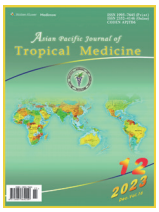

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Revisiting HPV infection pattern among urban Indonesian women in general population and its implication on health burden: A cross-sectional analysis from Indonesian Noncommunicable Disease Research 2016

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ABSTRACT

Objective: To identify circulating HPV types among urban Indonesian women and their specific co-infection patterns in bid to curb HPV infection in the general population and minimize its complications.

Methods: Urban Indonesian women from general population were selected as sample framework. Sample size and distribution across regions were determined by the Indonesian Bureau of Statistics (Badan Pusat Statistik, BPS), which represented the national level. Up to 35 408 cervical swab specimens were collected from August to September 2016 in 34 Indonesian provinces, categorized into six regions based on the development criteria set by the Ministry of National Development Planning (Badan Perencanaan Pembangunan Nasional, BAPPENAS). From all 1 874 samples identified as HPV-positive, hybrid capture was implemented to evaluate type-specific HPV. This study analyzed descriptive data to determine the core-cluster of HPV combination. Co-occurrence HPV network was assessed using 'qgraph' package version 1.6.3 and computed in R version 3.6.3. Two-HPV association was analyzed in logistic regression using bias-reduction generalized linear model (brglm2) package version 0.5.1 adjusted by age and six main Indonesian regions.

Results: The logistic regression analysis demonstrated that HPV type 52 had rare relationship despite its common co-occurrence, cementing its role in single HPV infection. HPV type 16 and 18 tended to form infection cluster and were strongly associated with other types.

Conclusions: HPV type 52 was the most frequent HPV type among urban Indonesian women and accounted for most single infection cases. Concurrently, HPV 16 and HPV 18 accounted for most multiple infection cases and had strong tendency to attract other types, which may add further complications. However, due to lack of cytology and histological examination and information for other potential determinants, further in-depth studies are necessary to confirm whether these infection patterns truly connect to certain clinical outcomes.

KEYWORDS: Human papilloma virus; HPV; Infection pattern; Urban women; Indonesia

Significance

Many studies have reported the proportion of single and multiple HPV infections, yet the information on a nationwide scale regarding the pattern of certain HPV types and their tendency to attract others in co-infection is still limited. This study provides an insight on circulating HPV types among urban Indonesian women and their two-way relationship with other types.

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1. Introduction

Cervical cancer remains a significant global health burden and is one of the leading causes of cancer-associated death. The majority of cases are attributed to HPV infection, particularly high-risk types, such as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68[1,2]. A nationwide study conducted by Indonesian Ministry of Health revealed that 5.2% of Indonesian urban women tested positive for HPV, primarily due to high-risk types such as HPV 16, 18 and 45[3]. Unfortunately, only a small number of these women had access to recommended doses of HPV vaccines.

While some HPV types may solely contribute to cervical infection, others may interact with each other to develop clinical symptoms, with precancerous lesion being the most concerned[4,5]. Several laboratory-based epidemiological studies have reported the patterns of HPV co-infection and their interaction as well as specific patterns of circulating HPV types documented in countries where these studies were conducted[6–9]. Since vaccination remains the most effective means of protection against HPV infection, it is important to gain insight into the circulating HPV types as well as their infection patterns (single or multiple HPV type infection) and whether they correspond to the HPV types commonly involved in the cervical cancer pathology[10].

The available HPV vaccine in Southeast Asia typically covers HPV type 6, 11, 16 and 18, but they are often unaffordable for those coming from low to middle socioeconomic class. The implementation of HPV vaccination program is still relatively new and limited in distribution, notably in developing countries[11]. Therefore, this study aims to provide information about HPV infection patterns and their implications on national health burden. In the long term, it is hoped that this effort will help control HPV prevalence and its potential complications.

2. Subjects and methods

2.1. Study design and sampling

This study was a laboratory-based cross-sectional analysis and a continuation of the Indonesian non-communicable disease research on breast tumors and cervical precancerous lesion in 2016. Specimen collection was done from August to September 2016 among urban Indonesian women aged 25-64. Indonesian provinces were categorized to 6 main regions (Figure 1) according to Badan Perencanaan Pembangunan Nasional or National Development Planning Agency (BAPPENAS) criteria based on the health development progress in each respective area: region 1: Sumatera; region 2: Java; region 3: Bali and Nusa Tenggara; region 4: Borneo (Kalimantan); region 5: Sulawesi; and region 6: Moluccas (Maluku) and Papuan island. Due to limited lab analysts with the ability to perform cytology and histology examination and the feasibility of conducting surveys in the field, visual inspection with 5% acetic acid (VIA) was chosen to screen for any sign of precancerous or cancerous lesions. The investigators were not allowed to track down participants with precancerous or cancerous signs due to ethical and personal considerations, therefore, data for these cases could not be presented. However, we were informed that up to 6 women showed precancerous signs and all of them resided in the region 6. Identification of HPV positive cases lasted from October 2016 to April 2017. Further genotyping analysis from June 2018 to March 2019 utilized specimens stored in Biorepository of National Institute of Health Research and Development (NIHRD), Ministry of Health Indonesia. All examinations took place at the Laboratory of Infectious Disease of Center for Research and Development of Biomedical and Basic Health Technology, Jakarta.

2.2. Specimen testing for HPV type

A subsample of up to 1 874 cervical swabs, all identified as

Figure 1. The map of Indonesia categorized to six development regions based on the health development progress (recreated through: https:// maps. com/ carte. php?num car+15295&lang=en).

Table 1. Characteristics of HPV single infection and co-infection among urban Indonesian women.

Parameters	∑ HPV infection		∑ involving high-risk type		Mean age among *n*1
	*n*1	Relative to total sample (%)	*n*2	Row of *n*2 relative to *n*1(%)	(years)
Total single HPV type	1234	65.85	936	75.85	41.0±9.1
Region 1	238	12.70	192	80.67	
Region 2	460	24.55	355	77.17	
Region 3	144	7.68	109	75.69	
Region 4	113	6.03	74	65.49	
Region 5	143	7.63	100	69.93	
Region 6	136	7.26	106	77.94	
Total combi-HPV type	640*	34.15	607	94.84	41.6±8.7
Region 1	129	6.88	120	93.02	
Region 2	196	10.46	183	93.37	
Region 3	74	3.95	71	95.95	
Region 4	82	4.38	81	98.78	
Region 5	92	4.91	85	92.39	
Region 6	67	3.58	67	100.00	
*Combi-HPV type details					
2 HPV types	457	24.39	428	93.65	
3 HPV types	148	7.90	144	97.30	
4 HPV types	32	1.71	32	100.00	
5 HPV types	3	0.16	3	100.00	

Number of total sample is 1874. *Denotes number of women with multiple HPV infection (≥1 HPV type), broken down by Indonesian development regions and number of concurrent HPV types. Notes: region 1: Sumatera; region 2: Java; region 3: Bali and Nusa Tenggara; region 4: Borneo (Kalimantan); region 5: Sulawesi; and region 6: Moluccas (Maluku) and Papuan island.

HPV-positive, was selected and tested for HPV specific type. The cervical swab had been stored in liquid media (®Liqui-PREP) and were divided into several aliquots prior to examination. HPV type identification was carried out using Hybrid Capture technique (®Qiagen & ®DiagCor) following the kit instructions. This method is based on the principle of viral DNA denaturation and the complementary chain of DNA and probe RNA hybridization, resulting in a complex DNA-RNA hybrid. The quantitative result was interpreted qualitatively using cut-off points determined by the standard, the positive control (marked by the formation of HPV DNA-RNA hybrid complex), and the negative. In case of ambiguous observation, an independent lab analyst would carry out the third repetition of test and the voting determined the final decision.

2.3. Data management and analysis

Data entry was performed using Microsoft Excel 2016. Descriptive analysis included the proportion of HPV single and combo infections as well as their core-clustering pattern. Core cluster was determined if minimum 2 different HPV types existed and their co-infection pattern was observed more than once. A matrix between two corresponding HPV types in Excel was created prior to co-occurrence network analysis using 'qgraph' package version 1.6.3, which was generated by Sacha Epskamp (main author), Giulio Costantini, Jonas Haslbeck, Adela Isvoranu, Angelique O. J. Cramer, Lourens J. Waldorp, Verena D. Schmittmann and Denny Borsboom in University of Amsterdam, Netherlands. This step runs in R environment version 3.6.3 created by Ross Ihaka and Robert Gentleman in University of Auckland, New Zealand. Bias-reduction logistic regression to evaluate association between two HPV types, adjusted by Indonesian age and regions concluded the analysis with the help of 'brglm2' package version 0.5.1 developed by Ioannis Kosmidis (main author), Euloge Clovis Kenne Pagui, Kjell Konis, and Nicola Sartori at University of Warwick, United Kingdom. The six main Indonesian regions proposed by BAPPENAS and BPS were included as the potential confounder since they might contribute to various development progress including in health sector. Each HPV type acts as dependent variable and the remaining HPV types as predictors alternately, but interaction effect among HPV types was not included in the analysis to minimize complexity of the full logistic regression model. Association between two HPV types presented as adjusted odds ratio (OR_{adj}) in form of exponent estimates along with their 95% confidence interval. Forest plot for the top 10 strongest and weakest 2-way HPV type associations was created using Microsoft Excel 2016. Due to the model's complexity, the threshold of statistical significance for logistic regression was determined at P value <0.001.

3. Results

From 1874 subjects examined based on selection criteria, most HPV infections, high-risk HPV types played an important role either in single or multiple cases. The proportion of HPV infection among 6 Indonesian regions was relatively similar. Multiple HPV type cases accounted for around one third of total HPV infections and as

Table 2. Top 10 strongest two-HPV type associations as evaluated with bias-reduction logistic regression.

Predictor (HPV type)	Dependent variable (HPV type outside predictor)	Lower 95% *CI* OR_{adj}	Upper 95% *CI* OR_{adj}	OR_{adj}	Association
16 (HR)	45 (HR)	1.4207	2.9862	2.0598	16.45 (HR-HR)
18 (HR)	45 (HR)	1.4035	3.0076	2.0545	18.45 (HR-HR)
45 (HR)	18 (HR)	1.3912	2.9913	2.0400	45.18 (HR-HR)
45 (HR)	16 (HR)	1.3476	2.8442	1.9578	45.16 (HR-HR)
51 (HR)	16 (HR)	0.2403	0.6722	0.4019	51.16 (HR-HR)
56 (HR)	16 (HR)	0.1932	0.5163	0.3158	56.16 (HR-HR)
16 (HR)	51 (HR)	0.1528	0.4671	0.2672	16.51 (HR-HR)
39 (HR)	18 (HR)	0.1368	0.5116	0.2646	39.18 (HR-HR)
42 (LR)	18 (HR)	0.1285	0.5155	0.2574	42.18 (LR-HR)
42 (LR)	43/44 (LR)	0.1427	0.4636	0.2572	42.43/44 (LR-LR)

HR=high-risk HPV. LR=low-risk HPV. Negative results of hybrid capture for each predictor serve as reference groups respectively. In the uppermost row, for example, negative HPV 16 as the reference and positive HPV 16 as a predictor for its association with HPV 45.

Table 3. Top 10 weakest two-HPV type associations as evaluated with bias-reduction logistic regression.

Predictor (HPV type)	Dependent variable (HPV type outside predictor)	Lower 95% *CI* OR_{adj}	Upper 95% *CI* OR_{adj}	OR_{adj}	Association
58 (HR)	84/26 (M)	0.000 0	0.049 8	0.000 8	58.84/26 (HR-M)
59 (HR)	11 (LR)	0.000 0	0.038 6	0.000 6	59.11 (HR-LR)
39 (HR)	11 (LR)	0.000 0	0.034 1	0.000 6	39.11 (HR-LR)
51 (HR)	11 (LR)	0.000 0	0.027 9	0.000 5	51.11 (HR-LR)
52 (HR)	53 (HR)	0.000 0	0.035 8	0.000 4	52.53 (HR-HR)
52 (HR)	84/26 (M)	0.000 0	0.028 0	0.000 4	52.84/26 (HR-M)
16 (HR)	11 (LR)	0.000 0	0.023 8	0.000 4	16.11 (HR-LR)
56 (HR)	11 (LR)	0.000 0	0.019 9	0.000 3	56.11 (HR-LR)
58 (HR)	11 (LR)	0.000 0	0.015 8	0.000 3	58.11 (HR-LR)
43/44 (LR)	11 (LR)	0.000 0	0.012 7	0.000 2	43/44.11 (LR-LR)

HR=high-risk HPV; LR=low-risk HPV; M=mixed type HPV. Negative results of hybrid capture for each predictor serve as reference groups respectively. In the most bottom row, for example, negative HPV 43/44 as the reference and positive HPV 43/44 as a predictor for its association with HPV 11.

this combination added from 2 types to 5-types, the proportion of high-risk types involved also increased (Table 1).

The core cluster pattern of HPV types was predominated by high-risk ones, notably HPV 16 and 18 being the most frequent combo, followed by a set of HPV 16-HPV 45 core and HPV 16-HPV 52 cluster in the third position (Supplementary Table 1).

Figure 2 visualizes network analysis for the co-occurrence pattern of HPV types as well as their degree of interaction as determined by the thickness of edge line in which the dominant network revolves around HPV type 16, 18, 45 and 52.

On the other hand, analysis of bias-reduction logistic regression by using R package brglm2 found up to 209 significant 2-way HPV associations (Supplementary Table 2). For simplicity, one can see the top 10 strongest and 10 weakest associations in Table 2 and Table 3, respectively. Similar with previous results, high-risk HPV types 16, 18 and 45 took the center stage when it comes to the strongest positive interactions. The weakest relationships belonged to heterogeneous HPV types containing low-risk and mixed ones.

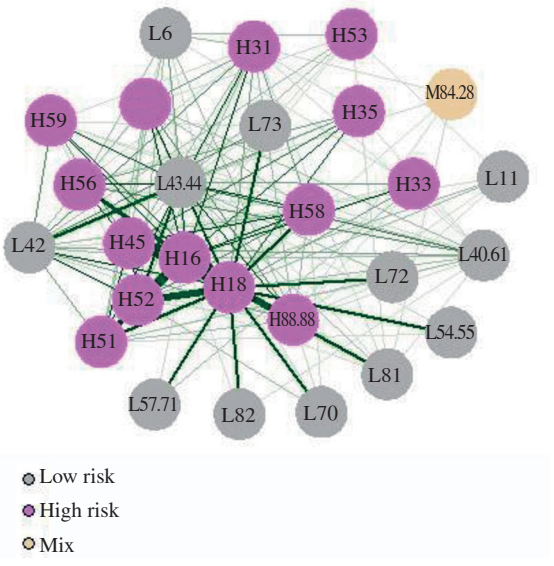

Figure 2. Co-occurrence network of HPV infections, analyzed by qgraph.

4. Discussion

This study was a continuation of the nationwide Noncommunicable Disease Research conducted by Ministry of Health among urban Indonesian women in 2016. Among this population, 5.2% tested positive for HPV and underwent further viral genotyping analysis. Our results revealed that around one third of HPV-positive individuals had multiple HPV infection, the overall proportion varies compared to studies in other countries, with Asian population tends to have lower percentage[4,12–14]. The combo HPV types tended to involve high-risk types in most cases, which is consistent with previous studies[12,14,15]. Therefore, mapping notable high-risk type and their interactions can help us determine their behavior in nature, particularly among general population. Meanwhile, the proportion of single and combo infections was concentrated in Java region (region 2), which is not surprising since its status as the most densely populated area in Indonesian[16].

Several studies have demonstrated certain HPV core clusters and their association with clinical manifestations. However, when it comes to cancer pathological process which manifests as precancerous or cancerous lesion, our findings regarding the association of HPV type 16 and HPV 18 with cervical intraepithelial neoplasia (CIN) are different from those reported in other studies[17]. We have to confirm whether this HPV co-infection occurs sporadically or in a specific manner since this association also varied among studies[18–20]. The different findings in our population might be due to different methods and criteria, but the genetic factors and their influence on HPV infection patterns cannot be excluded[21].

Our analysis revealed that HPV 16, 18, and 45 tended to form their distinct core cluster pattern. From the perspective of molecular interaction, this could be due to a phenomenon called superinfection exclusion when different HPV types might compete each other at early point of infection but synergize in later phase[22]. Meanwhile, the negative associations (ones which seemingly 'repulse' others) were mostly found among low-risk or mixed types. Interestingly, HPV 52 accounted for most infection cases with 213 occurrence of single infection among high-risk HPV, and rarely co-infects with other types. Apart from similar reports in other studies, the exact mechanism remains unknown[23]. Despite the involvement of HPV 52 in most cases of single infection, its established role in developing pre-cancerous lesion through genetic changes cannot be underestimated and require an effective approach to tackle it through proper vaccination[24,25].

Due to limited samples without any cytology and histology examination in this study, one may hypothesize that other HPV interaction pattern might be more commonly associated with HPV-related cancer development in the molecular level[17,26]. Further investigations are necessary to elucidate the exact molecular mechanism of one's susceptibility to a certain HPV type as well their interaction behavior in these two specific populations, which is crucial in developing an effective targeted prevention and therapy strategies.

The current HPV vaccines used in developing countries like Indonesia mainly targets HPV 6, 11, 16 and 18 (Gardasil®)[27]. Since most infection cases and their core clustering in our study also centered around two additional high-risk ones, *i.e.*, HPV 45 and HPV 52, and rarely interacted with type 6 and 11. The new Merck's HPV vaccine Gardasil (Gardasil 9®), may offer additional protection for this along with HPV type 31, 33 and 58. While this nonavalent vaccine has been already used in several developed countries[28], it is important to note that other low-risk types such as HPV 42 and HPV 43/44 contributed to infection in a considerable proportion. In addition, other high-risk types like HPV 51, 56, and 66/68 and their respective genome variants lead to single infection quite prominently[29].

The authors are fully aware that this analysis still has many limitations and therefore, one should make a careful interpretation from the results presented here. Besides restricted sample size, the examination took place mostly in general women population and did not include certain groups with known cervical cancers such as cancer patients in hospitals. Some HPV genotypes could not be determined using hybrid capture and needed further confirmation through sequencing. The cross-sectional design used to evaluate causal relationships also added more errors, compared to cohort studies[30]. Furthermore, cytology and histology examination should precede one's decision to associate certain HPV types with the cervical precancerous and cancerous lesion.

Although we already implemented bias-reduction technique in logistic regression analysis, we still observed notable errors as reflected by wide confidence interval. This might be attributable to limited sample size and the fact that all possible two-way combinations were included in the analysis, adding more complexity to the model. However, we set the threshold for statistical significance at P value less than 0.001 in the hope to minimize misinterpretation and this method was already utilized in research conducted by Elizabeth L. Dickson *et al*[31].

Most importantly, limited description about potential risk factors and lack of method consistency in data collection may serve as implicit bias when one considers linking HPV infection pattern to certain clinical outcomes. A systematic review by Rositch and colleagues found that the definition of HPV infection persistence may vary from one article to others, let alone failure to demonstrate clear distinction between true HPV infection persistence and remnants of HPV DNA in many studies. They also addressed the absence of specific age group information with regard to this persistence as it might interconnect with someone's immune response, sexual behavior besides sociodemographic factors[32]. Meanwhile, a similar work also discovered difficulties to determine whether an HPV persistence after CIN treatment is a true persistence from pretreatment infection, a recurrent infection that had actually resolved after CIN treatment

or newly acquired infection after CIN treatment. Taking together, all these variables including variability of HPV detection methods and testing interval among health facilities require meticulous judgement before one can come up with an assertion of HPV infection and its impact[33].

In conclusion, this investigation showed that HPV type 52 accounted for most single HPV infections but further studies are needed to confirm whether this type contribute to cervical precancerous and cancerous lesion. In the meantime, HPV 16 and HPV 18 accounted for most multiple infection cases and had strong tendency to form clusters with other types, which may add further complications. Due to lack of cytology and histological examination and limited information regarding the role of other risk factors or determinants, further thorough investigations should follow. These may include, but are not limited to, timely observation between each HPV type with clinical manifestation, genetic predisposition and molecular mechanisms, identification of core cluster pattern in specific populations, as well as minimization of bias including uniformity of operational definition and HPV detection method consistency. This kind of information will be helpful in developing a better strategy to curb HPV infection and its complications.

Conflict of interest statement

The authors have no conflict of interests in any substantial or financial terms pertaining to this study.

Data availability

Raw data in txt. format containing the HPV genotyping information along with R script to get the co-infection network and the logistic regression analysis can be accessed in the github repository (https://github.com/fransdany/HPV-Indonesian-NCD-Survey-2016). The data along with the R codes for forest plot optimization and top 10 associations are also provided.

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Authors' contributions

FD and KA served as main contributors equally in the writing of this manuscript from conceptualization of the study framework, data analysis, discussion and editing of the final draft for publication. SH and HAW assisted in the preparation of early draft and laboratory test validation. RMD and K helped in data interpretation as well as literature review. NLK and W contributed in sample and data management as well as laboratory workflow. All authors have read and checked the validity and legitimacy of the data. All authors have approved the final draft of this article prior to submission.

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