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Department of Human Biology
University of Cape Town

Network analysis of Diagnostic Medical Device Development for Infectious Diseases Prevalent in South Africa

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MPhil in Health Innovation

Nonku Nyathi (NYTANA001)

Supervisor: Prof. Tania Douglas
Co-supervisor: Dr Kylie de Jager
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DECLARATION

I, *……Nonku Nyathi…*, hereby declare that the work on which this dissertation/thesis 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.

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Abstract

Infectious diseases are a major health concern in South Africa and many other developing countries. The local development of medical devices for infectious diseases in such settings, utilizing the local knowledge base, has the potential to improve the accuracy of and access to diagnoses and to lead to the devices being more context-appropriate and affordable. The aim of this project was to examine the landscape of diagnostic medical device development targeting infectious diseases prevalent in South Africa for the period 2000-2016, particularly with regard to collaboration between institutions in different sectors and the contributions of different collaborators. Such knowledge would be beneficial to future technological and policy developments aimed at improving access to diagnostic services and treatment in the South African context.

Collaboration across four sectors was considered: university, hospital, industry and science councils and facilities. A bibliometric analysis was performed, and publications documenting medical device development for diagnosis of infectious diseases were extracted. Co-authorship of the journal and conference articles was used as a proxy for collaboration across organisations. Affiliation data extracted from the publications were used to generate a collaboration network. Netdraw, a network visualisation tool, was used to visualize the network, and network metrics such as degree centrality, betweenness centrality and closeness centrality, as well as group density measures, were produced using UCINET software. The collaboration network and the network metrics were used to determine which organisations have collaborated and which collaborators have played the most active and influential roles in diagnostic device development. The university sector was found to make the largest contribution to the development of diagnostic medical devices in South Africa, and also played a key role in transmitting information throughout the network due to its high frequency of connections to other organisations. The most prevalent type of inter-sectoral collaboration was between universities and science councils and facilities, while universities were found to collaborate most amongst themselves with regard to intra-sectoral collaboration. Foreign organisations played a prominent role in diagnostic device development between 2012 and 2016. Tuberculosis was the most prevalent infectious disease in diagnostic device development research, and computer-aided detection was a common feature of research on diagnostic device development.

1. Introduction

Infectious diseases continue to be a major health concern in many low income and developing countries with poorly resourced health systems (Mcnerney, 2015). Leading communicable diseases such as HIV/AIDS, tuberculosis, malaria, diarrheal diseases and lower respiratory tract infections collectively account for approximately a third of all deaths in these countries every year (Santoro et al., 2015). In the South African context, HIV/AIDS and tuberculosis were among the top ten leading causes of death in the years 2005 and 2016, as shown in Table 1-1.

Table 1-1: Top 10 causes of death in 2005 and 2016 (table adapted from Institute for Health Metrics and Evaluation, 2017)

2005	**2016**
HIV/AIDS	HIV/AIDS
Lower Respiratory Tract Infection	Ischemic Heart Disease
Tuberculosis	Lower Respiratory Tract Infection
Ischemic Heart Disease	Diabetes
Cerebrovascular Disease	Cerebrovascular Disease
Diabetes	Tuberculosis
Road Injuries	Road Injuries
Interpersonal Violence	Interpersonal Violence
Diarrheal Diseases	Chronic Obstructive Pulmonary Disease
Chronic Obstructive Pulmonary Disease	Diarrheal Diseases

A number of strategies have been implemented in an attempt to reduce this burden of disease, including vaccination programs, health education, the use of mosquito repellant bed nets in malaria-endemic areas, improved provision of clean water and sanitation and mass administration of drugs in remote communities; even so, appropriate clinical management of patients continues to present a significant challenge in global health (Peeling and Mabey, 2010).

The 20-year End-TB Strategy, adopted by the World Health Assembly in 2014, is one example of a global strategy aimed at eliminating one of the deadliest infectious diseases in the world, tuberculosis (World Health Organization, 2015). Similarly, the Sustainable Development Goals, which were approved by the General Assembly of the United Nations in 2015, have committed to ending epidemics of HIV/AIDS, tuberculosis, malaria and neglected tropical diseases, as well as to combating hepatitis, water-borne diseases and other communicable diseases by 2030 (Osborn et al., 2015). Targeted disease elimination and control programmes, including wider treatment and vaccination coverage and increased funding to support medical research have contributed to the decline in the incidence of communicable diseases between 2000 and 2015, however further expansion of these interventions, particularly in regions with a high disease burden, are required to reach the 2030 goals (UN, 2017).

The burden of infectious diseases falls mainly on vulnerable parts of the population, wherein financial, structural and geographical access to healthcare is limited. Lack of access to good quality diagnostic tests for infectious diseases results in the mistreatment of illnesses (Peeling and Mabey, 2010; Mcnerney, 2015). Clinical laboratories and diagnostic services in developing countries are typically sparsely distributed or under-resourced, and most diagnostic tests tend to be too expensive for healthcare providers and patients (Berkelman et al., 2006; Mcnerney, 2015). In such cases, diseases are typically diagnosed based on clinical symptoms and local disease prevalence; while this approach is able to identify most patients requiring treatment, it also results in the unnecessary treatment of misdiagnosed patients at the expense of limited funds and resources (Yager et al., 2008).

1.1 Diagnostic Devices

Laboratory testing has become increasingly automated, resulting in improved reliability and efficiency. However, the devices themselves remain centralized and require highly trained staff, specialised facilities (Drain et al., 2014) and developed-world resources not readily available in developing countries. Consequently, such tests are typically inaccessible to patients and clinicians in developing regions (Drain et al. 2014; Peeling & Mabey 2010). Therefore, while diagnostic tools are important for patient management and disease control, the effectiveness of these tools is dependent on how well the environment in which they were designed to be used, matches the environment in which they are implemented.

When it comes to health care services and research, there is a difference in priorities between high- and low-resource countries. While patients in high-resource countries focus on advanced diagnostic technologies, patients in low-resource countries would benefit from simple and affordable diagnostic tools which would improve accessibility to appropriate medical care (WHO, 2010). The mismatch in the supply and demand of diagnostic devices negatively impacts low-resource settings and thus creates a gap in the market for the development thereof (WHO, 2010).

Tests designed for use in developed countries are often not readily available or transferable to resource-limited countries. For example, rapid diagnostic tests for HIV (Ghani et al., 2015), the GeneXpert MTB/RIF test used for the detection of *Mycobacterium tuberculosis* DNA (Mcnerney and Zumla, 2015) and rapid diagnostic tests for malaria (Rao et al., 2013) have proven to be inconclusive and unreliable when used in low-income settings. Barriers include general lack of infrastructure, unreliable water and electricity resources, lack of staff training and incorrect specimen collection in developing countries (Peeling and Mabey, 2010; Begg, Young and Stone, 2011; Pai and Pai, 2012; Mcnerney, 2015). There is often a lack of knowledge in the clinical setting as to how to operate the devices and ensure consistent efficacy (Peeling and Mabey, 2010). Given that the sensitivity of diagnostic instruments and reagents may be reduced in resource-poor settings, there is a need for the development of simple, robust and cost-effective tests that can withstand extreme conditions and the lack of skilled technicians (Mehta and Cook, 2010). However, not many medical devices are manufactured in developing nations, instead the majority of devices used in healthcare in such countries have been imported (World Health Organization, 2010).

Decentralized diagnostic analysis carried out at the site of care is known as point-of-care testing (POCT) (Luppa et al., 2011). Examples of POC tests include blood glucose tests, pregnancy tests and urine tests, all of which provide some information about the patient’s physiology and prevent the delay of treatment (Choi, 2016). POCT can increase the speed with which clinicians receive results and reduce waiting times from days to hours, as the need for sample transport and laboratory processing is eliminated (Kost, 2002). The key objective of POCT is to generate a rapid result so that the appropriate treatment may be implemented, leading to a better clinical and economic outcome (Price, 2001). Furthermore, unlike laboratory testing methods, which require specific facilities and complex procedures, POCT offers a more distributable diagnostic analysis which includes benefits such as automation and portability (Choi, 2016). Simple and easy-to-use POCT devices would be beneficial in resource-limited areas.

Through improved access to fast and accurate diagnostic testing, both using POCT and other diagnostic devices, disease progression in developing countries would be mitigated, which could ultimately reduce disease transmission rates and mortality rates in disadvantaged communities. The local development of medical devices for infectious diseases in resource-limited settings, utilizing the local knowledge base, has the potential to improve the accuracy of and access to diagnoses and to lead to the devices being more context-appropriate and affordable. The End-TB Strategy identifies the lack of effective diagnostic tools as a barrier to ending the global TB epidemic, and considers a point-of-care test for the rapid diagnosis of TB disease and latent infection as one of the crucial elements for achieving complete TB elimination by the year 2035 (Uplekar et al., 2015).

1.2 Collaboration for Medical Device Development

Medical device development is a multi-disciplinary endeavour that requires contributions from different sectors. The sectors known to be involved (Hicks and Katz, 1996; Lander, 2013; Chimhundu et al., 2015), include the university sector, which contributes scientific research, the hospital sector which provides clinical expertise, and the industry sector which provides insight into product development and distribution. Additional sectors, such as government departments and non-governmental organizations sometimes participate in scientific research as collaborators (Lander, 2013). In South Africa, science councils are focused on conducting social, technological and scientific research in accordance with their commission by the South African government under the Scientific Research Council Act 46 of 1988 (South African Government, 1990) and play a role in collaboration for diagnostic device development (Chimhundu et al., 2015; de Jager et al., 2017)

Through collaboration, knowledge can be transferred between the different sectors (Lander, 2013; Chimhundu et al., 2015). Such collaborative interactions can be represented by a collaboration network, defined by Tijssen (1998) as a growing mutual dependency system based on the ability to exchange resources. By mapping collaboration networks, social network analysis tools can be used to develop an understanding of the collaboration activities. Examples exist in the literature where collaboration networks were used to explore the extent of collaboration between sectors, the strength of collaborations and the patterns of collaboration for health-related innovation (Lander, 2013, 2014; Chimhundu et al., 2015; Fonseca et al., 2016).

Some work has been done to understand the development of medical devices, and the associated collaborative activities within South Africa. For example, Chimhundu et al. (2015), analysed sectoral collaboration for cardiovascular medical device development in South Africa over a 15-year period with the purpose of establishing which sectors and organisations play a role in the development thereof, while de Jager et al. (2017) characterized the broad medical device landscape with regard to collaboration in South Africa over a 14-year period. Salie et al. (2017) showed that devices related to the immune system are one of four device types with the highest number of local organisations involved in their development. Although devices related to the immune system may address the diagnosis of infectious diseases (Salie et al., 2017) little is known about diagnostic devices as a category and the extent of activity for their development in South Africa.

1.3 Problem Statement

Diagnostic devices with local input are required to address the local burden of disease, however little is known about diagnostic device development for infectious diseases in South Africa. Mapping the South African landscape would provide a basis from which to promote local diagnostic device development.

Generating and analysing the collaboration network for diagnostic device development in South Africa is a first step in understanding the landscape. The network will help ascertain who the key role players are, to which sectors they belong, and what collaborations they have formed. Such knowledge may form a basis for analysis of success factors for productive collaboration, and may be beneficial to future technological and policy developments aimed at improving access to diagnostic services and treatment in the South African context.

1.4 Aims and Objectives

The aim of this project was to examine the landscape of diagnostic medical device development targeting the diagnosis of infectious diseases prevalent in South Africa, particularly with regard to collaboration between organisations in different sectors and the contributions of different collaborators.

In order to achieve the aim, the following objectives were pursued:

- Construct a collaboration network for diagnostic device development in South Africa thereby identifying the organisations which are collaborating.
- Analyse the collaboration network using social network analysis metrics to determine which collaborators play the most active and influential roles in diagnostic device development.

1.5 Chapter Overview

Chapter 2 provides insight into the literature that supports the different areas of the project. The methodology in Chapter 3 describes the steps that were taken to collect the bibliometric data on diagnostic device development for infectious diseases and outlines the collaborative network analysis approach. Chapter 4 provides a description and interpretation of the network analysis findings and compares them to the findings of other related publications. Chapter 5 summarises the results and makes recommendations for future work.

2. Literature Review

Africa has a high burden of infectious disease, and yet a low capacity to manage it (Karimuribo et al., 2011). Although some advances have been made towards the management and diagnosis of infectious diseases, they continue to pose a significant burden on global economies and public health (Jones et al., 2008). This burden is primarily driven by weak and poorly resourced health care systems, which prevent adequate treatment and reduce the chance of limiting further transmission of the diseases. The development of novel devices has the potential to overcome these challenges (Mcnerney, 2015). This purpose of this chapter is to provide an overview of the literature on the analysis of collaboration networks involved in medical device development, and in doing so to identify the gaps that exist in the literature which will be addressed by the study.

2.1 Collaborative Research

Collaboration is fundamental to scientific research (Abramo et al., 2011). Collaborative research and development has the ability to facilitate the transfer of knowledge between different sectors (Lander, 2013) and therefore has the potential to bridge the gaps in information and resources that exist in developing public health structures. Collaboration is beneficial in that it allows for the interaction of various networks, organizations and disciplines, either within or affiliated with the public health sector, which drives innovation and design (Sala et al., 2011).

Three sectors are known to be active within healthcare innovation (Hicks and Katz, 1996) namely universities, healthcare services, such as hospitals and clinics which are mainly focused on patient care, and industry. The university sector is primarily focused on public scientific research, and shows some development activity (Owen-smith, Arbor and Powell, 2002; Lander, 2013). The healthcare sector is important when it comes to determining medical device needs and ensuring that novel technologies and applications are appropriate and safe to be used within a clinical setting (Chimhundu et al., 2015). The industry sector is the driving force behind the manufacturing and distribution of biomedical devices (Ankrah et al., 2013). Another set of organisations that has been shown to be involved in medical device development in South Africa are science councils and science research facilities

(Chimhundu et al., 2015). Science councils are large-scale private or public organisations that typically engage in advanced projects that are perceived to be too risky for other sectors (Scholes et al., 2008).

The sectors, and their constituent organisations, that engage in healthcare innovation can be represented in collaborative networks as a tool towards further understanding how they engage in healthcare innovation. A variety of definitions for collaborative research networks have been proposed over the years, however Sala et al. (2011) cite the definition proposed by Tijssen (1998) as the most comprehensive and applicable to different types of networks. This definition states that a collaborative network is “an evolving mutual dependency system based on resource relationships in which their systemic character is the outcome of interactions, processes, procedures and institutionalisation.” Research and development networks have increasingly been established and networking activities studied by scholars and policy makers (Georghiou and Roessner, 2000) due to the growing interest in a multidisciplinary approach to technological and research advancements, and recognition of the need for various different skills to develop new ideas and products (Sala et al., 2011).

Scientific collaboration can be measured by co-authorship of written publications (Newman, 2001) within a given subject area. Although it is limited by the fact that it does not reflect all types of collaboration (Laudel, 2002) co-authorship is widely considered as a reliable proxy for scientific collaboration. Co-authorship analysis is an important tool that can be used to investigate collaborations between individuals, organisations and countries, and help interpret collaboration patterns (Newman, 2001; Meyer and Bhattacharya, 2004). Chimhundu et al. (2015) and de Jager et al. (2017) used co-authorship as an active indicator of collaboration in their respective studies on medical device development in South Africa. Collaborations can be visualised using network graphics, which allows for further analysis of the collaboration between different organisations (de Jager et al., 2017).

2.2 Bibliometric Strategies

The extraction and quantitative analysis of publications, often from available literature databases is known as a bibliometric analysis. As a first step, a search profile consisting of specific search terms that will yield the desired data set is created. The search terms are typically made up of a geographical aspect, an indicator of performance, such as development over a given time period, particular subject domains, types of authorship and publication types (e.g. journal article, review paper or conference proceeding) (Ellegaard and Wallin, 2015). For example Lander (2013), who conducted a bibliometric study of Vancouver, Canada's infection and immunity research and development network, searched for Canadian journal articles during a specific time period. This dataset was filtered and only articles discussing research relevant to infection and immunity research and development were retained. A similar process was followed by de Jager et al. (2017) who conducted a broad overview of medical device development in South Africa, and Chimhundu et al. (2015), who structured their search profile to yield a search output related to cardiovascular medical device development in South Africa.

2.3 Social Network Analysis

Newman (2001) describes a social network as a group of people that has a connection to some or all of the other individuals in the group. Social network analysis (SNA) is an approach that can be used to analyse the interactions within such groups (Hanneman and Riddle, 2005). Metrics such as density and centrality can be used to describe relationships between actors within the network (Schoen et al., 2014). These measures provide a means to assess research collaborations (Bian et al., 2014). SNA can provide a first step towards identifying infrastructural and geographical barriers in resource-limited settings (Perkins, Subramanian and Christakis, 2015), thereby creating a basis for overcoming them.

2.3.1 SNA of medical device collaboration networks

A number of studies have been conducted to examine cross-sectoral collaboration networks involved in the development of medical devices.

Lander (2013) conducted a study to assess collaborative research and development within the infection and immunity network in Vancouver, Canada with the purpose of examining the relative importance of different sectors in the network. The sectors considered included university, hospital, government, firms and NGOs. By examining network structure using various social network analysis tools, it was found that most sectors preferred to collaborate within as opposed to across sectors, and that university-hospital collaborations play a key role in the particular network studied. This finding was in agreement with a bibliometric study conducted by Hick and Katz (1996) wherein it was found that universities and hospitals collaborated more than expected in the United Kingdom science base.

Chimhundu et al. (2015) conducted a study to analyse the development of cardiovascular medical devices (CMD) in South Africa over a period of 15 years using co-publication of journal articles as an indicator of collaboration. The purpose of this study was to: identify the dominant organisations and sectors within the CMD development network, and the different ways they collaborate; measure the scope of collaboration within the network; and analyse the collaboration trends over time. Collaboration across four sectors was taken into consideration, namely healthcare services, industry, universities and science councils. This study found that in the South African network, the most prominent inter-sectoral collaboration was between the healthcare and university sectors. The science councils, healthcare and industry sectors were found to collaborate most with the university sector, thus indicating that the university sector is the foundation of the South African CMD co-publication network (Chimhundu et al., 2015). In a follow-up study, Chimhundu et al. (2016) investigated the focus of cardiovascular medical device research in South Africa using the same data set, and found that the research focused on diagnostic, monitoring and prosthetic cardiovascular medical devices.

De Jager et al. (2017) examined the broad South African medical device landscape between 2000 and 2013 through a bibliometric analysis of relevant scientific papers using co-authorship as an indicator of collaboration. A collaboration network was generated and used to: identify the most active and dominant organisations and the sectors to which they belong; determine the extent of collaboration within and between sectors; investigate the influence of foreign collaborators; and explore various collaboration types, focusing specifically on translational collaborations. The university sector was found to be the most dominant sectors, with the three highest ranking organisations being the University of Cape Town, Groote Schuur Hospital and the University of Stellenbosch. With regard to intra-sectoral collaboration, organisations within the university sector (A) collaborated most amongst themselves, followed by the hospitals (H) and science councils (S). The industry sector (I) was also considered in the analysis. Local and foreign organisations were equally present in the network, however local organisations were found to collaborate more with each other than with foreign organisations. Translational collaborations, which include three possible combinations of the four sectors (i.e. AHI, HIS and AHIS), were examined as they are considered key to implementation and commercialisation of medical devices. Few translational collaborations were present in the South African medical device development network, therefore leaving room for more collaborations of this nature to be established.

Salie et al. (2017) examined the focus areas of published research on medical device development in South Africa between 2001 and 2013. The results showed that device development was most frequently related to the cardiovascular, nervous, skeletal and muscular systems. Since devices related to the skeletal and muscular systems were the most prominent, Salie et al. (2017) further explored orthopaedic devices through actor and keyword collaboration networks. Co-authorship was used as an indicator of collaboration for the actors, and keywords were linked if they appeared on the same publication. While the relations between actors was sparse in the network of organisations involved in orthopaedic device development, a keyword network analysis revealed substantial potential for organisations to connect based on shared common areas of interest (as indicated by the keywords they use in their publications).

2.3.2 SNA of patent data

In addition to academic articles, patents can also be used as indicators of collaboration. According to the World Intellectual Property Organization, a patent is defined as “a document, issued, upon application, by a government office (or a regional office acting for several countries), which describes an invention and creates a legal situation in which the patented invention can normally only be exploited (manufactured, used, sold, imported) with the authorization of the owner of the patent" (WIPO, 2008). In the same way that publication author information is used to construct a collaboration network, information regarding an inventor can be retrieved from a patent and used to construct a patent network (Ma and Lee, 2008). Although patent data is considered more relevant for industry researchers, comparing this with publication data is a useful way to map the interaction between authors and inventors (Beaudry and Schiffauerova, 2011) and avoid losing relevant information pertaining to technological developments. Giglio et al. (2017) presented a social network analysis of patent activity related to cardiovascular medical device development in South Africa. The results were compared to those of an analysis of scientific publications. It was found that the university and healthcare sector, specifically the University of Cape Town, Groote Schuur Hospital and the University of Stellenbosch, were the biggest contributors towards cardiovascular medical device activity in both networks. The industry sector was more active in patenting than in scientific publication, however the local industry was less active in the patent collaboration network. It was also found that foreign organisations made a minimal contribution in both networks. Giglio et al. (2017) concluded that there is room for more collaboration across the university, hospital and industry sectors, which could promote the development of cardiovascular medical devices.

2.4 Network Development over Time

Networks develop over time as some actors either leave their professions they represent or form different scientific collaborations (Newman, 2001). In addition, short analysis periods (e.g. one year) may not reflect longer-term trends in collaboration patterns. As a result, researchers have used multi-year time windows to analyse collaboration networks. For example, Barabasi et al. (2002) constructed collaboration networks over an 8-year period for the purpose of studying the dynamics and evolution of a network, while Lander (2013) used a time period of 5 years to capture trends in a biomedical research and development network. According to Baum et al. (2003), networks that are constructed using a five-year window period are reliable and accurate in terms of the strength of the ties in the network. This idea has been supported by other researchers such as Eslami et al. (2013), as well as by Newman (2001), who stated that the five-year window period is ideal for capturing changes in collaboration patterns. Chimhundu et al. (2015) analysed changes in collaboration activity for the cardiovascular medical device networks of South Africa using a 5-year moving time window, to examine the activity of different organisations over time and identify gaps and potential for future collaboration. The study found a general increase in cardiovascular medical device development over a 15-year period, with the university and hospital sectors having the highest overall increase in collaboration over this period, and suggested that science councils and industry still had potential for greater participation by partnering with the dominant sectors.

2.5 Diagnostic Device Development: Gaps in the Literature

The Chimhundu et al. (2015) study was the first published attempt to characterise the medical device development landscape in South Africa using social network analysis. Studies by de Jager et al. (2017) and Salie et al. (2017) have characterised medical device development activity in South Africa broadly and for orthopaedic devices, respectively. Giglio (2017) examined patenting networks for cardiovascular devices

The aforementioned studies have indicated the growth in the development of medical devices broadly, of cardiovascular devices and of orthopaedic devices in South Africa. These studies have shown that there is room for increased collaboration and device development in the local context. Some of the research gaps that are mentioned across these studies include the need to investigate the motivating factors for collaboration (Chimhundu et al., 2015) the need for increased translational collaboration within South Africa (de Jager et al., 2017) and the need for knowledge transfer between researchers and innovators (Giglio, 2017). Investigating device development in South Africa in the context of infectious disease may reveal similar gaps and areas that require further research, and provide new insights into the future of medical device development in South Africa.

3. Methodology

The methodology presented in this chapter, which was used to identify and analyse data relevant to diagnostic devices, was based on the approach employed by Chimhundu et al. (2015) for cardiovascular medical devices.

3.1 Diagnostic Medical Device Definition

With the rapid growth in the medical device global market came the need harmonize national regulations in order to prevent barriers, facilitate trade and improve access to novel technologies (World Health Organization, 2003); this led to the formation of the Global Harmonization Task Force (GHTF), an organisation consisting of government and industry representatives from different parts of the world, which proposed a single definition that would encompass all the diverse aspects of medical devices. The widely accepted definition has been used by authors in the medical device research field, such as de Jager et al. (2017) and Chimhundu et al. (2015). In the former case the definition was used as is, while in the latter case the definition was revised to better suit the topic of interest, namely cardiovascular medical devices.

The purpose of the present study was to explore the landscape of diagnostic medical device development aimed at infectious diseases prevalent in South Africa. As such, a definition for diagnostic devices in particular was required. The word 'diagnostic' was therefore added to the original GHTF (World Health Organization, 2010) medical device definition for this study. Only the parts of the definition deemed relevant to disease diagnostics were retained, while amendments made to the definition are shown in square brackets:

> *A [diagnostic] medical device is any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article that does not achieve its primary intended action in or on the human body solely by pharmacological, immunological or metabolic means and that is intended for human beings for:*
>
> - *the diagnosis of disease;*
> - *providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body*

3.2 Data Collection

Journal and conference publications documenting medical device development for infectious diseases were used to analyse research and development (R&D) activity. Co-authorship was used as a proxy for collaboration. The publications were obtained from public journal databases for the period between January 2000 and December 2016.

Web of Science, Scopus and PubMed were used to access the literature on infectious disease related diagnostic device research using the search phrases shown in Table 3-1. The type of diagnostic device and method of diagnosis included in the search phrase were informed by the GHTF device definition. In addition, the search term ‘point-of-care’ was included, as this type of device is relevant in developing settings such as South Africa The Boolean operators – AND, OR and NOT – were used in the search phrase. The use of ‘AND’ limits the search to terms that occur together in one document, while the use of ‘OR’ broadens the search to every possible combination of the words or terms separated by it. The third Boolean operator, ‘NOT’, excludes the words in the subsequent search term so that they do not appear in the results (University of Alaska Fairbanks: Elmer E. Rasmuson Library, 2016). Another important component of the search phrase is the country of affiliation – South Africa – which ensures that all search results are affiliated with at least one South African co-author as stipulated in the aim of this study.

Table 3-1: Search phrases used to obtain scientific articles, with a South African affiliation, concerning medical devices that address infectious diseases

Database	Search Phrase
PubMed	(((south africa[Affiliation]) AND ("2000/01/01"[Date - Publication] : "2016/12/31"[Date - Publication]) AND (HIV OR AIDS OR TB OR tuberculosis OR "infectious disease*" OR "parasitic disease*" OR "communicable disease*")) AND (point-of-care OR microfluid* OR micro-fluid OR paper-based OR "paper based" OR microsys* OR sensor OR detect* OR analys* OR microstruct* OR microscop* OR "medical device" OR device OR tool OR instrument OR apparatus OR implement OR machine OR appliance OR calibrat* OR software OR material) NOT (pharmacolog* OR metabolic OR metabolism OR metabolite))
Scopus	AFFILCOUNTRY ("South Africa") AND TITLE-ABS-KEY (HIV OR AIDS OR TB OR tuberculosis OR "infectious disease*" OR "parasitic disease*" OR "communicable disease*") AND TITLE-ABS-KEY (point-of-care OR microfluid* OR micro-fluid OR paper-based OR "paper based" OR microsys* OR sensor OR detect* OR analys* OR microstruct* OR microscop* OR "medical device" OR device OR tool OR instrument OR apparatus OR implement OR machine OR appliance OR calibrat* OR software OR material) AND NOT (pharmacolog* OR metaboli*) AND PUBYEAR > 1999 AND PUBYEAR < 2017
Web of Science	CU = (South Africa) AND PY = (2000-2016) AND (TS = (((HIV OR AIDS OR TB OR tuberculosis OR “infectious disease*” OR “parasitic disease*” OR “communicable disease*”) AND (point-of-care OR microfluid* OR micro-fluid OR paper-based OR “paper based” OR microsys* OR sensor OR detect* OR analys* OR microstruct* OR microscop* OR “medical device” OR device OR tool OR instrument OR apparatus OR implement OR machine OR appliance OR calibrat* OR software OR material)) NOT (pharmacolog* OR metaboli*)))

The adequacy of the keywords used in the search was tested in order to ensure that all the relevant publications were captured in the dataset. PubMed was used for this exercise as it specifically covers health-related research. Keywords associated with the publications extracted from PubMed were scanned to determine whether new keywords not used in the searches were present. Any new keywords identified in the PubMed search results were applied to the existing search phrase, thus a new data set was extracted from PubMed. The new keywords included: reagent, screen, develop, design, manufacture and innovate. The additional results obtained in this manner were evaluated according to the inclusion and exclusion criteria listed below. Since no relevant new publications were identified, it was determined that the existing search phrase (shown in Table 3-1) was adequate and no additional keywords would be added to the search phrase.

3.2.1 Inclusion and exclusion criteria

Duplicate papers found across the three database outputs were discarded. The remaining search results were manually evaluated by scrutinizing the title, abstract and where necessary the body of the articles to ensure that the content related to the development of medical devices for infectious diseases in South Africa. Publications that did not relate to medical device development were excluded. In this study, the development of a device referred to the testing of a new device, or the testing of a new implementation of an existing device, such as a software tool or data processing method.

Below is a complete list of the inclusion and exclusion criteria applied to the search outputs:

1. Publications were required to explicitly focus on diagnostic device
2. At least one co-author from each publication was required to be affiliated with a South African organisation.
3. Conference and journal articles were included, while review articles were excluded as the latter does not present new developments but rather discusses existing technologies.
4. Publications discussing the development of new devices were included. The testing of a new device was considered as a contribution towards the development of the device, and therefore included.
5. Testing of commercially established devices (for example MRI machines, FDG-PET scans and microscopes) was not included unless a novel application of the device was being presented (for instance new software, or a new data processing method or component was incorporated into the device).
6. Studies that used animal models to test the efficacy of diagnostic devices were considered, provided the research paper made a link to the human healthcare implementation of the study outcome. However, if the paper was specifically aimed at diagnostic tests in the context of animal healthcare, it was excluded.
7. Studies were excluded if their primary mechanism of action of the intervention in or on the body was achieved only through pharmacological, metabolic and immunological means.

3.3 Sectors involved in Diagnostic Device Development

The same four sectors identified by Chimhundu et al. (2015), were expected to be found in the dataset of this project. The author affiliations, extracted from the publications retained for analysis, were assigned to each sector. The separation into different sectors is important as it provides a representation of how different sectors affect the functioning of a network (Lander, 2013). The four sectors contribute as follows:

- Industry (**I**): Companies, firms, organisations and individuals that are involved in the development of medical devices that will be made commercially available.
- Healthcare Services (**H**): Clinics, hospitals, medical centres and private practitioners that are solely focused on patient healthcare.
- Universities (**U**): Tertiary-level educational institutions that contribute to academic research for the development of medical devices.
- Science councils and facilities (**S**): Science councils and research centres that contribute to scientific research.

Other non-commercial sectors, such as government departments and non-governmental organizations (NGOs) were considered under the science councils and facilities sector. The role of science councils in the South African context is to promote science, engineering, technology and innovation, and to drive policy development (National Science and Technology Forum, 2014).

3.4 Analysis of the Diagnostic Device Landscape

Netdraw (Borgatti, 2002), a network visualization tool, was used to visualize the network of organisations to which publication authors were affiliated, and network metrics were calculated using UCINET(Borgatti et al., 2002).

The information in a network is defined by actors (nodes) and relations (edges) (Hanneman and Riddle, 2005) In this study, the nodes represent organisations that have contributed towards diagnostic device development. Each node was classified as either a South African entity, or a foreign entity. All foreign entities included in the network had collaborated with a South African organisation on a publication. Nodes were linked by edges only if co-authors affiliated with the nodes (organisations) had produced a publication together. The edges were weighted in proportion to the number of times two nodes have collaborated, as was done by Chimhundu et al. (2015). Furthermore, given that collaboration is a mutual relationship, the edges were undirected (Chimhundu et al., 2015).

Group density, average path length and three measures of centrality were used to quantify the structure of the network, and to identify the dominant actors:

- Group density quantifies the extent of interconnectedness between groups. It can therefore be used as a measure of the collaboration within and between sectors. Group density is calculated by dividing the number of edges actually present in the network by the total number of possible edges that could be present in the network provided all nodes were interconnected (Hanneman and Riddle, 2005)
- The power or influence of a given node in a network is dependent on how favorable the position of the node is with respect to other actors in the network (Hanneman and Riddle, 2005). Measures of centrality (degree, closeness and betweenness) can be used to identify influential nodes in a collaboration network (Chen et al., 2012) and describe the location of a node within the network in terms of how close it is to the centre of activity (Hanneman and Riddle, 2005). However, the definition of the “centre of activity” varies, and as such different centrality measures exist:
    - Degree centrality identifies which nodes are the most influential. This is measured by simply counting the number of other nodes directly connected to a given node (Abbasi et al., 2012).
    - Betweenness centrality measures the influence a node has over the spread of information across the network by calculating the number of times a particular node lies between the other nodes in the network (Abbasi et al., 2012).
    - Closeness centrality is a measure of how far information is spread from a given node to other reachable nodes in the network, and is calculated

as the sum of geodesic distances (the shortest path between any given node in a network) from a particular node to all the other nodes in a network (Abbasi et al., 2012).

The extent of diagnostic device research activity between 2000 and 2016 was determined by considering the number of papers published per year.

The dominant nodes in the network were identified by calculating the measures of degree, betweenness and closeness centrality.

Inter-sectoral collaboration is a collaborative relationship between two different sectors at any time during the study period, while intra-sectoral collaboration represents a collaboration between nodes from the same sector (Chimhundu et al., 2015). Inter-sectoral collaboration was calculated using the between group density metric, which measures the extent of interconnectedness between two different sectors, while intra-sectoral collaboration was calculated using the within group density metric, which measures the extent of interconnectedness between two of the same sectors. Group density was then separately used to investigate local-only versus local-foreign collaboration.

Given that five years is considered long enough to study the variations in publication rates (Newman, 2001; Baum et al., 2003; Eslami et al., 2013; Lander, 2013), five-year windows were used to asses changes in the collaboration patterns for diagnostic device development in South Africa over the study period.

Disease-specific device types that have been developed in the South African context were investigated by generating disease-specific networks from the publication dataset. The same five-year window previously used was also applied to the most prominent disease category, to examine changes in device development activity for the dominant infectious disease.

Finally, features of the diagnostic devices under development, as expressed in the publications, were examined to provide further insight into the types of devices being developed.

4. Results and Discussion

This chapter presents the bibliometric data extracted, the collaboration networks drawn, and the analysis of the networks, using the methodology described in the previous chapter.

4.1 Search Results

Figure 4-1 shows the number of results yielded from the search of the databases, and the total number of scientific articles retained.

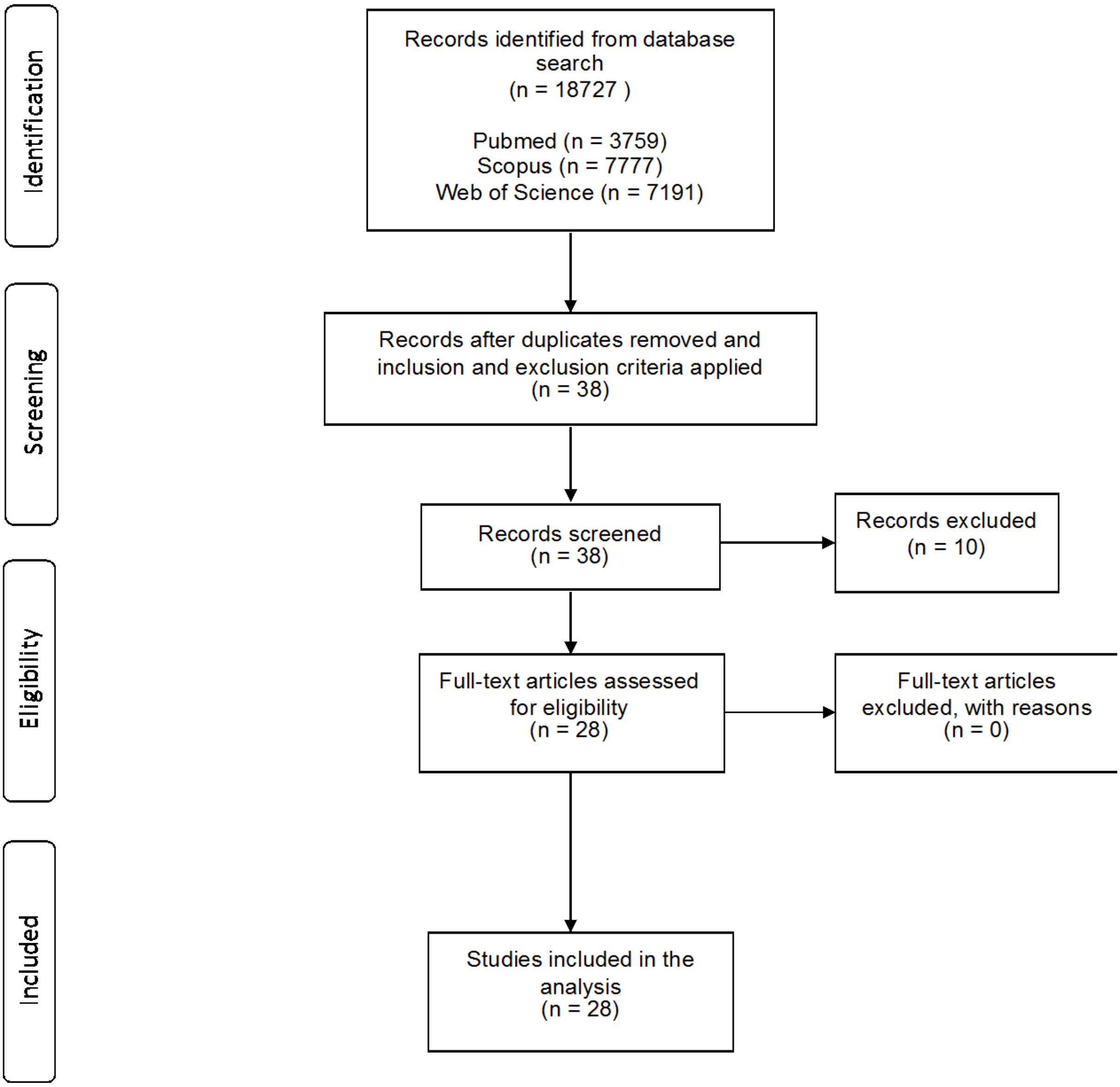

Figure 4-1: Number of studies yielded from the search of databases and the total number of studies retained for analysis

Figure 4-2 shows the number of publications plotted against time, thereby indicating the level of research activity per year over the 2000-2016 period. As no relevant publications were present in the data set before 2008, further analysis discusses 2008-2016 as the study period.

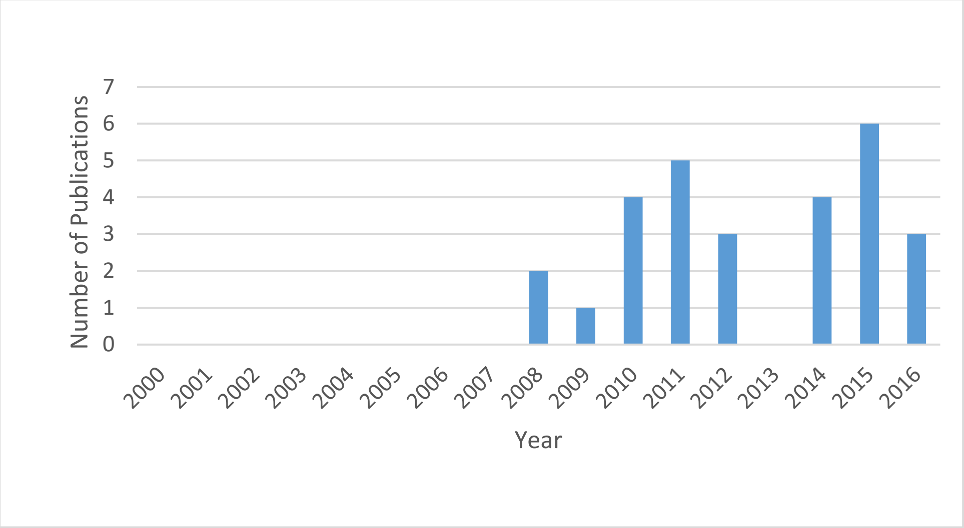

Figure 4-2: Number of publications per year addressing diagnostic device development for infectious diseases in South Africa during the period 2000-2016

A total of 42 organisations (to be visualized as network nodes) were found within the retained dataset. Table 4-1 shows the number of local and foreign nodes in each sector.

Table 4-1: Number of organisations (network nodes) between 2008 and 2016 forming the dataset of publications on South African diagnostic device development for infectious diseases.

	Sector				**Total**
	University	Healthcare services	Industry	Science councils and facilities	
Local	4	2	0	3	10
Foreign	16	8	4	5	32
Total	20	10	4	8	42

4.2 Collaboration Network

Figure 4-3 shows a collaboration network of local and foreign organisations that played an active role in medical device development for the diagnosis of infectious diseases during the period 2008-2016. Local and foreign nodes are differentiated by colour, sectors (U, H, I, S) are differentiated by node shape and the size of the nodes is scaled according to degree centrality. The edges were weighted according to the number of times two nodes have collaborated.

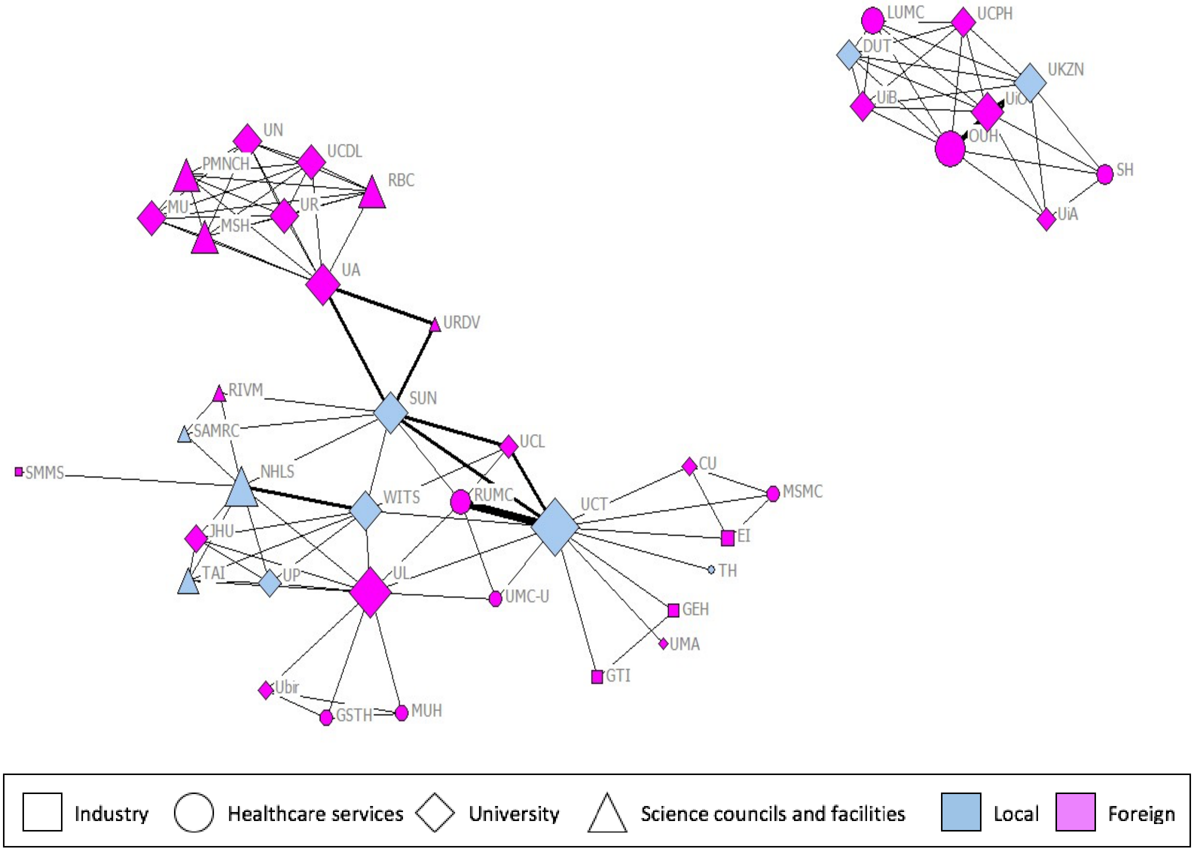

Figure 4-3: Collaboration network for diagnostic device development in South Africa during the period 2008-2016. Degree centrality was used to determine the size of the nodes. Edges were weighted according to the number of times collaboration occurred between two nodes. Abbreviations and full names of each node can be found in Appendix A.

Foreign (pink) nodes feature more prominently in the network than local (light blue) nodoes, while universities (diamonds) are the most dominant sectors, both locally and internationally. Thus universities in foreign countries played an active role in the development of diagnostic devices in South Africa between 2008 and 2016. Based on the varying sizes of the nodes, the University of Cape Town (UCT), Stellenbosch

University (SUN) and the University of London (UL) are among the most active institutions in the diagnostic medical device development network.

4.2.1 Dominant Nodes

Table 4-2 shows a list of the 10 highest ranking nodes for each measure of centrality. A high degree centrality indicates that the node has high influence over other nodes; a high betweenness centrality indicates that a node has high influence over the spread of information across the network; and a high closeness centrality indicates that a node is able to spread information across the network most efficiently.

Table 4-2: Top ten nodes ranked by highest to lowest measures of centrality (degree, closeness and betweenness). The full names of the organisations can be found in Appendix A.

Rank	**Degree Centrality**			**Closeness Centrality**			**Betweenness Centrality**		
	Institution	**Sector**	**Value**	**Institution**	**Sector**	**Value**	**Institution**	**Sector**	**Value**
1	UCT	U	13	SUN	U	9.404	SUN	U	236.917
2	UL	U	11	UCT	U	9.382	UCT	U	210.250
3	SUN	U	9	WITS	U	9.297	UA	U	175.000
4	NHLS	S		RUMC	H	9.213	UL	U	114.750
5	UA	U		UL	U	9.172	NHLS	S	71.667
6	OUH	H	8	NHLS	S		WITS	U	47.667
7	UKZN	U		UCL	S	9.131	RUMC	H	17.500
8	UiO	U		UA	U	9.071	UiO	U	2.667
9	WITS	U		RIVM	S	8.972	UKZN	U	
10	Seven organisations with equal degree*		7	SAMRC	S		OUH	H	

U, University; H, Healthcare Services; I, Industry; S, Science councils and facilities
*MSH (S), MU (U), PMNCH (S), RBC (S), UCDL (U), UN (U), UR (U).

The findings in Table 4-2 indicate that UCT (University of Cape Town) has the highest ranked degree centrality in the network, meaning that it is the most influential node with regard to level of activity. It also has a high impact on the spread of information in the network and how efficiently this occurs, which is indicated by its high betweenness centrality and closeness centrality. While SUN (University of Stellenbosch) is the third most influential node in the network based on degree centrality it has the highest impact on how information is spread (closeness centrality) and how efficiently this happens (betweenness centrality).

Degree centrality on its own does not provide a complete indication of influence in the network, as it only identifies the node at the centre of activity in the network, and does not take into account the location within the network of the nodes connected to the node in question (Chimhundu et al., 2015). For example consider WITS (University of Witwatersrand) which has the 9th highest degree centrality value but the 3rd highest closeness centrality. Although WITS may not have a very high influence due to the limited number of nodes directly connected to it (i.e. relatively low degree centrality) it is connected to pivotal nodes within the network that enable it to spread information effectively (as indicated by the high closeness centrality).

Chimhundu et al. (2015) presented an analysis of sectoral collaboration for cardiovascular medical device development over a period of 15 years by analysing two measures of centrality, namely degree and betweenness. In both the Chimhundu study and the present one, the U sector is in the most favourable position in the network, based on the degree centrality rankings (the majority of nodes ranked within the top 10 for degree centrality are from the U sector in both studies, and the top ranked nodes for degree centrality are from the U sector). Chimhundu et al. (2015) found that UCT, SUN and WITS were listed in the top five for both degree and betweenness centrality, while the present study showed that UCT and SUN are also present in the top 5 for both of these measures, however WITS is ranked 9th and 6th for degree and betweenness centrality respectively.

The U sector is able to reach other actors at the shortest path lengths (closeness centrality; 5/10 organisations in Table 4-2). Finally, the 7/10 organisations within the top 10 for betweenness centrality were from the U sector indicating that they most frequently act as a link between any two nodes in the network and therefore have the highest capacity to act as a channel for knowledge propagation within the collaboration network (Hanneman and Riddle, 2005).

4.2.2 Inter- and intra-sectoral collaboration

The density of a network gives an indication of the extent of overall collaboration within the network by measuring interconnectedness. It may also provide insight into how efficiently information is spread between groups within the network (Hanneman and Riddle, 2005). Table 4-3 shows the within-group densities (intra-sectoral collaboration) in bold and between-group densities (inter-sectoral collaboration) in normal text.

Another value included in the table is the sum of edge weights (∑ew); this represents the total number of edges in the network that connect the nodes belonging to a particular grouping, taking into account the weight of the edges (Hanneman and Riddle, 2005). For example, the ∑ew that connects institutions from the U sector to those of the H sector is 32, and the ∑ew that connects the U and I sectors is 4. This means that institutions from the U and H sectors have collaborated 8 times more frequently than those in the U and I sectors during the same period based on the number of edges that connect them.

*Table 4-3: Extent of sectoral collaboration as measured using group density (**ρ**) and sum of edge weights (∑ew). Within-group densities (intra-sectoral collaboration) are shown in bold and between-group densities (inter-sectoral collaboration) are in normal text.*

	U		**H**		**I**		**S**	
	ρ	∑ew	***ρ***	∑ew	***ρ***	∑ew	***ρ***	∑ew
U	**0.210**	**88**	0.169	32	0.048	4	0.185	31
H	0.169	32	**0.111**	**8**	0.028	1	0	0
I	0.048	4	0.028	1	**0.167**	**2**	0.031	1
S	0.185	31	0	0	0.031	1	**0.250**	**14**

U, University; H, Healthcare services; I. Industry; S. Science councils and facilities

Intra-sectoral collaboration, which serves as an indication of the extent to which sectors collaborate amongst themselves, can be ranked from highest to lowest as S, U, I and H. Previous studies have shown that universities collaborate extensively with one another. Chimhundu et al. (2015) showed intra-sectoral collaboration was highest in the I sector and second highest in the H sector (with regard to cardiovascular devices), while in de Jager et al. (2017) collaboration within the university sector was the highest (with regard to medical devices in general. In the present study the U sector has the second highest within group density (***ρ***=0.210). Although the results show that in the context of diagnostic device development, the S sector has the strongest intra-sectoral collaboration (***ρ***=0.250), the sum of edge weight values shows that the organisations within the U sector have worked on 88 instances of collaboration, while the organisations within the S sector have only worked on 14. Thus organisations within the S sector have worked on fewer published projects, but have preferred to collaborate within the S sector.

With regard to inter-sectoral collaboration, the strongest combinations include SU (***ρ*** = 0.185; ∑ew = 31) and HU (***ρ*** = 0.169; ∑ew = 32), and the weakest are HI (***ρ*** = 0.028; ∑ew = 1) and SI (***ρ*** = 0.031; ∑ew = 1). In the same way as shown in Chimhundu et al. (2015), the top two collaboration densities (SU = 0.185; HU = 0.169) indicate that the U sector acts as a liaison between the sectors.

Table 4-4 shows the extent of collaboration based on the location of the nodes (local only collaboration and local-foreign collaboration). The density for local-local (l-l) collaboration (0.356) is higher than for local-foreign (l-f) (0.150), which corresponds with de Jager et al.'s (2017) findings, and indicates that local organisations collaborate more with foreign organisations than with each other. When taking into account the local nodes and edges in the cardiovascular medical device network, compared to the local and foreign nodes and edges combined, Chimhundu et al. (2015) observed that foreign nodes serve to connect nodes that would otherwise not have been connected by providing alternate pathways for knowledge transfer. As seen in the current network, the local nodes form connections irrespective of the foreign nodes.

*Table 4-4: Extent of local and foreign collaboration as measured using group density (**ρ**) and sum of edge weights (∑ew). Within-group densities (local-local collaboration) are shown in bold and between-group densities (local-foreign collaboration) are in normal text.*

	Local	
	ρ	∑ew
Foreign	0.150	48
Local	**0.356**	**32**

4.2.3 Network Development over Time

In order to assess the change in activity for diagnostic device development over the period of study, two five-year windows, one at the beginning of the study period (2008-2012; Figure 4-4) and one at the end (2012-2016; Figure 4-5) were investigated. The degree centrality values were calculated for both networks and normalised to allow for comparison across the two networks (Freeman, 1978). The results are shown in Table 4-5 and Table 4-6 respectively.

For the 2008-2012 period, Figure 4-4 shows a similar presence of foreign and local nodes (8 foreign; 6 local), and at least three organisations contributing from each sector. The university sector is at the centre of device development activity, with UCT and SUN having the highest and third highest degree centrality measures at 0.615 and 0.385 respectively, as shown in Table 4-6.

UCT continues to hold a central position during the 2012-2016 period (Figure 4-5), with a degree centrality of 0.229 (Table 4-6), however two other local institutions have become prominent in this network, namely UKZN (degree centrality = 0.229) and WITS (degree centrality = 0.229). Also evident in Figure 4-5 is the dominant presence of foreign institutions (27 foreign nodes, 9 local nodes), most of which are universities (21 universities out of 36 total institutions). Narin et al. (1991) found that scientifically small countries tend to collaborate more with scientists outside of the country as there are more external scientists to with whom collaborate. Similarly, Boshoff (2009) noted that researchers in developed countries seek to collaborate with researchers in developing countries in order to access data. In the case infectious diseases, South Africa presents opportunities to foreign researchers to study diseases more prevalent here.

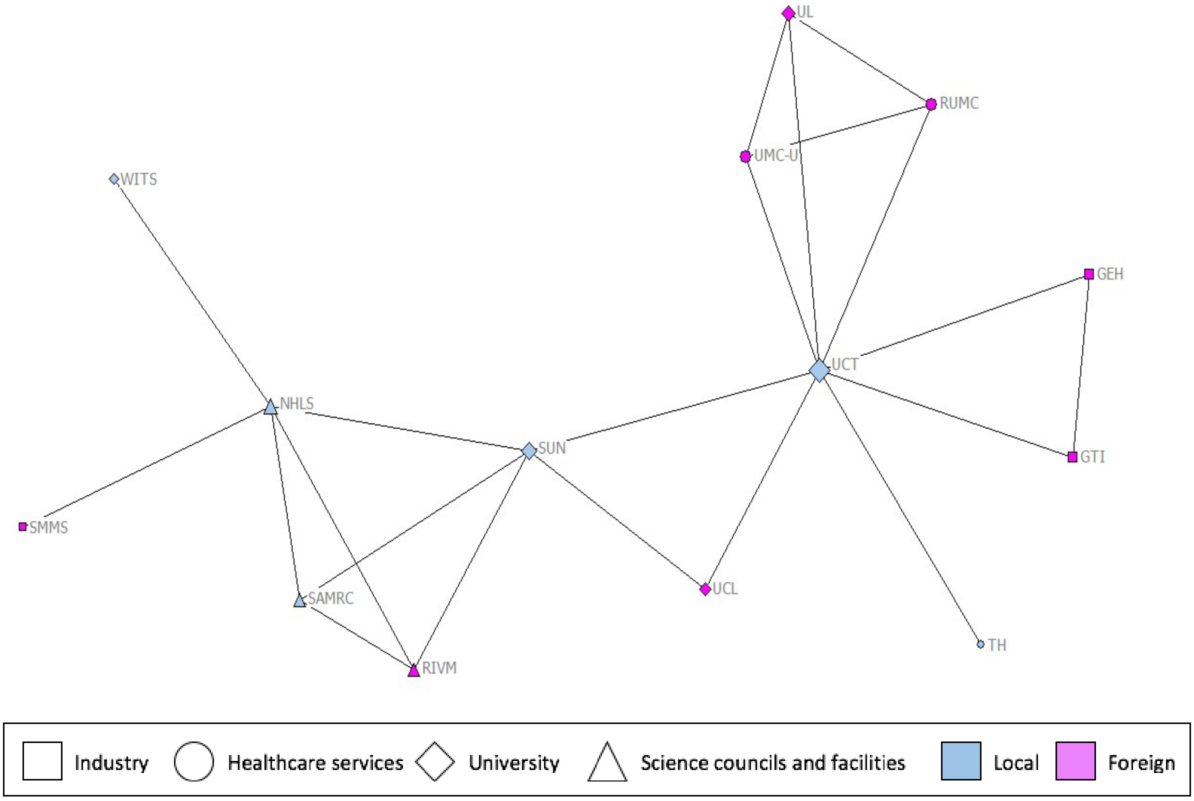

Figure 4-4: Collaboration network for diagnostic medical device development in South Africa during the period 2008-2012. Degree centrality was used to determine the size of the nodes. Edges were weighted according to the number of times collaboration occurred between two nodes.

Table 4-5: Top 10 organisations for degree centrality for 2008-2012. The values for institutions that had an identical degree centrality were merged. The full names of the organisations can be found in Appendix A.

Rank	**Degree Centrality**		
	Institution	**Sector**	**Value**
1	UCT	U	0.615
2	NHLS	S	0.385
3	SUN	U	
4	RUMC	H	0.231
5	UL	U	
6	UMC-U	H	
7	SAMRC	S	
8	RIVM	S	
9	UCL	U	0.154
10	GTI	I	

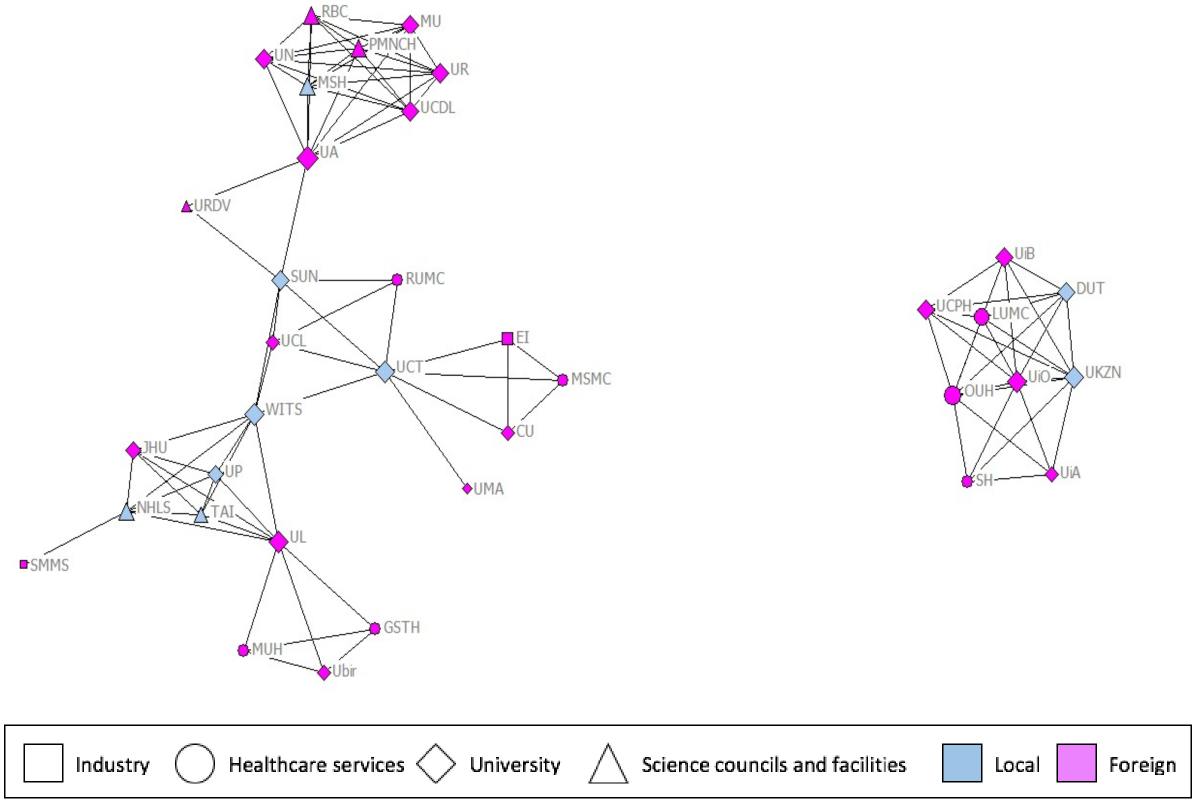

Figure 4-5: Collaboration network for diagnostic device development in South Africa during the period 2012-2016. Degree centrality was used to determine the size of the nodes. Edges were weighted according to the number of times collaboration occurred between two nodes.

Table 4-6: Top 10 organisations for degree centrality for 2012-2016. The values for institutions that had an identical degree centrality were merged. The full names of the organisations can be found in Appendix A.

Rank	**Degree Centrality**		
	Institution	**Sector**	**Value**
1	UA	U	0.257
2	UCT	U	0.229
3	OUH	H	
4	UKZN	U	
5	UiO	U	
6	UL	U	
7	WITS	U	
8	7 institutions with equal degree*		0.200
9			
10			

*RBC (S), MU (U), UN (U), PMNCH (S), UCDL (U), UR (U), MSH (S)

4.3 Disease-Specific Network

Four diseases appeared in the dataset (Table 4-8) and a collaboration network was constructed to show the collaborative diagnostic device research activity for each disease. Networks are shown in Figure 4-5 through 4-8; each disease (tuberculosis, HIV/AIDS, malaria and female genital schistosomiasis – FGS) is represented by different a colour and the size of each node represents how many publications the particular node has published on a specific disease. The edges were weighted according to the number of times two nodes have collaborated. The node sizes across Figures 4-5 – 4.10 are drawn to the same scale, with a particular node size representing the same number of publications. The institutions that have not published any papers on the given disease are coloured in black.

Table 4-7: Diseases addressed by diagnostic medical device research in South Africa between 2008-2016.

Disease	**Number of Publications**	**Number of local organisations**	**Number of foreign organisations**
Tuberculosis	57	5	20
HIV	1	3	5
Malaria	1	2	0
Female genital schistosomiasis	2	2	7

Figure 4-6 shows that while the majority of the nodes in the network are involved in TB diagnostic research, UCT, SUN and RUMC (Radboud University Medical Center) have contributed the most papers in the field (15, 7, and 4 respectively). On a sectoral level, research on device development for TB is dominated by the universities and hospitals based on the number of papers produced by each (U-19; H-8)). Very few actors (8) are involved in HIV device development and even fewer (2) in malaria device development, as shown in Figure 4-7 and Figure 4-8 respectively, and in addition, these networks only reflect one publication each.

Research aimed at FGS device development is dominated by foreign organisations, which make up 7 out of the 9 organisations that have contributed to publications addressing the disease. (Figure 4-9). The FGS cluster also appears as an isolated cluster of activity separate from the larger network. FGS is a waterborne parasitic disease that is primarily found in the poor regions of Sub-saharan Africa (Mbabazi et al., 2011) and primarily affects young women (Downs et al., 2011). Although South Africa does not fall under the top 5 countries in sub-Saharan Africa with the highest burden of FGS (Adenowo et al., 2015), it has been hypothesised that it increases the susceptibility of HIV in women (Magaisa et al., 2015), which is an important public health concern in the South African context. Studies have shown that women with FGS had a higher chance of contracting HIV than women who did not (Mbabazi *et al.*, 2011). The two local universities in the FGS network, Durban University of Technology (DUT) and the University of Kwazulu-Natal (UKZN) are located in Kwazulu-Natal, which had the highest provincial prevalence of HIV in South Africa in 2015 (National Department of Health, 2015). This is also a province of South Africa that is endemic for FGS.

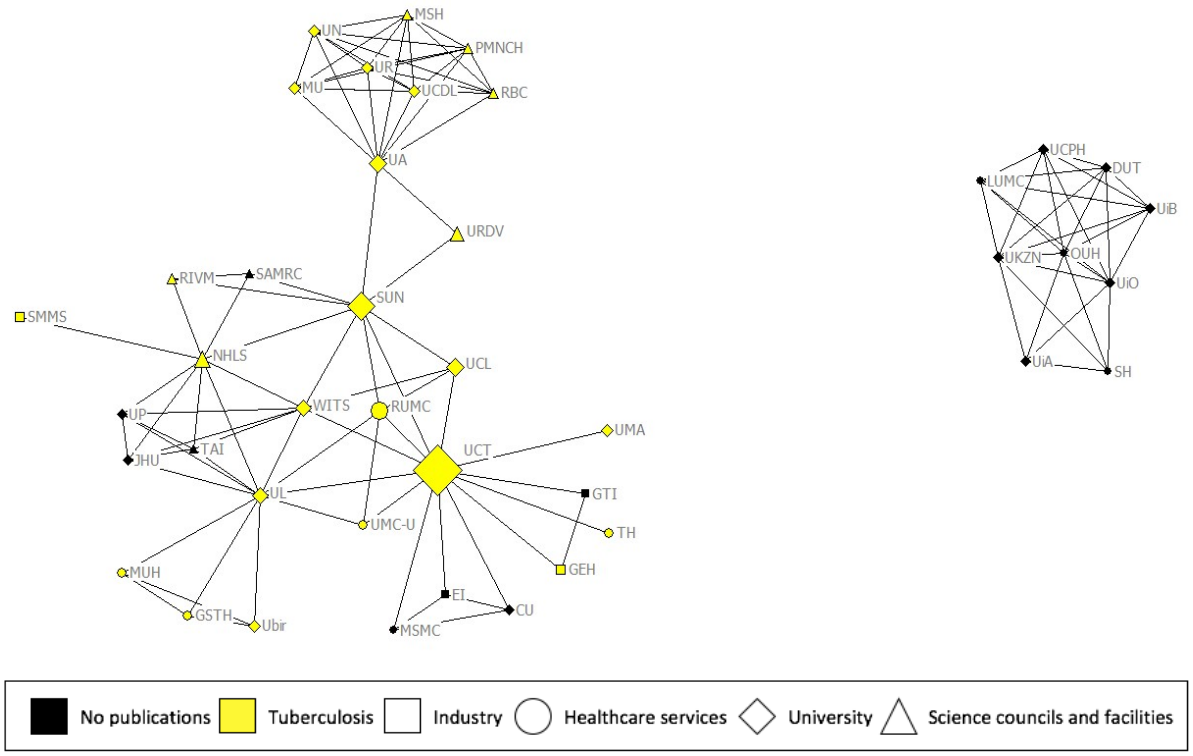

Figure 4-6: Network representation of diagnostic medical device research addressing tuberculosis (TB) in South Africa between 2008-2016. The size of the nodes was determined by the number of publications by each organisation. Edges were weighted according to the number of times collaboration occurred between two nodes.

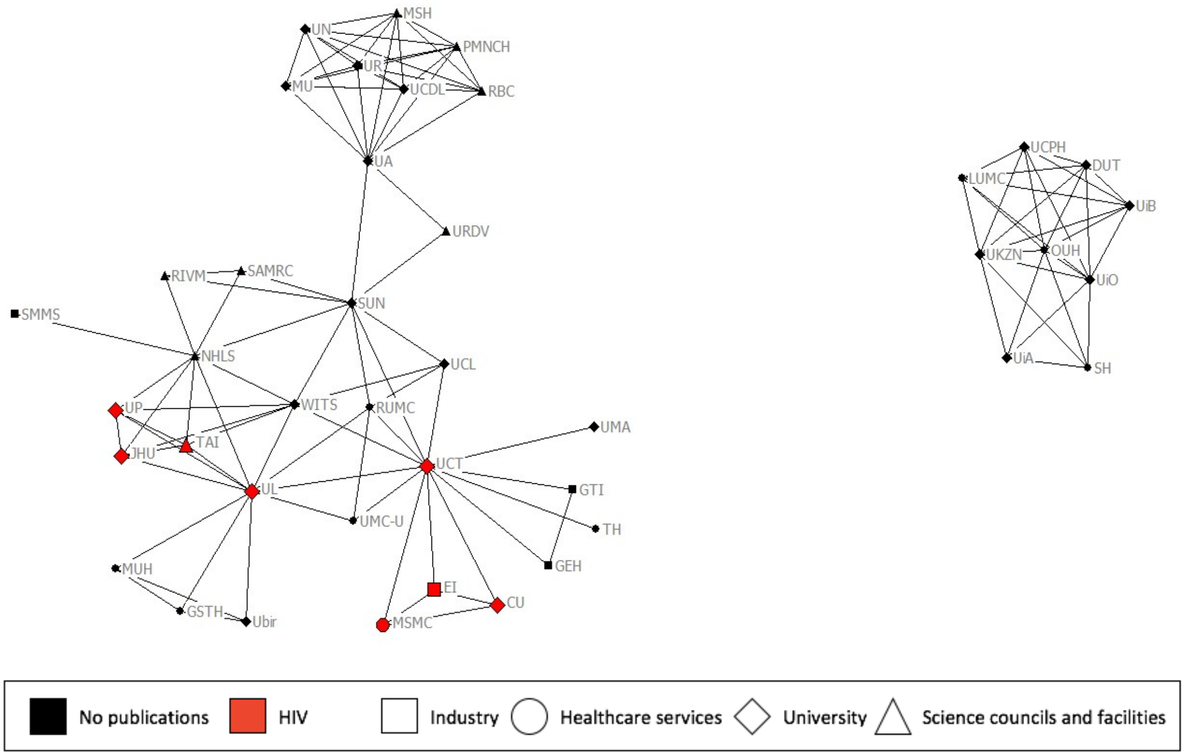

Figure 4-7: Network representation of diagnostic medical device research addressing HIV/AIDS in South Africa between 2008-2016. The size of the nodes was determined by the number of publications by each organisation. Edges were weighted according to the number of times collaboration occurred between two nodes.

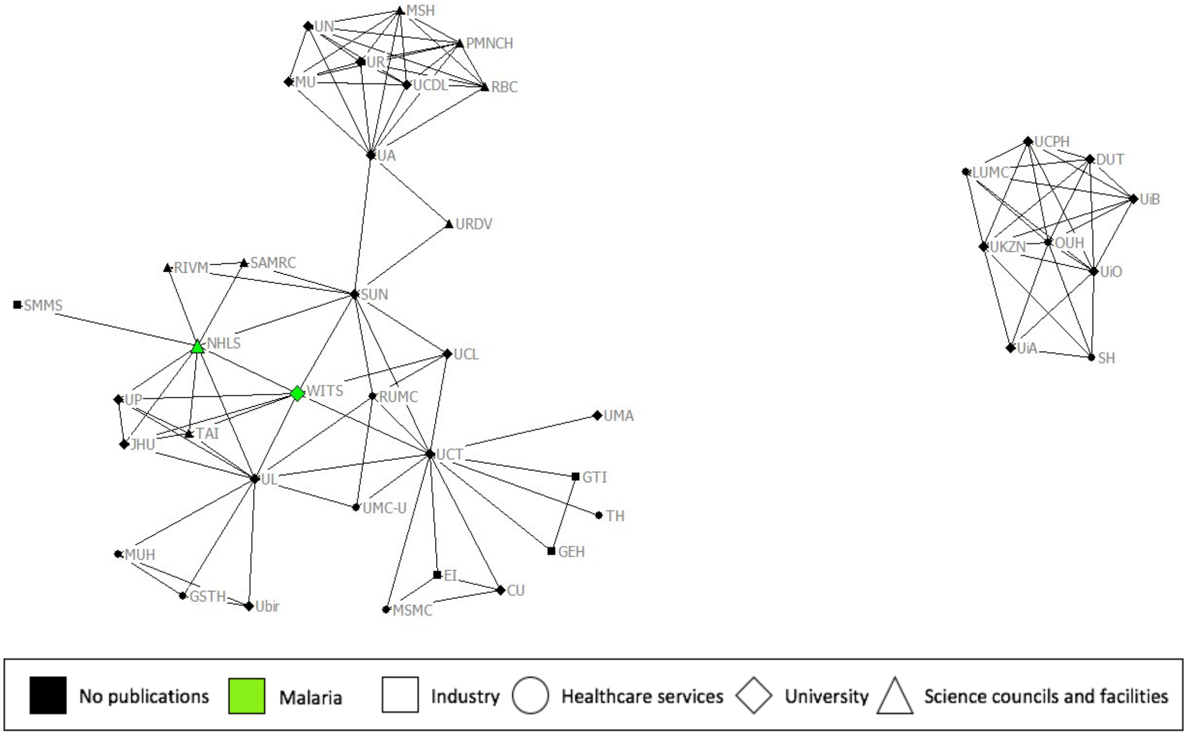

Figure 4-8: Network representation of diagnostic medical device research addressing malaria in South Africa between 2008-2016. The size of the nodes was determined by the number of publications by each organisation. Edges were weighted according to the number of times collaboration occurred between two nodes.

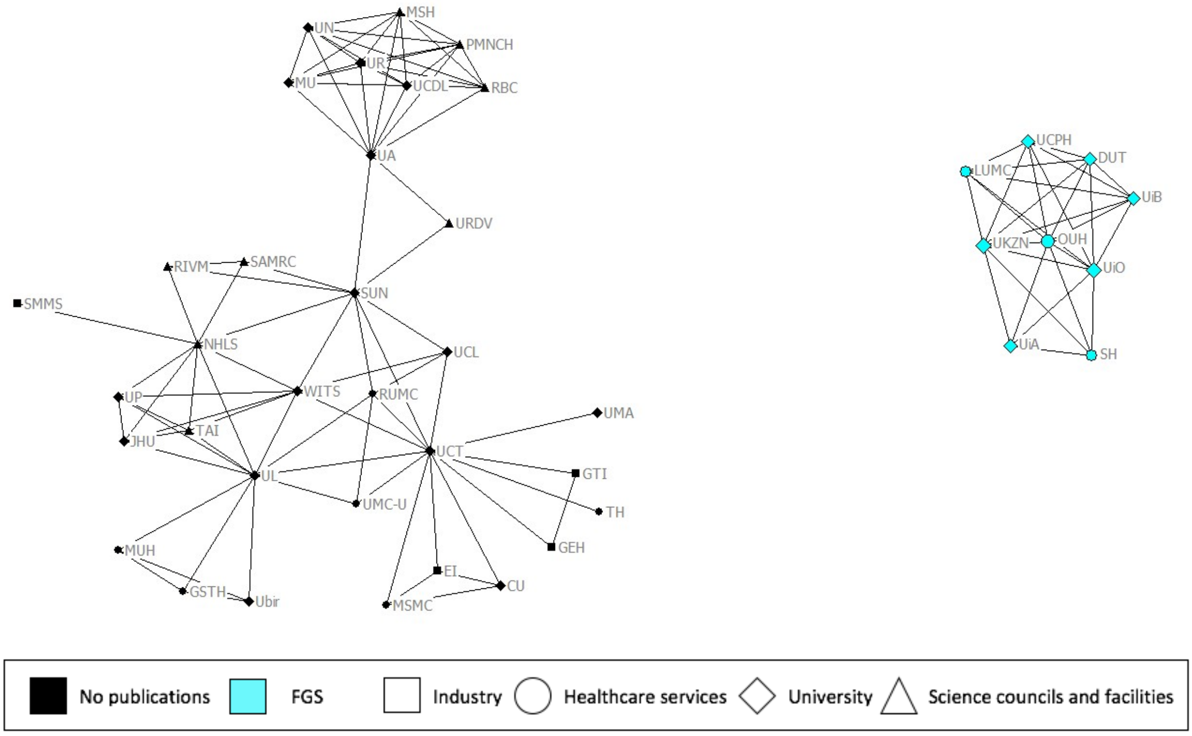

Figure 4-9: Network representation of diagnostic medical device research addressing female genital schistosomiasis (FGS) in South Africa between 2000-2016. The size of the nodes was determined by the number of publications by each organisation. Edges were weighted according to the number of times collaboration occurred between two nodes.

With TB being the disease that is most frequently addressed by diagnostic device development research, two additional networks were constructed to show the change over time of the TB network (Figure 4-10 and Figure 4-11). As in Figure 4-4 and Figure 4-5, the time periods considered were 2008-2012 and 2012-2016. The results show that UCT and SUN played a dominant role in publishing papers addressing diagnostic medical devices for TB, as shown by the sizes of the nodes, which represent the number of publications the institutions have published. TB diagnostic device research activity was higher during 2012-2016, despite its lower rank in Table 1-1, which shows that TB was the 6th out of 10 leading causes of disease in South Africa in 2016. The results presented in Figure 4-11 show that foreign organisations (SMMS, RIVM, UCL, GTI, GEH, UL, UMC-U, RUMC) were the most active during the 2012-2016 period.

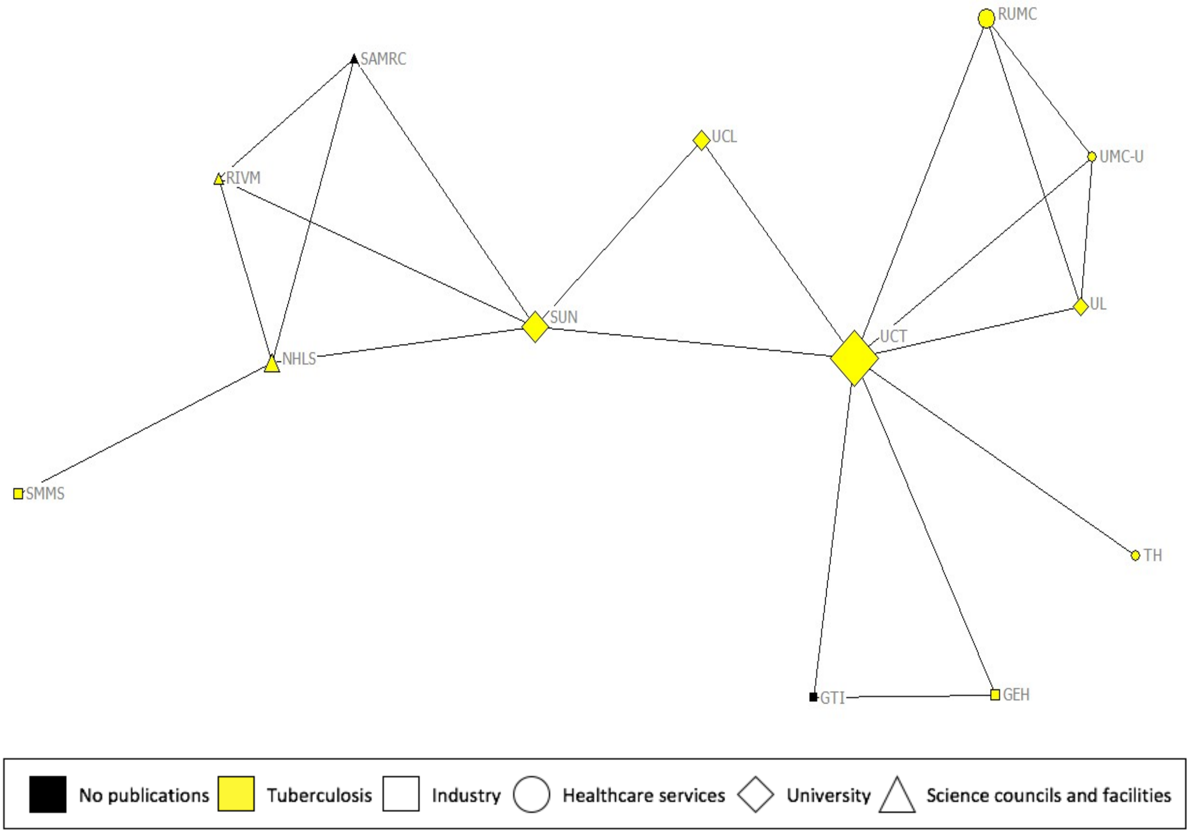

Figure 4-10: Network representation of diagnostic medical device research addressing TB in South Africa between 2008-2012. The size of the nodes was determined by the number of publications by each organisation. Edges were weighted according to the number of times collaboration occurred between two nodes.

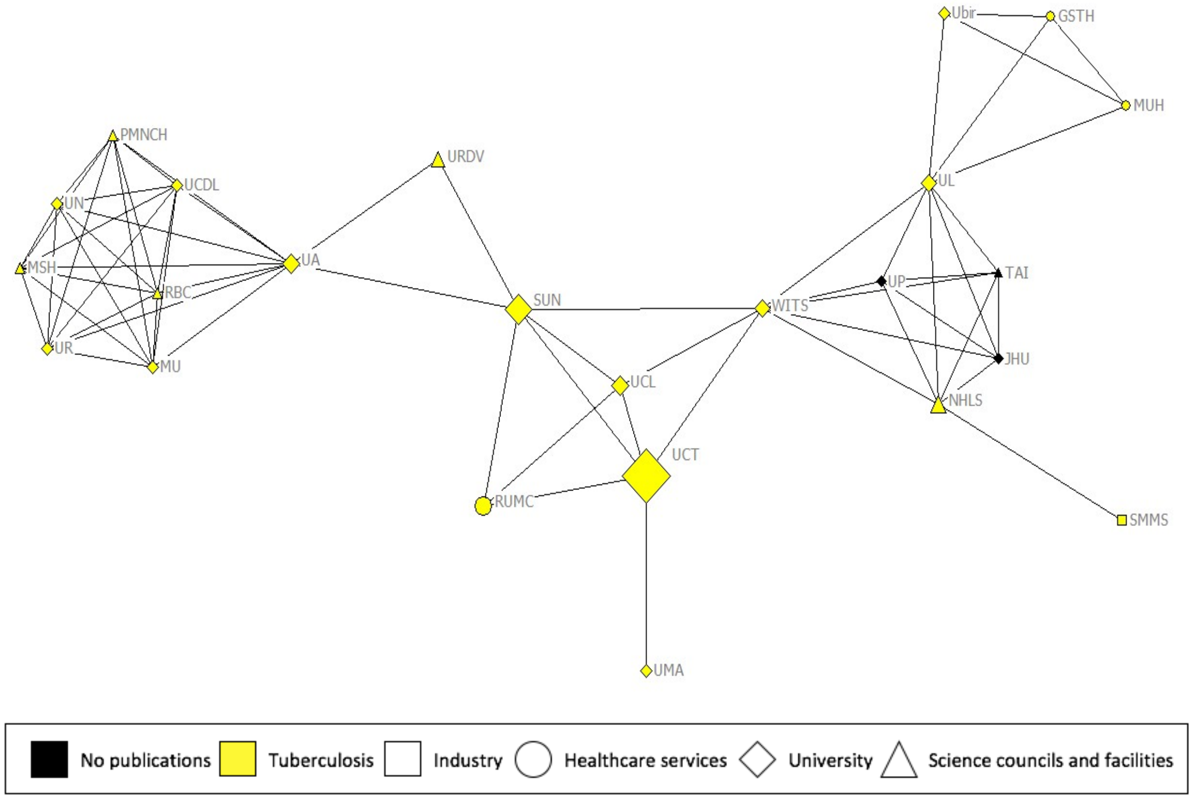

Figure 4-11: Network representation of diagnostic medical device research addressing TB in South Africa between 2012-2016. The size of the nodes was determined by the number of publications by each organisation. Edges were weighted according to the number of times collaboration occurred between two nodes.

4.4 Focus Areas

Table 4-8 shows the specific focus areas of diagnostic device development in South Africa with regard to infectious diseases. A list of diagnostic device features is presented along with the diseases that each one is intended to diagnose. The locations (local/foreign) of the co-authors involved in the development of each device as well as the funders of the research, have also been included in the table.

Of all the medical device features that appeared in the dataset, which consisted of the 28 publications listed in Table 4-8, computer-aided diagnosis was the most frequently addressed by diagnostic medical device research (12/28 publications). In terms of the motivation for each device type, the following observations were made from the relevant papers:

- Publication number 6 (Jager et al., 2014) stated that the purpose of their computer-aided diagnosis was to increase efficiency and improve detection accuracy, by reducing reliance on qualified technicians which are in short supply.

- Publication number 7 (Soobratty et al., 2014) presents a device uses nanomaterial-based sensors, which are sensitive and inexpenisive, to detect TB at the point of care through the analysis of exhaled alveolar breath.
- Publication 23 (Dang et al., 2015) and 27 (Mourão et al., 2016) present an adaptation to the GC/MS, which uses liquid extraction and solid phase extraction procedures to detect TB. Besides its high sensitivity, the authors claim that the device is also user-friendly and inexpensive, which is a useful characteristic in poor, resource-limited settings (Dang et al., 2015).

Although the table shows that the device development which has occurred between 2008 and 2016 has addressed some of the South African disease burden, there is a lack of point-of-care (POC) device activity. POC devices are known to be automated and portable and to provide a rapid result (Price, 2001; Choi, 2016) which helps to address the shortage of resources and skilled technicians in low-income settings. As such, at the outset of this study, it was expected to see POC devices in the diagnostic device development landscape. However, the study outcome showed that the focus has instead been on software for devices such as microscopes and X-ray machines, which are based in laboratories or health facilities (see Table 4-8). Two devices in the table qualify as POC diagnostic devices; publication number 19 (Robbins et al., 2014) presents a smartphone application for HIV diagnosis. Given that the application is able to run on any android device, it allows for screenings to be administered in any location (rural or urban) by any healthcare profession (Robbins et al., 2011). A limitation of this device would be that it can only be used on smartphones or tablets, which may not always be accessible in resource-limited areas. Publication number 7 is based on the use of organic nano-material sensors that are able to detect active TB through a breath test, and the authors claim it is also noninvasive and inexpensive (Soobratty et al., 2014).

Also shown in Table 4-8 is the source of funding for the research of each diagnostic medical device. While all the publications with a foreign author have at least one foreign funder, some of the local development activity also has foreign funders, which indicates that the funding source does not appear to determine whether or not foreign collaborators are involved.

Table 4-8: Features of diagnostic medical devices research and diseases addressed as discussed in the 28 South African affiliated journal articles between 2008 and 2016

	Author	**Diseases addressed**	**Device Type**	**Location of co-authors**	**Source of Funding**
1.	(Hogeweg et al., 2010)	Tuberculosis	Computer-aided detection – chest X-rays	Foreign/Local	
2.	(Khutlang et al., 2010)	Tuberculosis	Computer-aided detection – sputum smear microscopy	Local	
3.	(Irving et al., 2011)	Tuberculosis	Computer-aided detection – chest X-rays	Foreign/Local	Commonwealth Scholarship Commission
4.	(Dendere et al., 2011)	Tuberculosis	Image processing – automated microscopy	Local	
5.	(Divekar et al., 2012)	Tuberculosis	Computer-aided detection – sputum smear microscopy	Foreign/Local	
6.	(de Jager et al., 2014)	Tuberculosis	Image processing – automated microscopy	Local	
7.	(Soobratty et al., 2014)	Tuberculosis	Nanomaterial-based sensors	Foreign/Local	Sir Halley Stewart Trust
8.	(Hogeweg et al., 2015)	Tuberculosis	Computer-aided detection – chest X-rays	Foreign/Local	
9.	(Marais et al., 2008)	Tuberculosis	LED light source – fluorescence microscopy	Local	
10.	(Halberstadt and Douglas, 2008)	Tuberculosis	Computer-aided detection – CT images	Local	National Research Foundation, Abdus Salam International Centre for Theoretical Physics, Swedish International Development Cooperation Agency
11.	(Frean, 2009)	Malaria	Image processing –automated microscopy	Local	University of Witwatersrand, National Health Laboratory Services
12.	(Mouton et al., 2010)	Tuberculosis	Computer-aided detection – chest X-rays	Local	
13.	(Khutlang et al., 2010)	Tuberculosis	Computer-aided detection – sputum smear microscopy	Local	
14.	(Osibote et al., 2010)	Tuberculosis	Image processing – automated microscopy	Local	National Institutes of Health

15.	(Patel and Douglas, 2011)	Tuberculosis	Image processing –automated microscopy	Local	National Institutes of Health
16.	(Van Wyk et al., 2011)	Tuberculosis	LED light source –fluorescence microscopy	Local	SATBAT, National Institutes of Health, Fogarty International Center
17.	(Tezoo and Douglas, 2012)	Tuberculosis	Computer-aided detection – chest rays	Local	Lodox Systems, Technology and Human Resources for Industry Programme
18.	(Patel and Douglas, 2012)	Tuberculosis	Image processing – automated microscopy	Local	National Institutes of Health
19.	(Robbins et al., 2014)	HIV	Smartphone Application	Foreign/Local	National Institute of Mental Health to the HIV Center for Clinical and Behavioral Studies, Manhattan HIV Brain Bank at the Mount Sinai School of Medicine
20.	(Irving et al., 2014)	Tuberculosis	Computer-aided detection – CT images	Foreign/Local	Commonwealth Scholarship Commission
21.	(Ismail et al., 2015)	Tuberculosis	Image processing – automated microscopy	Local	
22.	(Holmen et al., 2015)	Female Genital Schistosomiasis	Image processing –automated microscopy	Foreign/Local	
23.	(Dang et al., 2015)	Tuberculosis	Adapted GC/MS based on liquid extraction and solid-phase clean-up	Foreign/Local	UBS Optimus Foundation, NanoNext NL
24.	(Holmen et al., 2015)	Female Genital Schistosomiasis	Image processing – automated microscopy	Foreign/Local	
25.	(Philipsen et al., 2015)	Tuberculosis	Computer-aided detection – chest X-ray	Foreign/Local	European and Developing Countries Clinical Trials Partnership
26.	(Melendez et al., 2016)	Tuberculosis	Computer-aided detection – chest X-ray	Foreign/Local	European and Developing Countries Clinical Trials Partnership
27.	(Mourão et al., 2016)	Tuberculosis	Adapted GC/MS based on liquid extraction and solid-phase clean-up	Foreign/Local	UBS Optimus Foundation, NanoNext NL
28.	(Ngabonziza et al., 2016)	Tuberculosis	LED light source– sputum smear microscopy	Foreign/Local	East African Public Health Laboratory Networking

4.5 Summary

The first diagnostic medical device publications within the 2000-2016 period appeared in 2008. Two independent collaboration networks were identified, one of which exhibited the collaborative research activity for the development of diagnostic tools for HIV/AIDS, TB and malaria, and the other which exhibited the research activity for FGS. The degree centrality results showed that UCT is the most influential institution, while the closeness and betweenness centrality results showed that SUN has a substantial impact on how information is transferred throughout the network. On a sectoral level, the local university sector was found to be an important link between other sectors and nodes, in that it formed the most inter-sectoral collaboration with the hospital and science council sectors. There was a high presence of foreign nodes in the network (32/42 nodes). TB was found to be the most frequently addressed disease in diagnostic device development in South Africa (57 publications), with UCT (15 publications) and SUN (7 publications) contributing the most research in this field. The development of automated detection methods, which was discussed in 12 out of the 28 articles, was the prominent focus of TB-related diagnostic device development activity during the 9-year period from 2008 to 2016.

5. Conclusion and Recommendations

The study investigated the landscape of diagnostic medical device development in South Africa by constructing a collaboration network and identifying influential institutions, collaboration trends and paths for knowledge propagation in the network. Future research could examine patenting activity for a richer analysis of diagnostic device activity. An analysis of the type of collaboration activity that successfully produced products that have reached the market or the clinic would also be useful. Insights into the barriers to and the drivers of successful diagnostic device innovation would be gained through detailed case studies of collaborations identified in the networks. Such knowledge would be beneficial to future technological and policy developments aimed at improving access to diagnostic services and treatment in the South African context.

While point-of-care tests are well suited to developing countries such as South Africa, the diagnostic device features listed in Table 4-10 indicate that little research has been directed at POCTs. According to a global market forecast published by Markets and Markets (2014), the global POC diagnostics market in developing countries has grown at a lower compound annual growth rate (CAGR) than in developed countries since 2013. However, the global market is expected to experience high growth in the future, particularly in emerging countries such as Brazil, Russia, India, China and South Africa. This is due to factors such as the increased prevalence of lifestyle diseases, persisting infectious diseases, increased usage of home-based POC devices and decreasing numbers of technicians in central labs (Markets and Markets, 2014). If reliance on internationally developed devices is to be avoided, countries like South Africa should consider investing in POC development research.

A limitation of this study is that only journal and conference articles were included. Given that the publishing of journal articles is considered as an academic exercise, the activity present in other sectors, particularly the industry sector, tends to be under-represented. It would therefore be useful to conduct a separate study to establish collaboration trends within the industry sector based on the analysis of patents as a way to account for this limitation. Another limitation is that although bibliometric studies typically use co-authorship as a proxy for collaboration, Laudel (2002) stated that collaborators are only awarded co-authorship status based on the type of contribution they have made to the publication (Laudel, 2002), and certain types of collaboration may not be reflected in co-authorship. Finally, the affiliation of multiple authors with one organization was not considered in the analysis and therefore collaboration within institutions has not been considered (Chimhundu, et al., 2015).

Further research is required to understand the motivations that underlie collaborations in medical device development, and to explore the unique contributions of different collaborators in medical device development.

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Appendix A

Full Name	**Abbreviation**	**Local/Foreign**
Universities		
Columbia University	CU	Foreign
Durban University of Technology	DUT	Local
Johns Hopkins University	JHU	Foreign
Makerere University	MU	Foreign
The Mannheim University of Applied Sciences	UMA	Foreign
Universite Catholique de Louvain	UCDL	Foreign
University College London	UCL	Foreign
University of Agder	UiA	Foreign
University of Amsterdam	UA	Foreign
University of Bergen	UiB	Foreign
University of Birmingham	UBir	Foreign
University of Cape Town	UCT	Local
University of Copenhagen	UCPH	Foreign
University of Kwazulu-Natal	UKZN	Local
University of London	UL	Foreign
University of Nairobi	UN	Foreign
University of Oslo	UiO	Foreign
University of Pretoria	UP	Local
University of Rwanda	UR	Foreign
University of Stellenbosch	SUN	Local
University of Witwatersrand	WITS	Local
Healthcare Services		
Guy’s and St. Thomas Hospital	GSTH	Foreign
Leiden University Medical Centre	LUMC	Foreign
Mount Sinai Medical Centre	MSMC	Foreign
Oslo University Hospital	OUH	Foreign
Radboud University Medical Centre	RUMC	Foreign
Sorlandet Hospital	SH	Foreign
Tygerberg Hospital	TH	Local
University Medical Centre Utrecht	UMC-U	Foreign
Industry		
Envisage IT	EI	Foreign

General Electric Healthcare	GEH	Foreign
Guardian Technologies International Inc.	GTI	Foreign
Signature Mapping Medical Sciences Inc.	SMMS	Foreign
Science Councils and Facilities		
Institute of Tropical Medicine Prince Leopold	PMNCH	Foreign
Management Sciences for Health	MSH	Local
National Health Laboratory Services	NHLS	Local
Rwanda Biomedical Centre	RBC	Foreign
South African Medical Research Council	SAMRC	Local
The Aurum Institute	TAI	Local
The National Institute for Public Health and Environment	RIVM	Foreign
Unilever Research and Development Vlaardingen	URDV	Foreign