# Prevalence of high-risk HPV genotypes in sub-Saharan Africa based on Human immunodeficiency virus Status: A 20-year systematic review

**Running title:** Systematic review on HPV genotypes in sub-Saharan Africa

**Jude Ogechukwu Okoye,[1*] Chukwudi Amaechi Ofordile,[1] Oluwaseun Kelechi Adeleke,[2] Okechi Obioma[3]**

[1]Department of Medical Laboratory Science, Faculty of Health Sciences and Technology, Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Nigeria.
[2]Department of Medical Laboratory Science, Afe Babalola University, Ado Ekiti, Ekiti State, Nigeria.
[3]Department of Medical Laboratory Science, Abia State University, Uturu, Abia State, Nigeria.

***Corresponding author:** Jude Ogechukwu Okoye, Department of Medical Laboratory Science, Faculty of Health Sciences and Technology, Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Nigeria. Email: jog.okoye@unizik.edu.ng. Tel: +2347031119994. ORCID iD: https://orcid.org/0000-0002-7194-5592

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ORCID
JO: https://orcid.org/0000-0002-7194-5592
CAO: https://orcid.org/0000-0003-0664-9698
OKA: https://orcid.org/0000-0001-9514-1639
OO: https://orcid.org/0000-0002-3726-1824

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**Abstract**

This review assessed the rate of high-risk Human papillomavirus (HPV) infection among women living in sub-Saharan Africa. It also determined the prevalence of high-risk HPV (hrHPV) among human immunodeficiency virus seropositive (HIV+) and seronegative (HIV-) women in sub-Saharan Africa, pre- and post-year 2010. In this systematic review, Google Scholar, PubMed Central, and EMBASE databases were searched to identify cohort and case-controlled studies that investigated the relationship between HIV and HPV infections. Database searches yielded 17 studies published between 1999 and 2018. In the general population, the prevalence of any HPV/multiple HPV infection was higher among HIV+ (53.6%/22.6%) than among HIV- women (26.5%/7.3%) with OR' 3.22/3.71, 95% confidence interval: 3.00-3.42/2.39- 5.75, p< 0.001). The prevalent HPV genotypes among HIV+ and HIV- women diagnosed with invasive cervical cancer (ICC) were HPV-16/18 and 45. The prevalence of HPV 16, 18 and 45 was lower in 1999-2010 (3.8%, 1.7% and 0.8%) than in 2011-2018 (19.1%, 6.0%, and 3.6%, respectively). Among women diagnosed of ICC, HIV+ women had higher prevalence of HPV-56, 31 and 51 (7.3%, 5.3% and 3.3%) than HIV- women (1.3%, 2.2% and 0.4%, p< 0.001, p= 0.050 and 0.013, respectively). In conclusion, this paper reveals that the prevalence of HPV infection, multiple HPV infection and non-vaccine HPV types were higher among HIV+ women than in HIV- women in sub-Saharan Africa. Although HIV infection influences the distribution of HPV types, this study suggests that cervical cancer incidence in sub-Saharan Africa is majorly driven by the prevalence of vaccine hrHPVs, especially HPV 16 and 18.

**Keywords:** Incidence, Viruses, Vaccine, Cervix, Africa

**Introduction**

Globally, cervical cancer is the third most common and deadly cancer among women [1]. The incidence of cervical cancer varies by race and region. According to GLOBOCAN 2018 estimate, the mean age-standardized incidence rates (ASIR) for cervical cancers in sub-Saharan Africa and Northern Africa were 34.9 and 7.2, respectively [1,2]. This suggests that the ASIR of cervical cancer is higher in sub-Saharan Africa than in North Africa. Up to 2016, Jedy-Agba et al. reported an increased incidence of cervical cancer in sub-Saharan Africa [3]. The reason for the increasing incidence of cervical cancer in sub-Saharan Africa is still unknown. It could be related to the prevalence of human immunodeficiency virus (HIV) and human papillomavirus (HPV). In 2019, according to the United Nations for acquired immunodeficiency syndrome (UNAIDS), the population of people living with HIV in sub-Sahara Africa and Northern Africa was 12.9 million (3.9-23.0 million) and 240,000 (170,000-400,000), respectively [4]. Interestingly, the prevalence of people accessing Anti-retroviral therapy (ART) across sub-Sahara Africa ranges from 59.2% to 72.5% while that of Northern Africa was 38.3%. As of 2019, women and girls accounted for approximately 59% of those that were living with HIV in sub-Saharan Africa [4]. In sub-Saharan Africa, the prevalence of the people living with HIV aged 15-49 years increased by 18.2% between 2000 and 2017 [5]. The human immunodeficiency virus facilitates HPV acquisition and delays its clearance with concomitant increased risk of invasive cervical cancer (ICC) [6-9]. Belglaiaa et al. maintained that HIV status is a strong predictor of high-risk HPV (hrHPV; OR' 4.16) [10]. Not just been HIV seropositive (HIV+), women who are positive for HIV1/2 are 52% and 90% more like to be positive for hrHPVs than HIV-1+ and HIV-2+ women [11]. This suggests that the prevalence of HIV, especially HIV-1/2, may be responsible for the variation of ASIR for cervical cancer between the African sub-regions. Additionally, longer duration of HIV infection and higher viral load, and lower CD4 T-cell counts <200/mm3 have also been implicated in the higher acquisition of HPV infection [12,13]. Considering race, in the United States (US), the incidence of HIV+ women diagnosed with CIN3+ was higher in African-Americans than Caucasians, with a ratio of 5:1. Still in the US, the prevalent hrHPV among HIV+ African-American women diagnosed with cervical cancer were HPV16 (26.8%), 53 (20.5%), 35 (15.2%) and 52/58 (14.3%) [14]. There is a paucity of data on the relationship between the types of HPV observed in African-American women and African women.

The introduction of National HPV immunization programs in countries within sub-Saharan Africa started in 2011 [2]. As of 2019, only 17 countries out of the 46 countries (37.0%) in sub-Saharan Africa had established nationwide HPV immunization [15]. Studies show that the HPV vaccine coverage is higher in Northern Africa (35.6%) than in sub-Saharan Africa (1.2%) [15,16]. The difference in vaccine coverage between the two regions may account for the higher ASIR of cervical cancer in the latter than the former. The prevalence of HPV infection could serve as an alternative index for assessing the impact of HPV vaccine on the risk of developing cancer. Widely distributed HPV vaccines targeted at reducing cervical cancer include bivalent (HPV16/18) and quadrivalent (HPV6/11/16/18). The third vaccine, 9-valent vaccines (Gardasil 9; 6/11/16/18/31/33/45/52/58), is yet to be widely distributed in most African countries [17]. Sexually transmitted HPV genotypes are grouped into high risk type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and low risk type (HPV-6, 11, 26, 40, 73, and 82) based on epidemiologic association and potential risk of cervical cancer [18-21]. Of note, individuals infected with multiple hrHPV genotypes are more likely to develop large tumors and have a poor treatment response [22], owing to a high propensity of co-existing with other hrHPVs than lrHPVs [23]. The co-existence of the non-vaccine hrHPV reduces the efficacy of vaccines in preventing cervical cancer. According to Yar et al., the involvement of non-vaccine hrHPV in hrHPV co-infection among African women was higher for HPV35 (19.6%), followed by HPV53 (15.0%), HPV56 (7.5%), HPV59/66 (6.5%), and HPV82 (5.6%) [23]. Since the introduction of HPV vaccination into the national immunization program, to the best of

our knowledge, no study has assessed the prevalence of HPV types, especially among HIV+ and HIV- women, in sub-Saharan Africa between years ≤2010 and ≥2011, hence this review. This review suggests that the high prevalence of non-vaccine hrHPV and multiple HPV infection could be associated with the high ASIR of cervical cancer in sub-Saharan Africa.

**Methods**

This systematic review was carried out (up to September 16th, 2020) in accordance with Preferred Reporting item for Systematic reviews and Meta-analysis [24,25].

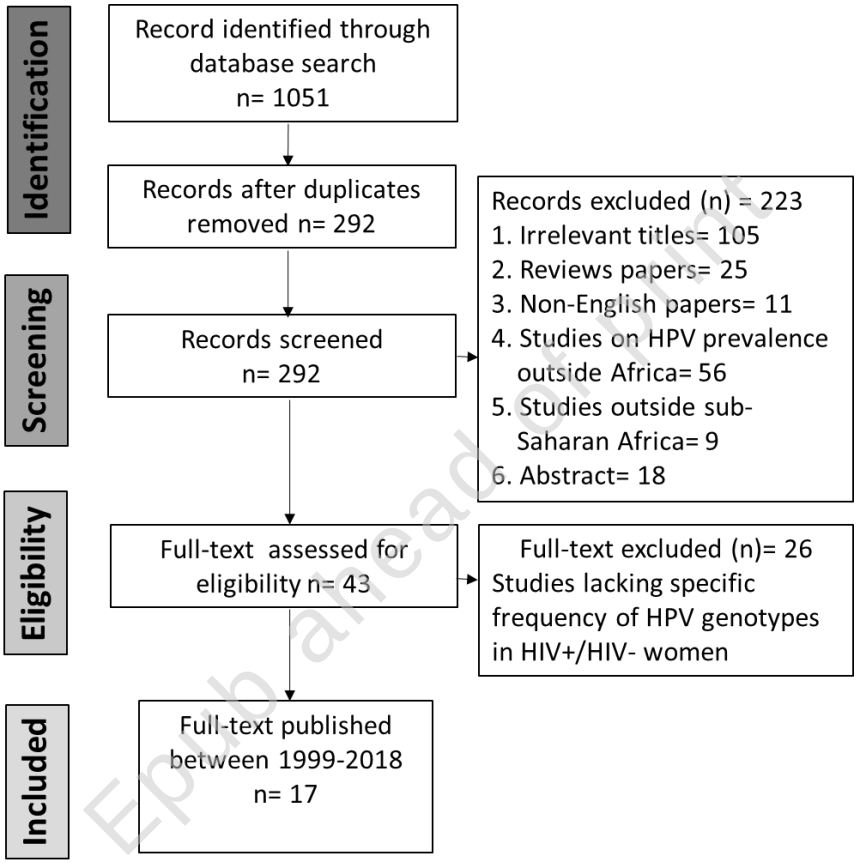




**Figure 1: PRISMA flow Diagram on prevalence of HPV among women living with and without HIV sub-Saharan Africa**

**Search strategy**

Studies that investigated the relationship between HIV status and HPV infection or acquisition was searched for in Google Scholar, Scopus, PubMed Central, and EMBASE databases and selected using the PRISMA guidelines (figure1). We screened the titles of cohort and case-controlled studies published between 1999 and 2018 using keywords and mesh terms: *('HPV' and 'human papillomavirus') AND ('HIV' and 'human immunodeficiency virus') AND ('ICC' and 'Invasive cervical cancer') AND ('prevalence' OR 'incidence' OR 'distribution' OR 'genotype'), AND ('sub-Saharan Africa')*. We also searched for unpublished studies (grey literature) by evaluating ClinicalTrials.gov (NIH), and International Clinical Trial Registry Platform (WHO).

**Study quality assessment and Study selection**

The included studies were assessed for quality using an adapted version of the NIH's 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [26]. Three authors assessed the risk of bias (as good, unclear or poor) in studies using the modified nonrandomized observational studies across five criteria: study population, imprecision, inconsistency, bias in study design, and disclosure of conflict of interest [27,28]. Exclusion criteria included: Articles not written in English, abstracts, non-full-length article, and articles without specific frequency of HPV types, articles not involving Africa and as well as articles not involving cervical cancer. Inclusion criteria included: Studies that tested for high-risk HPV DNA, studies with specific frequency of high-risk HPV infection, full-length articles involving sub-Saharan Africa.

Only studies that used polymerase chain reaction technique, which is the gold standard for HPV testing, were included in this study. Overall prevalence of an HPV type (for example HPV16) was dependent on the study size of studies that tested participants for the specific virus. For figure 2A and 2B, the study of Menon et al. [19] which was carried out between 2009 and 2015 was excluded because its data cut across the two timelines; ≤2010 and ≥2011. The study carried out by Diop et al. [35], Dols et al. [36] and Denny et al. [41] were excluded when the prevalence of multiple HPV infections were calculated due to lack of data. The mean age of HIV+ and HIV- women did not include data from Mpunga et al. [29], Mudini et al. [20], Marembo et al. [32], Maranga et al. [38] and Banura et al. [40] because they did not specify the mean age and age range of the two groups. The data presented in table 3 were only extracted from the studies carried out by Mpunga et al. [29], Mudini et al. [20] and Maranga et al. [38] due to the fact that their paper had the prevalence of HPV types for both HIV+ and HIV- women diagnosed with cancer.

**Table 1a: Findings of selected studies in sub-Saharan Africa based on HIV status**

| Author(s) | Location | Period of study | Mean age (age range) years | Study size | Multiple HPV (%) | Order of 6 most prev. HR-HPV types |
|---|---|---|---|---|---|---|
| **HIV Positive Studies** | | | | | | |
| Mpunga et al. [29]† | Rwanda | 2012-2018 | 54.3 (NA)[ap] | 99 | 7 (7.2) | 16, 35, 45, 31, 33, 52 |
| Yakub et al. [18] | Nigeria | 2016-2017 | NA (20-50) | 220 | 25 (11.4) | 35, 16, 45, 33, 18, 56 |
| Ndizeye et al. [30] | Burundi | 2013/2016 | 39.9 (NA) | 301 | 28 (9.3) | 16, 18, 51, 52, 58, 56/66 |
| Mudini et al. [20]† | Zimbabwe | 2014-2015 | NA (40-60)[ap] | 53 | 30 (56.6) | 16, 18, 56, 45, 33, 58 |
| Obiri et al. [31] | Ghana | 2017 | 43.8 (NA) | 160 | 77 (48.1) | 35, 52, 58, 16, 18, 68 |
| Marembo et al. [32] | Zimbabwe | 2015 | 39.8 (18-83)[ap] | 70 | 17 (24.3) | 52, 16, 18, 58, 51, 31/33/45 |
| Menon et al. [19]ǂ | Kenya | 2009-2015 | 28.0 (NA) | 74 | 48 (64.9) | 16, 53, 52, 56, 18/35/58, |
| Ezechi et al. [33] | Nigeria | 2014 | NA (NA) | 220 | 18 (8.2) | 16, 35, 31, 58, 52, 18/45 |
| Akarolo et al. [21] | Nigeria | 2012 | 36.6 (NA) | 149 | 21 (14.1) | 35, 56, 58, 59, 45, 33 |
| Kelly et al. [34] | S.A. | 2011-2012 | NA (20-50) | 594 | 147 (24.7) | 52, 51, 35, 16, 31, 39 |
| Kelly et al. [34] | Burkina Faso | 2011-2012 | NA (20-50) | 621 | 271 (43.6) | 52, 16, 35, 51, 18, 31 |
| Diop et al. [35]‡ | Senegal | 2010 | 36.0 (30-45) | 67 | NA | 52, 16, 68, 35, 45, 51 |
| Dols et al. [36] | Tanzania/S.A. | 2008-2010 | NA (NA) | 194 | NA | 52, 16, 51, 35, 58, 18 |
| Guthrie et al. [37] | Kenya | 2007-2009 | NA (18-50) | 283 | 122(43.1) | 52, 18, 16, 51, 35, 68 |
| Maranga et al. [38] | Kenya | 2008-2009 | 35.3 (21-50)[ap] | 113 | 22 (19.5) | 52, 56, 58, 53, 16, 35/39/66 |
| McDonald et al. [39] | S.A. | 1999-2006 | NA (26-38) | 1641 | 249(15.2) | 35, 16, 58, 18, 68, 45 |
| Banura et al. [40] | Uganda | 2002-2004 | NA (12-24)[ap] | 82 | 53 (64.6) | 52, 33, 16, 51, 68, 66 |
| Denny et al. [41] | S.A. | 2000-2003 | 29.3 (18-54) | 400 | NA | 16, 52, 53, 35, 18, 58 |
| **HIV Negative Studies** | | | | | | |
| Mpunga et al. [16]† | Rwanda | 2012-2018 | 54.3 (NA)[ap] | 501 | 21 (4.2) | 16, 18, 45, 33, 35, 52 |
| Ndizeye et al. [18] | Burundi | 2013/2016 | 36.4 (NA) | 299 | 9 (3.0) | 16, 18, 66, 45, 58, 53 |
| Mudini et al. [19]† | Zimbabwe | 2014-2015 | NA (40-60)[ap] | 54 | 25 (46.3) | 16, 13, 33, 35, 56, 45 |
| Obiri et al. [20] | Ghana | 2017 | 44.3 (NA) | 169 | 36 (21.3) | 35, 33, 58, 56, 52, 18/39/68 |
| Marembo et al. [21] | Zimbabwe | 2015 | 39.8 (18-83)[ap] | 66 | 10 (15.2) | 18, 16, 52, 31, 45/51/58 |
| Ezechi et al. [23] | Nigeria | 2014 | NA (NA) | 295 | 10 (3.4) | 18, 58, 16, 52, 31/35/51 |
| Akarolo et al. [24] | Nigeria | 2012 | 37.6 (NA) | 108 | 2 (1.9) | 52, 68, 18, 39, 45, 16/31/56/59 |
| Diop et al. [26]‡ | Senegal | 2010 | 34.0 (26-42) | 369 | NA | 52, 64, 16, 51, 35, 31/33 |
| Maranga et al. [29] | Kenya | 2008-2009 | 35.3 (21-50)[ap] | 111 | 15 (13.5) | 56, 16, 33, 35, 59, 51/52/82 |
| McDonald et al.[30] | South Africa | 1999-2006 | NA (33-45) | 8050 | 301(3.7) | 35, 16, 58, 45, 52, 18 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Banura et al. | [31] | Uganda | 2002-2004 | NA | (12-24)[ap] | 868 | 324(37.3) | 18, 52, 16, 51, 33, 68 |

Key: NA= Not available, HR= High risk, Prev.= prevalent, †= Cancer, ǂ = Female sex workers (FSW) with abnormal cytology, ‡= FSW, S.A.= South Africa

**Table 1b: Findings of selected studies in sub-Saharan Africa based on HIV status**

| Authors | | Countries | Study | Cases | hr-HPV | Multi-HPV | Order of 6 most prev. |
|---|---|---|---|---|---|---|---|
| **Cross-sectional studies (HIV+/HIV)** | | | **period** | **N** | **(%)** | **Prev. (%)** | **hr-HPV types** |
| Mpunga et al. | [16]† | Rwanda | 2012-2018 | 598 | 574 (96.0) | 28 (4.7) | 16, 18, 45, 33, 35, 52 |
| Mudini et al. | [19]† | Zimbabwe | 2014-2015 | 107 | 101 (94.4) | 55 (51.4) | 16, 18, 56, 33, 45, 35 |
| Banura et al. | [31] | Uganda | 2002-2004 | 950 | 707 (74.4) | 377 (39.7) | 52,16, 18, 51, 33, 56 |
| Diop et al. | [26]‡ | Senegal | 2010 | 436 | 316 (72.5) | NA | 52, 16, 68, 35, 51, 33 |
| Marembo et al. | [21] | Zimbabwe | 2015 | 136 | 70 (51.5) | 27 (19.9) | 18, 52, 16, 58, 51, 31 |
| Obiri et al. | [20] | Ghana | 2017 | 329 | 156 (47.4) | 113 (34.3) | 35, 58, 52, 18, 56, 16/56 |
| Maranga et al. | [29] | Kenya | 2008-2009 | 224 | 105 (46.9) | 37 (16.5) | 56, 52, 58, 16, 35, 33 |
| Akarolo et al. | [24] | Nigeria | 2012 | 257 | 64 (24.9) | 23 (8.9) | 82, 35, 56, 58, 45, 59 |
| Ndizeye et al. | [18] | Burundi | 2013/2016 | 600 | 142 (23.7) | 37 (6.2) | 16, 18, 58, 52, 51, 31 |
| Ezechi et al. | [23] | Nigeria | 2014 | 515 | 101 (19.6) | 28 (5.4) | 16, 35, 58, 31, 18, 52 |
| McDonald et al. | [30] | S. A. | 1999-2006 | 9691 | 1848 (19.1) | 550 (5.7) | 35, 16, 58, 45, 18, 52 |
| **Total** | [15,16,18-21,23,26,29,31] | Africa | 1999-2018 | 13843 | 4184 (30.2) | 1275 (9.5) | 16, 18, 35, 52, 45, 58 |
| **Cohort studies (HIV+ only)** | | | | | | | |
| Yakub et al. | [17] | Nigeria | 2016-2017 | 220 | 83 (37.7) | 25 (11.4) | 35, 16, 45, 33, 18, 56 |
| Menon et al. | [22]ǂ | Kenya | 2009-2015 | 74 | 52 (70.2) | 48 (64.9) | 16, 53, 52, 56, 18/35/58 |
| Kelly et al. | [25] | Burkina Faso | 2011-2012 | 621 | 491 (79.1) | 271 (43.6) | 52, 16, 35, 51, 18, 31 |
| Kelly et al. | [25] | S. Africa | 2011-2012 | 594 | 351 (59.1) | 147 (24.7) | 52, 51, 35, 16, 31, 39 |
| Dols et al. | [27] | Tanzania/S.A | 2008-2010 | 194 | 109 (56.2) | NA | 52, 16, 51, 35, 58, 18 |
| Guthrie et al. | [28] | Kenya | 2007-2009 | 283 | 176 (62.2) | 122 (43.1) | 52, 18, 16, 51, 35, 68 |
| Denny et al. | [32] | S. A. | 2000-2003 | 400 | 301 (75.3) | NA | 16, 52, 53, 35, 18, 58 |
| **Total** | [17, 22, 25, 27, 28, 32] | Africa | 2000-2017 | 2386 | 1563 (65.5) | 613 (34.2) | 52, 16, 35, 18, 51, 31 |

Key: NA= Not available, hr= High risk, HPV= Human papillomavirus, Prev.= prevalent, †= Cancer, ǂ = Female sex workers (FSW) with abnormal cytology, ‡= FSW, S.A.= South Africa



**Data extraction**

The vital information extracted for analysis included: participant characteristics such as sample size, cases of among HIV+ and HIV- women, prevalence of any HPV infection and multiple HPV infection, HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, and 82), mean age, recruitment method, period of data collection, and study location and region (according to WHO classification). We investigated the frequency of HPV infection in women living with HIV using HIV seronegative women as the comparison group. When calculating the prevalence of any HPV infection (women who tested positive for any HPV type), an individual may have acquired both HPV35 and HPV45 or more but it would only count as one event. The range of high-risk HPVs investigated in the selected studies varied, thus when calculating the prevalence of an HPV type, only studies or cases that investigated that particular HPV type were considered. To assess the impact of timelines on the prevalence of HPV infection, data points were categorized into pre-and during 2010 group, and post-2010 group.

**Table 1c: Findings of selected studies in Sub-Saharan Africa based on HIV status**

| Author(s) | Location | Summary/Inference |
|---|---|---|
| Mpunga et al. [29]† | Rwanda | There was minimal impact of HIV on HPV type distribution. |
| Yakub et al. [18] | Nigeria | HIV positive women with low CD4+T count are at a higher risk of cervical precancerous lesions. |
| Ndizeye et al. [30] | Burundi | There is a high burden of HR and pHR-HPV infections among women with HIV. Nonavalent vaccine covers most of the HR-HPV infections irrespective of residential area and HIV status. |
| Mudini et al. [20]† | Zimbabwe | HIV may influence distribution of some HPV genotypes given the significant increase in prevalence of HPV 18 among HIV+ women. The proportion with multiple genotypes is high and almost equal in both HIV+ and HIV- women. |
| Obiri et al. [31] | Ghana | HIV-1 infected women bear significant burden of HPV infection and related disease. The nonavalent HPV vaccine is likely the best means of cervical cancer prevention in Ghana. |
| Marembo et al.[32] | Zimbabwe | There is an increased risk of HR-HPV infection as well as multiple HR-HPV genotypes in HIV-positive women |
| Menon et al. [19]ǂ | Kenya | Co-infection with pHR/HR HPV genotypes was more strongly associated with abnormal cytology than any single hrHPV. There is high prevalence of multiple hrHPV genotypes in FSW, especially in HIV+ women. |
| Ezechi et al. [33] | Nigeria | HPV 16, 35, 58 and 31 were the most common hrHPV infections in the population and HIV positive women are at higher risk of acquiring HPV infection. Current HPV vaccines prevents genotype 16 and 18 which accounted for only a minority of hrHPV infection (21.7%) with no significant difference been HIV+ and HIV- women. |
| Akarolo et al. [21] | Nigeria | There is a high prevalence of non-16 and non-18 hrHPV among HIV+ women in Nigeria and other African countries. |
| Kelly et al. [34] | S.A. | HR-HPV infection and cervical lesions are very common among HIV+ women in |
| Kelly et al. [34] | Burkina Faso | Africa. Bi/quadrivalent vaccines could prevent up to 45% of treatable precursor lesions, the nonavalent vaccine could prevent up to 90% of cases in HIV+ women. |
| Diop et al. [35]‡ | Senegal | HPV-16 and -35 are the most prevalent HPV among HIV infected FSW. |
| Dols et al. [36] | Tanzania/S.A. | More than ⅓ (42%) of women with normal cytology tested positive for hrHPV. |
| Guthrie et al. [37] | Kenya | HrHPV prevalence was high in HIV+ women. Screening for hrHPV genotypes would identify a large majority of women who have a high-grade cervical lesion or more severe cytology. |
| Maranga et al. [38] | Kenya | HIV infection appears to alter the spectrum of HPV types found in both cervical smears and invasive cervical carcinomas. HPV infections were associated with a reduced level of immunity |
| McDonald et al.[39] | S.A. | HPV16 and 35 were the prevalent HPV types among HIV+ and HIV- women with or without cervical disease. |
| Banura et al. [40] | Uganda | There is an elevated prevalence of HPV infection in HIV+ and HIV- young women. |
| Denny et al. [41] | S.A. | There is a high level of hrHPV infection in HIV-1 infected women. |

Key: NA= Not available, Prev.= prevalence, †= Cancer, ǂ = Female sex workers (FSW) with abnormal cytology, ‡= FSW, S.A.= South Africa



### Statistical analysis

Odd ratios between HIV+ and HIV- women were also calculated in order to determine the risk of HPV acquisition and development of cervical cancer. Chi-square ($X^2$) analysis was used to calculate the difference in HPV infection between HIV+ and HIV- women in Africa (in GraphPad Prism, version 6.0), and significance was set at $p \leq 0.05$).

## Result

### Selected studies and sample size

Based on the inclusion criteria, there were eleven cross-sectional studies and six cohort studies. Overall, this review included 16237 participants (N) from 17 full-length articles (figure 1, table 1a). The number of HIV+ and HIV- women were 5,341 and 10,896, respectively. Southern Africa had the highest number

of participants (10285; n= 3 studies), followed by West Africa (3553; n= 9 studies), and East Africa (2399; n= 5 studies), and Southern Africa (10285; n= 3 studies). The mean age of HIV- women was insignificantly higher than that of HIV+ women (38.1 years vs 36.2 years, p= 0.590). The prevalence of HPV infection and multiple hr-HPV infection in the cohort studies (which involved HIV+ women only) were twice the prevalence in the cross-sectional studies (which included both HIV+ and HIV- women). No cohort study involving only HIV- women was identify during record identification. The three most prevalent HPV types in the cohort studies were HPV-52, 16, and 35, while that of the cross-sectional studies were HPV-16, 18, and 35 (table 1b). Table 1c shows the summary of the findings from each study.

**Table 2: Prevalence of high-risk HPV types in sub-Saharan Africa based on HIV status**

| Variables | Total Population | | HIV positive | | HIV negative | | % diff | OR' (95% CI) |
|---|---|---|---|---|---|---|---|---|
| HPV type | Cases N | HPV n (%) | Cases | HPV $n^1$ (%) | Cases | HPV $n^2$ (%) | $n^1$-$n^2$ | |
| **Any HPV** | 16237 | 5747 (35.4) | 5341 | 2865 (53.6) | 10896 | 2882 (26.5) | 27.1 | 3.22 (3.00- 3.42) |
| **Multiple** | 15001 | 1860 (12.4) | 4981 | 1128 (22.6) | 10020 | 732 (7.3) | 15.3 | 3.71 (2.39- 5.75) |
| **HPV-16** | 16237 | 1404 (8.6) | 5341 | 673 (12.6) | 10896 | 731 (6.7) | 5.9 | 2.00 (1.67- 2.39) |
| **HPV-18** | 16237 | 854 (5.2) | 5341 | 450 (8.4) | 10896 | 404 (3.7) | 4.7 | 2.39 (2.36- 2.41) |
| **HPV-31** | 16237 | 526 (3.2) | 5341 | 297 (5.6) | 10896 | 229 (2.1) | 3.5 | 2.74 (2.32- 3.25) |
| **HPV-33** | 16237 | 531 (3.3) | 5341 | 255 (4.8) | 10896 | 276 (2.5) | 2.3 | 1.93 (1.63- 2.29) |
| **HPV-35** | 16237 | 876 (5.4) | 5341 | 501 (9.4) | 10896 | 375 (3.4) | 6.0 | 2.90 (2.69- 3.10) |
| **HPV-39** | 16237 | 366 (2.3) | 5341 | 235 (4.4) | 10896 | 131 (1.2) | 3.2 | 3.78 (3.03- 4.71) |
| **HPV-45** | 16237 | 580 (3.6) | 5341 | 295 (5.5) | 10896 | 285 (2.6) | 2.9 | 2.19 (1.93- 2.46) |
| **HPV-51** | 16124 | 653 (4.0) | 5228 | 389 (7.4) | 10896 | 264 (2.4) | 5.0 | 3.23 (2.75- 3.78) |
| **HPV-52** | 16237 | 1018 (6.3) | 5341 | 644 (12.1) | 10896 | 374 (3.4) | 8.7 | 3.86 (3.60- 5.86) |
| **HPV-53** | 2528 | 174 (6.9) | 881 | 90 (10.2) | 1647 | 84 (5.1) | 5.1 | 2.12 (1.80- 2.48) |
| **HPV-56** | 16237 | 494 (3.0) | 5341 | 296 (5.5) | 10896 | 198 (1.8) | 3.7 | 3.17 (2.61- 3.82) |
| **HPV-58** | 16237 | 561 (3.5) | 5341 | 335 (6.3) | 10896 | 226 (2.1) | 4.2 | 3.16 (2.66- 3.76) |
| **HPV-59** | 16237 | 263 (1.6) | 5341 | 135 (2.5) | 10896 | 128 (1.2) | 1.3 | 2.18 (1.70- 2.80) |
| **HPV-66** | 2903 | 225 (7.8) | 1202 | 109 (9.1) | 1701 | 116 (6.8) | 2.3 | 1.26 (1.09- 1.45) |
| **HPV-68** | 16237 | 471 (2.9) | 5341 | 257 (4.8) | 10896 | 214 (2.0) | 2.8 | 2.52 (2.10- 3.00) |
| **HPV-82** | 1241 | 47 (3.8) | 707 | 40 (5.7) | 534 | 7 (1.3) | 4.4 | 4.51 (3.00- 6.82) |



**Prevalence of HPV and multiple HPV infection in the general population**

Here, the prevalence of HPV types and multiple HPV infections were higher in HIV+ women than HIV- women at p< 0.001 (table 2). In order of rank, the prevalent HPV types in the general population of sub-Saharan Africa were HPV- 16, 66, 53 and 52. The result also shows that HIV+ women in sub-Sahara Africa were approximately 3 and 4 times more likely to be HPV infected and acquire multiple HPV infection, respectively (table 2). Table 2 also shows that HIV+ women were approximately 2, 3, 4 and 5 times more likely to acquire HPV-16/18/33/45/53/59, HPV- 31/35/56/58/68, HPV-39/52 and HPV-82, respectively than their HIV- counterparts (table 2). It also shows that HIV+ women were 26% more likely to acquire HPV 66 than HIV- women.

**HPV infection and study timelines**

Between 1999-2010 and 2011-2018, result shows that the prevalence of HPV 16, 18 and 45 among HIV- and HIV+ women increased by 19.1% vs 3.8%, 6.0% vs 1.7% and 3.6% vs 0.8%, respectively (figure 2) while it also shows that the prevalence of HPV 53, 66, 59, 58, and 68 decreased by 12.6%, 6.7%, 2.4%, 2.2% and 1.7% among HIV+ women, respectively. Overall, the prevalence of HPV and multiple HPV infections increased in sub-Sahara Africa within the same study period (figure 2).

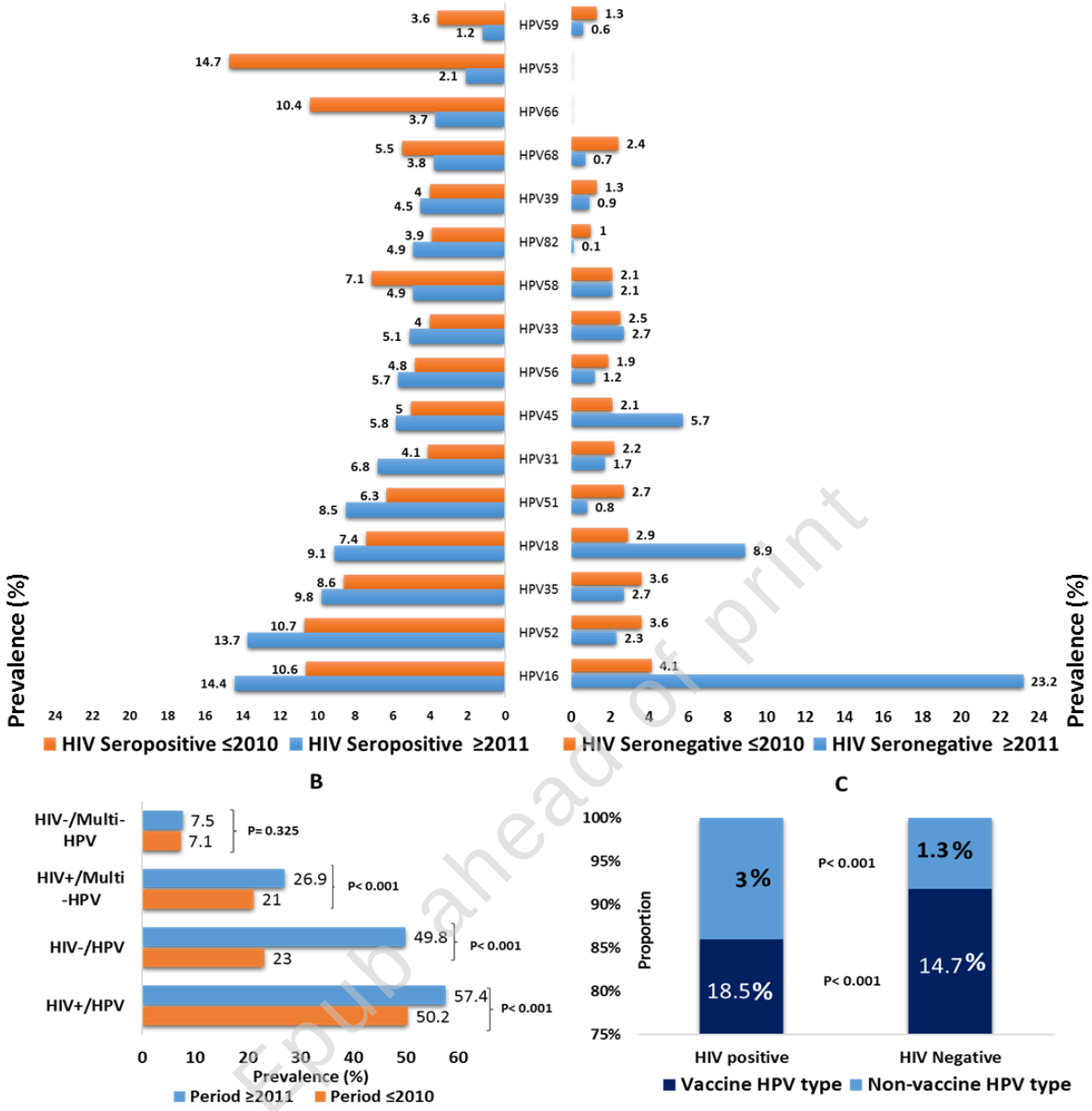




**Figure 2: prevalence of any HPV infection and multiple HPV infection, vaccine and non-vaccine HPV types in women living with and without HIV from 1999 to 2018 in sub-Saharan Africa (general population)**

Figure 2: In sub-Sahara Africa, the prevalence of HPV types among HIV- women in year ≤ 2010 was higher than in year ≥2011, except for HPV 16, 18 and 45 (figure 2A). It also shows that prevalence of HPV types among HIV+ women in year ≤ 2010 was lower than in year ≥2011, except for HPV 58, 68, 66, 53, and 59. Figure 2B: Based on timelines, higher prevalence of HPV infection was observed in ≥2011 than ≤2010 both in HIV+ and HIV- women. Considering the prevalence of HPV infection, the difference between ≥2011 and ≤2010 was higher among HIV- women than in HIV+ women (26.8% vs 7.2%). Among HIV- women, the prevalence of HPV infection doubled between 2010 and 2018 unlike HPV prevalence in HIV+ women that increased by 5.4% (figure 2B). More so, higher prevalence of multiple HPV infection was observed in year ≥2011 than in year ≤2010 both in HIV+ women ($p< 0.05$) and HIV- women ($p> 0.05$). Figure 2C shows higher prevalence of vaccine HPV types among HIV- women than

HIV+ women whereas higher prevalence of non-vaccine HPV types was observed among HIV+ women than HIV- women (p< 0.001).

**Table 3: Prevalence of high-risk HPV types in invasive cervical cancer patients based on HIV status**

| Variables | HIV positive | | HIV Negative | | % diff | Rank | OR' (95% CI) | $X^2$ |
|---|---|---|---|---|---|---|---|---|
| HPV type | Cases N | HPV $n^1$ (%) | Cases N | HPV $n^2$ (%) | ($n^1$-$n^2$) % | | | p-value |
| **Multiple** | 187 | 54 (28.9) | 595 | 78 (13.1) | 15.8 | | 2.69 (1.81-4.00) | **< 0.001** |
| HPV16 | 187 | 97 (51.9) | 595 | 346 (58.2) | -6.3 | 1 | 0.77 (0.56-1.08) | 0.150 |
| HPV18 | 187 | 46 (24.6) | 595 | 110 (18.5) | 6.1 | 2 | 1.43 (0.97-2.12) | 0.075 |
| HPV45 | 187 | 24 (12.8) | 595 | 75 (12.6) | 0.2 | 14 | 1.02 (0.62-1.67) | 0.900 |
| HPV56 | 150 | 11 (7.3) | 555 | 7 (1.3) | 6.0 | 3 | 6.18 (0.85-2.79) | **< 0.001** |
| HPV33 | 150 | 9 (6.0) | 555 | 31 (5.6) | 0.4 | 13 | 1.08 (0.51-2.32) | 0.843 |
| HPV31 | 150 | 8 (5.3) | 555 | 12 (2.2) | 3.1 | 4 | 2.55 (1.02-6.35) | **0.050** |
| HPV58 | 150 | 7 (4.7) | 555 | 9 (1.6) | 3.1 | 4 | 2.96 (1.08-8.08) | 0.060 |
| HPV66 | 53 | 2 (3.7) | 54 | 1 (1.9) | 1.8 | 7 | 2.08 (0.70-23.57) | 0.618 |
| HPV82 | 53 | 2 (3.7) | 54 | 1 (1.9) | 1.8 | 7 | 2.08 (0.70-23.57) | 0.618 |
| HPV51 | 150 | 5 (3.3) | 555 | 3 (0.4) | 2.9 | 6 | 6.34 (1.52-26.58) | **0.013** |
| HPV52 | 150 | 4 (2.7) | 555 | 14 (2.5) | 0.2 | 14 | 1.06 (0.34-3.29) | 1.000 |
| HPV68 | 97 | 2 (2.1) | 501 | 2 (0.4) | 1.7 | 9 | 5.25 (0.73-37.7) | 0.125 |
| HPV35 | 150 | 3 (2.0) | 555 | 22 (4.0) | 1.6 | 10 | 0.49 (0.15-1.67) | 0.325 |
| HPV39 | 150 | 3 (2.0) | 555 | 4 (0.7) | 1.3 | 11 | 2.81 (0.61-12.7) | 0.170 |
| HPV59 | 150 | 2 (1.3) | 555 | 3 (0.5) | 0.8 | 12 | 2.49 (0.41-15.0) | 0.289 |
| HPV53 | 37 | 0 (0.0) | 40 | 0 (0.0) | 0.0 | 16 | -- | -- |

Key: N= number of cases investigated (with adequate information on HPV positivity)



**Prevalence of multiple infection and HPV types among women with cervical cancer**

Among women diagnosed with invasive cervical cancer (ICC), the prevalence of multiple HPV infection was higher in HIV+ women than HIV- women (28.9% vs 13.1%, respectively; p< 0.001). In descending order of rank, the most prevalent hrHPV types among HIV+ and HIV- women diagnosed with ICC were HPV16 (51.9% vs 58.2%), HPV18 (24.6% vs 18.5%), and 45 (12.8% vs 12.6%, respectively). Significant differences between HIV+ and HIV- women diagnosed with ICC were only observed for the prevalence of HPV 56 (7.3% vs 1.3%), 31 (5.3% vs 2.2%), and 51(3.3% vs 0.4%, respectively) at p< 0.001, p= 0.050 and 0.013, respectively. Result shows that HIV+ women in sub-Sahara Africa who were positive for HPV 56/51 and HPV68 were 6 and 5 times more likely to develop cervical cancer than their HIV- counterparts (p <0.001/0.013 and 0.125, respectively). Figure 2 also shows that HIV+ women with multiple HPV infection, HPV 31/39/58 were approximately 3 times more likely to develop cervical cancer than HIV-negative women. It also shows that HIV+ women with HPV 16 and 35 were 23% and 51% less likely to develop cervical cancer than their HIV- counterparts (table 3). In table 3, the prevalence of all HPV types including multiple HPV types are higher among HIV+ women than among HIV- women, except HPV-16, and 35.

**Discussion**

This study assessed the prevalence of HPV types among HIV+ and HIV- women in regions of sub-Saharan Africa and between two timelines; ≤2010 and ≥2011. This study revealed that the prevalence of HPV and multiple HPV infection was higher among HIV+ women than in HIV- women living in sub-Saharan Africa. Between 2013 and 2016, this pattern of infection was also observed among HIV+ and

HIV- women in North Africa (65.7% vs 13.3% and 38.5% vs 7.6% respectively) [10,13]. The lower ASIR of cervical cancer in North Africa could be accrued to higher HPV vaccine coverage than in sub-Saharan Africa [16]. Conversely, the reason(s) for the differences between HIV+ and HIV- women are not well-understood. However, Hanisch et al. and Adebamawo et al. opined that HIV+ women initiate sex at a younger age, thus had a higher number of lifetime sexual partners which in turn increase their risk of acquisition and persistence of HPV infections than their HIV- counterparts [11,42]. As of 2016, the review carried out by Clifford et al. shows that HPV16 (46.6%), 18 (24.4%), and 45 (15.5%) were the prevalent HPV types in HIV+ women diagnosed with ICC in Africa [8]. Our findings go further show that HPV16, 18, and 45 were not only the prevalent HPV types among HIV+ women but also among HIV- women in sub-Saharan Africa. The prevalence of HPV-16 and 18 among HIV+ women in this review were higher than that of Clifford and his colleagues, possibly due to differences in study timelines and regions involved [11]. The differences observed between HIV+ and HIV- women suggest that the prevalence of HIV in a population increases the risk of acquiring HPV and multiple infections [20,35,38]. These factors in turn predict disproportionate ASIR of cervical cancer among HIV+ and HIV- women in sub-regions of Africa [19]. Additionally, in sub-Saharan Africa, the prevalence of HPV-16 and 35 infections was higher in HIV- women diagnosed with ICC than their HIV+ counterparts. The reason for this is unknown.

Studies show that HPV infected women, especially hrHPV types, are approximately 2 times at risk of acquiring HIV than HPV uninfected women [43.44]. A follow-up investigation carried out among HIV uninfected women shows that 28.4% of HPV infected women seroconverted after an average of 2.4years. The study revealed that women with multiple hrHPV infections were 4 times more likely to acquire HIV than those with single or no hrHPV infection [45]. The high risk of developing cervical cancer among HIV+ women and the risk of seroconversion among HIV- women due to the high prevalence of multiple HPV infection may account for the high ASIR of cervical cancer in sub-Saharan Africa [1]. According to Mccune et al., women with nonavalent vaccine types are 2.5 times more likely to acquire HIV than women with vaccine HPV types [46]. The high ASIR of cervical cancer in sub-Saharan Africa, when compared to North Africa, could be accrued to a higher prevalence of nonavalent hrHPV among HIV+ and HIV- women. Of note, the most prevalent HPV types among HIV+ women in North Africa were vaccine HPV types; HPV 58 (22.1%), 18 (7.8%), 16 (7.3%), 33 (6.0%) and 52 (3.7%) [10,13]. Conversely, in order of prevalence, the most prevalent HPV type(s) among people living with HIV in sub-Saharan Africa irrespective of cytology status were HPV-16, 52, 53, 35, and 66. This suggests that with the available vaccine, it could be easier to reduce or prevent cervical cancer attributable to HPV in North Africa than in sub-Sahara Africa. Taken together, HIV+ women in sub-Saharan Africa are at a higher risk of developing cervical cancer despite the available vaccine due to a higher prevalence of non-vaccine hrHPV types. Since women who are HPV 16 and 18 positive are 11-22 and 45-58 times capable of acquiring other hrHPVs, respectively [48] it could be argued that the lower prevalence of non-vaccine HPV types among HIV+ women in North Africa, when compared with their sub-Sahara African counterparts, was due to the low prevalence of HPV 16 and 18 (table 2).

This study revealed that the prevalence of HPV16, 18, and 45 increased from the timeline of ≤2010 to ≥2011 in both HIV+ and HIV- women. The increase could be due to increasing awareness of cervical cancer and uptake of screening services, better screening and testing techniques or protocols, or change in policy. Interestingly, the percentage difference in HPV infection between ≤2010 and ≥2011 was considerably higher in HIV- women. The reason for this is also unknown. Similarly, the changes in the prevalence of HPV16 between both timelines among HIV+ and HIV- women were significant ($p < 0.001$), but substantially higher among HIV- women than in HIV+ women (figure 1A). This agrees with the

findings of Dames et al. which shows lower HPV infection among women with CD4+ T-cell counts of ≥200 cell m/L [12]. On the other hand, increased sexual behaviour or activity and higher unprotected sex may be responsible for the marked increase in HPV prevalence among HIV- women in Sub-Saharan Africa. Low CD4+ T-cell counts, lower age, history of multiple sexual partners, a high number of unprotected sexual intercourse, especially among infected persons living with HIV [13,41] may also be responsible for multiple HPV infections among HIV+ women.

**Conclusion**

This paper reveals that the prevalence of HPV infection, multiple HPV infection and non-vaccine HPV types were higher among HIV+ women than in HIV- women in sub-Saharan Africa. This paper revealed that the prevalence of hrHPV, especially HPV 16 and 18, increased over the last decade irrespective of HIV status. Although HIV infection influences the distribution of HPV types, this study suggests that cervical cancer incidence in sub-Saharan Africa is majorly driven by the prevalence of vaccine hrHPVs, especially HPV 16 and 18.

**Limitation**

Based on searches on database, studies from Central Africa did not meet the inclusion criteria. Since Central Africa is a sub-region of Sub-Saharan Africa, the non-inclusion of studies from the sub-region constitutes a limitation in this study. More so, in this study, a meta-analysis was not carried out, hence there could be possibility of some publication bias or heterogeneity.



## Conflict of Interest

None.

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## Authors' contribution

Conceptualization: JOO. Data curation: JOO and OKA. Formal analysis JOO and CAO. Methodology: JOO, OKA and OO. Visualization: OO and CAO. Original draft JOO and OO. Writing-review and editing JOO, CAO, OKA and OO.

**ORCID ID:**

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