Assessing the impact of vaccinations and AI-based screening on cervical cancer prevention in low resource settings

by

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ABSTRACT

Cervical cancer disproportionately impacts lower-middle income countries (LMICs), with over 90% of cervical cancer related deaths occurring in these nations. Despite significant research and knowledge on how to prevent and manage cervical cancer, many women in low resource settings lack access to the necessary vaccinations, screening, and treatment. The WHO strategy for cervical cancer elimination recommends that: 90% of girls are vaccinated by the age of 15; 70% of women are screened using a high-performance test by the age of 35, and again at 45; and lastly that 90% of positively screened women are treated or their cancer is managed. These targets are optimistic relative to the current levels of prevention and treatment in LMICs.

Through this paper, we use HPVsim (an agent-based simulation model created by the Institute of Disease Modeling) to simulate the impact of vaccinations, screening, and treatment on health outcomes such as HPV prevalence, cervical cancer incidence, and mortality. We focus specifically on the impact of Automated Visual Evaluation (AVE); an AI based screening technology developed by Global Health Labs that leverages machine learning models to diagnose precancer.

Our results demonstrate that in the long term, HPV vaccination is more effective than screening and treatment strategies in reducing age standardized cervical cancer incidence rates (ASIR). Vaccinations are predicted to reduce ASIR by 41%, compared to 12% for screening and treatment interventions over the next 35 years. Although the impact of vaccinations is greater than the impact of screening and treatment in the long run, the effects of vaccinations take years to be realized. Therefore, the importance of screening is critical in the short run. The paper also evaluates the impact of AI based screening interventions (such as AVE). We find that in the long term (i.e., after 35 years), a 1% increase in screening probability is associated with a reduction in ASIR of 0.019, a 1% increase in treatment probability is associated with a reduction in ASIR of 0.015, and a 1% increase in AVE device sensitivity is associated with a reduction in ASIR of 0.09.

We supplement our analysis with primary research interviews, which focused on best practices for deploying AI based cancer screening technologies. Our interview findings emphasize the importance of a systems approach and underscore the need to implement screening tools within the behavioral and social contexts of the societies being served. Overall, our study provides insights into the potential impact of cervical cancer prevention strategies and highlights the importance of tailored and context-specific approaches to screening and treatment in LMICs.

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However, all views represented in this thesis are my own and do not constitute the views or any commitment from Global Health Labs, Inc.

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Abbreviations

AI	Artificial Intelligence
ASIR	Age standardized cervical cancer incidence rate
AVE	Automated Visual Evaluation
CIN	Cervical intraepithelial neoplasia
DHS	Demographic and Health Surveys
EVA	Enhanced Visual Assessment
HPV	Human papillomavirus
hrHPV	High risk human papillomavirus
LEEP	Loop electrosurgical excision procedure
LMIC	Low and middle-income countries
ML	Machine Learning
VIA	Visual inspection with acetic acid
VILI	Visual inspection with Lugol's iodine
WHO	World Health Organization

Introduction

"The huge burden of mortality related to cervical cancer is a consequence of <u>decades of neglect</u> by the global health community. However, the script can be <u>rewritten</u>.[1]"

WHO Assistant Director-General Dr Princess Nothemba (Nono) Simelela

Cervical cancer is the fourth most common cancer among women globally[2]. Over ninety percent of deaths due to cervical cancer occur in low- and middle-income countries (LMICs)[3]. Fortunately, most cervical cancer can be preventable and is curable if detected early[4]. There is extensive research and knowledge on how to treat, screen and prevent cervical cancer. Unfortunately, however, in low resource settings, many women do not and/or cannot access vaccinations, treatment, or screening. This limits their ability to prevent, diagnose and effectively manage cervical cancer.

In 2018, the World Health Organization (WHO) adopted the Global Strategy for cervical cancer elimination, which aims to achieve a cervical cancer incidence rate of below 4 per 100,000 women[5]. To achieve this threshold, the WHO devised a '90-70-90 approach': where 90% of girls are fully vaccinated with the HPV vaccine by the age of 15, 70% of women are screened using a high-performance test by the age of 35, and again by the age of 45, and lastly, 90% of positively screened women are treated or their palliative care is managed[6]. The reality of achieving the 90-70-90 targets is however still a distant ambition in many low resource settings.

Through this paper, we discuss the impact and relative importance of the recommended cervical cancer prevention strategies (i.e., vaccinations, screening, and treatment). Using HPVsim (an agent-based model for cervical cancer predictive modeling[7]), we simulate scenarios reflective of varying levels of success in implementing prevention interventions. Given the paper's specific focus on AI based

[1] "A Cervical Cancer-Free Future."
[2] Sung et al., "Global Cancer Statistics 2020."
[3] Sung et al.
[4] CDC, "CDC Vitalsign."
[5] Word Health Organization, "Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem."
[6] "Cervical Cancer Elimination Initiative."
[7] Stuart et al., "HPVsim."

screening tools, we explore the landscape and product characteristics of AI based screening tools for use in low resource settings. We also simulate the impact of such tools using HPVsim. Finally, we couple this research with insights from subject matter experts to provide recommendations for public health cervical cancer prevention strategies and implementation. The paper is structured as follows:

Section 1 provides a review of existing literature. This section is subdivided into three components: Section 1.1 provides background information on cervical cancer, the causes, risks, treatment and prevention strategies. Section 1.2 is a literature review of existing digital solutions for cervical cancer screening. Section 1.3 describes HPVsim (the simulation model used to conduct the analysis within the paper) and Automated Visual Evaluation (AVE, a type of AI based cervical cancer screening tool whose impact is explored through the paper).

Section 2 discusses the methods of analysis and outlines the simulations that were performed using HPVsim.

Section 3 provides the results of the analysis. Specifically, we discuss the impact of vaccination campaigns, AI based screening tool accuracy, screening probability, and treatment probability on cervical cancer incidence, HPV transmission and cancer deaths.

Section 4 provides consolidated results and discusses the implications and outcomes of the results.

Section 5 summarizes the insights from primary research through interviews with subject matter experts. Interviews focused on modeling disease progression as well as understanding existing AI based cervical cancer screening technologies (their development and best practices for deployment).

Section 6 outlines limitations of the study and further areas of research.

Lastly, Section 7 discusses the key takeaways and implications of the analysis

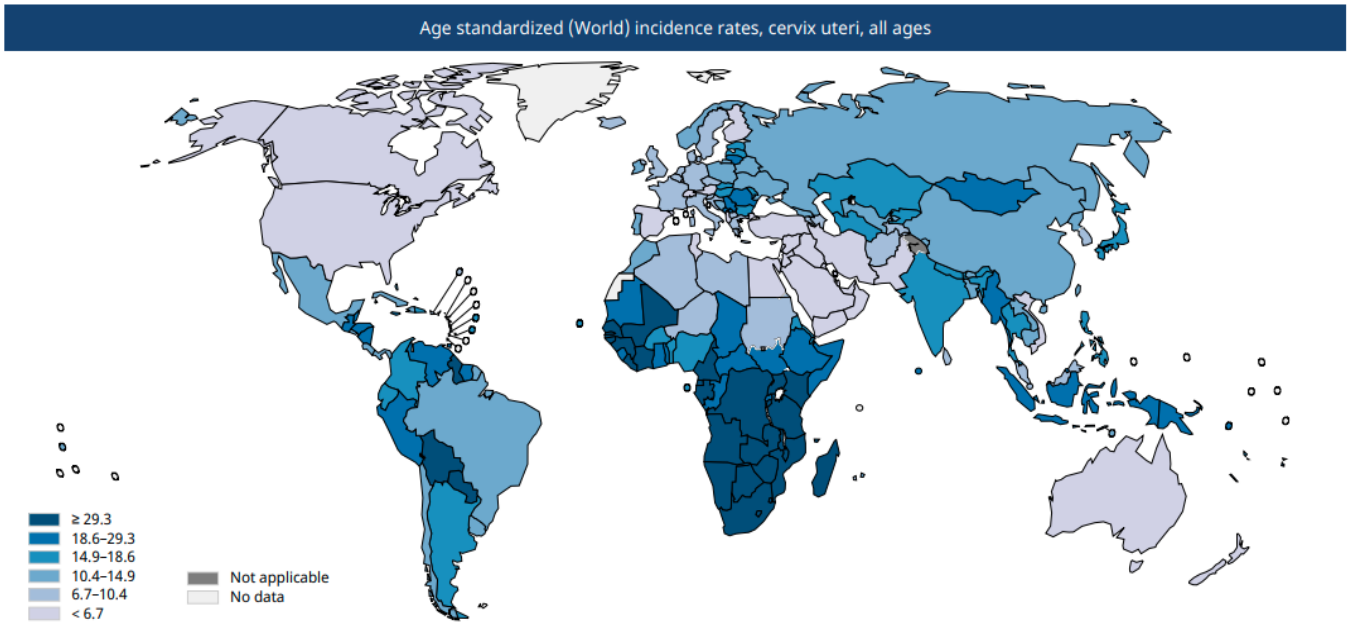
Section 1: Literature Review

1.1 Cervical cancer overview – global prevalence, causes, risk factors and interventions

Global prevalence of cervical cancer

Cervical cancer disproportionately affects LMICs with ninety percent of deaths due to cervical cancer (i.e., ~320,000 deaths in 2020) occurring in low middle income countries[8]. The global burden of cervical cancer is estimated to reach 700,000 cases in 2030[9]. The cervical cancer incidence rates are highest in sub-Saharan Africa and within countries with the lowest levels on the Human Development Index[10].

Figure 1: Age standardized cervical cancer incidence rates globally



Source: GLOBOCAN 2020[11], Map production: IARC (http://gco.iarc.fr/today)

[8] "Cervical Cancer."
[9] "Cervical Cancer."
[10] IARC, "Cervical Cancer Screening. IARC Handb Cancer Prev. 18:1–456."
[11] "Cancer Today."

Causes of cervical cancer

Nearly 95% of cervical cancer is due to the human papillomavirus (HPV)[12]. HPVs are a group of circular, double stranded, DNA viruses that infect human skin and mucosal epithelia[13]. There are more than 200 HPV related viruses which are classified into low risk and high-risk HPVs[14]. Low risk HPVs typically cause no disease, however, may cause warts. High risk HPVs (of which there are about 14 types), can cause various types of cancer including cervical, oral, vaginal, penile, vulva and anal cancers[15]. Two HPV types (i.e., 16 and 18) are responsible for over 70% of high grade cervical precancers[16]. HPV infections are often sexually transmitted and at least half of sexually active people will have HPV at some point in their lives[17]. In most cases HPV goes away on its own without health problems[18].

Disease progression

The transformation from HPV infection to cancer diagnosis can take decades[19]. Women can become infected with HPV at or soon after their first sexual encounter. Thereafter, cervical pre-cancers can develop (i.e., the extensive multiplication of abnormal cells). Precancerous cervical lesions can be classified into three grades using the cervical intraepithelial neoplasia (CIN) terminology. CIN 1 – refers to when abnormal cells are confined to the bottom third of the cervical epithelium[20]. CIN 2 is used to describe when the abnormal cells are confined to the bottom and the middle third of the cervical epithelium[21]. And CIN3 indicates that all three layers (bottom, middle and upper) contain abnormal cells[22]. Precancerous lesions progress to invasive cervical cancer over time. It can take 15 – 20 years for cervical cancer to develop for women with normal immune systems and only 5 – 10 years for those with weaker immune systems (such as those with HIV)[23].

[12] "Cervical Cancer."
[13] IARC, "Cervical Cancer Screening. IARC Handb Cancer Prev. 18:1–456."
[14] "HPV and Cancer - NCI."
[15] "HPV and Cancer - NCI."
[16] "Human Papillomavirus (HPV)."
[17] "Basic Information About Cervical Cancer | CDC."
[18] "STD Facts - Human Papillomavirus (HPV)."
[19] IARC, "Cervical Cancer Screening. IARC Handb Cancer Prev. 18:1–456."
[20] "Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginners' Manual."
[21] "Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginners' Manual."
[22] "Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginners' Manual."
[23] "Cervical Cancer."

Risk factors

There are a few factors that can affect one's risk of cervical cancer (and HPV transmission). These include having a weakened immune system, tobacco use, and a person's sexual history (multiple partners, unprotected sexual intercourse). Women with HIV are six times more likely to develop cervical cancer[24]; this is due to a weakened immune system which increases the risk of infections (including HPV). In addition, tobacco use and exposure to secondhand smoke, can cause cancer in many parts of the body including the cervix[25]. Since cervical cancer is a result of specific and persistent HPV infection, risk factors for cervical cancer also incorporate risk factors for HPV transmission. HPV is transmitted sexually; therefore, the use of condoms or dental dams can reduce the risk of HPV transmission, however this does not prevent transmission completely[26]. A person's sexual history, in terms of the number of partners or sexual interactions with partners that have HPV, can increase the risk of HPV transmission and ultimately the risk of cervical cancer.

Interventions

The WHO cervical cancer prevention guidelines stipulate primary, secondary, and tertiary prevention measures to manage and eliminate cervical cancer. These measures are HPV vaccinations, cervical cancer screening, and treatment, respectively.

HPV Vaccinations

There are currently six licensed prophylactic HPV vaccinations: three bivalent, two quadrivalent and one nonavalent vaccine[27]. All vaccines are highly efficacious in protecting against HPV 16 and 18 which cause over 70% of cervical cancer cases[28]. However, given that existing vaccinations today do not protect against all genotypes of HPV, there is still a need for additional measures (including screening and treatment) to prevent cervical cancer development and help treat those infected. The WHO recommends that girls aged 9-14 and 15 – 20 are on a one or two dose vaccination schedule and women older than 21 are given two doses with a 6-month interval[29]. For immunocompromised or HIV infected women, a minimum of 2 does, and when feasible, 3 doses, is recommended[30]. HPV

[24] "Cervical Cancer."
[25] "Tobacco and Cancer | CDC."
[26] "HPV and Cancer - NCI."
[27] "Human Papillomavirus (HPV)."
[28] "Human Papillomavirus (HPV)."
[29] "Human Papillomavirus (HPV)."
[30] "Human Papillomavirus (HPV)."

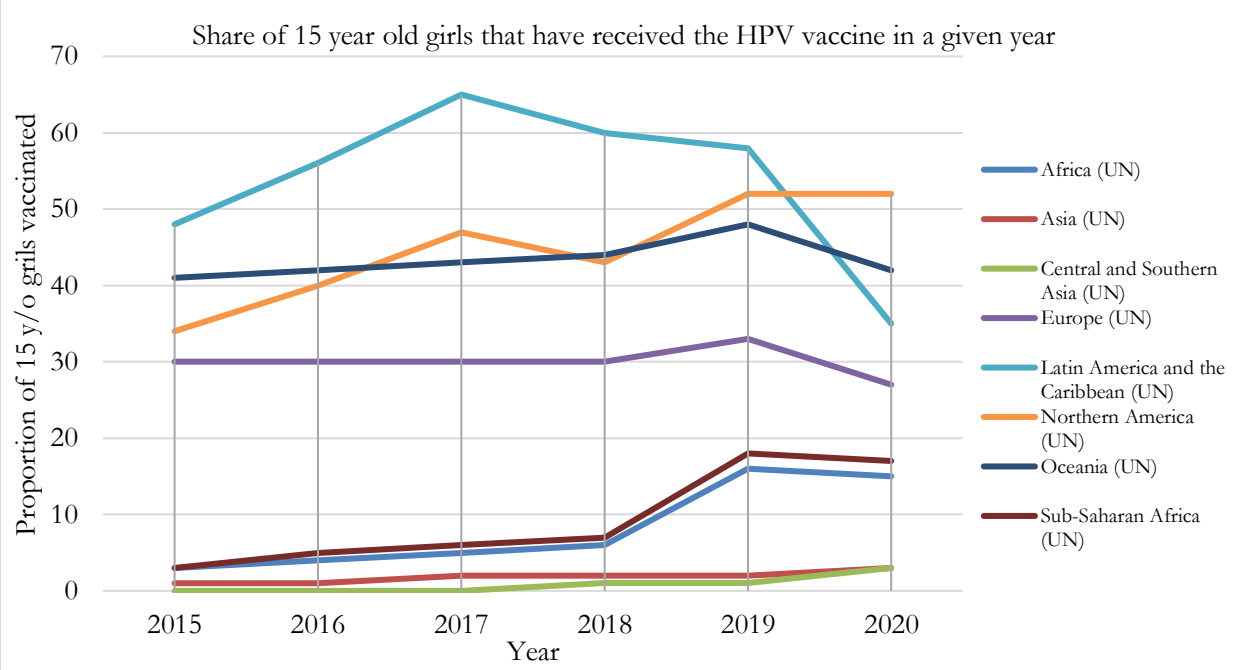
vaccines work best prior to HPV exposure and are therefore meant to be administered prior to sexual activity. Approximately 125 countries have introduced the HPV vaccine in their national immunization program for girls, and 47 countries have introduced this for boys[31].

HPV Vaccination uptake

Globally (between 2015 – 2020), HPV vaccination rates have ranged from 3% to 65% of 15-year-old girls in a given year[32]. In Africa for example, the vaccination rates (between 2015 – 2020) have ranged between 3% to 16% and in Asia from 0 – 3%[33]. In many countries, especially LMICs, the WHO 90% vaccination target has not been achieved. However, some lower-middle income countries have implemented HPV vaccination campaigns which have been successful with vaccination rates of above 80%. For example, through Rwanda's HPV vaccination program the screening rates of 15-year-old girls increased from 35% in 2011 to almost 90% in 2019[34]. There are few cases like Rwanda; in many LMICs additional progress is required and educational awareness is needed to achieve the desired vaccination rates.

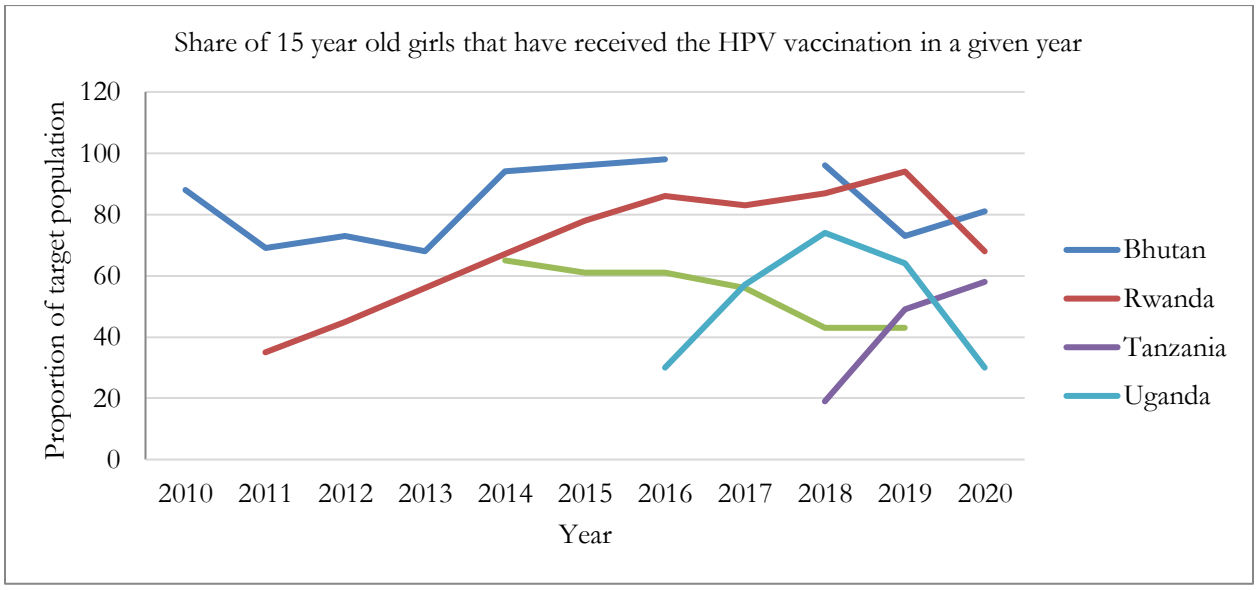
[31] WHO, "Weekly Epidemiological Record -Human Papillomavirus Vaccines: WHO Position Paper (2022 Update)."
[32] "Share of Adolescent Girls Vaccinated against the Human Papillomavirus."
[33] "Share of Adolescent Girls Vaccinated against the Human Papillomavirus."
[34] "Share of Adolescent Girls Vaccinated against the Human Papillomavirus."

Figure 2: Global Outlook – share of 15-year-old girls that have received the HPV vaccine in a given year



Source: OurWorld Data35

Figure 3: Selected LMIC outlook: Share of 15-year-old girls that have received the HPV vaccine in a given year



Source: Adapted from OurWorld Data[36]

[35] "Share of Adolescent Girls Vaccinated against the Human Papillomavirus."
[36] "Share of Adolescent Girls Vaccinated against the Human Papillomavirus."

Screening Methodologies

The WHO recommends that 70% of women are screened using a high-performance test by the age of 35, and again at 45[37]. For women that are HIV positive, screening is recommended at age 25[38]. There are three main types of screening methodologies:

1. DNA and mRNA HPV tests – These diagnostic tests are used to detect the presence of HPV, and to check cells for infection with high-risk HPV types (hrHPV). A sample of cells are removed from the cervix and the HPV test is performed[39]. HPV tests can be performed on a sample of cells collected from the vagina, which a person can collect on their own. These tests are more readily available in developed markets and may still be expensive in some low-middle income contexts[40].
2. Cytology - Commonly known as pap smears. During a pap smear, a speculum is inserted into the vagina and cervical cells are collected on a brush[41]. The cells are then checked for changes due to HPV[42].
3. Visual Inspection with acetic acid (VIA) or Visual Inspection with Lugol's iodine (VILI). These screening methods involve inserting a vaginal speculum and swabbing the cervix with acetic acid or Lugol's iodine, followed by a cervical inspection. VIA is often recommended for low resource settings due to its lower cost. However, given that inspection is dependent on the human eye, and this is prone to error, the repeatability and accuracy of VIA can vary. There is potential for computer aided diagnostics and AI to supplement the process of diagnosing cancer through visual inspection. Digital cervicography (the process of digitally capturing images of the cervix) can be performed after VIA. The analysis of the images through digital cervicography can be performed by medical experts (remotely or in person) or through machine learning algorithms. These algorithms are trained on numerous images of the cervix and can help diagnose a patient with cervical cancer.

[37] World Health Organization, "Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem."
[38] "Human Papillomavirus (HPV)."
[39] "Cervical Cancer - Screening and Prevention."
[40] Woo et al., "Accelerating Action on Cervical Screening in Lower- and Middle-Income Countries (LMICs) Post COVID-19 Era."
[41] "Definition of Pap Smear - NCI Dictionary of Cancer Terms - NCI."
[42] "Cervical Cancer Screening - NCI."

Cervical cancer screening rates in LMICs

Research by the WHO and the Catalan Institute of Technology, find that the current rates of screening are significantly lower in LMICs than in higher income countries[43]. In 2019, 84% of women aged 30 – 49 years living in high income countries have been screened in their lifetime, compared to 48% in upper middle-income countries, 9% in lower middle-income countries and 11% in low-income countries[44]. In Nigeria, for example, approximately 11% of women aged 35 – 49 had been screened for cervical cancer (between 2014-2019)[45]. We note however that accuracy and reporting of screening levels could potentially be even lower, especially in areas with limited healthcare access.

Treatment options

Diagnosis and treatment of cervical cancer is the tertiary prevention measure for cervical cancer. Tertiary prevention includes treatment through surgery, radiotherapy, chemotherapy, or palliative care[46]. Treatment of cervical cancer is typically dependent on the staging and tumor node metastasis[47]. In lower resource settings, treatment is often through thermal ablation, which is performed after visual inspection with acetic acid (VIA). Thermal ablation utilizes a heated probe to destroy precancerous lesions[48]. When thermal ablation occurs immediately after a woman screens positive for cervical cancer, this is known as the "screen and treat" approach[49]. Excisional treatments (also called cone biopsies or cervical conization) which includes cold knife colonization, loop electrosurgical excision procedure (LEEP) and laser conization are alternative mediums for treating cervical cancer. Additionally, cryotherapy, surgery, radiotherapy and chemotherapy are also additional treatment options.

[43] Bruni et al., "Cervical Cancer Screening Programmes and Age-Specific Coverage Estimates for 202 Countries and Territories Worldwide."
[44] Bruni et al.
[45] Bruni et al.
[46] "Cervical Cancer."
[47] Bruni et al., "Cervical Cancer Screening Programmes and Age-Specific Coverage Estimates for 202 Countries and Territories Worldwide."
[48] "Definition of Thermal Ablation - NCI Dictionary of Cancer Terms - NCI."
[49] Word Health Organization, "Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem."

1.2 Literature review of the existing digital/ AI diagnostics for cervical cancer screening

The potential use of AI in cancer diagnosis is increasingly being recognized, especially in low resource settings. The aim of this section is to provide context on the landscape of AI / computer aided technologies for cervical cancer screening in low resource settings. We identify different methodologies and devices in use (or that have been trialed) and detail their performance and accuracy. The process of this review involved an identification of papers and articles from PubMed and Web of Science in early 2023. Papers were selected based on the following criteria: First, papers must have been published in the last 10 years (i.e., from 2013 to March 2023). Second, papers must focus on AI or computer aided diagnosis of cervical cancer screening. Third, the keywords that were input into the databases' search bars included "AI based diagnostics for cervical cancer screening", "smartphone-based diagnostics for cervical cancer screening", "computer aided diagnostics for cervical cancer screening". Finally, papers had to be in English. Papers were prioritized if they referred to use in low resource settings. In addition to reviewing papers and studies, industry experts were consulted and asked to recommend well-known technologies used for cervical cancer screening in LMICs. It is worth noting that applications for AI based screening technologies in low resource settings have typically focused on automating diagnoses from VIA or VILI. Therefore, most papers that were reviewed discussed the use of machine learning models in classifying images of the cervix.

Results from this literature analysis are presented in Table 1. Papers were categorized based on the type of intervention (i.e., digital cervicography, portable colposcopy, etc.). The table presents key information about each study, including their objectives, the method or technology's performance in terms of sensitivity and specificity, as well as the geographical testing environment where the device or method was evaluated. In some studies, the device performance (sensitivity and specificity) was reported for detecting CIN1+ vs in other studies performance was provided for detecting CIN2+. Therefore, direct comparisons of device performance cannot be made from this literature review. The information is simply provided for contextual information of performance.

We find a number of studies that have employed mobile devices and cameras along with machine learning algorithms, to enhance the precision of cervical cancer diagnosis. Initially computer aided diagnosis for cervical cancer included digital cervicography and remote assessment of images by medical experts. Over time, machine learning algorithms have been incorporated into screening

technologies and processes. This enables image capture and automated diagnosis of potential cancerous lesions. Products such as the MobileODT and the Pocket Colposcope integrate image capture and diagnosis into one device.

Table 1: Selected studies on digital / AI based cervical cancer screening technology in LMICs

Type of digital tool	Study	Geography	Device / methodology description	Study objective / implementation	Outcomes
Digital cervicography and tele-medicine interpretation	Tran et.al., [2018] [50]	Madagascar	Smartphone – Samsung Galaxy used for image capture after VIA/ VILI; diagnosis performed by various gynecologists	Objective: Assess the performance of digital cervicography and tele-interpretation. Histopathological diagnosis (reference point), compared to smartphone based digital cervicography after VIA / VILI. 156 HPV positive women tested.	Sensitivity (CIN2+): 71.3%, Specificity (CIN2+): 67.4%
Digital Cervicography and image classification	Kudva et.al., [2018] [51]	India	Android smartphone (for image capture) and algorithm for image analysis	Objective: Assess the performance of a machine learning algorithm for cervical cancer diagnosis Medical expert interpretation of VIA images (reference point), compared to an algorithm predicted outcome. 102 images obtained	Sensitivity: 99.05%, Specificity: 97.16%
Portable colposcope / Smartphone based	Bae et.al., [2020][52]	South Korea	Smartphone based endoscope	Objective: Assess the performance of a smartphone-based endoscope Histopathology and physician	KNN (best performing algorithm) Sensitivity (CIN2+): 75%

[50] Tran et al., "PERFORMANCE OF SMARTPHONE-BASED DIGITAL IMAGES FOR CERVICAL CANCER SCREENING IN A LOW-RESOURCE CONTEXT.

[51] Kudva, Prasad, and Guruvare, "Andriod Device-Based Cervical Cancer Screening for Resource-Poor Settings."

[52] Bae et al., "Quantitative Screening of Cervical Cancers for Low-Resource Settings."

endoscope				interpretation of VIA result (reference point) was compared to image capture from the endoscope and interpretation through various ML models. 20 patients	Specificity:80.3%
	Goldstein et.al., [2020][53]	China (Yunnan Province)	MobileODT – cloud connected, mobile, digital colposcope	Objective: Assessing the performance of MobileODT Patients first tested through HPV DNA tests. Thereafter those with high-risk HPV genotypes underwent digital colposcopy with the Mobile ODT, and results checked with cervical biopsy. 3600 patients	Sensitivity / specificity: not reported however Mobile ODT was able to identify 93.8% of the CIN2+ lesions
	Rahatgaonkare et.al., [2020][54]	India	Smartscope[55] by Periwinkle Technologies- portable, handheld scope for image capture, attached to a tablet	Objective: Assess the performance of Smartscope Histopathology (reference point) was compared to Smartscope as well as VIA (with naked eye evaluation) and pap smear. 509 patients	Smartscope sensitivity (for CIN1+ identification): 100%, Specificity: 36.8%

[53]Goldstein et al., "Assessing the Feasibility of a Rapid, High-Volume Cervical Cancer Screening Programme Using HPV Self-Sampling and Digital Colposcopy in Rural Regions of Yunnan, China."
[54] Rahatgaonkar, Uchale, and Oka, "Comparative Study of Smart Scope® Visual Screening Test with Naked Eye Visual Screening and Pap Test."
[55] "Smart Scope."

	Mueller, et.al., [2018][56]	Peru	Pocket colposcope[57] by Calla Health Foundation and Department of Biomedical Engineering at Duke University – portable, low cost, colposcope	Objective: Assess the performance of Pocket Colposcope Expert medical review of VIA and VILI images through standard colposcopy (reference point) compared to Pocket colposcope. 200 patients	Pocket colposcope (for negative vs CIN+) sensitivity: 71.2%, specificity: 57.5%
	Nessa et.al., [2014][58]	Bangladesh	Gynocular[59] by Gynius Plus AB- portable, monocular, colposcope	Objective: Assess the performance or Gynocular Histologic diagnosis, stationary colposcope, liquid based cytology, HPV and cervical biopsies (reference points) compared Gynocular. 540 HPV positive patients	Gynocular (CIN2+) sensitivity: 83.3% and Specificity: 23.6%

[56] Mueller et al., "Portable Pocket Colposcopy Performs Comparably to Standard-of-Care Clinical Colposcopy Using Acetic Acid and Lugol's Iodine as Contrast Mediators – An Investigational Study in Perú."
[57] "Pocket Colposcope."
[58] Nessa et al., "Evaluation of Stationary Colposcope and the Gynocular, by the Swede Score Systematic Colposcopic System in VIA Positive Women."
[59] AB, "Gynius Plus AB."

Overall, the sensitivity and specificity of each of the technologies / methods in Table 1 has varied. Screening device /methodology sensitivities have ranged from 71% to 100% depending on the process and level of assessment (i.e., CIN1+ or CIN2+). Specificities have ranged from 36% to 90%. We also note that the accuracy and repeatability of cervical cancer screening can be influenced by more than just the technology or device itself. Factors such as the healthcare provider competency, appropriate lighting available and positioning of the cervix when images are captured, can impact the accuracy of screening processes. Therefore, it is difficult to make firm conclusions regarding the effectiveness of a particular method or device over another when factors such as those previously mentioned are not controlled for.

Through a Cochrane review by the WHO, the estimated sensitivity of VIA (for CIN2+ in a screening) ranged from 22% - 91% (with an average of 66%) and specificity ranged from 47% – 99% (with an average of 87%)[60]. Given the wide range of accuracy, there is potential for AI and digital technologies to improve the average sensitivity and specificity of VIA screening. AI based technologies can also help reduce the burden on healthcare professionals and can aid in the training of providers to accurately detect cancerous lesions[61]. Such technology however is intended to augment rather than replace healthcare professionals and gynecologists.

[60] Word Health Organization.
[61] Goldstein et al., "Assessing the Feasibility of a Rapid, High-Volume Cervical Cancer Screening Programme Using HPV Self-Sampling and Digital Colposcopy in Rural Regions of Yunnan, China."

Additional information regarding AI based screening devices (colposcopes)

In this section, we provide additional information on portable colposcopes, many of which are designed for use in low resource settings.

1. **Enhanced Visual Assessment (EVA) by Mobile ODT**

   Product: Digital Colposcope, speculum required

   Company: MobileODT, acquired by Liger Medical in 2022

   Company location: Israel

   Market suggested retail price: $1800[62]

   Power: Rechargeable battery (10 hours of constant use)[63]

   Currently product sales have been halted. Device was FDA approved.

Image retrieved from: MobileODT[64]

2. **Gynocular**

   Product: Mobile colposcope, speculum needed

   Company: Gynius Plus AB

   Company location: Sweden

   Cost (estimate)[65]: $3000

   Power: Rechargeable battery powered (at least 2 hours of continuous use)[66]

   Device is FDA and CE approved. It is pocket sized and can be used as a handheld device or mounted on a tripod.

Image retrieved from: Gynius Plus AB[67]

[62] "EVA System."
[63] Gonzalez et al., "Cervical Imaging in the Low Resource Setting."
[64] "FemTech Company MobileODT Awarded Prestigious National Cancer Institute (NCI) SBIR Grant of $2.3 Million."
[65] Gonzalez et al., "Cervical Imaging in the Low Resource Setting."
[66] "Gynocular™ - Video Colposcope by Gynius Plus AB | MedicalExpo."
[67] Gonzalez et al., "Cervical Imaging in the Low Resource Setting."

C. Pocket Colposcope

Product: Digital colposcope, no speculum needed

Company: Cala Health Foundation & Department of Biomedical Engineering at Duke

Company location: USA

Market suggested retail price: $500[68]

Power: Continuous power supply

Device has been FDA approved. Clinic testing has occurred in Ghana and the US. In both sites, 60% of participants found the device easy to use[69]. Procedure time estimated at 5 mins[70]

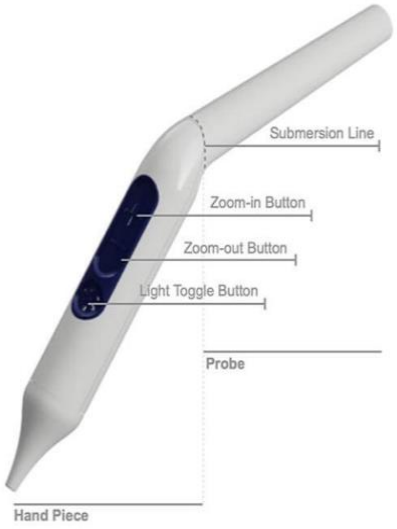


Image retrieved from Cala Health Foundation[71]

D. Smartscope

Product: Mobile colposcope, speculum needed

Company: Periwinkle Technologies

Company location: India

Device is ISO 13485:2016 certified. Procedure time is estimated at 7 mins[72].

Image retrieved from Periwinkle Technologies[73]

[68] "Pocket Colposcope."
[69] Gonzalez et al., "Cervical Imaging in the Low Resource Setting."
[70] "Pocket Colposcope."
[71] "Pocket Colposcope."
[72] "Smart Scope."
[73] "Smart Scope."

1.3 Human Papillomavirus Simulator (HPVSim) and Automated Visual Evaluation (AVE)

What is HPVsim?

HPVsim is an open source, mechanistic stochastic agent-based model that captures the process of HPV acquisition, persistent infection, and progression to cervical cancer[74]. The model was created by the Institute of Disease Modeling (IDM), with the purpose of enabling users to evaluate pathways toward cervical cancer elimination[75]. HPVsim incorporates country-specific dynamics, structured sexual networks, co-transmitting HPV genotypes, B- and T-cell mediated immunity and high-resolution disease natural history into the mathematical model[76]. HPVsim models people (agents) over time and simulates the transmission of HPV amongst sexual partners. Simulations reflect the progression of HPV to cervical dysplasia and cervical cancer. Simulations allow researchers and users of the model to predict outcomes (i.e., age standardized cervical cancer incidence rates, deaths, HPV transmission, among other outputs), based on various interventions such as vaccinations, screening policies, or treatment pathways.

HPVsim intended use and possible use cases

HPVsim was designed to foster collaboration across academia, industry, and policy makers. The model creators provide a platform for researchers and public health officials to test various scenarios and public health initiatives as well as understand the progression of disease in various contexts. This paper is an example of the former, where the model is used to predict and estimate the impact of cervical cancer prevention strategies on health outcomes. As the adoption of HPVsim grows, additional use cases will likely be identified.

Key inputs and parameters for simulations within HPVsim

Information in the section below draws heavily from the MedRxiv preprint published by Stuart.et al on HPVsim. Within this section, we aim to provide a baseline understanding of HPVsim in order to better understand the results of simulations that are shared later in this paper. To access HPVsim as

[74] Stuart et al., "HPVsim."
[75] Stuart et al.
[76] Stuart et al.

well as for details on the parameters and default values see Appendix 1. A summary of the calibration and key simulation components used within HPVsim is shown in Appendix 2.

a) Demographic information

HPVsim models health outcomes related to cervical cancer within pre-set calibrated countries. Demographic information such as population birth rates, death rates and migration are incorporated into the model calibration for a country[77]. For each simulation run through HPVsim, a population of agents is initialized, and country demographic data is scraped from World Bank data and the UN's 2022 World Population prospects[78].

b) Sexual Network

HPVsim models only heterosexual partnerships and cisgender individuals[79]. There are two built-in sexual network options in HPVsim (default and random)[80]. The 'default' sexual network (and what has been used in the analysis for this paper) considers three types of relationships: long-term, casual and one-off relationships. Across both network options ('default' and 'random'), variables for relationship duration, propensity for relationship concurrency, coital frequency, condom usage, sexual participation rates and age mixing are defined[81]. Data for these variables was typically obtained from the Demographic and Health Surveys (DHS)[82].

The demographic data and assumptions on sexual networks are used to define the population and behaviors of agents, on whom HPV transmission and cervical cancer progression will be simulated.

c) HPV transmission

Within HPVsim, a function is defined to predict the probability of a person transmitting HPV to a susceptible partner. Transmission is dependent on the per-act probability of transmission, efficacy of condoms, probability of condom use, number of sexual acts within the relationship and existing protective immunity to infection against a particular HPV genotype (for the susceptible partner).

[77] Stuart et al., "HPVsim."
[78] Stuart et al.
[79] Stuart et al.
[80] Stuart et al.
[81] Stuart et al.
[82] Stuart et al., "HPVsim."

Immunity occurs either through infection or vaccination. The probability of obtaining the necessary antibodies for immunity after infection is drawn from a beta distribution with mean of 0.35 and variance of 0.025[83]. HPVsim by default does not consider impacts to relative transmissibility based on the stages of infection (episomal, transforming or cancerous), however if desired HPVsim can be adapted to consider such differences[84]. For the purposes of the analysis in this paper, the default settings of no relative transmissibility were used.

d) Disease Natural History

HPVsim models the progression of HPV infection to cellular transformation and eventually invasive cervical cancer. HPVsim determines prognosis upon infection, including the time points at which a woman will clear infection or begin transformation and progress to cervical cancer. Key variables incorporated in modeling this process include the duration of episomal infection before clearance (which follows a log-normal distribution and varies by genotype) and the severity of infection[85]. Infection severity is determined based on to the proportion of epithelial layers with affected cells[86]. The severity of infection is used to determine whether clearance would occur or whether there would be a cellular transformation (i.e., invasive cervical cancer). Severity of infection is modeled based on a logistic function with a genotype specific inflection point[87]. Thereafter, the probability of the infection transforming and leading to invasive cancer is assumed to be a stochastic process and the risk of transformation grows with the severity of infection over time[88]. If a woman clears the infection, there is a possibility she obtains antibodies and seroconversion takes place, the probability of seroconversion occurring is genotype specific and results in the woman developing B and T-cell protection against future infection[89]. In HPVsim, clearance is assumed to represent complete clearance by default rather than a latent infection[90].

[83] Stuart et al.
[84] Stuart et al.
[85] Stuart et al.
[86] Stuart et al.
[87] Stuart et al.
[88] Stuart et al.
[89] Stuart et al.
[90] Stuart et al.

e) Cervical cancer prevention interventions

HPVsim also incorporates modules to assess public health interventions such as vaccinations, screening and treatment. These modules were utilized to simulate the scenarios required for our analysis in this paper. Parameters for the intervention modules are described below:

i) Prophylactic vaccines

HPVsim incorporates the ability to model vaccine campaigns by requiring the following parameters to be defined: vaccine coverage, eligibility criteria (age / gender at birth), start and end years of campaigns and type of vaccination products (ex. Bivalent vaccines). By default, single-dose delivery is modeled in HPVsim. Vaccinations provide neutralizing immunity to the genotypes that they target and cross immunity to other genotypes across the simulated population[91].

ii) Screening and triage

Various screening and triage methods can be simulated in HPVsim. Examples of screening methods that are included in HPVsim are: HPV DNA testing, visual inspection with acetic acid (VIA) and automated visual evaluation (AVE). Parameters incorporated in simulating the impact of screening technologies include: the probability of screening uptake, eligibility criteria (typically ages between 30 – 50), product types, timing of screening intervention, as well as the sensitivity and specificity of each screening technology / procedure. Screening interventions indirectly impact the disease progression, infection duration and severity of episomal infection. This is because screening may lead to treatment which will directly influence disease progression.

iii) Treatment

HPVsim models various types of treatment including thermal ablation and excisional treatments, which include cold knife conization, loop electrosurgical excision procedure (LEEP), and laser conization. The effectiveness of treatment strategies is estimated based on a meta-analysis of historical response rates for treatments[92]. Treatment interventions influence the duration of episomal infection and the severity of infection. HPVsim requires inputs on treatment probabilities, type of treatment, eligibility and start year of treatment intervention.

[91] Stuart et al.
[92] Stuart et al.

Automated visual evaluation (AVE)

Through this paper we use HPVsim to explore the value and potential impact of an AI based screening technology (i.e., Automated Visual Inspection, AVE) which has been developed by GHLabs. AVE is a smartphone-based app that applies machine learning to detect precancerous lesions[93]. AVE's machine learning models are trained on several images (of cervixes), which have already been labeled with the appropriate diagnosis. AVE is an assistive technology to VIA and offers an opportunity to improve the screening process and accuracy of VIA[94]. In practice, a healthcare provider performs VIA, by swabbing the cervix with acetic acid. Thereafter, images of the cervix are captured and interpreted using AVE which will provide a diagnosis. The use of AVE is expected to help improve the accuracy and reproducibility of VIA results[95]. Currently, in low resource settings VIA is frequently recommended due to its relatively lower cost[96]. However, VIA is often subjective and dependent on the expertise and experience of the healthcare provider analyzing the cervix. This variation in sensitivity and reliance on human expertise can potentially be overcome by leveraging deep learning models to evaluate cervical images. AVE is being tested across five African countries and India.

[93] "AI-Enabled Cervical Cancer Screening."
[94] Desai et al., "The Development of 'Automated Visual Evaluation' for Cervical Cancer Screening."
[95] Desai et al.
[96] Desai et al.

Section 2: Methods of Analysis

The analysis within this paper was structured into three components:

1. Sensitivity analyses – the impact of public health interventions (with varying levels of success) on cancer incidence, mortality and HPV transmission.

The global strategy to eliminate cervical cancer proposes targets for cervical cancer interventions. These targets must be met by 2030 in order for countries to be on the path towards cervical cancer elimination[97]. The 3 targets are:

- 90% of girls are fully vaccinated with the HPV vaccine by age 15
- 70% of women are screened with a high-performance test by 35 years of age and again by 45 years of age, and
- 90% of women identified with cervical disease should receive treatment (i.e., 90% of women with pre cancer are treated and 90% of women with invasive cancer are managed)[98].

These targets are optimistic based on the current levels of vaccination and screening in LMICs today.

Through this paper, we aim to model the impact of achieving various levels below the WHO targets for cervical cancer prevention strategies. We utilize HPVsim to model a less optimistic (or realistic) outlook and performed sensitivity analyses on key variables of the intervention strategies:

1) Vaccination uptake levels
2) Screening probabilities
3) Performance of AI based screening tools (sensitivity and specificity of AVE)
4) Probability for treatment

To perform the sensitivity analyses, code from HPVsim was altered to simulate each scenario. Each scenario that was run as well as the corresponding inputs and outputs are summarized in the table below.

[97] Word Health Organization, "Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem."
[98] Word Health Organization.

Table 2: Summary of simulations for sensitivity analysis performed

Input variable varied	**WHO expectation (and HPVsim model default value)**	**Sensitivity scenarios modeled**	**Model output**
Vaccination levels	90%	0 – 100%	Age standardized cervical cancer incidence rates, cancer deaths, HPV transmission
Screening probability	70%	No screening, 20%, 40%, 60%, 70% of eligible population screened (i.e., aged 30 -50) during the 20-year period	Age standardized cervical cancer incidence rates, cancer deaths
Performance of AI based screening tool	Not applicable or determined yet	The following sensitivity and specificity combinations were modeled: Sensitivity / Specificity 62%/86% 82%/86% 90%/83%	Age standardized cervical cancer incidence rates, cancer deaths
Probability of treatment	90%	20%, 40%, 60%, 80%, 90% probability of treatment for positively screened women	Age standardized cervical cancer incidence rates, cancer deaths

2. Linear regression to evaluate the impact of AVE, and the relative importance of screening probability, treatment probability and device accuracy in effective screening strategies

Given the paper's focus on AI based screening, we took a deeper dive to understand the potential impact of screening using AVE. We sought to understand the combined impact of screening probability, treatment probability and AVE accuracy on ASIR. For this analysis, we used HPVsim to generate a dataset of predictions of ASIR values in 2040 and 2060. Each predicted value represented a different combination of screening probability, treatment probability, and AVE sensitivity and specificity. A full breakdown of the combinations simulated to generate the predicted ASIR values is

shared in Appendix 3. We generated 100 predictions for 2040 and 100 for 2060 and then performed linear regression on the generated data sets. ASIR was the dependent variable, and the independent variables were screening probability, treatment probability and sensitivity / specificity of the AVE. The results of the linear regression (R squared, p values and coefficients) are presented and evaluated in Section 4.

Through an analysis of the results (i.e., the trend analysis in section 3 and the linear regression in section 4), we determine which strategies might have the most influence on age-standardized cervical cancer incidence and cancer mortality. These insights are then used to determine where the most urgent and impactful strategies might lie in eliminating cervical cancer (See Section 4).

Simulations for analyses 1 & 2 above were performed on a "Nigeria-like" country. Nigeria is already calibrated into HPVsim and offers a use case to investigate the impact of various interventions. HPVsim takes inputs based on current data of Nigerian demographics in order to calibrate a "Nigeria like country".

3. Primary research with subject matter experts

Primary research in the form of interviews with subject matter experts was conducted. Experts in the fields of epidemiology, public health simulation modeling, gynecology and AI based screening technologies for cervical cancer were conducted (See Appendix 4 for a list of interviewees). These interviews provided insights and feedback on simulations as well as on existing screening technologies (their development and best practices for deployment). These insights are consolidated and shared in section 5 of the paper.

Although HPVsim was the only mathematical model used in our analysis, we note that there are a variety of available models that estimate the outcomes of cervical cancer prevention strategies. These models include Cervix-1, HPVADVISE, and Harvard[99]. However, HPVsim was selected for this research due to the accessibility to the model developers.

[99] Brisson et al., "Impact of HPV Vaccination and Cervical Screening on Cervical Cancer Elimination," February 2020.

Section 3: Results

Utilizing HPVSim to model the impact of various intervention strategies and policies.

In the following section we describe the outcomes of the simulations that were referenced in section 2 (part 1). We first provide an overall view of the trends exhibited as each prevention strategy is altered. The results are subdivided into four categories, each representing a relevant prevention strategy (and set of simulations). The subsections are HPV vaccination rates, screening uptake, AVE accuracy (sensitivity and specificity) and treatment probability. Within each subsection, we provide context on the assumptions of the simulation and present the results from the sensitivity tests performed using HPVsim (referenced in section 2).

HPV Vaccination rates

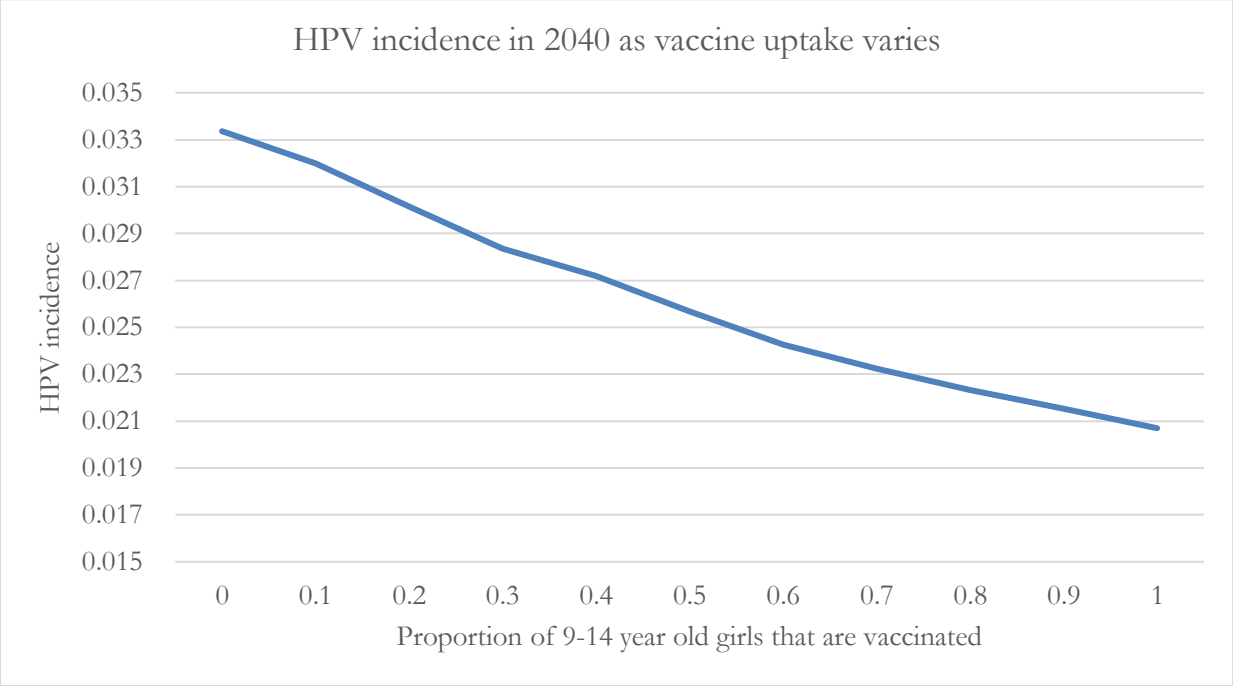
Using HPVsim, we model the impact of various vaccination uptake rates in a "Nigeria-like" country. The results below depict the impact on HPV incidence, age standardized cervical cancer incidence rates and cancer deaths as vaccination uptake is varied between 0 – 100%. Within these simulations, it is assumed that the vaccination campaign is structured as a single dose, bi-valent vaccination, provided to girls aged 9 – 14 years only. Vaccinations begin in 2025 and the simulation results in 2040 and 2060 are extracted. HPVsim also assumes that the bivalent prophylactic vaccinations have some cross-protective benefit (but not 100%) against other high risk HPV genotypes. HPVsim default settings for screening and treatment are maintained in the simulations below. These default settings assume 70% of women aged 30 – 50 are screened and 90% of positively screened cases are treated. In subsequent sections we isolate the impact of vaccinations from screening and treatment, however for the initial set of results the default settings of HPVsim for interventions are maintained.

Modeling the impact of varied vaccination uptake in the short term

In the short term, the impact of vaccinations on HPV transmission and age standardized cervical cancer incidence rates (ASIR) is limited. This is a result of two factors. First, that there is an unvaccinated but sexually active proportion of the population contributing to HPV transmission in the short term. These individuals might have passed the 15-year-old age bracket when the vaccination campaign was started. Second, from the point at which a girl is vaccinated (typically around ages 9 – 14) to the point where she reaches sexual debut and may contract or spread HPV, is a number of

years. Therefore, in the short term, the players within the sexual networks are a mix of individuals that may or may not have benefited from vaccinations. We present the impact of vaccinations in the short run only for comparative purposes. The actual impact of vaccinations can only be understood and realized when analyzing a longer time horizon.

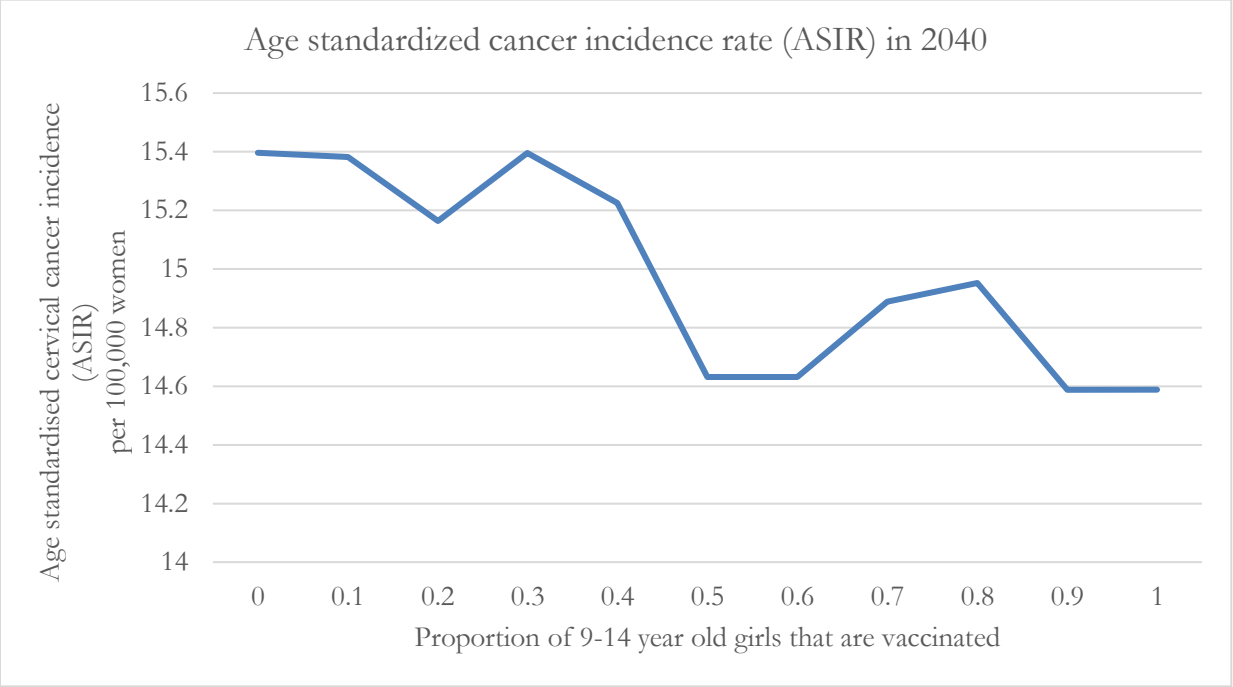
Figure 4: Projected HPV incidence rate in 2040, as the proportion of vaccinated girls (aged 9 – 14) is varied



HPVsim results for a vaccination campaign through which a bivalent, single dose vaccine is given to girls aged 9 – 14 (i.e., the vaccine target population). The proportion of 9–14-year-old girls vaccinated each year varies from 0 – 100%. The campaign begins in 2025 and the results (HPV incidence) are extracted after a 15-year simulation period (i.e., in 2040). We observe a decline in HPV incidence as the proportion of vaccinated girls each year (aged 9-14) increases from 0 – 100%.

As seen above, the general trend is that as vaccination proportions increase, HPV incidence rates decrease. In the short term (2040), we observe that vaccinating 90% of the target population (the WHO target) reduces HPV incidence by 35%. When 90% of the target population is vaccinated, HPV incidence is 0.022, whereas when no vaccinations are provided HPV incidence is projected at 0.033.

Figure 5: Projected age standardized cervical cancer incidence (ASIR) in 2040 as the proportion of vaccinated girls (aged 9 – 14) is varied.



HPVsim results for a vaccination campaign through which a bivalent, single dose vaccine is given to girls aged 9 – 14 (*i.e.,* the vaccine target population). The proportion of the target population vaccinated each year is varied from 0 – 100%. The campaign begins in 2025 and the result (age standardized cervical cancer incidence rate) is extracted after a 15-year simulation period (*i.e.,* in 2040). We observe a volatile but general decline in age standardized cervical cancer incidence as the proportion of vaccinated girls each year (aged 9-14) increases from 0 – 100%. Volatility in age standardized incidence rate is potentially a result of the randomness of simulations within HPVsim and that the true effect of vaccinations takes years to be realized.

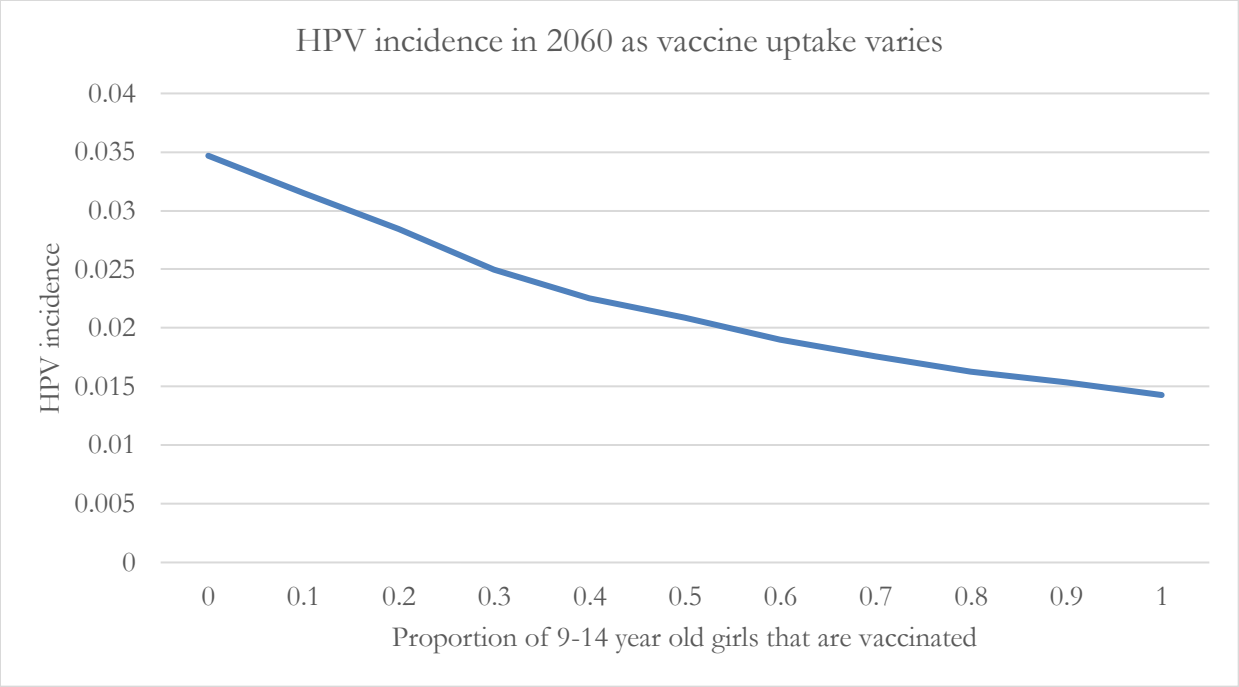
The impact on age standardized cervical cancer incidence rate (ASIR), shows an overall reducing but volatile decline as the proportion of the target population vaccinated increases. It is difficult to assume a relationship between the proportion of the target population that is vaccinated and the ASIR over such a short period of time (i.e., 15 years). This time period is not long enough to observe the full impact of the vaccination. Individuals that are contributing to sexual activity and the spread of HPV in 2040 are a mix of individuals that may or may not have been vaccinated through the vaccination campaign. Furthermore, the volatility in results is potentially due to randomness and the stochastic nature of HPVsim. Although it is difficult to make inferences about the relationship between vaccinations and health outcomes (ASIR and HPV incidence) in the short term, we perform this analysis to illustrate the immediate implications of a vaccination campaign and the expected levels of

ASIR in the short term. Importantly however, it brings to light the need for alternative prevention strategies such as screening, especially in the short term.

Modeling the impact of varied vaccination rate uptake in the long term

The following set of results depict HPV incidence, ASIR and cancer deaths in 2060 as a result of simulating the aforementioned vaccination campaign.

Figure 6: Projected HPV incidence rate in 2060, as the proportion of vaccinated girls (aged 9 – 14) is varied



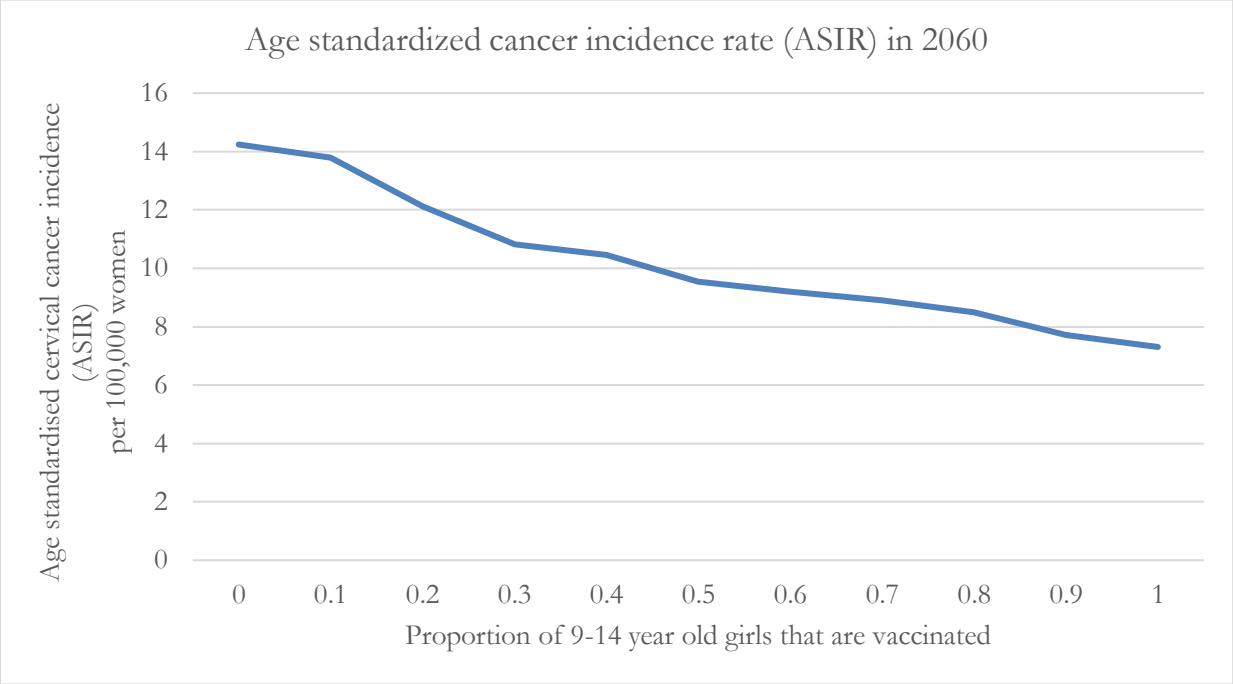
HPVsim results for a vaccination campaign through which a bivalent, single dose vaccine is given to girls aged 9 – 14 (i.e., the vaccine target population). The proportion of 9–14-year-old girls vaccinated each year is varied from 0 – 100%. The campaign begins in 2025 and the results (HPV incidence) are extracted after a 35-year simulation period (i.e., in 2060). We observe a decline in HPV incidence as the proportion of vaccinated girls each year (aged 9-14) increases from 0 – 100%. It appears that the rate of reduction in HPV incidence is front-loaded when the vaccinated proportion goes from 0 -30% of the population.

As exhibited above, we observe that the rate of reduction in HPV incidence is greatest when the proportion of the vaccine target population (9–14-year-old girls) that is vaccinated goes from 0 – 30%. Thereafter the rate of reduction in HPV incidence reduces. A possible reason for this observation is the influence of herd effects. However, even though the rate of reduction in HPV transmission slows down after ~30% of the population is vaccinated, it is still beneficial to promote vaccination. Firstly, the risk on an individual level of not being vaccinated is severe and from a public health perspective

it is desirable to target vaccination coverage across a greater proportion of the population. Secondly, HPVsim doesn't account for differences in sub-groups or socio-economic clusters, it simply assumes a defined vaccination coverage level across the entire set of agents modeled. In reality, this will be unlikely. Vaccination coverage may instead be concentrated amongst certain sub-groups and clusters (such as those in urban settings). Since HPV is sexually transmitted, and sexual interactions can be dependent on a person's subgroup, it is possible that there might be some sub-groups that are made vulnerable and are disproportionately affected by HPV. Therefore, it is possible that a 30% vaccination target would be lower than required to actually achieve herd effects. Although the greatest rate of reduction in HPV incidence occurs when ~30% of the targeted population is vaccinated, there is rationale therefore to pursue a much higher vaccination uptake target.

The vaccine modeled in this situation is a bivalent vaccination (primarily providing protection for HPV 16 and 18 (with some cross-protective benefit for other high risk HPV genotypes)). Therefore, we note that we do not see a complete reduction (i.e., absolutely no HPV transmission) even when 100% of the population is vaccinated. Although HPVsim assumes some cross-protective benefit from the bi-valent vaccination, the remaining HPV prevalence is possibly due to other high risk HPV genotypes that are not protected for through the bi-valent vaccination.

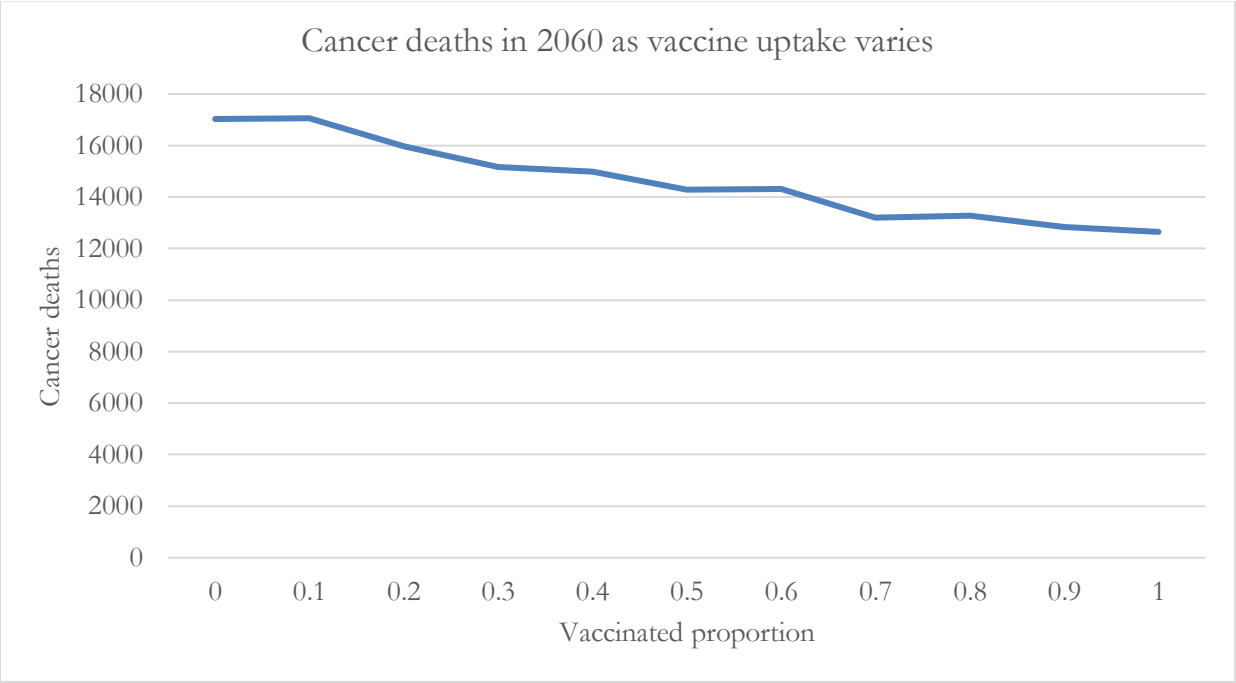
Figure 7: Projected age standardized cervical cancer incidence rates in 2060, as the proportion of vaccinated girls (aged 9 – 14) increases



HPVsim results for a vaccination campaign through which a bivalent, single dose vaccine is given to girls aged 9 – 14 (i.e., the vaccine target population). The proportion of 9–14-year-old girls vaccinated each year is varied from 0 – 100%. The campaign begins in 2025 and the results (age standardized cervical cancer incidence rate) is extracted after a 35-year simulation period (i.e., in 2060). We observe a decline in age standardized cervical cancer incidence as the proportion of vaccinated girls each year (aged 9-14) increases from 0 – 100%. The greatest decline is observed when vaccination uptake moves from 0 – 30%, thereafter the rate of reduction in ASIR reduces.

In the long-term vs, the short term, the relationship between ASIR and the proportion of the target population vaccinated is smoother. We observe a decline in incidence rates (ASIR) as a greater proportion of the target population is vaccinated. However, even with perfect (100%) uptake of the vaccine amongst the target population, the predicted ASIR is ~7 out of 100,000 women. This result is still above the WHO target for cervical cancer elimination which is set at 4 out of 100,000 women.

Figure 8: Projected cancer deaths in 2060, as the proportion of vaccinated girls (aged 9 – 14) increases



HPVsim results for a vaccination campaign through which a bivalent, single dose vaccine is given to girls aged 9 – 14 (i.e., the vaccine target population). The proportion of 9–14-year-old girls vaccinated each year is varied from 0 – 100%. The campaign begins in 2025 and the results (cervical cancer deaths) is extracted after a 35-year simulation period (i.e., in 2060). We observe a decline in cervical cancer deaths as the proportion of vaccinated girls each year (aged 9-14) increases from 0 – 100%.

Through the above simulation, we observe a decline in cancer deaths as a greater proportion of the target population is vaccinated. Cancer deaths in 2060 are projected to reduce from approximately seventeen thousand deaths annually (without a vaccination campaign) to approximately thirteen thousand (with 90% uptake through the vaccination campaign). Overall, we can infer that the greater the proportion of the target population vaccinated, the fewer the cancer deaths. It is important to recognize however that the progression from HPV transmission to cervical cancer can take decades[100], therefore the impact of a vaccination campaign will also take a long period of time to be realized and to influence cancer deaths.

In summary, we find that vaccinations and increasing vaccine uptake is beneficial, however it takes time for the impact of vaccinations to be realized. In the short term, there are many individuals that

[100] Brisson et al., "Impact of HPV Vaccination and Cervical Screening on Cervical Cancer Elimination," February 2020.

are sexually active, have not been vaccinated and have the potential to transmit HPV. For these individuals, their partners and communities, screening is increasingly important in order to reduce HPV transmission, cancer incidence rates and mortality. Both in the long and short term (i.e., in 2040 and 2060), we do not achieve the WHO required target for cervical cancer elimination (i.e., an ASIR of 4 per 100,000 women-years) in the simulated "Nigeria like" country. Based on the simulations conducted, even with 100% of the population vaccinated, by 2060, we would achieve an incidence rate of closer to 7 per 100,000 women-years, indicating there is further intervention needed beyond vaccination in order to achieve elimination.

Screening uptake

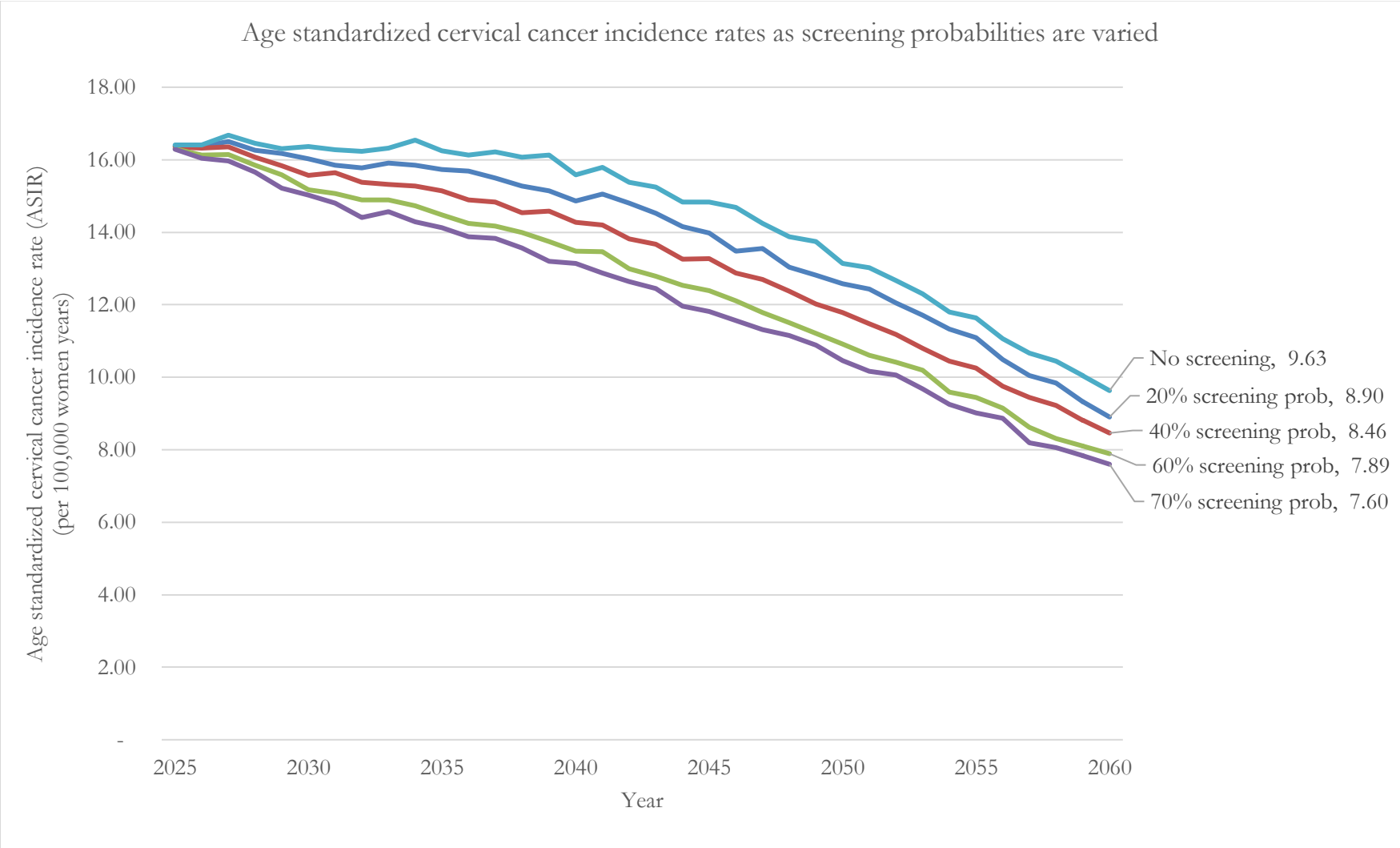
Within the WHO defined Africa region, many countries have not implemented cervical cancer screening programs with sufficient population coverage[101]. In Nigeria for example, screening rates have been documented at 11%[102] of women aged 30 – 50. Given the gap in screening uptake between the current levels and the WHO targets (i.e., 11% vs 70%), it was important to evaluate scenarios where various levels of screening uptake (below the 70% target) are reached.

The figures below show the results of simulations run through HPVsim, where the probability of screening amongst the eligible population was varied. The following screening campaign is modeled:

- Eligibility criteria: women aged 30 – 50 years old.
- Primary screening product: VIA followed by AVE (i.e., an AI based screening tool to diagnose the presence of precancerous cells, the performance of the AVE tool was assumed at 86% sensitivity and 82% specificity).
- Additional prevention / treatment measures in place: By default, HPVsim assumes a routine vaccination campaign where 90% of girls 9 – 14 are vaccinated and that 90% of positively screened cases are treated.

[101] IARC, "Cervical Cancer Screening . IARC Handbook Cancer Prev. 18:1–456."
[102] Bruni et al., "Cervical Cancer Screening Programmes and Age-Specific Coverage Estimates for 202 Countries and Territories Worldwide."

Figure 9: Impact over time on age standardized cervical cancer incidence rates (ASIR) as screening uptake is varied.



HPVsim results for a screening program through which women aged 30 – 50, are screened using VIA and AVE. 90% of positively screened women are assumed to be treated and 90% of 9–14-year-old girls are assumed to be vaccinated. Increased screening uptake results in lower cancer incidence rates. The reason for reduced incidence rates while no screening occurs is a result of vaccinations.

From the results above, we observe that over time, as screening uptake varies from 20% to 70% of the eligible population (i.e., women aged 30 – 50), the ASIR reduces. This is an expected output as the more women screened (and by extension treated), the lower the expected ASIR. When no screening takes place (depicted in Figure 9 by the light blue line labeled "No screening"), the reduction in ASIR is due to the effect of vaccinations.

We also show the impact of varying screening uptake in both the short and long term (i.e., by 2040 and 2060) in the tables below. We find that as screening probability increases there is a steady decrease in ASIR. Given the HPVsim default assumptions (90% vaccinated target population and 90% follow up treatment being provided), between 2025 and 2040, screening 70% of the eligible population results in a 14% reduction in ASIR and an aversion of ~2400 deaths relative to when no screening occurs. In the longer term (i.e., between 2025 and 2060), screening 70% of the population results in a 12% reduction in ASIR and an aversion of ~51,000 deaths relative to when no screening occurs.

Table 3: Age standardized cervical cancer incidence (ASIR) at various levels of screening uptake in the short (2040) and long term (2060).

	Reduction in age standardized cervical cancer incidence due to screening uptake	
Screening probability	Short term (between 2025 – 2040)	Long term (between 2025 – 2060)
20%	-4%	-4%
40%	-8%	-7%
60%	-12%	-10%
70%	-14%	-12%

HPVsim results when screening probabilities are varied, however vaccination levels remain at 90% of the eligible population and 90% of those screened are expected to be treated. Increased screening probability increases the reduction in ASIR. The impact of screening is slightly higher in the short-term vs in the long term; however, this is due to vaccination effects being realized in the long term.

Table 4: Cumulative cancer deaths averted in the long and short term based on varying estimates of screening probability.

	Cancer deaths averted	
Screening Probability	By 2040	By 2060
20%	828	13,965
40%	1,283	27,983
60%	2,013	42,486
70%	2,512	51,029

We highlight that these results reflect a scenario with default vaccination assumptions (i.e., 90% coverage). Therefore, the influence of screening (as a stand-alone strategy) is likely to be higher than the 12 – 14% impact shown above. Screening and vaccinations can be considered "substitutes" in terms of reducing ASIR therefore we are likely to observe an increased impact of screening on ASIR if we modeled a scenario where no vaccinations were provided. In addition, the difference in screening impact between the long and short term is likely due to the impact of vaccinations taking effect in the long term and reducing HPV prevalence, therefore screening has a lower relative impact in the long run.

Screening can be heavily resource intensive, requires appropriate technology, expertise, and healthcare provider accessibility, which can be limited in low resource settings. Therefore, public health officials and researchers would need to examine the cost implications and trade-offs for various types of screening interventions.

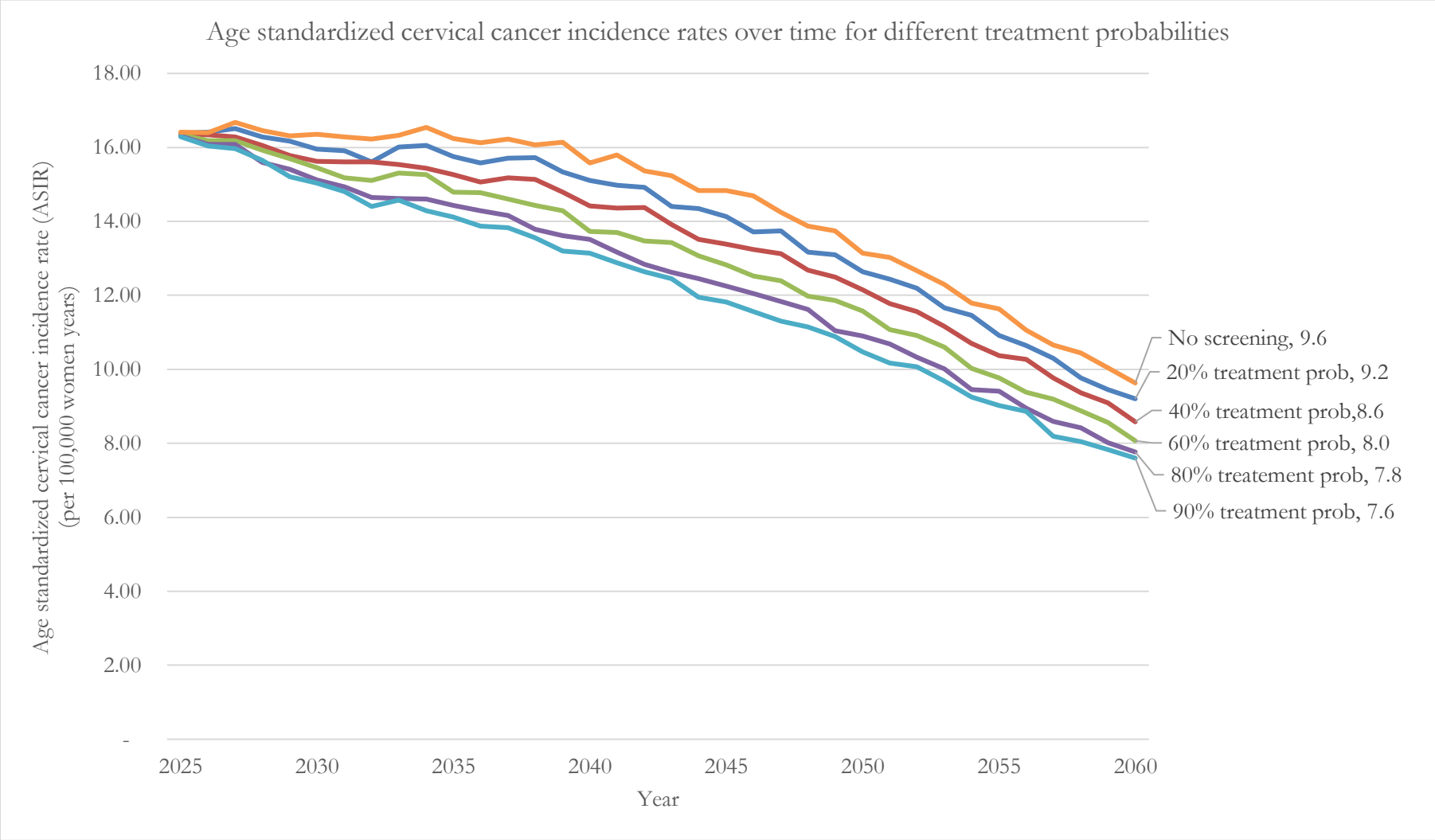
Treatment probability and loss to follow up

Screening and treatment go hand in hand, without treatment, the impact of screening is negated. Therefore, there is a case to be made for "screen and treat" strategies which involve screening and immediate (same day) treatment in order to minimize loss to follow up. Practically achieving immediate screening and treatment however can be difficult due to healthcare accessibility, resource constraints and patient fears regarding the treatment procedures.

The WHO targets a 10% loss to follow up ratio, which means that 90% of positively screened cervical cancer cases will be treated or that 90% of cancers will be managed. Similar to other targets for cervical cancer elimination, this loss to follow up target is also optimistic. Treatment probability influences the progression of cancer, the ASIR and cancer deaths averted. Loss to follow up ratios in lower-middle income countries have varied estimates, with some researchers reporting between 41% - 69% loss to follow up[103]. This means that the probability of treatment could range from ~30% - 60%. Such estimates of treatment probability might even be considered optimistic, as they typically reflect results in urban populations (where access to care is easier and more readily available). In light of this, we simulated the impact of varying treatment probabilities on ASIR and cancer deaths. The simulations assumed the standard default HPVsim interventions of a bivalent vaccination campaign being provided to 90% of the eligible population (girls age 9 – 14) and that 70% of the eligible population (30 – 50-year-old women) were screened. Results for the simulations are presented in Figure 10 and tables 5 and 6 below.

[103] Habinshuti et al., "Factors Associated with Loss to Follow-up among Cervical Cancer Patients in Rwanda."

Figure 10: Impact on age standardized cervical cancer incidence rates (ASIR) when treatment probability is varied



HPVsim results for various levels of treatment probability (post positive screening results). In this simulation, the default interventions are maintained (i.e., vaccination rates at 90% for girls aged 9 – 14 and 70% of women aged 30 – 50 are screened). As treatment probability increases, the ASIR reduces. The reduction in ASIR appears to occur evenly as probability of treatment increases.

Table 5: Change in age standardized cervical cancer incidence rates (ASIR) over time as the probability of treatment is varied

	Reduction in Age standardized cervical cancer incidence (ASIR) due to treatment probability	
Treatment probability	Short term (between 2025 – 2040)	Longer term (between 2025 – 2060)
20%	-3%	-3%
40%	-7%	-6%
60%	-11%	-9%
80%	-12%	-11%
90%	-14%	-12%

As treatment probability increases, the reduction in ASIR also increases. The difference in ASIR reduction in the long and short term is likely due to vaccination effects being realized in the long term which reduces the overall HPV prevalence and contributes to overall reductions in ASIR levels.

Table 6: Cumulative cancer deaths averted based on varying estimates of treatment probability

	Cumulative cancer deaths averted	
Treatment probability	By 2040	By 2060
20%	735	11,145
40%	1,221	22,558
60%	1,634	34,066
80%	2,041	43,124
90%	2,512	51,029

We observe that increasing treatment probability from 20% - 90% results in a 9% reduction in ASIR in the long run and an estimated additional ~40,000 deaths averted between 2025 – 2060. We observe a much smaller decrease in cancer deaths in the short run vs the long run, reflective perhaps of the time it takes between cancer diagnosis and death.

Automatic Visual Evaluation (AVE) Sensitivity and Specificity

The use of high-performance screening tests is recommended as part of the WHO targets for cervical cancer elimination[104]. However high-performance tests such as HPV DNA tests are often unavailable in LMICs due to their high costs[105]. Researchers and businesses (such as those referenced in Table 1) have developed or are in the process of developing lower cost, alternative screening technologies.

In this section we share the results of simulating the impact of a new type of AI based screening tool (AVE), which is used alongside VIA. In many low resource settings, VIA is often recommended as an approach to cervical cancer screening, due to its lower cost and that it does not require access to pathology facilities. However, VIA relies heavily on the healthcare providers' ability to visually identify cancerous lesions. There is a large spectrum of healthcare provider ability and therefore a broad range of sensitivity, specificity, and accuracy of VIA. Therefore, researchers and innovators are turning to AI based models to minimize the variations in VIA interpretation. By leveraging large machine learning models and image recognition, results of VIA can be interpreted automatically through trained algorithms. A critical question however is what level of sensitivity and specificity is sufficient for such AI based technologies. In this section, we provide results for simulations that explore the impact (on ASIR) of varying levels of AVE sensitivity and specificity. The AVE products are undergoing testing, and teams are in the process of proving the repeatability and accuracy of the products. We wanted to understand the impact that improvements in sensitivity and specificity of AVE could have on ASIR. This would enable innovators to understand the impact of each improvement in sensitivity or specificity of the product.

For the simulation below, we utilized HPVsim default settings (i.e., vaccination rates are maintained at 90% of the eligible population, screening is performed on 70% of women aged 30 – 50, and the probability of treatment after being screened positive is 90%). The only factor varied in this simulation was the performance of the AVE screening tool; three different performance levels of AVE were simulated. AVE was then compared to alternative screening methodologies including VIA (without

[104] Word Health Organization, "Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem."
[105] Woo et al., "Accelerating Action on Cervical Screening in Lower- and Middle-Income Countries (LMICs) Post COVID-19 Era."

AVE support i.e., VIA dependent on healthcare provider visual diagnosis only) and HPV DNA testing (which is known for superior performance[106]).

Table 7: List of screening technologies simulated and their estimated performance (sensitivity and specificity)

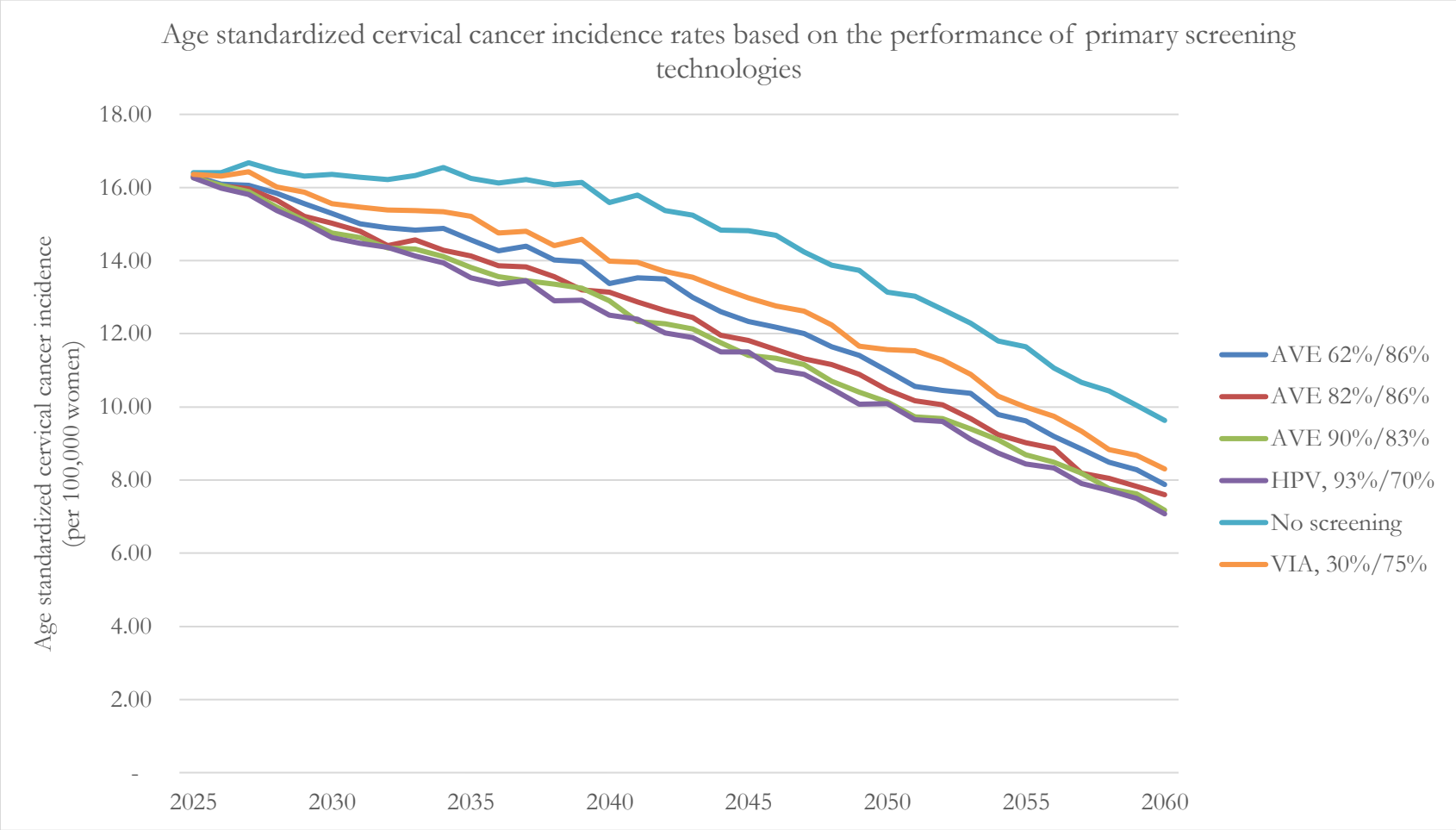
Screening technology	Sensitivity	Specificity
AVE (A)	62%	86%
AVE (B)	82%	86%
AVE (C)	90%	83%
VIA (human interpretation)	30%[107]	75%[108]
HPV test	93%[109]	70%[110]

The impact of AVE relative to alternative screening methodologies

As depicted in Figure 11, HPV DNA tests offer the greatest reduction in ASIR over time, followed by AVE then VIA. The reduction in ASIR shown in Figure 11 when no screening is performed is due to vaccinations (which are incorporated into the simulation by default). The impact however of screening only is isolated for further analysis in Table 8.

[106] Bruni et al., "Cervical Cancer Screening Programmes and Age-Specific Coverage Estimates for 202 Countries and Territories Worldwide."
[107] Stuart et al., "HPVsim."
[108] Stuart et al.
[109] Stuart et al.
[110] Stuart et al.

Figure 11: Impact on age standardized cervical cancer incidence rates (ASIR) at different levels of performance of AVE, compared to alternative screening technologies.



HPVsim results showing the impact on ASIR when various types of screening technologies are used as the primary screening method. In this simulation, the default interventions are maintained (i.e., vaccination rates at 90% for girls aged 9 – 14, 70% of women aged 30 – 50 are screened and 90% of women that are positively screened are treated). HPV DNA tests show the greatest reduction in ASIR, followed by AVE (with varying levels of reduction based on device sensitivity and specificity) and then VIA. Reductions in ASIR while no screening is performed are due to vaccination effects.

Table 8: Rate of reduction in ASIR between 2020 and 2060 for different screening methodologies / technologies

	Reduction in ASIR (due to screening)	
Screening technology (sensitivity / specificity)	Short term (between 2025 – 2040)	Long term (between 2025 – 2060)
No screening	0%	0%
VIA (30%/75%)	-9%	-8%
AVE (62%/86%)	-13%	-10%
AVE (82%/86%)	-14%	-12%
AVE (90%/83%)	-16%	-15%
HPV (93%/70%)	-18%	-15%

As sensitivity of the screening technology increases, ASIR reduces. The impact of AVE at high sensitivities is similar to that of HPV (which is the preferred methodology in developed markets). In the above scenario (that assumes 90% vaccination uptake and 90% probability of treatment for positively screened patients), the reduction in ASIR varies from 10% to 15% in the long-term depending on the sensitivity and specificity of AVE.

Through this simulation we observe that at high levels of sensitivity and specificity (90%/83%), AVE can have a similar impact on ASIR as HPV DNA testing. The reduction in ASIR between 2025 – 2060 is projected at 10% - 15%, for AVE at various levels of sensitivity and specificity. This reduction can be compared to the technologies in use today such as HPV tests and VIA. HPV tests show a potential reduction in ASIR of 15% and VIA shows a reduction of 8%. It seems AVE can have a similar impact (on ASIR) to the preferred testing technology (i.e., HPV DNA tests) and a 2%-7% greater impact than VIA. We note however that the performance of VIA is highly subjective and is dependent on a variety of factors including healthcare provider expertise, infrastructure of the healthcare facility, etc. In HPVsim the default performance for VIA is set at 30% sensitivity and 75% specificity, however it is possible that VIA may have higher sensitivity and specificity depending on the quality of healthcare provider and facility. Given the volatility in VIA performance however, it is difficult to determine an average sensitivity and specificity of VIA and by extension the benefit of AVE over VIA.

Table 9: Cumulative cancer deaths averted in the long and short term when using various screening technologies

	Cumulative cancer deaths averted due to screening	
Screening technology (sensitivity / specificity)	By 2040	By 2060
VIA (30%/75%)	1,451	29,905
AVE (62%/86%)	2,061	40,444
AVE (82%/86%)	2,512	51,029
AVE (90%/83%)	3,051	56,142
HPV (93%/70%)	3,218	60,623

The impact on cancer deaths was also simulated based on the type of equipment and the corresponding sensitivity and specificity. The cumulative cancer deaths averted in the long run (by 2060) range between ~40,000 to 56,000 as AVE performance improves from 62% / 86% to 90%/83%.

We find that if 70% of women aged 30 – 50 are screened and thereafter 90% of positive cases are treated, then AVE may provide a 10 – 15% reduction in ASIR by 2060 and avert between 40,000 to 56,000 deaths by 2060. We also observe that a 20% improvement in sensitivity (from 62% to 82%) results in a ~2% reduction in ASIR, whereas improvement in sensitivity of 8% at higher levels of specificity (from 82% -90%) results in a 3% improvement in ASIR. This suggests that the impact of sensitivity improvements on ASIR are greater at higher levels of sensitivity.

We summarize the potential impact of the use of AVE on ASIR and cancer deaths in the table below.

Table 10: Impact of various combinations of sensitivity and specificity of Automated Visual Evaluation (AVE) devices on age standardized cervical cancer incidence (ASIR) and cancer deaths from 2025 - 2060.

	AVE A	**AVE B**	**AVE C**
Sensitivity	62%	82%	90%
Specificity	86%	86%	83%
Impact to ASIR (2025 – 2060)	10% reduction	12% reduction	15% reduction
Impact to cancer deaths averted (2025 – 2060)	40,444 deaths averted	51,029 deaths averted	56,142 deaths averted

The impact to ASIR is greater at higher levels of sensitivity of AVE. Although cancer deaths reduce as sensitivity increases, the rate of reduction in cancer deaths appears to decrease as sensitivity goes up from 62% to 90%.

Section 4: Analysis and Implications

In the prior section, we provided results of various sensitivity analyses, where vaccination rates, screening uptake, treatment probability and AI device performance were varied. Within the section below, we summarize the impact on ASIR and cancer deaths of achieving WHO targets. In addition, we evaluate the relative importance of different components of a screening strategy through performing a regression analysis. And finally, we provide a high-level overview of the cost implications of vaccination and screening efforts.

The effect of achieving WHO targets

In the table below, we present the expected reduction in ASIR and cancer deaths if WHO targets are achieved. We assume the use of an AVE screening device as the primary screening technology (with sensitivity of 86% and specificity of 83%, which is indicative of the medium performance AVE). The combined WHO strategy for vaccinations and screening is projected to result in a 19% and 53% reduction in ASIR in by 2040 and 2060 respectively. In addition, achieving this strategy could potentially avert ~3600 deaths by 2040 and ~79,000 deaths by 2060.

In the short term, we observe that screening (and follow on treatment) has the most impact on ASIR as well as cancer deaths averted. 14% out of the projected 19% reduction in ASIR in the short term is attributable to screening (and treatment). Additionally, approximately 69% (2,512 out of the 3,661) cancer deaths averted are attributable to screening (and treatment).

In the long run vaccinations have the greatest effect on ASIR. By 2060, the model predicts a 53% reduction in ASIR, of which 41% of the reduction is attributable to vaccinations. In the longer term (by 2060), screening (and treatment) has the greatest effect on cancer deaths averted with ~64% of deaths averted being attributable to screening and treatment (51,000 out of the ~78,000). This provides a case for the importance of screening (and treatment) and emphasizes the immediate need for screening as the effect of vaccinations take time to be realized. The impact of screening and treatment is presented as a combined number as both strategies need to be implemented for their combined effect to be realized.

Table 11: Projected Impact on age standardized cervical cancer incidence (ASIR) and cancer deaths averted if all WHO targets are achieved.

Prevention strategy	**At WHO levels**	**Impact on ASIR by each year**			**Cumulative cancer deaths averted**	
		2025 – 2040	2025- 2060		2025 – 2040	2025- 2060
HPV vaccine	90%	-5%	-41%		1,149	28,783
Screening	70%	-14%	-12%		2,512	51,029
Treatment	90%					
Total impact of both strategies		-19%	-53%		3,661	79,812
Predicted ASIR at end of period (per 100,000 women)		13.1	7.6			

Results above assume AVE (with sensitivity of 86% and specificity of 83%) is used as the primary screening tool. Results show that screening (and treatment) have the greatest effect on ASIR and cancer deaths in the short term, while vaccinations have the greatest effect on ASIR in the long run.

In the aspirational scenario above, where the WHO targets are achieved (i.e., 90% of girls are vaccinated, 70% of eligible women are screened, 90% of women are treated and 90% of cancers are managed), the projected ASIR by 2060 is ~ 7.6 per 100,000 women. This can be compared to the ideal target for elimination of 4 per 100,000 women-years. Unfortunately, even with optimistic targets for vaccinations, screening and treatment, we predict that the elimination target may not be achieved by 2060. Therefore, there may be a need for additional interventions to speed up the process of elimination.

Optimal combinations of screening and treatment

Taking into consideration the possibility that WHO targets might not be achieved, and the paper's focus on screening tools, we investigate more realistic levels of screening uptake and treatment probability. Screening and treatment go hand in hand, in essence, screening is only effective when there is a follow up action of treatment, and therefore there is a need to maximize the probability of treatment in order for screening to be worthwhile and to influence cancer incidence rates.

In the table below, we show the impact on ASIR of various combinations of screening and treatment probability. We observe that when 20% of the eligible population (women aged 30 – 50) are screened, and 90% of positively screened women are treated, the impact on ASIR is a 4% reduction. At the same time, when 70% of the eligible population is screened and 30% of the positively screened population is treated, the impact on ASIR is also a 4% reduction. This example illustrates that even when screening uptake is increased significantly (from 20% - 70%), the corresponding impacts on ASIR can be the same depending on the probability of treatment. This highlights the importance of ensuring high treatment probabilities. Given the cost-intensive nature of screening, it's therefore worth noting that in certain instances it may be more impactful to improve follow up treatment probabilities rather than screening capabilities. However, we recognize that focusing solely on improving follow up / treatment probabilities within existing screening facilities only, can result in inequitable access to screening across populations.

Table 12: Impact on age standardized cervical cancer incidence rate (ASIR) of various combinations of screening uptake and treatment probability

Screening level	Treatment probability	Age standardized incidence rate (per 100,000 women)	Change in ASIR due to screening & treatment	Range in ASIR reduction achieved
20%	30%	9.43	-1%	1% - 4%
	60%	9.25	-2%	
	90%	8.90	-4%	
40%	30%	9.20	-3%	3% - 7%
	60%	8.92	-4%	
	90%	8.46	-7%	
60%	30%	9.08	-3%	3% - 10%
	60%	8.43	-7%	
	90%	7.89	-10%	
70%	30%	8.94	-4%	4% - 12%
	60%	8.07	-9%	
	90%	7.60	-12%	

The impact on ASIR of screening and treatment can range from 1% to 12% depending on the screening uptake and probability of treatment. Simulations above serve as an example to illustrate that the same impact on ASIR can be achieved at significantly different levels of screening deepening on the treatment probability achieved.

The relative influence of screening uptake, treatment probability and AVE performance on ASIR, estimated through linear regression.

In order to further understand the relationship and influence that screening uptake, treatment probability and AVE sensitivity and specificity have on ASIR, we performed an ordinary least squares (OLS) regression analysis. Data for the regression analysis is comprised of 100 data points (per year) which were generated using HPVsim. The data points are reflective of the predicted values of ASIR in 2040 and 2060, based on varying levels of screening probability, treatment probability and AVE sensitivity and specificity. See appendix 3 for full details of the combination inputs and the creation of the data set. We note that across all observations, a default vaccination campaign in which 90% of girls 9-14 are vaccinated was assumed.

Results of the regression analysis are shown below:

Table 13 :Results of linear regression, depicting the impact of screening probability, treatment probability, sensitivity, and specificity of AVE on age standardized cervical cancers incidence rate (ASIR) – Long term view (2060)

Regression Statistics	
R Square	0.892
Adjusted R Square	0.888
Standard Error	0.197
Observations	100

	Coefficients	Standard Error	t Stat	P-value
Intercept	10.09	1.45	6.95	0.00
Screen prob	-1.93	0.10	-18.82	0.00
Treatment prob	-1.54	0.08	-20.00	0.00
Sensitivity	-0.91	0.21	-4.33	0.00
Specificity	1.37	1.61	0.85	0.40

In 2060, (given default vaccination expectations that 90% of girls aged 9 – 14 are assumed to be vaccinated), a 1% increase in screening probability, treatment probability and sensitivity is expected to result in a 0.019, 0.015 and 0.01 reduction in ASIR respectively. All variables except for specificity are statistically significant, and high R squared is observed.

From the regression analysis, we observe and confirm the trends mentioned in Section 3. We find that screening probability, treatment probability and sensitivity are all significant variables in influencing ASIR (given their low p values <0.05). The increase in any of those variables results in a reduction in ASIR (as seen through their negative coefficients). From the results, we interpret that in 2060, (given a standard vaccination campaign impacting 90% of girls aged 9 - 14), increasing screening probability by 1% will reduce ASIR by 0.019, increasing treatment probability by 1% will reduce ASIR by 0.015 and increasing sensitivity by 1% will decrease ASIR by 0.09. As an illustrative example, if screening probability is increased from 11% (i.e., the current screening probability estimate in Nigeria[111]) to 70% (i.e., the WHO target), all else remaining equal, ASIR will reduce by ~1.13 per 100,000 individuals. Similarly, if treatment probability is increased from 30% to 90% (i.e., increased from predicted treatment probabilities in LMICs[112] to the WHO target), all else remaining equal, ASIR will reduce by 0.9 per 100,000 women. Additionally improving sensitivity from 62% to 92% (i.e., the lowest modeled sensitivity to the highest, and a 30% increase), all else remaining equal, ASIR will reduce by 0.27 per 100,000 women. It therefore appears that of most importance is improving screening probability followed by treatment probability and thereafter sensitivity of the screening device. Specificity of AVE does not appear to be significant, however this could be a result of modeling only small variations in specificity when generating the data points of ASIR (specificity was assumed between 83% - 86%). This was done as the potential levels of specificity anticipated fell within a smaller range. However, for further analysis and extension of this research, additional specificity levels could be included.

We also perform a regression analysis for datapoints that represent ASIR in 2040 (the short term). Results are shown below:

Table 14: Results of linear regression, depicting the impact of screening probability, treatment probability, sensitivity and specificity of AVE on age standardized cervical cancers incidence rate (ASIR) – Short term view (2040)

Regression Statistics	
R Square	0.904
Adjusted R Square	0.900
Standard Error	0.230
Observations	100

[111] Bruni et al., "Cervical Cancer Screening Programmes and Age-Specific Coverage Estimates for 202 Countries and Territories Worldwide."
[112] Habinshuti et al., "Factors Associated with Loss to Follow-up among Cervical Cancer Patients in Rwanda."

	Coefficients	Standard Error	t Stat	P-value
Intercept	16.751	1.695	9.880	0.000
screen prob	-2.449	0.120	-20.446	0.000
treatment prob	-1.900	0.090	-21.161	0.000
Sensitivity	-1.083	0.244	-4.430	0.000
Specificity	1.091	1.875	0.582	0.562

From the regression results above, we observe a similar relationship between all independent variables and the dependent variable (ASIR) as observed in the long run (2060) regression analysis. Screening probability, treatment probability and AVE sensitivity are all significant variables. The increase in any of those variables results in a reduction in ASIR (as seen through their negative coefficients). However, the magnitude of the impact of each independent variable is greater in the shorter time frame (i.e., in 2040 vs 2060). This reflects the importance of screening in the short term, perhaps due to the impacts of vaccinations taking time to be realized. From the results, we interpret that in 2040, (given a standard vaccination campaign impacting 90% of girls aged 9 - 14), increasing screening probability by 1% will reduce ASIR by 0.024, increasing treatment probability by 1% will reduce ASIR by 0.019 and increasing sensitivity by 1% will decrease ASIR by 0.0108.

This analysis helps us to understand the combined effect of all strategies and the relationship between all components of the screening strategy (screening, treatment and device accuracy) and ASIR. HPVsim utilizes a bottom-up, agent-based method of determining impact on health outcomes such as ASIR. However, the analysis above is helpful in understanding the magnitude and impact of each individual component of the screening strategy.

Cost implications of prevention strategies

Using HPVsim predictions (of the average number of individuals vaccinated, screened and treated between 2025 and 2060) and WHO cost estimates for cervical cancer prevention strategies in Nigeria[113], we estimate the potential cost of implementing a 90-70-90 prevention strategy. Combining results from table 11 and 15, we also estimate the cost per death averted by dividing the estimated cost per strategy by the deaths averted per prevention strategy.

From the estimated calculations, we observe that a 90-70-90 strategy could cost approximately $54m annually.

The cost estimates are based on the following assumptions:

- 90% of girls aged 9 – 14 being vaccinated at a cost of $1.8 per immunized girl[114]
- 70% of women aged 30-50 being screened at least twice per the 20-year period
- Screening is performed using AVE as the primary screening tool (with sensitivity and specificity of 82%/86% respectively). Since AVE is still in trials, the cost of AVE was not available, thus the cost of VIA (which must be performed alongside AVE) was used as a baseline, but we note that the actual cost of AVE will be higher due to costs of the product itself, consumables, maintenance etc.
- 90% of positively screened women obtaining treatment either through thermal ablation ($3.5 estimated cost) or LEEP ($107 estimated cost)[115]. The proportion of women treated with thermal ablation is estimated at 80%, and those treated with LEEP is estimated at 20% as per a study from Manga et.al[116].
- Screening is estimated to identify ~ 250,000 cases annually, of which 90% are assumed to be treated (i.e., treatment of ~230,000 cases annually) as per predictions from HPVsim
- Mortality rates if cancer is not treated is assumed at 100% within 8 years and if treatment occurs mortality rate is 7%[117].
- The estimated costs for vaccinations, screening and treatment are exclusive of program support activities costs, which we recognize are significant.

[113] 90% of girls vaccinated, 70% of women aged 30 – 50 screened and 90% of positively screened women treated / cancer managed.
[114] "Costing the National Strategic Plan on Prevention and Control of Cervical Cancer: Nigeria, 2017—2021."
[115] "Costing the National Strategic Plan on Prevention and Control of Cervical Cancer: Nigeria, 2017—2021."
[116] Manga et al., "Factors Associated with Treatment Uptake Among Women with Acetic Acid/Lugol's Iodine Positive Lesions of the Cervix in Cameroon."
[117] Stuart et al., "HPVsim."

Table 15: Estimated annual cost of a 90-70-90 cervical cancer prevention strategy in Nigeria

Prevention strategy	Estimated cost per strategy per person ($)[118]	Estimated no of individuals vaccinated / screened / treated annually[119]	Estimated annual cost per strategy	Cost per death averted
HPV vaccine	$1.80	3.5m	$6.4m	$7,825
Screening	$13	3.3m	$42.3m	$32,826
Treatment	$3.5 (thermal ablation) - $107 (LEEP)	0.23m	$5.6m	
Total cost			$54.3m	

The estimated cost of a 90-70-90 cervical cancer prevention strategy in Nigeria is approximately $54m annually. This estimate does not cover any program support activities costs and assumes that the cost of AVE will be at par with the cost of VIA. Therefore we expect the actual cost of such a strategy to be significantly higher. We also assume that the treatment cost is the weighted average cost of treatment through thermal ablation and LEEP based on estimated proportions for each type of treatment.

From the above analysis, we find that the estimated cost per death averted is much greater for screening and treatment rather than vaccinations. This is expected given the relatively higher unit cost of both treatment and screening relative to vaccinations. However, given the impact of vaccinations takes time to be realized, in the short term we will have to rely on screening in order to prevent cervical cancer. Screening costs per individual can be high and screening also requires additional infrastructure, program support, training, etc. which will further increase the cost of implementing such a prevention strategy. Therefore, any efforts to reduce the cost of screening, improve the speed of screening procedures and minimize burden on healthcare professionals and systems will be beneficial in the short run.

We note that the cost estimates used are understated and do not encompass the full suite of costs for prevention strategies. Further data collection, evaluation and updated cost estimates would be required to improve the accuracy of the estimate. A deeper dive into each of the costs was out of scope for this

[118] "Costing the National Strategic Plan on Prevention and Control of Cervical Cancer: Nigeria, 2017—2021."
[119] Annual estimates based on HPVsim simulations for a 35-year period (i.e., 2025 – 2060)

paper, however, this analysis was performed to directionally understand the cost implications of the 90-70-90 prevention strategy and to understand the cost implications of vaccinations vs screening and treatment. A further exploration of the cost per quality-adjusted-life-year saved would be a useful extension of this analysis in the future.

Section 5: Insights from Expert interviews

To supplement the simulations from HPVsim, interviews were conducted with subject matter experts in epidemiology, gynecology and the deployment of AI based screening tools for cervical cancer prevention. In the table below we summarize insights from these interviews. Insights have been categorized based on their relation to each of the prevention strategies discussed in previous sections.

Table 16: Summary of insights from primary research expert interviews

Prevention strategy	Summarized insights
Vaccinations	**The need for high vaccination rates** - Although herd immunity for many vaccines typically peaks when ~ 50 - 60% of the population is vaccinated, for HPV, the consequences of being unvaccinated are extreme for the patient (i.e., in the case where a woman gets cervical cancer). In addition, given cervical cancer can in many cases be prevented, we would rather focus on prevention than treatment. - A potential additional area of interest might be the impact and guidance for vaccinating mid-adult women due to uncertainties about HPV latency. **Vaccination implementation must be considered holistically and is influenced by a variety of factors outside of vaccine accessibility.** - HPV vaccination rates are significantly different across subsets of individuals, even in developed economies. HPV vaccination uptake is determined by social-cultural norms, awareness and advocacy efforts, availability of the vaccination, etc. These factors can differ greatly within a country, within an age demographic and within communities. In future analyses, the impact across different subsets of individuals could be incorporated into mathematical models such as HPVsim. - Vaccination rollouts require vaccine access as well as appropriate distribution channels. Some of the best-case examples of vaccination programs include combination programs with community health workers.
Screening Technologies: **Behavioral Insights**	**<u>Behavioral Insights:</u>** **Behavioral nuances across populations can influence screening technology receptiveness** - Behaviors and perceptions of patients and providers can vary across different settings (i.e., rural vs urban, public vs private settings). This variation can impact whether, how and at what speed the adoption and implementation of new technologies will take place. - Fear / stigma may impact some women's acceptance of screening. This potential aversion should be factored into our understanding an

	expectations of screening uptake. **Creative and community specific methods of screening & follow up implementation have been effective in increasing screening uptake** - Program ROSE[120] (Removing Obstacles to Cervical Screening) by Professor Yin Ling Woo incorporates HPV self-testing and an app for reporting is an example of one such method[121]. The project has been considered a success and recently won the Rachel Pearline Award (April 6, 2023). This is an example of a creative, community specific screening strategy. - Some studies have found that the incorporation of showers inside primary care facilities increased the receptiveness for women to get screened. The provision of a shower made women more comfortable and willing to be screened and treated. This is an example of a human centered design, focusing on user needs and creatively increasing uptake.
Screening Technologies: **Technological Insights**	**Technological insights:** **Although AI screening solutions are promising, equipment failure and device durability can cause disruptions in implementation** - Based on case studies of existing AI based screening technology, implementation has been hindered by equipment failure and device durability issues. Testing and validation in the country is a key part of the implementation process. There is also a need to identify alternative screening options to manage instances of equipment failure and disruption. **Device sterilization and disinfection can be a lengthy process and may limit uptake or device usage** - Based on case studies of existing AI screening technologies, the process of disinfection can require multiple steps and may add additional time to the patient workflow. This can limit overall screening proportions and willingness to utilize the screening device. Therefore, special design considerations should be made to account for the processes involved throughout the screening process with a new device. **New AI based screening tools can be cost prohibitive and maintenance pathways are unclear** - In countries such as Kenya, access to AI based screening tools has been made available. However, the cost of the equipment and the uncertainty around equipment maintenance and repair, limits the willingness of healthcare providers to adopt such technology.

[120] Woo et al., "The Implementation of a Primary HPV Self-Testing Cervical Screening Program in Malaysia through Program ROSE—Lessons Learnt and Moving Forward."
[121] Woo et al., "The Implementation of a Primary HPV Self-Testing Cervical Screening Program in Malaysia through Program ROSE—Lessons Learnt and Moving Forward."

	AI can be black box; therefore, providers may be hesitant in relying on outputs from such technologies - More needs to be done on 'AI explainability' to enable users and providers to trust AI based screening tools. - One concern from providers is the ability to detect errors in the machine learning algorithms or the ability to recognize when the diagnosis provided by AI may be incorrect. There is a fear of over-reliance on computer aided technologies and at times incorrect diagnosis. **Image quality can vary across healthcare facilities and patients, therefore impacting the accuracy of AI based devices.** - The exact location where an image of the cervix is captured has an effect on the image quality. For example, if the image is captured inside vs outside the vaginal canal, will affect the image quality. An image inside the vaginal canal is of higher quality. - The structure and physique of a woman may also impact the image quality. The vaginal wall can collapse in larger women, which causes limitations in image quality. - The way in which images are collected and the differences in image quality can have an impact on the reliability of the model. The impact of blur or out of focus images on an AI based technology's diagnosis is an area for further investigation. **AI based screening algorithms may not always be trained on the most representative or unbiased training data set.** - The data on which screening tools are trained are often based on images from women in the West, which is not representative of those in the markets that some of the AI based screening tools are being created for. Models and algorithms should be updated to encompass training data from the populations they intend to serve. **Data governance and privacy should be embedded within the implementation of AI based screening technologies.** - For AI based screening tools or digital cervicography tools, given that images are taken of a woman's cervix, key questions relating to data privacy, security of images and data must be addressed. Patient protection should be incorporated into the implementation plan of such technologies.
Screening Technologies: **Process / Systems Insights**	**<u>Process / Systems insights:</u>** **Implementation of new screening methods should consider the entire care cascade** - The screening process should not be assessed or influenced in isolation; instead, the consequences and impact along the entire care cascade should be evaluated. Integration across the EMR system, referral processes and

	treatment procedures are critical for successful implementation and uptake of novel screening technologies. **The quality and availability of existing infrastructure can impact screening adoption and implementation** - It is important to take into account factors such as access to reliable WIFI and electricity in the areas being served. The existing standard of infrastructure may have implications on device technology, user interfaces, EMR integration, etc. In certain regions, with limited resources and infrastructure, decisions on design must take into account the infrastructural capabilities of the context being served. **Maintaining the sustainability of donor led screening programs** - There are multiple NGOs that sponsor screening campaigns in LMICs. Although they may train the local healthcare providers, it's difficult for local providers to sustain the levels of care and rigor as the NGO or partner organization expects. This is due to limited resources, conflicting priorities, among other reasons. Ultimately this may leave screening programs unsustainable if not created and designed with local constraints in mind. **International support systems can influence the effectiveness of screening programs** - The uptake of AI based tools can be influenced by the level of international community participation in the country. For example, due to increased donor funding in Kenya, researchers have observed improved screening uptake percentages in Kenyan cities such as Kisumu relative to countries such as Peru where less donor funding and international support is received.
The use of mathematical simulation models	**Modeling helps to understand and bound a problem, as well as test certain assumptions. However, frequent iterations and updates to assumptions are required when using the model in different contexts.** - Models should be used as decision making aids, but with caution. - The creators of any model restrict the parameters of the model, and therefore, effectively control what explains the differences in outcomes generated by the model. - Simulation models should as much as possible be adapted to local contexts.

Section 6: Limitations

We identify some limitations of the paper which are described below.

First, the results and outcomes presented in the paper are based on simulations generated through HPVsim (version released in March 2023). HPVsim, like many mathematical models incorporates numerous parameters and assumptions. The model is still in development and is continuously being refined. This means that there could be changes in the model parameters or underlying assumptions which might impact or change the results and findings shared in the paper. The results of the simulations and the corresponding analyses are intended for discussion purposes and to understand the directional impacts of each prevention strategy. An area for future exploration could incorporate a comparison of results from HPVsim as well as other mathematical models that simulate HPV transmission and disease progression. This would provide multiple datapoints for potential predictions and expectations of health outcomes.

Secondly, our analysis does not incorporate differences in behavior, screening, vaccination and treatment uptake across different socio-economic or immunocompromised groups. For example, no distinctions or provisions have been made in this paper for individuals that are at higher risk, such as those with HIV. Although HPVsim incorporates capabilities to model individuals with HIV. HIV is a known risk factor for cervical cancer and the level of HIV prevalence within a society will influence the impact on health outcomes of various prevention strategies. However, modeling the impact of HIV was out of scope for this paper, but a critical area for further exploration.

In addition, we assume that only one type of screening method is in use (i.e., AVE alongside VIA). A more realistic scenario would incorporate a combination of devices or a triage system. One where the population screening strategy would incorporate a mix of screening methodologies. However, for the purposes of understanding and isolating the impact of AVE, we only modeled one type of screening method. We also note that the results and analysis within the paper often assume a default scenario where a vaccination campaign is in effect. Therefore, we do not quantify the impact of screening as a stand-alone strategy.

Finally, the paper focuses largely on the benefit of various prevention strategies rather than the cost (i.e., there is a focus on improved health outcomes rather than the cost effectiveness of each outcome). In this paper we provide a high-level directional understanding of costing for each strategy, on an

individual basis, however this is not comprehensive. The cost estimates used in this paper excluded programmatic costs which can influence the overall cost of a vaccination campaign or screening program. In addition, a cost per quality-adjusted-life-year saved would be a useful extension of this analysis in the future. We also do not model any additional benefits of minimizing HPV transmission such as reductions in other cancers that are caused by HPV (such as oropharyngeal cancers, anal, penile or vaginal cancers).

Section 7: Discussion

The results show that increasing screening, treatment and vaccination rates will lead to better outcomes (i.e., reduced age standardized cervical cancer incidence rates and a greater number of cancer deaths averted). However, even in the aspirational scenarios where the WHO targets are simulated, the modeled "Nigeria-like" country does not achieve the threshold required for cervical cancer elimination by 2060. In this section we synthesize key takeaways from the research and simulations as they pertain to cervical cancer prevention strategies and future analyses using mathematical models.

In the long run, vaccinations have a greater impact on ASIR than screening. However, screening impact is greater than vaccinations in the short run – therefore there is urgency to pursue screening initiatives and improvements as soon as possible.

In the long term, the simulations show that vaccinations can reduce age standardized cervical cancer incidence rates (ASIR) by 41% and that screening and treatment can reduce ASIR by ~12% if WHO targets are met (see Table 11). However, the impact and effect of HPV vaccinations takes time to be realized since it can be several years from the point at which a girl is vaccinated until she reaches sexual debut and may contract or spread HPV. Hence, in the short term, screening and treatment are more effective prevention strategies for cervical cancer. Specifically, to support those who have already passed the vaccination age group and are engaging in sexual activity. In the interim therefore, while public health officials ramp up vaccination coverage, screening and treatment serve as the main prevention strategies for cervical cancer. HPVsim simulations predict that screening and treatment in the short term can reduce ASIR by 14% if WHO targets are met.

On an individual level (per person level), the cost of vaccinations is significantly lower than the costs of screening and treatment.

The National Strategic Plan on Prevention and Control of Cervical Cancer estimates that the cost of vaccinating an individual in Nigeria is $1.8 and the cost of screening can range from $13 - $36 depending on the type of screening methodology[122]. This cost estimate however excludes program support activity costs. Vaccinations therefore are more cost effective, given their lower cost and greater reduction in ASIR as compared to screening and treatment. We note however, that a more

[122] "Costing the National Strategic Plan on Prevention and Control of Cervical Cancer: Nigeria, 2017—2021."

extensive assessment including program and support costs would be required to fully assess the cost implications.

Targeting a higher vaccination rate is beneficial, even though results suggest herd effects may be achieved after 30% of the targeted population is vaccinated.

HPVsim predictions indicate that there will be a diminishing but reducing effect on ASIR once 30% of the eligible population is vaccinated. However, we recognize that it is beneficial to set a vaccination target of greater than 30% of the eligible population. HPVsim doesn't account for differences in sub-groups or socio-economic clusters, it simply assumes a 30% vaccination coverage level across the entire set of agents modeled. In reality, this will be unlikely. A 30% vaccination coverage may be achieved but it may be disproportionately concentrated amongst certain sub-groups and clusters. Therefore, in order to achieve results simulated through HPVsim, a country would need to have a higher vaccination uptake in order to achieve a 30% average vaccination uptake among all sub-segments of the population. Therefore, we conclude that a 30% threshold of vaccination might be understated, and too low to achieve herd effects.

The importance of "screen and treat" strategies

Screening and treatment are both necessary to reduce the impact of cervical cancer on age-standardized incidence rates (ASIR) and cancer deaths. The two strategies work hand in hand, as the impact of one cannot be realized without the other. Once a positive screening result is obtained, it is important to maximize the probability of treatment. This is discussed in section 4, where we show it is possible that a similar reduction on ASIR can be achieved when the proportion of the population screened is small but follow up treatment probability is high, and when the proportion of the population screened is high but follow up treatment probability is low. Future work could explore strategies to increase the probability of treatment, such as combining screening and treatment technologies. Automated Visual Evaluation (AVE) technology, for example, could be combined with treatment technology to enable same-day screening and treatment, therefore maximizing the impact on ASIR and cancer deaths averted.

AVE (at high levels of sensitivity and specificity) can have similar impacts (on ASIR and cancer deaths) as HPV DNA tests.

At high levels of sensitivity and specificity AVE has the potential to yield similar reductions in ASIR to HPV DNA testing (which is the preferred screening methodology in developed markets). HPV DNA tests have historically been cost prohibitive and less readily available in LMICs. However, there are ongoing negotiations and advocacy for lower cost HPV DNA testing[123]. If lower cost HPV DNA tests become available, the relative cost effectiveness of VIA and AVE will need to be assessed further. It will be important to consider the viability of launching an AVE product if ultimately HPV DNA testing may replace traditional screening methods such as VIA. HPV DNA tests however pose a risk of overtreatment especially if used as the primary and only screening method[124].

The implementation of new AI based screening technologies requires a systems approach. Prevention strategies should be considered in the context of social and behavioral nuances of the country.

Utilizing a multi-stakeholder implementation strategy

Based on best practices of implementing AI based technologies in low resource settings, it is important to consider a systems approach with a multi-stakeholder perspective when implementing and launching new technology. An assessment of the impact to patients, providers, payers, governments, schools and community health workers will help determine the best approach for launching and sustaining new interventions and technologies.

Assessment of the entire care cascade

Another critical component of the technology launch is mapping out and integrating the technology into the existing care cascade. This will allow implementers to understand the ripple effects of the technology. In addition, understanding the cascade will help to identify weak points or opportunities that could influence screening uptake and follow up treatment. An analysis of the current screening

[123] "TogetHER Health: Rolling Out HPV Testing for Cervical Cancer Screening and Treatment: Experience from a Multi-Country Project."
[124] "Costing the National Strategic Plan on Prevention and Control of Cervical Cancer: Nigeria, 2017—2021."

workflow can also inform how the technology can be integrated into existing systems, EMRs and healthcare facility infrastructure. Ultimately easing the process of adoption and encouraging uptake.

Incorporating infrastructure variances and resource constraints into the design principles for AI based screening equipment.

Implementation of new technologies in low resource settings requires an understanding of the basic infrastructure (WIFI, electricity, sterilization capabilities, etc.) quality and standards in the context of operation. The infrastructure may ultimately impact the performance and accuracy of the technology. In addition, simple healthcare facility features such as lighting and availability of beds can have an impact on how the device is used and may influence the rational for additional product features (such as rechargeable batteries, integrated lighting or tripod connections). Therefore, accounting for infrastructure limitations and resource constraints within the design principles of the AI based screening tools can help to maximize uptake and usage.

Ethical considerations for AI based screening.

We reiterate the need to train AI based models on data that is as representative as possible of the communities and users of the equipment. This will ultimately improve the performance and output of the AI based screening technology. In addition, given images are being taken of a person's cervix, data privacy and protection is a critical consideration for any screening tool being introduced into the market.

The use of mathematical models in determining policies and business decisions.

Mathematical models are valuable decision-making aids, however, are constrained by the knowledge and assumptions built into the model. Therefore, it is important to validate assumptions and re-test models whenever they are applied to new contexts outside of their initial intended purpose.

Appendices

Appendix 1: HPVSim resources

The resources below are related to understanding HPVsim. HPVsim is an open-source simulator for exploring HPV.

HPVsim tutorial

HPVsim Manuscript and list of parameters[125]

[125] Stuart et al., "HPVsim."

Appendix 2 – Summary of a select HPVsim parameters

Country Calibration

Demographic information
Parameters: birth rates, death rates, migration
Information from World Bank data / UN World Population prospects

Sexual network
Parameters: Types of relationships and sexual behaviors, based on *relationship duration, propensity for concurrency, coital frequency, condom use, participation rates, age mixing*
Information from demographic health

Additional calibration parameters
Parameters: HPV prevalence over time, lifetime incidence of HPV, distribution of genotypes in detected cases

Simulations - each simulation models HPV transmission, immunity acquisition and disease progression

HPV transmission
The probability that a person infected with a particular HPV genotype, transmits HPV to another, is a function of

the per-act probability of transmission of a genotype, condom efficacy, condom use, and a person's immunity to infection against that particular genotype

B-cell mediated immunity
This is obtained if a person is vaccinated or clears an infection. A person's degree of protection against any HPV genotype is a function of:

a persons assigned level of immunity to a genotype they just cleared, and the cross immunity / protection obtained towards other genotypes.

Disease natural history
Progression from infection to invasive cervical cancer is modeled based on:

a) *duration of episomal infection which follows a log normal distribution where mean values vary based on genotype.*
b) *infection severity: Where severity grows over time according to a logistic function with a genotype specific inflection point of and a rate of growth*
c) *probability of episomal infection transforming*

Appendix 3 – Generating a dataset of predicted ASIR values

To create a database of ASIR values in 2040 and 2060, we used HPVsim to generate the predicted ASIR values for multiple combinations of screening probability, treatment probability and AVE accuracy (sensitivity and specificity). Each data point (predicted value of ASIR) was generated by applying a different combination of screening, treatment probability and AVE performance. In all instances we assumed the default vaccination uptake of 90% of 9–14-year-old girls.

Variable	Variable input options
Screening probability	20%, 40%, 60%, 70%
Performance of AI based screening tool	Sensitivity / Specificity 62%/86% 72% / 86% 82%/86% 90%/83% 92%/86%
Probability of treatment	20%, 40%, 60%, 80%, 90%

Variable combinations for each simulation / datapoint

Each datapoint is comprised of a unique combination of screening probability, treatment probability, sensitivity and specificity of AVE. We generated 100 datapoints per year (data was generated for 2040 and 2060). The unique combination included in each datapoint is defined in the table below.

As an example, datapoint1 represents a scenario where 20% of eligible women are screened, 90% of women are treated and screening was performed using AVE with sensitivity of 90% and specificity of 83%.

Simulation / datapoint	Screening probability	Treatment probability	Sensitivity	Specificity
1	0.2	0.9	0.9	0.83
2	0.2	0.8	0.9	0.83
3	0.2	0.6	0.9	0.83
4	0.2	0.4	0.9	0.83
5	0.2	0.2	0.9	0.83
6	0.4	0.9	0.9	0.83
7	0.4	0.8	0.9	0.83
8	0.4	0.6	0.9	0.83
9	0.4	0.4	0.9	0.83
10	0.4	0.2	0.9	0.83
11	0.6	0.9	0.9	0.83
12	0.6	0.8	0.9	0.83
13	0.6	0.6	0.9	0.83
14	0.6	0.4	0.9	0.83
15	0.6	0.2	0.9	0.83
16	0.7	0.9	0.9	0.83
17	0.7	0.8	0.9	0.83

18	0.7	0.6	0.9	0.83
19	0.7	0.4	0.9	0.83
20	0.7	0.2	0.9	0.83
21	0.2	0.9	0.82	0.86
22	0.2	0.8	0.82	0.86
23	0.2	0.6	0.82	0.86
24	0.2	0.4	0.82	0.86
25	0.2	0.2	0.82	0.86
26	0.4	0.9	0.82	0.86
27	0.4	0.8	0.82	0.86
28	0.4	0.6	0.82	0.86
29	0.4	0.4	0.82	0.86
30	0.4	0.2	0.82	0.86
31	0.6	0.9	0.82	0.86
32	0.6	0.8	0.82	0.86
33	0.6	0.6	0.82	0.86
34	0.6	0.4	0.82	0.86
35	0.6	0.2	0.82	0.86
36	0.7	0.9	0.82	0.86
37	0.7	0.8	0.82	0.86
38	0.7	0.6	0.82	0.86
39	0.7	0.4	0.82	0.86
40	0.7	0.2	0.82	0.86
41	0.2	0.9	0.62	0.86
42	0.2	0.8	0.62	0.86
43	0.2	0.6	0.62	0.86
44	0.2	0.4	0.62	0.86

45	0.2	0.2	0.62	0.86
46	0.4	0.9	0.62	0.86
47	0.4	0.8	0.62	0.86
48	0.4	0.6	0.62	0.86
49	0.4	0.4	0.62	0.86
50	0.4	0.2	0.62	0.86
51	0.6	0.9	0.62	0.86
52	0.6	0.8	0.62	0.86
53	0.6	0.6	0.62	0.86
54	0.6	0.4	0.62	0.86
55	0.6	0.2	0.62	0.86
56	0.7	0.9	0.62	0.86
57	0.7	0.8	0.62	0.86
58	0.7	0.6	0.62	0.86
59	0.7	0.4	0.62	0.86
60	0.7	0.2	0.62	0.86
61	0.2	0.9	0.72	0.83
62	0.2	0.8	0.72	0.83
63	0.2	0.6	0.72	0.83
64	0.2	0.4	0.72	0.83
65	0.2	0.2	0.72	0.83
66	0.4	0.9	0.72	0.83
67	0.4	0.8	0.72	0.83
68	0.4	0.6	0.72	0.83
69	0.4	0.4	0.72	0.83
70	0.4	0.2	0.72	0.83
71	0.6	0.9	0.72	0.83

72	0.6	0.8	0.72	0.83
73	0.6	0.6	0.72	0.83
74	0.6	0.4	0.72	0.83
75	0.6	0.2	0.72	0.83
76	0.7	0.9	0.72	0.83
77	0.7	0.8	0.72	0.83
78	0.7	0.6	0.72	0.83
79	0.7	0.4	0.72	0.83
80	0.7	0.2	0.72	0.83
81	0.2	0.9	0.92	0.83
82	0.2	0.8	0.92	0.83
83	0.2	0.6	0.92	0.83
84	0.2	0.4	0.92	0.83
85	0.2	0.2	0.92	0.83
86	0.4	0.9	0.92	0.83
87	0.4	0.8	0.92	0.83
88	0.4	0.6	0.92	0.83
89	0.4	0.4	0.92	0.83
90	0.4	0.2	0.92	0.83
91	0.6	0.9	0.92	0.83
92	0.6	0.8	0.92	0.83
93	0.6	0.6	0.92	0.83
94	0.6	0.4	0.92	0.83
95	0.6	0.2	0.92	0.83
96	0.7	0.9	0.92	0.83
97	0.7	0.8	0.92	0.83
98	0.7	0.6	0.92	0.83

99	0.7	0.4	0.92	0.83
100	0.7	0.2	0.92	0.83

Appendix 4 – List of expert interviewees

Interviews were conducted with various public health experts; their names and roles are listed below.

Interviewee	**Role**
Dr Meghan Huchko	Associate Professor Obstetrics & Gynecology, Global Health Director, Medical Scholars Program, Duke Global Health Institute, Director for the Center for Global Reproductive Health at Duke, Associate Chief – Division of Women's Community and Population Health
Emily Burger	Research Scientist, Center of Health Decision Scientists – Harvard
Libby Dotson	Duke Center of Global Women's Health Technologies
Erica Skerrett	PhD Student Duke Center for Women's Health Technologies
Dr Maina Board	Physician, Obstetrics and Gynecology Kenya

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