
Other fistula			
Fever over 37.8^0C			
Loperamide or diphenoxylate for diarrhoea (none=0, yes=1)	- - -	30	- - -
Abdominal mass (none=0, questionable=2, definite=5)	- - -	10	- - -
Haematocrit [males 47-Ht(%), females 42-Ht(%)]	- - -	6	- - -
Body weight [1-(Body weight/standard weight)] X 100 =	- - -	1	- - -
		CDAI total	- - -

[1] Pain score per day: 0=none, 1=mild, 2=moderate, 3=severe. [2] General well-being score per day: 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible. [3]Total number of complications from the list that are present.

APPENDIX C: TRUELOVE AND WITTS CRITERIA

	Mild	Moderate	Severe
Bloody stools/day	<4	4-5	≥6 and
Pulse	≤90 bpm	≤90 bpm	>90 bpm or
Temperature	<37.5ºC	≤37.8ºC	>37.8ºC or
Haemoglobin	>11.5 g/dl	≥10.5 g/dl	<10.5 g/dl or
ESR	<20 mm/hr	≤30 mm/hr	>30 mm/hr or
CRP	Normal	≤30 mg/L	>30 mg/L

APPENDIX D: South African IBD Registry Datasheet

Fax: 021 531-6403

Personal Details	Answer
1. Surname	
2. Initials	
3. Male / Female	
5. ID number	
6. Date of birth	
7. Postal code	

IBD Details	Description	Answer
1. Type of IBD	Crohns, Ulcerative colitis, Not sure	
2. Year of diagnosis	In what year were you diagnosed with IBD?	
3. Age at diagnosis	How old were you at diagnosis?	
4. Duration of symptoms	How many months were you ill before you were found to have IBD?	
5. Smoking status at diagnosis	At diagnosis were you a smoker (more than 2 cigs a day), a non-smoker or an ex-smoker?	
6. Family history	Do you have a parent, brother or sister with either Crohn's or UC?	
7. Tuberculosis	Have you ever been treated for TB?	
8. Cancer	Have you ever been diagnosed or treated for cancer?	

Crohn's disease phenotype at diagnosis	
Disease Extent at diagnosis	*Montreal Classification (Appendix 5)*
CD L4	*Upper GI disease- Montreal Classification*
CD L4a or L4b	*For paediatric patients as per Paris Classification(Appendix 6)*
Peri-anal disease	*Documented abscess or fistula – not anal tags or fissures.*
CD Behaviour	*Penetrating, Stricturing or Inflammatory as per Montreal Classification at diagnosis.*
Ulcerative colitis phenotype at diagnosis	
Disease extent at diagnosis	*Proctitis, Left sided (to splenic flexure) or extensive (beyond splenic flexure) Montreal Classification*
Extra-intestinal Disease / Complications	
PSC	*Yes or No or Under investigation. Description of diagnosis.*
Osteoporosis	*BMD results and date with vertebral fracture assessment.*
Extra-intestinal manifestations	*Arthritis (not arthralgia), ankylosing spondylitis, uveitis/episcleritis, pyoderma gangrenosum, erythema nodosum*
Thrombosis	*Any venous or arterial thrombosis since diagnosis*
Comorbidity	
Previous TB	*Yes / No - brief description. Excludes empiric TB treatment in Crohn's disease patients.*
Mantoux and date of last test	*Not done, Outstanding, Negative, Positive (>5mm)*
IFGRA and date of last test	*Not done, Outstanding, Positive, Negative, Indeterminate*
CXR	*Outstanding, Normal, Previous TB (CDC Criteria Appendix 7) or Not done. Preferably at diagnosis*
HIV and year of diagnosis	*Positive / Negative/ Unknown*
Cancer	*Any history of cancer, including non-melanoma skin cancer, with description*
Fertility	*Number of pregnancies since diagnosis with IBD*

Immunomodulator Treatment	
Medication	*Methotrexate, Azathioprine, 6-mercaptopurine.*
Duration of treatment	*Date started and stopped*
Reason for stopping treatment	*E.g. Non-adherence, surgery, side effects (neutropaenia, hepatitis, pancreatitis, infection etc), other, unknown, lost to follow-up*
Biological Treatment	
Drug	*Humira, Revellex, Simponi, Vedolizumab, Other*
Treatment start and stop	
Dose escalation	*Any increase in treatment with either dose increase or interval shortening*
Access	*Biological treatment indicated but access denied by funder or institution. See SAGES Guidelines for Rx indications*
Reason for stopping biological treatment	*Primary or Secondary Non-response, Surgery, Side effect, Infection, Other serious adverse event, Cost, Unknown*
Surgical Treatment	
Crohn's disease	*Small bowel resection (includes ileo-caecal or ileo-hemicolectomy) and number of resections*
	Colon surgery (includes segmental colectomy or total colectomy)
	Other Crohn's surgery with description
Ulcerative colitis	*Total colectomy, Other colectomy*
	Indication: 1.Fulminant colitis 2.Chronic disease 3.Dysplasia/Cancer
	Ileal pouch anal anastomosis
Years from diagnosis to first IBD surgery	*IBD diagnosis may be made at surgery (1 year) or surgery required after diagnosis. Duration in years.*
Patient death	*Alive or dead or unknown. Patients > 100 years assumed dead.*
	Cause of death (IBD related or non-IBD related) with description
	IBD related includes 30-day post-operative mortality for IBD surgery, immune suppression related infection, short bowel syndrome complications, IBD related cancers.

APPENDIX E: CONSENT FORM

CONSENT TO ACT AS A PARTICIPANT IN THE SOUTH AFRICAN INFLAMMATORY BOWEL DISEASE REGISTRY

PRINCIPAL INVESTIGATOR: Dr D Epstein

CO-INVESTIGATORS: Complete, current listing available upon request

SOURCE OF SUPPORT: SA Gastroenterology Society

What is the purpose of the South African IBD Registry?
Many advancements in medicine have resulted from research involving the collection and analysis of the medical record information of patients with a certain disease or condition. Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease or IBD, are important, emerging health conditions in South Africa. The South African Gastroenterology Society is asking for your permission to allow us to place your past, current and future medical record information into the SA IBD Registry. By placing the medical record information of many patients such as you, into a research registry, researchers will be able to conduct research studies aimed at increasing our knowledge about ulcerative colitis and Crohn's disease in South Africa. Results of these studies could lead to better care for IBD patients in South Africa.

What will my participation in this IBD Registry involve?
If you agree to participate in the SA IBD Registry your past, current and future medical record information will be placed into the Registry. This will permit research studies to be conducted on the medical record information contained within the registry.

What are the possible risks of my participation in the SA IBD Registry?
There are no risks of physical injury associated with your participation in the SA IBD Registry. Participation in this Registry does involve the possible risk that information about your health might become known to individuals other than your usual healthcare providers. We will attempt to preserve your medical record confidentiality by assigning a code number to your medical record information stored in the Registry, and by removing personal identifiers (for example, your name, address, contact details) from information stored about you in the Registry. Only the SA IBD Registry staff will have access to this information.

What are the possible benefits of my participation in the SA IBD Registry?
It is unlikely that you will receive any direct benefit as a result of your participation in the SA IBD Registry. However, medical record information contained within the Registry will be used for research studies directed at improving our knowledge and treatment of Crohn's disease and ulcerative colitis and this knowledge may benefit patients with these diseases in the future.

Will I or my medical aid be charged for my participation in the SA IBD Registry?
There will be no costs to you or your medical aid to participate in this Registry.

Will I be paid for my participation in the SA IBD Registry?
No, you will not receive any payment for participating in this Registry.

Who will know about my participation in the SA IBD Registry?
Information from your medical records that is placed into this Registry will be kept as confidential (private) as possible. In addition, you will not be identified by name in any publication of the results of research studies involving the use of your medical record information.

What is the nature of my medical record information that will be placed into the SA IBD Registry?
All of your past, current and future medical record information related to your IBD will be recorded into the Registry. Since medical conditions and treatments not related directly to your IBD may affect IBD and/or its treatment, it is likely that all of your existing and future medical record information will be placed in the registry. This information can be submitted personally, or obtained from your hospital or private healthcare provider's medical records.

Who will have access to my identifiable medical record information contained in the SA IBD Registry?
Access to your identifiable medical record information contained within this Registry will be limited to investigators and staff associated with SA IBD Registry. A current, complete listing of these individuals will be provided to you upon your written request.

For how long will my medical record information continue to be placed in the SA IBD Registry and for how long will this information be used for research purposes?
We will continue to place your medical record information into the SA IBD Registry until 1) you are no longer living; or 2) you withdraw your permission for participation in the Registry. Your medical record information contained within the Registry will be used for research purposes for an indefinite period of time.

Is my participation in the SA IBD Registry voluntary?
Your participation in the Registry, to include the use of your medical record information for the research purposes described above, is completely voluntary. Whether or not you provide your permission for participation in this Registry will have no effect on your current or future medical care.

May I withdraw, at a future date, my consent for participation in the SA IBD Registry?
You may withdraw, at any time, your consent for participation in the Registry, to include the additional collection of your medical record information and its further use for the research purposes described above. To formally withdraw your permission for participation in the Registry you should provide a written and dated notice of this decision.

Has the SA IBD Registry project been approved by an ethics committee?
The SA IBD Registry protocol has been approved by the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee (Ref: R048/2013)

****

VOLUNTARY CONSENT
All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of my participation in the SA IBD Registry at any time, and that such future questions will be answered by the doctors associated with the SA IBD Registry or their research staff. I understand that a copy of this consent form will be given to me.

By signing below, I agree to participate in the SA IBD Registry.

_____ _____
Participant's (or guardian's) Signature Date

CERTIFICATION OF INFORMED CONSENT
I certify that I have explained the nature and purpose of the SA IBD Registry to the above-named individual, and I have discussed the possible risks and potential benefits of participation in this Registry. Any questions the individual has about this Registry have been answered, and the doctors and research staff associated with SA IBD Registry will be available to address future questions as they arise.

_____
Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

APPENDIX F: ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-44 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arlefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 January 2017

HREC REF: 804/2016

Prof Sandie Thomson
Division of Gastroenterology
Room 93, E23
NGSH

Dear Prof Thomson

PROJECT TITLE: INCIDENCE OF TUBERCULOSIS IN THE INFLAMMATORY BOWEL DISEASE REGISTRY IN CAPE TOWN, SOUTH AFRICA (MMed candidate- Mitesh Kanthi Pema)

Thank you for your response letter dated 18 January 2017, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 January 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Dr M Pema will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 804/2016

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

APPENDIX G: INSTRUCTIONS TO AUTHORS

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.
To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:
www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.
We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g.
  guidelines,
  conference/congress
  abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 565 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publicaiton fee is payable when your manuscript is editorially accepted and before production commences for

publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.
Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.
If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please

refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Patient Consent

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The **Author Agreement form** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice

Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.
- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The

conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.
Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.
From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.
In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant

- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996. In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)
Rex v Jopp and Another: Name of the parties concerned
1949: Date of decision (or when the case was heard)
(4): Volume number
SA: SA Law Reports
11: Page or section number
(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.
NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

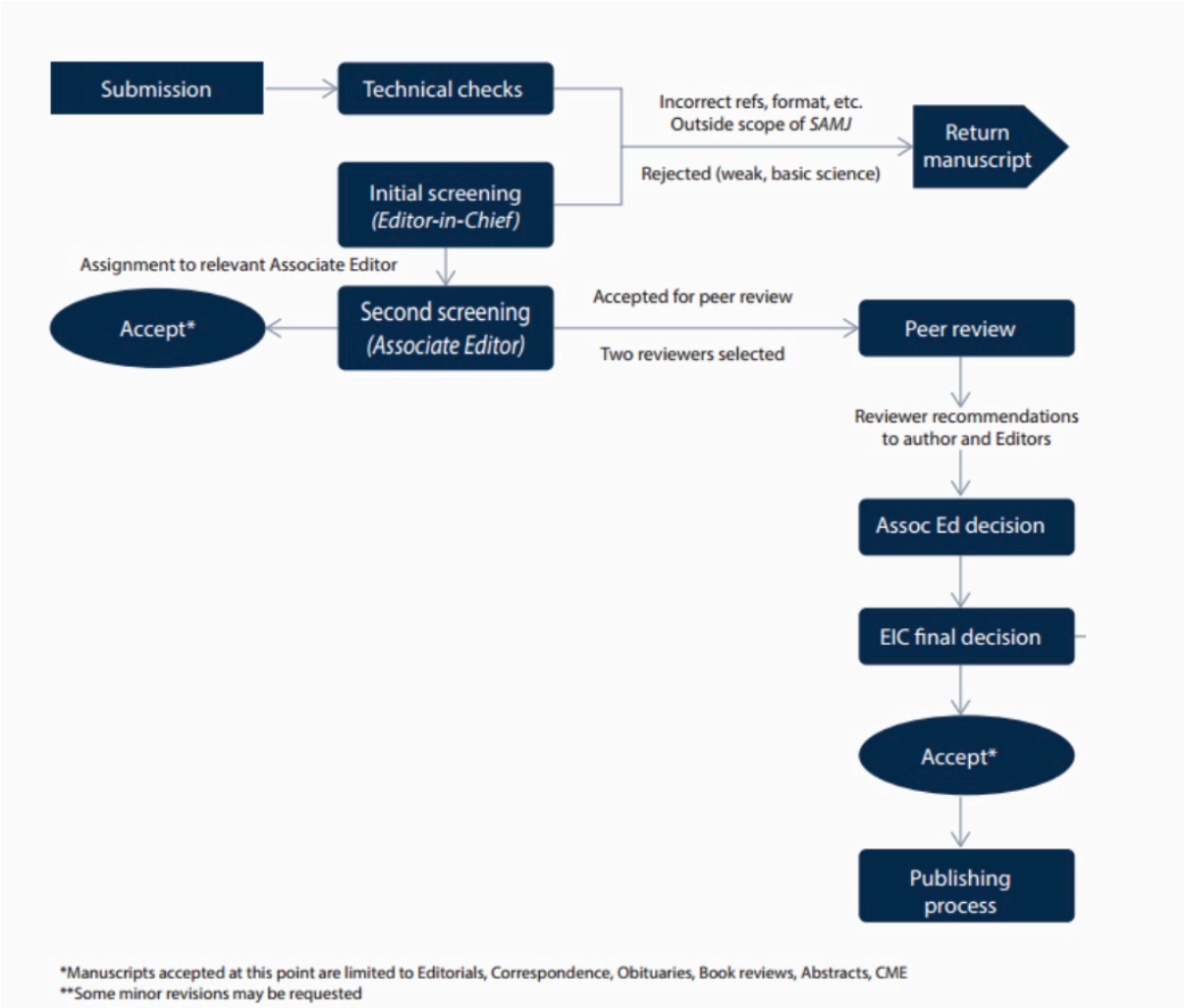
Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who

will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1 An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).

2 The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3 If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.

4 The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.

5 The CE will finalise the article and then it will be typeset.
6 Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7 The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8 The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All

investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.
Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.
Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

Copyright Notice

Privacy Statement

The *SAMJ* is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the *SAMJ* for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

The South African Medical Journal | Online ISSN: 2078-5135 | Print ISSN: 0256-9574 | © 2014 Health & Medical Publishing Group