Mathematical modelling of human immunodeficiency virus and human papillomavirus disease transmission dynamics, natural history, and control interventions

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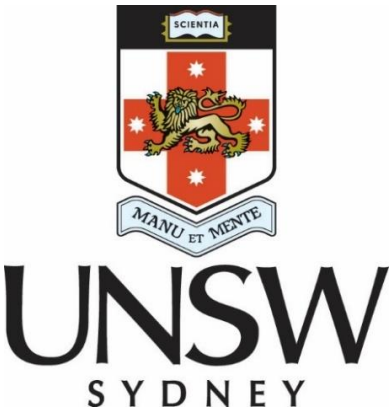
A thesis in fulfilment of the requirements of the degree of

Doctor of Philosophy



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Thesis Title

Mathematical modelling of human immunodeficiency virus and human papillomavirus disease transmission dynamics, natural history, and control interventions.

Thesis Abstract

Human immunodeficiency virus (HIV) control is one of the most heavily studied diseases of our time, as an estimated 32.7 million people have lost their lives to HIV-related illnesses. The scientific community has collectively made considerable advancements in HIV prevention and treatment methods, with the implementation of programmes for voluntary medical male circumcision (VMMC), antiretroviral therapy (ART), and behavioural interventions successfully reducing HIV-related deaths globally by 60% in 2019, compared to the peak in 2004. Cervical cancer is caused by a persistent infection with an oncogenic strain of human papillomavirus (HPV), which in rare cases, facilitates the development of a lesion that progresses to cervical cancer. New evidence suggests that women living with HIV are at a six-fold greater risk of cervical cancer compared to women without HIV, as the presence of an HIV infection increases HPV infection persistence and escalates progression to cervical cancer. Cervical cancer is largely preventable through HPV vaccination and cervical screening; however, despite this, there were still over 600,000 cervical cancer cases and over 340,000 cervical cancer deaths globally in 2020. Therefore, the World Health Organisation (WHO) has called for all nations to contribute to a concerted global effort to eliminate cervical cancer as a public health problem and has launched a global strategy to accelerate this. As HIV control such as VMMC and behavioural interventions directly impact HPV transmission, and since HIV is implicated in 5% of cervical cancers, future predictions of cervical cancer incidence and mortality rates in regions with endemic HIV must account for HIV epidemic metrics and uptake of HIV control. The body of work presented in this thesis utilises a detailed model platform of HIV and HPV infection and natural history to systematically address the combined and standalone impacts of HIV and HIV control on cervical cancer incidence and mortality in Tanzania, an example country broadly representative of sub-Saharan Africa. This thesis builds on the Tanzanian example to assess the impact of the implementation and scale-up of HPV vaccination and screening for cervical cancer prevention under the WHO global strategy for cervical cancer elimination in terms of direct health benefits and cost-effectiveness and resource utilisation. The results presented in this thesis illustrate the importance of continuing to invest in sustained HIV control, which has the secondary benefit of preventing cervical cancer incidence and mortality and provides arguments for the adoption and rapid scale-up of HPV vaccination and cervical screening for all women, with particular emphasis on women living with HIV. From a broader perspective, this body of work highlights the valuable role of detailed mathematical modelling to assess population health policy.

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Contents

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List of abbreviations

The following is a list of abbreviations, in alphabetical order, used throughout this thesis.

ART – antiretroviral therapy

CIN – cervical intraepithelial neoplasia

HIV – human immunodeficiency virus

HPV – human papillomavirus

HSIL – high-grade squamous intraepithelial lesion

ICER – incremental cost-effectiveness ratio

LMIC- low- and middle-income country

LSIL – low-grade squamous intraepithelial lesion

LY – life-year

MSM – men who have sex with men

NNT – number needed to treat

PLHIV – people living with HIV

UNAIDS – The Joint United Nations Programme on HIV/AIDS

USD – United States dollar

VIA – visual inspection with acetic acid

VMMC – voluntary medical male circumcision

WLHIV – women living with HIV

WHO – World Health Organisation

WTP – willingness to pay

Abstract

Human immunodeficiency virus (HIV) control is one of the most heavily studied diseases of our time, as an estimated 32.7 million people have lost their lives to HIV-related illnesses. The scientific community has collectively made considerable advancements in HIV prevention and treatment methods, with the implementation of programmes for voluntary medical male circumcision (VMMC), antiretroviral therapy (ART), and behavioural interventions successfully reducing HIV-related deaths globally by 60% in 2019, compared to the peak in 2004. Cervical cancer is caused by a persistent infection with an oncogenic strain of human papillomavirus (HPV), which in rare cases, facilitates the development of a lesion that progresses to cervical cancer. New evidence suggests that women living with HIV are at a six-fold greater risk of cervical cancer compared to women without HIV, as the presence of an HIV infection increases HPV infection persistence and escalates progression to cervical cancer. Cervical cancer is largely preventable through HPV vaccination and cervical screening; however, despite this, there were still over 600,000 cervical cancer cases and over 340,000 cervical cancer deaths globally in 2020. Therefore, the World Health Organisation (WHO) has called for all nations to contribute to a concerted global effort to eliminate cervical cancer as a public health problem and has launched a global strategy to accelerate this. As HIV control such as VMMC and behavioural interventions directly impact HPV transmission, and since HIV is implicated in 5% of cervical cancers, future predictions of cervical cancer incidence and mortality rates in regions with endemic HIV must account for HIV epidemic metrics and uptake of HIV control. The body of work presented in this thesis utilises a detailed model platform of HIV and HPV infection and natural history to systematically address the combined and standalone impacts of HIV and HIV control on cervical cancer incidence and mortality in Tanzania, an example country broadly representative of sub-Saharan Africa. This thesis builds on the Tanzanian example to assess the impact of the implementation and scale-up of HPV vaccination and screening for cervical cancer prevention under the WHO global strategy for cervical cancer elimination in terms of direct health benefits and cost-effectiveness and resource utilisation. The results presented in this thesis illustrate the importance of continuing to invest in sustained HIV control, which has the secondary benefit of preventing cervical cancer incidence and mortality and provides arguments for the adoption and rapid scale-up of HPV vaccination and cervical screening for all women, with particular emphasis on women living with HIV. From a broader perspective, this body of work highlights the valuable role of detailed mathematical modelling to assess population health policy.

List of publications

Thesis publications

Chapter 2 contains original research published in the following paper:

Hall M.T., Smith M.A., Simms K.T., Barnabas R.V., Canfell K., Murray J.M. The past, present and future impact of HIV prevention and control on HPV and cervical disease in Tanzania: a modelling study. PLoS One. 2020;15(5): e0231388.

Chapter 3 contains original research published in the following paper:

Hall M.T., Simms K.T., Smith M.A., Barnabas R.V., Murray J.M., Canfell K. Elimination of cervical cancer in Tanzania: Modelled analysis of elimination in the context of endemic HIV infection and active HIV control. International Journal of Cancer. 2021. DOI: 10.1002/ijc.33533

Accepted author versions of these publications are included as thesis chapters and may contain additional material. Figures, tables, associated captions, and references have been reformatted to be consistent throughout the thesis.

Chapter 1: Introduction and Literature Review

Biology and epidemiology of human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV) is a transmissible retrovirus that infects human immune cells that express the CD4 receptor. Susceptible cells include monocytes, macrophages and $CD4^+$ T cells(Dalgleish et al., 1984, Barre-Sinoussi et al., 1983). The virus is acquired through contact with the bodily fluids of an infectious individual, most commonly during sexual intercourse(Moore et al., 2001, National Institutes of Health, 2017, De Cock et al., 2000). Following HIV acquisition, an infected individual enters an acute stage of infection that typically lasts for less than 12 weeks (Table 5) and is characterised by non-descript flu-like symptoms(U.S. Department of Health & Human Services, 2017, Hightow-Weidman et al., 2009). Following acute infection, the World Health Organisation recognises four clinical (symptom-defined) stages of HIV infection(World Health Organization, 2013). Clinical stage 1 refers to the asymptomatic stage of disease, otherwise known as chronic infection. In the absence of HIV treatment, chronically infected individuals remain in this stage for approximately five years, while their immune system is gradually depleted(AVERT, 2017, U.S. Department of Health & Human Services, 2017). Once the infected individual's immune system has been sufficiently depleted, they enter clinical stage 2, the first symptomatic stage(World Health Organization, 2013). Identifying symptoms for this stage are unexplained weight loss (<10% of bodyweight), and recurrent bacterial, viral, or fungal infections. The second symptomatic stage (clinical stage 3) is identified by a set of more severe symptoms, for example, weight loss of greater than 10% of body weight, severe/chronic infection and persistent diarrhoea, fever and anaemia(World Health Organization, 2013). On average, untreated individuals spend an additional five years in clinical stages 2 and 3(Palk et al., 2018). The final stage (clinical stage 4) is often characterised by an increase in viral load alongside the presence of AIDS-defining conditions(World Health Organization, 2013, Vergis and Mellors, 2000, U.S. Department of Health & Human Services, 2017).

Following the emergence and classification of HIV in the early 1980s, fear of the deadly infection swept the globe. As infection rates grew, HIV was quickly identified as a global public health concern, with the United Nations declaring a global crisis. Estimates suggest that global HIV incidence peaked at 3.3 (3.1-3.4) million new infections in 1997, before rapidly declining over 1998-2005 following the introduction and scale-up of highly effective anti-retroviral therapy (ART)(Wang et al., 2016). Early forms of anti-retroviral drugs such as zidovudine were first approved for use in the late 1980s; however, these early drugs were used as monotherapy and were quickly

overcome with HIV evolving drug resistance. However, the era of anti-retroviral therapies progressed rapidly. The current standard for HIV treatment referred to throughout the thesis as ART involves a combination of anti-retroviral drugs that inhibit at least two stages in the viral infection cycle, effectively suppressing viral activity and transmission through lifelong adherence(Palmer, 2003, Cohen et al., 2011).

As a testament to the effectiveness of ART as both a treatment and prevention, and, to the global commitment to ending HIV, in 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) unveiled '90-90-90: An ambitious treatment target to help end the AIDS epidemic', intending to increase testing and treatment rates such that 90% of all people living with HIV are aware of their status, 90% of people diagnosed with HIV are receiving treatment, and 90% viral suppression of treated individuals(Joint United Nations Programme on HIV/AIDS (UNAIDS), 2014).

While ART plays a prominent role in HIV prevention efforts, there is a range of other effective tools for HIV prevention that cannot be overlooked. Findings from three gold standard efficacy trials indicate that voluntary medical male circumcision (VMMC) reduced the risk of HIV acquisition by 44-70%(World Health Organisation (WHO), 2020b). As a result, the World Health Organisation (WHO) has recommended VMMC for HIV prevention, with updated policy recommendations published in 2020(World Health Organisation (WHO), 2020b). In practice, ART for treatment and prevention and VMMC work in conjunction with a slew of other behavioural and social interventions targeted towards increasing HIV testing rates, increasing safe sexual practices such as monogamy and condom use, and decreasing the need for young women to engage in transactional or commercial sex through social security enterprise. More recently, particularly in high-income settings, pre-exposure prophylaxis (PrEP) has emerged and is an effective way for HIV negative individuals to protect themselves against HIV infection(Centers for Disease Control and Prevention, 2018b, World Health Organisation 2018b). PrEP involves administering an anti-viral drug, either orally or as a topical gel, before HIV exposure(World Health Organisation 2018b). Taken orally every day, PrEP is highly effective at reducing the risk of HIV acquisition by >90%(Grulich et al., 2018, Centers for Disease Control and Prevention, 2018b). Due to this efficacy, the WHO recommends that individuals who are considered high-risk of HIV infection receive PrEP(World Health Organisation 2018b). Therefore, PrEP may be appropriate for commercial sex workers and men who have sex with men.

HIV acquisition risk is significantly affected by geographical, social, and economic factors. The majority of all people living with HIV reside in low- and middle-income

countries (LMICs), and marginalised members of society, such as sex workers, injection-drug users and men who have sex with men (MSM), are at disproportionate risk. Sub-Saharan African countries carry the highest global burden of HIV, with 75.4% (71.7-75.4) of all new HIV infections in 2015 occurring in this region(Wang et al., 2016).

The landscape of global HIV epidemiology has changed substantially over time and will continue to change. As the scientific community continues to discover and refine effective HIV treatment and prevention technologies, some studies report increased levels of complacency and potential occurrences of risk compensation following the successful implementation of HIV control interventions such as male medical circumcision, treatment with ART, and pre-exposure prophylaxis. However, there is conflicting evidence surrounding the magnitude or directionality of community-wide behavioural changes(Kalichman et al., 2018, MacKellar et al., 2011, Crepaz et al., 2004, Lal et al., 2017). The current global focus has shifted towards achieving equity of access to these technologies to eliminate transmission in low-income (and all) countries. Notably, even once HIV transmission is eliminated, if viral suppression in people living with HIV is not staunchly maintained throughout their lifetime, there is a risk of resurgence of their disease and throughout the community.

Biology and epidemiology of human papillomavirus (HPV)

Human papillomavirus (HPV) is a double-stranded DNA virus, which infects human stratified epithelial cells(Doorbar, 2006, McMurray et al., 2001). Over 150 HPV genotypes have been discovered, with some resulting in the development of either non-genital or genital warts. Most HPV infections are asymptomatic and cleared naturally(Loo and Tang, 2014, Ljubojevic and Skerlev, 2014, Doorbar et al., 2015, World Health Organisation 2018a). Persistent infection with a class of HPV genotypes known as the “high-risk” types can cause oropharyngeal and anogenital lesions and cancers, particularly cervical cancer(Ljubojevic and Skerlev, 2014, Doorbar et al., 2015). There are 15 high-risk oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82); types 16 and 18 are generally considered to be the highest risk and are responsible for around 70% of all cervical cancer cases(Winer et al., 2006, Division of STD prevention (Department of health and human services), 1999, Munoz et al., 2003). Even so, the majority of high-risk HPV infections do not result in any clinical disease and are cleared by the immune system(Ault, 2006). However, persistent infection within the cervix can induce neoplastic cell changes within the epithelium, resulting in the development of a cervical lesion(Ault, 2006). Cervical lesions are identified as cervical intraepithelial neoplasia (CIN) and are graded by severity (i.e., low-grade CIN1 to high-grade CIN3). The majority of cervical lesions

regress and are eventually cleared; however, some lesions eventually progress to invasive cervical carcinoma(Ault, 2006).

HPV is one of the most common sexually transmitted infections. In the United States, the Centres for Disease Control (CDC) estimates that 80% of women become infected with HPV by the time they are 50 years old(Centers for Disease Control and Prevention, 2018a). Globally, the World Health Organisation estimates that in 2016 more than 290 million women were living with a current HPV infection, and estimates that HPV infection causes 528,000 cervical cancer cases and 266,000 cervical cancer deaths each year(World Health Organisation 2016). Low human development index (HDI) countries shoulder the greatest burden of cervical cancer, with 2018 age-standardised rates (ASR) of cervical cancer incidence and mortality rates being 29.8 per 100,000 women and 23.0 per 100,000 women(International Agency for Research on Cancer (IARC), 2018a, International Agency for Research on Cancer (IARC)), which are 2.3 and 3.3 times higher, respectively, than the global average(International Agency for Research on Cancer (IARC), 2018b, International Agency for Research on Cancer (IARC), 2018c).

HPV and cervical cancer control interventions

Fortunately, health departments and policymakers have access to two safe and highly effective tools for preventing cervical cancer: HPV vaccination and cervical screening. HPV vaccination is a first-line primary prevention method, as vaccinated females are protected against oncogenic HPV infection and subsequent cervical cancer. As of 2020, there are three commercially available HPV vaccines: the bivalent vaccine, which protects against HPV types 16 and 18; the quad-valent vaccine, which protects against HPV types 16, 18, 6 and 11; and a 9-valent vaccine which protects against HPV types 16, 18, 6, 11, 31, 33, 45, 52 and 58 (responsible for >90% of all cervical cancer, globally)(The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), 2018). The 9-valent vaccine (Gardasil® 9) has the highest coverage of protection against cervical cancer, in that the vaccine-included types are responsible for >90% of cervical cancers worldwide, and is highly safe and effective, preventing infection in >95% of vaccinated individuals(The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), 2018, Joura et al., 2015).

Cervical screening is a safe and effective method for detecting HPV-related cervical disease among HPV positive women. Early detection of pre-cancerous cell changes allows for preventative treatment against the development of cervical cancer(World

Health Organisation 2018c). The most used (and oldest) test, the Papanicolaou (Pap) smear is a cytology test involving the staining and visual inspection of cervical cells by a pathologist to check for cellular changes; this test is used for the detection of cervical pre-cancer (that is, CIN) and cancer and has been highly successful(Michael, 1999, Tambouret, 2013). However, cytology is not sufficient to perfectly determine the severity or degree of cellular changes. Women with cytologically detected abnormalities would receive one of two possible results depending on what was visualised on the slide: low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL). In general, women with CIN1 may receive an LSIL diagnosis, and women with CIN2+ may receive an HSIL result, noting substantial variability in the classification of CIN1/2 lesions in practice. Once a pre-cancerous cervical lesion is detected, women may be offered either an ablative or excisional treatment option, depending on the severity of their lesion, whose goal is to remove the lesion and prevent further progression to cervical cancer.

More recently, many countries have been moving towards implementing HPV DNA testing instead of cytology- or visual inspection with acetic acid (VIA) based screening programs in response to evidence from large scale international clinical trials(Ronco et al., 2014). The HPV test is more sensitive and capable of detecting HPV infection before cell changes start to occur; this allows women with potentially oncogenic HPV types to be managed more cautiously and for earlier treatment of pre-cancer. It is possible that through a combination of HPV vaccination and cervical screening with appropriate treatment for pre-cancerous lesions, the burden of cervical cancer can be drastically reduced(Brisson et al., 2020, Simms et al., 2019).

HIV and cervical cancer: the link

Emerging studies are reporting links between HIV and HPV acquisition and progression. Women living with HIV, particularly those who are not receiving ART and at later stages of HIV disease, are at an elevated risk of new HPV detection (pooled relative risk, RR_{pooled} 2.64), reduced clearance rates (pooled hazard ratio, HR_{pooled} 0.72), and increased incidence of LSIL (RR_{pooled} 3.73), HSIL (HR_{pooled} 1.32) and cervical cancer (RR 6.01)(Liu et al., 2018, Stelzle et al., 2021). Recent WHO estimates of the global burden of cervical cancer associated with HIV report that globally, 5.8% of women diagnosed with cervical cancer are living with HIV(Stelzle et al., 2021). In regions with a substantially higher burden of HIV, such as the WHO African region, more than a quarter (25.1%) of cervical cancers diagnosed are among HIV-positive women(Stelzle et al., 2021). Furthermore, women with HIV and cervical cancer are 40-95% more likely to die from cervical cancer than women without HIV(Dryden-Peterson

et al., 2016, Coghill et al., 2015). Adherence to ART is understood to lower the risk of HPV acquisition and progression; however, effects are contingent on other factors such as HPV genotype, duration of ART use and $CD4^+$ T cell count, where CD4 count is inversely associated with risk(Liu et al., 2018). Nevertheless, the specific impact of ART on HPV incidence and progression risk is difficult to quantify. As authors Liu et al. concluded, more studies are needed to investigate the effect of objective levels of ART adherence, such as viral suppression, on HPV-related cervical disease(Liu et al., 2018).

Emerging evidence also suggests that the relationship between HIV and HPV may not be one-sided. An analysis of clinical trial data, published by Liu et al. in 2021, has reported that the presence of a high-risk HPV infection increases HIV acquisition risk (adjusted odds ratio of 1.5-4.6) in females. Furthermore, females infected with multiple HPV types simultaneously are at even greater risk of HIV acquisition, with a 20% increase in HIV acquisition risk for each additional HPV type present(Liu et al., 2021).

Sub-Saharan Africa stands out as a region with high disease burdens of both HIV and cervical cancer(Bray et al., 2018). Women living in sub-Saharan Africa may be more subject to social inequities, such as reduced access to essential health care, incomplete educational attainment and financial distress. Such equity disparities increase cervical cancer and HIV risk, with 20.6 million of the 37.9 million people living with HIV (PLHIV) living in Eastern or Southern Africa(UNAIDS, 2020b, UNAIDS, 2019). The WHO African region's cervical cancer incidence and mortality rates were 30.9 and 21.5 cases and deaths per 100,000 women in 2020, which dwarf the global averages of 13.3 and 7.3 cervical cancer cases and deaths, respectively(International Agency for Research on Cancer, 2020).

Despite these high rates of both HIV and cervical cancer, for women living in sub-Saharan Africa, in fact in many low- and middle-income countries (LMIC), there is limited access to essential cervical cancer prevention, with only nine countries in Africa having implemented national HPV immunisation programmes as of 2018 and an average cervical screening uptake of 13% across sub-Saharan Africa(World Health Organisation 2019b, Yimer et al., 2021). Further, for women diagnosed with cervical cancer, there may be limited access to appropriate cancer treatment services such as radiotherapy, chemotherapy and palliative care(Canfell et al., 2020, Lott et al., 2020, Bruni et al., 2016).

Existing modelling literature

From the initial phase of the global HIV epidemic, mathematicians, policymakers, and epidemiologists looked to modelling to increase our depth of understanding of the transmission dynamics and epidemiology of HIV. The earliest models of HIV, published by Anderson and May in the 1980s, utilised Kermack-McKendrick SIR (susceptible, infectious, recovered/removed) modelling to study the transmission dynamics of HIV and largely popularised the field of mathematical epidemiology(Anderson et al., 1986, Anderson and May, 1992). In the following years, many models of HIV, both continuous and discrete, were developed and published, with varying levels of complexity, to quantify the effects of behaviours, demographic factors and preventative interventions on HIV transmission, natural history and mortality(Blower et al., 2003, Smith and Blower, 2004, Van der Ploeg et al., 1998, Vissers et al., 2011, Andersson et al., 2007, Kaldor and Wilson, 2010, Herbeck et al., 2014, Anderson et al., 2009, Edward et al., 1998, Freedberg et al., 2001, Hontelez et al., 2016, Long and Owens, 2011, Weinstein et al., 2001, Mishra et al., 2012). Despite the expanse of HIV models published in scientific literature, there were no modelling studies simulating the transmission of HIV in Tanzania specifically at the time of writing this thesis. However, the Spectrum/AIM model is a platform used by UNAIDS and country-level HIV monitoring programs to supplement observed data in estimating HIV epidemic metrics in 170 countries, including Tanzania(Stover et al., 2019).

Many other communicable diseases have been modelled to better understand epidemics and the effects of various interventions, whose effectiveness may be driven by a range of biological, economic, and behavioural factors(Velentzis et al., 2017, Schmidt-Ott et al., 2016, Lang, 2011). HPV and cervical cancer modelling are no different, and many international research groups have established well-supported and extensively validated HPV and cervical cancer modelling programmes. The first published analyses of epidemiological modelling of cervical cancer with HPV as a causative agent emerged in the late 1980s from the 'MISCAN' group based at Erasmus University in Rotterdam, The Netherlands(Canfell and Berkhof, 2019, Koopmanschap et al., 1990, Habbema et al., 1985). These analyses simulated the Dutch cervical cancer screening programme and economic aspects of screening. The second group to enter the HPV/cervical cancer modelling space was a team from the University College London (UCL). The UCL team developed a detailed and widely parameterised model of HPV natural history, assessing not only cytology-based (Pap) cervical screening programmes but also identifying the potential for HPV-based programmes to

improve cervical cancer outcomes in a range of countries(Canfell and Berkhof, 2019, Sherlaw-Johnson et al., 1994, Jenkins et al., 1996).

Following the detailed characterisation of HPV infection and natural history in an influential paper published by Shiffman and Castle in 2007(Schiffman et al., 2007), and successful HPV vaccine trials(Koutsky et al., 2002), the field of HPV and cervical cancer epidemiological modelling took off(Canfell and Berkhof, 2019). Building on the work of SIR modellers in the HIV epidemic space, many models of HPV and cervical cancer incorporated transmission dynamics to model the impacts of vaccination and changing risk factors over time(Brisson et al., 2016).

Many of these programmes of work have centred around predicting future cervical cancer incidence and mortality rates among a multitude of populations and quantifying the impacts of interventions such as cervical screening and precancer treatment, cervical cancer treatment and HPV vaccination. In recognition of these research groups and their established model platforms, international collaborative groups were formed to undertake a series of comparative modelling exercises. These groups, such as the Cervical Cancer Elimination Modelling Consortium (CCEMC)(Brisson et al., 2020) and the National Cancer Institute (NCI) funded Cancer Intervention and Surveillance Modelling Network (CISNET)(National Cancer Institute (NCI), 2015), produce reliable estimates of intervention impacts by utilising platforms which differ in structure, parametrisation, or modelling paradigm, to assess the same research question.

At the time of writing, all HPV transmission and infection-dynamic models which are deterministic compartment models in nature, operate on discrete time-steps. This approach simulates the mean force of infection without the need to simulate individuals and their partnerships explicitly. The benefit of this is that it is computationally inexpensive and can be minimally parameterised. In systems with large populations and established epidemics, or where detailed information about the system is limited, deterministic models are often preferred as they are reliable and straightforward to execute. However, the consequence of their computational inexpensiveness is reduced design flexibility and a combinatorially increasing number of compartments for each desired stratification. Stochastic variation is increasingly being incorporated into previously entirely deterministic compartment models, strengthening confidence in the ranges of outcomes produced while maintaining a degree of the original model simplicity and computational inexpensiveness. As we gain access to increased computing power, the use of agent-based stochastic modelling is growing in popularity, as it allows a more nuanced investigation of the impact of individual variability and

provides the modeller greater control over input parameters and the tracking of individual agents over their lifetime.

The HPV and cervical cancer modelling community are increasingly looking towards the incorporation of HIV to facilitate greater accuracy of predictions of HPV acquisition and progression to cervical cancer and the efficacy of cervical screening and HPV vaccination in regions with moderate to high levels of endemic HIV. In 2011, authors from the University of Buea in Cameroon published a cohort-model analysis assessing the potential for ART and cervical screening to reduce cervical cancer mortality rates in sub-Saharan Africa(Atashili et al., 2011). The authors found that, for a cohort of women infected with HIV at age 25, antiretroviral therapy initiation and sustained treatment effectively doubled the cumulative lifetime risk of cervical cancer mortality(Atashili et al., 2011). Other cohort-based analyses, such as Vanni et al. (2012) and Campos et al. (2018), have assessed the effectiveness and cost-effectiveness of cervical cancer screening programmes in a cohort of HIV positive women in low/middle-income countries(Vanni et al., 2012, Campos et al., 2018). These models, however, are cohort models that assume all simulated women are HIV positive. These do not account for HIV and HPV transmission dynamics, variable ART uptake, or preventative interventions over time.

Currently, two model platforms have been published in recent literature with characteristics comparable to the platforms developed for this thesis. The first platform, published in 2018 by authors from the University of Washington presented a detailed dynamic model of HIV and HPV infection and natural history, which assessed the effectiveness of HPV vaccination among HIV-negative and HIV-positive women in South Africa(Tan et al., 2018). Their model platform is detailed and thorough, but their analysis did not incorporate changing uptake of HIV prevention interventions and excluded the direct effect of current and future cervical screening. The second platform is more recent and was published just prior to the submission of this thesis in June 2021. In their analysis, authors from Stellenbosch University in South Africa comprehensively assess the long-term impacts of HPV vaccination and cervical screening on cervical cancer incidence in South Africa, accounting for the South African HIV epidemic(van Schalkwyk et al., 2021). The Stellenbosch University platform is individual-based and has been carefully parametrised to incorporate South Africa's existing cytology-based cervical screening programme and HPV immunisation schedule involving the bivalent HPV vaccine.

Thesis aims and outline

The overarching goal of this programme of work was to build upon the limited body of modelling evidence in support of expanding and sustaining HIV and cervical cancer control interventions in low-income countries, particularly in the context of sub-Saharan Africa. More specifically, the aim was to develop and parametrise a detailed transmission-dynamic model of HIV and HPV transmission and natural history, which accounts for over-time changes in behavioural characteristics and uptake of control interventions for HIV and cervical cancer. This model was utilised to perform three evaluations, set in the example context of the United Republic of Tanzania. Tanzania was chosen as an example country within this region due to the availability of data for HIV diagnosis, prevalence, and treatment and data informing genotype-specific HPV and CIN prevalence, stratified by HIV positivity status - empiric data which is relatively difficult to source. While parameterised to fit the epidemic metrics observed in Tanzania, these analyses are broadly representative of sub-Saharan Africa in general, as the region is generally low- to middle-income and subject to a moderately high prevalence of HIV and elevated cervical cancer incidence and mortality rates.

The first analysis, presented in Chapter 2, quantified the historical, current, and potential ongoing benefits of maintaining and expanding specific HIV control interventions, including ART, VMMC and PrEP with respect to both HIV and cervical cancer. This chapter provides background information essential to the conceptualisation of the potential future impacts of cervical cancer interventions, such as HPV vaccination and cervical screening.

Building upon this work, Chapter 3 explicitly addressed the impact of HPV vaccination and cervical screening, independently and combined, on cervical cancer incidence and mortality rates in Tanzania. This analysis is contextualised in the World Health Organisation’s timely call to action, mobilising countries to implement cervical cancer elimination strategies worldwide. This chapter aimed to assess the achievability of cervical cancer elimination in Tanzania for all women and highlight the need to plan specifically for women living with HIV when defining and implementing national cervical screening programmes.

Recognising the high effectiveness and cost-effectiveness of HPV vaccination, in addition to the HPV vaccination programme currently being scaled up in Tanzania, Chapter 4 quantified the cost-effectiveness of routine cervical screening in Tanzania. Here, detailed estimates were reported for resource utilisation, programme costs, and harms versus benefits of potential cervical screening regimes. This analysis solidifies

the argument for implementing comprehensive cervical screening regimes, including specifically accounting for increased screening in women living with HIV. Prior to the finalisation of this chapter, the World Health Organisation released updated cervical screening and treatment guidelines for the prevention of cervical cancer; therefore, model assumptions for cervical screening were updated to reflect these new recommendations.

Finally, Chapter 5 presented a calibrated stochastic agent-based HIV and HPV co-infection model parameterised to the Tanzanian setting. The modelled impact of HIV control interventions, including VMMC and ART, on HIV prevalence and cervical cancer incidence are reported and compared to outcomes generated by the compartment-based model presented in Chapter 2. Additionally, this chapter extends our understanding of the dynamic impact of ART on cervical cancer incidence by quantitatively reporting on the time to cervical cancer detection for HIV infected women who are untreated versus treated with ART.

Chapter 2: The impact of HIV and HIV control on cervical cancer in Tanzania: an example country in sub-Saharan Africa

This chapter aimed to quantify the historical, current, and potential ongoing benefits of maintaining and expanding specific HIV control interventions, including ART, VMMC and PrEP with respect to both HIV and cervical cancer. In doing so, the analysis provides essential background for understanding the potential impacts of specific cervical cancer interventions, such as HPV vaccination and cervical screening.

This chapter contains original research published in the following paper:

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The published study was conceptualised for this thesis by the candidate (Michaela Hall) and supervisors Professors John Murray and Karen Canfell. The candidate's estimated contribution to this analysis is approximately 80%, involving conceptualisation, study design and methodology, formal analysis, interpretation of results and visualisation, and development of original and revised manuscript drafts. The accepted author version of this publication has been included with minor modifications to improve clarity, and contains additional material sourced from the published supplementary appendix. Figures, tables, associated captions, and references have been reformatted to be consistent throughout the thesis.

Work from this chapter was presented at the International Papillomavirus Conference 2020 as a poster and was awarded 'Best E-Poster for outstanding research work'.

The past, present and future impact of HIV prevention and control on HPV and cervical disease in Tanzania: a modelling study

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Abstract

Background

Women with HIV have an elevated risk of HPV infection, and eventually, cervical cancer. Tanzania has a high burden of both HIV and cervical cancer, with an HIV prevalence of 5.5% in women in 2018 and a cervical cancer incidence rate among the highest globally, at 59.1 per 100,000 per year and an estimated 9,772 cervical cancers diagnosed in 2018. We aim to quantify the impact that interventions aimed at controlling HIV have had and will have on cervical cancer in Tanzania over a period from 1995 to 2070.

Methods

A deterministic transmission-dynamic compartment model of HIV and HPV infection and natural history was used to simulate the impact of voluntary medical male circumcision (VMMC), anti-retroviral therapy (ART), and targeted pre-exposure prophylaxis (PrEP) on cervical cancer incidence and mortality from 1995-2070.

Findings

From 1995 to 2020, we estimate that VMMC has prevented 2,843 cervical cancer cases and 1,039 cervical cancer deaths; by 2070, we predict that VMMC will have lowered cervical cancer incidence and mortality rates by 28% (55.11 cases per 100,000 women in 2070 without VMMC, compared to 39.93 with VMMC) and 26% (37.31 deaths per 100,000 women in 2070 without VMMC compared to 27.72 with VMMC). We predict that ART temporarily increases cervical cancer diagnoses and deaths due to the removal of HIV death as a competing risk but will ultimately lower cervical cancer incidence and mortality rates by an additional 7% (to 37.31 cases per 100,000 women in 2070) and 5% (to 26.44 deaths per 100,000 women in 2070), respectively, relative to a scenario with VMMC but no ART.

Conclusions

HIV treatment and control measures in Tanzania will result in long-term reductions in cervical cancer incidence and mortality. Although, in the near term, the life-extending capability of ART has resulted in the opportunity for additional cervical cancer cases and deaths, continued efforts towards HIV prevention will reduce cervical cancer incidence and mortality. To achieve further reductions and to eliminate cervical cancer, the implementation of HPV vaccination and cervical screening and scale-up of cervical pre-cancer and cancer treatment services will be required.

Background

For many years human immunodeficiency virus (HIV) has been one of the most heavily researched infectious diseases, and now, controlling HIV is beginning to look achievable(endinghiv.org, 2019). Improved methods of HIV prevention and control such as pre-exposure prophylaxis (PrEP), anti-retroviral therapy (ART) and even voluntary medical male circumcision (VMMC) are at the forefront of health policy recommendations(Joint United Nations Programme on HIV/AIDS (UNAIDS), 2014, endinghiv.org, 2019, Joint United Nations Programme on HIV/AIDS (UNAIDS), 2009, PrEP Watch, 2019). If these interventions are effectively implemented at the population level, they may substantially reduce HIV transmission and eventually end the HIV epidemic. Many modelling studies have attempted to quantify the impact of these interventions on HIV prevalence and related mortality in a range of settings(Mishra et al., 2012, Blower et al., 2003, Van der Ploeg et al., 1998, Vissers et al., 2011, Kaldor and Wilson, 2010, Herbeck et al., 2016).

HIV positivity has been linked to higher rates of human papillomavirus (HPV) acquisition, and, among those infected with HPV, the presence of HIV co-infection is known to reduce the likelihood of HPV clearance, regression of pre-cancerous lesions, and increase the risk of carcinogenesis(Liu et al., 2018). For this reason, modelling studies evaluating cervical cancer prevention policies are increasingly considering, either directly or indirectly, the impacts of endemic HIV in relevant settings(Campos et al., 2018, Tan et al., 2018, Van der Ploeg et al., 1998).

Methods of HIV control may have a substantial impact on prevalence and deaths due to HIV and HPV prevalence and, subsequently, cervical cancer incidence and mortality rates(Liu et al., 2018, Yuan et al., 2019). As the inner mucosal surface of the foreskin is highly susceptible to HIV infection, the removal of this vulnerable surface via circumcision reduces the risk of HIV acquisition(Szabo and Short, 2000). In particular, male circumcision has been shown to reduce the risk of HIV-1 acquisition in heterosexual men over a time period of 18-24 months by at least 60%, and reduce HPV prevalence among heterosexual men by 63%(Prodger and Kaul, 2017, Castellsague et al., 2002, Gray et al., 2007, Bailey et al., 2007, Auvert et al., 2005). Reduction in male HIV and HPV prevalence then results in women also experiencing less HIV and oncogenic HPV infection, and subsequently, less cervical cancer(Castellsague et al., 2002, Grund et al., 2017). A global ecological analysis classifying VMMC into high (>80%), intermediate (20-80%) and low (<20%) prevalence has reported that for each categorical shift in VMMC prevalence, cervical cancer

incidence was reduced by 3.65 (0.54-6.76) cases per 100,000 women per year(Drain et al., 2006).

The United Republic of Tanzania has a high burden of both HIV and cervical cancer. It is estimated that in 2018, 5.5% of Tanzanian women aged 15-49 years were living with HIV(UNAIDS, 2018b), while the incidence of cervical cancer was among the highest globally, at 59.1 cases diagnosed per 100,000 women (9,771 cervical cancers detected) in 2018(Bray et al., 2018). The 2018 incidence rates of cervical cancer in Southern Africa and Eastern Africa were 43.1 cases per 100,000 women per year, and 40.1 cases per 100,000 women per year, respectively(Bray et al., 2018). Tanzania is within the East and Southern African region, which in 2018 contained 53% of all people living with HIV globally and had an estimated HIV prevalence among adults aged 15-49 years of 7%(UNAIDS Joint United Nations Programme on HIV/AIDS, AVERT, 2019). The two main interventions against HIV currently in place in Tanzania are ART for HIV positive individuals and VMMC, which are both being actively scaled up(Ministry of Health et al., 2017); while the Tanzanian Ministry of Health recommends PrEP use for those at significant risk of HIV acquisition, scale-up of access to PrEP has been minimal(Ministry of Health, 2019). Considering Tanzania's high burden of cervical cancer and the known impact of HIV, it is important to assess the effect of HIV control interventions that are currently being scaled up (ART and VMMC) or considered (PrEP) on not only HIV incidence and prevalence, but also rates of cervical cancer incidence and mortality. While there exists significant variation in national laws pertaining to sexual identity and orientation, sex-work and access to contraception across the African continent affecting rates of sexually transmitted diseases(UNAIDS Joint United Nations Programme on HIV/AIDS), the relative impact of HIV interventions on cervical cancer incidence rates in Tanzania is likely to be broadly representative of the region.

Therefore, the aim of this analysis was to quantify the effect of HIV control actions to date on cervical cancer incidence and mortality in terms of cancer diagnoses and lives saved and to predict future cervical cancer incidence and mortality rates in Tanzania, in the context of scaled-up HIV control interventions.

Methods

Model overview and parameterisation

A detailed deterministic transmission-dynamic compartment model was developed to concurrently simulate the transmission and natural history of HIV, HPV 16/18, HPV 31/33/45/52/58 (referred to as HPV H5) and other oncogenic high-risk HPV (referred to as HPV OHR) in the United Republic of Tanzania. While there are a range of

transmission modalities for HIV and HPV, this platform simulates heterosexual transmission only (a simplifying assumption) as this is the dominant mode of transmission for both HIV and HPV in sub-Saharan Africa(Kharsany and Karim, 2016, Mbulawa et al., 2018). The platform can simulate dual HIV and HPV infections and infections with multiple HPV types, with and without ART. The model incorporates comprehensive demographic, sexual behaviour and natural history assumptions, and accounts for VMMC, ART and PrEP. The simulated population includes males, females, and a separate subgroup of female commercial sex workers (which females may be hired into or retire from), ages 5 to 79 years, stratified by sex, five-year age group, sexual activity level, HIV and HPV infection, and treatment status. This model is comprised of 9,644,670 compartments, where simulated populations move between the states described in Table 1. Note that some combination of attributes categorises all persons in the simulated population: sex/career, age, risk, HIV infection status and natural history, HIV treatment status (note that no HIV negative individuals are treated with the exception of PrEP which may be provided prophylactically for HIV prevention in HIV negative individuals only), HPV 16/18 infection status and natural history, HPV H5 infection status and natural history, HPV OHR infection status and natural history and cervical cancer detection status and treatment (note that only women can progress from HPV infections to cervical pre-cancer, and only women with cervical cancer may have cancer detected). It is essential here to note that the Tanzanian population size in 2018 was estimated to be 56,310,000(THE WORLD BANK, 2018); that this population is not evenly distributed throughout model compartments, with some compartments being functionally impossible to enter (e.g., cervical precancer and cancer in males) and others being highly populated (e.g., pre-sexual-debut males and females who are both HIV and HPV negative). The existence of functionally impossible compartments impacts computational efficiency by unnecessarily accounting for a proportion of available memory, however, contributes minimally to the CPU load as the model code was designed to avoid performing matrix operations on such compartments.

The entire simulated population, and defined compartments, was simulated using a multi-dimensional matrix representing the cartesian product of sets defined in Table 1. Movement between model compartments was simulated using a system of difference equations, defined bespoke for this model platform and implemented in MATLAB R2018b. The model was run on a four-core personal computer with a 3.40 GHz processor and 16GB of installed RAM. The current model implementation utilises a quarterly timestep (13 weeks). The majority of data informing HIV and HPV prevalence is, at best, annual and therefore, any reductions in step size could not provide any finer

degree of data fitting. In this case, the quarterly step-size was determined in consideration of the smallest necessary time increments driven by observed and estimated time-in-state for HIV and HPV disease stages, while balancing the requirement for run-time efficiency. This approach was validated by close model agreement with a range of observed data and compares well with similarly described models in the field (Tan et. al. 2018, van Schalkwyk et. al. 2021, chapter 5). Finally, we performed extensive sensitivity analysis on influential model parameters; with the net effect of varying state transition probabilities at this timescale is equivalent to investigating the impact of investigating the possible model sensitivity to step-size. The model was instantiated to the year 1960, and takes on average, 45 seconds to simulate one calendar year.

Table 1 Model compartments exist for the cartesian product of sets (A) to (I).

SEX/CAREER (A)	**AGE (YEARS) (B)**	**RISK (C)**	**HIV NATURAL HISTORY (D)**	**HIV ART STATUS (E)**	**HPV 16/18 NATURAL HISTORY (F)**	**HPV H5 NATURAL HISTORY (G)**	**HPV OHR NATURAL HISTORY (H)**	**CERVICAL CANCER DETECTION AND TREATMENT (I)**
Male	5-9	General population sexual activity	Immune (PrEP)	Untreated	Immune (HPV vaccine)	Immune (HPV vaccine)	Immune (HPV vaccine)	No cervical cancer detected
Female	10-14	Elevated sexual activity	Susceptible	ART (no viral suppression)	Susceptible	Susceptible	Susceptible	Symptomatically detected localised cervical cancer
Female sex-worker	15-19		Acute infection	ART (viral suppression)	HPV 16/18 infection	HPV 16/18 infection	HPV 16/18 infection	Symptomatically detected regional cervical cancer
	20-24		Stage 1 (WHO clinical)		CIN 1	CIN 1	CIN 1	Symptomatically detected distant cervical cancer
	…		Stage 2 (WHO clinical)		CIN 2	CIN 2	CIN 2	Screen detected localised cervical cancer

	60-64		Stage 3 (WHO clinical)		CIN 3	CIN 3	CIN 3	Screen detected regional cervical cancer
	65-69		Stage 4 / AIDS (WHO clinical)		Undetected localised cervical cancer	Undetected localised cervical cancer	Undetected localised cervical cancer	Screen detected distant cervical cancer
	70-74				Undetected regional cervical cancer	Undetected regional cervical cancer	Undetected regional cervical cancer	
	75-79				Undetected distant cervical cancer	Undetected distant cervical cancer	Undetected distant cervical cancer	

There are two classes of parameters used in the model: static parameters which were held constant over the entire simulated time horizon, and time-dependent parameters. The term ‘parameter set’ is used to define a parameter which varies over age and/or time. There are a total of 21 sets of parameters, which are described in detail in the upcoming subsections. Briefly, there are three parameter sets specified in the demography module, two of which are time-dependent reflecting year-on-year variation in fertility (annual) and mortality (age-specific and annual) rates and the other (sex ratio at birth) is static. There are ten parameter sets specifying sexual behaviour characteristics, with a mixture of static and time-dependent parameters. These are described at length in Table 2. Parameter sets informing stage-specific HIV transmission and type-specific HPV transmission (Tables 3 and 4) are static and based on scientific literature. Disease natural history is governed by three static parameter sets, namely, HIV progression and mortality (Table 5), HPV-type-specific progression/regression (Tables 13 and 14) and the impact of HIV on HPV natural history (Table 7). Finally, there are three time-dependent parameter sets which govern interventions of interest in this analysis: VMMC uptake, ART initiation and adherence, and PrEP uptake, which are described in Table 8. This constitutes a total 21 sets of parameters, which are described and justified in detail in the subsequent sections.

The input parameters are specified primarily using empirical data; however, some parameters, particularly those which are either unobservable or informed by survey data, were found through calibration using MATLAB’s inbuilt non-linear least-squares solver for data fitting called ‘lsqnonlin’ (trust-region reflective algorithm option). This algorithm was selected to leverage MATLAB’s pre-existing functionality, with the options readily amenable to the optimisation problem of minimising an objective function (weighted sum of squared differences between calibration targets and model output) in the context of biologically acceptable parameter upper and lower bounds. The parameter inputs found through calibration were sex-, age- and activity-group specific volumes of high-risk sexual contacts per timestep, the degree of age-assortative sexual mixing, annual fluctuations in population-level risk aversive behaviour, and the relative per-sex-act probability of HIV acquisition for females compared to males. These inputs were calibrated to estimated HIV prevalence over time and stratified sex and annual rates of new HIV infections obtained from UNAIDS(UNAIDS, 2018c, UNAIDS, 2018b, UNAIDS, 2018a). Note that different groupings in the age range of calibration/validation results are due to variation in reported age ranges in the observed data.

Demography

Population demography encompasses compartments for sex/career (male, female, commercial sex-worker), age (five-year age-groups from 5-9 to 75-79 years) and risk index (specify age- and sex-specific rates of propensity towards sexual risk-taking), and, the demography module simulates population ageing, recruitment, natural mortality and assigns risk groups. The youngest simulated age group is 5-9 years; therefore, recruitment represents the number of children born who survive to age five and accounts for the age- and year-specific fertility rates of the simulated female population, as well as infant mortality. The probability in each timestep of any individual ageing to the next five-year age group is calculated using the number of single-year ages, the age group, and the number of model iterations per year. For example, we assume that $\frac{1}{5}$ of individuals in the 10–14-year age group turn 15 in any given year, and since there are four timesteps simulated per year, the probability of ageing from the 10–14-year group to the 15–19-year group is $\frac{1}{5} \times \frac{1}{4} = 0.05$. In calculating recruitment rates, annual fertility rates (which follow changing fertility rates over time) were sourced from the World Bank using the median fertility variant(The World Bank, 2017a), whereas data on maternal age at birth was sourced from the United Republic of Tanzania Ministry of Finance and is based on the 2012 census(National Bureau of Statistics, 2015). The simulated population is then subject to an age-specific probability of death resulting from any cause other than HIV or cervical cancer (other cause mortality). Age-and-year-specific mortality rates (which vary by both age and year) are specified using the projected year-on-year life tables reported by the United Nations Population Division(United Nations Department of Economic and Social Affairs Population Division, 2019). Finally, the demography module redistributes the simulated population into two sex- and age-specific sexual activity groups (high-activity and general-activity) and simulates the recruitment of women into a career of commercial sex work and their eventual retirement. The initial age distribution is based on the 1960 Tanzanian population(United Nations DESA / Population Division, 2017), with a sex ratio of 1 male to 1.03 females based on data from the World Bank(The World Bank, 2017b).

Force of infection

The model simulates HIV and HPV transmission between sexual partners, including interactions between commercial sex workers (CSWs) and their male clients. The population is compartmentalised into ‘high activity’ and ‘general activity’ sexual activity groups which differ in their assumed number of sexual contacts per timestep; notably,

'high activity' and 'general activity' risk groups are assumed to mix freely (non-assortative). The number of sexual interactions per time-step implicitly accounts for new partners, the per-partner frequency of sex and relationship type (casual or monogamous). An age-dependent proportion of the female population is assumed to be CSWs, with an age-specific probability of seeking commercial sex defined for males. Furthermore, CSWs are assumed to engage in both personal and commercial sexual interactions, with a pre-defined age-specific client volume per timestep.

The sex- and age-specific per-timestep force of infection is calculated using age-specific partnership preferences, sexual activity group, HIV/HPV prevalence among sex partners, the per-sex-act probability of pathogen transmission (stratified by disease stage where applicable) and uptake of preventative interventions such as condom use (specified separately for commercial sex and general partnerships), voluntary medical male circumcision (VMMC) and anti-retroviral therapy (ART) use. For example, the force of infection for HIV for a male aged a in sexual activity group r at time t is calculated using equation (1).

$$\Lambda_M^{\mathrm{HIV}}(a,r,t) = c_M(a,r,t)\big(1-\kappa_{HIV}(t)\big)\big(1-\upsilon_{HIV}(t)\big)\times \sum_i\left(\sum_{Tx}\rho_M(a)\cdot T_{FM}^{HIV(Tx)}(i)I_F^{HIV(Tx)}(i,t)\right)+\lambda_M^{\mathrm{HIV}}(a,t) \quad (1)$$

$c_M(a,r,t)$ denotes the average number of sexual contacts assumed for a male aged a, in sexual-activity group r, at time t, $\kappa_{HIV}(t)$ denotes the per-sex-act probability that a condom is worn and prevents HIV acquisition, $\upsilon_{HIV}(t)$ denotes the probability that the male has undergone VMMC and the per-sex act-probability that this prevents HIV acquisition; i is the stage of HIV disease among potential female sex-partners; $T_{FM}^{HIV(Tx)}(i)$ is the HIV-stage-specific per sex-act female-to-male transmission probability for females with treatment status Tx; $\rho_M(a)$ is a vector of the distribution of preferences for female partners of each age-group for males aged a (vector over all ages summing to unity); $I_F^{HIV(Tx)}(i,t)$ is a vector specifying the age-specific probability of a female being HIV positive (simulated), stage i, and with treatment status Tx; $\lambda_M^{\mathrm{HIV}}(a,r,t)$ is the probability of acquiring a HIV infection from a commercial sex worker. Note that

$$\lambda_M^{\mathrm{HIV}}(a,r,t) = \varsigma_M(a,r,t)\big(1-\kappa_{HIV}(t)\big)\big(1-\upsilon_{HIV}(t)\big)\times \sum_i\left(\sum_{Tx}\rho_M(a)\cdot T_{FM}^{HIV(Tx)}(i)I_{CSW}^{HIV(Tx)}(i,t)\right) \quad (2)$$

where $\varsigma_M(a,r,t)$ denotes the average number of commercial sexual contacts assumed for a male aged a, in sexual risk group r, at time t; $\upsilon_{HPV}(t)$ denotes the probability that

the male has undergone VMMC and the per-sex act-probability that this prevents HIV acquisition; $I_{CSW}^{HIV(Tx)}(i,t)$ is a vector specifying the age-specific probability of a commercial sex worker is HIV positive, stage i and with treatment status Tx.

The HPV 16/18 force of infection for a high activity male aged a at time t is calculated in a similar way but simplified by the assumption that the probability of HPV transmission is fixed irrespective of HPV disease stage. That is,

$$\Lambda_M^{HPV_{1618}}(a,r,t) = c_M(a,r,t)\big(1-\kappa_{HPV}(t)\big)\big(1-\upsilon_{HPV}(t)\big)\times T_{FM}^{HPV_{1618}}\left(\rho_M(a)\cdot \mathrm{I}_{\mathrm{F}}^{\mathrm{HPV}_{1618}}(t)\right)+\lambda_M^{HPV_{1618}}(a,r,t) \quad (3)$$

where $\kappa_{HPV}(t)$ denotes the per-sex-act probability that a condom is worn and prevents HPV acquisition; $T_{FM}^{HPV_{1618}}$ is the per sex-act female-to-male HPV16/18 transmission probability; $I_F^{HPV_{1618}}(t)$ is a vector specifying the age-specific probability of a female being HPV 16/18 positive; and $\lambda_M^{HPV_{1618}}(a,r,t)$ is given by:

$$\lambda_M^{HPV_{1618}}(a,r,t) = \varsigma_M(a,r,t)\big(1-\kappa_{HPV}(t)\big)\big(1-\upsilon_{HPV}(t)\big)\times T_{FM}^{HPV_{1618}}\left(\rho_M(a)\cdot \mathrm{I}_{\mathrm{CSW}}^{\mathrm{HPV}_{1618}}(t)\right). \quad (4)$$

Following on from the calculation of the force of infection for HIV and HPV 16/18, the HPV H5 and HPV OHR forces of infection for high activity males age a and time t are calculated using equations (5) to (8). Recall that HPV H5 refers to HPV types 31, 33, 45, 52 and 58, whereas HPV OHR refers to all oncogenic HPV types excluding HPV 16/18 and HPV H5. Therefore,

$$\Lambda_M^{HPV_{H5}}(a,r,t) = c_M(a,r,t)\big(1-\kappa_{HPV}(t)\big)\big(1-\upsilon_{HPV}(t)\big)\times T_{FM}^{HPV_{H5}}\left(\rho_M(a)\cdot \mathrm{I}_{\mathrm{F}}^{\mathrm{HPV}_{H5}}(t)\right)+\lambda_M^{HPV_{H5}}(a,r,t) \quad (5)$$

where

$$\lambda_M^{HPV_{H5}}(a,r,t) = \varsigma_M(a,r,t)\big(1-\kappa_{HPV}(t)\big)\big(1-\upsilon_{HPV}(t)\big)\times T_{FM}^{HPV_{H5}}\left(\rho_M(a)\cdot \mathrm{I}_{\mathrm{CSW}}^{\mathrm{HPV}_{\mathrm{H5}}}(t)\right) \quad (6)$$

and

$$\Lambda_M^{HPV_{OHR}}(a,r,t) = c_M(a,r,t)\big(1-\kappa_{HPV}(t)\big)\big(1-\upsilon_{HPV}(t)\big)\times T_{FM}^{HPV_{OHR}}\left(\rho_M(a)\cdot \mathrm{I}_{\mathrm{F}}^{\mathrm{HPV}_{OHR}}(t)+\lambda_M^{HPV_{OHR}}(a,r,t)\right) \quad (7)$$

where

$$\lambda_M^{HPV_{OHR}}(a,r,t) = \varsigma_M(a,r,t)\big(1-\kappa_{HPV}(t)\big)\big(1-\upsilon_{HPV}(t)\big)\times T_{FM}^{HPV_{OHR}}\left(\rho_M(a)\cdot \mathrm{I}_{\mathrm{CSW}}^{\mathrm{HPV_{OHR}}}(t)\right). \quad (8)$$

Here, $T_{FM}^{HPV_{H5}}$ and $T_{FM}^{HPV_{OHR}}$ are per sex-act female-to-male HPV H5 and HPV OHR transmission probabilities, and $I_F^{HPV_{H5}}(t)$ and $I_F^{HPV_{OHR}}(t)$ are vectors specifying the age-specific probability of a female being HPV H5 and HPV OHR positive, respectively.

We can define the force of infection for females similarly for males, except that we have no need to account for the protective effects of VMMC, and we instead consider HIV acquisition among commercial sex workers from their male clients. Therefore, we define the force of HIV, HPV16/18 and HPV OHR infection in females as follows:

$$\Lambda_F^{\mathrm{HIV}}(a,r,t) = c_F(a,r,t)\big(1-\kappa_{HIV}(t)\big)\times \sum_i\left(\sum_{Tx}\rho_F(a)\cdot T_{MF}^{HIV(Tx)}(i) I_M^{HIV(Tx)}(i,t)\right) + \lambda_F^{\mathrm{HIV}}(a,t) \quad (9)$$

where

$$\lambda_F^{\mathrm{HIV}}(a,r,t) = \varsigma_F(a,r,t)\big(1-\kappa_{HIV}(t)\big)\times \sum_i\left(\sum_{Tx}\rho_F(a)\cdot T_{MF}^{HIV(Tx)}(i) I_{Client}^{HIV(Tx)}(i,t)\right), \quad (10)$$

$$\Lambda_F^{HPV_{1618}}(a,r,t) = c_F(a,r,t)\big(1-\kappa_{HPV}(t)\big)\times T_{MF}^{HPV_{1618}}\left(\rho_F(a)\cdot \mathrm{I}_M^{\mathrm{HPV_{1618}}}(t)\right) + \lambda_F^{HPV_{1618}}(a,r,t) \quad (11)$$

where

$$\lambda_F^{HPV_{1618}}(a,r,t) = \varsigma_F(a,r,t)\big(1-\kappa_{HPV}(t)\big)\times T_{MF}^{HPV_{1618}}\left(\rho_F(a)\cdot \mathrm{I}_{Client}^{\mathrm{HPV_{1618}}}(t)\right), \quad (12)$$

$$\Lambda_F^{HPV_{H5}}(a,r,t) = c_F(a,r,t)\big(1-\kappa_{HPV}(t)\big)\times T_{MF}^{HPV_{H5}}\left(\rho_F(a)\cdot \mathrm{I}_M^{\mathrm{HPV_{H5}}}(t)\right) + \lambda_F^{HPV_{H5}}(a,r,t) \quad (13)$$

where

$$\lambda_F^{HPV_{H5}}(a,r,t) = \varsigma_F(a,r,t)\big(1-\kappa_{HPV}(t)\big)\times T_{MF}^{HPV_{H5}}\left(\rho_F(a)\cdot \mathrm{I}_{Client}^{\mathrm{HPV_{H5}}}(t)\right), \quad (14)$$

and finally,

$$\Lambda_F^{HPV_{OHR}}(a,r,t) = c_F(a,r,t)\big(1-\kappa_{HPV}(t)\big)\times$$
$$T_{MF}^{HPV_{OHR}}\left(\rho_F(a)\cdot \mathrm{I}_M^{\mathrm{HPV}_{OHR}}(t) + \lambda_F^{HPV_{OHR}}(a,r,t)\right) \quad (15)$$

where

$$\lambda_F^{HPV_{OHR}}(a,r,t) = \varsigma_F(a,r,t)\big(1-\kappa_{HPV}(t)\big)\times$$
$$T_{MF}^{HPV_{OHR}}\left(\rho_F(a)\cdot \mathrm{I}_{Client}^{\mathrm{HPV}_{\mathrm{OHR}}}(t)\right). \quad (16)$$

Model input parameter assumptions specific to sexual behaviour and force of infection are summarised in Table 2. We additionally define the following equations, which are referred to in Table 2:

$$y = \lambda e^{-\left(\frac{x-\mu}{\sigma}\right)^2}, \quad (17)$$

$$y = \frac{a_1 x - a_2}{b_1 x^2 - b_2 x + b_3}. \quad (18)$$

Table 2 Model parameters relating to sexual behaviour in Tanzania.

Parameter Description	**Parameter Value**	**Data Source and/or Rationale**
Commercial sex worker population size and distribution. Used to calculate $\varsigma_M(a,r,t)$.	1% of females aged 15-54 are sex workers. These 1% are broken down into the following age-groups: 36% of CSW are aged 15-24 years, 40% are 25-34 years, 22% are 35-49 years and 2% are 50-54 years.	The total CSW population size is based on UNAIDS 2018 update (UNAIDS estimate of 155,450 CSWs in 2014)(UNAIDS, 2018e). The age distribution of CSW's is based on the NACP report on Female Sex Workers in Dar es Salaam (2010)(United Republic of Tanzania Ministry of Health and Social Welfare National AIDS Control Programme (NACP), 2012).
Age-specific per timestep CSW client volume. Used to calculate $\varsigma_M(a,r,t)$.	Normally distributed around a mean age of 39 for female sex workers aged 15-49 years. Defined by equation (17) where	This is based on the age-distributions provided in the NACP report on FSW in Dar es Salaam, in addition to qualitative data which indicates that on average, Tanzanian FSWs have 26 clients

Parameter Description	Parameter Value	Data Source and/or Rationale
	x is equal to the youngest age in each specified age group. Here, $\lambda_{CSW} = 20$, $\mu_{CSW} = 39$ and $\sigma_{CSW} = 42$.	per month, as reported in qualitative data(United Republic of Tanzania Ministry of Health and Social Welfare National AIDS Control Programme (NACP), 2012, Research International (on behalf of T-MARC), 2009).
Age-specific per-timestep probability of a male paying for commercial sex	Specified by equation (18) for males aged 15 years and over where x is equal to the youngest age in the specified age group, and $a_1 = 0.5294$, $a_2 = 7.608$, $b_1 = 1$, $b_2 = 23.34$ and $b_3 = 153.6$.	This was based on fitting the age-specific probability of a male having paid for sex in the last 12 months, as published in the 2007-08 HIV/AIDS and Malaria indicator survey(Tanzania Commission for AIDS (TACAIDS) et al., 2008).
Probability of condom usage for commercial sex interactions	Specified by equation (18) where x is equal to the calendar year (for 1993 onwards), and $a_1 = 1.01$, $a_2 = 2016$, $b_1 = 0$, $b_2 = 1$ and $b_3 = 1987$.	Parameter equation specified to fit survey data on condom use among commercial sex interactions(Tanzania Commission for AIDS (TACAIDS) et al., 2008, Tanzania Commission for AIDS (TACAIDS) et al., 2013, Ministry of Health et al., 2016).
Age-specific probability of males being in the high-activity sexual activity group	The age-specific probability of a male being in the high-activity groups are as follows: 15-19 years: 0.05 20-24 years: 0.13 25-44 years: 0.12 45+ years: 0.03	Specified for consistency with the observed data(Munguti et al., 1997). The 'high-activity' group is equivalent to having 5+ sexual partners in a 12-month period as published in Munguti et al.

Parameter Description	Parameter Value	Data Source and/or Rationale
Age-specific probability of females being in the high-activity sexual activity group (excludes commercial sex workers).	The age-specific probability of a female being in the high-activity groups are as follows: 15-24 years: 0.03 25+ years: 0.01	Specified for consistency with the observed data(Munguti et al., 1997). Note that the probability of being in the high-risk sexual activity group for females aged 25 years and over was modified from zero to one percent. The 'high-activity' group is equivalent to having 5+ sexual partners in a 12-month period as published in Munguti et al.
Volume of sexual interactions possibly resulting in HIV transmission per timestep for high-activity males and females $c_M(a,1,t)$ and $c_F(a,1,t)$. NB $r = 1$ for high-activity individuals.	Normally distributed around a mean age of 30 for males and 17 for females. Defined by equation (17) where x is equal to the youngest age in each specified age group. For males: $\lambda_{HAM} = 162$, $\mu_{HAM} = 30$ and $\sigma_{HAM} = 19$. And for females: $\lambda_{HAF} = 294$, $\mu_{HAF} = 17$ and $\sigma_{HAF} = 6$. Note that λ_{HAM} and λ_{HAF} are varied in sensitivity analysis.	Determined via calibration algorithm.
Volume of sexual interactions possibly resulting in HIV transmission per timestep for general-	Normally distributed with mean age of 30 for males and 28 for females. Defined by equation (17) where	Determined via calibration algorithm.

Parameter Description	Parameter Value	Data Source and/or Rationale
activity males and females $c_M(a,0,t)$ and $c_F(a,0,t)$. NB $r = 1$ for general-activity individuals.	x is equal to the youngest age in each specified age group. For males: $\lambda_{GAM} = 9.45$, $\mu_{GAM} = 30$ and $\sigma_{GAM} = 12$. And for females: $\lambda_{GAF} = 9.50$, $\mu_{GAF} = 28$ and $\sigma_{GAF} = 6.8$. Note that λ_{GAM} and λ_{GAF} are varied in sensitivity analysis.	
Probability of condom use for non-commercial sex interactions and condom efficacy.	Specified by a smoothed piece-wise linear interpolant from 0 in 1993, to 0.55 in 2011, to 0.37 in 2016 and constant thereafter. Therefore $\kappa_{HIV}(t) = p_{CUse}$ and $\kappa_{HPV}(t) = p_{CUse} \times 0.46$ for males and $\kappa_{HPV}(t) = p_{CUse} \times 0.3$ for females.	Specified to fit survey data on condom use among non-commercial sex interactions(Kapiga and Lugalla, 2003, Adair, 2008, Tanzania Commission for AIDS (TACAIDS) et al., 2008, Tanzania Commission for AIDS (TACAIDS) et al., 2013, Ministry of Health et al., 2016, Reynolds et al., 2012).
Year-specific reduction in the number of high-risk sexual interactions among both sexes and all activity groups. Parameter reflects nationwide behavioural change	Specified by equation s13 where x is equal to the calendar year between 1995 and 2010, and $\lambda_{SB} = 0.5$, $\mu_{SB} = 2002$, $\sigma_{SB} = 8$. From 2010 onwards, this function is set to	Determined via calibration algorithm. This parameter reflects the behavioural change in Tanzania in response to public fear of HIV infection at the peak of the AIDS epidemic.

Parameter Description	Parameter Value	Data Source and/or Rationale
in response to the HIV epidemic.	a constant value of 0.05.	

For each female age group, the age distribution of male partners is determined by the probability density function of the Poisson distribution over a maximum of five age groups (her current age group and the four groups above her, if possible), with a Poisson parameter decreasing linearly with age from a maximum of 1.5 (i.e., this is an average of 7.5 years older than the female age) to 0. This assumption was based on observed data indicating that males tend to have sex with females younger than themselves, and determines $\rho_M(a)$ and $\rho_F(a)$ used to calculate force of infection(Munguti et al., 1997).

Model input parameters for the per-sex-act HIV transmission probability is given in Table 3. These parameters reflect the variability in the probability of transmission among HIV discordant couples, depending on the stage of disease of the HIV positive partner. The stage-specific per-contact transmission probabilities were based on observed data(Quinn et al., 2000).

Table 3 Stage-specific per-contact probability of HIV transmission.

	Acute infection	WHO clinical stage 1	WHO clinical stage 2	WHO clinical stage 3	WHO clinical stage 4 (AIDS)
Transmission multipliers which operate on base HIV transmission probability (0.0006)[+]	$T_{FM}^{HIV(0)}(1) = 0.0006 \times 7$	$T_{FM}^{HIV(0)}(2) = 0.0006$	$T_{FM}^{HIV(0)}(3) = 0.0006 \times 5.8$	$T_{FM}^{HIV(0)}(4) = 0.0006 \times 6.8$	$T_{FM}^{HIV(0)}(5) = 0.0006 \times 11.8$

[+]*Note that these probabilities are for female to male transmission; for male to female transmission, we note that* $T_{MF}^{HIV(Tx)} = 2.5\ T_{FM}^{HIV(Tx)}$*; the probabilities assume no ART treatment* ($Tx = 0$)*. For contacts with treated individuals* ($Tx = 1$) *we assume that the transmission probability is reduced by 96%.*

HPV type-specific per sex-act transmission probabilities are given in Table 4. These values were found through calibration and are consistent with estimates that the probability of HPV transmission among discordant general partnerships is 20% over a six-month period(Burchell et al., 2011).

Table 4 Transmission probabilities per sex-act for HPV 16/18, HPV H5 and HPV OHR

Parameter*	**Value**	**Probability of transmission over a six-month period⁺**
HPV 16/18 transmission probability per high-risk-sex-act $T_{FM}^{HPV_{1618}}$	0.0560	46% - 76%
HPV H5 transmission probability per high-risk-sex-act $T_{FM}^{HPV_{H5}}$	0.0123	14% - 47%
HPV OHR transmission probability per high-risk sex-act $T_{FM}^{HPV_{OHR}}$	0.0179	19% - 57%

* Note that $T_{FM}^{HPV} = T_{MF}^{HPV}$ for all HPV types. ⁺*Calculated for males and females in the general activity group assuming condom use and efficacy (46% for males and 30% for females) as observed in 2011; ranges provided reflect variation in sexual frequency due to age; number included for comparison with Burchell et al 2011 (Burchell et al., 2011).*

Disease natural history

Disease progression for HIV infection is governed by the following state diagram (Figure 1), where specific progression rates are dependent on the current stage of disease and treatment status.

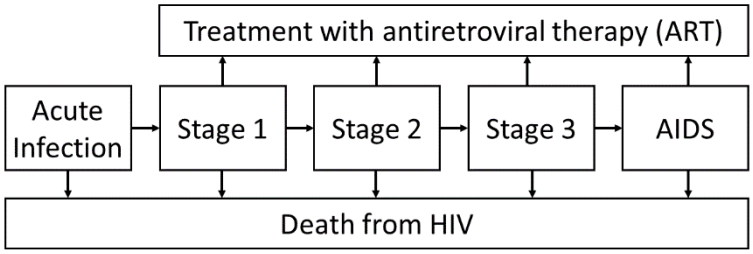

Figure 1 State-space diagram for HIV disease progression. Note that we assume viral suppression halts disease progression and that all states are subject to other cause mortality.

The natural history of HIV infection is assumed to progress from acute HIV infection through four clinical disease stages. These stages align with the World Health

Organisation (WHO) 'Clinical Staging of HIV/AIDS for Adults and Adolescents' and are defined in terms of patient symptoms(Weinberg and Kovarik, 2010). Input parameters specifying HIV progression rates in the model are described in Table 5.

Table 5 Average length of time spent in each disease stage, and the probability of HIV-death for each HIV disease stage.

	Acute infection	**WHO clinical stage 1**	**WHO clinical stage 2**	**WHO clinical stage 3**	**WHO clinical stage 4 (AIDS)**
Average length of time spent in HIV disease stage(Palk et al., 2018).	< 3 months	1 year 6 months	1 year 3 months	6 years 6 months	1 year 3 months
Per-timestep probability of HIV-death while in each disease stage for ages 15-49 years and ages 50+, respectively+(Tan et al., 2018).	3%, 5%	0.2%, 0.5%	0.4%, 0.4%	1%, 2%	14%, 27%

+The per-timestep probability of HIV death was derived from absolute stage-specific HIV mortality rates and necessarily accounts for the average time-in-state for clinical HIV disease stages and other competing risks.

The model platform accounts for the detailed and well-understood natural history of HPV. Disease progression and regression for HPV infection is governed as per Figure 2, where specific progression rates are dependent on HPV type, age, disease stage, HIV positivity and ART treatment status. HPV types 16 and 18 are more aggressive than other oncogenic HPV types, with elevated disease progression rates and suppressed regression rates. Women with an HIV co-infection also experience more aggressive HPV infections; however, viral suppression through ART can help mitigate this(Liu et al., 2018). The model contains interacting compartments for all of HPV susceptibility, infection, and natural history states. These stages are described in Table 6, and their interactions are summarised in Figure 2, which describes the state transitions possible from each state at the start of a new timestep, including the case where no state transition is made.

Table 6 List and description of HPV transmission and natural history compartments.

Compartment name	**Description**
Vaccinated	Vaccinated individuals are unable to become infected with HPV.
Susceptible	Individuals are recruited into this compartment and are susceptible to HPV infection.
Naturally immune	Once clearing an HPV infection, some individuals retain temporary natural immunity.
HPV infected	Susceptible individuals may become infected with HPV. Initial model conditions specify a small number of HPV infected individuals to start the simulation.
CIN 1	Cervical intraepithelial neoplasia (abbreviated as CIN) stage 1 is a low-grade pre-cancerous lesion.
CIN 2	CIN stage 2 is a high-grade pre-cancerous lesion.
CIN 3	CIN stage 3 is a high-grade pre-cancerous lesion.
Localised cervical cancer (undetected)	Localised cervical cancer (undetected) is the early-stage cervical cancer state.
Localised cervical cancer (detected)	Women with detected cancer (any stage) are not explicitly subject to disease progression or regression. Women with detected cancer (any stage) are subjected to a probability of cervical cancer mortality, which increases with stage, and which removes them from the model; alternatively, they may survive their disease.
Regional cervical cancer (undetected)	Regional cervical cancer (undetected) is the mid-stage cervical cancer state.
Regional cervical cancer (detected)	See localised cervical cancer (detected).
Distant cervical cancer (undetected)	Distant cervical cancer (undetected) is the late-stage cervical cancer state (cancer has metastasised and has a low survival probability).
Distant cervical cancer (detected)	See localised cervical cancer (detected).

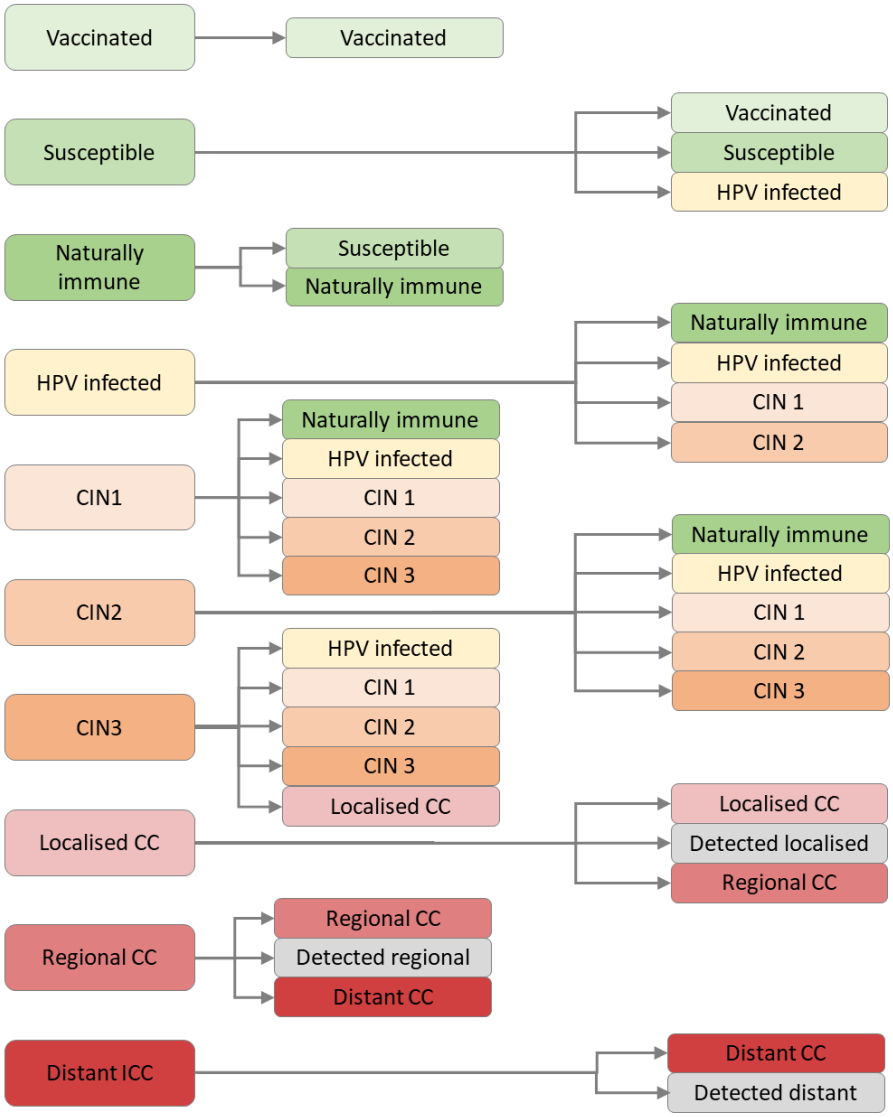

Figure 2 State-space diagram for the natural history of HPV and cervical cancer carcinogenesis; note that all compartments are subject to natural mortality and detected cancer (grey) compartments are subject to stage-specific cervical cancer mortality or survival; CIN = cervical intraepithelial neoplasia; cervical cancer = cervical cancer.

The natural history of human papillomavirus infection is explicitly simulated for HPV types 16, 18, the HPV types included in the 9-valent vaccine (31/33/45/52/58 abbreviated as HPV H5) and other oncogenic HPV types (abbreviated as HPV OHR). The stage-, age- and HPV type-specific progression and regression rates have been adapted from previous analyses and reproduced in the section titled 'Additional tables' (Table 13, Table 14)(Tan et al., 2018). HIV positivity status and viral suppression through ART are both assumed to affect HPV acquisition and natural history;

assumptions regarding the impact of HIV positivity on HPV natural history are summarised in Table 7.

Table 7 HPV-type specific multipliers for eventual risk of acquisition, progression and regression of HPV associated disease for HIV positive individuals(Liu et al., 2018).*

Parameter description	**Parameter value[+]**
Multiplier increasing HPV acquisition for HIV positive individuals	2.75 (1.17-2.75)
Clearance of an HPV infection (no CIN)	0.6
Progression from HPV infection to CIN1	3.73 (2.62-3.73)
Progression from HPV infection to CIN2	1.3 (1.1-1.33)
Regression from CIN1 to clearance or HPV infected	0.7 (0.56-0.7) for HIV 16/18 0.67 (0.56-0.67) for all other HPV types.
Regression from CIN2/3 to clearance, HPV infection or CIN1	0.57 (0.26-0.57)
Progression from CIN3 to invasive cervical cancer	2.5 (2.3-2.5)

**Ranges specified are those considered in the sensitivity analysis. For more information is contained in the section titled 'Sensitivity analysis'. [+]Note that these parameters are the same for all HPV types except where otherwise stated.*

Interventions

The model accounts for the impact of a range of HIV control interventions, including uptake of ART, PrEP, VMMC, and behavioural factors, including the use of condoms. Effective use of ART in an individual infected with HIV not only acts to reduce disease progression and HIV death but also significantly reduces the infectivity of virally suppressed patients. Further, PrEP, VMMC and condoms all lower the probability of acquisition to varying degrees. VMMC is specified by year, with rates reported in the literature and Tanzanian DHS reports and explicitly described in the footnote to Table 8(The United Republic of Tanzania Ministry of Health and Social Welfare, 2013, Forbes et al., 2012, Ministry of Health et al., 2016). The circumcision rate is applied to males of all ages and reduces female to male transmission by 63%, consistent with the available evidence(World Health Organisation (WHO), 2020b).

ART is considered in two categories: those receiving ART, and those receiving ART who are 'virally suppressed'. The model assumes some mortality benefit for all individuals receiving ART; however, viral suppression is assumed to halt disease progression and/or HIV death completely and reduces infectivity by 96%(Tan et al.,

2018). The percentage of people living with HIV in Tanzania who are virally suppressed is assumed to match rates published in 2018 by UNAIDS(UNAIDS, 2018d).

Scenarios and outcomes

A range of counterfactual and potential future HIV epidemic control scenarios were simulated, as described in Table 8. For each scenario, we estimate cervical cancer incidence and cervical cancer mortality (stratified by HIV positivity) from 1995-2020 and project these outcomes from 2020 to 2070. The absolute numbers of cervical cancer cases and deaths prevented by interventions to 2020 are presented, in addition to an age-standardised rates. Here, the age-standardised rate (ASR) is a weighted mean of the age-specific rates where weights (summing to one) are derived from the estimated world female population(United Nations DESA / Population Division, 2017), and is presented per 100,000 women.

Table 8 Modelled scenarios of HIV control.

Scenario name and description	**VMMC assumptions $v(t)$[1]**	**ART assumptions[2]**	**PrEP assumptions**
No interventions. This is an exploratory worst-case counterfactual scenario.	No VMMCs carried out.	No ART uptake.	No PrEP offered.
VMMC only. This is an exploratory pessimistic counterfactual scenario.	VMMC is as historically observed and is maintained at 80% from 2018 onwards.	No ART uptake.	No PrEP offered.
VMMC and ART (baseline). This scenario is the baseline scenario and reflects the current situation in Tanzania.	VMMC is as historically observed and is maintained at 80% from 2018 onwards.	The proportion of people living with HIV who are receiving ART and virally suppressed is as historically observed and is	No PrEP offered.

Scenario name and description	VMMC assumptions $v(t)$[1]	ART assumptions[2]	PrEP assumptions
		maintained at 47% from 2018 onwards.	
VMMC and target ART. This is an exploratory optimistic scenario.	VMMC is as historically observed and is maintained at 80% from 2018 onwards.	The proportion of people living with HIV who are receiving ART, and virally suppressed, is as historically observed but assumes this is scaled up from 47% in 2018 to meet WHO '90-90-90' targets[3] in 2020 and onwards.	No PrEP offered.
VMMC, target ART and PrEP. This is an exploratory best-case scenario.	VMMC is as historically observed and is maintained at 80% from 2018 onwards.	The proportion of people living with HIV who are receiving ART and virally suppressed is as historically observed and is scaled up from 47% in 2018 to meet WHO '90-90-90' targets in 2020 (onwards).	Daily PrEP use for offered to women engaging in commercial or transactional sex and their clients (90% uptake, 99% efficacy) from 2020.

[1]VMMC, as historically observed, assumes 8% VMMC (or traditional circumcision where applicable) until 1995, after which it increased to 23% in 1998 and then increases quadratically to 80% in 2015 as observed(The United Republic of Tanzania Ministry of Health and Social Welfare, 2013, Ministry of Health et al., 2016). [2]ART, as historically observed, assumes the introduction of ART in 2005, with a linear scale-up to 47% virally suppressed in 2017(UNAIDS, 2018d). [3] The 90-90-90 targets refer to the global goal of achieving the following: 90% of all people living with HIV know their HIV status, 90% of all people diagnosed with HIV receive sustained ART, and 90% of all people receiving HIV achieve viral suppression(UNAIDS, 2017).

Sensitivity analysis (methods)

A multivariate sensitivity analysis was carried out to assess the robustness of model outcomes with variation in a range of parameters. The parameters selected for sensitivity analysis are those which are difficult to observe/report on, those to which the model is suspected to be sensitive, and parameters directly affecting the interventions assessed in the scenario analysis. The modelled effect of HIV control interventions is dependent on assumptions about the magnitude of their effectiveness. The literature indicates uncertainty surrounding the effect of VMMC, ART and PrEP(Castellsague et al., 2002, Tobian et al., 2014, Minkoff et al., 2010, Liu et al., 2018, Anderson et al., 2012). Furthermore, any population- or individual-level behavioural change driven by implementing these interventions is challenging to quantify as perceptions of risk are constantly changing; however, evidence suggests that the availability and uptake of HIV control interventions may facilitate an increase in risky sexual practices to the order of up to 20%(Ramchandani and Golden, 2019, Hoornenborg et al., 2019, Chen et al., 2002, Dukers et al., 2001, Katz et al., 2002, Scheer et al., 2001). A Latin hypercube sampling (LHS) analysis of 6,000 possible parameter sets was utilised (200 simulations for each of 30 varied parameters), the values of which are described in Table 9.

Table 9 Parameter values considered in Latin hypercube sampling analysis and the rationale for selecting these parameters/ranges. Parameters are described in Table 2.

Parameter	**Value ranges in the sensitivity analysis**	**Rationale**
Volume of sexual interactions possibly resulting in HIV transmission per timestep for high- and general activity males and females. The parameters varied are $c_M(a,r,t)$ and $c_F(a,r,t)$.	The age-specific volumes are each varied by $\pm 5\%$ of the baseline value. The baseline value for these parameters is specified in Table 2.	The selected variation is sufficient to assess the model's sensitivity to these parameters while not producing excessive variation in simulation outcomes.
Age-assortative mixing. The parameter varied is λ_{max}.	The maximum Poisson parameter λ_{max} is varied over a range $\lambda_{max} = 1.5\ (1.4, 1.6)$.	This is based on observed data indicating that males tend to mate with females younger than

Parameter	Value ranges in the sensitivity analysis	Rationale
		themselves(Munguti et al., 1997).
The relative risk of HIV acquisition per sexual contact for females compared to males. The parameter varied is p_f.	The multiplier p_f was found to be 2.5 through calibration and is varied between 2.2 and 2.8 for the sensitivity analysis.	Based on observed data(Quinn et al., 2000).
Stage-specific per-contact probability of HIV transmission	Multipliers against the base HIV transmission probability: Multiplier for 'WHO clinical stage 2' (p_2)= 4.3 (2.25, 17.91) Multiplier for 'WHO clinical stage 3' (p_3)= 6.5 (2.93, 19.97) Multiplier for 'WHO clinical stage 4' (p_4)= 8.7 (5.28, 36.99)	Ranges are derived from confidence intervals given in Quinn et al. (Quinn et al., 2000).
HPV-type specific multipliers for acquisition, progression and regression of HPV associated disease for HIV positive individuals.	The ranges considered here are as described in Table 7.	Ranges are considered in sensitivity analysis are as published(Liu et al., 2018).
Type-specific HPV transmission probabilities per sex act.	$T_{FM}^{HPV_{1618}} = 0.056 - 0.078$ $T_{FM}^{HPV_{H5}} = 0.0134 - 0.0448$ $T_{FM}^{HPV_{OHR}} = 0.0202 - 0.056$ Where $T_{FM}^{HPV} = T_{MF}^{HPV}$ for all HPV types.	The selected variation is sufficient to assess the model's sensitivity to these parameters while not producing excessive variation in simulation outcomes.
Per sex-act reduction in HPV acquisition risk for	Relative risk reduction assumed in sensitivity	Based on the result of a pooled study which

Parameter	Value ranges in the sensitivity analysis	Rationale
circumcised males (compared to uncircumcised males).	analysis: 0.16 – 0.85 (0.63 assumed at baseline).	indicated circumcised men are 37% (95% CI: 16%-85%) less likely to have an HPV infection than uncircumcised men(Castellsague et al., 2002).
Per sex-act reduction in HIV acquisition risk for circumcised males (compared to uncircumcised males).	Relative risk reduction assumed in sensitivity analysis: 0.53 – 0.6 (0.6 assumed at baseline).	Based on the result of a study which indicated that circumcised men are 60% (53%-60%) less likely to acquire an HIV infection than uncircumcised men.(Tobian et al., 2014)
Impact of viral suppression through ART on HPV persistence and natural history among HIV infected women.	Baseline scenario: ART reduces additional risk of HPV/pre-cancer progression due to HIV positivity by 50%. Sensitivity analysis: ART reduces additional risk of HIV/pre-cancer progression by 0-100%. The specific values of multipliers specifying progression/regression of HPV related disease in HIV positive women compared to HIV negative women are outlined in Table 7.	A study comparing relative risk of HPV acquisition among virally suppressed women with those not receiving ART found that ART decreased HPV incidence (OR 0.64; 95% CI 0.46-0.88), but that this was not the case for high-risk HPV (OR 0.62; 95% CI 0.38-1.02)(Minkoff et al., 2010). Another study found that women receiving ART are at lower LSIL risk (RR 0.67; 95% CI 0.45-1), and were 2.29 times more likely to regress from LSIL (95% CI 1.56-3.37)(Liu et al., 2018). Overall, a systematic review and

Parameter	Value ranges in the sensitivity analysis	Rationale
		meta-analysis by Liu et al reported that the impact of ART on HPV-related disease is unclear(Liu et al., 2018).
Per sex-act reduction in HIV acquisition for daily PrEP users compared to non-PrEP users.	Baseline relative risk reduction: 0.99. Range assumed in sensitivity analysis: 0.92 – 0.99.	The iPrEx study found that PrEP can reduce HIV risk by 92%-99% for daily use among HIV-negative individuals(Anderson et al., 2012).
Population-level behavioural change (i.e., disinhibition) resulting from uptake/availability of HIV control.	Condom usage from 1990 to 2016 is as reported in Table 2 and reflects observed usage in Tanzania, with the assumption that a condom was used in 37% of all high-risk interactions from 2016 onwards. In sensitivity analysis we consider variation in condom use from 2020 onwards, and the percentage of all high-risk interactions where a condom is used varies uniformly in the interval 32-42%.	A range of studies have found that availability of HIV control interventions ART and PrEP can facilitate behavioural disinhibition where risk behaviour is increased in a population(Ramchandani and Golden, 2019, Hoornenborg et al., 2019, Chen et al., 2002, Dukers et al., 2001, Katz et al., 2002, Scheer et al., 2001).

Results

Calibration and validation

Simulations from the calibrated model were consistent with observed HIV-specific outcomes, including male and female HIV prevalence, total HIV incidence and number

of HIV deaths (Figure 3), in addition to age-specific 2018 cervical cancer incidence and age-specific 2018 cervical cancer mortality rates (Figure 4).

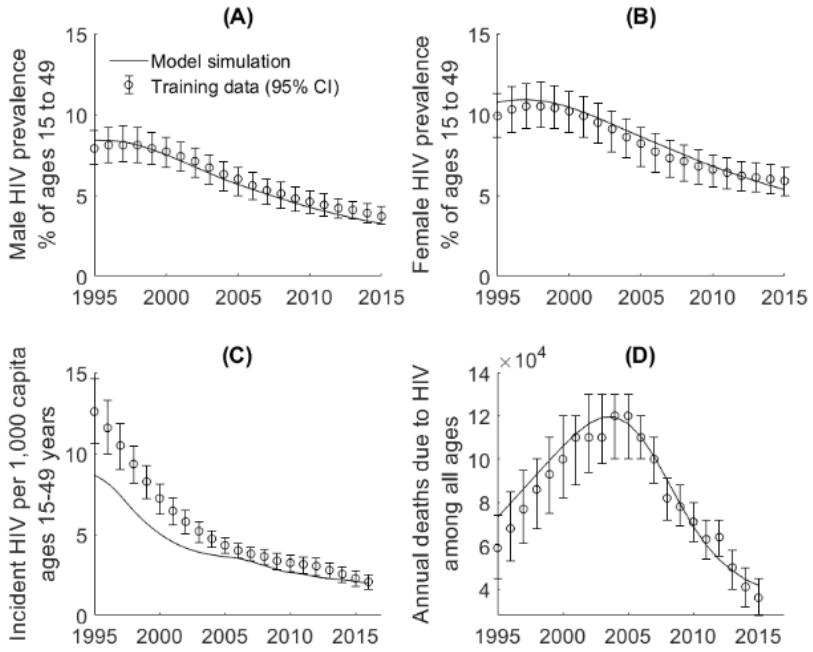

Figure 3 Calibrated HIV outcomes. (A) and (B): male and female HIV prevalence from 1995 to 2015; (C) HIV incidence from 1995 to 2015; (D) the number of HIV deaths from 2015 to 1995. Error bars are 95% CI of observed data. Training data sourced from UNAIDS(UNAIDS, 2018c, UNAIDS, 2018b) (UNAIDS, 2018a) (UNAIDS, 2018e).

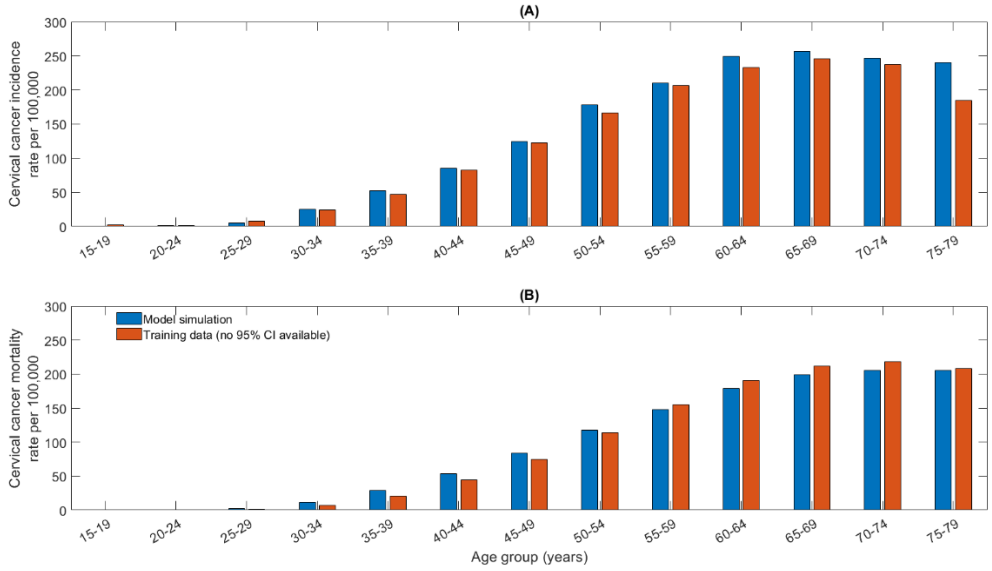

Figure 4 (A) Calibrated age-specific cervical cancer incidence and (B) mortality for the year 2018 compared to estimated data sourced from the International Agency for Research on Cancer IARC(Bray et al., 2018).

Following the model calibration procedure, where parameters were chosen such that the model was a good fit to UNAIDS and Globocan (IARC) data(UNAIDS, 2018c, UNAIDS, 2018b, UNAIDS, 2018a, Bray et al., 2018), the model was validated against independent datasets. These include sex- and age-specific HIV prevalence (Figure 5 A-B) and the sex-specific age distribution of age at AIDS diagnosis (Figure 5 C-D), and age-specific HPV prevalence (Figure 6) and the prevalence of HSIL (high-grade squamous intra-epithelial lesion; considered equivalent to a diagnosed CIN 2/3) prevalence among HIV negative versus positive women (Figure 7) from the PROTECT study(Dartell et al., 2012).

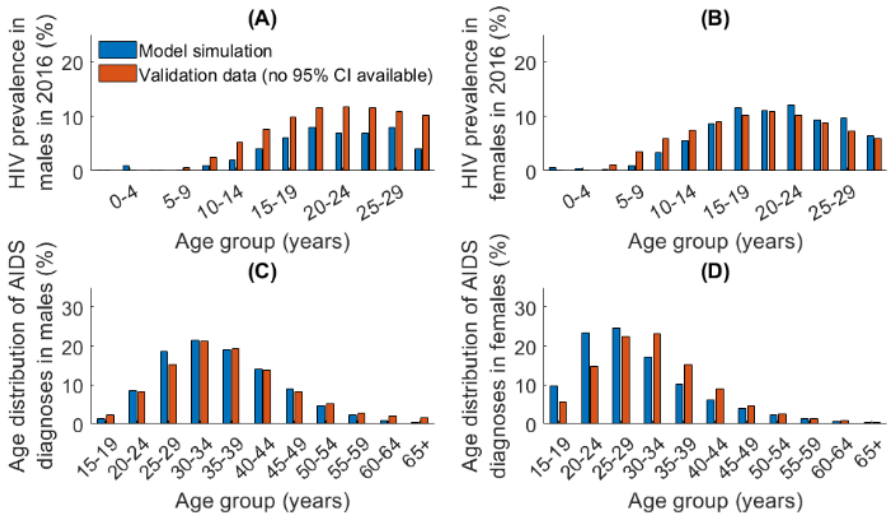

Figure 5 (A) and (B): age-specific HIV prevalence for males and females in 2016 compared to observed data; Figure 5 (C) and (D): Age distribution of AIDS diagnoses for males and females in 2011 compared to observed data. Observed data from the Tanzanian Ministry of Finance (no confidence intervals available)(Ministry of Health et al., 2017, Tanzania Commission for AIDS (TACAIDS) et al., 2013).

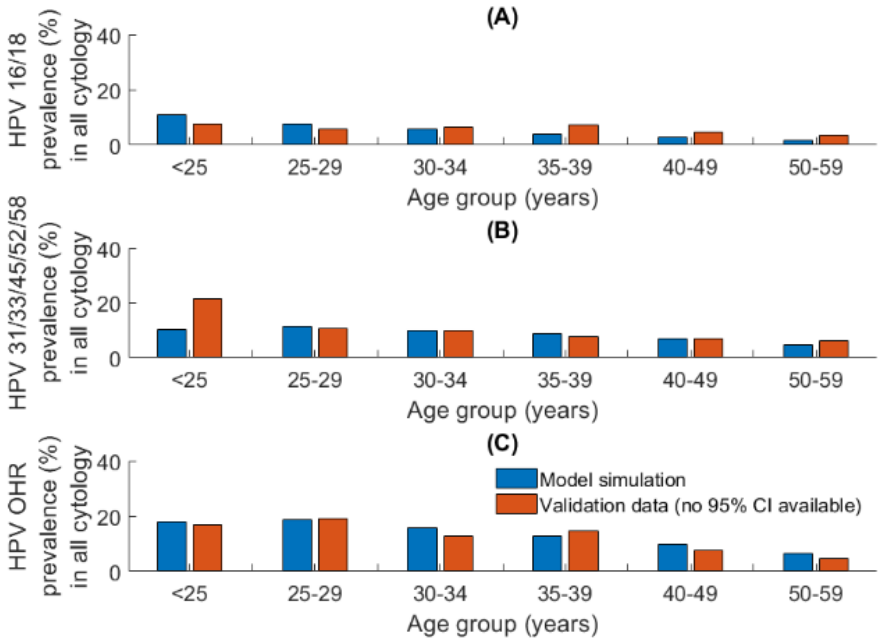

Figure 6 age-specific HPV prevalence in cervical cytology (all cytological results) of (A) HPV 16/18, (B) HPV H5 and (C) HPV OHR compared to observed data. Observed data from Dartell et al. 2012 (no confidence intervals available)(Dartell et al., 2012).

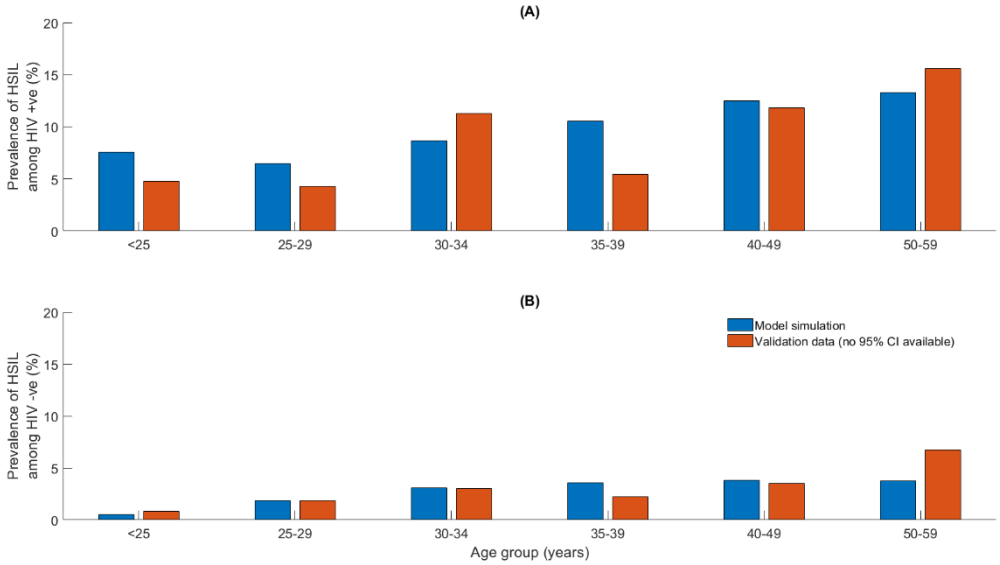

Figure 7 Age-specific rates of HSIL (detected high-grade squamous intraepithelial lesion consistent with CIN2/3) prevalence for (A) HIV positive and (B) HIV negative women. Observed data from Dartell et al. 2012 (no confidence intervals available)(Dartell et al., 2012).

Scenario analysis

It is estimated that there will be 2,843 (and 1,039) fewer cervical cancer cases (and deaths), and 33,648 fewer total deaths (HIV and cervical cancer combined) from 1995 to 2020 because of the introduction and scale-up of VMMC. Assuming VMMC is maintained at 2018 levels, by 2070, VMMC is expected to have averted 330,400 (and 186,260) cervical cancer cases (and deaths) and save 3.47 million lives (HIV and cervical cancer combined) (Table 10; Figure 8 B and D). ART use to date is predicted to lead to an additional 1,573 (and 1,222) cervical cancer cases (and deaths) from 1995-2020; this is due to ART reducing the competing risk of mortality due to HIV. The cumulative number of deaths averted by ART is predicted to reach 2,253,700 by 2070 and prevent 52,430 (and 16,390) additional cervical cancer cases (and deaths) by 2070 (Table 10; Figure 8 B and D).

Table 10 Number of prevented cervical cancer cases (and deaths) due to VMMC and ART (incremental benefit of each intervention). Negative values denote additional cases/deaths.

	Prevented by VMMC	**Prevented by ART**
Cervical cancer cases (deaths) prevented cumulatively from 1995 to 2020	2,843 (1,039)	-1,573 (-1,221)
Deaths due to HIV or cervical cancer prevented cumulatively from 1995 to 2020	33,648	147,262
Cervical cancer cases (deaths) prevented cumulatively from 1995 to 2070	330,400 (186,260)	52,430 (16,390)
Deaths due to HIV or cervical cancer prevented cumulatively from 1995 to 2070	3,469,800	2,253,700

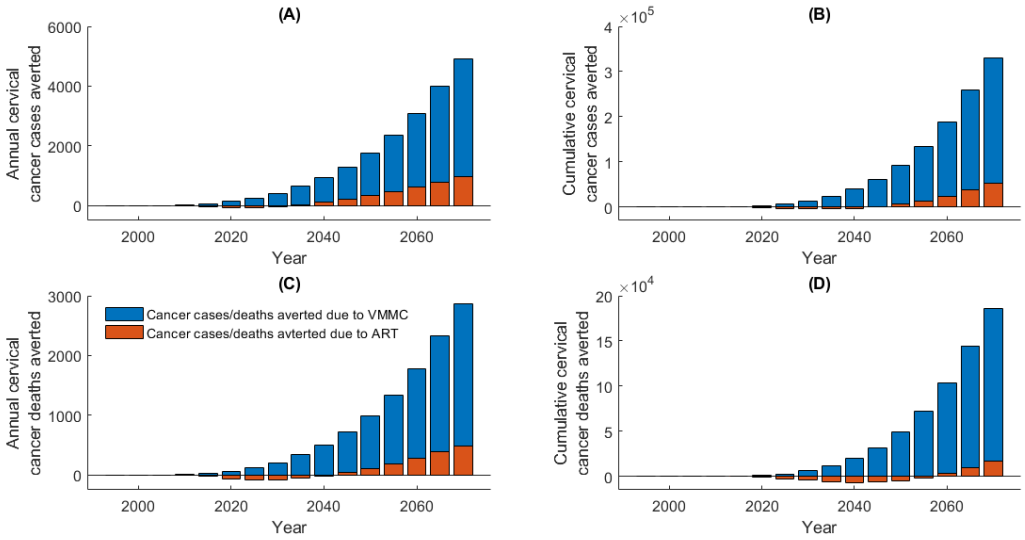

Figure 8 A: annual cervical cancer cases averted due to VMMC and ART (negative values under ART denote additional cases rather than cases averted). B: cumulative cervical cancer cases averted due to VMMC and ART. C: annual cervical cancer

deaths averted due to VMMC and ART. D: cumulative cervical cancer deaths averted due to VMMC and ART.

VMMC is predicted to substantially reduce both HPV and HIV prevalence in Tanzanian men and women (Table 11). By 2070, VMMC is predicted to reduce HPV prevalence in men and women by 28% (44.71% under 'No interventions' to 32.13% under 'VMMC only' in 2070) and 17% (46.39% under 'No interventions' to 38.59% under 'VMMC only'), respectively. Similarly, the estimated reduction in HIV prevalence due to VMMC is 75% (7.59% under 'No interventions' to 1.86% under 'VMMC only') and 71% (8.47% under 'No interventions' to 2.46% under 'VMMC only'), respectively, for men and women. Compared to the 'No intervention' scenario, the introduction and scale-up of ART and PrEP are estimated to reduce HIV prevalence in men and women by ~99% (to 0.05% in males and 0.11% in females in 2070.

Table 11 Simulated HPV and HIV prevalence for males and females in 2070 (and 2020) under five scenarios. Note that intervention start-year occurs pre-2020 for simulated interventions.

	HPV prevalence in 2070 (2020 value)		**HIV prevalence in 2070 (2020 value)**	
	Males	*Females*	*Males*	*Females*
No interventions	44.71% (47.43%)	46.39% (49.42%)	7.59% (5.22%)	8.47% (6.07%)
VMMC only	32.13% (34.43%)	38.56% (42.45%)	1.86% (3.19%)	2.46% (4.89%)
VMMC and ART (baseline)	31.9% (34.38%)	38.28% (42.3%)	0.41% (2.57%)	0.59% (4.24%)
VMMC and target ART	31.85% (34.38%)	38.22% (42.3%)	0.12% (2.57%)	0.19% (4.24%)
VMMC, target ART and PrEP	31.83% (34.38%)	38.2% (42.3%)	0.05% (2.57%)	0.11% (4.24%)

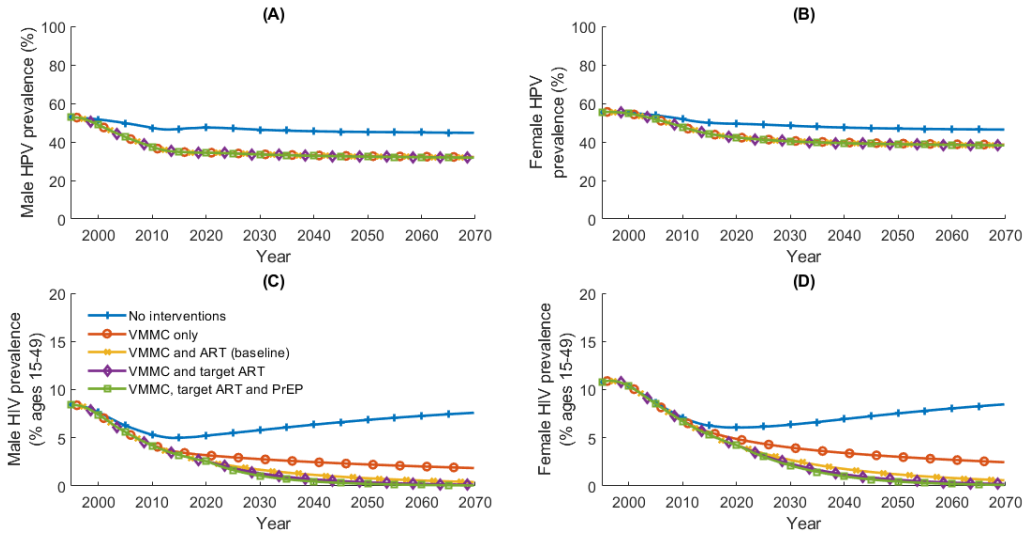

Figure 9 A: Male HPV prevalence; B: male HIV prevalence; C: female HPV prevalence; D: female HIV prevalence from 1995 to 2070 under five intervention scenarios.

The introduction and scale-up of HIV preventions are predicted to reduce the age-standardised rates of cervical cancer incidence and mortality over time. VMMC is expected to reduce cervical cancer incidence and mortality rates by 36-40% in 2070 compared to 2020 rates (under 'VMMC and ART (baseline)' scenario), whereas the provision and scale-up of ART to meet World Health Organisation 90-90-90 targets reduce cervical cancer incidence and mortality rates by 41-45% in 2070 compared to the current rates in 2020. Absolute rates of cervical cancer incidence and mortality are presented in Table 12. Here, we note that the reductions in cervical cancer incidence and mortality due to ART among all women are driven by reductions among HIV positive women.

Table 12 Simulated cervical cancer incidence and mortality rates per 100,000 women per year for all women (and stratified by HIV positivity) in 2070 (and 2020) under five scenarios. Rates are standardised to the WFP2015 population(United Nations DESA / Population Division, 2017).

	Cervical cancer incidence in 2070 (2020 value)			**Cervical cancer mortality in 2070 (2020 value)**		
	All women	*HIV negative women*	*HIV positive women*	*All women*	*HIV negative women*	*HIV positive women*

No interventions	55.11 (64.39)	40.52 (44.69)	269.89 (291.46)	37.31 (41.99)	28.43 (29.7)	182.27 (198.01)
VMMC only	39.93 (63)	35.04 (42.99)	256.25 (286.92)	27.72 (41.47)	24.61 (28.91)	176.04 (197.85)
VMMC and ART (baseline)	37.31 (65.42)	35.17 (42.99)	220.23 (288.57)	26.44 (43.27)	24.68 (28.88)	168.01 (204.14)
VMMC and target ART	36.28 (65.42)	35.19 (42.99)	208.82 (288.57)	25.72 (43.27)	24.7 (28.88)	166.81 (204.14)
VMMC, target ART and PrEP	35.82 (65.42)	35.2 (42.99)	192.9 (288.57)	25.35 (43.27)	24.71 (28.88)	158.74 (204.14)

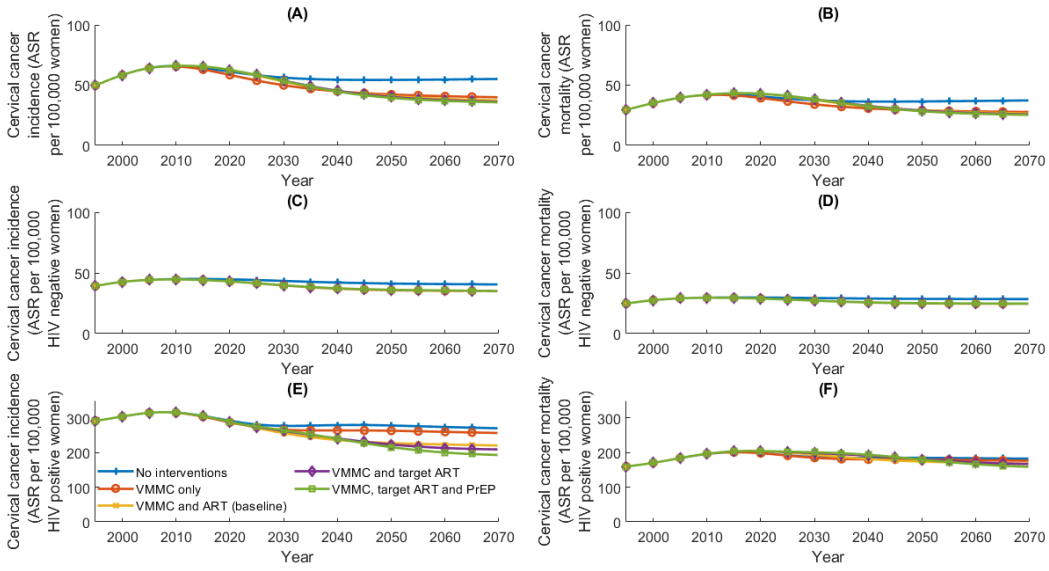

Figure 10 A Age-standardised cervical cancer incidence and B: mortality rates among all women aged 0-99 years. C: cervical cancer incidence and D: mortality rates among HIV negative women aged 0-99 years. E: cervical cancer incidence and F: mortality rates among HIV positive women aged 0-99 years. Age-standardised rates are calculated using the 2015 World Female Population(United Nations DESA / Population Division, 2017).

Sensitivity analysis (results)

The multivariate sensitivity analysis indicates that the findings of this analysis are highly sensitive to variation in the following parameters specifying sexual behaviour, disease transmission and natural history, and intervention effectiveness. Figure 11 summarises the baseline and total variation in endpoint predictions for all simulated outcomes over the five intervention scenarios.

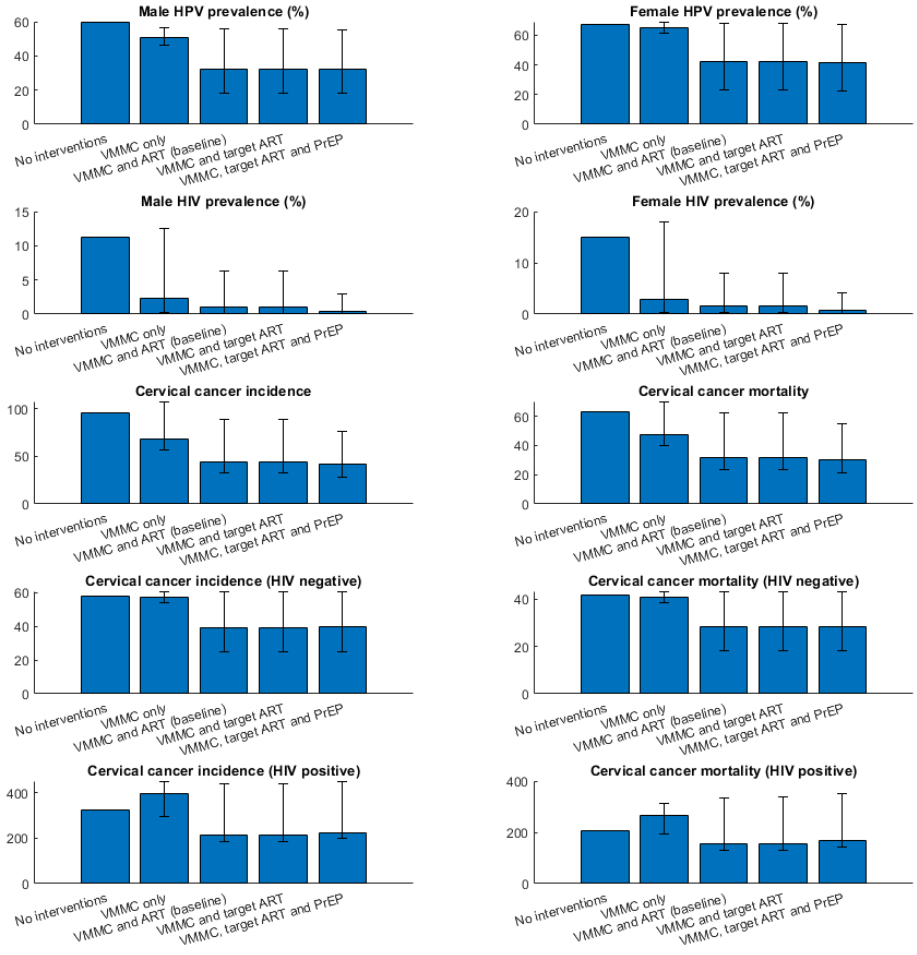

Figure 11 (A) and (B): male and female HPV prevalence; (C) and (D) male and female HIV prevalence; (E) and (F) cervical cancer incidence and mortality among all women; (G) and (H) cervical cancer incidence and mortality among HIV negative women; (I) and (J) cervical cancer incidence and mortality among HIV positive women, simulated in the year 2070 (error bars correspond to the total variation generated by the sensitivity analysis).

An analysis of partial rank correlation coefficients indicates that cervical cancer incidence is most strongly correlated with VMMC efficacy for HPV prevention

(correlation coefficient: 0.25; Figure 12), followed by VMMC efficacy for HIV prevention (correlation coefficient: 0.13).

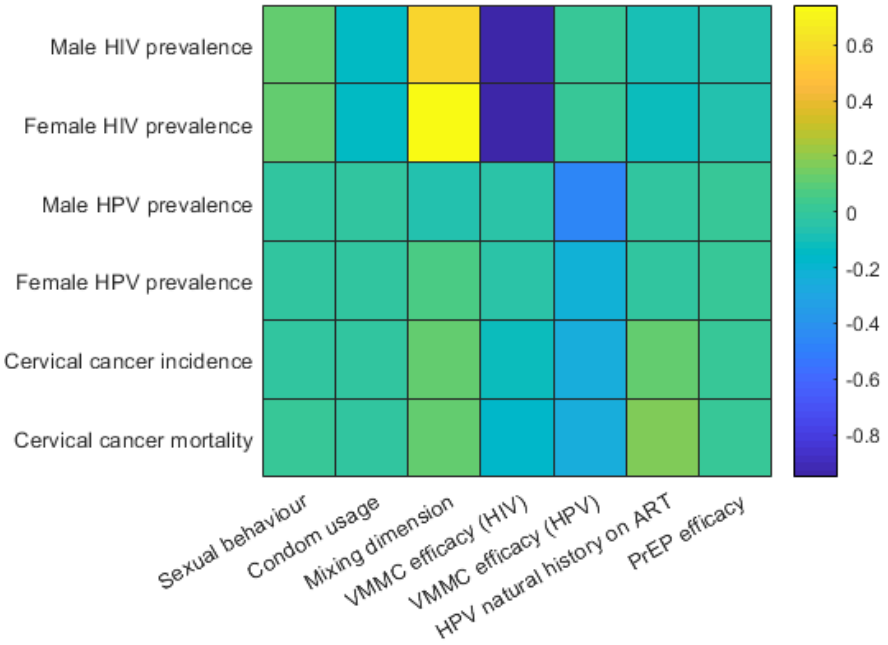

Figure 12 Correlation strength of selected outputs (HPV and HPV prevalence for males and females, and cervical cancer incidence and mortality) and parameters varied in the multivariate sensitivity analysis. Partial rank correlation analysis was performed on the 'VMMC, target ART and PrEP' scenario, as it is the only scenario to assessing all modelled interventions.

Discussion

This novel analysis is the first to estimate the impact over time of changing VMMC prevalence, ART utilisation and PrEP uptake on cervical cancer in any setting; and findings from this analysis are likely to be broadly applicable to other low-income settings with high HIV prevalence and cervical cancer incidence rates, particularly in sub-Saharan Africa. These HIV control interventions were found to substantially impact cervical cancer incidence and mortality in Tanzania. Using a simulation model of HIV and HPV transmission to estimate cervical cancer cases, cervical cancer deaths and total deaths (including HIV deaths) in Tanzania from 1995 to 2070 in the context of currently implemented HIV control measures, we estimated that VMMC has prevented 2,843 cervical cancer cases and 1,039 cervical cancer deaths from 1995 to 2020. Perhaps a less intuitive finding is that, while the addition and scale-up of ART in HIV-positive women reduce both overall HIV and HPV prevalence (women effectively treated with ART are less likely to acquire HPV and more likely to clear an HPV

infection than their untreated counterparts), ART is expected to result in some 1,573 additional cervical cancer diagnoses and 1,221 additional cervical cancer deaths, cumulatively, from 1995 to 2020. These additional cases and deaths are among HIV infected women and are caused by the removal of HIV-related death as a competing risk, as some women who would have otherwise died from HIV-related causes develop cervical cancer and subsequently die from it in the absence of scaled-up cervical cancer prevention. In the longer-term, the protective effect of ART prevails, as scale-up to meet World Health Organisation 90-90-90 targets would result in cervical cancer incidence and mortality rates that are 43% (37.31 c.f. 65.42 cases per 100,000 women per year) and 39% (26.44 c.f. 43.27 deaths per 100,000 women per year) lower, respectively, in 2070 compared to the current rates in 2020.

The model prediction for HIV prevalence over time is consistent with empirical data for Tanzania(UNAIDS, 2018b, UNAIDS, 2018c), and future predictions are broadly consistent with the findings from HIV modelling studies specific to sub-Saharan Africa(Hontelez et al., 2013). A comparative modelling study utilising predictions from four independent models predicts that under a scenario assuming universal HIV testing and treatment (up to 90% coverage), HIV prevalence will be reduced to 0-3% in sub-Saharan Africa in 2050. The current analysis predicts that HIV prevalence in Tanzania in 2050 will be 0.12% in males and 0.19% in females aged 15-49 years in the 'VMMC and target ART' scenario. In addition to this, predicted HPV prevalence in males (35.4% in 2017) under the 'VMMC and ART (baseline)' scenario showed relatively consistent agreement with an observed HPV prevalence in South Africa in 2017 of 40%(Mbulawa et al., 2017), and, predictions published by another modelling group(Tan et al., 2018). Similarly, Tan et al. predict that the cervical cancer incidence rates in KwaZulu Natal women will be ~31 cases per 100,000 among HIV negative women in 2070 and ~145 cases per 100,000 among HIV positive women(Tan et al., 2018). For Tanzania, this analysis predicts 35.17 cases per 100,000 women among HIV negative women and 220.23 cases per 100,000 among HIV positive women under the 'VMMC and ART (baseline)' scenario in 2070. For both analyses, the cervical cancer incidence rate in HIV positive women is approximately five times higher than the rate among HIV negative women.

The dynamic and highly detailed nature of the HIV and HPV co-infection model is a strength of this study. The model is stratified by sex, age, sexual activity (including women engaging in transactional or commercial sex), HIV positivity (including disease stage and treatment status) and HPV positivity (including disease stage/detection status) for multiple HPV types; which allows exploration of disease transmission and

progression dynamics in detail, accounting for herd protective effects and the protective effects of ART. This platform was extensively calibrated to high quality data including HIV incidence, prevalence and mortality data prepared and published by UNAIDS, and informed by routine data collected by the Tanzanian Ministry of Health(UNAIDS, 2018e), and, cervical cancer incidence and mortality rates published by the International Agency for Research on Cancer (IARC) which are informed by patient data from the Ocean Road Cancer Institute, a tertiary hospital in Tanzania specialising in cancer care(Bray et al., 2018). By performing a separate comparison to external data, including AIDS diagnoses from DHS reports, and HPV and precancer prevalence from cross-sectional studies, not only is the model validated, but the perceived quality of the combined data is increased(Tanzania Commission for AIDS (TACAIDS) et al., 2013, Dartell et al., 2012).

This analysis was limited by the inherent uncertainty surrounding input parameter assumptions, particularly sexual behaviour assumptions, including condom usage, which has been the focus of widespread public campaigns throughout sub-Saharan Africa. Due to the uncertainty surrounding underlying consistent condom use, the standalone impact of this intervention is difficult to quantify. Additionally, in many settings which have implemented specific HIV control, a reduction in safe sex practices and an increase in other sexually transmitted infections is often observed(Ramchandani and Golden, 2019, Hoornenborg et al., 2019, Chen et al., 2002, Dukers et al., 2001, Katz et al., 2002, Scheer et al., 2001). A recent study into the sexual behaviour of PrEP users in Amsterdam found that daily PrEP use among HIV negative men who have sex with men (MSM) was associated with a 2-9% increase in condomless sex acts(Hoornenborg et al., 2019). Another study has reported a 21% increase in risky sexual practice, and an increase in HIV incidence, among the San Franciscan MSM population since the advent of ART(Katz et al., 2002). Sensitivity analysis findings indicate that HPV and HIV prevalence and cervical cancer incidence and mortality are highly sensitive to variations in condom usage; therefore, if condom usage trends over time vary, model predictions could substantially under-estimate or over-estimate disease burden. The model used for this analysis simulates disease at the national scale, averaging sub-national variation in attitudes towards risk and access to HIV control interventions. Tanzanian HIV prevalence and access to health services varies considerably by province(Runge et al., 2019, Kim et al., 2019). As infection rates for HIV and HPV are driven down, this geographical heterogeneity may substantially impact real-world disease transmission dynamics.

A number of simplifying assumptions were also made regarding the effect of ART on HPV natural history in HIV positive women; we assume that ART affects all HPV types to the same degree and that commencing ART has the same effect on HPV natural history regardless of CD4+ count or HIV disease stage. Furthermore, the HIV transmission component of this model accounts for heterosexual transmission only, which is based on the assumption that the impact of HIV transmitted via sexual contact between men, and injection drug use, has negligible impacts on cervical cancer in women. Cervical cancer is an AIDS-defining disease; therefore, there is a degree of uncertainty surrounding the true cervical cancer mortality rates in Tanzania, that is, whether a cervical cancer death in an HIV positive woman was attributed to cervical cancer or HIV(World Health Organization, 2013). The grouping of many individual HPV genotypes in the model, for example, HPV 16/19, HPV 31/33/45/52/58 (HPV H5) and a category for “other high-risk HPV types”, may impact the overall simulated HPV prevalence in addition to the overall transmission dynamics of the model. For example, in this model, it is impossible to discern whether individuals are infected with only one or any combination of the HPV genotypes in each simulated HPV subgroup, which may result in an overestimation of the effectiveness of interventions targeted at HPV reduction. Finally, the findings of this study must be interpreted in the context of the lengthening life expectancy in Tanzania. Due to reductions in HIV mortality in addition to other-cause mortality (e.g. driven by improvements in sanitation and health care), the life expectancy at birth is expected to rise to 75 years in 2065-2070 (compared to 54 years in 1995-2000)(United Nations Department of Economic and Social Affairs Population Division, 2019); this necessarily results in an increased opportunity to develop cervical cancer (and other diseases), irrespective of additional effects due to HIV treatment.

In November 2020, the World Health Organisation released their global strategy for the elimination of cervical cancer as a public health problem, which defines that cervical cancer is eliminated as a public health problem when all countries achieve an incidence rate of fewer than four cases per 100 000 women per year.(World Health Organisation, 2020) To achieve this target, the WHO recommends that each country implement HPV vaccination programmes whereby 90% of girls are vaccinated by the age of 15, organised cervical screening programmes whereby 70% of women are screened at least twice per lifetime, and effective management of 90% of women diagnosed with invasive cervical cancer(World Health Organisation (WHO), 2020a). While VMMC and ART can reduce the burden of cervical cancer in Tanzania in the long term, they are not sufficient to bring cervical cancer incidence beneath the

threshold (ASR <4 per 100,000 women) proposed by the WHO for cervical cancer elimination. Our finding that even under the best-case scenario, the rate of cervical cancer incidence in all Tanzanian women is not reduced below 35 cases per 100,000 women per year (more than eightfold higher than the elimination threshold). This persistently high cervical cancer incidence rate demonstrates the importance and urgency of scaling up cervical cancer prevention programs, such as HPV vaccination and cervical screening, as well as HIV control, in order to avoid the situation that lives saved from HIV-related death are instead lost to cervical cancer. The WHO call for global action to eliminate cervical cancer as a public health problem is an important opportunity to galvanise and unite efforts to prevent cervical cancer in Tanzania and globally.

Additional tables

The natural history transition probabilities for HPV infection are adapted from previously published models (see Tan et al 2018 supplementary appendix Table S25 a)(Tan et al., 2018).

Table 13 Per-timestep disease transition probabilities for HPV 16/18 infections and associated disease, by age, in HIV negative women.

Age	From HPV infected to:					From CIN 1 to:					From CIN 2 infected to:					From CIN 3 to:					
	Well+	HPV	CIN 1	CIN 2	CIN 3	Well+	HPV	CIN 1	CIN 2	CIN 3	Well+	HPV	CIN 1	CIN 2	CIN 3	Well+	HPV	CIN 1	CIN 2	CIN 3	Undet ICC
10-14	0.2013	0.035	0.05 69	0.01 71	0	0.06 84	0.00 56	0.28 44	0.00 88	0.00 88	0.06 79	0.00 66	0.02 38	0.16 13	0.03 69	0	0	0.01 34	0.00 97	0.5	0
15-19	0.2013	0.035	0.05 69	0.01 71	0	0.06 84	0.00 56	0.28 44	0.00 88	0.00 88	0.06 79	0.00 66	0.02 38	0.16 13	0.03 69	0	0	0.01 34	0.00 97	0.5	0
20-24	0.2013	0.03 49	0.05 69	0.01 71	0	0.06 84	0.00 56	0.28 43	0.00 88	0.00 88	0.06 79	0.00 66	0.02 38	0.16 13	0.03 69	0	0	0.01 34	0.00 97	0.5	0.001
25-29	0.13 81	0.12 22	0.03 12	0.00 68	0	0.06 84	0.00 56	0.27 67	0.01 02	0.01 02	0.06 79	0.00 66	0.02 38	0.13 52	0.05 32	0	0	0.01 34	0.00 97	0.5	0.0014
30-34	0.13 81	0.12 14	0.03 12	0.00 68	0	0.06 84	0.00 56	0.27 51	0.01 02	0.01 02	0.06 79	0.00 66	0.02 38	0.13 43	0.05 32	0	0	0.01 34	0.00 97	0.5	0.0033
35-39	0.13 81	0.12 46	0.03 12	0.00 34	0	0.06 84	0.00 56	0.27 19	0.01 02	0.01 02	0.06 79	0.00 66	0.02 38	0.11 83	0.06 46	0	0	0.00 56	0.00 97	0.5	0.0033
40-44	0.12 1	0.14 03	0.03 12	0.00 34	0	0.06 84	0.00 56	0.26 63	0.01 02	0.01 13	0.06 79	0.00 66	0.02 38	0.11 67	0.06 46	0	0	0.00 56	0.00 38	0.5	0.0063
45-49	0.10 52	0.16 89	0.02 41	0.00 17	0	0.06 84	0.00 56	0.25 27	0.01 36	0.01 13	0.06 79	0.00 66	0.02 38	0.10 5	0.07 23	0	0	0.00 56	0.00 38	0.5	0.0063
50-54	0.09 06	0.18 97	0.03 62	0.00 25	0	0.06 84	0.00 56	0.25 44	0.02 04	0.01 69	0.06 79	0.00 66	0.02 38	0.10 6	0.10 85	0	0	0.00 56	0.00 28	0.5	0.0095

55-59	0.077	0.2114	0.041	0.0029	0	0.0684	0.0056	0.2554	0.0232	0.0191	0.0679	0.0066	0.0238	0.098	0.1363	0	0	0.0056	0.0028	0.5	0.015
60-64	0.0642	0.2344	0.0458	0.0032	0	0.0684	0.0056	0.2561	0.0259	0.0214	0.0679	0.0066	0.0238	0.0983	0.1523	0	0	0.0019	0.0019	0.5	0.0168
65-69	0.0642	0.2358	0.0506	0.0035	0	0.0684	0.0056	0.2576	0.0286	0.0236	0.0679	0.0066	0.0238	0.0909	0.1852	0	0	0.0019	0.0019	0.5	0.0186
70-74	0.0642	0.2341	0.0554	0.0039	0	0.0684	0.0056	0.2557	0.0314	0.0259	0.0679	0.0066	0.0238	0.0899	0.2028	0	0	0.0019	0.0019	0.5	0.0203
75-79	0.0642	0.2279	0.0603	0.0042	0	0.0684	0.0056	0.2699	0.0341	0.0281	0.0679	0.0066	0.0238	0.0783	0.2408	0	0	0.0019	0.0009	0.5	0.0253
80-84	0.0642	0.2153	0.0241	0.0017	0	0.0684	0.0056	0.2352	0.0136	0.0113	0.0679	0.0066	0.0238	0.071	0.0963	0	0	0.0019	0.0009	0.5	0.0101

[+] *Well refers to the per-timestep probability of clearance of HPV infection or CIN.*

Table 14 Per-timestep disease transition probabilities for high-risk HPV not 16/18 infections and associated disease, by age, in HIV negative women.

Age	From HPV infected to:					From CIN 1 to:					From CIN 2 infected to:					From CIN 3 to:					
	Well[+]	HPV	CIN 1	CIN 2	CIN 3	Well[+]	HPV	CIN 1	CIN 2	CIN 3	Well[+]	HPV	CIN 1	CIN 2	CIN 3	Well[+]	HPV	CIN 1	CIN 2	CIN 3	Undet ICC
10-14	0.3298	0.012	0.0334	0.01	0	0.0804	0.0097	0.2268	0.0051	0.0051	0.1143	0.0114	0.0407	0.0984	0.0203	0	0	0.023	0.0163	0.4044	0
15-19	0.3298	0.012	0.0334	0.01	0	0.0804	0.0097	0.2268	0.0051	0.0051	0.1143	0.0114	0.0407	0.0983	0.0203	0	0	0.023	0.0163	0.4042	0
20-24	0.3298	0.0119	0.0334	0.01	0	0.0804	0.0097	0.2267	0.0051	0.0051	0.1143	0.0114	0.0407	0.0983	0.0203	0	0	0.023	0.0163	0.4002	0.0006
25-29	0.2273	0.0764	0.0182	0.0039	0	0.0804	0.0097	0.2212	0.0059	0.0059	0.1143	0.0114	0.0407	0.087	0.0312	0	0	0.023	0.0163	0.3989	0.0008

30-34	0.2273	0.0757	0.0182	0.0039	0	0.0804	0.0097	0.22	0.0059	0.0059	0.1143	0.0114	0.0407	0.0841	0.0312	0	0	0.023	0.0163	0.3887	0.0019
35-39	0.2273	0.0767	0.0182	0.002	0	0.0804	0.0097	0.2175	0.0059	0.0059	0.1143	0.0114	0.0407	0.0769	0.038	0	0	0.0097	0.0163	0.5	0.0019
40-44	0.2	0.0923	0.0182	0.002	0	0.0804	0.0097	0.214	0.0059	0.0065	0.1143	0.0114	0.0407	0.0735	0.038	0	0	0.0097	0.0065	0.5	0.0036
45-49	0.1769	0.115	0.0141	0.001	0	0.0804	0.0097	0.2059	0.0079	0.0065	0.1143	0.0114	0.0407	0.066	0.0426	0	0	0.0097	0.0065	0.5	0.0036
50-54	0.1512	0.1366	0.0211	0.0015	0	0.0804	0.0097	0.2072	0.0119	0.0098	0.1143	0.0114	0.0407	0.0668	0.0639	0	0	0.0097	0.0069	0.5	0.0053
55-59	0.1291	0.1601	0.0239	0.0017	0	0.0804	0.0097	0.2081	0.0135	0.0111	0.1143	0.0114	0.0407	0.0623	0.1161	0	0	0.0097	0.0069	0.5	0.0085
60-64	0.1081	0.1862	0.0267	0.0019	0	0.0804	0.0097	0.2086	0.0151	0.0124	0.1143	0.0114	0.0407	0.0626	0.1298	0	0	0.0032	0.0032	0.5	0.0095
65-69	0.1081	0.1873	0.0295	0.0021	0	0.0804	0.0097	0.2099	0.0167	0.0137	0.1143	0.0114	0.0407	0.0584	0.1094	0	0	0.0032	0.0032	0.5	0.0105
70-74	0.1081	0.1859	0.0323	0.0022	0	0.0804	0.0097	0.2083	0.0182	0.015	0.1143	0.0114	0.0407	0.0577	0.1199	0	0	0.0032	0.0032	0.5	0.0115
75-79	0.1081	0.1808	0.0351	0.0024	0	0.0804	0.0097	0.2027	0.0198	0.0164	0.1143	0.0114	0.0407	0.0493	0.1426	0	0	0.0032	0.0016	0.5	0.0143
80-84	0.1081	0.1704	0.0141	0.001	0	0.0804	0.0097	0.1914	0.0079	0.0065	0.1143	0.0114	0.0407	0.0427	0.057	0	0	0.0032	0.0016	0.5	0.0057

[+] *Well refers to the per-timestep probability of clearance of HPV infection or CIN.*

Chapter 3: Elimination of cervical cancer as a public health problem

The previous chapter describes a detailed HIV and HPV infection dynamics and natural history model, accounting for over-time changes in sexual behaviour and advancement in HIV control interventions such as VMMC, ART, and PrEP. Chapter 2 reported that the implementation and scale-up of VMMC and ART can reduce the burden of cervical cancer in Tanzania, although, are not enough to eliminate cervical cancer below a threshold of four cases per 100,000 women. As a natural continuation of this, and in response to the cervical cancer elimination strategy outlined by the World Health Organisation, Chapter 3 presents a modelled assessment of the predicted impact of implementing the WHO cervical cancer elimination strategy in the United Republic of Tanzania. The fundamental aim of this chapter was to assess the achievability of cervical cancer elimination in Tanzania for all women, including those with HIV, and with a focus on explicitly planning for these women when instituting national programmes for cervical screening and HPV vaccination.

This chapter contains original research published in the following paper:

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The published study was conceptualised for this thesis by the candidate (Michaela Hall) and supervisors Professors John Murray and Karen Canfell. The candidate's estimated contribution to this analysis is approximately 80%, involving conceptualisation, study design and methodology, formal analysis, interpretation of results and visualisation, and development of original and revised manuscript drafts. The accepted author version of this publication has been included with minor modifications to improve clarity, and contains additional material sourced from the published supplementary appendix. Figures, tables, associated captions, and references have been reformatted to be consistent throughout the thesis.

Work from this chapter was additionally presented at the International Papillomavirus Conference 2020 as an oral presentation.

Elimination of cervical cancer in Tanzania: Modelled analysis of elimination in the context of endemic HIV infection and active HIV control

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Novelty and Impact Statement

This is the first modelled analysis to directly assess the impact and feasibility of implementing the World Health Organisation's cervical cancer elimination strategy in the context of HIV and ongoing HIV control. This analysis shows that high coverage cervical screening and HPV vaccination could eliminate cervical cancer for all Tanzanian women, including those living with HIV, by the end of the century and provides elimination projections specifically for women living with HIV.

Abstract

The World Health Organisation (WHO) has launched a strategic initiative for cervical cancer elimination, which involves scaling up three interventions: human papillomavirus (HPV) vaccination, twice-lifetime HPV-screening screening, and precancer/cancer treatment by 2030. Cervical cancer is challenging to control in countries with endemic human immunodeficiency virus (HIV), as women living with HIV (WLHIV) are at elevated risk of HPV infection, persistence, and progression. This analysis estimated the impact of the elimination interventions on cervical cancer incidence and mortality but considering more intensive screening for WLHIV, using Tanzania as an example. A dynamic HIV/HPV model was used to simulate the elimination strategy for vaccination, screening, and precancer/cancer treatment, with three-yearly HPV screening in WLHIV, in the context of sustained HIV control in Tanzania over 2020-2119. Without vaccination or HPV screening, cervical cancer incidence rates per 100,000 women are predicted to fall from 58.03 in 2020 to 41.60 (range:39.14-44.68) in 2119 due to existing HIV control. HPV vaccination and twice-lifetime HPV-screening would reduce cervical cancer incidence to 1.30 (range:1.30-2.47) by 2119, with elimination (<4/100,000) in 2076 (range:2076-2092). cervical cancer mortality rates per 100,000 women are predicted to reach 1.15 (range:1.15-2.12) with further reductions contingent on increased cervical cancer treatment access. Vaccination and three-yearly HPV screening for WLHIV are predicted to achieve elimination in WLHIV by 2061 (range:2061-2078), with a 2119 cervical cancer incidence rate of 1.66 (range:1.66-3.28). Scaling-up vaccination and HPV screening to meet WHO targets will substantially reduce cervical cancer incidence in Tanzania, with elimination predicted within a century. Three-yearly HPV screening and HPV vaccination at high coverage rates may also facilitate cervical cancer elimination among WLHIV.

Introduction

Despite the preventability of cervical cancer, it remains the most frequent cause of cancer death in women in 42 countries(Bray et al., 2018). Vaccination against human papillomavirus (HPV), the agent responsible for cervical cancer, is safe and effective at preventing infection in females and males. While the GAVI vaccine alliance heavily subsidises the cost of many vaccines, including the HPV vaccine in eligible low-income countries, many countries do not have established population-wide HPV vaccination programmes(Brisson et al., 2020, Gavi the vaccine alliance, 2020, World Health Organisation (WHO), 2020a). The detection and treatment of cervical pre-cancer through routine cervical screening programmes effectively prevent cervical cancer and provide a means of downstaging cervical cancer through early detection; however, routine screening is not universally available in many low and middle-income countries (LMICs). The World Health Organisation (WHO), in November 2020, launched a cervical cancer elimination strategy which recommends national implementation of HPV vaccination programmes achieving coverage levels of 90% of nine-year-old girls and twice-lifetime HPV-screening programmes at 70% participation to achieve cervical cancer elimination at a threshold of <4/100,000 cases per annum. In practice, this threshold represents a 'stretch-goal' to mobilise substantial action and investment in cervical cancer prevention, while being functionally achievable in the majority of countries(Simms et al., 2019). Additionally, the WHO recommends that 90% of women diagnosed with either cervical pre-cancer or cervical cancer have access to appropriate treatment(World Health Organisation (WHO), 2020a). Women with human immunodeficiency virus (HIV) are at higher risk of persistent HPV infection, cervical pre-cancer and cervical cancer compared to HIV negative women(Liu et al., 2018). In July 2021, the WHO released their revised guidelines for cervical screening, which recommend that HIV positive women are screened with HPV-DNA-testing at a frequency of every three to five years(World Health Organisation 2021).

In the global context, the United Republic of Tanzania has high rates of cervical cancer incidence and mortality, with 59.1 cases and 42.7 deaths (per 100,000 women) in Tanzania versus the global average of 13.1 cases and 6.9 deaths in 2018, and a moderate HIV prevalence of 5.5% among women aged 15-49 years(UNAIDS, 2018b, Bray et al., 2018). Recent estimates suggest that, on average, only 9.5% of women in sub-Saharan Africa diagnosed with cervical cancer have access to treatment(Canfell et al., 2020). In 2018, Tanzania commenced the roll-out of a pilot HPV vaccination programme, offering a quadrivalent HPV vaccine to girls aged 9-15 years, although an organised cervical screening programme is yet to be financed(Runge et al., 2019).

While VIA-based cervical screening clinics are available in some northern provinces of Tanzania, these are relatively sparse, with few women having ever received a screening test(Bakiewicz et al., 2020, Runge et al., 2019, Cunningham et al., 2015).

A modelled analysis published by the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) predicts that HPV vaccination combined with cervical screening at high coverage can achieve the elimination of cervical cancer in LMICs, with cervical screening expediting the timeline and also the primary means of achieving intermediate-term reductions in cervical cancer cases and deaths(Brisson et al., 2020, World Health Organisation (WHO), 2020a, Canfell et al., 2020). This analysis used comparative modelling to simulate the draft WHO elimination strategy, including 2030 scale-up targets for HPV vaccination (90% coverage) and cervical screening (70% twice-lifetime coverage) in 78 LMICs. Due to the scale of the analysis, the authors necessarily made a range of simplifying assumptions; for example, two out of the three models assumed static rates of cervical cancer incidence in the absence of intervention going forward, and the models did not explicitly account for the known effects of HIV infection on HPV progression and cervical cancer natural history, and the differential efficacy of treatment for precancer in WLHIV. The CCEMC models implemented a simplified screening algorithm and assumed that as part of elimination implementation, 90% of all women, including HIV positive women, received effective pre-cancer treatment, which is not necessarily currently the case(De Vuyst et al., 2014). Therefore, there is value in performing detailed country-level analyses as a complementary exercise, which explicitly incorporates sexual behaviour, the transmission of both HPV and HIV, and HPV natural history as influenced by HIV co-infection and anti-retroviral therapy (ART) uptake. By incorporating this level of detail, combined with a screening algorithm that allows for specific management and treatment success for HIV positive women, it is possible to provide greater specificity for the country-specific cervical cancer elimination predictions. It is also possible to explicitly address the question of whether it is possible to achieve cervical cancer elimination, at a threshold of 4/100,000 women, for the subgroup of HIV positive women by implementing more frequent screening strategies.

Using Tanzania as an example country, this analysis provides detailed country-level modelling of cervical screening with HPV, accounting for HIV prevalence and ART, considering different screening recommendations and pre-cancer treatment success rates for women who are HIV positive. We have previously reported a model of cervical cancer in Tanzania, finding that in the absence of HPV vaccination and cervical screening, HIV interventions would lower cervical cancer incidence and mortality rates

by 43% and 39%, respectively, in 2070 compared to rates in 2020(Hall et al., 2020). Building on this work, our primary aims in the current analysis were to 1) estimate the expected year of cervical cancer elimination in Tanzania at the WHO threshold of <4/100,000 cases per annum, 2) examine the impact of more intensive screening in HIV positive women and determine whether elimination is feasible in this subgroup and, 3) quantify the mortality benefits of achieving elimination in Tanzania, with scaled-up access to cervical cancer treatment for women with screen-detected cervical cancer.

Methods

Model description and parameterisation overview

A dynamic compartment model of the heterosexual transmission and natural history of HIV, HPV16/18, HPV31/33/45/52/58, and other oncogenic HPV types, calibrated to the Tanzanian setting, was utilised to simulate cervical cancer prevention and control in Tanzania. This model simulates transmission, co-infection and natural history of HIV and multiple HPV types, stratified by sex, age and HIV treatment status, and was extensively calibrated and validated against data local to the United Republic of Tanzania. Disease transmission probabilities are informed by a force of infection, which accounts for detailed sexual behaviour and intervention parameters, including the number of sexual partners, condom usage, circumcision rates and HIV treatment. Cervical carcinogenesis is followed by stage-specific assumptions about cancer progression, symptom onset and detection, treatment, and survival. This analysis focused on the impact of HIV and HIV/HPV interventions on cervical cancer incidence and mortality; therefore, other modes of transmission, such as injection drug use (HIV only) and via men who have sex with men (HIV and HPV), were not included. This model was implemented in Matlab version R2018b. Table 15 provides a detailed overview of model compartments and is an extension of the previously reported Table 1. Input parameter values are reported in Chapter 2(Hall et al., 2020).

Table 15 Description of all possible model compartments, as defined by the cartesian product of columns (all logical combinations of a single box from each column are possible).

Population sub-group	**Age**	**Sexual activity level**	**HIV disease status**	**HIV treatment status**	**HPV 16/18 disease status**	**HPV 31/33/ 54/52/58 disease status**	**HPV OHR disease status**	**Cervical cancer detection, treatment, and survival**	**Screening behaviour and history**
Male	5-9	General population sexual activity	Immune (PrEP)	No treatment	Immune (HPV vaccination)	Immune (HPV vaccination)	Immune (HPV vaccination)	No cervical cancer	Never-screeners
Female (general population)	10-14	Elevated sexual activity	Susceptible	ART (partial treatment)	Immune (natural)	Immune (natural)	Immune (natural)	Undetected cervical cancer (localised)	Routine-screeners
Female (commercial sex worker)	15-19		Infected (acute)	ART (viral suppression)	Susceptible	Susceptible	Susceptible	Undetected cervical cancer (regional)	Post-ablation follow-up
	20-24		Stage 1 (WHO clinical)		HPV infection	HPV infection	HPV infection	Undetected cervical	Post-excision follow-up

								cancer (distant)	
	…		Stage 2 (WHO clinical)		CIN 1	CIN 1	CIN 1	Symptomatically detected cervical cancer (localised)	
			Stage 3 (WHO clinical)		CIN 2	CIN 2	CIN 2	Symptomatically detected cervical cancer (regional)	
			AIDS^{+}		CIN 3	CIN 3	CIN 3	Symptomatically detected cervical cancer (distant)	
	60-64				Invasive cervical cancer*	Invasive cervical cancer*	Invasive cervical cancer*	Screen-detected cervical cancer (localised)	

	65-69							Screen-detected cervical cancer (regional)	
	70-74							Screen-detected cervical cancer (distant)	
	75-79							Cancer survivor	

[+]*Acquired immunodeficiency syndrome. *Once a woman develops invasive cervical cancer attributable to any HPV genotype, their HPV disease status for all genotypes ceases to change, and their disease is tracked through 'cervical cancer detected, treatment and survival' compartments. Cervical cancer survivors are assumed to be at no further risk of acquiring an HPV infection (cervical) and developing subsequent disease.*

To simulate cervical screening, an additional function was created to examine the health states of women who are eligible for screening in any given year with eligibility influenced by age, HIV status, and screening behaviour and history. For each screen-eligible compartment of women, a proportion receive precancer treatment ($p_{treatment} = [screening\ participation] \times [test\ positivity] \times [treatment\ compliance]$) which either completely removes the cervical disease (women become HPV negative), partially removes the cervical disease (lesions are removed, but women remain HPV positive), fails completely (women remain in their health state), or detects an underlying case of cervical cancer. Further details describing screening parameters, including screening compliance, test positivity, precancer treatment compliance and precancer treatment efficacy are provided in a subsequent subsection titled 'Cervical screening and treatment'.

HIV control assumptions

The prevalence of male circumcision, which lowers a male's risk of both HIV and HPV acquisition, is assumed to be 23% in 1998 and to increase to 80% in 2015, in line with observational data obtained from the Tanzanian Ministry of Health and Social Welfare (The United Republic of Tanzania Ministry of Health and Social Welfare, 2013, Ministry of Health et al., 2016). The World Health Organisation currently recommends voluntary medical male circumcision (VMMC) to control the spread of HIV(World Health Organisation (WHO), 2020b). Male circumcision is assumed to reduce HIV acquisition in males by 60% and HPV acquisition by 63%(Prodger and Kaul, 2017, Castellsague et al., 2002). As reported in a previous analysis, VMMC is predicted to lower the prevalence of HIV and HPV infection in Tanzanian males and females, as protecting men against infection secondarily protects all subsequent sexual partners(Hall et al., 2020).

ART is explicitly simulated for HIV positive individuals. Here, we assume two tiers of HIV treated individuals: virally-suppressed, and incomplete suppression, which accounts for individuals who have commenced treatment but have experienced either treatment failure or discontinuation of treatment. However, we do not directly model switching to second/third-line therapies following treatment failure. Rates of ART uptake and viral suppression are assumed to be as reported in Tanzania and maintained at the current rate of 62% of people living with HIV knowing their status and are receiving treatment such that 47% of people with HIV are virally suppressed(UNAIDS, 2018d).

HPV vaccination assumptions

In HPV vaccination scenarios, it is assumed that a completed course of the broad-spectrum HPV vaccine is administered to females at the age of nine years, that the vaccine is 100% effective against vaccine-included HPV types (with lower vaccine efficacies considered in sensitivity analysis), and that it confers lifelong immunity. HPV vaccination is assumed to be introduced for nine-year-old females in 2020, with modelled full-dose vaccine uptake rates increasing linearly from 0-90% over 2020-2030. Catch-up HPV vaccination was not offered to older cohorts.

Cervical screening and treatment

In all cervical screening scenarios, twice lifetime HPV screening for women (at ages 35 and 45) is assumed for HIV negative women and women of unknown HIV status, with three-yearly testing for WLHIV. In practice we assume that only WLHIV who are aware of their HIV status (79% of all WLHIV, UNAIDS 2018 data) receive more frequent screening(UNAIDS, 2021b). We assumed that an HPV DNA test was used, with sensitivity and specificity as stated in Table 16. Cervical screening participation rates were assumed to increase linearly from 0% in 2019 to 70% in 2030, and for all years, we assume 90% of women with a positive HPV test receive either ablative or excisional treatment, following a treatment eligibility test with VIA (visual inspection with acetic acid). Women who have received either treatment type are assumed to be re-screened in 12 months (modelled participation for follow-up is 90%) to determine treatment success and re-treated with excisional treatment if this test is positive. Scenarios involving scaled-up access to treatment for cervical cancer assumed that cervical cancer treatment access rates increased from the sub-Saharan African average of 9.5% to 90%, as specified by the WHO draft elimination strategy(Canfell et al., 2020). Cervical cancer survival is modelled by cervical cancer stage at detection, with current ten-year survival rates ranging between 8.3% for early-stage to 0.9% for end-stage cervical cancer. Increasing cervical cancer treatment access to 90% is assumed to increase these ten-year survival rates to 78.3% and 8.1%, respectively. These rates were chosen for consistency with the CCEMC modelling study(Canfell et al., 2020).

Table 16 Description of input parameters considered for baseline and sensitivity analysis

Parameter description	**Parameter values**
Screening test and pre-cancer treatment	

HPV test characteristics (screening test positivity by underlying health-states irrespective of HIV positivity status)	Well[a]: 0.014 (0.014 – 0.042) (Sandri et al., 2006, Venturoli et al., 2002, Riethmuller et al., 1999, Kulmala et al., 2004, Safaeian et al., 2007) HPV positive: 0.56 (0.497 – 0.667) (Wahlstrom et al., 2007, Yamazaki et al., 2001) CIN1[b]: 0.8415 (0.694 – 0.989) (Zuna et al., 2005, Soderlund-Strand et al., 2005) CIN2: 0.93 (0.901 – 0.989) (Soderlund-Strand et al., 2005) CIN3+[c]: 0.984 (0.928 – 1) (Soderlund-Strand et al., 2005) Although HPV test sensitivity and specificity are consistent given a particular underlying health state, the composite summary values of effect HPV test sensitivity and specificity depend on the composition of underlying health states seen in the population of women screened, which vary by year, age, and age and HIV positivity status. In the year 2020, at a CIN2+ threshold, the following cross-sectional values are obtained: Sensitivity: 95-98% (HIV negative) and 96-95% (HIV positive) Specificity: 70-97% (HIV negative) and 54-97% (HIV positive)
Cryotherapy treatment efficacy (assumes clearance of lesion and infection)	HIV negative women: 0.842 – 0.91 HIV positive women: 0.595 – 0.77
Cancer treatment and survival	
Ten-year cervical cancer survival by stage at diagnoses without scaled-up treatment access (versus with scaled-up treatment access)[d]	Localised: 8.3% (and 78.3%) Regional: 5.5-7.3% (and 52.2-69.3%) Distant: 0.9% (and 8.1%)
Variation for sensitivity analysis	

Sexual behaviour	The per-timestep volume of sexual partnership formations, for high and general-activity males and females, was varied by ± 5%, as similarly explored in (Hall et al., 2020).
Protective effect of male circumcision against HIV and HPV acquisition	RR reduction of HIV (and HPV) acquisition for males was varied over 0.53-0.6 (and 0.16-0.85). Values at baseline were 0.6 and 0.63, respectively, as reported in (Hall et al., 2020).
HPV natural history on ART[e]	Modelled relative risk (RR) of HPV acquisition and natural history for WLHIV virally suppressed through ART, compared to untreated WLHIV. Acquisition: 1.17 – 2.75 HPV to CIN1 progression: 2.62 – 3.73 HPV to CIN2 progression: 1.1 – 1.33 CIN1 clearance: 0.56 – 0.7 (HPV 16/18), 0.56-0.67 (HPV not 16/18) CIN2/3 clearance: 0.26-0.57 CIN3 to cancer: 2.3-2.5
HPV vaccine efficacy	90– 100%

a. Well = no current HPV infection or cervical disease; b. CIN = cervical intraepithelial neoplasia; c. CIN3+ = CIN 3 or cervical cancer; d. Access to cervical cancer treatment for diagnosed women is assumed to increase from 9.5% in 2020 to 90% in 2030 under scaled-up treatment access scenarios(Canfell et al., 2020). [e] *As consistent with HPV natural history parameters reported in Chapter 2 (Hall et al., 2020).*

Sensitivity analysis

A multivariate sensitivity analysis was carried out on transmission, HPV vaccination and screening parameters (Table 16) to account for parameter uncertainty. For each scenario, we considered variation in a range of HIV/HPV transmission and prevention parameters, including sexual behaviour, the protective effect of voluntary medical male circumcision against HIV and HPV acquisition, the impact of anti-retroviral therapy (ART) on the natural history of HPV, HPV vaccine efficacy, HPV test sensitivity and pre-cancer treatment efficacy with lower- and upper-bounds for each as described in Table 16. For each scenario, we simulated possible parameter variations sampled over a randomly generated Latin hypercube, with 480 parameter combinations per scenario. The total variation in simulated outcomes because of this sensitivity analysis are presented as ranges with the primary results. An additional sensitivity analysis was later performed on cervical cancer prevention parameters only in the ‘WHO 90-70-90’

scenario, where HPV test sensitivity, pre-cancer treatment efficacy and HPV vaccine efficacy were each varied between 90-100% of their values assumed at baseline, with the interval split uniformly into five parts. For each parameter, every possible combination of these variations in sensitivity/efficacy was simulated to determine the individual and combined impact of variation in these parameters, which of the three is more influential over the final simulated outcome. The result of this additional analysis is presented separately.

Scenarios and outcomes

Four scenarios were considered to assess cervical cancer incidence rates over time and were simulated over a 100-year time horizon from 2020 to 2119: 1) a status-quo scenario assuming no HPV vaccination and no cervical screening called 'status quo'; 2) a vaccination only scenario assuming that a broad spectrum HPV vaccination programme is introduced in 2020 for females aged nine, with vaccine coverage linearly scaled from 0% in 2020 to 90% in 2030 called 'HPV vaccination only'; 3) a screening only scenario assuming that a twice-lifetime HPV-screening (at ages 35 and 45) programme was introduced, where three-yearly HPV-screening is available to HIV positive women over the age of 20 years, with participation increasing from 0% in 2020 to 70% in 2030 called 'cervical screening only'; 4) a WHO elimination strategy scenario assuming a combination of HPV vaccination (as per scenario 2) and HPV-screening (as per scenario 3) called 'WHO 90-70-90'. Cervical cancer mortality rates over time were estimated for eight scenarios, which are scenarios 1-4, as described above, both with and without scaled-up cervical cancer treatment access. Cervical cancer incidence and mortality rates were estimated per 100,000 women, standardised to the WHO 2015 standard female population over ages 0-99 years.

Results

CC elimination at a threshold of <4/100,000 women among all Tanzanian women was achieved under both the 'HPV vaccination only' and 'WHO 90-70-90' scenarios (Table 17). Under the WHO 90-70-90 scenario, cervical cancer elimination is predicted to occur as early as 2076 (range: 2076 - 2092) and was predicted for all parameter sets included in sensitivity analysis, which included variations in sexual behaviour, HIV/HPV acquisition parameters, the impact of HIV on HPV natural history and vaccination and screening parameters. In the HPV vaccination only scenario, cervical cancer elimination was not predicted to occur for all parameter sets, with the elimination year delayed until 2106 (range: 2103-2119) for sets that did achieve elimination in the simulated timeframe. Cervical cancer elimination in WLHIV, at a threshold of 4/100,000 women, is also predicted to occur for all parameter sets in 2061 (range:2061-2078), for

the ‘WHO 90-70-90’ scenario, which notably assumes that WLHIV are screened more frequently, at three-yearly intervals from diagnosis with HIV. Cervical cancer elimination is achieved sooner among WLHIV than the general population; this is due to the compounding effectiveness of multiple rounds of three-yearly HPV screening detecting and removing prevalent cervical disease among WLHIV, as compared to the twice-lifetime testing strategy assumed for women without HIV. An additional sub-analysis was performed to assess the magnitude to which cervical cancer elimination may be delayed by failing to meet the WHO 90-70-90 targets for HPV vaccination and cervical screening, the methodology and results of which are written up in detail in the supplementary material. Broadly, we note that if screening participation of only 40% were achieved by 2050, cervical cancer elimination among the general population and WLHIV would each be delayed by eight years. If vaccination coverage of only 70% could only be achieved by 2050, cervical cancer elimination would be delayed by 24 and 30 years for the general population and WLHIV, respectively. It is important to note that it is not only elimination per se, but lives saved on the path to elimination, which is critical, given that elimination is a long-term goal. Delays or impacts to screening coverage will have a profound effect on the number of lives that can be saved over the next half-century, as pointed out by colleagues(Simms et al., 2019).

Over the simulated time-horizon, we predict that age-standardised cervical cancer incidence rates among all Tanzanian women will fall from 58.03 per 100,000 to 41.60 (range: 39.14-44.68) under status quo assumptions, 3.50 (range: 3.31-5.95) in the scenario assuming HPV vaccination only; 15.98 (range: 15.50-18.01) in the cervical screening only scenario (whereby cervical screening aims to detect and treat cervical pre-cancer, thereby preventing progression to cervical cancer); and 1.30 (range: 1.30-2.42) in the WHO 90-70-90 scenario (Table 17). These long-term predictions largely reflect the HIV negative sub-population, as a diminishing proportion of the female population is predicted to be HIV positive (0.11-0.12%)(Hall et al., 2020). Under WHO 90-70-90 HPV vaccination and screening assumptions, assuming three-yearly HPV screening for HIV positive women, cervical cancer incidence rates among HIV positive women are predicted to fall to 1.66 (range: 1.66-3.28) per 100,000 women by 2119. For all women and WLHIV, we predict a temporary increase in cervical cancer detection following the implementation of cervical screening. Screening brings forward the diagnosis of cervical cancer, which would have otherwise been detected later, and therefore the temporary increase in detection should be seen as an indicator of programme success rather than program failure. We have previously discussed this phenomenon in detail(Hall et al., 2018).

Similarly, for cervical cancer mortality, we predict that age-standardised cervical cancer mortality rates among all Tanzanian women will fall to 30.27 (range: 29.29-32.01) per 100,000 women under status quo assumptions; 2.54 (range: 2.48-4.41) in the scenario assuming HPV vaccination only; 13.82 (range: 13.43-15.4) in the cervical screening only scenario; and 1.15 (range: 1.15-2.12) in the WHO 90-70-90 scenario (Table 17). However, scaling-up access to appropriate treatment for women diagnosed with cervical cancer, such that 90% of women with cervical cancer receive disease-stage-appropriate treatment, is expected to substantially reduce mortality rates over all scenarios. Here, we predict the ASR of cervical cancer mortality can be reduced to 0.79 (range:0.71 – 1.29) per 100,000 women by 2119 if scaled-up cervical cancer treatment is combined with WHO 90-70-90 prevention interventions (Table 17). Reductions in cervical cancer mortality due to cervical screening are associated with the prevention of cervical cancer cases and downstaging due to early detection.

Table 17 Predicted age-standardised rates of cervical cancer incidence and mortality per 100,000 women in 2119, under a range of modelled scenarios.

		Simulated scenario in the year 2119 (range generated by sensitivity analysis)			
		Status quo	*HPV vaccination only*	*Cervical screening only*	*WHO 90-70-90*
Cervical cancer incidence	*All women*	41.6 (39.15-44.71)	3.5 (3.31-5.95)	15.98 (15.5-18.01)	1.3 (1.3-2.42)
	HIV positive women	239.77 (235.59-244.91)	29.05 (28.81-45.2)	13.78 (13.73-18.48)	1.66 (1.66-3.28)
Cervical cancer mortality	*All women*	30.27 (28.96-31.64)	2.54 (2.44-4.36)	13.82 (13.43-15.4)	1.15 (1.15-2.12)
	HIV positive women	218.47 (214.72-223.08)	26.61 (26.39-41.25)	11.34 (11.32-15.81)	1.44 (1.44-2.87)
Cervical cancer mortality+	*All women*	21.77 (15.15-16.56)	1.83 (1.27-2.27)	9.57 (8.04-9.22)	0.79 (0.71-1.29)
	HIV positive women	153.71 (137.65-143.01)	19.05 (17.3-27.05)	7.28 (5.98-8.35)	0.92 (0.84-1.59)

+ Cervical cancer mortality rate if access to cervical cancer treatment were scaled up from the current observed rate of 9.5% to 90% for all women diagnosed with cervical cancer(Canfell et al., 2020).

HPV vaccination and cervical screening, independently of each other, are predicted to substantially reduce cervical cancer incidence in Tanzania over the long term (Figure 13). For the general population, the long-term impact of screening only is less pronounced than HPV vaccination only, despite outperforming the vaccination only scenario over the next 50 years as vaccinated cohorts slowly realise the benefit of their protection. This is not the case for WLHIV, where three-yearly screening (assumed for WLHIV under the 'WHO 90-70-90' scenario) outperforms HPV vaccination in the long term (Figure 13). Gradual reductions in cervical cancer incidence and mortality reductions are predicted in all scenarios, including 'status quo', due to changes in sexual behaviour and uptake in condom use, voluntary medical male circumcision (which prevents both HIV and HPV acquisition) and uptake in ART (which lowers HIV transmission, and protects against HPV acquisition and progression in WLHIV); Figure 13, (Hall et al., 2020).

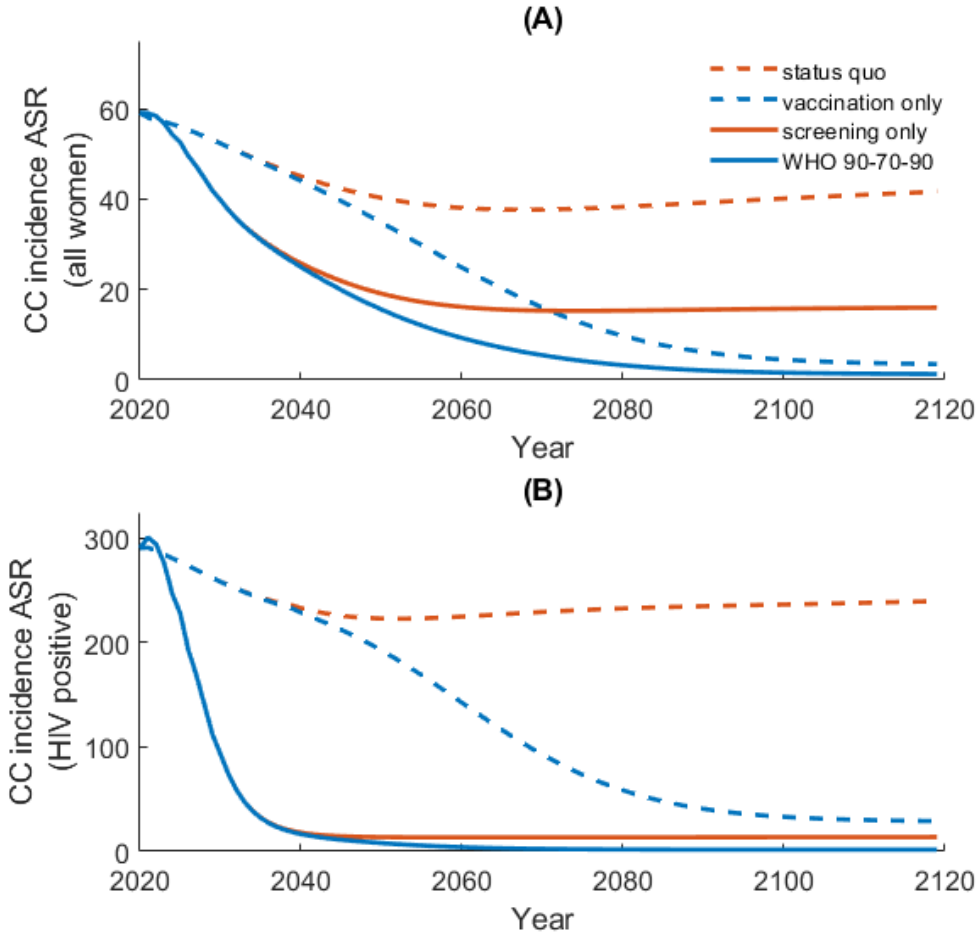


Figure 13 Age-standardised cervical cancer incidence in (A) all women and (B) HIV positive women, over time, for the status quo scenario, compared to intervention scenarios. CC = cervical cancer.

Dynamically, cervical cancer mortality rates are expected to behave in much the same way as cervical cancer incidence rates, such that the introduction and scale-up (by 2030) of cervical screening is predicted to have a substantial effect on reducing the cervical cancer mortality rate as cervical cancer cases are prevented (Figure 14). This impact is highly pronounced in the WLHIV population subgroup, which experiences more frequent screening. Scaling up access to cervical cancer treatment for women diagnosed with cancer rapidly and significantly reduces cervical cancer mortality in all scenarios (Figure 14).

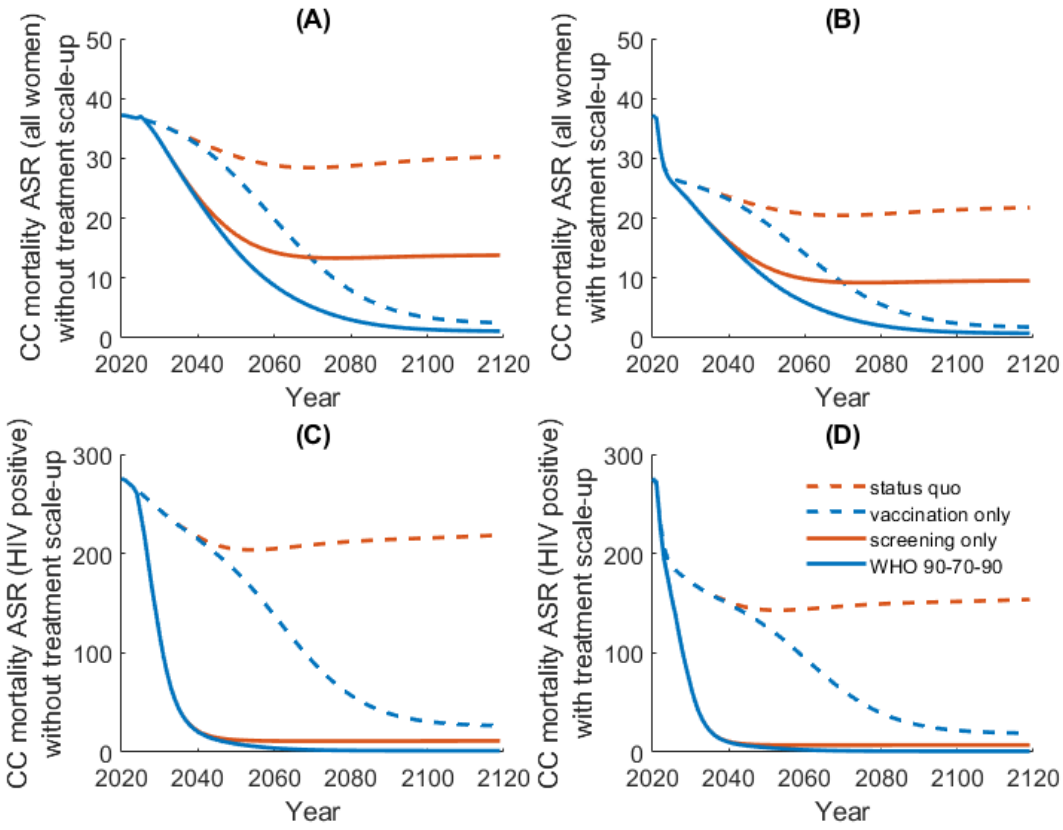


Figure 14 Age-standardised cervical cancer mortality in (A-B) all women, and (C-D) HIV positive women, over time, for the status quo scenario compared to intervention scenarios without (A, C) and with (B, D) scale-up of access to cervical cancer treatment for women diagnosed with cervical cancer. CC = cervical cancer.

The introduction of HPV vaccination is expected to avert 2.35 million cervical cancer cases and 1.83 million cervical cancer deaths, cumulatively, between 2021 and 2119 (Figure 15). Cervical screening is anticipated to avert over 496,500 and 368,200 additional cervical cancer cases and deaths cumulatively over 2021-2119. If access to cervical cancer treatment is scaled up to 90% by 2030, it is predicted to prevent 735,100 cumulatively over 2021-2119.

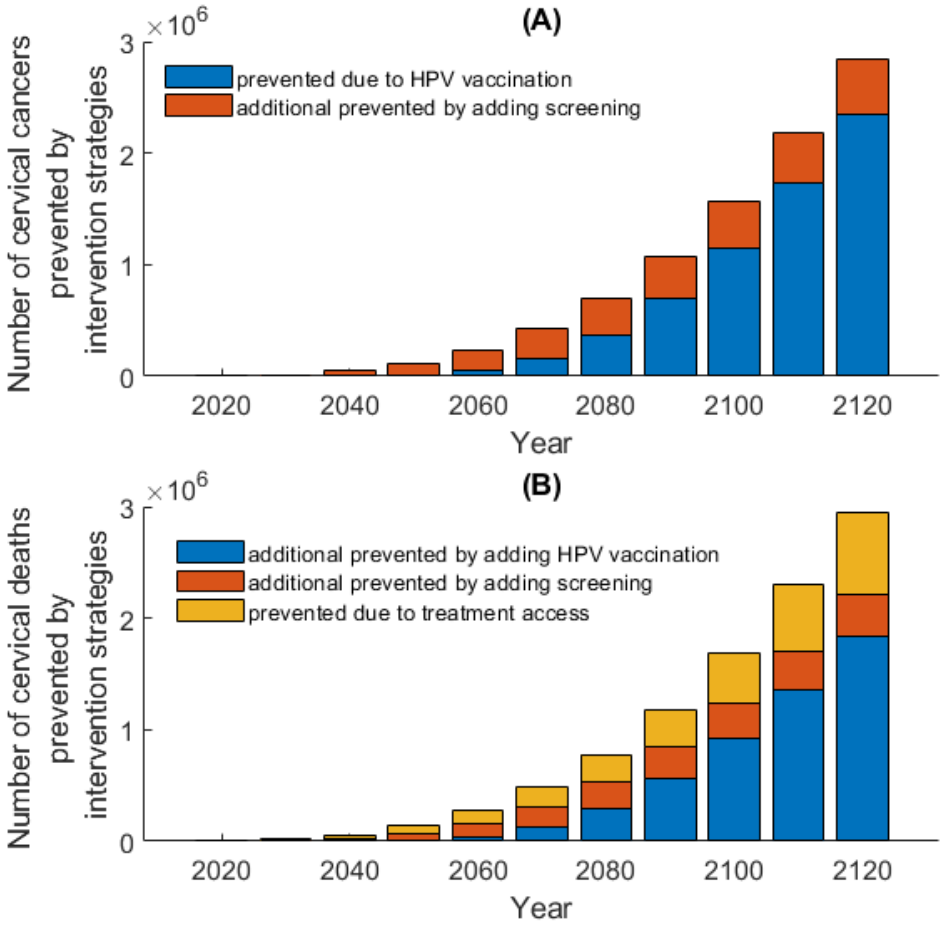


Figure 15 Cumulative (A) cervical cancer diagnoses and (B) cervical cancer deaths prevented by the incremental addition of first HPV vaccination, then cervical screening, and lastly increased cervical cancer treatment access (mortality only).

Results of the additional sensitivity analysis, performed for the WHO 90-70-90 scenario only, indicate that HPV vaccination is the most influential parameter when it comes to the elimination of cervical cancer, as analysis of the Pearson coefficients of the predictor and outcome variables determined that HPV vaccine efficacy has a partial correlation co-efficient < -0.99 (increased vaccine efficacy decreased cervical cancer incidence). Cervical cancer elimination was achieved for all scenarios combining vaccination with cervical screening, decreasing pre-cancer treatment efficacy and HPV test sensitivity delay elimination by up to seven years (Figure 16).

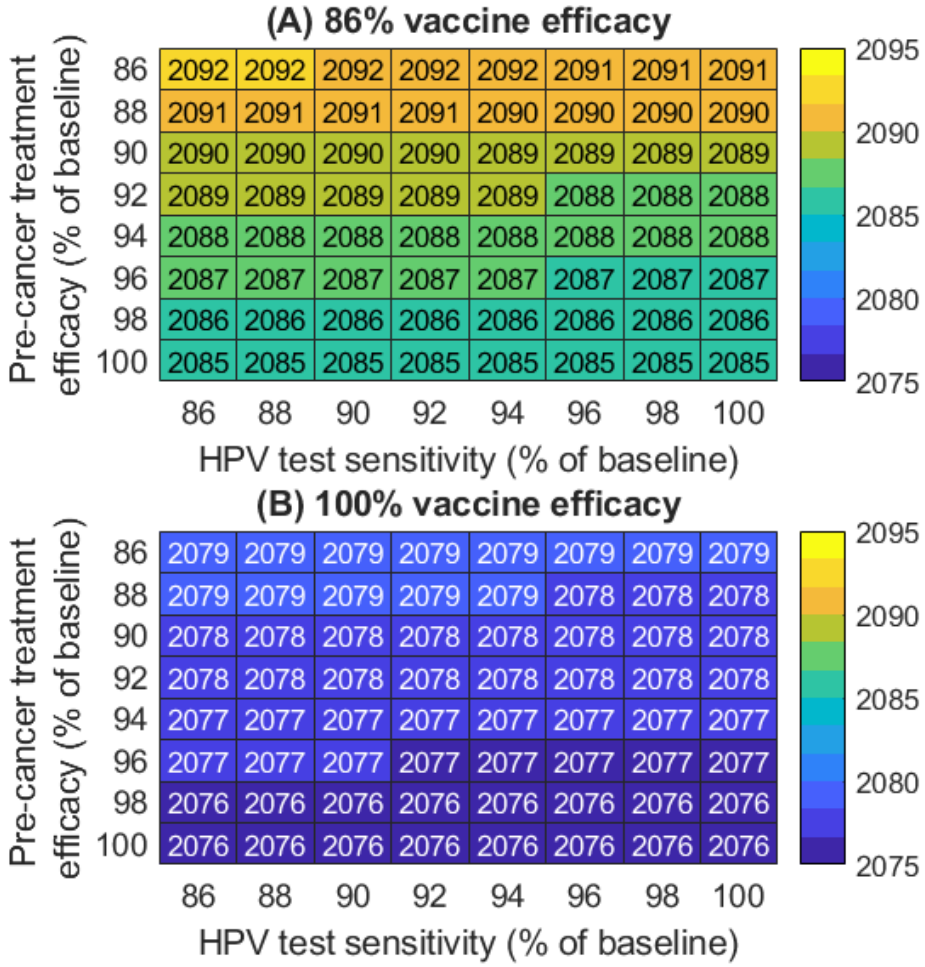


Figure 16 Heatmap of the predicted year of cervical cancer elimination under the' WHO 90-70-90' scenario, for parameter sets with variation in pre-cancer treatment and vaccination efficacy, and HPV test sensitivity.

Discussion

The primary finding of this work is that through combined HPV vaccination and HPV-screening, including three-yearly HPV-screening for WLHIV, at high levels of coverage, cervical cancer may be eliminated in Tanzania by 2076 (range: 2076-2092), with cervical cancer incidence and mortality rates of 1.30 and 1.15 cases and deaths, respectively per 100,000 women, achieved in 2119. Combining HPV vaccination with a more intensive cervical screening programme, involving three-yearly HPV screening from HIV diagnosis, is predicted to eliminate cervical cancer among WLHIV by 2061 (2061 – 2078). In the short term, we predict that rapid scale-up of three-yearly HPV-screening can immediately and substantially reduce cervical cancer incidence in WLHIV, from an age-standardised incidence rate of 291 per 100,000 in 2020 to <20 by the year 2040, providing strong arguments for the prioritisation of directing screening

efforts for WLHIV in particular. However, this group is only expected to form 0.11-0.12% of women aged 15-49 years in Tanzania in 2119 due to continued efforts to end HIV transmission. The scale-up of access to cervical cancer treatment, such that 90% of women diagnosed with cervical cancer receive appropriate treatment, is predicted to reduce cervical cancer mortality rates by 28-36% (range over all scenarios and population subgroups).

This analysis predicts the elimination of cervical cancer in Tanzania (<4 per 100,000 women threshold) by 2076-2092, which is broadly consistent with findings published by the CCEMC, where two out of three models predicted the elimination of cervical cancer in Tanzania, with the elimination year of 2085-2086(Brisson et al., 2020). Additionally, the CCEMC predicted that cervical cancer incidence and mortality rates in 2120 would be 1.95-7.63 and 0.7-1.02 per 100,000, under the WHO 90-70-90 triple intervention strategy (HPV vaccination at 90% coverage, twice-lifetime HPV-screening at 70% participation, treatment of 90% of cervical pre-cancer and cancer) with cancer treatment scale-up. In comparison, the current analysis predicts cervical cancer incidence and mortality rates of 1.30-2.42 and 1.15-2.12 per 100,000 women, respectively, under comparable assumptions but without cervical cancer treatment scale-up. Unlike the CCEMC's analysis, the current analysis explicitly accounts for the impact of HIV infection, treatment and prevention, and simulates more frequent screening (with lower pre-cancer treatment efficacy) among HIV positive women who know their HIV positivity status.

The strength of this analysis lies in the level of detail incorporated in this transmission-dynamic model, which was not incorporated into the modelled analyses referenced above. By explicitly accounting for HIV transmission, disease progression, treatments and prevention, we captured the intermediate-term impacts of the changing landscape of HIV prevalence, prevention and treatment in Tanzania. For example, a previous analysis using the same model platform which explores the implications of scaled-up HIV treatment (ART) and prevention (male circumcision, ART and pre-exposure prophylaxis) found that, in the short term, the life-extending capabilities of ART will result in an approximate 4% increase in cervical cancer diagnoses in 2020. However, the preventative and protective effects of ART and male circumcision will ultimately reduce cervical cancer incidence and mortality rates by 39-43% over a fifty-year time horizon, compared to 2020 rates; an artefact which is additionally reported in the current study(Hall et al., 2020). The present analysis incorporates this critical background to the analysis of cervical cancer prevention and can also simulate

differential management and treatment success of HIV positive women compared to HIV negative women and women with unknown HIV status.

As for all modelled projections of this kind, long term findings of this analysis are limited by the need to make assumptions regarding birth and natural mortality rates, sexual behaviour and uptake of HPV and HPV prevention strategies, in addition to the assumption of no further development in vaccine and screening technologies. In addition, a number of simplifying assumptions were made, including (1) simulating five-year age groupings instead of single-year ages, (2) grouping HPV types into HPV 16/18, HPV 31/33/45/52/58, and other oncogenic HPV, and (3) simplifying the modelled transmission modalities to accommodate heterosexual transmission of HIV and HPV only. These simplifications are widely considered to be acceptable for modelling studies of this nature, as they reflect data availability, are not expected to influence the results of this analysis, mainly since the groupings of HPV genotypes reflect very similar levels of risk of progression to cervical cancer and vaccine coverage. Finally, this analysis utilises conservative estimates for progress towards the WHO 90-90-90 targets for HIV intervention and PrEP utilisation, whereby we assume lower rates of viral suppression among all WLHIV (47%) than the target of 73%, and no pre-exposure prophylaxis (PrEP) utilisation. This is because we have aimed to produce conservative estimates for what may be achieved by way of future HIV prevention, detection and treatment, especially given that very few Tanzanians (<0.05%) currently utilise PrEP, as it has only just become available through demonstration and implementation projects with no nationally available roll-out (PrEP Watch, 2020, Harling et al., 2019). Our previous analysis has reported that meeting the WHO 90-90-90 intervention targets for HIV prevention, combined with targeted PrEP uptake, could reduce cervical cancer incidence rates by a further 4% on top of current HIV control interventions(Hall et al., 2020).

Low and middle-income countries looking to implement and scale-up interventions targeted to eliminating cervical cancer may face a range of financial, logistical and acceptability-based challenges. Multiple studies in LMIC, and high-income, settings report that the HPV vaccine is safe, effective and highly acceptable on both individual and national levels(Brotherton and Bloem, 2018, Brisson et al., 2020). Tanzania has the capacity to draw on the knowledge and past experiences from over 82 countries(Brotherton and Bloem, 2018), and the potential for Gavi funding(Gavi the vaccine alliance, 2020). Achieving high coverage rates as quickly as possible is an essential component for achieving timely cervical cancer elimination in Tanzania, with delays in vaccine and screening scale-up predicted to impact the timing of elimination

and lives saved on the path to elimination. Traditional cervical screening programmes are costly and resource-intensive to implement, as accessible clinics must be set up and funded with equipment and trained staff. This shortage in screening services, in combination with added costs, travel and time-lost for individual women, has resulted in a small number of women in Tanzania (and sub-Saharan Africa in general) having ever received a cervical screening test(Anaman-Torgbor et al., 2020, Runge et al., 2019). However, a range of possibilities exists for minimizing the challenges involved in the roll-out of national organised cervical screening programmes, such as the implementation of "screen-and-treat" models, which aim to reduce the number of clinic visits offering pre-cancer treatment in the same visit as a women's initial screening test(Poli and Petignat, 2020), and implementation of self-collection based HPV-screening, which may increase programme participation without sacrificing effectiveness(Mezei et al., 2017, Sultana et al., 2016, Arbyn et al., 2018). Furthermore, there exist additional options for opportunistic screening of women in these settings, for example, during antenatal care or at sexual health clinics, and for WLHIV, there is the potential to incorporate regular cervical screening within the infrastructure of HIV testing and treatment clinics(Coleman et al., 2016, Fitzpatrick et al., 2019). While opportunistic screening may help to increase screening participation or accessibility for certain groups of women, this analysis intended to estimate the impact of a national routine screening programme, whereby asymptomatic women attend clinics for routine screening. Cervical screening is predicted to rapidly and substantially reduce cervical cancer incidence and mortality rates in the near term for all women, including WLHIV, and cannot be overlooked as an essential component of health care.

In this study, we present a modelled analysis of the impact of adopting the WHO 90-70-90 triple-intervention targets to eliminate cervical cancer, which incorporates recommendations for more intensive screening in HIV-positive women and reducing preventable cervical cancer deaths. The findings from this analysis support the achievability of cervical cancer elimination at a threshold of four cases per 100,000 women in Tanzania within the coming century. Additionally, we find that cervical cancer elimination may be achieved earlier for the subgroup of women who are HIV positive due to sustained high coverage of HPV vaccination and frequent HPV screening. These findings indicate the necessity to plan for WLHIV when defining cervical cancer elimination thresholds and implementing intervention strategies, and in particular, respond to the World Health Organisation's revision of screening guidelines specifically for WLHIV, which were released in July 2021(World Health Organisation 2021). HIV positive women experience higher rates of persistent HPV infection, including non-

vaccine-included subtypes, and are subject to lower rates of precancer treatment success; therefore, WLHIV may require more frequent screening with more sensitive test technologies and precancer treatment with a higher chance of success. The results for WLHIV need to be interpreted in the context of the changing cervical cancer risk among WLHIV and the greater opportunity for cervical screening among WLHIV. As WLHIV are more likely to attend sexual health clinics and receive anti-retroviral therapy treatment for their HIV, this presents a greater opportunity for cervical screening and increases the likelihood that women attend at least some of their cervical screening tests. The effectiveness of HPV vaccination, cervical screening, and cervical cancer treatment scale-up among the general and HIV-positive populations highlights the urgent and ongoing need to engage relevant stakeholders in implementing the triple-intervention targets and setting interim and achievable goals.

Supplementary Material

Impact of delays in meeting HPV vaccination and screening participation targets

The 'WHO 90-70-90' scenario, as described in the main text, considers the impact of HPV vaccination and cervical screening scale-up to target participation rates by the year 2030 (90% vaccination coverage of pre-adolescent girls, and 70% screening participation where 90% of detected pre-cancerous lesions are treated). These targets, set by the World Health Organisation, and modelled in a range of predictive analyses, are aspirational targets designed to motivate the systematic scale-up of cervical cancer prevention interventions. However, it is generally recognised that some countries, especially low-and-middle-income countries including Tanzania, may not necessarily reach these targets within the next ten years. While the Gavi vaccine alliance subsidises HPV vaccine doses for low-income countries, there are still costs and logistical considerations associated with vaccine storage, transportation, and delivery in addition to reaching young females in rural communities or those who have discontinued formal education. In addition, cervical screening in Tanzania is not widespread and predominately VIA-based. As such, implementation of a national far-reaching HPV-based cervical screening program is likely to require significant time and resource investment. This additional sub-analysis aims to quantify the impact that reduction and/or delays in achieving target HPV vaccination and cervical screening rates would have on the predicted timeline to cervical cancer elimination in Tanzania. For both HPV vaccination coverage and cervical screening participation, we consider reductions in achieved rates by up to 30 percentage points and delays in scale-up of up to 20 years. HPV vaccination coverage and screening participation rates were varied

independently of each other. Here, we report the numbers of years that cervical cancer elimination, at a threshold of four cases per 100,000 women per year, is delayed.

Screening participation and vaccine coverage implementation and variation

Screening participation is implemented in the model such that if 70% participation in screening is assumed, 70% of women receive each screening test, and this 70% is randomly selected over the population. Therefore, for HIV negative women who are managed under twice-lifetime HPV testing for their entire lifetime, 9% (0.3^2) will not receive any screening tests, 42% ($2 \times 0.3 \times 0.7$) are screened once in their lifetime, and 49% (0.7^2) receive both their screening tests. However, for women living with HIV, who are managed under three-yearly HPV testing from the time of their diagnosis, the proportion of women who are never screened approaches zero as HIV positive women are eligible for many screens over their lifetime, that is $P(never\ screened) = 0.3^n$ where *n* is the maximum possible number of screening events for that woman. For women diagnosed with HIV at the age of 25, n could be as high as 17 as screening is offered at three-yearly intervals from 25 to 74 years. In this exploratory analysis, we consider eight variations in screening participation over time, which includes a "baseline" assumption of 70% participation achieved by 2030. These variations (Figure 17A) account for participation scaling up to a maximum level of 40%, 50%, 60% or 70%, achieved by 2030, as well as "slow" uptake assumptions, in which the maximum participation is achieved by 2050.

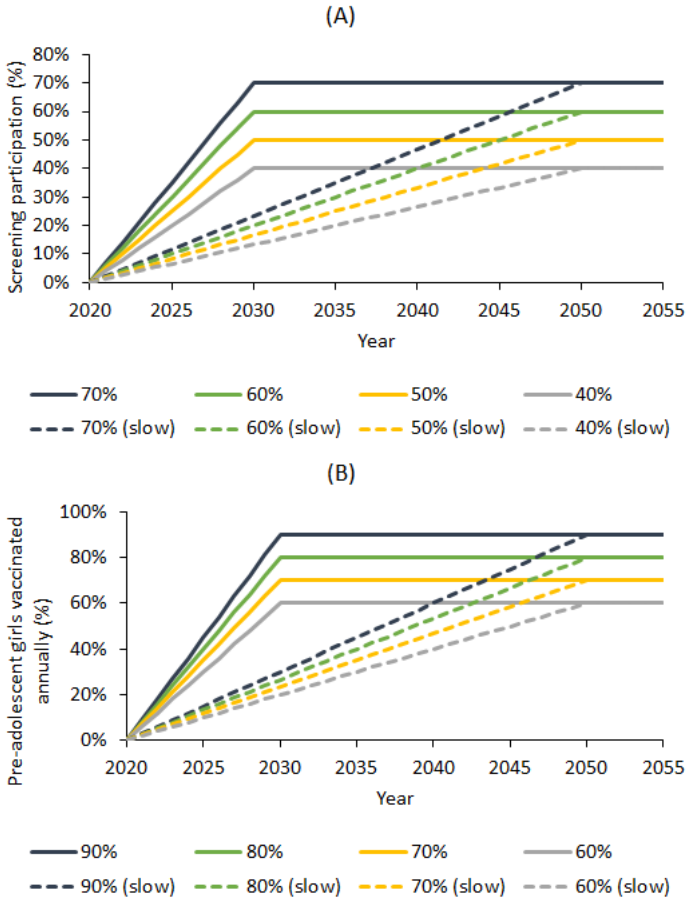


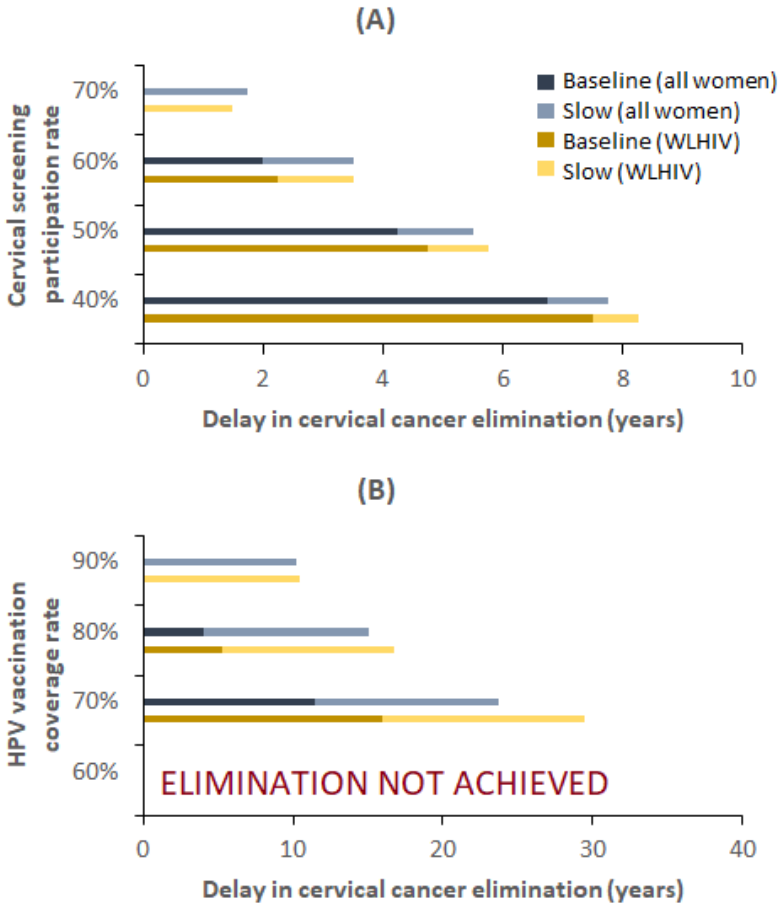
Figure 17 A: annual screening participation, and B: vaccination coverage for baseline and additional scenarios

Vaccination is implemented in the model such that a vaccine coverage of 90% means that, in the specified year, 90% of girls turning ten in that year receive the full HPV vaccine schedule. Here, we do not assume there are opportunities for catch-up vaccination after this time. In a similar vein to the screening participation exploration, we consider vaccination coverage which varies between a maximum of 60-90% achieved by 2030, with slow uptake scenarios that are achieved by 2050. Here, the "baseline" assumption is 90% vaccine coverage achieved by 2030.

The two sets of scenarios, with variations to screening participation and vaccination coverage, are completely independent. That is, where screening participation is varied from 40-70%, we always assume that vaccination coverage is as per the WHO 90-70-90 scenario (90% achieved by 2030). Similarly, where vaccination coverage is varied from 60-90%, screening participation of 70% by 2030 is always assumed.

Modelled impact on the achievement and timing of cervical cancer elimination

Assuming an HPV vaccination coverage of 90% achieved by 2030, if the WHO target for screening participation of 70% is achieved in 2050 rather than in 2030, we predict that the elimination of cervical cancer will be delayed by approximately two years, for all women and for women living with HIV (WLHIV) (Supplementary Figure 18). In the worst-case scenario, where cervical screening participation rates of 40% are achieved by 2050, cervical cancer elimination is delayed by seven years and nine months for all women and eight years and three months for WLHIV.



Supplementary Figure 18 Predicted delay (in years) of cervical cancer elimination compared to the WHO-90-70-90 scenario (90% vaccine coverage and 70% screening participation by 2030) for scenarios assuming (A) screening participation of 40-70% and (B) HPV vaccine coverage of 60-90%. Note that 'baseline' assumptions refer to scenarios where coverage and participation rates hit their maximum by 2030, and 'slow' scenarios achieve these rates 20 years later in 2050.

HPV vaccination coverage and scale-up timing had a substantial impact on cervical cancer elimination timing. Here, assuming screening participation rates of 70% are

achieved by 2030, achieving the 90% vaccine coverage by 2050 rather than 2030 delayed cervical cancer elimination by over ten years for all women, including WLHIV. Achieving an HPV vaccine coverage of 70% by 2030 delayed cervical cancer elimination by over 11 years for all women and 16 years for WLHIV; the impact of delaying achievement of this coverage to 2050 delayed elimination by a further 12 and 14 years, respectively, for all women and WLHIV. Notably, cervical cancer elimination is not predicted to occur in the simulated time horizon (up to the years 2119) for scenarios assuming vaccine coverage of 60% (or lower).

Impression

These results support the findings of the main analysis, which indicate that for the general Tanzanian population, rapid scale-up of HPV vaccination and cervical screening plays an important role in the achievement of cervical cancer elimination. Furthermore, it highlights the necessity to scale up HPV vaccination coverage as quickly as possible, as on average, cervical cancer elimination is delayed by at least six months for every year of delay in maximum HPV vaccination coverage. In addition, WLHIV were more affected than the general population by reductions in the maximum achieved cervical screening participation. Finally, the findings of this sub-analysis must be interpreted in the greater context of reducing cervical cancer incidence and mortality for all women. While the elimination of cervical cancer is an important goal and milestone, saving lives is most important, and any delays to the achievement of cervical cancer elimination necessitate substantial reductions to the number of lives saved along the way.

Chapter 4: The cost-effectiveness of elimination

The previous chapter simulates the WHO triple-pronged intervention strategy for the elimination of cervical cancer in the context of Tanzania, with more frequent screening for women living with HIV. The analysis unpicks the independent and combined impact of high coverage HPV vaccination and cervical screening for all Tanzanian women, including WLHIV, and ultimately concludes that elimination at a threshold of four cases per 100,000 women per year is feasible over the next century. Further, the analysis highlights that while HPV vaccination is a better predictor for eventual cervical cancer elimination, the implementation and rapid scale-up of high-quality cervical screening programmes will be essential for saving lives on the path to cervical cancer elimination.

In July 2021, the WHO released their revised guidelines for cervical screening, which includes specific recommendations for WLHIV. As part of an evaluation of various screening technologies and schedules, the WHO Guidelines Development Group (GDG) performed a detailed assessment of benefits and harms over a range of different screening algorithms/technologies and schedules. These were simulated for all women and WLHIV in the context of an unvaccinated Tanzanian cohort of 100,000 women born in 2005. The model utilised for the GDG's analysis in WLHIV is the same platform developed for this thesis as described in Chapter 2 and Chapter 3; however, that work will not form part of this thesis and is being drafted as a separate body of work.

This chapter, prepared independently of the WHO GDG process, is a detailed harms, benefits and cost-effectiveness analysis of primary HPV testing at various screening intervals and age ranges in a Tanzanian population vaccinated against HPV at 90% coverage from 2030. Two screening algorithms, primary HPV testing with VIA to determine treatment eligibility, and, primary screening with VIA, are simulated for a swathe of possible screening schedules commencing at ages 25, 30 and 35 years with sequentially increasing numbers of lifetime screens. The aim of this chapter is to inform policy surrounding cervical screening schedules in women, including WLHIV, who have been vaccinated against HPV, while recognising that over the short to medium term, where the benefit of HPV vaccination is yet to be realised, more frequent screening is be the most appropriate option.

This study has been submitted for publication, and was conceptualised for this thesis by the candidate (Michaela Hall) and supervisors Professors John Murray and Karen Canfell. The candidate's estimated contribution to this analysis is approximately 80%, involving conceptualisation, study design and methodology, formal analysis,

interpretation of results and visualisation, and development of original and revised manuscript drafts.

Can cervical screening be reduced in future cohorts of women with high HPV vaccination coverage in Tanzania?

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Abstract

Background

HPV vaccination, cervical screening and pre-cancer/cancer treatment underpin the WHO cervical cancer elimination strategy, with target coverage rates by 2030 of 90%, 70% and 90%, respectively. As vaccinated cohorts become eligible for screening in decades to come, they may eventually require fewer screens, with the optimal approach not yet determined. We assessed screening approaches for women offered HPV vaccination in Tanzania, including women living with HIV (WLHIV).

Methods

We used a detailed model of HIV and HPV in Tanzania to estimate the benefits, harms, and cost-effectiveness of screen-and-treat approaches to cervical screening in a cohort born in 2020, assuming 90% vaccine uptake ('vaccinated cohort'), 70% cervical screening participation and 90% treatment of detected cervical pre-cancer/cancer. We evaluated 3-, 5- and 10-yearly primary HPV and VIA screening approaches, starting from ages 25, 30 and 35 years.

Findings

For the general vaccinated population, HPV testing at ages 35 and 45 was the most cost-effective approach while reducing screening harms, with an incremental cost-effectiveness ratio (ICER) of $975.05 at a willingness to pay threshold of $1,061 (2018 GDP per-capita in USD) and a number needed to treat (NNT) of 15.58. In WLHIV, three-yearly HPV testing from age 30 (eight lifetime tests) was cost-effective (ICER=$1015.57, NNT=9.89), although HPV testing at ages 35 and 45 was also on the cost-effectiveness frontier and had a more favourable NNT (ICER=$88.13, NNT=5.33). Population-level implementation of these cost-effective approaches is predicted to achieve cervical cancer elimination longitudinally by 2057 nationally and 2083 for WLHIV in Tanzania.

Conclusion

For younger cohorts of women in HIV-endemic settings, if high (90%) HPV vaccination coverage is achieved, twice-lifetime HPV testing (ages 35, 45) with 3-yearly screening for WLHIV from age 30 (no more than eight lifetime tests) could maximise benefits and cost-effectiveness without compromising the feasibility of cervical cancer elimination.

Background

In November 2020, the World Health Organisation launched a cervical cancer elimination strategy that outlines a three-pronged approach to eliminate cervical cancer as a public health problem(World Health Organisation, 2020). To achieve this, the WHO has set 2030 targets for each country of 90% female HPV vaccination coverage, 70% of women screened with an HPV test at least twice in a lifetime, and 90% treatment of all detected cervical pre-cancer and cancer, referred to as the 90-70-90 targets(World Health Organisation, 2020). Many countries are have already started implementing publicly-funded national HPV vaccination programmes(Bruni et al., 2016). Despite these concerted efforts and the support of charitable organisations such as the GAVI Vaccine Alliance, only 12% of girls in low- and middle-income countries (LMICs) are fully vaccinated, and 70% of girls globally live in countries that have not yet been introduced vaccination(Bruni et al., 2021). There is potential to reduce the disproportionately high burden of cervical cancer in LMICs, as countries find ways to overcome the financial and logistical barriers to vaccinating girls against HPV and delivering cervical screening to women. As of 2015, only five countries in the WHO African region had implemented HPV vaccination in females; however, by 2018, this number had more than doubled, reaching 31% of African countries by June 2020(World Health Organisation 2019b, Bruni et al., 2021). Of these countries, the United Republic of Tanzania is well placed to expand their HPV vaccination programme, which, as of 2019, has achieved 49% HPV vaccination coverage (final dose) of girls aged 9-14 years(Bruni et al., 2021).

An analysis of the impact of HPV vaccination and cervical screening in 78 LMICs, undertaken by the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC), demonstrated that achieving the 90-70-90 targets in LMICs will reduce the median cervical cancer incidence rate by 42% and 97%, by 2045 and the end of 2119, respectively, averting over 73 million cervical cancer cases over the period 2020-2119(Brisson et al., 2020). Assessments of the cost-effectiveness of HPV vaccination reported that HPV vaccination is likely to be cost-effective, possibly even cost-saving, in LMICs(Fesenfeld et al., 2013, Jit et al., 2014). Cervical screening in Tanzania has been opportunistic and has generally used visual inspection with acetic acid (VIA) rather than HPV testing, which is the approach called for in the WHO elimination strategy and other cervical screening guidelines encompassing LMICs(Runge et al., 2019, World Health Organisation, 2020, World Health Organisation 2013b). A cross-sectional study of 478 women in rural and urban Tanzania in 2012 reported that only 6.8% of women have ever received a screening test. Many women were unaware that

screening was available (66.5%), unable to afford the test (49.3%), unable to take time off work to receive a test (25.6%) or were not able to travel the distance required to receive the test (20.0%). Only 4.13% reported that they would not accept cervical screening if available to them(Cunningham et al., 2015). HPV self-collection offers an avenue to increase uptake of cervical screening, and a recent study into the acceptability and feasibility of HPV self-collection in Tanzania found that the women involved preferred self-sampling rather than clinician-collected sampling for HPV testing(Bakiewicz et al., 2020).

In July 2021, the WHO released revised cervical screening guidelines, recommending screening with HPV for women aged 30-50 years at five- or ten-yearly intervals. Women living with HIV (WLHIV) are recommended to screen more frequently at three- or five-year intervals, from age 25 to 50(World Health Organisation 2021). These recommendations are based on accumulated evidence from systematic reviews, meta-analyses and modelling studies, which assessed a range of cervical screening algorithms for all women and for WLHIV, which were generally conducted in the absence of HPV vaccination. The rationale for grounding these cervical screening recommendations in the assumption that women in LMIC are unvaccinated is that it is essential to ensure that maximum cervical cancer cases are prevented through screening while countries implement and scale-up HPV vaccination to meet 90-70-90 targets and because it takes decades for the benefit of HPV vaccination against cervical cancer to be realised. However, taking a long term view, the benefits, harms and cost-effectiveness of cervical screening will likely change over time, with active HPV vaccination scale-up underway and sustained HIV prevention and control further driving down HIV and cervical cancer incidence rates. An analysis that accounts for changing cervical cancer risk over time, driven by HPV vaccination and reducing HIV prevalence, will be necessary for countries to assess the long-term health and budget implications of cervical screening.

This analysis aimed to address this need for a detailed resource, cost, and benefit estimates of implementing cervical screening in all women and women living with HIV, taking into account scaled up pre-adolescent HPV vaccination in the United Republic of Tanzania. We additionally considered whether implementing cost-effective screening strategies would cervical cancer elimination timing in Tanzania, which we had previously estimated could be achieved by 2076-2092 if the 90-70-90 elimination targets were met by 2030(Hall et al., 2021).

Methods

Model description and parameterisation

A dynamic model platform of HIV and HPV transmission, natural history, prevention, and treatment was used to simulate cervical cancer prevention strategies over all ages in Tanzania over 2020 to 2119 inclusive. This platform (first described in Chapter 2 and expanded in Chapter 3) was used to directly support the development of the WHO 2021 cervical screening guidelines specific to WLHIV and has been extensively calibrated and validated using Tanzanian data, accounting for the impact of HIV on the natural history of HPV, in addition to the HIV control interventions currently in place in Tanzania(Hall et al., 2020). Figure 19 is a simplified flowchart depicting the natural histories of HIV and HPV independently, noting that these processes are linked since HPV natural history parameters vary depending on HIV positivity and treatment status. The model reflects the HIV epidemic in Tanzania, utilising observed uptake of HIV control interventions, including voluntary medical male circumcision (VMMC), antiretroviral therapy (ART), and condom usage. Over the HIV-positive population (that is, across all birth cohorts), the proportion who are virally suppressed through ART is assumed to be 47%, where WLHIV have their infection detected and treated throughout their life. A detailed description of the model and parameters, including sexual behaviour, the impact of HIV positivity and ART on HPV natural history, calibration and validation outcomes including HIV epidemic metrics, HPV and CIN prevalence and cervical cancer incidence and mortality, has been described in Chapters 2 and 3(Hall et al., 2020). The current analysis adheres to consensus guidelines for reporting modelled evaluations of HPV-related cancer control (HPV-FRAME), with relevent information appearing in the supplementary material to this chapter(Canfell et al., 2019).

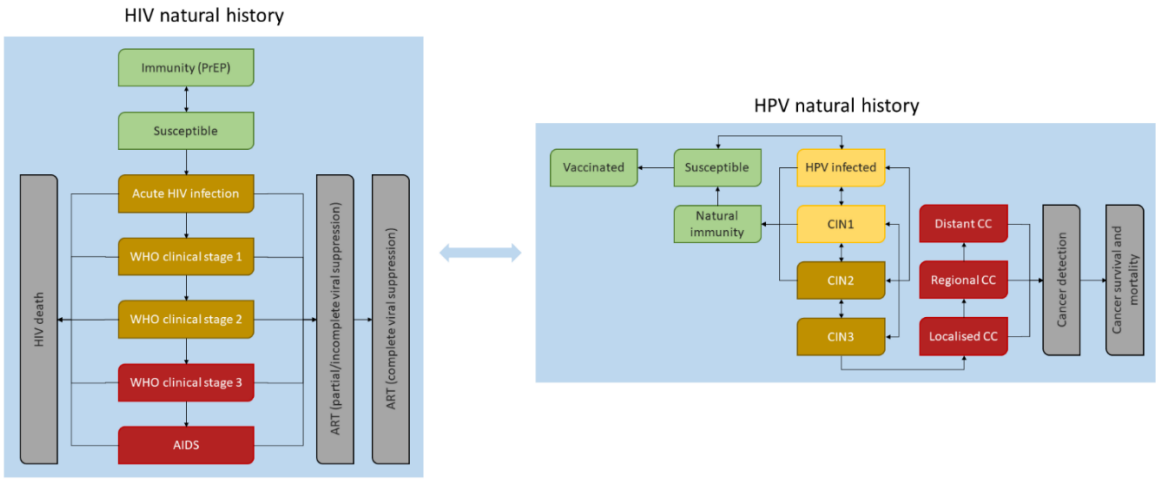

Figure 19 Interacting HIV and HPV model natural history compartments.

Modelled screening approaches

This analysis assumes use of a broad-spectrum vaccine protecting against approximately 90% of invasive cervical cancer, as might be achieved via either direct protection (e.g. with 9-valent vaccine) or cross-protection (e.g. with bivalent vaccine)(Kavanagh et al., 2017). It considers a cohort of women born in 2020, who are the first cohort to receive HPV vaccination at 90% coverage in their tenth year, and receive cervical screening at 70% participation. We assumed that in 2020 9.5% of women diagnosed with cervical cancer would receive appropriate cervical cancer treatment, as is currently the case in Tanzania, but that cervical cancer treatment access will increase to 90% from 2030 to meet WHO 90-70-90 targets(Canfell et al., 2020, World Health Organisation, 2020). To estimate cost-effectiveness and the number of pre-cancer treatments needed to avert one cervical cancer case (NNT), we simulated a baseline *status quo* comparator scenario of no screening, in addition to the potential screen-and-treat cervical screening intervention approaches. A screening approach is a combination of screening technology/algorithm (HPV testing versus primary screening with VIA), screening interval (three-, five-, or ten-yearly), screening age-range (starting from ages 25, 30 and 35, and ending no later than age 54), and a maximum number of cervical screens offered per lifetime (from one to eight lifetime). Each possible screening approach listed in Table 18 was considered for primary HPV testing and primary screening with VIA (86 scenarios in total, with 'no screening' the 87th).

In this evaluation, for simplicity of comparisons of the number of screening events in a lifetime, we focused on screen-and-treat rather than screen-triage-and-treat strategies - although noting that new WHO guidelines specifically recommend that WLHIV are

always triaged after an HPV positive screen. Therefore, the current evaluation and our findings should not be considered directly relevant to current 'real world' screening algorithm decision-making; instead, this provides a high-level analysis of the future effects of screening at different ages for different numbers of lifetime screening events in vaccinated cohorts. In future, the role of triaging in WLHIV and the general population will likely require detailed re-examination in the context of vaccination. Under a screen-and-treat framework, primary HPV testing involves immediate pre-cancer treatment directly following a positive test, with treatment eligibility (excisional or ablative) determined by VIA, and primary screening with VIA involves immediate pre-cancer treatment following an abnormal test, with the type of treatment directly informed by the initial test. In all simulated screening approaches, women who have received pre-cancer treatment are assumed to return at 12 months (90% participation in follow-up testing) for surveillance to confirm treatment success.

Table 18 Screening approaches simulated for both HPV testing and primary screening with VIA strategies.

	Number of lifetime screens
3-yearly screening starting at age 25 years	1 (screen at age 25)
	2 (screen at age 25, 28)
	3 (screen at age 25, 28, 31)
	4 (screen at age 25, 28, 31, 34)
	5 (screen at age 25, 28, 31, 34, 37)
	6 (screen at age 25, 28, 31, 34, 37, 40)
	7 (screen at age 25, 28, 31, 34, 37, 40, 43)
	8 (screen at age 25, 28, 31, 34, 37, 40, 43, 46)
	9 (screen at age 25, 28, 31, 34, 37, 40, 43, 46, 49)
	10 (screen at age 25, 28, 31, 34, 37, 40, 43, 46, 49, 52)
5-yearly screening starting at age 25 years	2 (screen at age 25, 30)
	3 (screen at age 25, 30, 35)
	4 (screen at age 25, 30, 35, 40)
	5 (screen at age 25, 30, 35, 40 45)
	6 (screen at age 25, 30, 35, 40, 45, 50)
10-yearly screening starting at age 25 years	2 (screen at age 25, 35)
	3 (screen at age 25, 35, 45)
	1 (screen at age 30)

3-yearly screening starting at age 30 years	2 (screen at age 30, 33)
	3 (screen at age 30, 33, 36)
	4 (screen at age 30, 33, 36, 39)
	5 (screen at age 30, 33, 36, 39, 42)
	6 (screen at age 30, 33, 36, 39, 42, 45)
	7 (screen at age 30, 33, 36, 39, 42, 45, 48)
	8 (screen at age 30, 33, 36, 39, 42, 45, 48, 51)
	9 (screen at age 30, 33, 36, 39, 42, 45, 48, 51, 54)
5-yearly screening starting at age 30 years	2 (screen at age 30, 35)
	3 (screen at age 30, 35, 40)
	4 (screen at age 30, 35, 40, 45)
	5 (screen at age 30, 35, 40, 45, 50)
10-yearly screening starting at age 30 years	2 (screen at age 30, 40)
	3 (screen at age 30, 40, 45)
3-yearly screening starting at age 35 years	1 (screen at age 35)
	2 (screen at age 35, 38)
	3 (screen at age 35, 38, 41)
	4 (screen at age 35, 38, 41, 44)
	5 (screen at age 35, 38, 41, 44, 47)
	6 (screen at age 35, 38, 41, 44, 47, 50)
	7 (screen at age 35, 38, 41, 44, 47, 50, 53)
5-yearly screening starting at age 35 years	2 (screen at age 35, 40)
	3 (screen at age 35, 40, 45)
	4 (screen at age 35, 40, 45, 50)
10-yearly screening starting at age 35 years	2 (screen at age 35, 45)

Note that strategies involving 3-yearly screening for all women (not HIV positive) were simulated for explorative purposes and are not compatible with the current WHO cervical screening guidelines (2021). These revised guidelines recommend five- to ten-yearly HPV testing for women in the general population aged 30-50 years, and three- to five-yearly HPV testing for WLHIV aged 25-50 years(World Health Organisation 2021). For this single-cohort cost-effectiveness analysis, when comparing cervical screening approaches for the general female population and WLHIV, we have assumed that all women, including WLHIV, are managed under the same cervical

screening schedule. While this does not reflect the reality of the recommendations, this assumption ensures continuity of screening schedule regardless of age at HIV acquisition and ensures a fair comparison between screening approaches at the single-cohort level. Furthermore, this assumption was necessary considering the combinatorially large number of possible simulations that would arise from assuming independent approaches based on HIV positivity. For all screening approaches considered for Tanzanian women born in 2020, screening participation was assumed to be 70% throughout their lifetime. Screening test parameters (HPV and VIA test sensitivity and specificity), pre-cancer treatment rates, and pre-cancer treatment success rates are as reported in Chapter 3(Hall et al., 2021).

All simulations assume that vaccination of Tanzanian females occurs at age 10 with two doses of a high valency HPV vaccine (100% lifelong protection against HPV types 16, 18, 31, 33, 45, 52 and 58 was assumed, which could conceptually be conveyed either by direct or cross-protection) with coverage scaling-up linearly from 0% in 2020 to 90% in 2030. Due to the linear scale-up of HPV vaccination coverage and cervical screening participation to reach target rates of 90% and 70%, respectively, in 2030, the cohort born in 2020 will be the first simulated cohort to receive both HPV vaccination and screening at target rates.

Benefits, harms, and cost-effectiveness

For a cohort of Tanzanian females born in 2020, we estimated age-specific cervical cancer cases and deaths, screening events including pre-cancer treatments and costs incurred through screening and treatment for cervical pre-cancer/cancer. Utilising these outcomes, we report life-years (LYs) saved in relation to lifetime costs to determine an efficiency frontier of screening approaches which is determined by starting with the lowest cost screening approach and iteratively including screening approaches that reflect the greatest increase in LYs relative to incremental cost (i.e. the lowest possible gradient between points)(Drummond et al., 1987). Screening approaches above the efficiency frontier are not considered cost-effective, and we report incremental cost-effectiveness ratios (ICERs) for screening approaches on the efficiency frontier. We additionally report cervical cancer cases prevented as a function of treatments for cervical pre-cancer and calculate the number of treatments needed (NNT) to prevent one cervical cancer case as a measure of the ratio of screening benefits (cervical cancer prevented) versus screening harms (pre-cancer treatments).

Aggregate item costs were obtained via a review of published data (Table 19). All costs are reported from a health-services perspective and incorporate the cost of cervical

cancer treatment and cervical screening programme costs, which include test kits, supplies, equipment, and personnel time. All costs have been inflated to 2018 USD and are discounted annually at 3% from age 25, the youngest age of cervical screening initiation for any of the simulated screening approaches. Decisions regarding cost-effectiveness analysis methodology, including the discounting of costs, and the decision to utilise undiscounted as opposed to discounted life-years, were based on 2019 WHO recommendations for the standardisation of economic analyses, and are consistent with a separate cost-effectiveness analyses being undertaken by the WHO to inform the updated cervical screening guidelines(World Health Organisation 2021, World Health Organisation 2019a).

Table 19 Description of direct medical costs excluding overheads (costs inflated to 2018 USD)

Item	**Assumption (base-case analysis)**	**Assumptions (sensitivity analysis)**
HPV DNA test cost without genotyping.*	$16.43. Assuming a base HPV test cost of $9(The Economist Intelligence Unit Limited, 2021), with personnel ($2.55), supply ($1.23) and equipment ($3.65) costs relevant to South Africa(Lince-Deroche et al., 2015).	Lower bound primary HPV test cost: $11.11 ($9.00, $1.12, $0.62, and $0.37 for an HPV test, personnel, supply, and equipment costs, respectively).
		Upper bound primary HPV test cost: $18.29 ($9.00, $3.19, $1.53, and $4.57 for an HPV test, personnel, supply, and equipment costs, respectively).
Primary VIA screening cost.*	$9.12 Accounting for supplies, equipment and personnel time(Lince-Deroche et al., 2015).	Lower bound VIA test cost: $2.98 ($1.26, $1.00, and $0.71 for personnel, supply, and equipment costs, respectively).
		Upper bound VIA test cost: $12.31 ($2.83, $2.31, and $7.17 for personnel,

Item	Assumption (base-case analysis)	Assumptions (sensitivity analysis)
		supply, and equipment costs, respectively).
Pre-cancer treatment cost for women testing HPV or VIA positive.	$30.31 Accounting for supplies, equipment and personnel time(Nelson et al., 2016).	Not considered in sensitivity analysis.
Treatment cost for women diagnosed with cervical cancer who receive appropriate treatment.+	Localised cancer per treated case: $3,138 Regional cancer per treated case: $1,825 Distant cancer per treated case: $1,822 (Nelson et al., 2016)	Not considered in sensitivity analysis.

**All costs are in 2018 USD and (except for the HPV test cost) have been adapted from ranges published in Lince-Deroche et al. (2015)(Lince-Deroche et al., 2015). The HPV test cost remained as published in the report for the global action on financing cervical cancer elimination(The Economist Intelligence Unit Limited, 2021). +A cohort of females born in 2020 is assumed to receive treatment access at rates of 90% over their lifetime with stage-specific survival as reported in Canfell et al. 2020.(Canfell et al., 2020) Note that before 2020, we assume 9.5% of women diagnosed with cervical cancer receive appropriate treatment (as observed); from 2020 to 2030, this is linearly scaled up to 90% (elimination strategy target) and maintained at 90% thereafter irrespective of treatment modality (screen- versus symptomatic-detection)(Canfell et al., 2020, World Health Organisation, 2020).*

We performed multiple one-way sensitivity analyses on test costs, the discount rate for effects (Lys), and screening approaches offered to WLHIV before HIV diagnosis to determine cost-effective screening approaches under different assumptions. Here, we repeated the initial cost-effectiveness analysis six times, each with a single variation in either HPV or VIA test cost or method of health-benefit calculation. Cost assumptions relating to sensitivity analyses are reported in Table 19. For the sensitivity analysis assessing the impact of undiscounted LYs, we instead calculated ICERs using LYs discounted at 3% from age 25. Finally, we considered a scenario for WLHIV only, where no screening is offered before diagnosis with HIV.

Population-level analysis

To illustrate the real-world expected impact of a transition to lower frequency screening for cohorts receiving HPV vaccination at high (90%) coverage, we simulated the following scenarios at population (i.e. not cohort) level from 2020 to 2119: (i) women

born in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, and WLHIV are screened at 3-yearly intervals from ages 30-54 years (8 lifetime tests), and (ii) women born in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, regardless of HIV status. In both scenarios, women born before 2020 are screened with HPV 5-yearly from ages 30-50, or 3-yearly screening from ages 25-50 for WLHIV, per the WHO 2021 cervical screening guidelines(World Health Organisation 2021). Screening approaches simulated for vaccinated cohorts were chosen *a priori* based on the outcome of the cost-effectiveness analysis for Tanzanian women born in 2020. The chosen screening approaches were either most cost-effective or had the most favourable ratio of benefits to harms (for the general population, this was the same strategy).

Screening participation rates increase linearly from 0-70% over 2020-2030 (remaining stable thereafter), and vaccination coverage rates of pre-adolescent females increase linearly from 0-90% over 2020-2030. Screening approaches for women born in 2020 or later for all women and WLHIV were selected based on being the most cost-effective screening approach or having the most favourable balance of benefits to harms as found in the single-cohort analysis. This population-level analysis differs from the single-cohort benefits, harms and cost-effectiveness analysis by assuming specific, differential screening recommendations for WLHIV from the general population; therefore, it presents a more accurate and detailed prediction for how these screening approaches, if implemented, would affect the population.

Results

Analysis outcomes

Results for the 2020 birth cohort were extracted from a simulation of the entire Tanzanian population over 2020-2119, ensuring women in the cohort were subject to appropriate year-specific risks of HPV and HIV incidence and control interventions. For the general population of Tanzanian women born in 2020, primary HPV testing was more effective and more expensive than primary screening with VIA. For WLHIV, primary testing with HPV was more effective and less costly than primary screening with VIA (Figure 20). Screening approaches involving the same number of lifetime screens cluster together, with a broadly linear increase in both effects (LYs) and costs as the number of lifetime screens increases. The increase in costs was smaller in relation to the incremental benefits for schedules involving primary HPV testing (bolder markers) than for primary screening with VIA (fainter markers). Screening approaches above the efficiency frontier in Figure 20 are not cost-effective, and approaches on the

efficiency frontier are summarised in Table 20 10-yearly HPV testing from age 35 (2x lifetime) is cost-effective for the general vaccinated population (ICER=$975.05, WTP=$1,061) with screening no more than eight times per lifetime (3-yearly HPV testing from age 30) being cost-effective for vaccinated WLHIV (ICER=$1,015.57). Generally, the costs are higher for WLHIV than for women in the general population due to their increased (5-6x) rates of cervical cancer and subsequent treatment (even in the context of vaccination); however, for the same reason, the expected benefit of cervical screening is also higher for WLHIV.

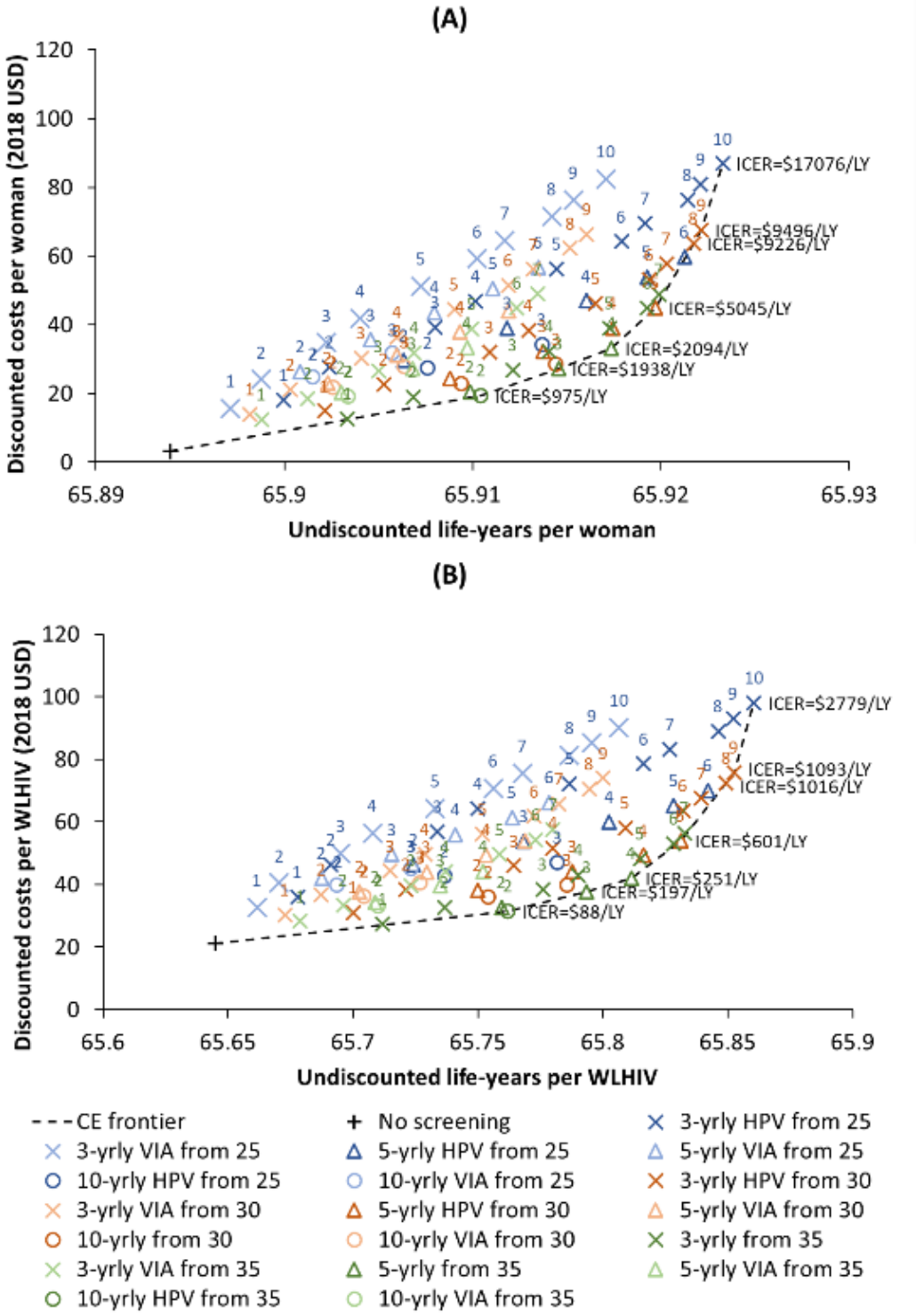

Figure 20 Screening programme costs (3% annual discounting from age 25) versus undiscounted life-years (LYs) for HPV-testing and primary VIA screening approaches per (A) Tanzanian woman and (B) Tanzanian WLHIV, born in 2020 (90% vaccine uptake). Note that panels (A) and (B) appear on different scales.

Table 20 Screening approaches identified on the efficiency frontier. Note that all approaches assume primary HPV testing and that strategies with an ICER < $1,061/LY (Tanzania 2018 per-capita GDP in USD) are considered cost-effective.

Population group	**Primary HPV screening schedules falling along the efficiency frontier**
Average population (irrespective of HIV status)	• No screening • 10-yearly from 35 years (2 lifetime screens, ICER=$975.05/LY) • 5-yearly from 35 years (3 lifetime screens, ICER=$1,938.49/LY) • 5-yearly from 35 years (4 lifetime screens, ICER=$2,094.16/LY) • 5-yearly from 30 years (5 lifetime screens, ICER=$5,045.03/LY) • 3-yearly from 30 years (8 lifetime screens, ICER=$9,225.95/LY) • 3-yearly from 30 years (9 lifetime screens, ICER=$9,495.74/LY) • 3-yearly from 25 years (10 lifetime screens, ICER=$17,076.33/LY)
Women living with HIV	• No screening • 10-yearly from 35 years (2 lifetime screens, ICER=$88.13/LY) • 5-yearly from 35 years (3 lifetime screens, ICER=$196.76/LY) • 5-yearly from 35 years (4 lifetime screens, ICER=$251.01/LY) • 5-yearly from 30 years (5 lifetime screens, ICER=$601.15/LY) • 3-yearly from 30 years (8 lifetime screens, ICER=$1,015.57/LY) • 3-yearly from 30 years (9 lifetime screens, ICER=$1,093.00/LY) • 3-yearly from 25 years (10 lifetime screens, ICER=$2,778.52/LY)

Primary HPV testing was associated with a greater number of cervical cancer cases prevented and required fewer pre-cancer treatments than primary screening with VIA with the same number of lifetime screens (Figure 21). In Figure 21, schedules involving

the same number of lifetime screens cluster together, with a linear increase in both the number of treatments and cancers prevented as the number of lifetime screens increases. The gradient of this increase was lower for schedules involving primary HPV testing (bolder markers) than for primary screening with VIA (fainter markers), indicating that fewer additional pre-cancer treatments are required for the incremental gain in the number of cervical cancer cases prevented. The only exception is 3-yearly screening from age 25 (1-2 lifetime tests), where primary HPV testing resulted in more pre-cancer treatments for the general population and WLHIV compared to VIA.

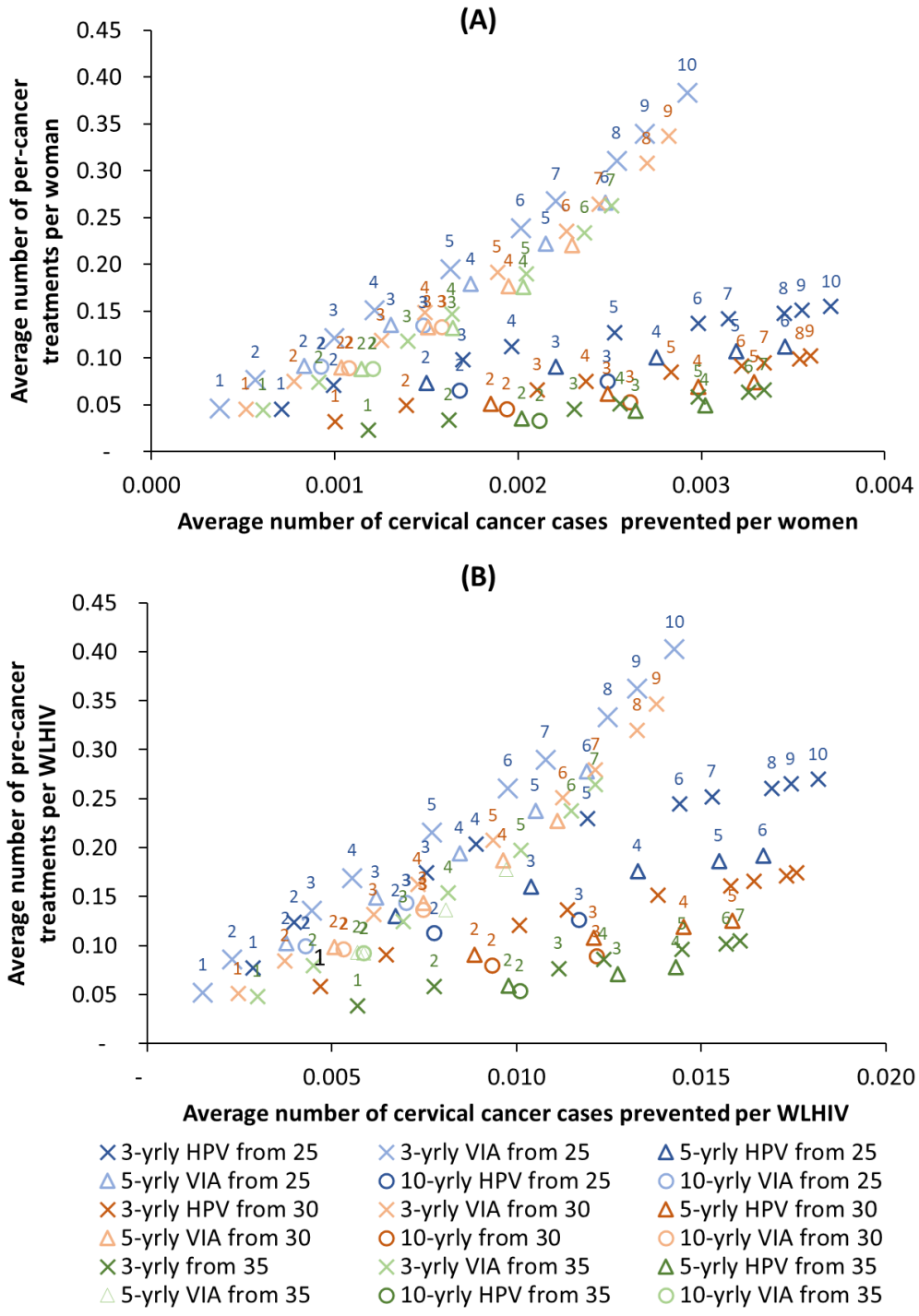

Figure 21 Average lifetime number of pre-cancer treatments versus cases of cervical cancer prevented for HPV-testing and primary VIA screening schedules per (A) Tanzanian woman and (B) Tanzanian WLHIV, born in 2020. Schedules in the lower-right quadrant have a favourable balance of benefits to harms.

We calculated the number of cervical pre-cancer treatments (ablative/excisional) required to prevent one cervical cancer case (NNT) (Figure 22). NNTs are stratified by HIV positivity and screening technology and colour coded from most efficient (lowest NNT = blue) to least efficient (highest NNT = red). The schedule with the lowest NNT for all women, including WLHIV, is 10-yearly HPV testing from age 35 (2 lifetime tests), with an NNT=15.58 for the general population and NNT=5.33 for WLHIV. The next best was 5-yearly HPV testing from age 35 (4x lifetime tests), with NNT=16.41 and NNT=5.42 for the general population and WLHIV. For each screening schedule, primary HPV screening was associated with a lower NNT than the corresponding primary VIA strategy. Similarly, for each screening approach, the NNT was lower for WLHIV than for the general population due to WLHIV with cervical pre-cancer being at greater risk of cervical cancer than HIV-negative women, and therefore a higher probability that a pre-cancer treatment will prevent cervical cancer in WLHIV.

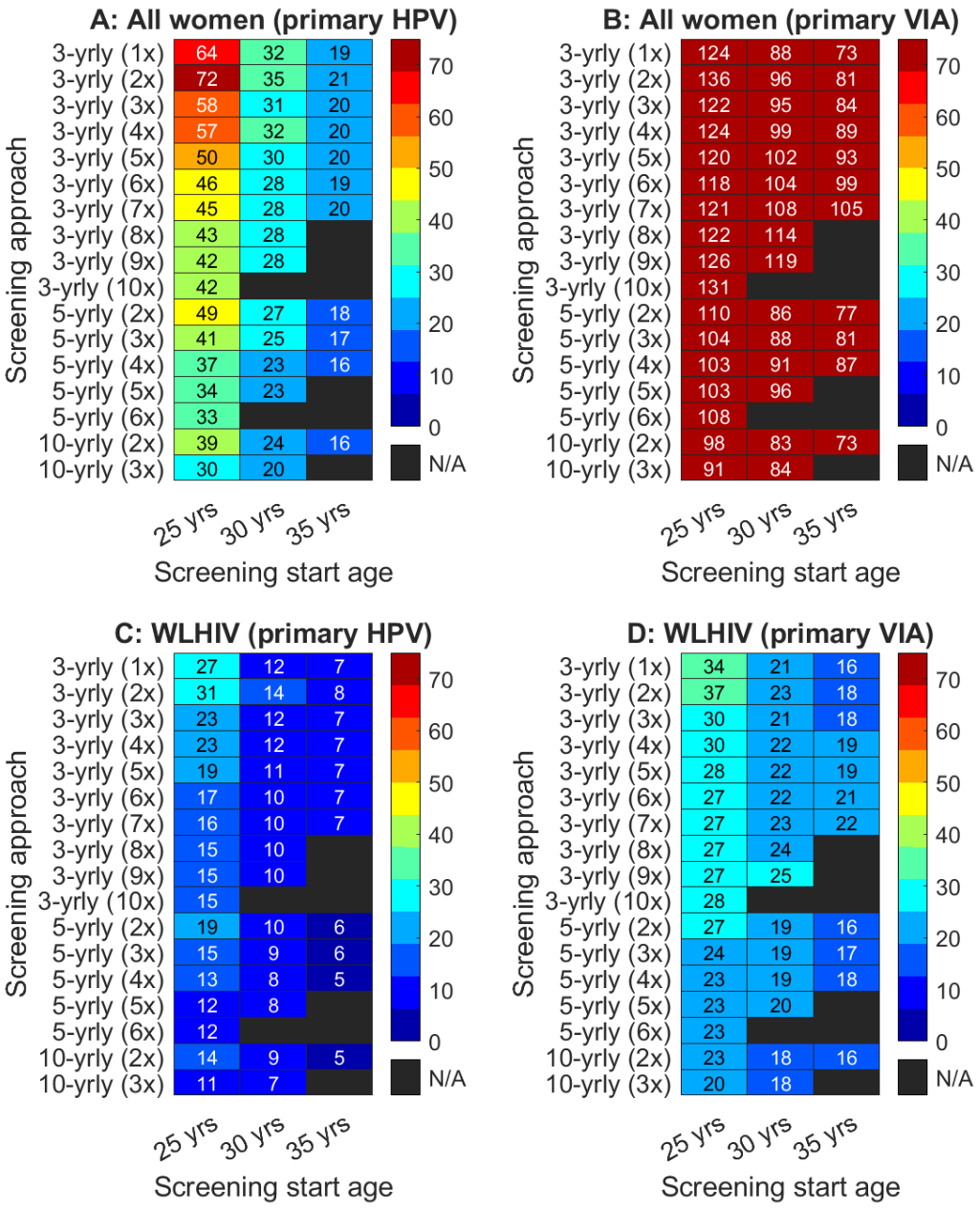

Figure 22 Number needed to treat (NNT) of cervical pre-cancer treatments (either ablative or excisional) required to prevent one case of cervical cancer for a vaccinated cohort of Tanzanian women born in 2020, stratified by HIV positivity status. Screening approaches where the calculated NNT appears as "N/A" were not simulated.

Sensitivity analysis outcomes

In one-way sensitivity analysis, we re-estimated the cost, life-years and incremental cost-effectiveness ratios for each strategy for each parameter variation, presented in

the supplementary material (Figure 25 to Figure 28). In summary (Table 21), the parameter ranges considered in sensitivity analysis impacted which cervical screening approaches were on the efficiency frontier and which were cost-effective at a WTP of $1,061 (2018 USD). In particular, cost-effectiveness was sensitive to reductions in VIA test costs (lower assumed cost of $2.98 per visit) and utilisation of annually discounted (3% from age 25) LYs (instead of undiscounted LYs as per the base-case assumption). Assuming lower-bound VIA cost assumptions, primary screening approaches using VIA were on the efficiency frontier for the cheapest screening approaches; however primary HPV testing was on the frontier for screening approaches assuming more than 4 lifetime screens. For each screening approach, the ICER calculated using discounted life-years (3% annually from age 25) was less favourable (higher) than when ICERs used undiscounted LYs. For the general population of women, it was not cost-effective under this discounting assumption to offer any screening to cohorts of women receiving high-valency HPV vaccination at 90% coverage (ICER ≥ $2,588); however, it was still cost-effective to screen cohorts of WLHIV vaccinated with HPV9, with the most cost-effective strategy being 5-yearly HPV from age 35 (4 lifetime tests, ICER=$876.87).

Table 21 Screening approaches on the efficiency frontier and cost-effective screening approach for a cohort of general female population and WLHIV born in 2020 in scenarios considered in the sensitivity analysis.

Sensitivity analysis scenario	**Screening approaches on the efficiency frontier (all women)**	**Screening approaches on the efficiency frontier (WLHIV)**	**Cost-effective screening approach (WTP $1,061)**
HPV test costs (lower-bound)	Same as baseline scenario, that is: No screening, 10-yearly from 35 years (2 lifetime tests), 5-yearly from 35 years (3 lifetime tests),	Same as the baseline scenario, that is: No screening, 10-yearly from 35 years (2 lifetime tests), 5-yearly from 35 years (3 lifetime tests),	General population: 10-yearly HPV testing from age 35 (2 lifetime tests, ICER=$644.317) WLHIV: 3-yearly HPV testing from age 30 (9 lifetime tests, ICER=$725.16).

	5-yearly from 35 years (4 lifetime tests), 5-yearly from 30 years (5 lifetime tests), 3-yearly from 30 years (8 lifetime tests), 3-yearly from 30 years (9 lifetime tests), 3-yearly from 25 years (10 lifetime tests)	5-yearly from 35 years (4 lifetime tests), 5-yearly from 30 years (5 lifetime tests), 3-yearly from 30 years (8 lifetime tests), 3-yearly from 30 years (9 lifetime tests), 3-yearly from 25 years (10 lifetime tests)	
HPV test costs (upper-bound)	Same as the baseline scenario (see above).	Same as the baseline scenario (see above).	General population: No screening (ICER for 10-yearly HPV from age 35 (2 lifetime tests) = $1,091.47) WLHIV: 5-yearly HPV testing from age 30 (9x lifetime tests, ICER=$749.54).
VIA test costs (lower-bound)	No screening, 10-yearly VIA from age 35 (2 lifetime tests), 5-yearly VIA from age 35 (4 lifetime tests), 3-yearly VIA from 35 years (7 lifetime tests), 5-yearly HPV from age 35 (4 lifetime tests),	No screening, 5-yearly VIA from age 35 (3 lifetime tests), 3-yearly VIA from age 35 (6-7 lifetime tests), 5-yearly HPV testing from 35 (4 lifetime tests), 5-yearly HPV from age 30 (5 lifetime tests),	General population: 5-yearly VIA from age 35 (4 lifetime tests, ICER=$1,002.05). WLHIV: 3-yearly HPV from 30 (8 lifetime tests, ICER=$1,027.92).

	5-yearly HPV from age 30 (5 lifetime tests), 3-yearly HPV from age 30 (8-9 lifetime tests), 3-yearly HPV from age 25 (10 lifetime tests).	3-yearly HPV from 30 (8-9 lifetime tests), 3-yearly HPV from 25 (10 lifetime tests).	
VIA test costs (upper-bound)	Same as the baseline scenario (see above).	Same as the baseline scenario (see above).	Same as the baseline scenario (see above).
Life-years (3% annual discounting)	No screening, 10-yearly HPV from age 35 (2 lifetime tests), 5-yearly HPV from 35 (3-4 lifetime tests), 5-yearly HPV from age 25 (5 lifetime tests), 3-yearly HPV from age 25 (10 lifetime tests)	No screening, 3-yearly HPV from age 35 (1 lifetime test), 10-yearly HPV from age 35 (2 lifetime tests), 5-yearly HPV from age 35 (3-4 lifetime tests), 5-yearly HPV from age 30 (5 lifetime tests), 3-yearly HPV from age 30 (8-9 lifetime tests), 3-yearly HPV from age 25 (10 lifetime tests).	General population: No screening WLHIV: 5-yearly HPV from age 35 (4 lifetime tests, ICER=$876.87)

Population-level outcomes

For the population-level analysis, we simulated two scenarios that were chosen based on cost-effectiveness and harms versus benefits outcomes in the single-cohort

analysis. These screening approaches are: (i) women born in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, and WLHIV are screened at 3-yearly intervals from age 30 (8 lifetime tests), and (ii) women born in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, regardless of HIV status. In both scenarios, women born before 2020 were screened with HPV at 5-yearly intervals from ages 30-54. WLHIV received 3-yearly HPV screening from ages 25-54 according to the current WHO recommendations.

Table 22 summarises cervical cancer cases averted cumulatively by 2069 (and 2119) and age-standardised cervical cancer incidence rates in 2069 (and 2119) among the Tanzanian population (cross-sectional, all birth cohorts), assuming screening approaches simulated for the general female Tanzanian population and the subpopulation of WLHIV. Compared to a no screening comparator, we predict that under scenario (i) assumptions 318,925, and 602,561 cervical cancer cases would be averted by 2069 and 2119, respectively. Among these averted cervical cancer cases, 53,291(17%) and 96,977 (16%) are attributable to the population subgroup of WLHIV. Compared to scenario (i), scenario (ii) assumptions, that is, 10-yearly HPV testing at ages 35 and 45 for all women, including WLHIV, would result in 13,797 fewer cervical cancers averted in WLHIV, over the period 2020-2119 inclusive. For both scenarios (i) and (ii), cervical cancer elimination (age-standardised rate [ASR] <4/100,000 per year) is predicted to occur for all women, including WLHIV, within the simulated timeframe (2057 for the whole population; 2083 or 2111 for the subgroup WLHIV depending on screening approach for WLHIV).

Table 22 Cervical cancer cases averted compared to no screening and age-standardised rates (ASR) of cervical cancer incidence per 100,000 women for the general population of Tanzanian women and WLHIV.[+]

	Simulation outcomes across the general Tanzanian female population (includes HIV-negative and WLHIV)		**Simulation outcomes specific to WLHIV only in Tanzania**	
	Scenario (i): WLHIV born in 2020 or later are screened 3-	*Scenario (ii): WLHIV born in 2020 or later are screened at*	*Scenario (i): WLHIV born in 2020 or later are screened 3-*	*Scenario (ii): WLHIV born in 2020 or later are screened at*

	yearly from 30-54 years	*ages 35 and 45 years*	*yearly from 30-54 years*	*ages 35 and 45 years*
Total cervical cancer cases averted over 2020-2069 inclusive (and over 2020-2119 inclusive), compared to no screening	316,449 (591,622)	316,734 (583,054)	52,232 (91,747)	52,516 (83,179)
Age-standardised rate (ASR) of cervical cancer per 100,000 women in 2069 (and 2119)	1.74 (0.34)	1.95 (0.44)	7.87 (1.17)	11.97 (3.16)
Predicted year of cervical cancer elimination (ASR<4/100,000)	2057	2057	2083	2111

+ ASRs are calculated using the United Nations 2019 World Female Population for ages 0-99 years(United Nations DESA / Population Division, 2017).

For the general Tanzanian female population, the number of primary tests (routine HPV tests) is predicted to increase over time in line with population growth until approximately 2050, when vaccinated cohorts born in 2020 or later begin to enter the cervical screening program and are therefore screened only twice per lifetime at ages 35 and 45, rather than 5-yearly from ages 30-50. There is a slight, steady decrease in primary test numbers as women born before 2020 slowly age out of the target age for cervical screening, before they steadily increase again from 2080 onwards, again reflecting population growth. Eventually, in the decade of 2110-2119, we predict approximately 134,775,000 HPV tests across the population, assuming WLHIV born in 2020 or later are screened 3-yearly from age 30 (8x lifetime tests). If WLHIV born in 2020 or later are screened twice per lifetime, at ages 35 and 45, we predict that in the decade spanning 2110-2119, there will be approximately 3,646,000 fewer primary HPV tests, compared to scenario (ii) (Figure 23, right axis). Pre-cancer treatment numbers (ablative and excisional) will follow a broadly similar pattern to that predicted for primary screening tests. Under scenario (i) assumptions, we expect a total of 186,000

pre-cancer treatments performed over 2110-2119, with only 107,000 performed under scenario (ii) assumptions (Figure 23, left-axis).

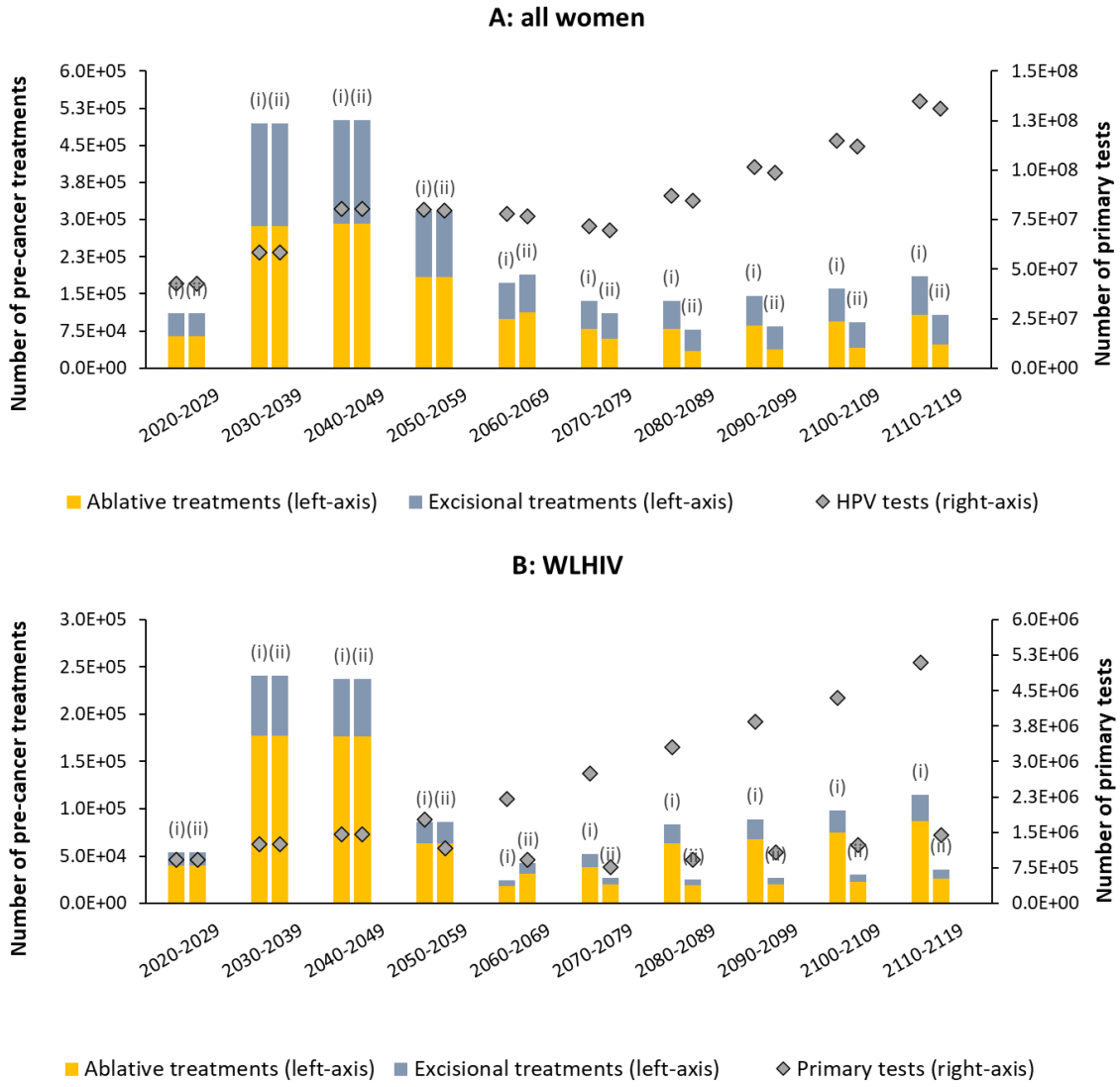

Figure 23 Number of cervical pre-cancer treatments (left axis) compared to the number of primary tests with HPV (right axis) in vaccinated cohorts of (A) all women and (B) WLHIV : (i) women born in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, and WLHIV are screened at 3-yearly intervals from age 30 (8 lifetime tests)(left bar in paired series), and (ii) women born in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, regardless of HIV status. Women born before 2020 are assumed to have been screened with HPV 5-yearly from ages 30-54, with 3-yearly screening from ages 25-54 for WLHIV (right bar in paired series).

Once 70% participation in cervical screening is reached in 2030, we predict near-linear increases in annual screening programme costs until the gradual phase-in of less frequent screening, by birth year, occurs in 2050 for the general Tanzanian female

population and WLHIV (Figure 24, bold lines). However, this analysis assumes that 90% of cervical cancers are appropriately treated, per the WHO 90-70-90 targets. Therefore, these increasing screening programme costs are offset by expected savings in cancer treatment costs due to cervical cancer cases being prevented (Figure 24, dashed lines). This cost offset brings the overall cost due to cervical screening, from a healthcare perspective, to approximately $209,653,000 annually by 2119, assuming 3-yearly HPV testing from age 30 (8 lifetime tests) for WLHIV (i.e. scenario (i) assumptions). This annual cost would be reduced by $3,927,000 under scenario (ii) assumptions where WLHIV born in 2020 or later are screened twice-lifetime at ages 35 and 45. Assuming increasing cervical screening program costs (excluding overheads) are offset by expected savings in cancer treatment costs due to prevented cases, screening in WLHIV is predicted to be cost-saving from 2046 to 2066 under scenario (i) assumptions and from 2046 to 2081 under scenario (ii) assumptions.

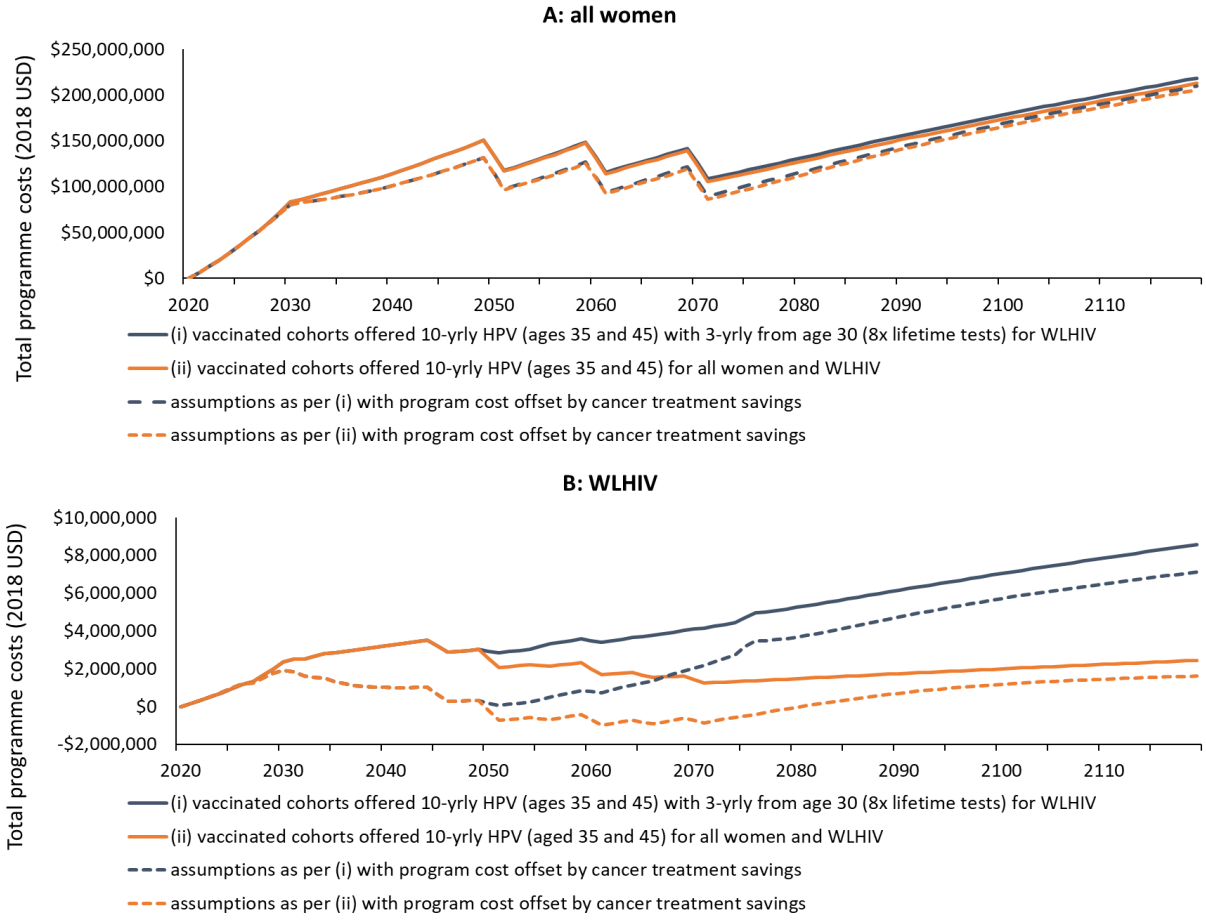

Figure 24 Annual cervical screening programme costs for (A) the general population of Tanzanian women and (B) WLHIV for simulated screening approaches: (i) women born in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, and WLHIV are screened at 3-yearly intervals from age 30 (8x lifetime tests) years, and (ii) women born

in 2020 or later receive twice-lifetime HPV testing at ages 35 and 45, regardless of HIV status. Women born before 2020 are screened with HPV 5-yearly from ages 30-54, with 3-yearly screening from ages 25-54 for WLHIV.

Discussion

In this study, we analysed the high-level benefits, harms, and cost-effectiveness of a range of potential screening regimes in the context of HPV vaccination, focussing on the relative impacts and harms of alternative approaches to the number of lifetime screes, age at screening and primary screening test. We considered both the general (overall) population of Tanzanian women and the subgroup of WLHIV in Tanzania, assuming that cohorts born in 2020 would be offered HPV vaccination with high uptake. For the general population (i.e. not WLHIV specifically), the most cost-effective screening approach (at a WTP of $1,061) was 10-yearly HPV testing at ages 35 and 45 (2 lifetime tests; ICER=$975.05). For the population subgroup of WLHIV, the most cost-effective screening approach was 3-yearly HPV testing from age 30 (8 lifetime tests; ICER=$1,015.57). Regarding minimising harms compared to screening benefits, 10-yearly HPV from age 35 (2 lifetime tests) was the most favourable strategy for the general Tanzanian female population and for WLHIV, with NNTs of 15.58 5.33, respectively. However, the most cost-effective screening strategy for WLHIV, despite not minimising harms versus benefits for this population subgroup (NNT=9.89), had a lower NNT than the most favourable screening approach for the general population (NNT=15.58). Across all screening intervals and age ranges, primary HPV testing was more cost-effective and resulted in a lower NNT than primary screening with VIA. For both HPV and VIA-based screening schedules, it was more favourable to delay the start age for cervical screening until age 35, with substantially lower cost-effectiveness and greater harms predicted for schedules starting at age 25 years.

We focused on screen-and-treat rather than screen-triage-and-treat approaches for simplicity of comparisons of the number of screening events in a lifetime. However, the revised WHO guidelines specifically recommend triage after an HPV positive screen(World Health Organisation 2021). Therefore, the current evaluation and our findings should not be considered directly relevant to current ‘real world’ screening algorithm decision-making; but instead provides a high-level analysis of the future effects of screening at different ages for different numbers of lifetime screening events in vaccinated cohorts. In future, the role of triaging, which will impact the ratio of benefits to screening harms, in WLHIV and the general population will likely require detailed re-examination in the context of vaccination. Additionally, many screening

approaches, for example, 3-yearly screening in the general population, were simulated for completeness and illustrative purposes; screening in these women need be more frequent than 5-yearly from age 30, as recommended by the revised WHO screening guidelines(World Health Organisation 2021). From a programmatic standpoint, implementation of tailored screening programmes which account for HPV vaccination status may be complicated, therefore, it is not necessarily realistic to assume two concurrent screening programs will be in operation while unvaccinated cohorts are phased out of cervical screening. Furthermore, current cervical screening initiatives in Tanzania are predominately limited to VIA-based screening in the Northern Provinces, and significant investment will be required to achieve WHO screening recommendations(Runge et al., 2019). This analysis extends on the existing literature assessing the cost and effectiveness of various cervical screening programs in sub-Saharan African countries, as these do not consider cost-effectiveness over time, HPV vaccination scale-up, and the transmission, prevalence and treatment of human immunodeficiency virus (HIV)(Mezei et al., 2018, Zimmermann et al., 2017, Campos et al., 2017, Ralaidovy et al., 2018). Despite the protection against cervical cancer afforded by high-coverage HPV vaccination, the most cost-effective screening approach for vaccinated WLHIV was found to involve relatively frequent screening (3-yearly HPV testing from age 30; 8 per lifetime), which is considerably more intensive than the optimal approach for the general population (twice lifetime at ages 35 and 45). Nonetheless, this finding is not inconsistent with a cost-effectiveness analysis assessing cervical screening approaches in unvaccinated WLHIV in South Africa, which reported 2-yearly HPV testing starting at age 25 was cost-effective, despite assuming HPV test costs of up to $45.35 (in 2011 USD)(Campos et al., 2018). An analysis of the cost-effectiveness of HPV testing in Uganda reported that in the absence of HPV vaccination, provider-collected HPV testing once per lifetime could achieve cervical cancer incidence reductions of 21.6%, and an ICER ($/life-years saved) of $190 (reported in 2011 USD as $170)(Campos et al., 2017). The Uganda analysis also investigates the potential for HPV self-collection campaigns to reduce cost and increase screening participation, which has already been piloted in Tanzania(Bakiewicz et al., 2020). Based on the ASPIRE trial in Uganda, a retrospective cost analysis simulated HPV screen-and-treat screening schedules for once, twice, and five-times lifetime cervical screening, compared to primary VIA screening(Mezei et al., 2018). The authors found that HPV screen-and-treat schedules dominated VIA-based screening strategies and could achieve ICERs of $138 (reported in 2014 USD as $130), $255 (reported in 2014 USD as $240) and $499 (reported in

2014 USD as $470)(Mezei et al., 2018). While the current study found that for all women, including WLHIV, and most screening schedules, primary HPV testing dominated primary screening with VIA, additional analysis may need to be performed to determine whether this would still be the case should an additional clinic visit be required following testing.

A WHO-CHOICE analysis assessed the cost-effectiveness of combined HPV vaccination and cervical screening and found that HPV vaccination with VIA screening for women aged 30-49 years was more cost-effective than HPV vaccination with five-yearly HPV testing for women aged 30-49 years(Ralaidovy et al., 2018). These findings (presented in International Monetary Units '*I'* which are equivalent to the US dollar), which are inconsistent with ours, were based on an assumption of higher costs associated with primary HPV testing (I$31.37 overall assuming an I$21.03 recall cost) compared to primary screening with VIA (I$2.79) and may not have utilised more recent data syntheses on VIA's relative (in)effectiveness for cervical cancer prevention(Shastri et al., 2014, International Agency for Research on Cancer (IARC), 2021). This difference highlights the uncertainty of intervention assumptions without future knowledge of technological advancements and changes in supply and demand and the importance of updating analyses as evidence on interventions and data on screening and treatment costs change. In the present study, the costs utilised were based entirely on recently published literature for regions representative of Tanzania. Nonetheless, these may not reflect the true cost of cervical screening and omit the cost of infrastructure scale-up, although such infrastructure investment may be considered as part of universal healthcare and have uses extending beyond that of cervical cancer prevention and treatment. In addition to cost uncertainty, the findings of this analysis may be limited by an incomplete understanding of the long-term efficacy of HPV vaccines in women living with HIV. While studies report good immunogenicity following HPV vaccination, there is insufficient published data on CIN and cervical cancer in WLHIV vaccinated against HPV(Zizza et al., 2021). Our findings that it is safe to reduce cervical screening (to some degree) in vaccinated WLHIV are based on the assumption that HPV vaccination is as protective for WLHIV as it is for HIV negative; should this be found not to be the case, the safety of reduced screening for this subgroup would need to be revised.

Our previous analysis (in Chapter 3) assessing the feasibility and timing of cervical cancer elimination in Tanzania for all women and WLHIV estimated cervical cancer elimination could be achieved for all women by 2076-2092 and for WLHIV by 2061-2078(Hall et al., 2021). The population-level predictions provided in this current

analysis estimate that cervical cancer elimination for the general Tanzanian population will occur in 2057 and no sooner than 2083 for WLHIV. This inconsistency in the estimated elimination year is attributed to differences in screening frequency and age-range assumptions for the general population and WLHIV, which were informed by the release of the updated WHO cervical screening guidelines(World Health Organisation 2021). In short, the current analysis assumes that the general population are screened more (5-yearly from age 30 versus 10-yearly from age 35), WLHIV are screened less (screening cessation before age 55, versus no screening cessation), and that screening is reduced for HPV vaccinated cohorts. This study additionally differs from other published WHO elimination analyses, which do not assume gradual scale-up of participation and coverage rates but rather assume a step-wise increase in coverage of cervical screening and treatment to meet the 90-70-90 targets, and further scale-up beyond 2030(Canfell et al., 2020, Brisson et al., 2020).

The cost-effectiveness component of this analysis is based on calculations over a single birth cohort of Tanzanian women (born in 2020) rather than the population-level simulated outcomes. Utilising this cohort allowed a fair comparison between screening programmes offered over the course of a woman's life while directly accounting for the anticipated ongoing reduction in cervical cancer risk among cohorts vaccinated against HPV at 90% coverage. Future analyses of this nature may incorporate quality of life or health-adjusted life-year estimates if appropriate utility weights become available for women living with HIV. Finally, the overall conclusions of this analysis were found to be sensitive to discount rates applied to effects; namely, for a scenario assuming life-years were discounted at 3%, cervical screening was found to be not cost-effective in the general population of vaccinated Tanzanian women at a threshold of $1,061, a finding which must be interpreted in the context of the low (relative to global standards) willingness-to-pay threshold. In order to provide illustrative cost estimates and cervical cancer predictions over time, we present population-level outcomes in Figure 23 and Figure 24. The primary finding of this analysis is that for cohorts of women vaccinated against HPV, it is cost-effective to delay the commencement of cervical screening to age 30 for WLHIV and age 35 for all other women. These findings indicate that it is safe and cost-effective to reduce the lifetime number of screening events in women who have received broad-spectrum HPV vaccination, with optimal screening dependent on HIV status. While there is an ongoing need to protect unvaccinated women against cervical cancer, future screening programmes may be designed to account for the changing underlying cervical cancer risk due to HPV vaccination. This

work provides guidance as to when it may be appropriate to consider disinvestment in cervical screening programmes and what degree of disinvestment may be acceptable.

Supplementary material

Additional charts: sensitivity analysis

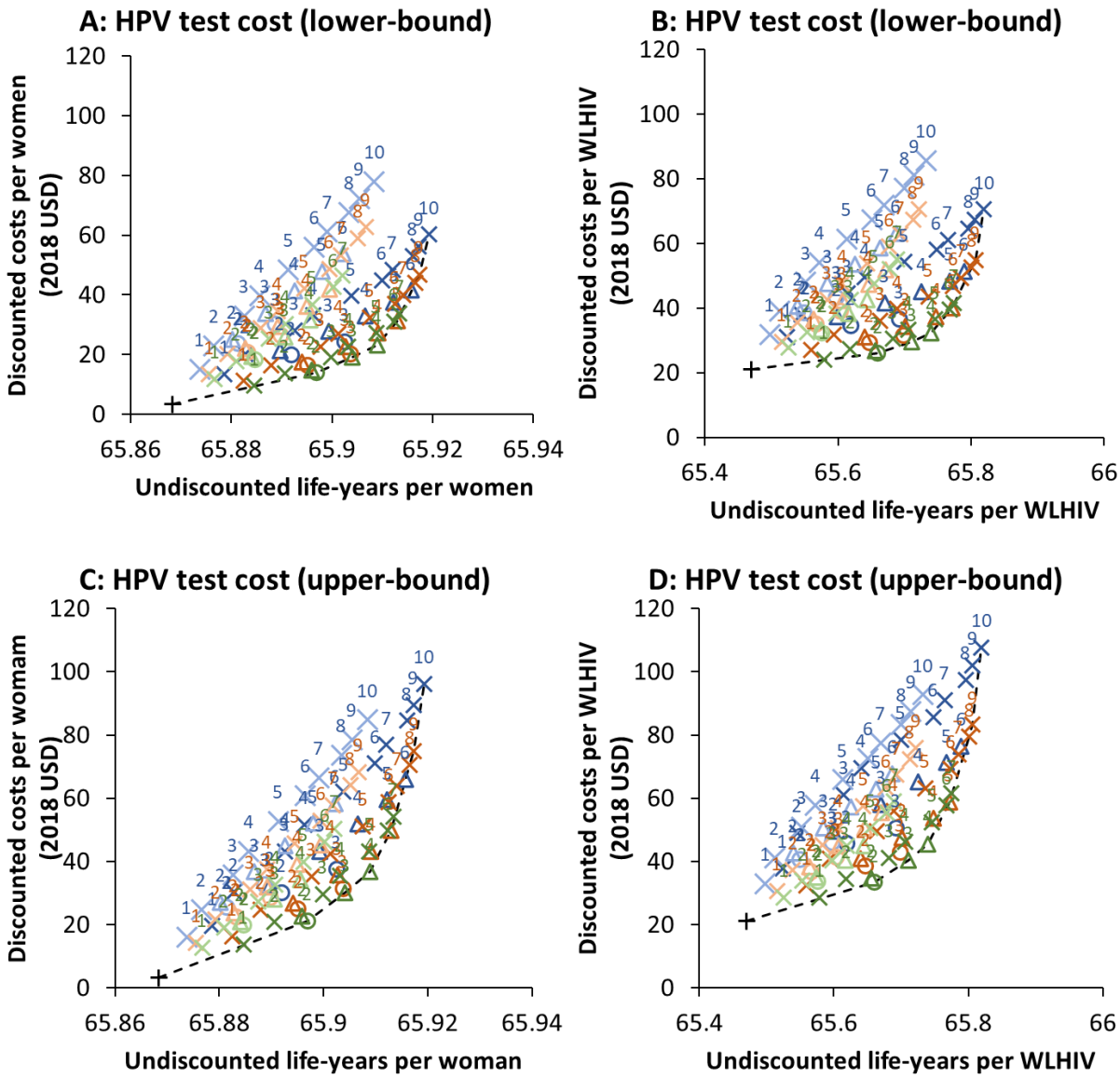

Figure 25 Discounted costs versus undiscounted LYs for all women and WLHIV, for sensitivity analysis scenarios assuming lower- and upper-bound HPV test costs.

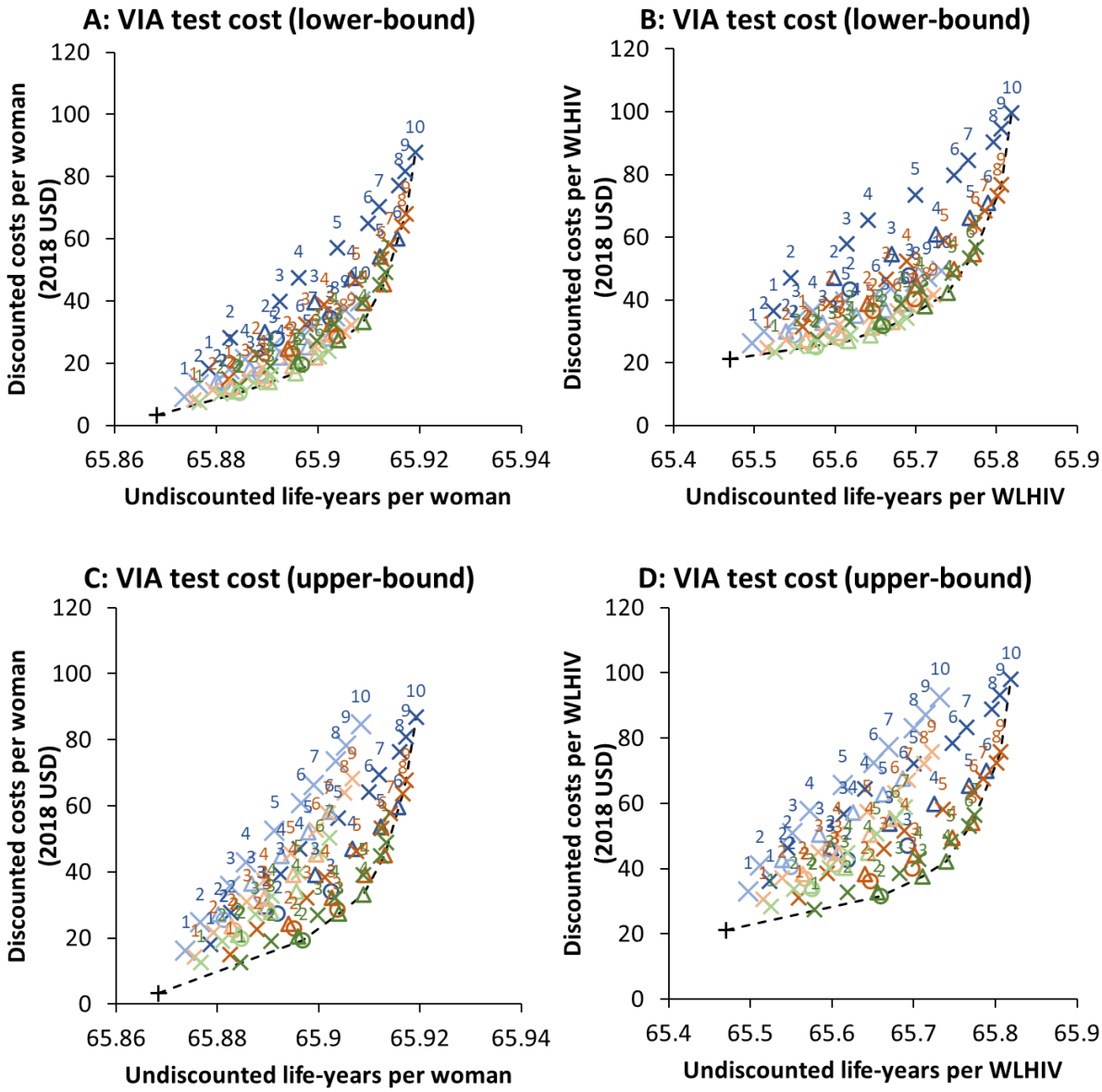

Figure 26 Discounted costs versus undiscounted LYs for all women and WLHIV, for sensitivity analysis scenarios assuming lower- and upper-bound VIA test costs.

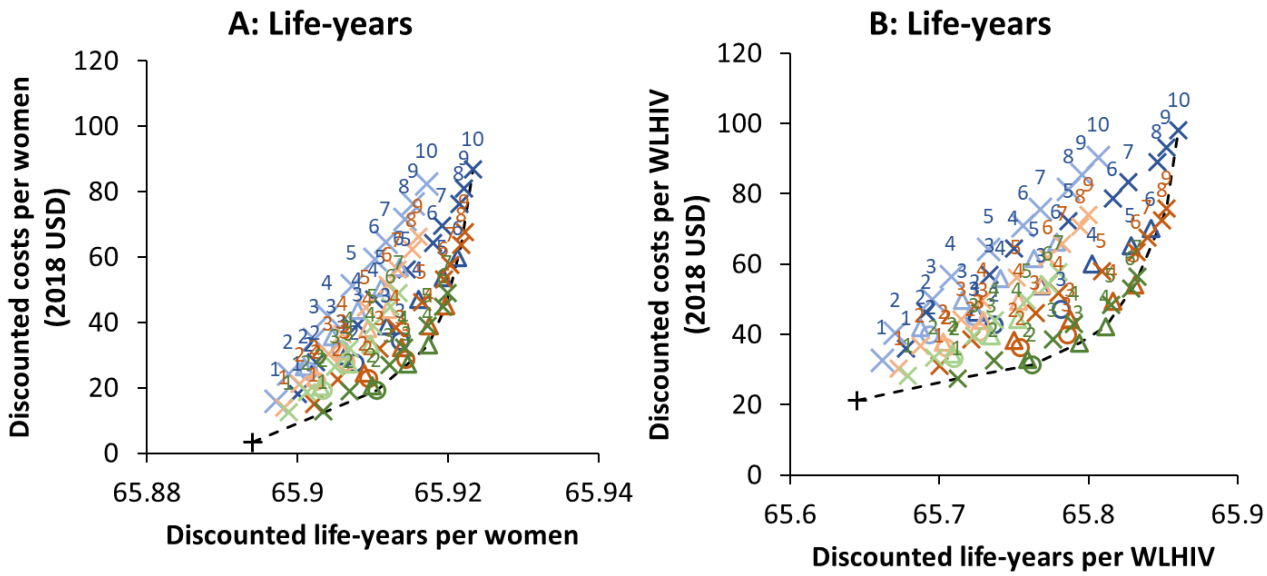

Figure 27 Discounted costs versus discounted life-years for all women and WLHIV, assuming baseline costs.

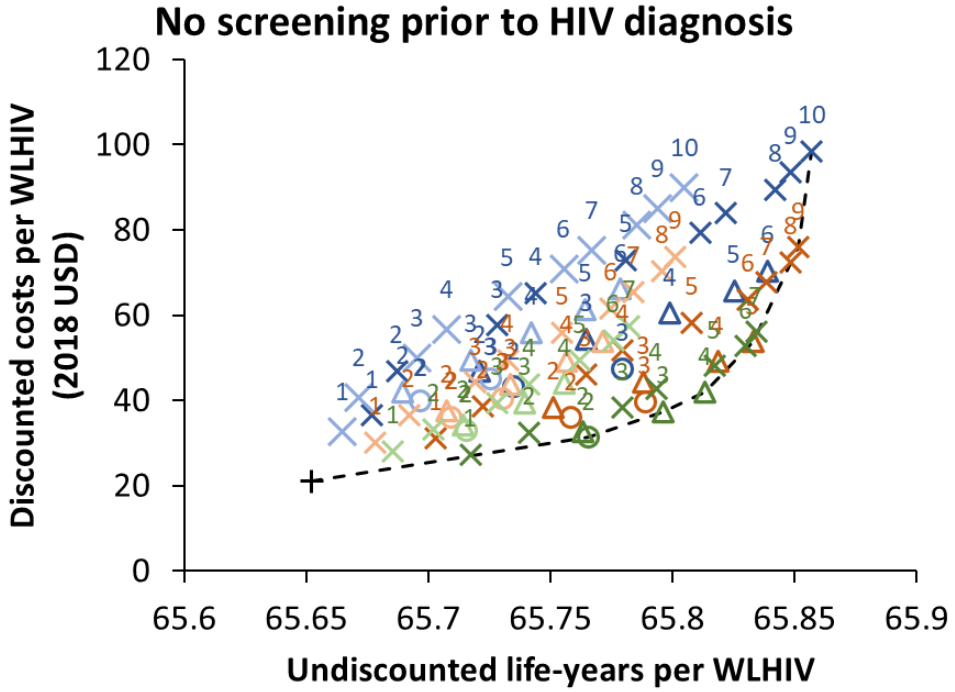

Figure 28 Discounted costs versus undiscounted life-years for WLHIV, assuming baseline costs, assuming that women are not offered screening prior to HIV diagnosis.

HPV-FRAME

Table 23 HPV-FRAME analysis domain descriptions.

Domain	Description
CRS	Core reporting standards
1	Vaccination in adolescents
2	Vaccination in adults
3	Vaccination in MSM
4	Models of HPV-associated cancers among individuals living with HIV (ILWH).
5	HPV prevention in LMIC
6	Cervical screening (including integrated vaccination and screening)
7	Alternative vaccine types or reduced-dose schedules

6 screening should be included for countries where significant screening exists*

Table 24 Reportable model input and output descriptions for this analysis.

Domain	Inputs	Reported by age? (Y/N)	Report by sex (F/M/Both)?	Comments
CRS	Target population for intervention	Y	F	Reported in methods sub-section titled 'Modelled screening approaches'.
CRS	Sexual behaviour	Y	Both	Reported in the methods sub-section titled ‘Model description and parameterisation’ and a previous

				publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
CRS	Cohort examined for evaluation/ time horizon	Y	F	Reported in methods sub-section titled 'Benefits, harms and cost-effectiveness', and in 'Population-level analysis'.
CRS	Quality of life assumptions	N/A	N/A	Not applicable.
CRS	Calibration	Y	Both	Reported in the methods sub-section titled ‘Model description and parameterisation’ and a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
CRS	Validation (where possible)	Y	Both	Reported in the methods sub-section titled ‘Model description and parameterisation’ and a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
CRS	Costs	N/A	F	Costs are reported in Table 19.
2	Vaccine coverage at older ages	N/A	N/A	Not applicable.
1	Vaccine uptake	Y	F	Reported in methods sub-section titled 'Modelled screening approaches'.
1	Vaccine efficacy	N/A	F	Reported in methods sub-section titled 'Modelled screening approaches'.
1	Vaccine cross-protection	N/A	F	Reported in methods sub-section titled 'Modelled screening approaches'.

1	Duration vaccine protection and waning	Reported but not by age	F	Reported in methods sub-section titled 'Modelled screening approaches'.
1	Vaccine and delivery costs	N/A	N/A	Not applicable.
1	Pre-vaccination disease burden (including population attributable fractions for HPV)	Y	F	Identified in the methods sub-section titled ‘Model description and parameterisation’ and fully reported in a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
1	Heterogeneity in sexual behaviour	Y	Both	Identified in the methods sub-section titled ‘Model description and parameterisation’ and fully reported in a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
1	Duration of natural immunity	N/A	Both	Identified in the methods sub-section titled ‘Model description and parameterisation’ and fully reported in a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
2	Natural history parameters, specifically for older individuals: structure; rate of infection clearance; loss of natural immunity; simulation of latency	N/A	N/A	Not applicable.
3	MSM-specific disease burden	N/A	N/A	Not applicable.
3	Interaction between HIV and HPV	N/A	N/A	Not applicable.
3	Prior exposure	N/A	N/A	Not applicable.

4	HPV prevalence, CIN prevalence and cervical cancer incidence by HIV status	Y	F	Identified in the methods sub-section titled 'Model description and parameterisation' and fully reported in a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
4	HPV disease multipliers on HPV acquisition, progression from HPV infection to cancer (or relevant precursors, if modelled) for HIV-infected women/men	N/A	F	Identified in the methods sub-section titled 'Model description and parameterisation' and fully reported in a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
4	HPV-associated cancer mortality by HIV status (and CD4 count if modelled)	Y	F	Identified in the methods sub-section titled 'Model description and parameterisation' and fully reported in a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
4	Relevant co-morbidities	N/A	N/A	Not applicable.
4	HPV-associated screening sensitivity/specificity by HIV status	N/A	F	Identified in the methods sub-section titled 'Modelled screening approaches' and fully reported in a previous publication (Hall et. Al. IJC 2021)(Hall et al., 2021).
5	HIV prevalence rates if endemic in country	Y	Both	Identified in the methods sub-section titled 'Model description and parameterisation' and fully reported in a previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).

5	Description of any opportunistic or pilot/demonstration screening projects ongoing	Y	F	Reported in the introduction.
6	Routine screening behaviour (routine and follow-up and test-of-cure)	Y	F	Reported in methods sub-section titled 'Modelled screening approaches' and in previous publication (Hall et. Al. IJC 2021)(Hall et al., 2021).
6	Screening test(s) and colposcopy accuracies	N/A	F	Identified in the methods sub-section titled ‘Modelled screening approaches’ and fully reported in a previous publication (Hall et. Al. IJC 2021)(Hall et al., 2021).
6	Abnormal test management (primary and triage)	N/A	F	Identified in the methods sub-section titled ‘Modelled screening approaches’ and fully reported in a previous publication (Hall et. Al. IJC 2021)(Hall et al., 2021).
6	Diagnostic follow-up of abnormal tests	N/A	F	Identified in the methods sub-section titled ‘Modelled screening approaches’ and fully reported in a previous publication (Hall et. Al. IJC 2021)(Hall et al., 2021).
6	Management by disease grade (confirmed disease)	N/A	F	Identified in the methods sub-section titled ‘Modelled screening approaches’ and fully reported in a previous publication (Hall et. Al. IJC 2021)(Hall et al., 2021).

6	Sources of information for screening structure and parameterisation	N/A	F	Simplified screen-and-treat screening algorithm based off un-revised 2013 WHO cervical screening guidelines, and as previously published (Hall et. Al. IJC 2021)(Hall et al., 2021, World Health Organisation 2013a).
6	Herd effect	N/A	F	Model is transmission dynamic, so inclusion of herd effects is intrinsic to the model structure.
6	Association between vaccination and screening uptake	N/A	N/A	Not applicable.
6	Fixed – variable costs	N/A	F	Fixed costs.
7	Timing between doses (for 2-dose)	N/A	N/A	Not applicable.
	Outputs	**Reported by age? (Y/N)**	**Report by sex (F/M/Both)?**	**Comments**
CRS	Cancer incidence, mortality, life years, QALYs/DALYs (as appropriate)	Reported but not by age	F	Reported in the results sub-sections 'Analysis outcomes' and 'Population-level outcomes'.
CRS	HPV prevalence, pre-intervention	Y	F	Reported in previous publication (Hall et. al. PLoS ONE 2020)(Hall et al., 2020).
CRS	CIN2/3 detected	Reported but not by age	F	Pre-cancer treatments are reported (in leu of CIN2/3 detection) in results subsections 'Analysis outcomes' and 'Population-level outcomes'.

CRS	Sensitivity analysis on key inputs	Reported but not by age	F	Reported in results subsection 'Sensitivity analysis outcomes'.
CRS	Incremental cost-effectiveness ratios and costs saved	Reported but not by age	F	Reported in results subsection 'Analysis outcomes'.
1	Absolute reductions in HPV infections, and/or warts, post-vaccination	N/A	N/A	Outcome not reported.
1	Absolute reductions in CIN2+ post-vaccination	N/A	N/A	Outcome not reported.
1	Absolute reductions in invasive cancer (cervical and other HPV cancers, as relevant) post-vaccination	N/A	N/A	Outcome not reported.
4	Reduction in cervical cancer incidence over time by HIV status (and CD4 count and ART status if modelled)	Y	F	Reported in results sub-section 'Population-level outcomes'. Not reported by age or ART treatment status.
7	Threshold cost per vaccine dose	N/A	N/A	Not applicable.

Chapter 5: Impact of model paradigm and structure on transmission- dynamic models of HIV and HPV: development of an agent-based model

The model platform developed and utilised in Chapters 2, 3 and 4 is a highly detailed and well-calibrated and validated deterministic compartment model. Models of this paradigm tend to be Markovian (or semi-Markovian) and often face two fundamental limitations: it is impossible to determine which individuals are contained within each compartment, and, how long they have been there or from where they might have come. Agent-based models are increasing in popularity because, due to their structure, they are not limited by Markovian constraints and are relatively flexible. In the field of HIV and HPV epidemiological modelling, an advantage of the agent-based paradigm is that influential time-dependent factors, such as duration of ART adherence and the relationship between HPV infection persistence and cervical cancer, can be more comprehensively included. In addition, the role of heterogeneity of control intervention uptake (for example, circumcised males and partnership-specific condom use) and behaviours (commercial sex-workers and men who have sex with men) is readily assessable. This chapter aimed to develop an agent-based model that could improve upon some of the aspects built into the deterministic compartment model, noting that the extensive foundations of development, calibration, and testing undertaken for the compartment model could not feasibly be undertaken a second time during one thesis. Nonetheless, this chapter describes the development of the best possible agent-based model of HIV and HPV infection and natural history in Tanzania, which simulates the impact of HIV control interventions, VMMC and ART, on HIV prevalence and cervical cancer incidence both historically and into the future. Findings from the agent-based model are compared to those presented in Chapter 2, alongside some new results which could not be generated using the compartment model framework.

Introduction

Mathematical modelling is frequently used to further our understanding of pathogen transmission and epidemic dynamics, and the HIV and HPV viruses are particularly amenable to this. The majority of HIV and HPV epidemic models are deterministic compartment models that simulate movement between these compartments and often operate on a discrete time-step(Canfell and Berkhof, 2019). This type of modelling, or model paradigm, simulates the mean of a population which is assumed to be homogeneous. Here, factors such as the force of infection or uptake of disease prevention interventions are the same for everyone in a particular compartment and are based on population averages(Brauer, 2008, Lin, 2008, Vynnycky and White, 2010, Diekmann and Heesterbeek, 2000, Kermack and McKendrick, 1927, Anderson and May, 1992). In the classic example of the Kermack-McKendrick S-I-R epidemic model, we would define compartments for susceptible (S), infected (I) and recovered (R) (Kermack and McKendrick, 1927). However, many modern implementations are adapted to contain substantially more states and detail. The movement of individuals between compartments may be modelled using difference equations or ordinary or partial differential equations, depending on the model complexity and computational resources available. In HIV and HPV epidemiology, it is common to see difference equation-based models operating on a time-step of weeks to months with millions of possible states. In systems with large populations and established epidemics, or where detailed information about the system is limited, deterministic compartment models are often preferred as they are reliable, straightforward to execute, and appropriate for modelling large populations by representing the average population or expected outcome(Giesecke, 2017).

The cost of compartment models' ease and computational inexpensiveness is a lack of design flexibility and a combinatorially increasing number of compartments. Deterministic models also exclude random chance or stochasticity, which may be influential when modelling small populations or the early epidemic growth phase(Lin, 2008, Vynnycky and White, 2010, Giesecke, 2017, Roberts et al., 2015). As we gain access to increased computing power, the use of computationally-demanding agent-based modelling is growing in popularity since it allows a more nuanced investigation of the impact of heterogeneity in individual attributes and behaviours, provides the modeller greater control over input parameters and allows the tracking of agents over their lifetime(Rocha and Masuda, 2016, Vynnycky and White, 2010). To increase computational efficiency in individual-based models, many have fully (or partially) adopted an event-driven framework, which means that models are based on an event

queue rather than a discrete time-step. In this case, stochasticity may describe the amount of time between events and the next event to occur, which means that the model does not waste resources simulating time when nothing happens(Kiss et al., 2017, Lin, 2008, Vynnycky and White, 2010).

In the fields of both HIV and HPV epidemiological modelling, there is discussion surrounding the choice of one model paradigm over the other(Roberts et al., 2015, Britton et al., 2015). Scientific literature contains many examples of deterministic and stochastic compartment models, and agent-based models on a discrete time-step or an event-driven framework. Due to these differences, research teams with separate independent models of HIV or HPV and cervical cancer are increasingly forming larger groups or consortiums to undertake exercises in comparative modelling(Hontelez et al., 2013, Kim et al., Brisson et al., 2020, de Kok et al., 2020). Comparative modelling aims to utilise models with different structures and model paradigms to answer the same research question and ultimately increase our understanding of the dynamic system itself and the impact that model structure has on simulated outcomes.

Previous chapters in this thesis have described analyses of the impact of various control interventions for HIV and cervical cancer on HIV prevalence and cervical cancer incidence in the United Republic of Tanzania, a country with high rates of cervical cancer and endemic HIV with active HIV control(Hall et al., 2020, Hall et al., 2021). The model utilised for these analyses was a deterministic compartment model, simulating the transmission dynamics and natural history of HIV and numerous HPV genotypes. This deterministic model platform was extensively parameterised and validated against empiric data local to, or representative of, Tanzania and was used to inform the WHO 2021 guidelines development for the screening and treatment of cervical pre-cancer in women living with HIV(World Health Organisation 2021). That platform, while as detailed and comprehensive as practical, faces limitations in terms of the number of compartments required to simulate HIV and HPV properly; in fact, the latest development of the compartment model used in this thesis required over 42,577,000 compartments (Chapter 3), which given Tanzania's current population (58,000,000 in 2019), means that on average each compartment contains less than 1.5 people. Therefore, an agent-based model is likely to be more efficient in simulating individual attributes and potentially decreases the computational cost of differentiating between disease and intervention categories. Additionally, the mechanism of action of many of the simulated control interventions, especially where the duration of the intervention for an individual is important, may benefit from being modelled in the agent-based framework. For example, anti-retroviral therapy has greater efficacy for individuals

adhering to treatment for more than two years(Ali and Yirtaw, 2019), and qualitative data suggest that condom use is more likely to be partnership-specific than applied as an average across all sexual interactions in a population(Outwater et al., 2000). Therefore, this chapter aims to lay the groundwork for improving upon the previously described deterministic compartment model by developing and parameterising a detailed agent-based model of HIV and HPV co-infection and cervical cancer. Finally, this model will be used to validate the findings reported in Chapter 2, which presents the impact of HIV control interventions, VMMC and ART, on cervical cancer incidence rates in Tanzania from 2020 to 2070.

Methods: model design and parameterisation

Development of an agent-based model

A stochastic agent-based HIV and multi-type HPV co-infection model has been developed to simulate the transmission and natural history of HIV, HPV16/18, HPV 31/33/45/52/58, and other oncogenic HPV types. In keeping with the previous model iteration, this model has been parametrised to simulate the United Republic of Tanzania (Chapter 2-4). Broadly, this platform contains programmed modules governing population demography, sexual partnership formation and dissolution, HIV and HPV transmission among heterosexual couples and men who have sex with men (MSM), vertical (mother-to-child) HIV transmission, disease natural-history (progression and regression of HIV and HPV disease stages) and the uptake of prevention interventions such as voluntary medical male circumcision (VMMC), antiretroviral therapy (ART) and condom use over time.

Each simulated agent is instantiated into the model with a series of personal attributes, some of which change over time. While the model operates on a monthly time-step, computational performance is enhanced as some processes are simulated via an event-driven or 'time-in-state' mechanism rather than via per-timestep state-transition probabilities. The following sections provide in-depth descriptions of each module. The model was developed using Matlab version R2018b and is represented as an $N \times A$ array of N individuals with A individual attributes, and these attributes (of which there are 14) are described in Table 25. The model was run on a four-core personal computer with a 3.40 GHz processor and 16GB of installed RAM. Due to the constantly increasing number of individuals to simulate, each successive year takes longer. However, on average the model takes 0.04 milliseconds to simulate a single individual over the course of a year, or approximately 140 minutes to simulate 500,000 individuals starting in 1955 and ending in 2070.

Table 25 Attributes ascribed to each simulated agent or individual.

Attribute	**Description**
Unique identifier	Each simulated agent/individual is provided with a unique identifying number. This is assigned at birth and does not change.
Age	The age of simulated individuals (in years) from birth (zero) to 99 years. This is updated annually.

Natural mortality	The year that an individual will die from natural causes (i.e., not HIV or cervical cancer) is assigned at birth and may be interrupted by HIV or cervical cancer death.
Partnership status	The partnership status of simulated individuals, who may be: unpartnered and unavailable, unpartnered and available, or partnered. Relationship formation/dissolution may occur as frequently as every simulated month, with the probability of relationship formation and the average length of a relationship dependent on male age and the relationship status of both individuals.
Partnership attitude towards monogamy	Partnership attitude refers to the attitude towards monogamy for each simulated individual, which is either: 'monogamous' (does not form other relationships while partnered) or 'flexible' (forms concurrent partnerships). This attribute is age-specific and applied to a proportion of individuals as they enter a specified age range and is also used to account for the possibility of an individual having multiple short relationships (< one-month duration) over the simulated time step, which implicitly includes transactional and sex-worker activity.
Men who have sex with men (MSM)	A binary value specifying whether a male is available for sexual partnerships with other males.
Circumcision status (males only)	A binary value referring to whether a specific male has undergone voluntary medial male circumcision (VMMC).
HIV status	The HIV status of simulated individuals encompasses both HIV positivity status and disease stage. Acquisition of HIV is simulated monthly via heterosexual and MSM partnership interactions or applied at birth via vertical transmission.
HIV progression (time to event)	For HIV positive individuals, 'HIV progression (time to event)' specifies the date that this individual is due to progress to the next stage of HIV disease. This is decided based on their age, current disease stage, and ART treatment status. This parameter is modelling using a 'time-in-state' or event-driven mechanism, although, it may occur as frequently as every month.

ART status	For HIV positive individuals, ART treatment status governs treatment uptake and success. Individuals may be untreated, partially/ineffectually treated, or virally suppressed. The simulated proportion of PLHIV receiving ART is updated monthly to reflect observed ART utilisation in Tanzania. This model does not currently account for ART discontinuation.
HPV type	The HPV type parameter specifies whether a simulated individual is HPV negative or HPV positive with a single or multi-type HPV infection and the genotypes of any present HPV infections. Acquisition of HPV is simulated via heterosexual partnership interactions only.
HPV stage	For HPV positive individuals, this attribute specifies the stage of their infection, which may be an infection only (males and females) or cervical pre-cancer or cervical cancer (females only).
HPV stage evolution (next regression/progression)	For HPV positive individuals, this attribute specifies the next (pre-determined) disease stage to which they will progress or regress. This is decided based on their age, current disease stage, and HPV type.
HPV stage evolution (time to event)	For HPV positive individuals, this attribute specifies the date at which they will progress or regress to their next disease stage (HPV stage evolution). This parameter is modelled using an event-driven mechanism, although it may occur as frequently as every month.

Demographic processes

The demography module is executed at the start of every simulated year and governs ageing (0-99 years), fertility (including vertical transmission where appropriate) and other-cause mortality (i.e., year of death due to any reason other than HIV or cervical cancer). The starting population used for model initialisation directly reflects the Tanzanian population structure (by age and sex) in 1955(United Nations DESA / Population Division, 2017, The World Bank, 2017b). Notably, this model is instantiated five years earlier than the deterministic compartment model instantiated in 1960, due to the longer time required for sexual partnership formation and dissolution to stabilise.

Table 26 Model characteristics governing population demography for the agent-based stochastic model compared to the previously described deterministic compartment model.

Structural or parameterisation element description	**Stochastic agent model**	**Deterministic compartment model (Chapters 2-4)**
Age groups (structure)	Single year ages from birth to 99 years.	Five-year age groups from 5-9 to 75-79 years.
Sex-based population subgroups (structure)	Males and females. Unlike the compartment model, sex work is governed by sexual behavioural characteristics.	Males, females, and commercial sex workers.
Recruitment rate (parameter)	The number of recruits R is calculated using the fertility and maternal age data, combined with the female population structure and the early childhood mortality (ages 0-4) rate. The sex is chosen such that if $x \leq \frac{1}{2.03}$ for $x \in U(0,1)$, the individual is male. Otherwise, the individual is female.	The number of new recruits R is calculated using the fertility and maternal age data, combined with the female population structure and overlayed with a probability of survival to age five years. The ratio of recruited males to females is 1:1.03.
All-cause mortality rate (parameter)	A year to die naturally is drawn from a random normal distribution at birth (at model instantiation in the starting population). Note that since only individuals who survive infancy are modelled, infant mortality rates are not considered.	Per time-step age- and sex-specific probabilities of natural mortality, $m(sex, age)$, are derived from year-specific life tables and applied directly to the simulated population.

The annual number of live births is calculated for each year using the estimated (up to 2019) and projected (to 2100) fertility rates per 1,000 population; it is not assumed to depend on the simulated partnership status of women of childbearing age. The World Bank (median fertility variant) published estimated and projected fertility rates, indicating a decrease in birth rate from 48.49 per 1,000 capita in 1950 to 16.95 in 2100(The World Bank, 2017a, National Bureau of Statistics, 2015). Simulated births are corrected for infant mortality (as reported in life tables), and therefore simulated births more accurately reflect the number of babies born who will survive to age 5.

The year of natural mortality for each individual is based on the individual's year of birth and is drawn from a normal distribution $N(m, \frac{1}{4}m)$. Here, m is equal to the mean expected years of life for males and females in each birth cohort, and the data underpinning this was sourced from life tables estimated and projected by the United Nations Population Division(United Nations Department of Economic and Social Affairs Population Division, 2019).

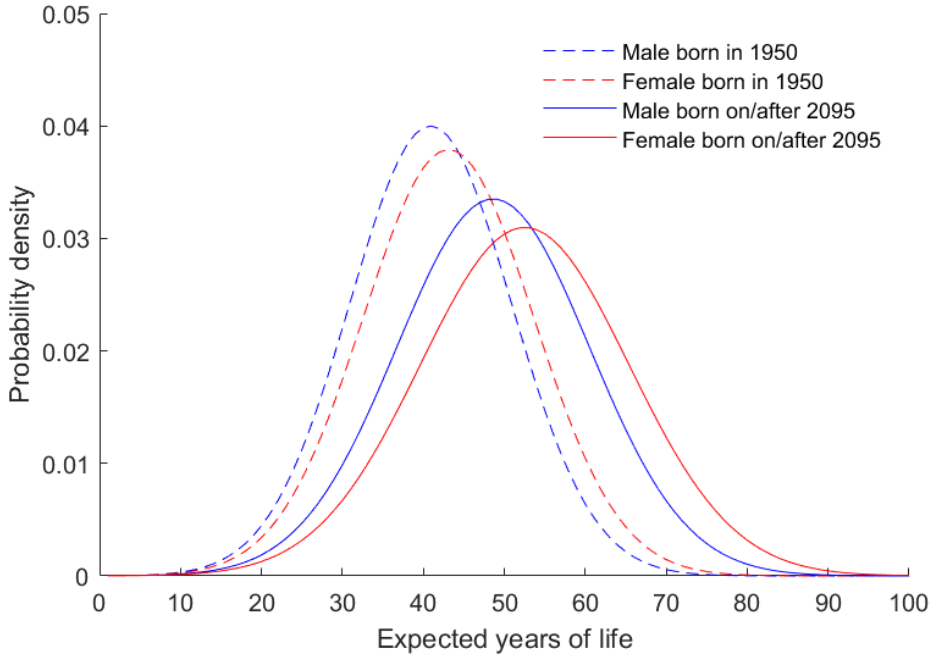

Figure 29 Probability density function for expected years of life for males and females born in 1950 (earliest simulated cohort) and in/after 2095 (latest simulated cohorts). Note that infant mortality is captured in the birth rate(United Nations Department of Economic and Social Affairs Population Division, 2019).

Partnership formation and dissolution

The model explicitly simulates the formation and dissolution of sexual partnerships between individuals. All individuals are recruited into the model with a partnership status of 'unpartnered and unavailable', which changes to 'unpartnered and available' at age 15 for females and 18 years for males. Individuals who are either 'unpartnered and available' or 'partnered' but with a 'flexible' attitude towards monogamy at the start of each monthly time-step are pooled for potential partnering. The category specifying a flexible attitude towards monogamy is designed to encompass females who engage in commercial sex work. Based on data collected in 2016, the assumed prevalence of commercial sex workers in the female population aged 15-49 years is 5.6%(Wambura et al., 2020). In general, there is limited data that specifies behavioural attitudes to sexual preferences, partnership longevity and turnover rates among different subgroups of individuals. Therefore, the age-specific probability of having a flexible attitude towards monogamy, including commercial and transactional sex for females, was based on calibration findings, ensuring a reasonable fit to observed age-, sex- and year-specific HIV incidence and prevalence in Tanzania (Figure 30).

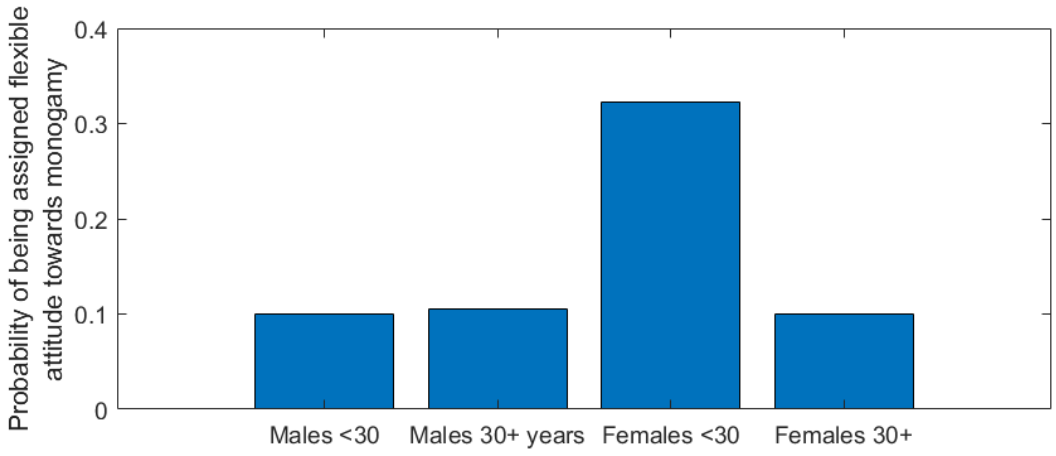

Figure 30 Age-specific probability (obtained via model fitting) that a male or female is assigned as having a flexible attitude towards monogamy upon entry to each age group.

From here, partnership formation is driven entirely by parameters acting on the male population. In the first instance, males are removed from the pool of individuals available for partnering by an age-specific function $r(a)$, where a is male age. The purpose of removing these males from the pool of men available for partnering is to account for lack of opportunity or unwillingness to form a partnership; it is possible (albeit unlikely) that some simulated individuals never form partnerships. Males are

randomly removed from the pool of available males such that a mean age-specific per-timestep probability of partnership formation $r(a)$ is maintained as per Figure 31.

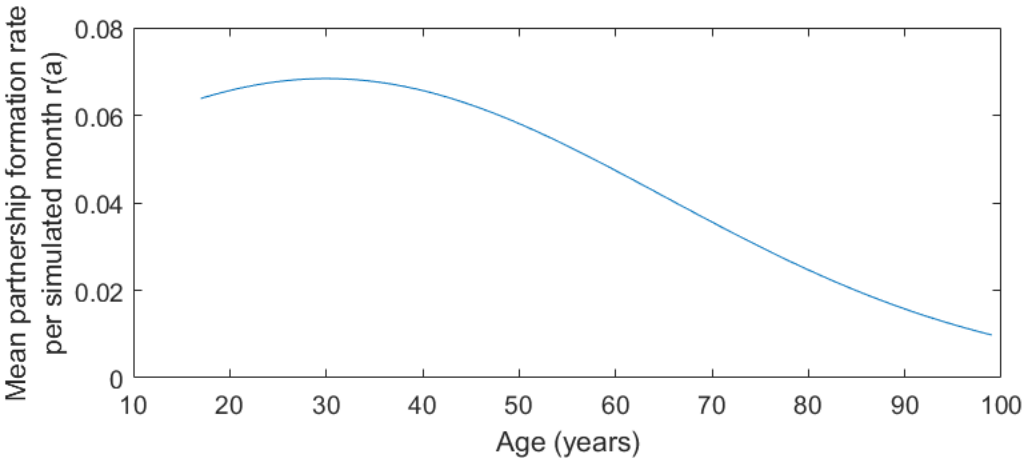

Figure 31 Monthly probability (obtained via model fitting) of partnership formation availability/opportunity for simulated males by age.

For the formation of general partnerships, males and females are split into ten-year age groups, offset by three years. For example, the male partnering group aged 18-27 will be able to select from females aged 15-24 years, and males aged 23-32 years will partner with women aged 20-29 years. Male partners are randomly selected within each partnering group for each female in order of ascending (female) age. Females aged 15–30 years with flexible attitudes towards monogamy, therefore incorporating commercial sex workers and those who engage in transactional sex, are partnered with available males aged 18-59. Once again, males are randomly selected from the available pool, with younger females partnered first. Partnership formation was simulated in this way in order to optimise computational efficiency while still broadly conforming to the observed phenomenon of males partnering with females who are younger than them(Munguti et al., 1997). The per-partnership frequency of simulated age differences (in years) is presented in Figure 32. In general, male partners are four years and one month (or 18%) older than their female partners, a lower age difference than the 5-10 year age gap reported for marriages in Tanzania in the 1990s (Munguti et al., 1997).

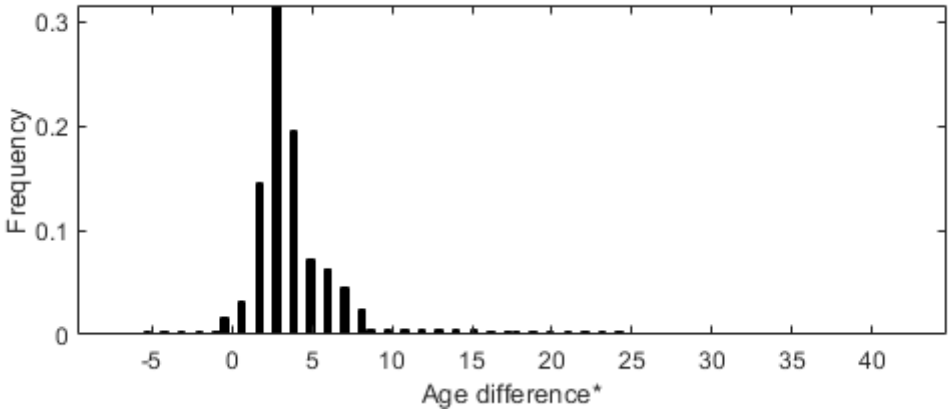

*Figure 32 Simulated frequency (probability out of 1) of the age difference (in years) between male and female sexual partnerships. *A positive age difference indicates an older male; a negative age difference indicates a younger male.*

Due to the small simulated MSM population, which is 1.3% of males aged 15-49 years(Wambura et al., 2020), MSM partnerships are simulated with sexual mixing assumed to be completely age-assortative short partnership durations of 1-6 months. A cross-sectional survey of MSM in southern Africa found that of men having ever reported anal sex with another man, 53% reported both male and female sexual partners in the past six months(Beyrer et al., 2010); therefore, the proportion of MSM assumed to also engage in heterosexual partnership formation is 0.53.

Once a suitable partner is selected, a partnership is formed, and each individual's partnership status is updated to 'partnered'. A separate array keeps track of each partnership that has been formed, storing the following information: unique identifiers for the male and female, HIV status, HPV type, and the age of each partner at partnership formation, a binary parameter for condom use, and the date d that the partnership is scheduled to end. Here $d = l + D$ where D is the current date and l is the length of the relationship which is drawn from a uniform distribution where $l \in U(f(a) - 5, f(a) + 5)$ and $f(a)$ is a function specifying the mean relationship length for men aged a; the mean partnership duration by male age is represented in Figure 33. Comprehensive data informing the duration of steady relationships in Tanzania is not available, and therefore the decision to use a uniform distribution is an assumption based on model calibration findings and to explore the impact of parameter uncertainty. The sexual partnership will end when either $d \geq D$, or either party dies. The model does not assume that HIV acquisition or positivity affects partnership formation or duration. The mean duration of relationships is a function of male age at formation, assuming that both parties are not already in another partnership.

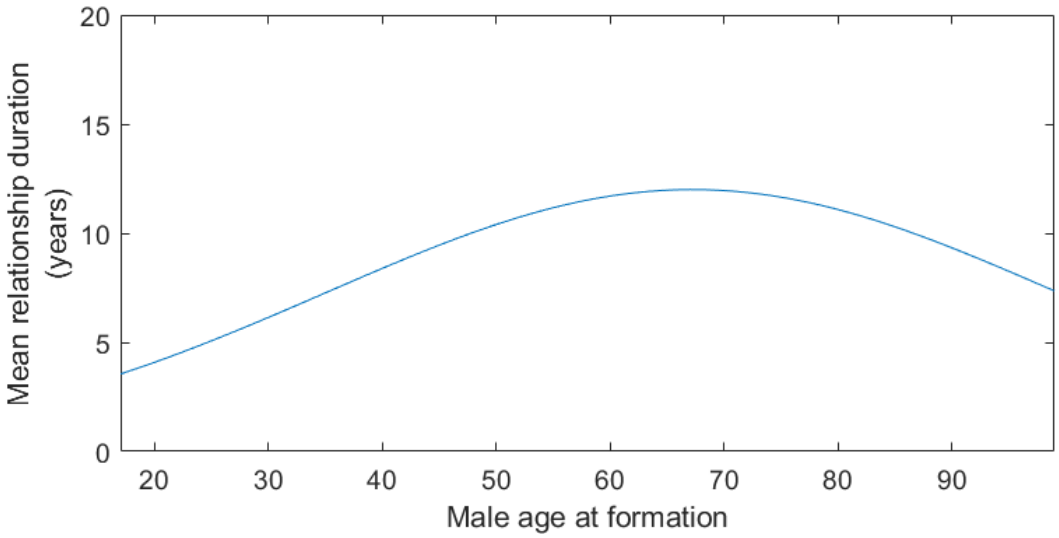

Figure 33 Mean relationship duration as a function of male age at formation. Assumes that neither party is currently in another partnership.

Partnerships formed where one or both parties are already partnered, or formed in the context of commercial sex work, are assumed to have a much shorter mean duration of 1 month. A limitation of this approach is that it does not reflect the reality of sex worker interactions, which are likely to occur as a single interaction where sex workers have multiple clients per month(United Republic of Tanzania Ministry of Health and Social Welfare National AIDS Control Programme (NACP), 2012).

Table 27 Model characteristics governing sexual behaviour for the agent-based stochastic model compared to the previously described deterministic compartment model.

Structural or parameterisation element description	**Stochastic agent model**	**Deterministic compartment model (chapters 2-4)**
Sexual partnerships.	Individual sexual partnerships are explicitly simulated, accounting for variation in sexual debut and individual-specific rates of becoming available for partnerships. Opportunity for partnership formation and relationship	Partnerships are not explicitly simulated. The force of infection λ for HIV and HPV transmission accounts for: sex- age- and sexual activity level-specific per time-step probabilities of forming sexual partnerships and the frequency

	length is specified for each male where a new partnership is formed.	of sexual interactions within partnerships by male age. This is weighted by the probability of forming partners in each possible age group, and the proportion of that age group with either HIV or HPV.[a]
Partnership concurrency.	Partnership concurrency is explicitly simulated. An age- and sex-specific probability of being either 'monogamous' or 'flexible' specifies whether an individual will remain available despite forming a new partnership. In each simulated timestep, individuals can form a maximum of one general partnership and one additional high-risk (concurrent, transactional, or commercial) partnership.	Partnership concurrency is not accounted for among general partnerships. However, commercial sex workers are assumed to have both personal and professional sexual partnerships.
Sexual activity/risk groups.	Individuals with higher rates of partner turnover (flexible attitudes towards monogamy, commercial/transactional sex and MSM) may be considered 'high-risk' individuals. Mixing between sexual activity groups is assumed to be non-assortative.	Males and females are split into general sexual activity and high sexual activity groups. This reflects increased sexual partnership turnover and elevated risk among a smaller proportion of the population. Commercial sex workers are assumed to be in the high sexual activity group for females, although not all high activity females are commercial sex workers.

Non-assortative mixing (age-based).[b]	Males and females are assumed to potentially mix with partners of all ages, depending on partnership type. On average, across all partnerships, males are four years older than their female partners. The mixing of MSM is assumed to be completely assortative.	Males and females are assumed to mix with partners of all ages, with strong preferences for partnerships where the male is approximately five years older than the female.
Condom use.[c]	Condom use (Y/N) is added as an attribute for each partnership when formed. Couples are assumed to either always or never use condoms in that partnership. Condom use in partnerships is decided by a biased coin toss, with the mean 'Y' specified by empirical data for condom use among males by year.	The probability of condom use, combined with condom efficacy, is applied as a multiplier reducing the force of infection of HIV and HPV acquisition for high- and general-activity males and females.

[a]*More details regarding the calculation of force of infection for the deterministic compartment model are provided in subsequent sections.* [b]*Input assumptions regarding age-assortative mixing were based on Munguti et al. (Munguti et al., 1997).* [c]*Input assumptions for both models are specified to fit survey data on condom use among non-commercial sex interactions(Kapiga and Lugalla, 2003, Adair, 2008, Tanzania Commission for AIDS (TACAIDS) et al., 2008, Tanzania Commission for AIDS (TACAIDS) et al., 2013, Ministry of Health et al., 2016, Reynolds et al., 2012). The assumption that condom use is specified per partnership rather than per interaction is broadly based on observation(Outwater et al., 2000), but may not represent all relationships in reality, particularly where family planning needs change throughout a partnership.*

HIV transmission and natural history

The HIV transmission and natural history modules are executed every monthly time-step. HIV transmission is simulated to occur between members of an HIV discordant partnership. For each such partnership, a per time-step probability of HIV transmission $P(T_{HIV})$ is calculated using: stage-specific per-sex-act HIV transmission probabilities, the sex of the HIV-negative partner (and circumcision status if male), the ART

treatment status of the HIV-positive partner, the mean frequency of sexual interactions per partnership (calculated based on male age) and the probability of condom use; all are described in Table 28 and have been parametrised in agreement with the deterministic compartment model (Chapter 2-4). For each HIV discordant partnership, HIV transmission in each timestep is simulated using a biased coin toss, where the mean probability of transmission is dependent on HIV stage, ART status, condom use and circumcision status (female to male transmission only).

Table 28 Factors influencing the HIV transmission probability $P(T_{HIV})$ and their value.

Factor influencing HIV transmission	**Value/description**
Stage-specific per-sex-act HIV transmission probabilities.	A base per-sex-act HIV transmission probability of 0.0006 is assumed. For each HIV stage, this probability is subject to the following multipliers: 7 for acute infection, 1 for WHO clinical stage 2, 5.8 for WHO clinical stage 2, 6.8 for WHO clinical stage 3, and 11.8 for WHO clinical stage 4 (AIDS)(Quinn et al., 2000).
Sex of the HIV negative partner.	An additional multiplier of 2.5 is used to increase the transmission probability for male to female transmission.
Circumcision status (male).	An additional multiplier of 0.40 is used to decrease the transmission probability for female to male transmission where the male has been circumcised(Tobian et al., 2014). Circumcision rates are assumed to be stable at 8% until 1995, where they increase quadratically to 80% in 2015, where they remain. This assumption is comparable with observed data and consistent with previous analyses(The United Republic of Tanzania Ministry of Health and Social Welfare, 2013, Ministry of Health et al., 2016). At the start of each year, the number of circumcisions needed to maintain observed circumcision prevalence is calculated, which informs the number of randomly selected simulated males to be circumcised in that year.
ART treatment status (viral suppression).	For HIV discordant partnerships where HIV-positive individuals are virally suppressed through ART, a multiplier of 0.04 is utilised to reduce transmission probability by 96%.

Frequency of sexual intercourse per partnership.	The frequency of sexual interactions per partnership was found to be 12 acts per month via calibration. It is assumed to apply to both general and sex-worker interactions and is broadly consistent with self-reported data(Dasgupta et al., 2018).
Probability of condom use.	In partnerships with a condom-use value of 'Y', the HIV transmission probability is reduced by 46% for males and 30% for females.

When an individual becomes infected with HIV, their infection status changes from 'uninfected' to 'acute infection'; the date that this individual is scheduled to progress to 'WHO stage 1' is chosen, in addition to the date of HIV mortality. This date is drawn from a random normal distribution, calculated using the initial infection date and the mean length of time for an individual to remain in the acute infection stage. The mean time for individuals to remain in each HIV disease stage and stage-specific HIV mortality rates are provided in Table 29.

Table 29 Average length of time spent in each disease stage and the probability of HIV-death for each HIV disease stage.

	Time in acute infection	**Time in WHO clinical stage 1**	**Time in WHO clinical stage 2**	**Time in WHO clinical stage 3**	**Time in WHO clinical stage 4 (AIDS)**	**Time from acute infection to HIV mortality**
Mean	2 months[1]	1 year 6 months[1]	1 year 3 months[1]	6 years 6 months[1]	1 year 3 months[1]	Males: 11 years, Females: 10 years[2]
Standard deviation	-	4 months	3 months	16 months	3 months	Sex-specific distribution as published.[2]

[1].As published in Palk et al. 2018 (Sci Rep)(Palk et al., 2018). [2]Assuming no ART uptake, as published by the CASCADE collaboration in 2000 (Lancet)(CASCADE, 2000).

Individuals are randomly selected from the pool of stages 3 and 4 HIV-positive people to commence ART; if there no untreated stage 3 or 4 HIV positive individuals available,

treatment uptake is assumed to occur for individuals in stages 1 and 2. Year-specific ART uptake rates are assumed to mirror those reported in the UNAIDS 2020 update report for the United Republic of Tanzania, reaching a viral suppression rate of 63% of all people living with HIV by 2019(UNAIDS, 2021b). In addition, it is assumed that 55% of individuals commencing ART are female; a figure which was found through the calibration procedure and is broadly consistent with evidence that ART uptake and adherence is higher among females than males(Sharma et al., 2017).

HPV transmission and natural history

The transmission of multiple HPV types is simulated similarly to HIV transmission, with slightly fewer factors influencing the transmission probability. The 'HPV type' attribute specifies whether an individual is either: (1) HPV negative, (2) HPV16/18 positive only, (3) HPV 31/33/45/52/58 (HPV H5) positive only, (3) other HPV positive only, (4) HPV 18/19 and H5 positive, (5) HPV 16/18 and other positive, (6) HPV H5 and other positive, or (7) positive for HPV 16/18, H5 and other. Here, a per-timestep probability for HPV transmission $P(T_{HPV})$ is calculated for couples with differing HPV type attributes and accounts for HPV type-specific per-sex-act transmission probabilities, circumcision status of the male partner and the mean frequency of sexual interactions per partnership (calculated based on male age). HPV types are ranked in order of severity/transmissibility (HPV 16/18 > HPV H5 > HPV other). If both partners are HPV positive, both partners can become infected with additional HPV types. Sexual behaviour parameters, including circumcision status, ART treatment status, and per-partnership frequency of intercourse related to HPV transmission (and HIV transmission), have already been reported in Table 28. All other factors relating to HPV transmission are reported in Table 30.

Table 30 Factors influencing the HPV transmission probability $P(T_{HPV})$ and their value.

Factor influencing HIV transmission	**Value/description**
HPV type-specific per-sex-act transmission probabilities.[+]	HPV transmission probabilities, per sex act, were found via calibration. The transmission probability $P(T_{HPV})$ is 0.018 for HIV negative individuals and virally suppressed HIV positive individuals, and 0.045 for HIV positive individuals.
Circumcision status (male).	For female to male transmission where the male has been circumcised, an additional multiplier of 0.53 is used to

	decrease the transmission probability(Castellsague et al., 2002).
Probability of condom use.	Condom use is not predicted to have any bearing on HPV transmission probabilities.

+Note that we assume an average of 12 sex acts per monthly timestep per partnership and that HPV transmission occurs at the end of each month.

When individuals become infected with HPV, their 'HPV stage' attribute is updated to 'HPV positive'. At this point, the time-to-event, that is, the length of time that this individual will remain in the 'HPV positive' stage, and the HPV stage that the individual will be progressing or regressing to, is decided based on an unfair coin toss, and is dependent on that individual's sex, disease stage, and HPV type. Men are assumed to move between two possible states: HPV negative and HPV positive, and the mean probability of HPV clearance is 0.0184.

Female natural history is substantially more complex, as HPV disease in women may progress and regress through multiple pre-cancer states before eventually becoming invasive cervical cancer. Progression and regression pathways through multiple pre-cancer states, and possibly to cervical cancer, is governed by Figure 34.

$$[HPV\ negative] \leftrightarrow [HPV\ positive] \leftrightarrow [CIN1] \leftrightarrow [CIN2] \leftrightarrow [CIN3] \rightarrow [Cervical\ cancer]$$

Figure 34 HPV natural history states and possible transitions.

Once females develop invasive cervical cancer, they are no longer able to regress and are governed by a different cervical cancer natural history, which includes progression through multiple cancer stages, which are broadly defined to reflect FIGO staging for carcinoma of the cervix uteri(Bhatla et al., 2019). Once cancer is detected, stage-specific mortality and, if relevant, time to cervical cancer death is decided. While the implication is that women diagnosed with early-stage cervical cancer will progress through all stages before cervical cancer death, this is not explicitly simulated (Figure 35).

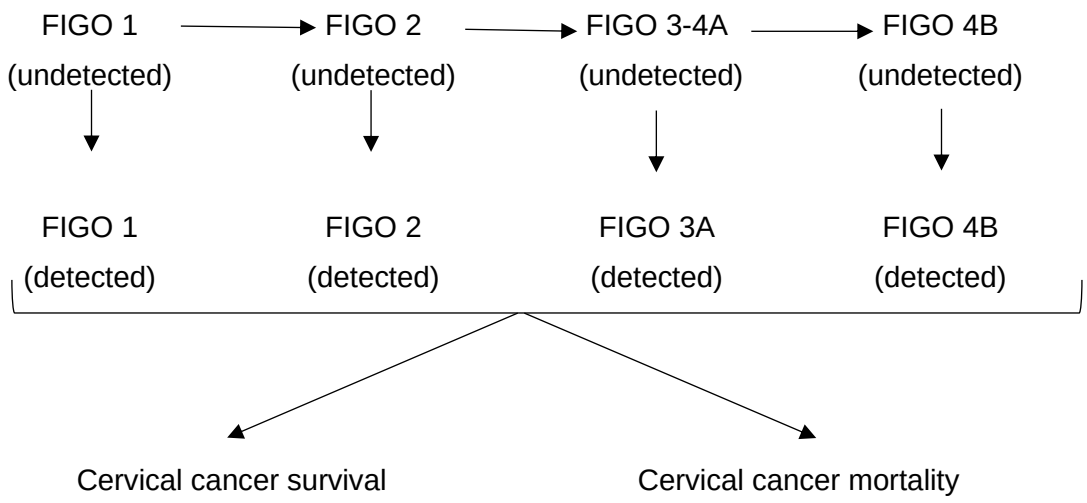

Figure 35 Cervical cancer natural history and detection profile.

The length of time that a female remains in a pre-cancer state is randomly drawn upon entry into that state from a normal distribution with mean μ_t and standard deviation $\frac{1}{3}\mu_t$. Human ethics excludes the possibility of designing studies that measure the time to cervical cancer progression; as such limited empiric data is available to inform the time spent in each pre-cancer state; therefore, a large standard deviation is assumed to reflect the uncertainty in this parameter. The mean time in state is dependent on female age, disease state, and the most dominant HPV type present, and these are presented in Table 31. The values for time in state were found through model calibration to HPV prevalence and cervical cancer incidence and are broadly consistent with other modelling studies that simulate a time from HPV acquisition to cervical cancer of 17.5-26.0 years(Burger et al., 2020).

Table 31 Mean years in state for health states attributable to HPV types 16/18 and other high-risk HPV types. If an individual is infected with multiple HPV types, HPV 16/18 natural history is assumed if present.

	Cervical pre-cancer time in state (years) with HPV 16/18				**Cervical pre-cancer time in state (years) with HPV not 16/18**			
Age	**HPV**	**CIN1**	**CIN2**	**CIN3**	**HPV**	**CIN1**	**CIN2**	**CIN3**
< 30	1.4	7.5	5.2	1.4	0.4	4.8	2.6	1.3
30-39	4.2	7.4	4.5	1.4	2.1	4.8	2.3	1.3
40-44	4.2	7.3	4.0	1.4	2.1	4.7	2.0	1.3
45-49	4.6	7.2	4.0	1.4	2.4	4.7	2.0	1.4
50-54	5.3	7.0	3.7	1.4	2.9	4.6	1.8	1.4

55-59	5.8	7.0	3.7	1.4	3.4	4.6	1.8	1.4
60-64	6.3	7.0	3.5	1.4	3.8	4.6	1.7	1.4
65+	6.7	7.1	3.5	1.4	4.3	4.6	1.7	1.4

The assumed time in state for undetected cervical cancer states (Figo stages 1, 2, 3-4A and 4B) are described in Table 32. Women leaving each cervical cancer state (undetected) progress to the next cervical cancer state or have their disease symptomatically detected.

Table 32 Time in state (years) for undetected cervical cancer stages.

Age	**Time in state (years) for women in cervical cancer FIGO stage 1**	**Time in state (years) for women in cervical cancer FIGO stage 2**	**Time in state (years) for women in cervical cancer FIGO stage 3-4A**	**Time in state (years) for women in cervical cancer FIGO stage 4B**
<49	2.1	0.9	0.9	0.4
50-64	1.8	0.9	0.9	0.3
65-74	1.2	0.9	0.9	0.3
75+	0.45	0.45	0.9	0.3

When the time in state is drawn, the next stage is also decided using an unfair coin toss, with the probability of progressing to the next pre-cancer (or cancer) state based on the state transition probabilities reported in Chapter 2 for the deterministic compartment model and reported in Table 33. These probabilities of progression are relatively consistent with retrospective observations that 50.3% (37.3-64.9%) of women with persistent CIN3 will develop cervical cancer(McCredie et al., 2008).

Table 33 Probability of progression for health states attributable to HPV types 16/18 and other high-risk HPV types. If an individual is infected with multiple HPV types, HPV 16/18 natural history is assumed.

	Probability of cervical pre-cancer progression (HPV 16/18)*				**Probability of cervical pre-cancer progression (HPV not 16/18)***				**Probability of cervical cancer progression (any HPV)⁺**	
Age	**HPV**	**CIN1**	**CIN2**	**CIN3**	**HPV**	**CIN1**	**CIN2**	**CIN3**	**FIGO1-2**	**FIGO3-4A**

< 30	0.42	0.37	0.38	0.15	0.19	0.13	0.14	0.02	0.33	0.70
30-34	0.36	0.40	0.45	0.20	0.14	0.15	0.19	0.04	0.33	0.70
35-39	0.36	0.40	0.45	0.28	0.14	0.15	0.19	0.08	0.32	0.69
40-44	0.35	0.41	0.49	0.37	0.14	0.16	0.22	0.14	0.32	0.69
45-49	0.37	0.43	0.49	0.57	0.15	0.17	0.23	0.30	0.31	0.69
50-54	0.36	0.47	0.52	0.61	0.15	0.21	0.25	0.36	0.51	0.68
55-59	0.38	0.46	0.52	0.62	0.15	0.20	0.25	0.36	0.51	0.68
60-64	0.40	0.46	0.53	0.66	0.17	0.20	0.26	0.39	0.51	0.68
65-69	0.43	0.45	0.53	0.80	0.18	0.19	0.26	0.57	0.75	0.68
70-74	0.43	0.45	0.55	0.80	0.18	0.19	0.28	0.57	0.75	0.68
75-79	0.42	0.45	0.55	0.79	0.17	0.19	0.27	0.55	0.93	0.69
80+	0.46	0.48	0.58	0.89	0.21	0.23	0.31	0.74	0.91	0.67

**All females who do not progress to the next highest pre-cancer stage are assumed to regress to the next lowest pre-cancer stage (or HPV negative if appropriate)—individuals in CIN3 progress to FIGO1. +All females who do not progress to the next highest cancer stage are assumed to have their cancer detected. FIGO stage 4B is not assumed to progress; therefore, the probability of cancer detection is 1.*

Once cervical cancer has been detected, a woman's next state, either cancer survival or cancer mortality, is stochastically decided using survival probabilities of 0.083, 0.073, 0.055 and 0.009 for FIGO stages 1, 2, 3-4A and 4B, respectively. These survival probabilities are based on 10-year survival probabilities estimated for Tanzania(Canfell et al., 2020). For females with terminal cervical cancer, the time to death is drawn from a normal distribution with mean 4 years and standard deviation 3 years; females who survive cervical cancer are assumed to enter a cancer survivor state after 7 years in remission.

Results: model calibration and validation outcomes

For calibration, the model was instantiated with 500,000 individuals in the year 1955 and run until 2020, by which time the simulated population had grown to approximately 3.4 million individuals; on average a single simulation run completed in 48 minutes. The starting population size (>5% of the actual 1955 population size in Tanzania) was chosen for computational efficiency; noting that the model would need to cope with the 2.3-3.4% growth rate that Tanzania has maintained since that time. The year 1955 was chosen as the start year because it allowed sufficient time for partnership formation and dissolution rates to stabilise and HPV infection and cervical pre-cancer rates to mature. The model was parametrised to match observed demographic, behavioural, and natural history data. Where empirical data were not available, model parameters were chosen to obtain a reasonable fit to observational data. This calibration procedure

was performed entirely independently of the calibration of the deterministic compartment model to prevent the artificial convergence of model outcomes. During this calibration process, the seed for the random number generator was set to 1. Following parametrisation, the model was run 1,000 times to determine the stochastic range for modelled outcomes, and confidence intervals (CI) reflect the total variation in simulated outcomes.

Sexually active population structure

The validity of assumed demographic parameters, expected years of life and fertility rates was confirmed by comparing the simulated population age structure to observational data(United Nations Department of Economic and Social Affairs Population Division, 2019). This comparison is presented in Figure 36.

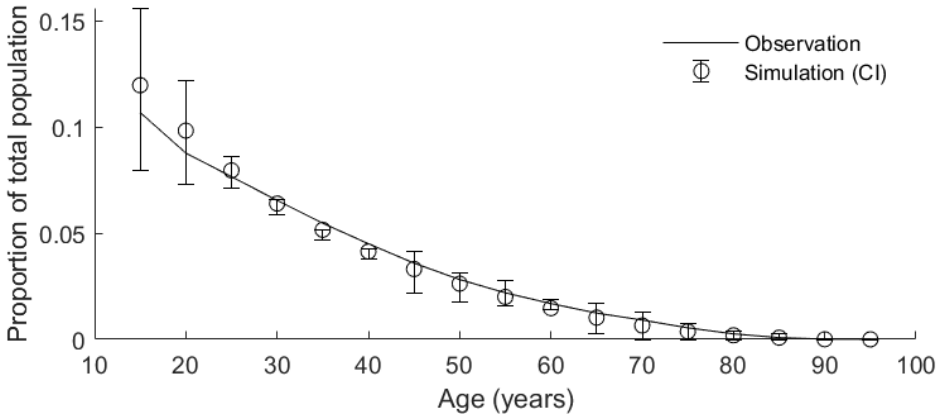

Figure 36 Observed 2019 female population structure in Tanzania compared to the simulated range (mean and CI over 1,000 simulations).

HIV epidemiological outcomes

HIV epidemic outcomes were calibrated to HIV incidence and mortality, age- and sex-specific HIV prevalence (for years 2007 and 2016), and annual sex-specific HIV prevalence. Observed data for HIV incidence, mortality and year-on-year prevalence is as reported by UNAIDS in 2018 (UNAIDS, 2018c, UNAIDS, 2018b, UNAIDS, 2018e), and age-specific HIV prevalence was sourced from Tanzania's HIV Impact Survey (THIS) reports(Ministry of Health et al., 2017).

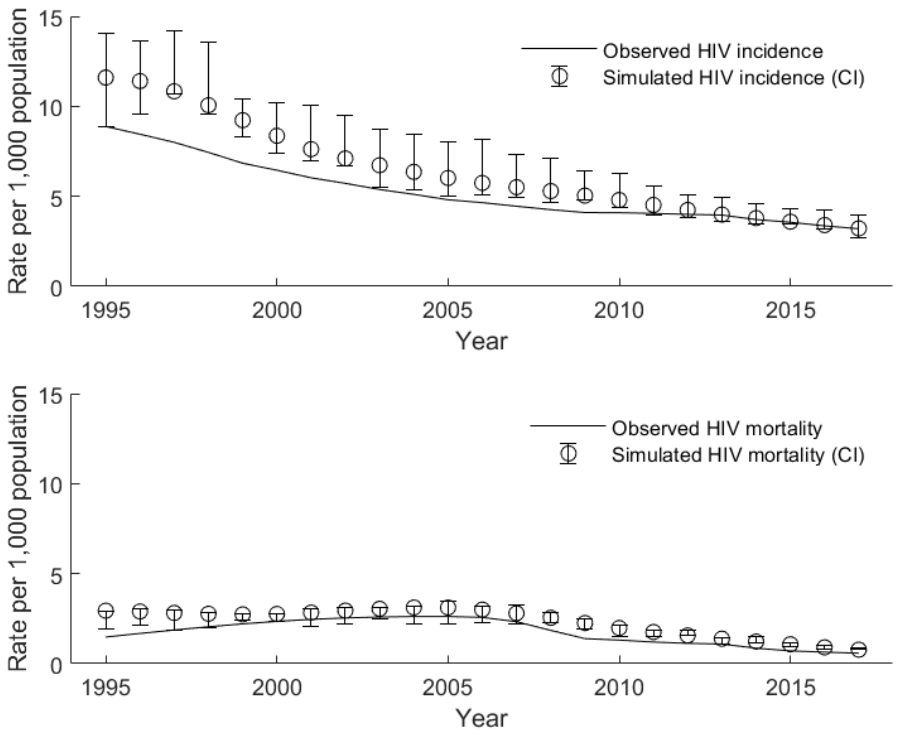

Figure 37 Estimated HIV incidence and mortality rates (UNAIDS, 2018a) compared to the simulated range (mean and CI over 1,000 simulations).

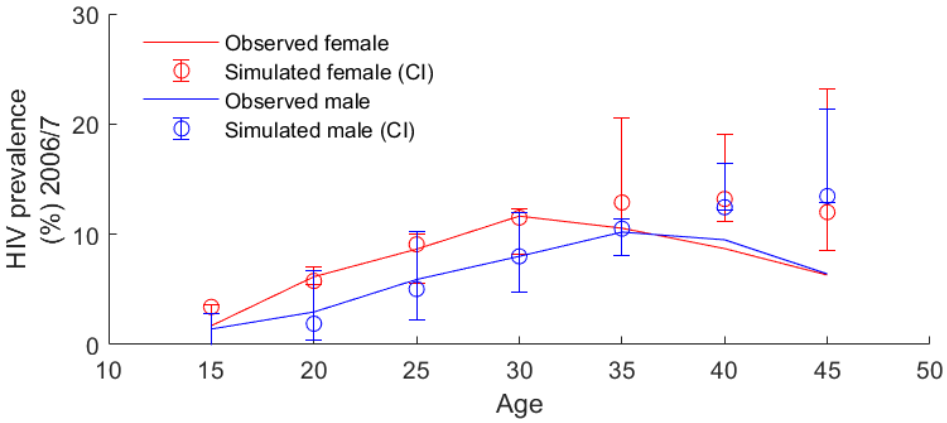

Figure 38 Observed age-specific HIV prevalence compared to simulated ranges (mean and CI over 1,000 simulations) for females and males in 2005-7(Tanzania Commission for AIDS (TACAIDS) et al., 2008).

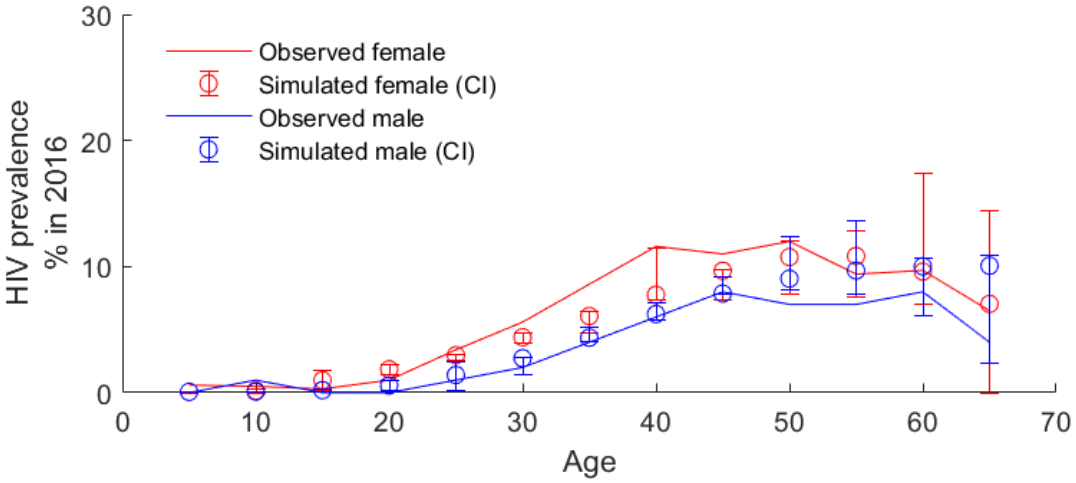

Figure 39 Observed age-specific HIV prevalence compared to simulated ranges (mean and CI over 1,000 simulations) for females and males in 2016(Ministry of Health et al., 2017).

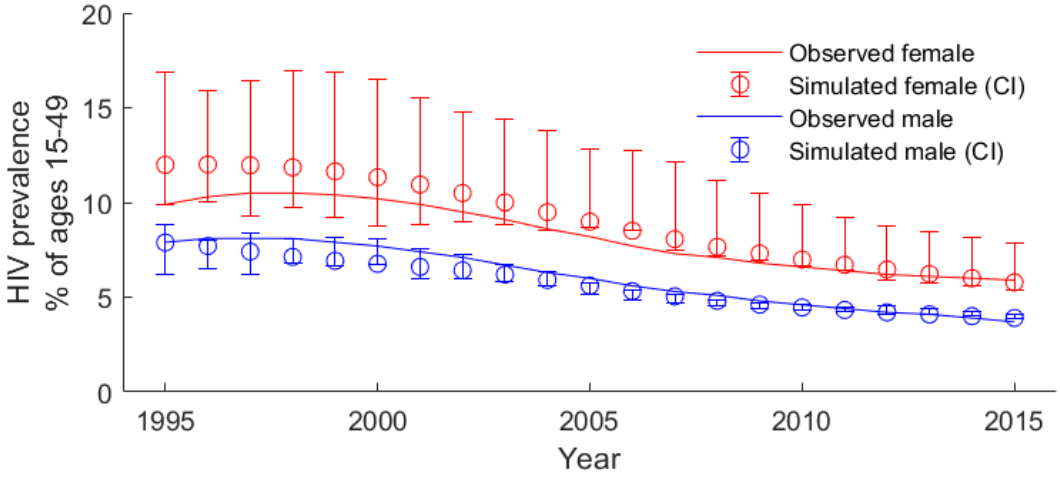

Figure 40 Observed HIV prevalence for adults aged 15-49 years compared to the simulated range (mean and CI over 1,000 simulations) for males and females from 1990 to 2016(UNAIDS, 2018c, UNAIDS, 2018b).

HPV and cervical cancer outcomes

The model was additionally calibrated to age-specific cervical cancer incidence and mortality rates, as reported by GLOBOCAN for the year 2016, in addition to age-specific high-risk HPV prevalence in 2012, as reported in the PROTECT study(Dartell et al., 2012, International Agency for Research on Cancer, 2018). Notably, this model is not calibrated to match the observed distribution of HPV types, or HSIL prevalence in

HIV negative versus HIV positive women in Tanzania, which are both significant limitations. For HPV and cervical cancer outcomes, model-generated confidence intervals (total variation) were wide and asymmetric; in order to better understand this occurrence, further investigations, including a univariate sensitivity analysis (where non-target parameters are defined probabilistically), must be performed. Additionally, as cervical cancer is still not a common occurrence, with a 2018 incidence rate of 59.1/100,000(<0.06 per 100 women), the initial starting population size of 500,000 individuals (or approximately 250,000 women) may need to be increased. Therefore, future model developments will focus on calibrating the model with a larger starting population size and to a broader, more comprehensive range of outcomes, which will increase confidence in the predicted outcomes and allow parameter inputs to be refined with smaller allowable variance.

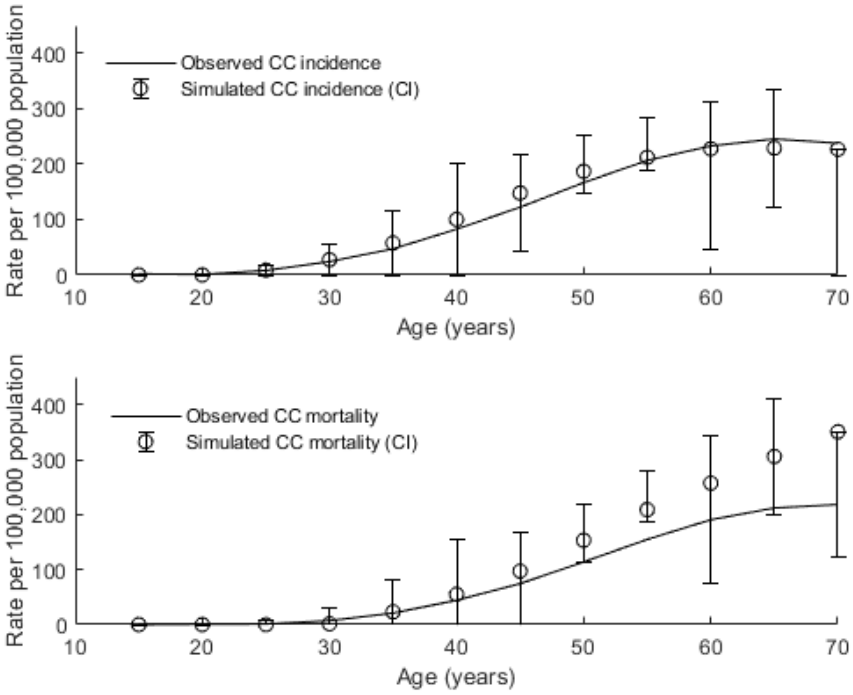

Figure 41 Observed age-specific cervical cancer incidence and mortality rates per 100,000 women compared to simulated ranges (mean and CI over 1,000 simulations) in 2016(International Agency for Research on Cancer, 2018).

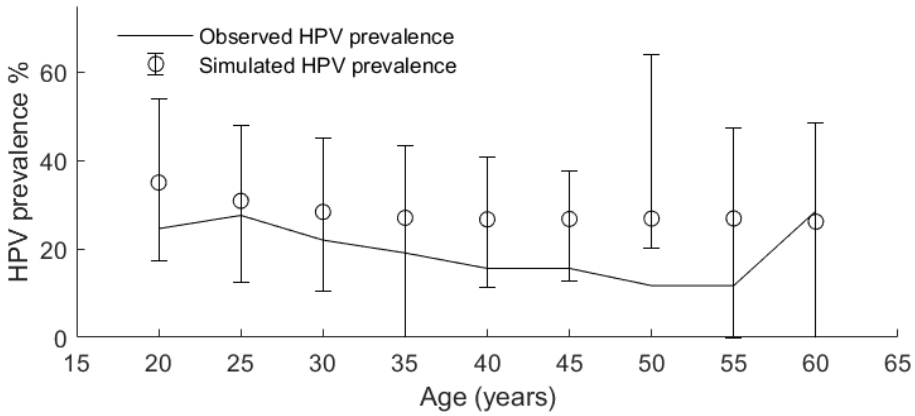

Figure 42 Observed age-specific high-risk HPV prevalence compared to simulated ranges (mean and CI over 1,000 simulations) in 2012(Dartell et al., 2012).

Validation to the deterministic compartment model

Using the parameterised agent-based model, we simulated cervical cancer incidence and mortality rates from 1995 to 2070, assuming incrementally added VMMC and ART, to estimate the impact of current HIV control interventions on HIV prevalence in females aged 15-49 years and the age-standardised (2015 world female population) rate of cervical cancer incidence for HIV-negative and HIV-positive women(United Nations DESA / Population Division, 2017). The outcomes of these simulations were directly compared to the results presented in Chapter 2. Because the agent model will be further developed for future applications, it was parametrised with the most recent data available, including updated estimates for viral suppression in Tanzania (63% in 2019)(UNAIDS, 2020a). Since agent model viral suppression assumptions fall between the baseline (47% from 2018) and 90-90-90 (73% from 2020) viral suppression assumptions presented in Chapter 2, the agent model was compared to the range generated by these two scenarios. Additionally, because the purpose of this exercise was to determine differences in model impact of HIV control interventions on HIV and cervical cancer outcomes in a broad sense, a scenario involving scale-up to meeting WHO 90-90-90 targets for HIV testing and control was not explicitly simulated. In addition, this exercise does not consider the modelled impact of PrEP use among high-risk individuals, as this has not yet been incorporated into the agent-based model. Scenario assumptions considered for the current analysis are presented in Table 34.

Table 34 HIV control intervention assumptions for modelled scenarios.

Scenario name and description	**VMMC assumptions[1]**	**ART assumptions[2]**	**Deterministic model comparison (Chapter 2)**
VMMC and ART. This scenario is the baseline scenario and reflects the current situation in Tanzania.	VMMC is as historically observed and is maintained at 80% prevalence in men aged 15-49 years from 2018 onwards.	The proportion of people living with HIV who are receiving ART and virally suppressed is as historically observed and is maintained at 63% from 2019 onwards.	VMMC and ART (baseline) and VMMC and ART (90-90-90) scenario. Assumed VMMC prevalence is the same for the agent-based and compartment models. Agent-model assumptions for viral suppression (63%) are higher than baseline ART assumptions for the deterministic model (47%) and lower than the target viral suppression (73%) under 90-90-90 assumptions.
VMMC only. This is an exploratory pessimistic counterfactual scenario.	VMMC is as historically observed and is maintained at 80% prevalence in men aged 15-49 years from 2018 onwards.	No ART uptake.	VMMC only, with no ART. Assumed VMMC prevalence is the same for the agent-based and compartment models.
No interventions. This is an exploratory worst-case counterfactual scenario.	No VMMCs carried out.	No ART uptake.	No interventions (including VMMC or ART).

[1]VMMC, as historically observed, assumes 8% VMMC (or traditional circumcision where applicable) prevalence until 1995, increasing to 23% in 1998 and then increases quadratically to 80% in 2015 as observed(The United Republic of Tanzania Ministry of Health and Social Welfare, 2013, Ministry of Health et al., 2016). [2]ART, as historically observed, assumes the introduction of ART in 2005, with a linear scale-up to 47% virally suppressed in 2017(UNAIDS, 2018d).

For all simulated scenarios, the agent-based and deterministic-compartment models predicted similar female HIV prevalence from 1995 to 2070 (Figure 43). For the realistic VMMC and ART scenario, the agent-based model predicts a 2070 female HIV

prevalence of 0.86-1.15%, compared to the deterministic compartment model prediction of 0.19-0.56% depending on viral suppression rate. For the scenario which assumes VMMC only and no ART, the agent-based and deterministic compartment models predict that HPV prevalence in 2070 would be 2.00-5.45% and 2.46%, respectively. Without any intervention, the agent-based and compartment models respectively predict 2070 HIV incidence rates of 9.00-9.91% and 8.47%, respectively. Across all three scenarios, simulated HIV prevalence was generally higher for the agent model compared to the deterministic compartment model; this may be due to differences in the way that preventative interventions are simulated (i.e., at the individual level compared to an average across the population), or, due to the additional simulated modes of HIV transmission in the agent-based model. However, both additional transmission modalities are suppressed by ART uptake.

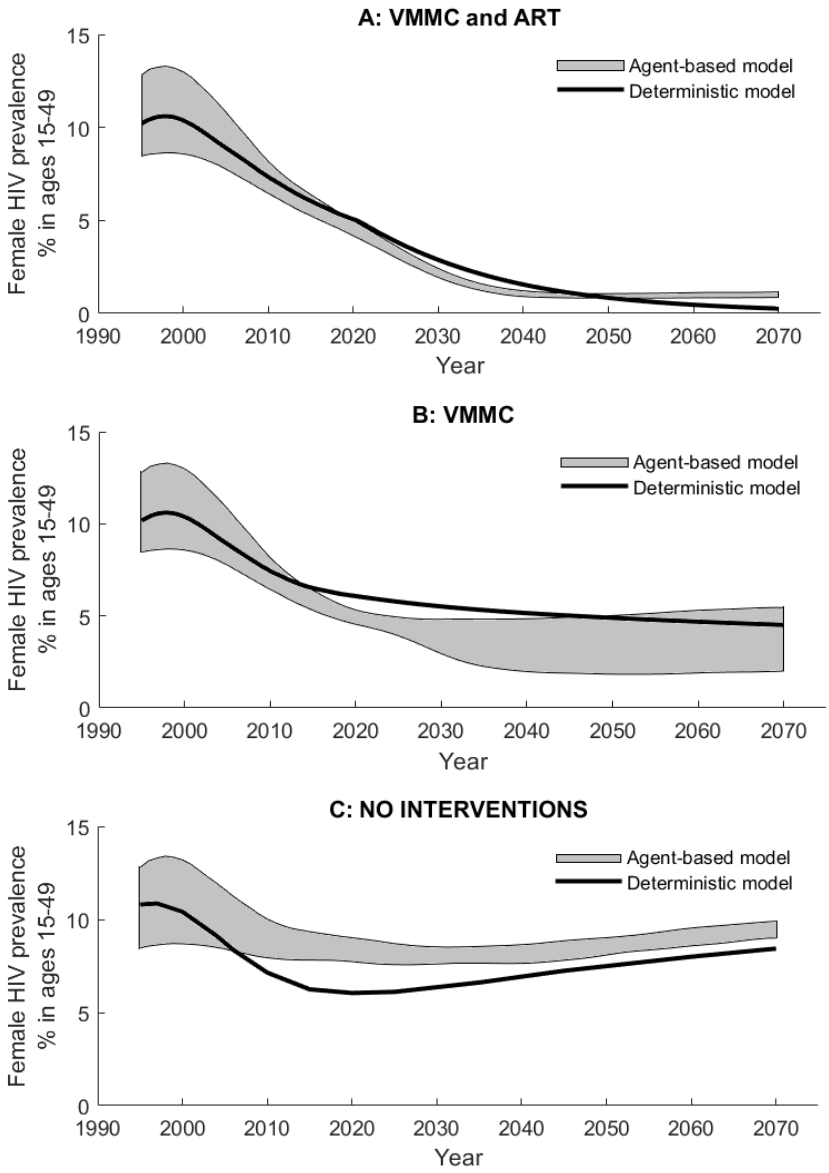

Figure 43 Simulated female HIV prevalence (ages 15-49 years) from 1995-2070 for scenarios assuming A: VMMC and ART, B: VMMC only, and C: no interventions for the agent-based model (CI range over 1,000 simulations) compared to the deterministic compartment model.

For HIV negative women, the agent-based model predicts a lower cervical cancer incidence rate in 2070 than the compartment model (ASR of 38.09 c.f. 40.52 per 100,000 women). VMMC is predicted to decrease the rate of cervical cancer incidence by 16.54% in 2070, compared to the deterministic compartment model prediction of a 13.52% reduction (Table 35). Both models predict a slight increase in cervical cancer incidence rate in HIV negative women of less than 1 ASR point, due to ART for WLHIV extending their life expectancy and therefore increasing their contribution to the spread of HPV. For HIV positive women, the agent model predicted, across all simulated

scenarios, a lower cervical cancer incidence rate than the deterministic model, noting some overlap due to large confidence bounds in the 'VMMC and ART (baseline)' and 'No interventions' scenarios. As with HIV negative women, the impact of VMMC (in terms of percentage decrease) was larger in the agent-based model (13.97% reduction compared to the 5.05% reduction predicted by the deterministic compartment model) .

Table 35 Agent-based (mean and CI over 1,000 simulations) versus deterministic compartment model estimates of age-standardised cervical cancer incidence rates (ASR) per 100,000 women in 2070 for HIV negative and HIV positive women.

	ASR of cervical cancer incidence in 2070 per 100,000 HIV negative women		**ASR of cervical cancer incidence in 2070 per 100,000 HIV positive women**	
Scenario	**Agent-based model (mean and CI[a])**	**Deterministic compartment model[b]**	**Agent-based model (mean and CI[a])**	**Deterministic compartment model[b]**
VMMC and ART	32.43 (30.99-43.50)	35.17-35.19	189.55 (156.17-210.91)	208.82-220.23
VMMC only	31.79 (30.38-53.74)	35.04	224.97 (204.22-239.82)	256.25
No interventions	38.09 (32.68-54.81)	40.52	261.51 (241.36-281.65)	269.89

[a]*Confidence interval (CI) refers to the total range of outcomes generated by stochastic variation.*
[b] *All quoted findings relevant to the deterministic compartment model are reported in Chapter 2; the VMMC and ART scenario range reflects variation in ongoing viral suppression rates between 47-73%.*

The magnitude of the differences between the agent-based and compartment model predictions for cervical cancer incidence among HIV positive women may be due to model paradigm or limitations in the parametrisation of sexual behaviour, such as lower sex-worker client volume and smaller assumed difference in age between partnered males and females than what was assumed for the deterministic compartment model. Additionally, relative risk of HPV acquisition and progression to cervical pre-cancer/cancer for HIV positive compared to HIV negative women has been well defined and is easily translatable into multipliers for pre-cancer state transition probabilities in a deterministic setting. The same multipliers were utilised similarly in the agent model;

however, given the event-driven mechanism for time-in-state, it may also be necessary to translate these multipliers into quickened progression rates.

Additional findings

By capitalising on the flexible agent-based model structure, it is possible to further nuance our understanding of HIV positivity and viral suppression's impact on progression to cervical cancer. Women with HIV have an increased risk of HPV acquisition and disease progression across all states in the cervical pre-cancer pathway; however, viral suppression is known to substantially offset this increase in risk. As demonstrated above, ART can prevent cervical cancer incidence in some WLHIV; however, the capacity of ART to delay cervical cancer onset has not yet been quantified. Not only would delaying cervical cancer onset give back valuable years of life to WLHIV, but it would also expand the window of opportunity to detect and treat cervical precancer through screening, therefore preventing cervical cancer. Under the 'VMMC and ART' scenario assumptions described above, the time between HPV acquisition and onset of cancer was tracked for all women diagnosed with cervical cancer. HPV infections were counted only if that specific infection eventually resulted in cervical cancer; therefore, infections that cleared or were acquired on top of existing HPV infections were excluded. Results were stratified by HIV positivity and ART treatment status. Additionally, HPV infections acquired before 2019, the year that viral suppression rates reach 63%, were excluded to ensure a fair comparison between untreated and virally suppressed WLHIV.

The most common predicted time between HPV acquisition and cervical cancer incidence for women who developed cervical cancer was 22 years for HIV negative women, 20 years for virally suppressed women living with HIV, and 16 years for untreated women living with HIV (Figure 44). Therefore, on average, viral suppression through ART delays cervical cancer onset by four years.

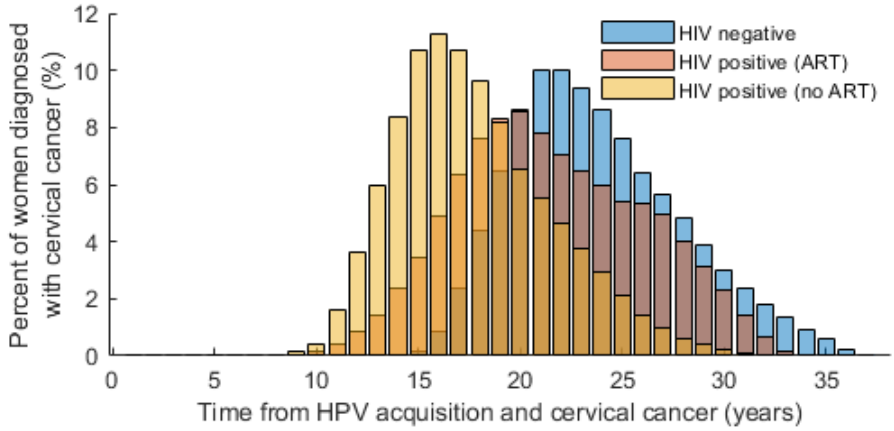

Figure 44 Years (mean over all simulated women in 1,000 simulations) between HPV acquisition and incidence of cervical cancer for all cervical cancer diagnoses in women who acquired their HPV infection in 2020 or later.

Discussion

This chapter describes the development and parametrisation of an agent-based model of HIV and HPV transmission, (co-)infection, natural history, and prevention. The model platform was developed to complement and expand upon the deterministic compartment model presented in Chapters 2-4, as the agent-based structure enables the incorporation of greater detail and the generation of more nuanced results. While still in preliminary form, this achieves a reasonable fit to training data for HIV incidence, prevalence, and mortality, as well as HPV prevalence and cervical cancer incidence and mortality rates. Furthermore, predicted HIV and cervical cancer outcomes under a range of HIV control scenarios were reasonably comparable to predictions made by the deterministic compartment model. Finally, the model estimated the time from HPV infection to cervical cancer incidence for HIV negative compared to HIV positive women, depending on ART treatment status. On average, the estimated time from HPV infection to cervical cancer incidence was 22 years for HIV negative women, 20 years for HIV positive women, and 16 years for HIV positive women on ART.

By directly comparing predictions for the agent-based model to the deterministic compartment model, we have found that, in general, the agent model produced similar end-point estimates for HIV prevalence and cervical cancer incidence over a range of intervention scenarios. Incrementally, VMMC and ART were predicted to reduce HIV prevalence by up to 80% and 84% (assuming viral suppression of 63%) considering confidence intervals, whereas the compartment-based model reported reductions of up to 71% and 92% (assuming viral suppression of 73%) for VMMC and ART, respectively. For cervical cancer incidence rates among HIV negative and HIV positive

women, VMMC reduced cervical cancer incidence rates by 17% (2-45%) and 14% (1-27%) respectively, which are larger than the reported reductions for the deterministic model, of 14% and 5%. These differences substantiate the argument that comparative modelling has an important place in epidemiology, as it can verify or contradict the overall conclusions of an analysis. A comparative study undertaken by the Cancer Intervention and Surveillance Modelling Network (CISNET) assessed the impact of introducing cervical screening in an unscreened setting and reported the percentage reduction in cervical cancer incidence rate. The author's compared findings from three separate model platforms (two deterministic compartment models and one stochastic agent-based model) and reported that cervical cancer incidence reductions ranged from 55-74% across the models(de Kok et al., 2020). While a total difference of 19 percentage points may seem substantial, it highlights the inherent uncertainty of modelling and contextualises the findings from the comparative exercise presented in this chapter.

The agent model outlined in this chapter is an effective proof of concept; however, it should be further developed to address a range of limitations. Firstly, this model was calibrated to a smaller number of observed targets than the deterministic compartment model described in Chapters 2-4, and due to significant uncertainty in HPV natural history parameters, the simulations produced large confidence bounds. This model has not yet been calibrated to match Tanzanian HPV-type specific prevalence or HSIL (i.e., cytologically detected CIN2/3) prevalence among HIV-negative versus HIV positive women. Ensuring an acceptable fit to these targets will be essential to guarantee the validity of future model applications, which may assess the impact of HPV vaccination or specific interventions targeted to WLHIV, such as more intensive cervical screening and adult HPV vaccination. Another limitation of this analysis is that individuals who clear their HPV infections are not conferred any natural immunity to reinfection, which may ultimately result in an overestimation of HPV re-infection and cervical cancer incidence. While this was not found to substantially impact the calibration result, it will be addressed in future model developments. Finally, simplifications in the simulation of sexual behaviour may impact modelled HIV infection dynamics. In particular, the assumption that commercial sex workers form a maximum of two new sexual partnerships per month, chosen largely for computational efficiency, is significantly lower than the monthly client volume of 26, reported in a qualitative analysis of sex worker behaviour in Dar es Salaam(Research International (on behalf of T-MARC), 2009); however, this reported monthly client volume is low-quality data, and gives no information confirming the ratio of new clients to recurring clients. The impact of

underestimating sex-worker client volumes is likely to have impacted the early HIV epidemic growth phase; however, as the HIV epidemic matures and the role of general partnerships increases, this is expected to have less of an impact. Despite this limitation, the model fit to observed HIV prevalence data was not severely impacted.

Due to their inherent individualised structure, this exercise highlights that agent-based models can be more challenging to parametrise than their compartment-based counterparts and require a greater number of parameters specifying sexual partnership interactions. In addition, to provide meaningful estimates for the incidence of relatively uncommon diseases, including cervical cancer, which is usually reported in units of 100,000 women, agent models must necessarily simulate many individuals at a great computational cost. Future development of this platform, which is expected to take place during my post-doctoral research, will address these specific limitations in addition to a range of other improvements.

The agent model developed for this chapter has several strengths, including its detailed simulation of multimodal HIV transmission, event-driven natural history, and individual-level incorporation of behavioural and control interventions, such as per-partnership condom use, VMMC and ART uptake and viral suppression. Furthermore, compared to deterministic compartment models, which tend to be (semi-)Markovian in nature, the agent-based paradigm facilitates the output of time-dependent results that would be impractical to generate from a compartment-based model; for example, estimating the time between disease acquisition and various milestones, and quantifying the potential for prevention interventions to delay acquisition. Time-dependent results are impractical to generate using Markovian models, as, by definition, it is not possible to track time in state. The finding that, for HIV positive women, viral suppression due to ART delays the onset of cervical cancer is an important result. This finding implies that virally suppressed women may experience an even greater benefit from cervical screening, as the delay in onset of cervical cancer provides an expanded window for pre-cancer detection and treatment.

Additionally, the individualised nature of this model ensures its suitability for simulating next generation cervical screening technologies that utilise early-stage biomarkers, and for nuancing ART treatment impacts, which are highly dependent on the length of time that an individual has been receiving treatment. Further strengths of this model include its capacity to capture heterogeneity without the need to exponentially increase model size, for example, in this model, circumcision is applied to individual males, and condom use is applied to partnerships, rather than being protective factors

homogeneously applied across the entire population. Finally, this model iteration operates at a finer granularity than the compartment-based model, as it simulates individuals in single-year age groups (0-99 years) compared to five-year age groups (5-9 to 75-79 years), and on a monthly rather than quarterly time-step. When cervical screening is implemented in subsequent versions of this model, single year age-groups will enable screening frequency and events to be more accurately captured. Further, the shorter time-step facilitates a more precise representation of short sexual relationships and allows HPV natural history progression and regression to be simulated linearly, without needing to assume that individuals' jump' states (for example, transitioning from HPV infection to CIN2 in a single time-step). The choice of such a small timestep was balanced against the need for computational efficiency and is unlikely to impact the findings of this analysis. Most processes performed by this model are event-driven and directly informed by data and are therefore not influenced by any choice of time-step. Processes which may be influenced by choice of discrete time-step are limited to the formation of new sexual partnerships, HIV/HPV acquisition per existing partnership and uptake of interventions. Since uptake of interventions is specified based on annual observed data, the only potential time-step-sensitive processes are new partnership formation and the per-timestep probability of HIV/HPV transmission among discordant couples (a result of ‘coital acts per timestep’). Because new partnership formation rates and the number of coital acts per timestep were found via model calibration to observed data, and are additionally subject to stochastic variation, it is unlikely that a reduced timestep could improve model findings. Nonetheless, future model iterations will investigate the use of a reduced timestep, which will come at substantial computational cost.

Deterministic compartment modelling is a useful and valid modelling approach for simulating complex epidemic interactions, such as HIV and HPV; however, there is a practical limit to what can be achieved with that model paradigm. As it becomes necessary to include more detail, a compartment-based model’s Markovian and size limitations necessitate a transition to agent-based approaches. Modelling studies utilising multiple independent model platforms to make predictions, known as comparative modelling, is quickly becoming the gold standard for model generated evidence. By defining, parametrising, and comparing two separate models of HIV and HPV infection and natural history, with substantial variation in underlying structure, this thesis can provide, through comparative modelling, validated estimates of the quantitative impact of HIV control interventions on cervical cancer outcomes in Tanzania.

Chapter 6: Discussion and Conclusion

This body of work was constructed to comprehensively assess the impact of endemic human immunodeficiency virus, and ongoing HIV control, on HPV transmission dynamics, natural history, and cervical cancer control. For this work, a deterministic model platform was developed to dynamically simulate the transmission, natural history, and potential for control of HIV and multiple HPV genotypes. This model platform was extensively calibrated and validated against data specific to the United Republic of Tanzania, a country with endemic HIV (4.6% in 2020) and ongoing scale-up of HIV control interventions such as voluntary medical male circumcision (up to 80% from 2018), antiretroviral therapy (up to 47% viral suppression in 2018) and programmes targeted at increasing safe sex practices and condom use(UNAIDS, 2018e, Kim et al., 2019). Tanzania was the chosen setting for parametrisation of the model as it is broadly representative of the sub-Saharan African region in terms of human development index, income, endemic HIV, and cervical cancer incidence, and, due to the availability of detailed empiric data describing national HIV diagnoses, prevalence, and treatment, in addition to data informing HPV and CIN prevalence by HPV genotype and HIV positivity status.

Summary of findings

The historical, present, and future impact of Tanzania's implemented and sustained HIV control interventions on HIV and HPV prevalence and cervical cancer incidence and mortality were quantified. These interventions included voluntary medical male circumcision (VMMC) scale-up to cover 80% of Tanzanian males by 2018, progress towards the WHO 90-90-90 HIV testing and treatment targets, and access to pre-exposure prophylaxis for at-risk females and males. The modelling estimated that, to 2020, VMMC had prevented 2,843 cervical cancer cases and 1,039 cervical cancer deaths. The expansion of Tanzania's antiretroviral treatment coverage, while ultimately lowering cervical cancer incidence and mortality rates over the next fifty years, is estimated to have indirectly resulted in 1,573 additional cervical cancer cases and 1,221 additional cervical cancer deaths. This temporary increase in cancer burden is not a failure of antiretroviral utilisation but rather should be seen as a success, as the life-extending capability of antiretroviral therapy has, for many women, removed HIV-related mortality as a competing risk to cervical cancer incidence. The scale-up of antiretroviral coverage and viral suppression rates to meet the WHO's 90-90-90 targets in combination with VMMC was predicted to lower cervical cancer incidence and mortality rates by 43% and 39%, respectively, in 2070 compared to the 2020 rates. Unfortunately, even the best-case assumptions for HIV control were not predicted to

drive the incidence rate of cervical cancer below 35 cases per 100,000 women, which is substantially higher than the elimination threshold of four cases per 100,000 women. It is therefore important to scale up dedicated cervical cancer prevention programmes, in addition to sustained HIV control, such that lives saved through HIV prevention are not instead lost to cervical cancer.

Therefore, the subsequent analysis examined the impact of scaling up HPV vaccination, screening, and treatment in Tanzania to meet the WHO 90-70-90 elimination targets (independently and combined), considering variation in HPV and cervical cancer risk for all women, and specifically for WLHIV. This work assumed twice-lifetime HPV testing, with intensive three-yearly HPV testing for women living with HIV as per the original (now superseded) 2013 WHO cervical screening guidelines. The principal finding was that cervical cancer elimination, at the four per 100,000 threshold, was predicted to occur in 2076 for the general population of Tanzanian women and in 2061 for WLHIV. Cervical cancer elimination aside, the scale-up of cervical screening on its own was projected to rapidly reduce cervical cancer incidence among all Tanzanian women by more than 50% in 10-20 years, with even greater reductions predicted for WLHIV. Additionally, increasing access to cervical cancer treatment from 9.5% to 90% reduced the predicted cervical cancer mortality rate by 28-35% for all women and WLHIV. These findings strengthen the case for implementing the WHO cervical cancer elimination strategy with increased screening available for women living with HIV and highlight the urgency for delivering high-quality screening to populations with endemic HIV.

In the intermediate term, while the protective benefits of pre-adolescent HPV vaccination are yet to be realised, there is a substantial benefit in terms of lives saved by rolling out cervical screening quickly and at high coverage rates. However, as HPV vaccination combined with HIV control drives down the risk of cervical cancer, the optimal cervical screening regimen for women in Tanzania, or any country, is likely to change. Therefore, Chapter 4 aimed to take a closer look at possible cervical screening approaches (a combination of technology, frequency, and age range) tailored for cohorts of women vaccinated at high (≥90%) coverage against HPV. Detailed cost-effectiveness and harms-versus-benefits analyses identified that, for the general population of Tanzanian women, primary HPV testing at age 35 and 45 was the most cost-effective approach (ICER=$957.05/LY, WTP=$1,061) and minimised harms associated with cervical screening relative to cervical cancer cases prevented (NNT=15.58). In the subgroup of WLHIV, three-yearly HPV testing from age 30 (8 lifetime tests) was the most cost-effective approach (ICER=$1,015.57, NNT=9.89);

however, HPV testing at age 35 and 45 was also cost-effective and further minimised screening harms (NNT=5.33). Longitudinally, transitioning from revised (2021) WHO screening recommendations to cost-effective screening approaches for vaccinated cohorts is still predicted to achieve cervical cancer elimination, despite less frequent screening in WLHIV.

The final piece of work, presented in Chapter 5, outlines the preliminary development of an agent-based model of HIV and HPV (co-)infection, natural history, and HIV control. The purpose of this additional model is to complement and expand on the capabilities of the deterministic compartment model, and in the process, address several identified limitations. This chapter presents a description of model structure and parametrisation, validation against compartment model findings (Chapter 2) and additional model outcomes to further our understanding of the impact of ART on cervical cancer onset in WLHIV. The model achieved an acceptable fit to limited observed data targets, with large, simulated confidence intervals produced by stochasticity for cervical cancer outcomes. The agent-based model validated reasonably against findings from the deterministic compartment model. Under current HIV control assumptions, the agent and deterministic compartment models predict that the 2070 prevalence of HIV among females will be 2.00-5.45% and 2.46%, respectively, and that the age-standardised rate of cervical cancer incidence will be 32.43 and 35.17 per 100,000 women, respectively. The agent-based model also predicts that, on average, women who are diagnosed with cervical cancer have carried their high-risk HPV infection for 22 years if they are HIV negative and 16 years if they are HIV positive and untreated. In WLHIV, viral suppression was predicted to delay the onset of cervical cancer by approximately four years, increasing the opportunity to detect and treat cervical precancer before it progresses to cancer.

Strengths and comparison to the literature

The overarching strengths of this thesis are the novelty of the research, which addresses an important public health problem in sub-Saharan Africa, and, the detail incorporated into the model platform supporting this research. This doctoral research was the first to directly explore the dynamic relationship between HIV control interventions and cervical cancer incidence and mortality, report on the feasibility and timing of cervical cancer elimination using an integrated dynamic HIV/HPV model and assess the cost-effectiveness of continued cervical screening among vaccinated women with and without HIV. Findings from this thesis contribute to evidence for public health interventions that can minimise unnecessary morbidity and mortality to African women. Furthermore, this model platform was used to perform detailed analyses

(separate to this thesis) of cervical screening algorithms, including variation in primary and triage test technology, screening interval and age-range in unvaccinated cohorts of WLHIV; an analysis which directly informed the World Health Organisation 2021 guidelines for cervical screening in women living with HIV(World Health Organisation 2021).

The model is highly detailed, capable of simulating HIV and multi-type HPV transmission dynamics, accounting for age-, sex-, and risk-profile-specific sexual behaviour over time, in addition to VMMC, PrEP, condom-use, HIV-stage-specific ART uptake rates, including partial and complete viral suppression, and cervical cancer control interventions such as HPV vaccination and cervical screening. This platform has been carefully calibrated and validated against a wealth of empiric data sourced primarily from Tanzania and supplemented by South African or Ugandan data when Tanzanian data was unavailable. From a pragmatic standpoint, this platform has pushed its computational and size limits; therefore, the development of an agent-based platform has commenced to support it. This additional agent model, which will be the focus of further development and improvement, can incorporate greater detail and has already produced estimates that were not possible for the compartment model to determine, such as the length of time between initial HPV infection and the onset of cervical cancer.

Prior to the commencement of this doctoral research, the existing modelling literature was largely cohort-based in strictly HIV positive populations, not accounting for age- and year-specific dynamics in HIV and HPV acquisition risk, or changing access to control interventions(Atashili et al., 2011, Vanni et al., 2012, Campos et al., 2018). In more recent years, while this thesis was being prepared, two relevant model platforms have also featured in the literature: a dynamic compartment model developed by authors at the University of Washington, and a stochastic individual-based model developed at Stellenbosch University in South Africa(Tan et al., 2018, van Schalkwyk et al., 2021). The University of Washington model was published in a 2018 analysis assessing the long-term impact of HPV vaccination programmes in HIV-negative and HIV-positive women in Kwa-Zulu Natal, South Africa(Tan et al., 2018). The authors found that increasing HPV vaccination coverage in South Africa from 50% (with a bivalent vaccine) to 90% (with a 9-valent vaccine) may reduce cervical cancer incidence rates by 74%, in the context of existing cytology-based cervical screening, over a 70-year time horizon; Chapter 3 reports greater reductions of 91% in cervical cancer incidence due to 9-valent HPV vaccination. Potential causes of this difference in cervical cancers preventable through HPV vaccination may be caused by differences in

underlying assumptions about HPV type distribution in cervical cancer. While this 2018 study incorporated essential HIV transmission dynamics and HIV control, it did not explicitly explore the direct and indirect effects of HIV and HIV control on HPV prevalence, cervical precancer and cervical cancer rates over time in HIV-positive and HIV-negative women.

The Stellenbosch University model, published online in June 2021, utilised an individual-based HIV and HPV infection model to assess the historical and potential future impact of HPV vaccination and cervical screening in South Africa(van Schalkwyk et al., 2021). Their analysis is very comparable to Chapter 3 of this thesis, except for differences in model paradigm (individual versus compartment), setting (South Africa versus Tanzania), and screening algorithm/s (screening with triage versus screen-and-treat without triage). The authors predict that under current observed HIV control (ART and condom-use), HPV vaccination (bivalent HPV vaccine) and cervical screening (cytology) in South Africa, cervical cancer incidence will fall by 76% over the next century, from an age-standardised rate of 49.4 in 2020 to 12.0 per 100,000 women in 2120. Cervical cancer incidence rates may be further reduced to 4.7/100,000 women if the HPV vaccination programme switches to a 9-valent HPV vaccine, combined with a screening programme transition to primary HPV testing with 16/18 genotyping and cytology triage for women with high-risk HPV not 16/18. An additional reduction to 4.0/100,000 is predicted for a scenario assuming three-yearly screening (ages 25-50) for women living with HIV. These findings for South Africa are highly comparable to other published estimates that do not explicitly account for HIV, which similarly estimate that screening and HPV vaccination will reduce cervical cancer incidence (ASR) to 4.9/100,000 women in 2099(Simms et al., 2019). Such a reduction in cervical cancer is not as substantial as those reported under similar assumptions for Tanzania in Chapter 3, which predicts that over the same 100-year timeframe, cervical cancer incidence may be reduced from 58.0 to 1.3-2.5 cases per 100,000 women annually(Hall et al., 2021). This disagreement in the magnitude of cervical cancer incidence reduction may be attributed to differences in local HPV type distribution and setting-specific variation in voluntary medical male circumcision prevalence, which is assumed to reduce male HPV acquisition risk by 63%, and is significantly higher in Tanzania (80%) than in South Africa (53%)(Cork et al., 2020). Additionally, Tanzania has a higher starting cervical cancer incidence rate (58.0 compared to 49.4/100,000 in South Africa), and this may reflect the current availability of screening, as women in Tanzania are for the most part unscreened, whereas women living in South Africa have access to cytology-based cervical screening.

To date, there are no published studies that assess optimal cervical screening frequency in the context of endemic HIV and HPV vaccination as presented in Chapter 4, or which report on delay in cervical cancer onset due to viral suppression in HIV positive women as presented in Chapter 5. While this research fills a current literature gap, this field is rapidly maturing, and there will ideally be similar analyses to compare these findings to in the future.

Limitations and avenues for future research

Considering the findings and the limitations of this thesis, there are extensive opportunities for future work, as described below.

Improved and updated parameter information

As with all modelled analyses of this nature, the best one can do is use the observational data available at the time; however, future analyses must be updated to incorporate new data as it emerges. While this thesis was being prepared, updated data has emerged which will inform future model assumptions. In particular, priority areas for data updates include ART uptake and viral suppression (up to 69% viral suppression among all people living with HIV in 2019), progress towards target HPV vaccination rates (49% full-dose coverage of 9-14-year-old females by the end of 2019), and if/when data becomes available, updates reflecting changes in behaviour, uptake of interventions and all-cause mortality attributable to the COVID-19 pandemic(UNAIDS, 2020a, Mphuru et al., 2021).

Increased model detail and complexity

Due to practical and computational limitations imposed by a compartment-based structure, it may not be feasible to incorporate additional detail into the compartmental model utilised in Chapters 2, 3 and 4. However, in leveraging the flexibility inherent in agent-based models, the model described in Chapter 5 represents an excellent opportunity to include this detail. Many limitations that were previously noted for the compartmental model have been, or will be, addressed in the agent-based model structure, including simulating single-year age groups and individual HPV genotypes, the impact of HIV stage on HPV natural history, and alternate HIV transmission modalities. Furthermore, by modelling individuals rather than groups of people with similar characteristics, it is feasible to integrate individual variability in CD4 counts, ART failure and uptake of second-line therapies, the length of time on ART and discontinuation, HIV-stage reversion and HIV anti-viral resistance in ART users.

While heterosexual transmission is the modality most applicable to HPV transmission in relation to cervical cancer, HIV transmission is known to be elevated among high-risk

population subgroups such as men who have sex with men (MSM) and injection drug users (IDU), and can be transmitted from mother to child in utero; with MSM estimated to make up 1.3% of the Tanzanian (male) population, and over 10,000 infant HIV infections in 2019 due to mother-to-child transmission(UNAIDS, 2021a, Wambura et al., 2020). The agent model presented in Chapter 5 specifically incorporates additional HIV transmission modalities, including transmission among MSM and mother to child transmission; however, it is subject to substantial limitations in simulating sexual mixing patterns and behaviour for commercial sex workers and their clients, which will need to be addressed. Future model iterations will additionally incorporate within-country geographic heterogeneity for parameters such as sexual mixing, sexual behaviour and access to prevention interventions, as observational data demonstrate that severe inequities exist across geographic regions in Tanzania(Runge et al., 2019). In many sub-Saharan African countries, national averages for HIV prevalence and cervical cancer incidence reflect elevated disease transmission in regional hot spots(Dwyer-Lindgren et al., 2019). A clear example of this is the case of South Africa, where a study reported that geospatially across the greater Durban region, HIV incidence rates ranged from 3 to 12 new cases per 100 woman-years(Ramjee et al., 2019).

The simplified screen-and-treat screening approaches modelled in Chapters 3-4 are unlikely to reflect real-world cervical screening pathways, with the WHO recommending in their revised guidelines that national screening programmes follow a 'screen, triage and treat' approach for WLHIV(World Health Organisation 2021). Under a screen, triage and treat screening algorithm, women who screen positive at their primary screening test then receive a second 'triage test', which determines whether they are at high risk of CIN 3 or cervical cancer (to receive immediate precancer treatment), or, whether they are at intermediate risk (to receive surveillance testing). The WHO recommends HPV DNA testing as the primary screening test, with either partial genotyping (for HPV 16/18), colposcopy, VIA or cytology to triage women. Detailed screening algorithms, including screen, triage, and treat approaches, have been implemented in the compartment model to perform evaluations informing these WHO recommendations, although they have not been utilised for analyses in this thesis.

Finally, the cervical screening analyses presented in Chapters 3 and 4 assume that a screening participation rate of 70% is uniformly applied across the entire female Tanzanian population for each independent screening test. In reality, we know that there are a range of barriers and facilitators to cervical screening, and that it is likely a population would be divided into never-screeners, inconsistent screeners, and those who consistently screen when they are due(Pedersen et al., 2017). By ignoring these

individual behaviours as assuming that a random 70% of women participate in each recommended screening event, scenarios assuming frequent screening invariably also assume that all women are screened at least once, an assumption which maximises potential simulated cervical cancer incidence reductions and is unlikely to reflect the reality of implemented screening programmes. Individual screening behaviours can be incorporated into the agent-based model structure to account for heterogeneity in screening behaviour to overcome this limitation.

Optimal scale-up strategies

Future studies assessing the optimal introduction of cervical cancer prevention strategies may consider temporary 'catch-up' vaccination or screening for women older than the usual target age range but still at risk of cervical cancer(Bosch et al., 2016). This approach may help reduce cervical cancer incidence in women outside of the intervention age range and may be targeted towards WLHIV, noting that the effectiveness of HPV vaccination in this population subgroup is still disputed and under active investigation(Zizza et al., 2021). In the case of catch-up screening, this may be offered to women older than the screening cut-off as an 'exit-test' to reduce their cervical cancer risk, as they have not benefited from a lifetime of cervical screening under recommended management.

New screening strategies

As more data on the safety and efficacy of new cervical screening test technologies emerges, it will be prudent to model their potential incorporation into new and existing cervical screening programmes. This includes emerging evidence for primary screening with an mRNA test and triaging with dual-stained cytology for women with screen-detected HPV. Unlike HPV DNA testing, which utilises PCR to detect HPV DNA present in a cervical sample, mRNA testing aims to detect only HPV infections where there is over-expression of the viral oncogenes E6 and E7. While slightly reducing test sensitivity to CIN2+ detection by approximately 2%, this approach has been shown to increase specificity by 4%, which will reduce costs and harms associated with unnecessary follow-ups and precancer treatments by up to 23%(Iftner, 2018). Dual-stained cytology can be used as a triage test to determine the severity of disease or urgency of follow-up for women who screen positive with either an HPV DNA or mRNA test and refers to the detection through staining of the biomarkers p16 and Ki-67. Recent studies from Kaiser Permanente and the National Institutes of Health have reported that dual-stained cytology is superior to cytology testing alone for stratifying screen-positive women by risk and may be an effective triage test by reducing overall screening-associated harms(Wentzensen et al., 2019).

Impact of coronavirus pandemic

Finally, a timely and relevant analysis assessing the impact of the 2019 novel coronavirus pandemic (SARS-COV-2) on HIV epidemic outcomes and uptake of cervical cancer control interventions could be performed. Data from many countries indicate that uptake and availability of the usual health services have been reduced during the pandemic for a range of reasons, including supply, workforce closures, and patient fear to attend clinics(Dorward et al., 2021, Waterfield et al., 2021, Smith et al., 2021). This has the potential to reduce rates of viral suppression through ART in countries with endemic HIV and stall the scale-up of HPV vaccination and cervical screening services in many countries.

Open-source code sharing

At the time of writing this thesis, the executable model code for both the deterministic compartment model and the agent-based model has not been made publicly-accessible.

Policy implications of findings

Synthesis of model findings presented throughout this thesis, combined with existing evidence-based guidelines, yields seven key policy recommendations specific to HIV and cervical cancer control in Tanzania. For each recommendation, the rationale or evidence is described, in addition to an assessment of Tanzania's current status in that specific domain as well as potential barriers and challenges. Tanzania's progress in each domain is defined as one of three possible categories:

Achieved	The policy recommendation has been implemented in Tanzania, and utilisation is at target levels.
On-track	The policy recommendation has been implemented in Tanzania, and utilisation is moderately high or close to target levels.
Urgent	The policy recommendation has not been implemented in Tanzania, or the policy recommendation has been implemented in Tanzania, and utilisation is low.

Policy recommendation 1: voluntary medical male circumcision

Policy:	Maintain high (≥80%) prevalence of VMMC among the sexually active male population.
Status:	Achieved.

Evidence from randomised controlled trials, cohort studies and modelling informed the 2020 WHO recommendation that VMMC should be utilised as an effective means of

HIV prevention in males aged 15 and over in settings with endemic HIV. The risk of HIV infection is 44-56% lower for circumcised men and 41% lower for their female partners(World Health Organisation (WHO), 2020b). Model findings from this thesis (Chapter 2) indicate that compared to a scenario with no VMMC or ART, VMMC at 80% prevalence would reduce HIV prevalence by more than 70%, with an additional benefit of reducing cervical cancer incidence by 28%.

Acceptability and uptake of VMMC in Tanzania have been high, with the latest estimates reporting 80% prevalence of VMMC among adult (ages 15+) Tanzanian males in 2019(Cork et al., 2020). Nevertheless, there are still potential barriers to maintaining this programmatic success, particularly when the perceived threat of HIV incidence subsides. When performed beyond infancy, circumcision comes with associated harms, including pain\discomfort, interruption to sexual function, and risk of infection as associated with any surgical procedure(World Health Organisation (WHO), 2020b). To reduce these risks, infant circumcision may be considered; however, circumcision of infants is not voluntary and removes choice and bodily autonomy.

Policy recommendation 2: HIV testing and treatment

Policy:	Meet UNAIDS 90-90-90 targets (and 95-95-95 targets if possible) for HIV testing, treatment and viral suppression**.**
Status:	On track.

Strong accumulated evidence on the benefit of viral suppression through ART, on both the individual (normalised survival) and community (96% reduction in transmission), has resulted in the 2014 Joint United Nations Programme on HIV/AIDS (UNAIDS) setting the' 90-90-90' targets for HIV testing and treatment(UNAIDS, 2017). These UNAIDS targets specified a 2020 deadline to achieve these targets and defined additional 'Fast-Track Targets', increasing the initial targets to 95-95-95 by 2030(UNAIDS, 2015). Model findings presented for Tanzania in Chapter 2 indicate that scale-up to meet the UNAIDS 90-90-90 targets, compared to the maintenance of rates observed in 2018, will reduce HIV prevalence by 68-71% by 2070, with the added benefit of reducing cervical cancer incidence by 3%. Furthermore, agent-model findings presented in Chapter 5 indicate that for WLHIV who develop cervical cancer, viral suppression can delay onset of this disease by approximately four years.

Data published up to 2019 indicate that Tanzania is on track to achieve the UNAIDS 90-90-90 targets, with an estimated 85% of PLHIV aware of their status, 90% of people diagnosed with HIV receiving ART, and 92% of these people virally suppressed(UNAIDS, 2020a). HIV diagnosis among PLHIV is the only domain currently

falling short of the 90-90-90 targets, and in order to achieve this, personal barriers (fear of positive test, stigmatisation), health system barriers (proximity to clinics and long wait times), and interpersonal barriers (disclosure to sexual partners) must be overcome(Alfred Meremo et al., 2016, Mohlabane et al., 2016).

Policy recommendation 3: broad-spectrum HPV vaccination

Policy:	Vaccinate 90% of females aged 9-14 with a broad-spectrum HPV vaccine by 2030 per the WHO cervical cancer elimination strategy**.**
Status:	On track.

There is a wealth of evidence in support of widespread use of the safe and highly efficacious HPV vaccine; as such, the WHO has recommended that, by 2020, countries fully vaccinate 90% of girls by the age of 15(World Health Organisation, 2020). The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) results indicate that over the 100 years from 2020-2120, 9-valent HPV vaccination at 90% will reduce cervical cancer incidence rates by 89%(Brisson et al., 2020). Modelled results from this thesis specific to Tanzania and accounting for HIV prevalence and control indicate that (in the absence of screening), implementation of 9-valent HPV vaccination at 90% will reduce cervical cancer incidence rates in Tanzania by 92% for the general female population, and 87% in WLHIV.

Recent HPV vaccine coverage data indicate that Tanzania is on the way to achieving the target HPV vaccine coverage rate by 2030, with 49% of girls aged 14 in 2019 having completed their HPV vaccine course(Mphuru et al., 2021). However, Tanzania's HPV immunisation programme currently delivers a 4-valent HPV vaccine and may consider switching to a 9-valent or bivalent (with cross-protection) HPV vaccine(Runge et al., 2019). While general vaccine acceptability is high, barriers to the effective roll-out of HPV vaccination in Tanzania include vaccine availability and service delivery, costs associated with vaccination (from both a healthcare and individual perspective) and individual concerns surrounding vaccine safety, the potential to encourage early sexual initiation, and perceived low risk of HPV infection(Cunningham et al., 2015, Ports et al., 2013).

Policy recommendation 4: cervical screening with HPV

Policy:	(1) Screen at least 70% of women with HPV DNA testing at least twice per lifetime, once by age 35 and again by age 45. (2) Screen at least 70% of WLHIV with HPV DNA testing at 3- to 5-yearly intervals, starting from age 25.

Status:	Urgent.

Cervical screening prevents cervical cancer by detecting and treating HPV infection or cervical precancer and increases cervical cancer survival through early detection. Following an extensive systematic review and meta-analysis, and specialised modelling studies, the WHO has recommended that women aged 30-50 years are screened with HPV DNA testing at 5- to 10-yearly intervals; which incorporates the minimum WHO cervical cancer elimination strategy, or twice per lifetime at ages 35 and 45 years. WLHIV are recommended to be screened with HPV DNA testing every 3- to 5-years, from age 25 to 50(World Health Organisation, 2020, World Health Organisation 2021). Combined, the findings from Chapters 3 and 4, regarding the feasibility, timing and cost-effectiveness of cervical cancer elimination provide a strong case for swift investment in cervical screening, with particular attention for WLHIV. In the absence of HPV vaccination, Chapter 3 model findings indicate that over 2020-2119, twice-lifetime HPV testing (with 3-yearly testing for WLHIV) will reduce cervical cancer incidence rates by 62% overall and by 94% in WLHIV; the majority of this reduction predicted to occur in the decade following full screening programme implementation. Furthermore, as reported in Chapter 4, under some circumstances, cervical screening may even be cost-saving as dollars spent on cervical cancer prevention may be saved on cervical cancer treatment costs.

Women in Tanzania are eligible for nationally or (in some cases) church-funded primary screening with VIA; uptake is low, with an estimated 6-21% of women having ever received a cervical screening test(Mabelele et al., 2018, Runge et al., 2019). Barriers to uptake of cervical screening in Tanzania include: patient awareness, travel to testing facilities, costs associated with travel, testing or time off work, fear of a positive result and stigmatisation(Cunningham et al., 2015, Bateman et al., 2019). However, self-collection and integration of cervical screening with existing HIV care structures may help overcome some of these identified barriers to screening.

Policy recommendation 5: cervical precancer treatment

Policy:	At least 90% of women with detected cervical precancer receive ablative or excisional treatment, as appropriate, and additional follow-up to confirm treatment success, by 2030.
Status:	On-track.

The efficacy of cervical screening to prevent cervical cancer is dependent on the removal of detected cervical precancer. Based on this, the WHO's 2021 revised

guidelines for cervical screening and precancer treatment outline detailed precancer treatment and follow-up recommendations to ensure that the benefit of cervical screening is maximised while not causing unnecessary harms(World Health Organisation 2021). The WHO cervical cancer elimination strategy calls for at least 90% of women with detected cervical precancer to receive treatment by 2030. The potential impact of losses in precancer treatment efficacy is reported in Chapter 3 in sensitivity analysis, which finds that for a 10% decrease in precancer treatment efficacy, cervical cancer elimination may be delayed by up to five years.

In Tanzania, 10-15% of screen-positive women receive same-visit precancer treatment; however, one study reports that only 52.2% of women who postpone precancer treatment return to receive it(Masalu et al., 2017, Anderson et al., 2015). Loss to follow-up due to lack of patient recall mechanisms, or clinic inaccessibility, is a primary barrier for women receiving precancer treatment, as many women need to travel for screening attendance(Anderson et al., 2015). Therefore, screen-and-treat cervical screening approaches may be beneficial in this setting, reducing the probability of loss to follow-up.

Policy recommendation 6: cervical cancer treatment

Policy:	At least 90% of women diagnosed with cervical cancer receive appropriate treatment (surgery, radiation, chemotherapy and palliative care) by 2030.
Status:	Urgent.

The WHO cervical cancer elimination strategy calls for 90% of all women diagnosed with cervical cancer to receive treatment appropriate to the severity of their disease(World Health Organisation, 2020). Modelling undertaken by the WHO CCEMC estimates that HPV vaccination combined with cervical screening and cervical cancer treatment scale-up can reduce projected 2120 cervical cancer mortality rates by 98.6%, compared to a scenario without vaccination, screening, or cervical cancer treatment scale-up(Canfell et al., 2020). Chapter 3 addresses the impact of cervical cancer treatment scale-up alone, specific to Tanzania, reporting that scale-up of cancer treatment rates to 90% could reduce cervical cancer mortality rates by a further 28-36%, depending on HIV infection status and the implementation of other interventions.

Estimated 2020 cervical cancer treatment access rates in Tanzania are 9.5%, indicating that cancer treatment services should be prioritised in this region(Canfell et al., 2020). The primary challenge in improving cervical cancer treatment rates in Tanzania is the current deficit of medical centres delivering specialised cancer care.

For many years, the Ocean Road Cancer Institute (ORCI) in the nation's capital (Dar es Salaam) was the only cancer treatment centre but has recently been joined by the Kilimanjaro Christian Medical Centre and the Arusha Lutheran Medical Centre, which do not offer all treatment services. Additionally, it is estimated that at the ORCI, approximately 70% of patients are not correctly medicated due to insufficient supply(Henke et al., 2021, Runge et al., 2019).

Policy recommendation 7: tailored screening for cohorts vaccinated against HPV

Policy:	Re-assess cervical screening needs as vaccinated cohorts dominate the age range of cervical screening eligibility.
Status:	Not applicable (future recommendation).

Findings from Chapter 4, in addition to accruing evidence from a range of other settings, indicate that as HPV infection and cervical cancer risk change due to HPV vaccination, the optimal frequency of cervical screening will also change. For the general population of Tanzanian women, Chapter 4 indicates that it is not cost-effective to screen more than twice per lifetime; for WLHIV it is not cost-effective to screen before age 30 and more than 8 times per lifetime. Based on this, it is recommended that as the HPV vaccination programme matures and the screening age range is comprised of vaccinated cohorts, a re-assessment of cervical screening needs should be carried out.

Concluding remarks

Population interventions for HIV and cervical cancer control have achieved substantial success in reducing the disease burden of both HIV and cervical cancer. This thesis solidifies arguments for sustained investment in HIV control interventions, and scale-up of HPV vaccination and cervical screening, given the encouraging potential for lives saved. Furthermore, this thesis provides actionable policy-relevant recommendations for reducing the burden of cervical cancer in a sub-Saharan African country.

References

ADAIR, T. 2008. Men's condom use in higher-risk sex: Trends in five sub-Saharan African countries. *Journal of Population Research,* 25**,** 51-62.

ALFRED MEREMO, BEATI MBOYA, DAVID NGILANGWA, ROBERT DULLE, EDITH TARIMO, DAVID URASSA, EMILLIAN MICHAEL, NYASIRO GIBORE, BONAVENTURA MPONDO, GABRIEL MCHONDE, ALEX ERNEST, RITA NORONHA & ILAKO, F. 2016. Barriers to accessibility and utilization of HIV testing and counseling services in Tanzania: experience from Angaza Zaidi programme. *Pan African Medical Journal,* 23:189.

ANAMAN-TORGBOR, J., ANGMORTERH, S. K., DORDUNOO, D. & OFORI, E. K. 2020. Cervical cancer screening behaviours and challenges: a sub-Saharan Africa perspective. *The Pan African medical journal,* 36**,** 97-97.

ANDERSON, J., WILSON, D., TEMPLETON, D. J., GRULICH, A., CARTER, R. & KALDOR, J. 2009. Cost-Effectiveness of Adult Circumcision in a Resource-Rich Setting for HIV Prevention among Men Who Have Sex with Men. *The Journal of Infectious Diseases,* 200**,** 1803-1812.

ANDERSON, J., WYSONG, M., ESTEP, D., BESANA, G., KIBWANA, S., VARALLO, J., SUN, K. & LU, E. 2015. Evaluation of Cervical Cancer Screening Programs in Côte d'Ivoire, Guyana, and Tanzania: Effect of HIV Status. *PLOS ONE,* 10**,** e0139242.

ANDERSON, P. L., GLIDDEN, D. V., LIU, A., BUCHBINDER, S., LAMA, J. R., GUANIRA, J. V., MCMAHAN, V., BUSHMAN, L. R., CASAPÍA, M., MONTOYA-HERRERA, O., VELOSO, V. G., MAYER, K. H., CHARIYALERTSAK, S., SCHECHTER, M., BEKKER, L.-G., KALLÁS, E. G. & GRANT, R. M. 2012. Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men. *Science Translational Medicine,* 4**,** 151ra125.

ANDERSON, R. & MAY, R. M. 1992. *Infectious Diseases of Humans*, Oxford Science Publications.

ANDERSON, R. M., MEDLEY, G. F., MAY, R. M. & JOHNSON, A. M. 1986. A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *IMA Journal of Mathematics Applied in Medicine and Biology,* 3**,** 229-63.

ANDERSSON, K. M., OWENS, D. K., VARDAS, E., GRAY, G. E., MCINTYRE, J. A. & PALTIEL, A. D. 2007. Predicting the impact of a partially effective HIV vaccine and subsequent risk behavior change on the heterosexual HIV epidemic in low- and middle-income countries: A South African example. *Journal of Acquired Immune Deficiency Syndrome,* 46**,** 78-90.

ARBYN, M., SMITH, S. B., TEMIN, S., SULTANA, F. & CASTLE, P. 2018. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ,* 363**,** k4823.

ATASHILI, J., SMITH, J. S., ADIMORA, A. A., ERON, J., MILLER, W. C. & MYERS, E. 2011. Potential impact of antiretroviral therapy and screening on cervical cancer mortality in HIV-positive women in sub-Saharan Africa: a simulation. *PLoS One,* 6**,** e18527.

AULT, K. A. 2006. Epidemiology and Natural History of Human Papillomavirus Infections in the Female Genital Tract. *Infectious Diseases in Obstetrics and Gynecology,* 2006.

AUVERT, B., TALJAARD, D., LAGARDE, E., SOBNGWI-TAMBEKOU, J., SITTA, R. & PUREN, A. 2005. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLOS Medicine,* 2**,** e298.

AVERT. 2017. *Symptoms and stages of HIV infection* [Online]. avert.org. Available: https://www.avert.org/about-hiv-aids/symptoms-stages [Accessed 20/09/2017].

AVERT. 2019. *HIV AND AIDS IN EAST AND SOUTHERN AFRICA REGIONAL OVERVIEW* [Online]. United Kingdom: AVERT. Available: https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/overview [Accessed 08/01/2020].

BAILEY, R. C., MOSES, S., PARKER, C. B., AGOT, K., MACLEAN, I., KRIEGER, J. N., WILLIAMS, C. F., CAMPBELL, R. T. & NDINYA-ACHOLA, J. O. 2007. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet,* 369**,** 643-56.

BAKIEWICZ, A., RASCH, V., MWAISELAGE, J. & LINDE, D. S. 2020. "The best thing is that you are doing it for yourself" – perspectives on acceptability and feasibility of HPV self-sampling among cervical cancer screening clients in Tanzania: a qualitative pilot study. *BMC Women's Health,* 20**,** 65.

BARRE-SINOUSSI, F., CHERMANN, J. C., REY, F., NUGEYRE, M. T., CHAMARET, S., GRUEST, J., DAUGUET, C., AXLER-BLIN, C., VEZINET-BRUN, F., ROUZIOUX, C., ROZENBAUM, W. & MONTAGNIER, L. 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science,* 220**,** 868-71.

BATEMAN, L. B., BLAKEMORE, S., KONERU, A., MTESIGWA, T., MCCREE, R., LISOVICZ, N. F., ARIS, E. A., YUMA, S., MWAISELAGE, J. D. & JOLLY, P. E. 2019. Barriers and Facilitators to Cervical Cancer Screening, Diagnosis, Follow-Up Care and Treatment: Perspectives of Human Immunodeficiency Virus-Positive Women and Health Care Practitioners in Tanzania. *The Oncologist,* 24**,** 69-75.

BEYRER, C., TRAPENCE, G., MOTIMEDI, F., UMAR, E., IIPINGE, S., DAUSAB, F. & BARAL, S. 2010. Bisexual concurrency, bisexual partnerships, and HIV among Southern African men who have sex with men. *Sexually Transmitted Infections,* 86**,** 323.

BHATLA, N., BEREK, J. S., CUELLO FREDES, M., DENNY, L. A., GRENMAN, S., KARUNARATNE, K., KEHOE, S. T., KONISHI, I., OLAWAIYE, A. B., PRAT, J. & SANKARANARAYANAN, R. 2019. Revised FIGO staging for carcinoma of the cervix uteri. *International Journal of Gynecology & Obstetrics,* 145**,** 129-135.

BLOWER, S., SCHWARTZ, E. J. & MILLS, J. 2003. Forecasting the future of HIV epidemics: the impact of antiretroviral therapies & imperfect vaccines. *AIDS Rev,* 5**,** 113-25.

BOSCH, F. X., ROBLES, C., DÍAZ, M., ARBYN, M., BAUSSANO, I., CLAVEL, C., RONCO, G., DILLNER, J., LEHTINEN, M., PETRY, K. U., POLJAK, M., KJAER, S. K., MEIJER, C. J., GARLAND, S. M., SALMERÓN, J., CASTELLSAGUÉ, X., BRUNI, L., DE SANJOSÉ, S. & CUZICK, J. 2016. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. *Nat Rev Clin Oncol,* 13**,** 119-32.

BRAUER, F. 2008. Compartmental Models in Epidemiology. *In:* BRAUER, F., VAN DEN DRIESSCHE, P. & WU, J. (eds.) *Mathematical Epidemiology.* Berlin, Heidelberg: Springer Berlin Heidelberg.

BRAY, F., FERLAY, J., SOERJOMATARAM, I., SIEGEL, R. L., TORRE, L. A. & JEMAL, A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *A Cancer Journal for Clinicians,* 68**,** 394-424.

BRISSON, M., BÉNARD, É., DROLET, M., BOGAARDS, J. A., BAUSSANO, I., VÄNSKÄ, S., JIT, M., BOILY, M. C., SMITH, M. A., BERKHOF, J., CANFELL, K., CHESSON, H. W., BURGER, E. A., CHOI, Y. H., DE BLASIO, B. F., DE VLAS, S. J., GUZZETTA, G., HONTELEZ, J. A. C., HORN, J., JEPSEN, M. R., KIM, J. J., LAZZARATO, F., MATTHIJSSE, S. M., MIKOLAJCZYK, R., PAVELYEV, A., PILLSBURY, M., SHAFER, L. A., TULLY, S. P., TURNER, H. C., USHER, C. & WALSH, C. 2016. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. *Lancet Public Health,* 1**,** e8-e17.

BRISSON, M., KIM, J. J., CANFELL, K., DROLET, M., GINGRAS, G., BURGER, E. A., MARTIN, D., SIMMS, K. T., BÉNARD, É., BOILY, M.-C., SY, S., REGAN, C., KEANE, A., CARUANA, M., NGUYEN, D. T. N., SMITH, M. A., LAPRISE, J.-F., JIT, M., ALARY, M., BRAY, F., FIDAROVA, E., ELSHEIKH, F., BLOEM, P. J. N., BROUTET, N. & HUTUBESSY, R. 2020. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *The Lancet,* 395**,** 575-590.

BRITTON, T., HOUSE, T., LLOYD, A. L., MOLLISON, D., RILEY, S. & TRAPMAN, P. 2015. Five challenges for stochastic epidemic models involving global transmission. *Epidemics,* 10**,** 54-57.

BROTHERTON, J. M. L. & BLOEM, P. N. 2018. Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage. *Best Practice & Research Clinical Obstetrics & Gynaecology,* 47**,** 42-58.

BRUNI, L., DIAZ, M., BARRIONUEVO-ROSAS, L., HERRERO, R., BRAY, F., BOSCH, F. X., DE SANJOSÉ, S. & CASTELLSAGUÉ, X. 2016. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *The Lancet Global Health,* 4**,** e453-e463.

BRUNI, L., SAURA-LÁZARO, A., MONTOLIU, A., BROTONS, M., ALEMANY, L., DIALLO, M. S., AFSAR, O. Z., LAMONTAGNE, D. S., MOSINA, L., CONTRERAS, M., VELANDIA-GONZÁLEZ, M., PASTORE, R., GACIC-DOBO, M. & BLOEM, P. 2021. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. *Prev Med,* 144**,** 106399.

BURCHELL, A. N., COUTLÉE, F., TELLIER, P.-P., HANLEY, J. & FRANCO, E. L. 2011. Genital transmission of human papillomavirus in recently formed heterosexual couples. *The Journal of infectious diseases,* 204**,** 1723-1729.

BURGER, E. A., DE KOK, I., GROENE, E., KILLEN, J., CANFELL, K., KULASINGAM, S., KUNTZ, K. M., MATTHIJSSE, S., REGAN, C., SIMMS, K. T., SMITH, M. A., SY, S., ALARID-ESCUDERO, F., VAIDYANATHAN, V., VAN BALLEGOOIJEN, M. & KIM, J. J. 2020. Estimating the Natural History of Cervical Carcinogenesis Using Simulation Models: A CISNET Comparative Analysis. *The Journal of the National Cancer Institute,* 112**,** 955-963.

CAMPOS, N. G., LINCE-DEROCHE, N., CHIBWESHA, C. J., FIRNHABER, C., SMITH, J. S., MICHELOW, P., MEYER-RATH, G., JAMIESON, L., JORDAAN, S., SHARMA, M., REGAN, C., SY, S., LIU, G., TSU, V., JERONIMO, J. & KIM, J. J. 2018. Cost-Effectiveness of Cervical Cancer Screening in Women Living With HIV in South Africa: A Mathematical Modeling Study. *Journal of Acquired Immune Deficiency Syndrome,* 79**,** 195-205.

CAMPOS, N. G., TSU, V., JERONIMO, J., NJAMA-MEYA, D., MVUNDURA, M. & KIM, J. J. 2017. Cost-effectiveness of an HPV self-collection campaign in Uganda: comparing models for delivery of cervical cancer screening in a low-income setting. *Health Policy Plan,* 32**,** 956-968.

CANFELL, K. & BERKHOF, J. 2019. The key role of mathematical modelling and health economics in the public health transitions in cervical cancer prevention. *Human Papillomavirus: Proving and Using a Viral Cause for Cancer.*

CANFELL, K., KIM, J. J., BRISSON, M., KEANE, A., SIMMS, K. T., CARUANA, M., BURGER, E. A., MARTIN, D., NGUYEN, D. T. N., BÉNARD, É., SY, S., REGAN, C., DROLET, M., GINGRAS, G., LAPRISE, J.-F., TORODE, J., SMITH, M. A., FIDAROVA, E., TRAPANI, D., BRAY, F., ILBAWI, A., BROUTET, N. & HUTUBESSY, R. 2020. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *The Lancet,* 395**,** 591-603.

CANFELL, K., KIM, J. J., KULASINGAM, S., BERKHOF, J., BARNABAS, R., BOGAARDS, J. A., CAMPOS, N., JENNETT, C., SHARMA, M., SIMMS, K. T., SMITH, M. A., VELENTZIS, L. S., BRISSON, M. & JIT, M. 2019. HPV-FRAME: A consensus statement and quality framework for modelled evaluations of HPV-related cancer control. *Papillomavirus Res,* 8**,** 100184.

CASCADE 2000. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet,* 355**,** 1131-7.

CASTELLSAGUE, X., BOSCH, F. X., MUNOZ, N., MEIJER, C. J., SHAH, K. V., DE SANJOSE, S., ELUF-NETO, J., NGELANGEL, C. A., CHICHAREON, S., SMITH, J. S., HERRERO, R., MORENO, V. & FRANCESCHI, S. 2002. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *New England Journal of Medicine,* 346**,** 1105-12.

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2018a. *HPV and Cancer* [Online]. Atlanta, GA, USA. Available: https://www.cdc.gov/cancer/hpv/index.htm [Accessed 25/01/2019].

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2018b. *PrEP* [Online]. Atlanta, GA, USA. Available: https://www.cdc.gov/hiv/basics/prep.html [Accessed 21/10/2018].

CHEN, S. Y., GIBSON, S., KATZ, M. H., KLAUSNER, J. D., DILLEY, J. W., SCHWARCZ, S. K., KELLOGG, T. A. & MCFARLAND, W. 2002. Continuing increases in sexual risk behavior and sexually transmitted diseases among men who have sex with men: San Francisco, Calif, 1999-2001, USA. *American Journal of Public Health,* 92**,** 1387-8.

COGHILL, A. E., SHIELS, M. S., SUNEJA, G. & ENGELS, E. A. 2015. Elevated Cancer-Specific Mortality Among HIV-Infected Patients in the United States. *J Clin Oncol,* 33**,** 2376-83.

COHEN , M. S., CHEN , Y. Q., MCCAULEY , M., GAMBLE , T., HOSSEINIPOUR , M. C., KUMARASAMY , N., HAKIM , J. G., KUMWENDA , J., GRINSZTEJN , B., PILOTTO , J. H. S., GODBOLE , S. V., MEHENDALE , S., CHARIYALERTSAK , S., SANTOS , B. R., MAYER , K. H., HOFFMAN , I. F., ESHLEMAN , S. H., PIWOWAR-MANNING , E., WANG , L., MAKHEMA , J., MILLS , L. A., DE BRUYN , G., SANNE , I., ERON , J., GALLANT , J., HAVLIR , D., SWINDELLS , S., RIBAUDO , H., ELHARRAR , V., BURNS , D., TAHA , T. E., NIELSEN-SAINES , K., CELENTANO , D., ESSEX , M. & FLEMING , T. R. 2011. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine,* 365**,** 493-505.

COLEMAN, J. S., CESPEDES, M. S., CU-UVIN, S., KOSGEI, R. J., MALOBA, M., ANDERSON, J., WILKIN, T., JAQUET, A., BOHLIUS, J., ANASTOS, K. & WOOLS-KALOUSTIAN, K. 2016. An Insight Into Cervical Cancer Screening and Treatment Capacity in Sub Saharan Africa. *Journal of lower genital tract disease,* 20**,** 31-37.

CORK, M. A., WILSON, K. F., PERKINS, S., COLLISON, M. L., DESHPANDE, A., EATON, J. W., EARL, L., HAEUSER, E., JUSTMAN, J. E., KINYOKI, D. K., MAYALA, B. K., MOSSER, J. F., MURRAY, C. J. L., NKENGASONG, J. N., PIOT, P., SARTORIUS, B., SCHAEFFER, L. E., SERFES, A. L., SLIGAR, A., STEUBEN, K. M., TANSER, F. C., VANDERHEIDE, J. D., YANG, M., WABIRI, N., HAY, S. I. & DWYER-LINDGREN, L. 2020. Mapping male circumcision for HIV prevention efforts in sub-Saharan Africa. *BMC Medicine,* 18**,** 189.

CREPAZ, N., HART, T. A. & MARKS, G. 2004. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA,* 292**,** 224-36.

CUNNINGHAM, M. S., SKRASTINS, E., FITZPATRICK, R., JINDAL, P., ONEKO, O., YEATES, K., BOOTH, C. M., CARPENTER, J. & ARONSON, K. J. 2015. Cervical cancer screening and HPV vaccine acceptability among rural and urban women in Kilimanjaro Region, Tanzania. *BMJ Open,* 5**,** e005828.

DALGLEISH, A. G., BEVERLEY, P. C., CLAPHAM, P. R., CRAWFORD, D. H., GREAVES, M. F. & WEISS, R. A. 1984. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature,* 312**,** 763-7.

DARTELL, M., RASCH, V., KAHESA, C., MWAISELAGE, J., NGOMA, T., JUNGE, J., GERNOW, A., EJLERSEN, S. F., MUNK, C., IFTNER, T. & KJAER, S. K. 2012. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. *Sexually Transmitted Diseases,* 39**,** 201-8.

DASGUPTA, A. N. Z., UEFFING, P. & KANTOROVÁ, V. 2018. *Sexual Activity by Marital Status and Age: A Comparative Perspective* [Online]. New York. Available:

https://www.un.org/en/development/desa/population/publications/pdf/technical/TP2017-11.pdf [Accessed 29/04/2021].
DE COCK, K. M., FOWLER, M., MERCIER, E. & ET AL. 2000. Prevention of mother-to-child hiv transmission in resource-poor countries: Translating research into policy and practice. *JAMA,* 283**,** 1175-1182.
DE KOK, I., BURGER, E. A., NABER, S. K., CANFELL, K., KILLEN, J., SIMMS, K., KULASINGAM, S., GROENE, E., SY, S., KIM, J. J. & VAN BALLEGOOIJEN, M. 2020. The Impact of Different Screening Model Structures on Cervical Cancer Incidence and Mortality Predictions: The Maximum Clinical Incidence Reduction (MCLIR) Methodology. *Med Decis Making,* 40**,** 474-482.
DE VUYST, H., MUGO, N. R., FRANCESCHI, S., MCKENZIE, K., TENET, V., NJOROGE, J., RANA, F. S., SAKR, S. R., SNIJDERS, P. J. & CHUNG, M. H. 2014. Residual disease and HPV persistence after cryotherapy for cervical intraepithelial neoplasia grade 2/3 in HIV-positive women in Kenya. *PLoS One,* 9**,** e111037.
DIEKMANN, O. & HEESTERBEEK, J. A. P. 2000. *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, Wiley.
DIVISION OF STD PREVENTION (DEPARTMENT OF HEALTH AND HUMAN SERVICES). 1999. *Prevention of Genital HPV Infection and Sequelae: Report of an External Consultants' Meeting* [Online]. Atlanta, Georgia Available: https://www.cdc.gov/std/hpv/HPVSupplement99.pdf [Accessed 19/10/2018].
DOORBAR, J. 2006. Molecular biology of human papillomavirus infection and cervical cancer. *Clin Sci (Lond),* 110**,** 525-41.
DOORBAR, J., EGAWA, N., GRIFFIN, H., KRANJEC, C. & MURAKAMI, I. 2015. Human papillomavirus molecular biology and disease association. *Reviews in Medical Virology,* 25**,** 2-23.
DORWARD, J., KHUBONE, T., GATE, K., NGOBESE, H., SOOKRAJH, Y., MKHIZE, S., JEEWA, A., BOTTOMLEY, C., LEWIS, L., BAISLEY, K., BUTLER, C. C., GXAGXISA, N. & GARRETT, N. 2021. The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. *The Lancet HIV,* 8**,** e158-e165.
DRAIN, P. K., HALPERIN, D. T., HUGHES, J. P., KLAUSNER, J. D. & BAILEY, R. C. 2006. Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. *BMC Infectious Diseases,* 6**,** 172.
DRUMMOND, M. F., SCULPHER, M. J., CLAXTON, K., STODDARD, G. L. & TORRANCE, G. W. 1987. *Methods for the Economic Evaluation of Health Care Programmes,* United Kingdom, Oxford University Press.
DRYDEN-PETERSON, S., BVOCHORA-NSINGO, M., SUNEJA, G., EFSTATHIOU, J. A., GROVER, S., CHIYAPO, S., RAMOGOLA-MASIRE, D., KEBABONYE-PUSOENTSI, M., CLAYMAN, R., MAPES, A. C., TAPELA, N., ASMELASH, A., MEDHIN, H., VISWANATHAN, A. N., RUSSELL, A. H., LIN, L. L., KAYEMBE, M. K. A., MMALANE, M., RANDALL, T. C., CHABNER, B. & LOCKMAN, S. 2016. HIV Infection and Survival Among Women With Cervical Cancer. *Journal of Clinical Oncology,* 34**,** 3749-3757.
DUKERS, N. H., GOUDSMIT, J., DE WIT, J. B., PRINS, M., WEVERLING, G. J. & COUTINHO, R. A. 2001. Sexual risk behaviour relates to the virological and immunological improvements during highly active antiretroviral therapy in HIV-1 infection. *Aids,* 15**,** 369-78.
DWYER-LINDGREN, L., CORK, M. A., SLIGAR, A., STEUBEN, K. M., WILSON, K. F., PROVOST, N. R., MAYALA, B. K., VANDERHEIDE, J. D., COLLISON, M. L., HALL, J. B., BIEHL, M. H., CARTER, A., FRANK, T., DOUWES-SCHULTZ, D., BURSTEIN, R., CASEY, D. C., DESHPANDE, A., EARL, L., EL BCHERAOUI, C., FARAG, T. H., HENRY, N. J., KINYOKI, D., MARCZAK, L. B., NIXON, M. R., OSGOOD-ZIMMERMAN, A., PIGOTT, D., REINER, R. C., ROSS, J. M., SCHAEFFER, L. E., SMITH, D. L., DAVIS WEAVER, N., WIENS, K. E., EATON, J. W., JUSTMAN, J. E., OPIO, A., SARTORIUS, B., TANSER, F., WABIRI, N., PIOT, P., MURRAY, C.

J. L. & HAY, S. I. 2019. Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. *Nature,* 570**,** 189-193.
EDWARD, D. M., SHACHTER, R. D. & OWENS, D. K. 1998. A Dynamic HIV-Transmission Model for Evaluating the Costs and Benefits of Vaccine Programs. *Interfaces,* 28**,** 144-166.
ENDINGHIV.ORG. 2019. *Ending HIV 2020* [Online]. ACON. Available: https://endinghiv.org.au/# [Accessed 27/06/2019].
FESENFELD, M., HUTUBESSY, R. & JIT, M. 2013. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: A systematic review. *Vaccine,* 31**,** 3786-3804.
FITZPATRICK, M. B., EL-KHATIB, Z., KATZENSTEIN, D., PINSKY, B. A., CHIRENJE, Z. M. & MCCARTY, K. 2019. Community-based self-collected human papillomavirus screening in rural Zimbabwe. *BMC Public Health,* 19**,** 603.
FORBES, H. J., DOYLE, A. M., MAGANJA, K., CHANGALUCHA, J., WEISS, H. A., ROSS, D. A. & HAYES, R. J. 2012. Rapid Increase in Prevalence of Male Circumcision in Rural Tanzania in the Absence of a Promotional Campaign. *PLOS ONE,* 7**,** e40507.
FREEDBERG , K. A., LOSINA , E., WEINSTEIN , M. C., PALTIEL , A. D., COHEN , C. J., SEAGE , G. R., CRAVEN , D. E., ZHANG , H., KIMMEL , A. D. & GOLDIE , S. J. 2001. The Cost Effectiveness of Combination Antiretroviral Therapy for HIV Disease. *New England Journal of Medicine,* 344**,** 824-831.
GAVI THE VACCINE ALLIANCE. 2020. *Human papillomavirus vaccine support* [Online]. Available: https://www.gavi.org/types-support/vaccine-support/human-papillomavirus [Accessed 28/02/2020].
GIESECKE, J. 2017. *Modern Infectious Disease Epidemiology, Third Edition*, CRC Press.
GRAY, R. H., KIGOZI, G., SERWADDA, D., MAKUMBI, F., WATYA, S., NALUGODA, F., KIWANUKA, N., MOULTON, L. H., CHAUDHARY, M. A., CHEN, M. Z., SEWANKAMBO, N. K., WABWIRE-MANGEN, F., BACON, M. C., WILLIAMS, C. F., OPENDI, P., REYNOLDS, S. J., LAEYENDECKER, O., QUINN, T. C. & WAWER, M. J. 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet,* 369**,** 657-66.
GRULICH, A. E., GUY, R., AMIN, J., JIN, F., SELVEY, C., HOLDEN, J., SCHMIDT, H.-M. A., ZABLOTSKA, I., PRICE, K., WHITTAKER, B., CHANT, K., COOPER, C., MCGILL, S., TELFER, B., YEUNG, B., LEVITT, G., OGILVIE, E. E., DHARAN, N. J., HAMMOUD, M. A., VACCHER, S., WATCHIRS-SMITH, L., MCNULTY, A., SMITH, D. J., ALLEN, D. M., BAKER, D., BLOCH, M., BOPAGE, R. I., BROWN, K., CARR, A., CARMODY, C. J., COLLINS, K. L., FINLAYSON, R., FOSTER, R., JACKSON, E. Y., LEWIS, D. A., LUSK, J., O'CONNOR, C. C., RYDER, N., VLAHAKIS, E., READ, P., COOPER, D. A., SMITH, D., OOI, C., MARTIN, S., SOO, T. M., TEMPLETON, D., TOWNSON, D., FORSSMAN, B., DOONG, N., HAN THAI, G., ANDERSON, B., MACLEOD, H. & PARKHILL, N. 2018. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. *The Lancet HIV,* Nov;5(11):e629-e637.
GRUND, J. M., BRYANT, T. S., JACKSON, I., CURRAN, K., BOCK, N., TOLEDO, C., TALIANO, J., ZHOU, S., DEL CAMPO, J. M., YANG, L., KIVUMBI, A., LI, P., PALS, S. & DAVIS, S. M. 2017. Association between male circumcision and women's biomedical health outcomes: a systematic review. *The Lancet Global Health,* 5**,** e1113-e1122.
HABBEMA, J. D., VAN OORTMARSSEN, G. J., LUBBE, J. T. & VAN DER MAAS, P. J. 1985. Model building on the basis of Dutch cervical cancer screening data. *Maturitas,* 7**,** 11-20.
HALL, M. T., SIMMS, K. T., LEW, J.-B., SMITH, M. A., SAVILLE, M. & CANFELL, K. 2018. Projected future impact of HPV vaccination and primary HPV screening on cervical cancer rates from 2017-2035: Example from Australia. *PLoS One,* https://doi.org/10.1371/journal.pone.0185332.

HALL, M. T., SMITH, M. A., SIMMS, K. T., BARNABAS, R. V., CANFELL, K. & MURRAY, J. M. 2020. The past, present and future impact of HIV prevention and control on HPV and cervical disease in Tanzania: a modelling study. *PLoS One,* 15(5): e0231388.

HALL, M. T., SMITH, M. A., SIMMS, K. T., BARNABAS, R. V., MURRAY, J. M. & CANFELL, K. 2021. Elimination of cervical cancer in Tanzania: Modelled analysis of elimination in the context of endemic HIV infection and active HIV control. *International Journal of Cancer*.

HARLING, G., MUYA, A., ORTBLAD, K. F., MASHASI, I., DAMBACH, P., ULENGA, N., BARNHART, D., MBOGGO, E., OLDENBURG, C. E., BÄRNIGHAUSEN, T. & SPIEGELMAN, D. 2019. HIV risk and pre-exposure prophylaxis interest among female bar workers in Dar es Salaam: cross-sectional survey. *BMJ Open,* 9**,** e023272.

HENKE, A., KLUGE, U., BORDE, T., MCHOME, B., SERVENTI, F. & HENKE, O. 2021. Tanzanian women´s knowledge about Cervical Cancer and HPV and their prevalence of positive VIA cervical screening results. Data from a Prevention and Awareness Campaign in Northern Tanzania, 2017 – 2019. *Global Health Action,* 14**,** 1852780.

HERBECK, J. T., MITTLER, J. E., GOTTLIEB, G. S., GOODREAU, S. M., MURPHY, J. T., CORI, A., PICKLES, M. & FRASER, C. 2016. Evolution of HIV virulence in response to widespread scale up of antiretroviral therapy: a modeling study. *Virus Evol,* 2**,** vew028.

HERBECK, J. T., MITTLER, J. E., GOTTLIEB, G. S. & MULLINS, J. I. 2014. An HIV Epidemic Model Based on Viral Load Dynamics: Value in Assessing Empirical Trends in HIV Virulence and Community Viral Load. *PLOS Computational Biology,* 10**,** e1003673.

HIGHTOW-WEIDMAN, L. B., GOLIN, C. E., GREEN, K., SHAW, E. N. P., MACDONALD, P. D. M. & LEONE, P. A. 2009. Identifying People with Acute HIV Infection (AHI) – Demographic Features, Risk Factors, and Use of Health Care among Individuals with AHI in North Carolina. *AIDS and behavior,* 13**,** 1075-1083.

HONTELEZ, J. A., CHANG, A. Y., OGBUOJI, O., DE VLAS, S. J., BARNIGHAUSEN, T. & ATUN, R. 2016. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. *Aids,* 30**,** 2341-50.

HONTELEZ, J. A. C., LURIE, M. N., BÄRNIGHAUSEN, T., BAKKER, R., BALTUSSEN, R., TANSER, F., HALLETT, T. B., NEWELL, M.-L. & DE VLAS, S. J. 2013. Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study. *PLOS Medicine,* 10**,** e1001534.

HOORNENBORG, E., COYER, L., ACHTERBERGH, R. C. A., MATSER, A., SCHIM VAN DER LOEFF, M. F., BOYD, A., VAN DUIJNHOVEN, Y., BRUISTEN, S., OOSTVOGEL, P., DAVIDOVICH, U., HOGEWONING, A., PRINS, M. & DE VRIES, H. J. C. 2019. Sexual behaviour and incidence of HIV and sexually transmitted infections among men who have sex with men using daily and event-driven pre-exposure prophylaxis in AMPrEP: 2 year results from a demonstration study. *Lancet HIV*.

IFTNER, T. 2018. *Are HPV DNA or HPV E6/E7 mRNA assays the better solution for Cervical Cancer Screening?* [Online]. Available: https://www.hpvworld.com/articles/are-hpv-dna-or-hpv-e6-e7-mrna-assays-the-better-solution-for-cervical-cancer-screening/ [Accessed 27/05/2021].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. 2018. *Cancer Today* [Online]. Available: https://gco.iarc.fr/today/home [Accessed 13/10/2020].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. 2020. *Cancer Today* [Online]. Available: https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%252

2%253Atrue%252C%2522mort%2522%253Afalse%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D [Accessed 01/03/2021].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). *Estimated number of new cases in 2018, cervix uteri, females, all ages* [Online]. Lyon, France. Available: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=population&mode_population=hdi&population=900&populations=900&key=asr&sex=2&cancer=23&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1 [Accessed 20/10/2018].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). 2018a. *Estimated number of deaths in 2018, cervix uteri, females, all ages* [Online]. Lyon, France. Available: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=population&mode_population=hdi&population=900&populations=900&key=asr&sex=2&cancer=23&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1 [Accessed 20/10/2018].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). 2018b. *Estimated number of deaths in 2018, worldwide, females, all ages* [Online]. Lyon, France. Available: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=hdi&population=900&populations=900&key=asr&sex=2&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1 [Accessed 20/10/2018].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). 2018c. *Estimated number of new cases in 2018, worldwide, females, all ages* [Online]. Lyon, France. Available: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=hdi&population=900&populations=900&key=asr&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1 [Accessed 20/10/2018].

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) 2021. *IARC Handbooks of Cancer Prevention*.

JENKINS, D., SHERLAW-JOHNSON, C. & GALLIVAN, S. 1996. Can papilloma virus testing be used to improve cervical cancer screening? *International Journal of Cancer,* 65**,** 768-73.

JIT, M., BRISSON, M., PORTNOY, A. & HUTUBESSY, R. 2014. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. *The Lancet Global Health,* 2**,** e406-e414.

JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS) 2009. Making decisions on male circumcision for HIV risk reduction: modelling the impact and costs. *Report from a UNAIDS/WHO/SACEMA consultation, Stellenbosch, South Africa, November 15-16, 2007.*

JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS). 2014. 90-90-90 An ambition treatment to help end the AIDS epidemic. Available: https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf [Accessed 27/06/2019].

JOURA, E., BAUTISTA, O. & LUXEMBOURG, A. 2015. A 9-Valent HPV Vaccine in Women. *New England Journal of Medicine,* 372**,** 2568-9.

KALDOR, J. M. & WILSON, D. P. 2010. How low can you go: the impact of a modestly effective HIV vaccine compared with male circumcision. *Aids,* 24**,** 2573-8.

KALICHMAN, S., MATHEWS, C., KALICHMAN, M., EATON, L. A. & NKOKO, K. 2018. Male circumcision for HIV prevention: Awareness, risk compensation, and risk perceptions among South African women. *Glob Public Health,* 13**,** 1682-1690.

KAPIGA, S. H. & LUGALLA, J. L. 2003. Male condom use in Tanzania: results from a national survey. *East Afr Med J,* 80**,** 181-90.

KATZ, M. H., SCHWARCZ, S. K., KELLOGG, T. A., KLAUSNER, J. D., DILLEY, J. W., GIBSON, S. & MCFARLAND, W. 2002. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *American Journal of Public Health,* 92**,** 388-94.

KAVANAGH, K., POLLOCK, K. G., CUSCHIERI, K., PALMER, T., CAMERON, R. L., WATT, C., BHATIA, R., MOORE, C., CUBIE, H., CRUICKSHANK, M. & ROBERTSON, C. 2017. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. *Lancet Infectious Diseases,* 17**,** 1293-1302.

KERMACK, W. O. & MCKENDRICK, A. G. 1927. A Contribution to the Mathematical Theory of Epidemics. *Proceedings of the Royal Society of London,* Series A 115**,** 700-721.

KHARSANY, A. B. M. & KARIM, Q. A. 2016. HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. *The open AIDS journal,* 10**,** 34-48.

KIM, H., BRANSCUM, A., DEWOLFE MILLER, F. & CUADROS, D. F. 2019. Geospatial assessment of the voluntary medical male circumcision programme in Tanzania, 2011–2016. . *BMJ Global Health,* 4:e001922.

KIM, J., BALLEGOOIJEN, M. V., CANFELL, K. & KULASINGAM, S. Comparative Modeling to Inform Cervical Cancer Control Policies. National Cancer Institute: Cancer Intervention and Surveillance Modeling Network.

KISS, I. Z., MILLER, J. C. & SIMON, P. L. 2017. *Mathematics of Epidemics on Networks: From Exact to Approximate Models*, Springer International Publishing.

KOOPMANSCHAP, M. A., LUBBE, K. T., VAN OORTMARSSEN, G. J., VAN AGT, H. M., VAN BALLEGOOIJEN, M. & HABBEMA, J. K. 1990. Economic aspects of cervical cancer screening. *Social Science & Medicine,* 30**,** 1081-7.

KOUTSKY, L. A., AULT, K. A., WHEELER, C. M., BROWN, D. R., BARR, E., ALVAREZ, F. B., CHIACCHIERINI, L. M. & JANSEN, K. U. 2002. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine,* 347**,** 1645-51.

KULMALA, S. M., SYRJANEN, S., SHABALOVA, I., PETROVICHEV, N., KOZACHENKO, V., PODISTOV, J., IVANCHENKO, O., ZAKHARENKO, S., NEROVJNA, R., KLJUKINA, L., BRANOVSKAJA, M., GRUNBERGA, V., JUSCHENKO, A., TOSI, P., SANTOPIETRO, R. & SYRJANEN, K. 2004. Human papillomavirus testing with the hybrid capture 2 assay and PCR as screening tools. *Journal of Clinical Microbiology,* 42**,** 2470-5.

LAL, L., AUDSLEY, J., MURPHY, D. A., FAIRLEY, C. K., STOOVE, M., ROTH, N., MOORE, R., TEE, B. K., PURATMAJA, N., ANDERSON, P. L., LESLIE, D., GRANT, R. M., DE WIT, J., WRIGHT, E. & ON BEHALF OF THE VICPR, E. P. S. T. 2017. Medication adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users. *AIDS,* 31.

LANG, P. O. 2011. [Adverse effects of the herd immunity or when childhood vaccination becomes deleterious for the epidemiology of infectious diseases in adults]. *Geriatr Psychol Neuropsychiatr Vieil,* 9**,** 11-9.

LIN, C. Y. 2008. Modeling Infectious Diseases in Humans and Animals by KEELING, M. J. and ROHANI, P. *Biometrics,* 64**,** 993-993.

LINCE-DEROCHE, N., PHIRI, J., MICHELOW, P., SMITH, J. S. & FIRNHABER, C. 2015. Costs and Cost Effectiveness of Three Approaches for Cervical Cancer Screening among HIV-Positive Women in Johannesburg, South Africa. *PLOS ONE,* 10**,** e0141969.

LIU, G., MUGO, N. R., BROWN, E. R., MGODI, N. M., CHIRENJE, Z. M., MARRAZZO, J. M., WINER, R. L., MANSOOR, L., PALANEE-PHILLIPS, T., SIVA, S. S., NAIDOO, L., JEENARAIN, N.,

GAFFOOR, Z., NAIR, G. L., SELEPE, P., NAKABIITO, C., MKHIZE, B., MIREMBE, B. G., TALJAARD, M., PANCHIA, R., BAETEN, J. M., BALKUS, J. E., HLADIK, F., CELUM, C. L. & BARNABAS, R. V. 2021. Prevalent HPV infection increases the risk of HIV acquisition in African women: advancing the argument for HPV immunization. *Aids*.

LIU, G., SHARMA, M., TAN, N. & BARNABAS, R. V. 2018. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *Aids,* 32**,** 795-808.

LJUBOJEVIC, S. & SKERLEV, M. 2014. HPV-associated diseases. *Clin Dermatol,* 32**,** 227-34.

LONG, E. F. & OWENS, D. K. 2011. The cost-effectiveness of a modestly effective HIV vaccine in the United States. *Vaccine,* 29**,** 6113-24.

LOO, S. K. & TANG, W. Y. 2014. Warts (non-genital). *BMJ Clinical Evidence,* 2014.

LOTT, B. E., TREJO, M. J., BAUM, C., MCCLELLAND, D. J., ADSUL, P., MADHIVANAN, P., CARVAJAL, S., ERNST, K. & EHIRI, J. 2020. Interventions to increase uptake of cervical screening in sub-Saharan Africa: a scoping review using the integrated behavioral model. *BMC Public Health,* 20**,** 654.

MABELELE, M. M., MATERU, J., NG'IDA, F. D. & MAHANDE, M. J. 2018. Knowledge towards cervical cancer prevention and screening practices among women who attended reproductive and child health clinic at Magu district hospital, Lake Zone Tanzania: a cross-sectional study. *BMC Cancer,* 18**,** 565.

MACKELLAR, D. A., HOU, S. I., WHALEN, C. C., SAMUELSEN, K., VALLEROY, L. A., SECURA, G. M., BEHEL, S., BINGHAM, T., CELENTANO, D. D., KOBLIN, B. A., LALOTA, M., SHEHAN, D., THIEDE, H. & TORIAN, L. V. 2011. HIV/AIDS complacency and HIV infection among young men who have sex with men, and the race-specific influence of underlying HAART beliefs. *Sexually Transmitted Diseases,* 38**,** 755-63.

MASALU, N., SERRA, P., AMADORI, D., KAHIMA, J., MAJINGE, C., RWEHABURA, J., NANNI, O., BRAVACCINI, S., PUCCETTI, M., TUMINO, R. & BUCCHI, L. 2017. Setting up a community-based cervical screening service in a low-income country: a pilot study from north-western Tanzania. *International Journal of Public Health,* 62**,** 755-762.

MBULAWA, Z. Z. A., VAN SCHALKWYK, C., HU, N.-C., MEIRING, T. L., BARNABAS, S., DABEE, S., JASPAN, H., KRIEK, J.-M., JAUMDALLY, S. Z., MULLER, E., BEKKER, L.-G., LEWIS, D. A., DIETRICH, J., GRAY, G., PASSMORE, J.-A. S. & WILLIAMSON, A.-L. 2018. High human papillomavirus (HPV) prevalence in South African adolescents and young women encourages expanded HPV vaccination campaigns. *PloS one,* 13**,** e0190166-e0190166.

MBULAWA, Z. Z. A., WILKIN, T., GOEIEMAN, B. J., JONG, E., MICHELOW, P., SWARTS, A., SMITH, J. S., KEGORILWE, P., FIRNHABER, C. S. & WILLIAMSON, A. L. 2017. Prevalence of Anal Human Papillomavirus (HPV) and Performance of Cepheid Xpert and Hybrid Capture 2 (hc2) HPV Assays in South African HIV-Infected Women. *The American Journal of Clinical Pathology,* 148**,** 148-153.

MCCREDIE, M. R., SHARPLES, K. J., PAUL, C., BARANYAI, J., MEDLEY, G., JONES, R. W. & SKEGG, D. C. 2008. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol,* 9**,** 425-34.

MCMURRAY, H. R., NGUYEN, D., WESTBROOK, T. F. & MCANCE, D. J. 2001. Biology of human papillomaviruses. *International Journal of Experimental Pathology,* 82**,** 15-33.

MEZEI, A. K., ARMSTRONG, H. L., PEDERSEN, H. N., CAMPOS, N. G., MITCHELL, S. M., SEKIKUBO, M., BYAMUGISHA, J. K., KIM, J. J., BRYAN, S. & OGILVIE, G. S. 2017. Cost-effectiveness of cervical cancer screening methods in low- and middle-income countries: A systematic review. *International Journal of Cancer,* 141**,** 437-446.

MEZEI, A. K., PEDERSEN, H. N., SY, S., REGAN, C., MITCHELL-FOSTER, S. M., BYAMUGISHA, J., SEKIKUBO, M., ARMSTRONG, H., RAWAT, A., SINGER, J., OGILVIE, G. S., KIM, J. J. & CAMPOS, N. G. 2018. Community-based HPV self-collection versus visual inspection

with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial. *BMJ Open,* 8**,** e020484.
MICHAEL, C. W. 1999. The Papanicolaou smear and the obstetric patient: a simple test with great benefits. *Diagnostic Cytopathology,* 21**,** 1-3.
MINISTRY OF HEALTH, C. D., GENDER, ELDERLY AND CHILDREN (MOHCDGEC), 2019. National guidelines for the management of HIV and AIDS.
MINISTRY OF HEALTH, C. D., GENDER, ELDERLY AND CHILDREN (MOHCDGEC), , MINISTRY OF HEALTH (MOH), NATIONAL BUREAU OF STATISTICS (NBS), OFFICE OF THE CHIEF GOVERNMENT STATISTICIAN (OCGS) & ICF 2016. Tanzania Demographic and Health Survey and Malaria Indicator Survey 2015-16.
MINISTRY OF HEALTH, C. D., GENDER, ELDERLY AND CHILDREN (MOHCDGEC), GOVERNMENT OF TANZANIA,, MINISTRY OF HEALTH ZANZIBAR (MOH), NATIONAL BUREAU OF STATISTICS (NBS) & OFFICE OF CHIEF GOVERNMENT STATISTICIAN (OCGS) 2017. Tanzania HIV Impact Survey (THIS) 2016-2017. *In:* MOHCDGEC, M., NBS, OCGS (ed.) *Summary Sheet: Preliminary Findings.* Dar es Salaam, Tanzania.
MINKOFF, H., ZHONG, Y., BURK, R. D., PALEFSKY, J. M., XUE, X., WATTS, D. H., LEVINE, A. M., WRIGHT, R. L., COLIE, C., D'SOUZA, G., MASSAD, L. S. & STRICKLER, H. D. 2010. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. *The Journal of infectious diseases,* 201**,** 681-690.
MISHRA, S., STEEN, R., GERBASE, A., LO, Y. R. & BOILY, M. C. 2012. Impact of high-risk sex and focused interventions in heterosexual HIV epidemics: a systematic review of mathematical models. *PLoS One,* 7**,** e50691.
MOHLABANE, N., TUTSHANA, B., PELTZER, K. & MWISONGO, A. 2016. Barriers and facilitators associated with HIV testing uptake in South African health facilities offering HIV Counselling and Testing. *Health SA Gesondheid,* 21**,** 86-95.
MOORE, A., HERRERA, G., NYAMONGO, J., LACKRITZ, E., GRANADE, T., NAHLEN, B., OLOO, A., OPONDO, G., MUGA, R. & JANSSEN, R. 2001. Estimated risk of HIV transmission by blood transfusion in Kenya. *The Lancet,* 358**,** 657-660.
MPHURU, A., LI, A. J., KYESI, F., MWENGEE, W., MAZIGE, F., NSHUNJU, R., SHAYO, B., GIATTAS, M. R., LOHARIKAR, A. & LYIMO, D. 2021. National introduction of human papillomavirus (HPV) vaccine in Tanzania: Programmatic decision-making and implementation. *Vaccine*.
MUNGUTI, K., GROSSKURTH, H., NEWELL, J., SENKORO, K., MOSHA, F., TODD, J., MAYAUD, P., GAVYOLE, A., QUIGLEY, M. & HAYES, R. 1997. Patterns of sexual behaviour in a rural population in north-western Tanzania. *Social Science & Medicine,* 44**,** 1553-61.
MUNOZ, N., BOSCH, F. X., DE SANJOSE, S., HERRERO, R., CASTELLSAGUE, X., SHAH, K. V., SNIJDERS, P. J. & MEIJER, C. J. 2003. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine,* 348**,** 518-27.
NATIONAL BUREAU OF STATISTICS 2015. Mortality and Health. *In:* FINANCE, M. O. (ed.). Dar es Salaam, Tanzania.
NATIONAL CANCER INSTITUTE (NCI). 2015. *Cervical cancer models overview* [Online]. Available: https://resources.cisnet.cancer.gov/registry/site-summary/cervical/ [Accessed 01/03/2021].
NATIONAL INSTITUTES OF HEALTH. 2017. *The Basics of HIV Prevention* [Online]. U.S. Department of Health and Human Services. [Accessed 19/09/2017].
NELSON, S., KIM, J., WILSON, F. A., SOLIMAN, A. S., NGOMA, T., KAHESA, C. & MWAISELAGE, J. 2016. Cost-Effectiveness of Screening and Treatment for Cervical Cancer in Tanzania:

Implications for other Sub-Saharan African Countries. *Value in Health Regional Issues,* 10**,** 1-6.
OUTWATER, A., NKYA, L., LWIHULA, G., O'CONNOR, P., LESHABARI, M., NGUMA, J., MWIZARUBI, B., LAUKAMM-JOSTEN, U., GREEN, E. C. & HASSIG, S. E. 2000. Patterns of partnership and condom use in two communities of female sex workers in Tanzania. *The Journal of the Association of Nurses in AIDS Care,* 11**,** 46-54.
PALK, L., GERSTOFT, J., OBEL, N. & BLOWER, S. 2018. A modeling study of the Danish HIV epidemic in men who have sex with men: travel, pre-exposure prophylaxis and elimination. *Sci Rep,* 8**,** 16003.
PALMER, C. 2003. HIV treatments and highly active antiretroviral therapy. *Australian Prescriber,* 26.
PEDERSEN, K., BURGER, E. A., CAMPBELL, S., NYGÅRD, M., AAS, E. & LÖNNBERG, S. 2017. Advancing the evaluation of cervical cancer screening: development and application of a longitudinal adherence metric. *European Journal of Public Health,* 27**,** 1089-1094.
POLI, U. R. & PETIGNAT, P. 2020. Screen and treat with hpv testing in lmic countries. *HPV World.*
PORTS, K. A., REDDY, D. M. & RAMESHBABU, A. 2013. Barriers and facilitators to HPV vaccination: perspectives from Malawian women. *Women & health,* 53**,** 630-645.
PREP WATCH. 2019. *National Policies and Guidelines for PrEP* [Online]. Available: https://www.prepwatch.org/prep-planning/national-policies-guidelines/ [Accessed 27/06/2019].
PREP WATCH. 2020. *Tanzania* [Online]. Available: https://www.prepwatch.org/country/tanzania/ [Accessed 21/01/2021].
PRODGER, J. L. & KAUL, R. 2017. The biology of how circumcision reduces HIV susceptibility: broader implications for the prevention field. *AIDS Research and Therapy,* 14**,** 49.
QUINN, T. C., WAWER, M. J., SEWANKAMBO, N., SERWADDA, D., LI, C., WABWIRE-MANGEN, F., MEEHAN, M. O., LUTALO, T. & GRAY, R. H. 2000. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *New England Journal of Medicine,* 342**,** 921-9.
RALAIDOVY, A. H., GOPALAPPA, C., ILBAWI, A., PRETORIUS, C. & LAUER, J. A. 2018. Cost-effective interventions for breast cancer, cervical cancer, and colorectal cancer: new results from WHO-CHOICE. *Cost Effectiveness and Resource Allocation,* 16**,** 38.
RAMCHANDANI, M. S. & GOLDEN, M. R. 2019. Confronting Rising STIs in the Era of PrEP and Treatment as Prevention. *Curr HIV/AIDS Rep,* 16**,** 244-256.
RAMJEE, G., SARTORIUS, B., MORRIS, N., WAND, H., REDDY, T., YSSEL, J. D. & TANSER, F. 2019. A decade of sustained geographic spread of HIV infections among women in Durban, South Africa. *BMC Infectious Diseases,* 19**,** 500.
RESEARCH INTERNATIONAL (ON BEHALF OF T-MARC) 2009. Women engaged in sex work and transactional sex in Tanzania.
REYNOLDS, H. W., LUSENO, W. & SPEIZER, I. S. 2012. The Measurement of Condom Use in Four Countries in East and Southern Africa. *AIDS and behavior,* 16**,** 1044-1053.
RIETHMULLER, D., GAY, C., BERTRAND, X., BETTINGER, D., SCHAAL, J. P., CARBILLET, J. P., LASSABE, C., ARVEUX, P., SEILLES, E. & MOUGIN, C. 1999. Genital human papillomavirus infection among women recruited for routine cervical cancer screening or for colposcopy determined by Hybrid Capture II and polymerase chain reaction. *Diagnostic Molecular Pathology,* 8**,** 157-64.
ROBERTS, M., ANDREASEN, V., LLOYD, A. & PELLIS, L. 2015. Nine challenges for deterministic epidemic models. *Epidemics,* 10**,** 49-53.
ROCHA, L. E. C. & MASUDA, N. 2016. Individual-based approach to epidemic processes on arbitrary dynamic contact networks. *Scientific Reports,* 6**,** 31456.

RONCO, G., DILLNER, J., ELFSTROM, K. M., TUNESI, S., SNIJDERS, P. J., ARBYN, M., KITCHENER, H., SEGNAN, N., GILHAM, C., GIORGI-ROSSI, P., BERKHOF, J., PETO, J. & MEIJER, C. J. 2014. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet,* 383**,** 524-32.

RUNGE, A. S., BERNSTEIN, M. E., LUCAS, A. N. & TEWARI, K. S. 2019. Cervical cancer in Tanzania: A systematic review of current challenges in six domains. *Gynecologic oncology reports,* 29**,** 40-47.

SAFAEIAN, M., HERRERO, R., HILDESHEIM, A., QUINT, W., FREER, E., VAN DOORN, L. J., PORRAS, C., SILVA, S., GONZALEZ, P., BRATTI, M. C., RODRIGUEZ, A. C. & CASTLE, P. 2007. Comparison of the SPF10-LiPA system to the Hybrid Capture 2 Assay for detection of carcinogenic human papillomavirus genotypes among 5,683 young women in Guanacaste, Costa Rica. *Journal of Clinical Microbiology,* 45**,** 1447-54.

SANDRI, M. T., LENTATI, P., BENINI, E., DELL'ORTO, P., ZORZINO, L., CAROZZI, F. M., MAISONNEUVE, P., PASSERINI, R., SALVATICI, M., CASADIO, C., BOVERI, S. & SIDERI, M. 2006. Comparison of the Digene HC2 assay and the Roche AMPLICOR human papillomavirus (HPV) test for detection of high-risk HPV genotypes in cervical samples. *Journal of Clinical Microbiology,* 44**,** 2141-6.

SCHEER, S., CHU, P. L., KLAUSNER, J. D., KATZ, M. H. & SCHWARCZ, S. K. 2001. Effect of highly active antiretroviral therapy on diagnoses of sexually transmitted diseases in people with AIDS. *Lancet,* 357**,** 432-5.

SCHIFFMAN, M., CASTLE, P. E., JERONIMO, J., RODRIGUEZ, A. C. & WACHOLDER, S. 2007. Human papillomavirus and cervical cancer. *Lancet,* 370**,** 890-907.

SCHMIDT-OTT, R., SCHWEHM, M. & EICHNER, M. 2016. Influence of social contact patterns and demographic factors on influenza simulation results. *BMC Infectious Diseases,* 16**,** 646.

SHARMA, M., BARNABAS, R. V. & CELUM, C. 2017. Community-based strategies to strengthen men's engagement in the HIV care cascade in sub-Saharan Africa. *PLoS medicine,* 14**,** e1002262-e1002262.

SHASTRI, S. S., MITTRA, I., MISHRA, G. A., GUPTA, S., DIKSHIT, R., SINGH, S. & BADWE, R. A. 2014. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. *The Journal of the National Cancer Institute,* 106**,** dju009.

SHERLAW-JOHNSON, C., GALLIVAN, S., JENKINS, D. & JONES, M. H. 1994. Cytological screening and management of abnormalities in prevention of cervical cancer: an overview with stochastic modelling. *The Journal of Clinical Pathology,* 47**,** 430-5.

SIMMS, K. T., STEINBERG, J., CARUANA, M., SMITH, M. A., LEW, J.-B., SOERJOMATARAM, I., CASTLE, P. E., BRAY, F. & CANFELL, K. 2019. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study. *The Lancet Oncology,* 20**,** 394-407.

SMITH, M. A., BURGER, E. A., CASTANON, A., DE KOK, I., HANLEY, S., REBOLJ, M., HALL, M. T., JANSEN, E. E. L., KILLEN, J., O'FARRELL, X., KIM, J. J. & CANFELL, K. 2021. Impact of disruptions and recovery for established cervical screening programs across a range of high-income country program designs, using COVID-19 as an example: A modelled analysis. *Prev Med***,** 106623.

SMITH, R. J. & BLOWER, S. M. 2004. Could disease-modifying HIV vaccines cause population-level perversity? *Lancet Infectious Diseases,* 4**,** 636-9.

SODERLUND-STRAND, A., RYMARK, P., ANDERSSON, P., DILLNER, J. & DILLNER, L. 2005. Comparison between the Hybrid Capture II test and a PCR-based human papillomavirus detection method for diagnosis and posttreatment follow-up of cervical intraepithelial neoplasia. *Journal of Clinical Microbiology,* 43**,** 3260-6.

STELZLE, D., TANAKA, L. F., LEE, K. K., IBRAHIM KHALIL, A., BAUSSANO, I., SHAH, A. S. V., MCALLISTER, D. A., GOTTLIEB, S. L., KLUG, S. J., WINKLER, A. S., BRAY, F., BAGGALEY, R.,

CLIFFORD, G. M., BROUTET, N. & DALAL, S. 2021. Estimates of the global burden of cervical cancer associated with HIV. *The Lancet Global Health,* 9**,** e161-e169.
STOVER, J., GLAUBIUS, R., MOFENSON, L., DUGDALE, C. M., DAVIES, M.-A., PATTEN, G. & YIANNOUTSOS, C. 2019. Updates to the Spectrum/AIM model for estimating key HIV indicators at national and subnational levels. *AIDS,* 33.
SULTANA, F., ENGLISH, D. R., SIMPSON, J. A., DRENNAN, K. T., MULLINS, R., BROTHERTON, J. M., WREDE, C. D., HELEY, S., SAVILLE, M. & GERTIG, D. M. 2016. Home-based HPV self-sampling improves participation by never-screened and under-screened women: Results from a large randomized trial (iPap) in Australia. *International Journal of Cancer,* 139**,** 281-90.
SZABO, R. & SHORT, R. V. 2000. How does male circumcision protect against HIV infection? *BMJ (Clinical research ed.),* 320**,** 1592-1594.
TAMBOURET, R. H. 2013. The evolution of the Papanicolaou smear. *Clinical Obstetrics and Gynecology,* 56**,** 3-9.
TAN, N., SHARMA, M., WINER, R., GALLOWAY, D., REES, H. & BARNABAS, R. V. 2018. Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa. *Vaccine,* 36**,** 4830-4836.
TANZANIA COMMISSION FOR AIDS (TACAIDS), ZANZIBAR AIDS COMMISSION (ZAC), NATIONAL BUREAU OF STATISTICS (NBS), OFFICE OF CHIEF GOVERNMENT STATISTICIAN (OCGS) & ICF INTERNATIONAL 2013. Tanzania HIV/AIDS and Malaria Indicator Survey 2011-2012. *In:* TACAIDS, Z., NBS, OCGS, AND ICF INTERNATIONAL. (ed.). Dar es Salaam, Tanzania.
TANZANIA COMMISSION FOR AIDS (TACAIDS), ZANZIBAR AIDS COMMISSION (ZAC), NATIONAL BUREAU OF STATISTICS (NBS), OFFICE OF CHIEF GOVERNMENT STATISTICIAN (OCGS) & MACRO INTERNATIONAL INC. 2008. Tanzania HIV/AIDS and Malaria Indicator Survey 2007-2008. *In:* TACAIDS, Z., NBS, OCGS, AND MACRO INTERNATIONAL INC. (ed.). Dar es Salaam, Tanzania.
THE ECONOMIST INTELLIGENCE UNIT LIMITED. 2021. *Global action on financing cervical cancer elimination: Funding secondary prevention services in low resource settings* [Online]. Available: https://eiuperspectives.economist.com/sites/default/files/eiu_uicc_global_action_on_financing_cervical_cancer_elimination.pdf [Accessed 21/04/2021].
THE ROYAL AUSTRALIAN AND NEW ZEALAND COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS (RANZCOG). 2018. *Guidelines for HPV vaccine* [Online]. Available: https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women's%20Health/Statement%20and%20guidelines/Clinical%20-%20Gynaecology/Guidelines-for-HPV-Vaccine-(C-Gyn-18)-Review-July-2015.pdf?ext=.pdf [Accessed 21/10/2018].
THE UNITED REPUBLIC OF TANZANIA MINISTRY OF HEALTH AND SOCIAL WELFARE 2013. Report Number 23. *HIV/AIDS/STI Surveillance Report.* Dar es Salaam, Tanzania: National AIDS Control Programme.
THE WORLD BANK. 2017a. *Fertility rate, total (births per woman)* [Online]. WORLD BANK GROUP. Available: https://data.worldbank.org/indicator/SP.DYN.TFRT.IN?locations=TZ [Accessed 30-04-2018].
THE WORLD BANK. 2017b. *Sex ratio at birth (male births per female births)* [Online]. Available: https://data.worldbank.org/indicator/SP.POP.BRTH.MF?end=2017&locations=TZ&start=2017&view=bar [Accessed 2018-09-07].
THE WORLD BANK. 2018. *Population, total* [Online]. World Bank Group. Available: https://data.worldbank.org/indicator/SP.POP.TOTL?locations=TZ [Accessed 03/05/2018].

TOBIAN, A. A. R., KACKER, S. & QUINN, T. C. 2014. Male circumcision: a globally relevant but under-utilized method for the prevention of HIV and other sexually transmitted infections. *Annual review of medicine,* 65**,** 293-306.

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES. 2017. *The Stages of HIV Infection* [Online]. AIDS info. Available: https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/46/the-stages-of-hiv-infection [Accessed 20/09/2017].

UNAIDS. 2015. *Understanding fast-track: accelerating action to end the AIDS epidemic by 2030* [Online]. Available: https://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf [Accessed 16/07/2021].

UNAIDS. 2017. *90–90–90 - An ambitious treatment target to help end the AIDS epidemic* [Online]. Available: https://www.unaids.org/en/resources/documents/2017/90-90-90 [Accessed 13/01/2019].

UNAIDS. 2018a. *Data Sheet - HIV Incidence Per 1000 Population* [Online]. Geneva, Switzerland. Available: http://aidsinfo.unaids.org?did=55da49cd64e925b94e70b0ce&r=world&t=2016&tb=d&bt=dnli&ts=0,0&tr=world&aid=5970eccef7341ed11f26de5d&sav=Population: Adults (15-49)&tl=2 [Accessed 03/05/2018].

UNAIDS. 2018b. *Data Sheet - HIV Prevalence Population: Female adults (15-49)* [Online]. Geneva, Switzerland. Available: http://aidsinfo.unaids.org?did=554ca08005b5b281750af20a&r=world&t=2016&tb=d&bt=dnli&ts=0,0&tr=world&aid=577bfcca880284565dfd2ebf&sav=Population: Female adults (15-49)&tl=2 [Accessed 03/05/2018].

UNAIDS. 2018c. *Data Sheet - HIV Prevalence Population: Male adults (15-49)* [Online]. Geneva, Switzerland: UNAIDS. Available: http://aidsinfo.unaids.org?did=554ca08005b5b281750af20a&r=world&t=2016&tb=d&bt=dnli&ts=0,0&tr=world&aid=577bfcca880284565dfd2ebf&sav=Population: Male adults (15-49)&tl=2 [Accessed 03/05/2018].

UNAIDS. 2018d. *Data Sheet - PEOPLE LIVING WITH HIV RECIEVING ART (%)* [Online]. Geneva, Switzerland: UNAIDS. Available: http://aidsinfo.unaids.org?did=554c8ceac904ab29709ecd3b&r=world&t=null&tb=d&bt=dnli&ts=0,0&tr=world&aid=5ae071a462abc329969a8de1&sav=Population: All ages&tl=2 [Accessed 03/05/2018].

UNAIDS. 2018e. *UNITED REPUBLIC OF TANZANIA* [Online]. Available: http://aidsinfo.unaids.org/ [Accessed 2018-09-10].

UNAIDS 2019. The little-known links between cervical cancer and HIV.

UNAIDS. 2020a. *HIV estimates with uncertainty bounds 1990-2019* [Online]. Available: https://www.unaids.org/en/resources/documents/2020/HIV_estimates_with_uncertainty_bounds_1990-present [Accessed 06/2021].

UNAIDS. 2020b. *UNAIDS DATA 2019* [Online]. Available: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf [Accessed 01/03/2021].

UNAIDS. 2021a. *New child infections due to gaps in prevention of vertical transmission* [Online]. Available: https://aidsinfo.unaids.org/ [Accessed 15/07/2021].

UNAIDS. 2021b. *Treatment cascade* [Online]. Available: https://aidsinfo.unaids.org/?did=5fbeb5cb94831556e11c4517&r=world&t=null&tb=g&bt=gnli&ts=&gid=5977091c3ba08432558d099c&gr=TZA [Accessed 29/04/2021].

UNAIDS JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS. *Miles to go: the response to HIV in Eastern and Southern Africa* [Online]. Available: https://www.unaids.org/sites/default/files/media_asset/miles-to-go_eastern-and-southern-africa_en.pdf [Accessed 08/01/2020].

UNITED NATIONS DEPARTMENT OF ECONOMIC AND SOCIAL AFFAIRS POPULATION DIVISION. 2019. *World Population Prospects 2019, Online Edition.* [Online]. Available: https://population.un.org/wpp/Download/Standard/Population/ [Accessed 01/08/2019].

UNITED NATIONS DESA / POPULATION DIVISION. 2017. *World Population Prospects: The 2015 Revision, DVD Edition.* [Online]. Available: https://esa.un.org/unpd/wpp/Download/Standard/Population/ [Accessed 21/03/2017].

UNITED REPUBLIC OF TANZANIA MINISTRY OF HEALTH AND SOCIAL WELFARE NATIONAL AIDS CONTROL PROGRAMME (NACP) 2012. HIV Behavioral and Biological Surveillance Survey Among Female Sex Workers in Dar es Salaam, 2010. *In:* TANZANIA, M. O. H. A. S. W. (ed.). Dar es Salaam.

VAN DER PLOEG, C. P. B., VAN VLIET, C., DE VLAS, S. J., NDINYA-ACHOLA, J. O., FRANSEN, L., VAN OORTMARSSEN, G. J. & HABBEMA, J. D. 1998. STDSIM: a microsimulation model for decision support in STD control. *Interfaces,* 28**,** 84-100.

VAN SCHALKWYK, C., MOODLEY, J., WELTE, A. & JOHNSON, L. F. 2021. Modelling the impact of prevention strategies on cervical cancer incidence in South Africa. *International Journal of Cancer*.

VANNI, T., LUZ, P. M., GRINSZTEJN, B., VELOSO, V. G., FOSS, A., MESA-FRIAS, M. & LEGOOD, R. 2012. Cervical cancer screening among HIV-infected women: an economic evaluation in a middle-income country. *International Journal of Cancer,* 131**,** E96-104.

VELENTZIS, L. S., CARUANA, M., SIMMS, K. T., LEW, J. B., SHI, J. F., SAVILLE, M., SMITH, M. A., LORD, S. J., TAN, J., BATESON, D., QUINN, M. & CANFELL, K. 2017. How will transitioning from cytology to HPV testing change the balance between the benefits and harms of cervical cancer screening? Estimates of the impact on cervical cancer, treatment rates and adverse obstetric outcomes in Australia, a high vaccination coverage country. *International Journal of Cancer*.

VENTUROLI, S., CRICCA, M., BONVICINI, F., GIOSA, F., PULVIRENTI, F. R., GALLI, C., MUSIANI, M. & ZERBINI, M. 2002. Human papillomavirus DNA testing by PCR-ELISA and hybrid capture II from a single cytological specimen: concordance and correlation with cytological results. *Journal of Clinical Virology,* 25**,** 177-85.

VERGIS, E. N. & MELLORS, J. W. 2000. Natural history of HIV-1 infection. *Infectious Disease Clinics of North America,* 14**,** 809-25, v-vi.

VISSERS, D. C., SJ, D. E. V., BAKKER, R., URASSA, M., VOETEN, H. A. & HABBEMA, J. D. 2011. The impact of mobility on HIV control: a modelling study. *Epidemiol Infect,* 139**,** 1845-53.

VYNNYCKY, E. & WHITE, R. 2010. *An Introduction to Infectious Disease Modelling*, OUP Oxford.

WAHLSTROM, C., IFTNER, T., DILLNER, J. & DILLNER, L. 2007. Population-based study of screening test performance indices of three human papillomavirus DNA tests. *Journal of Medical Virology,* 79**,** 1169-75.

WAMBURA, M., NYATO, D. J., MAKYAO, N., DRAKE, M., KURINGE, E., CASALINI, C., MATERU, J., NNKO, S., MBITA, G., SHAO, A., KOMBA, A., CHANGALUCHA, J. & SAIDEL, T. 2020. Programmatic mapping and size estimation of key populations to inform HIV programming in Tanzania. *PLOS ONE,* 15**,** e0228618.

WANG, H., WOLOCK, T. M., CARTER, A., NGUYEN, G., KYU, H. H., GAKIDOU, E., HAY, S. I., MILLS, E. J., TRICKEY, A., MSEMBURI, W., COATES, M. M., MOONEY, M. D., FRASER, M. S., SLIGAR, A., SALOMON, J., LARSON, H. J., FRIEDMAN, J., ABAJOBIR, A. A., ABATE, K. H., ABBAS, K. M., RAZEK, M. M. A. E., ABD-ALLAH, F., ABDULLE, A. M., ABERA, S. F., ABUBAKAR, I., ABU-RADDAD, L. J., ABU-RMEILEH, N. M. E., ABYU, G. Y., ADEBIYI, A. O., ADEDEJI, I. A., ADELEKAN, A. L., ADOFO, K., ADOU, A. K., AJALA, O. N., AKINYEMIJU, T. F., AKSEER, N., LAMI, F. H. A., AL-ALY, Z., ALAM, K., ALAM, N. K. M., ALASFOOR, D., ALDHAHRI, S. F. S., ALDRIDGE, R. W., ALEGRETTI, M. A., ALEMAN, A. V., ALEMU, Z. A.,

ALFONSO-CRISTANCHO, R., ALI, R., ALKERWI, A. A., ALLA, F., MOHAMMAD, R., AL-RADDADI, S., ALSHARIF, U., ALVAREZ, E., ALVIS-GUZMAN, N., AMARE, A. T., AMBERBIR, A., AMEGAH, A. K., AMMAR, W., AMROCK, S. M., ANTONIO, C. A. T., ANWARI, P., ÄRNLÖV, J., ARTAMAN, A., ASAYESH, H., ASGHAR, R. J., ASSADI, R., ATIQUE, S., ATKINS, L. S., AVOKPAHO, E. F. G. A., AWASTHI, A., QUINTANILLA, B. P. A., BACHA, U., BADAWI, A., BARAC, A., BÄRNIGHAUSEN, T., BASU, A., BAYOU, T. A., BAYOU, Y. T., BAZARGAN-HEJAZI, S., BEARDSLEY, J., BEDI, N., BENNETT, D. A., BENSENOR, I. M., BETSU, B. D., BEYENE, A. S., BHATIA, E., BHUTTA, Z. A., BIADGILIGN, S., BIKBOV, B., BIRLIK, S. M., BISANZIO, D., BRAININ, M., BRAZINOVA, A., BREITBORDE, N. J. K., BROWN, A., BURCH, M., BUTT, Z. A., CAMPUZANO, J. C., CÁRDENAS, R., et al. 2016. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. *The Lancet HIV,* 3**,** e361-e387.

WATERFIELD, K. C., SHAH, G. H., ETHEREDGE, G. D. & IKHILE, O. 2021. Consequences of COVID-19 crisis for persons with HIV: the impact of social determinants of health. *BMC Public Health,* 21**,** 299.

WEINBERG, J. L. & KOVARIK, C. L. 2010. The WHO Clinical Staging System for HIV/AIDS. *American Medical Association Journal of Ethics,* 12**,** 202-206.

WEINSTEIN, M. C., GOLDIE, S. J., LOSINA, E. & ET AL. 2001. Use of genotypic resistance testing to guide hiv therapy: Clinical impact and cost-effectiveness. *Annals of Internal Medicine,* 134**,** 440-450.

WENTZENSEN, N., CLARKE, M. A., BREMER, R., POITRAS, N., TOKUGAWA, D., GOLDHOFF, P. E., CASTLE, P. E., SCHIFFMAN, M., KINGERY, J. D., GREWAL, K. K., LOCKE, A., KINNEY, W. & LOREY, T. S. 2019. Clinical Evaluation of Human Papillomavirus Screening With p16/Ki-67 Dual Stain Triage in a Large Organized Cervical Cancer Screening Program. *JAMA Intern Med,* 179**,** 881-888.

WINER, R. L., HUGHES, J. P., FENG, Q., O'REILLY, S., KIVIAT, N. B., HOLMES, K. K. & KOUTSKY, L. A. 2006. Condom use and the risk of genital human papillomavirus infection in young women. *New England Journal of Medicine,* 354**,** 2645-54.

WORLD HEALTH ORGANISATION 2013a. *WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention* [Online]. World Health Organization. Available: https://apps.who.int/iris/bitstream/handle/10665/94830/9789241548694_eng.pdf [Accessed].

WORLD HEALTH ORGANISATION 2013b. *WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention*, World Health Organization.

WORLD HEALTH ORGANISATION 2016. *Sexually transmitted infections (STIs)* [Online]. Geneva, Switzerland. Available: http://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis) [Accessed 20/10/2018].

WORLD HEALTH ORGANISATION 2018a. *Human papillomavirus (HPV) and cervical cancer* [Online]. Geneva, Switzerland. Available: http://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer [Accessed 19/10/2018.].

WORLD HEALTH ORGANISATION 2018b. *Pre-exposure prophylaxis* [Online]. Geneva, Switzerland. Available: http://www.who.int/hiv/topics/prep/en/ [Accessed 21/10/2018].

WORLD HEALTH ORGANISATION 2018c. *Screening for cervical cancer* [Online]. Geneva, Switzerland. Available: http://www.who.int/cancer/detection/cervical_cancer_screening/en/ [Accessed 21/10/2018].

WORLD HEALTH ORGANISATION 2019a. *WHO guide for standardization of economic evaluations of immunization programmes, 2nd edition* [Online]. Geneva. Available: https://apps.who.int/iris/rest/bitstreams/1257211/retrieve [Accessed 20/01/2021].

WORLD HEALTH ORGANISATION. 2020. *Global strategy to accelerate the elimination of cervical cancer as a public health problem* [Online]. Geneva. Available: https://www.who.int/publications/i/item/9789240014107 [Accessed 12/01/2021].

WORLD HEALTH ORGANISATION 2021. *WHO guidelines for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition* [Online]. Available: https://www.who.int/publications/i/item/9789240030824 [Accessed 07/07/2021].

WORLD HEALTH ORGANISATION (WHO). 2020a. *A cervical cancer-free future: First-ever global commitment to eliminate a cancer* [Online]. Geneva, Switzerland. Available: https://www.who.int/news/item/17-11-2020-a-cervical-cancer-free-future-first-ever-global-commitment-to-eliminate-a-cancer [Accessed 25/01/2021].

WORLD HEALTH ORGANISATION (WHO). 2020b. *Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key considerations. Policy Brief* [Online]. Geneva, Switzerland. Available: https://apps.who.int/iris/rest/bitstreams/1295920/retrieve [Accessed 25/01/2021].

WORLD HEALTH ORGANISATION , D. O. I., VACCINES AND BIOLOGICALS. 2019b. *WHO estimates of Human papillomavirus immunization coverage 2010-2018* [Online]. Available: http://www.who.int/immunization/monitoring_surveillance/data/HPVadmin.xls?ua=1 [Accessed 19/05/2020].

WORLD HEALTH ORGANIZATION. 2013. *Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children.* [Online]. Geneva, Switzerland: WHO. Available: http://www.who.int/hiv/pub/guidelines/arv2013/annexes/WHO_CG_annex_1.pdf [Accessed 20/10/2018].

YAMAZAKI, H., SASAGAWA, T., BASHA, W., SEGAWA, T. & INOUE, M. 2001. Hybrid capture-II and LCR-E7 PCR assays for HPV typing in cervical cytologic samples. *International Journal of Cancer,* 94**,** 222-7.

YIMER, N. B., MOHAMMED, M. A., SOLOMON, K., TADESE, M., GRUTZMACHER, S., MEIKENA, H. K., ALEMNEW, B., SHAREW, N. T. & HABTEWOLD, T. D. 2021. Cervical cancer screening uptake in Sub-Saharan Africa: a systematic review and meta-analysis. *medRxiv***,** 2020.12.26.20248864.

YUAN, T., FITZPATRICK, T., KO, N. Y., CAI, Y., CHEN, Y., ZHAO, J., LI, L., XU, J., GU, J., LI, J., HAO, C., YANG, Z., CAI, W., CHENG, C. Y., LUO, Z., ZHANG, K., WU, G., MENG, X., GRULICH, A. E., HAO, Y. & ZOU, H. 2019. Circumcision to prevent HIV and other sexually transmitted infections in men who have sex with men: a systematic review and meta-analysis of global data. *Lancet Global Health,* 7**,** e436-e447.

ZIMMERMANN, M. R., VODICKA, E., BABIGUMIRA, J. B., OKECH, T., MUGO, N., SAKR, S., GARRISON, L. P. & CHUNG, M. H. 2017. Cost-effectiveness of cervical cancer screening and preventative cryotherapy at an HIV treatment clinic in Kenya. *Cost Effectiveness and Resource Allocation,* 15**,** 13.

ZIZZA, A., BANCHELLI, F., GUIDO, M., MAROTTA, C., DI GENNARO, F., MAZZUCCO, W., PISTOTTI, V. & D'AMICO, R. 2021. Efficacy and safety of human papillomavirus vaccination in HIV-infected patients: a systematic review and meta-analysis. *Scientific Reports,* 11**,** 4954.

ZUNA, R. E., WANG, S. S., ROSENTHAL, D. L., JERONIMO, J., SCHIFFMAN, M. & SOLOMON, D. 2005. Determinants of human papillomavirus-negative, low-grade squamous intraepithelial lesions in the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesions triage study (ALTS). *Cancer,* 105**,** 253-62.