Construction of plasmids expressing recombinant B cell epitopes of PD1

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Abstrak

Latar Belakang: *Pengobatan kanker di Indonesia umumnya menggunakan pengobatan dengan kemoterapi atau dengan operasi. Efek samping dari pengobatan ini antara lain adalah kerontokan rambut, mual dan penurunan berat badan. Saat ini sedang berkembang alternatif terapi kanker dengan menggunakan immunoterapi. Kemampuan sel kanker untuk menghindar dari sistem imun disebabkan adanya protein PD-1 pada sel T yang berikatan dengan ligannya PD-L1.*

Metode: *Penelitian ini merupakan penelitian awal yaitu pembuatan rekombinan PQE PD-1 dan menggunakan bagian soluble dari PD-1 yang disebut dengan EP2PD1 yang akan digunakan untuk pembuatan antibodi monoklonal dan sistem pendeteksi antibodi monoklonal. Metode pembuatan rekombinan PD-1 dan EP2PD1 dengan cara penentuan sekuens epitop sel B yang paling imunogenik dilanjutkan dengan amplifikasi sekuen tersebut dengan PCR dan diligasi ke vektor pengekspresi PQE80.*

Hasil: *Telah terbentuk konstruksi rekombinan PQE80 PD-1 dan PQEEP2PD1 yang diverifikasi menggunakan PCR koloni, pemotongan enzimatik dan sekuensing. Hasil penelitian menunjukkan bahwa epitop PD1 telah terklona ke PQE 80 dan tidak ditemukan mutasi dalam urutan asam amino.*

Kesimpulan: *Konstruksi yang dibuat tidak mempunya mutasi dan dapat dilanjutkan untuk pembuatan antibodi monoklonal. **(Health Science Journal of Indonesia 2019;10(1):1-7)***

Kata Kunci: *PD1, Epitop, Kanker, Immunotherapy*

Abstract

Background: Medications on cancer to date in Indonesia is mostly by surgical or chemotherapy, this type of medications is not always curing the patients. The side effect of the chemotherapy drugs sometimes more challenging such as hair loss, nausea and lost weight. One of the promising targets for cancer is using immune therapy. Cancer cells can avoid immune response by surprising immunity through activation of specific inhibitory signalling pathways, referred to as immune checkpoints. Immune check points like PD-1, PD-L1 are breakthrough therapies in oncology and this monoclonal antibody have been approved by the FDA for treatment. In this research we develop full PD-1 and part of PD1 sequence as an insert then we construct with plasmid PQE80L. This recombinant called PQE PD-1 and PQEEP2PD1. The aim of this study is to make recombinant which would be used to detect PD1 full clone monoclonal antibodies.

Methods: In this study, we designed our recombinants using Indonesian HLA and others using in silico models, this prototype will not only cover Indonesian patients but also other country.

Result: The result showed that the epitope sequence of PD1 has been clone to PQE 80 wt and verified using colony PCR, Enzyme Digestion and Sanger Sequencing. The Clone than will be expressed and injected to animal model to produce antibody.

Conclusion: Construction of recombinant PQE PD-1 and PQE EP2PD1 are constructed without any mutation in the sequence, this recombinant can be used in the next study for protein expression of PQE PD-1 and PQE EP2PD1. **(Health Science Journal of Indonesia 2019;10(1):1-7)**

Keywords: PD1, Epitope , Cancer, Immunotherapy

Current treatment of cervical dysplasia is limited to excisional or ablative procedures that remove or destroy cervical tissue. These procedures have efficacy rates of approximately 90% but are associated with morbidity and expense. Additionally, surgical treatments remove only the dysplastic tissue, leaving normal-appearing HPV-infected tissue untreated.[1]

There are five main therapeutic modalities for cancer: surgery, radiation, chemotherapy, targeted therapy, and immunotherapy. With a few exceptions, the first four modalities are focused squarely on cancer itself. Immunotherapy represents conceptually a unique way of dealing with cancer which is to focus on eliminating cancer indirectly by harnessing the power of the host's immune system.[1] The presence of tumour – associated inflammatory cells in tumours raises an important question, which is one of the most important challenges in oncology. During the early stage of tumour development, cytotoxic immune cells such as NK cells, and CD8+ recognize and eliminate the more immunogenic cancer cells.[2]

In 2011 the immune check point inhibitor (ipilimumab) that used CTLA-4 antibodies was approved by the FDA for melanoma therapy. There are currently 2 types of immune FDA approved therapy as treatment cancer (1) inhibitors of either the programmed death receptor 1 (PD-1) or its ligand (PD-L1), or (2) cytotoxic T cell lymphocyte-associated protein 4 (CTLA-4).[3,4] A good example of the advanced checkpoint molecules that mediates tumour -induced immune suppression is programmed death-1 (PD-1). Physiologically, the PD-1/PD-L1 pathway had emerged as a result of the need to control the degree of inflammation at locations expressing the antigen, in order to protect normal tissue from damage. There was a remarkable expression of the PD-1 protein on the surface of all activated T cells. When a T cell recognizes the antigen expressed by the MHC complex on the target cell, inflammatory cytokines are produced, initiating the inflammatory process.[5,6]

These cytokines result in PD-L1 expression in the tissue, activating the PD-1 protein on the T cell leading to immune tolerance, a phenomenon where the immune system lose the control to mount an inflammatory response, even in the presence of actionable antigens.[5]

The evolution of immune checkpoint inhibitors as anticancer treatment options represents one of the most successful approaches in cancer drug discovery in the past few years. Someday might be possible to make cancer an easy disease to cure.

In this study, we constructed recombinant PQE80 with PD1 full sequences and recombinant of part of epitopes from PD1. The purpose of obtaining a full PD1 sequence construction was to obtain PD1 protein to be injected into mice and to obtain PD1 monoclonal antibody after going through the stages of making monoclonal antibodies. Whereas the making of part of PD1 epitope which we call PQEEP2PD1 is intended as a detection and selection of monoclonal antibody of full PD1 sequence. We designed sequence of Full PD1 and EP2PD1 with unique epitope for single B-cell. Because monoclonal antibodies generated from a single B cell, it is important to get sequence epitope with high affinity. To get this we analyze our full sequence PD1 using in silico method. We use www.IEDB .org epitope B linear prediction with Kolaskar and Tongaonkar antigenicity method, with threshold number 1,007. From the result we find that locations 145-217 of protein have threshold above 1,007. We amplified this sequence and become EP2PD1 sequence. This study gives a preliminary data in DNA level that is important for the future research in expression of PD1 protein and production of PD 1-anti monoclonal antibodies as therapies of cancerous diseases.

MATERIAL AND METHODS

Analysis of PD-1 Gene

The PD1 gene was made by conducting alignment genes from the genebank. After the alignment, codon optimization was done so that the gene that is ordered is easy to express. Codon optimization was performed using in silico. The optimized genes were added with B*amHI* and S*acI*. The gene were synthesised by *Macrogene.*

Analysis in-Silico of PD-1 Protein

In silico analysis (*www.IEDB.org*) was carried out to determine epitopes of B cells that play a role in the immunology process. The analysed PD-1 DNA sequence was applied to websites and its results some epitopes for targeting PD-1 anti monoclonal antibodies.

Construction of Recombinant PQE80−PD-1and PQE EP2PD-1

The Synthetic PD-1 DNA fragment was restricted using *Bam*HI and *Sac*I enzymes .The restricted PD-1 DNA fragment was inserted to vector PQE 80 that had been restricted by the same enzymes. The EP2PD1

were amplified using PCR with synthetic PD-1 as a template. Locations of EP2PD1 was at 147-217 as mentions above and amplified using primers and TaqHifi enzyme from *Invitrogen*. After amplified, the amplicon then purified using PCR purification from Qiagen and digested using *Bam*HI and *Sac*I enzymes. The ligation was performed by using T4 enzyme and T4 DNA ligase. The ratio of vector and insert DNAs for ligation is 1: 3. Transformation was conducted by chemical induction method using heat shock. The transformant value was 7.664 x 103 cfu efficiency is 1.15 x 105 cfu / µgIn the results of the negative control transformation, no growing colonies were found so that there was no bacterial contamination when making competent TOP 10 E. *coli* cells. Selection of transformants was performed by PCR colonies. PCR. Primers PQE F: CCCGAAAAGTGCCACCTG and PQE R: GTTCTGAGGTCATTACTGG were used for PCR. The PCR was performed by the following compositions: 95^{0}C for 2 minutes for early denaturation, For denaturation we at 95^{0}C for 10 seconds, annealing at 95^{0}C for 30 seconds extended time at 68^{0}C for 1 minute and final extension at 68^{0}C for 2 minutes the PCR cycle is 35 cycle. The thermal cycler (BioRad) was performed by the following condition. The PCR results were visualized at 0.8% agarose gel.

Sequencing

DNA sequencing was conducted to determine the correctness of DNA sequences and in-frame between DNA insert and plasmid DNA backbone. Sequencing were using sanger method and for analysis sequencing was analysed with Bio Edit software. Based on the sequencing results, the DNA insert was successfully inserted in the frame on the PQE80 vector. The sequencing results were then aligned with the reference sequence and initial DNA PD1 gene to known any mutations that were caused by cloning process.

Ethical Clearence

The study is laboratory experiment which does not involve any human and animal as an object.

RESULTS

B Cell Epitop Prediction

A study was performed to determined which epitope might elicit cellular or humoral immune response. B-cell epitopes can be defined as a surface accessible clusters of amino acids, which are recognized by secreted antibodies or B-cell receptors. Figure 1, analysis of linear epitope prediction was using with Kolaskar and Tongaonkar antigencity method, with threshold number 1,007 at www.IEDB.org. Briefly we input the PD-1 sequence to find which position have the highest rank. The threshold of peptide prediction is 1,007, epitope give score above the threshold is the epitope were amplified.
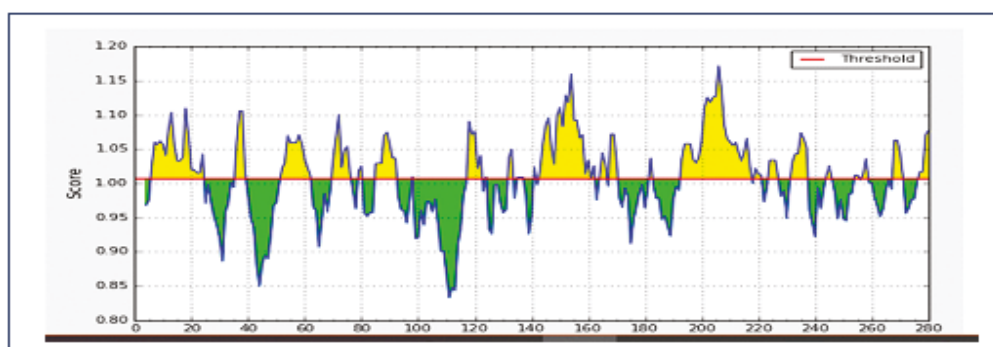

Figure 1. Result of linear epitop B cell Prediction using Kolaskar and Tongaonkar antigencity method

Table 1. The score of prediction PD-1 epitop to B cell

No	Start	End	Peptide	Lenght	Score
1	6	24	TQRLCATRTICATTTCRAA	19	0,998
2	52	62	FTPLKIQFTII	11	1,011
3	70	76	ARIFFQR	7	0,963
4	85	92	GTTCCTAT	8	0,961
5	143	160	FCTQAFFNLCFRCQANCT	18	1,026
6	193	217	LTRLATIFRKCCQFIGLIARAHTIP	25	1,022
7	232	237	KGCIIT	6	1,052

From the result we choose peptide position at 145- 217 for amplification of EP2PD1 insert. As a template we use PD-1 full length (Table 1).

Amplification of EP2PD1

Full-length PD-1 sequence it was used to amplify EP2PD1 insert. Primer used in this amplification was purchase from IDT with forward sequence : 5'-ccggaagcttatgcagattccg-3' and reverse sequence : 5'-ggccaagcttgctcgggctcat-3'.
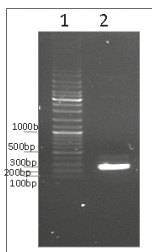

Figure 2. Amplification of EP2PD1 using PCR Taq Hifi Invitrogen.

Next, the amplification of EP2PD1 using PCR with Taq Hifi Polymerase, the amplicon had a molecular base pair 220 bp (figure 2, lane 2) which is consistent with the design of epitope prediction .

Detection of Insert PD-1 By PCR Colony

Verification of recombinant was using PCR colony. This PCR performed as early step to identified cloned that have PD1 insert. The colony use for this analysis

is the colony from replica plating at ligation and transformation procedure which is 12 colony (Figure 3).
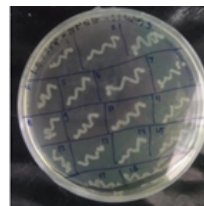

Figure 3. Replica plate of PQE80 PD-1

The Primer were use are PQE-*forward* and PQE-*reverse*. Those primer amplified Multiple Cloning Site (MCS) of PQE 80 which about ± 175 bp. To confirm the colony has insert of PD-1, length of amplified DNA from PCR colony is ± 1056 bp (175 bp + 881 bp). Electrophoresis visualisation showed that colony number 2,3,4,6,and 8 are predicted carrying PD-1 insert, showed with band at ± 1056 bp.

PCR colony also conducted to PQEEP2PD1 using primer PQE-*forward* and PQE-*reverse* confirm, to confirm the colony has insert of EP2PD-1, length of amplified DNA from PCR colony is ± 395 bp (175 bp + 220 bp). Electrophoresis visualisation at Figure 5 showed that colony number 1,2,3,4, are predicted carrying EP2PD-11 insert.

Figure 4. PCR Colony result, lane M: Gene ruler marker from Invitrogen, Lane 1: colony PQE PD-1 No:1, Lane 2: colony PQE PD-1 No:2, Lane 3,: colony PQE PD-1 No:3 Lane 4 : colony PQE PD-1 No:4, Lane 5 : colony PQE PD-1 No:5, Lane 6: colony PQE PD-1 No:6, Lane 7: colony PQE PD-1 No:7, Lane 8: colony PQE PD-1 No:8, Lane 9: colony PQE PD-1 No:9 Lane 10 : colony PQE PD-1 No:10, Lane 11 ; colony PQE PD-1 No:11, Lane 12 : colony PQE PD-1 No:1
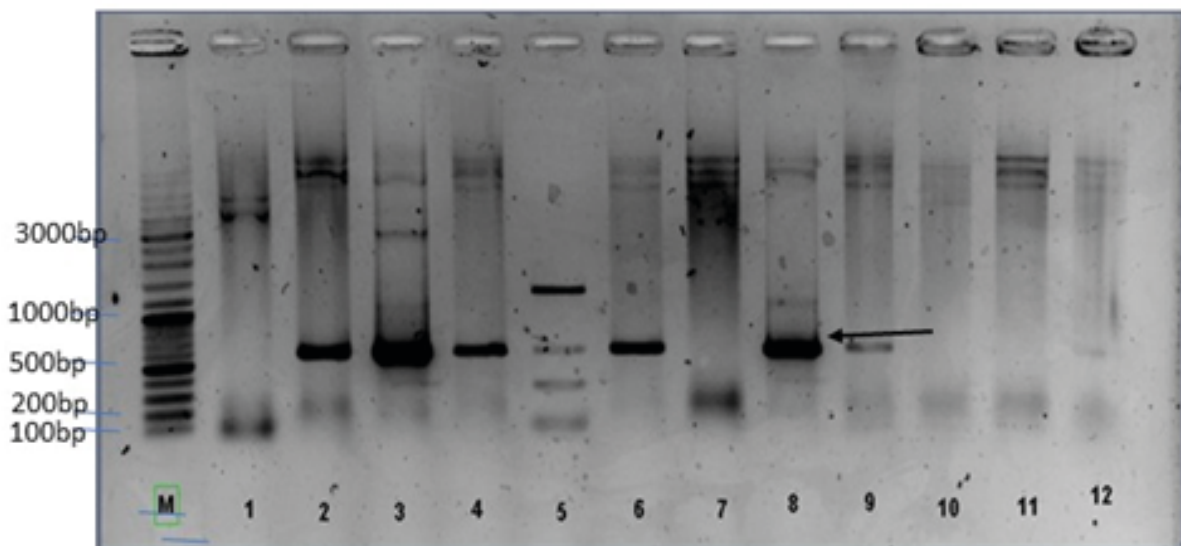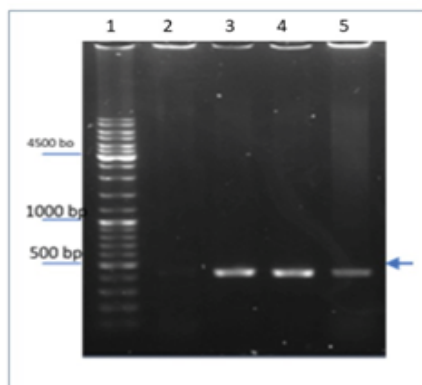
Figure 5. PCR Colony result, lane 1: Gene ruler marker from Invitrogen, Lane 2: colony PQE EP2PD1 No:1, Lane 3: colony PQE EP2PD1 No:2, Lane 4,: PQE EP2PD1 No:3 Lane 5 : PQE EP2PD1 No:4

Verification of the insert PD-1 and EP2 PD-1 by restriction enzymes

Colony that predicted have insert of PD-1, then inoculate to Luria Berthani medium with volume of culture 3 ml overnight. The next day culture were performed plasmid isolation using QIAprep Spin Miniprep Kit. The concentration of DNA plasmid was 111,6 ng/μL with total volume of 41 μL and the ratio of A260/280 value is 1,92. After plasmid isolation we performed verification of insert using enzyme digestion with B*am*HI and S*ac*I. The purpose of this method is to excrete PD-1 insert. Colonies containing insert will showed 4068 bp and 818 bp band (Figure 6).
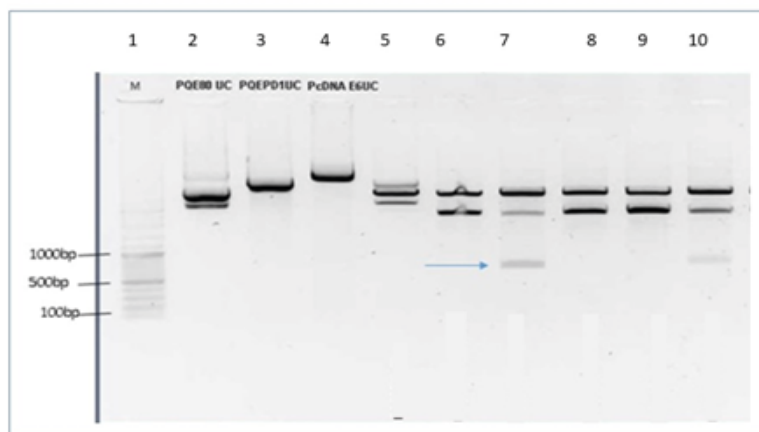

Figure 6. Verification of insert PQE PD-1 colony number 2,3,4,6,and 8 using BamHI and SacI. lane 1: Gene ruler marker from Invitrogen, Lane 2: PQE80 Uncut colony, Lane 3: PQE PD-1 Uncut, Lane 4,:PcDNA E6 Lane 5 : PQE 80 cut BamHI-SacI, Lane 6 : PQE PD-1 (2) cut BamHI-SacI , Lane 7: PQE PD-1 (3) cut BamHI-SacI, Lane 8: PQE PD-1 (4) cut BamHI-SacI, Lane 9: PQE PD-1 (6) cut BamHI-SacI, Lane 10: PQE PD-1 (8) cut BamHI-SacI

From the digestion result using agarose 0,8% tells that colony with DNA fragment expected (818 bp) are colony PQE PD-1(3) and PQE PD-1(8).

The same protocol also conducted to colony of PQE EP2PD1, for this colony the insert were excrete using B*am*HI and H*ind*III. All the digest verification protocol was performed single digest only, B*am*HI then followed by H*ind*III using NEB buffer 3 and incubate at 37⁰C for 4 hours. After incubation period the plasmid was ran at agarose gel 0,8% for visualisation.

DNA Sequencing

DNA sequencing was conducted to determine nucleotide bases of inserted DNA. DNA sequencing was using Sanger method, and for analysis was using BioEdit. To find out if there is any mutation analysis was compare to reference gene from gene bank for PQE PD-1 (8) and fpr PQE EP2PD1 (1) was compare with full length of PQE PD-1(8). From

data sequencing result (Figure 8) we can find out that there is no mutation of PQE EP2PD1 (1) in the recombinant, also with the PQE PD-1 (8).
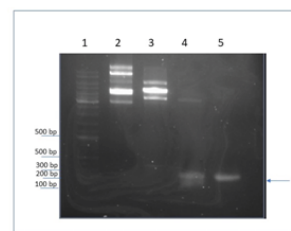
Figure 7. Verification of insert PQE EP2 PD-1 colony number 1,2, using BamHI and HindIII lane 1: Gene ruler marker from Invitrogen, Lane 2: PQE80 Uncut, Lane 3: PQE80 cut with BamHI and HindIII , Lane 4,: PQE EP1PD-1 (1) cut BamHI and HindIII,   Lane 5 : PQE EP1PD-1 (2) cut BamHI and HindIII

From Visualisation of digested plasmid was using agarose 0,8% we can find that expected band (220 bp) was inserted to PQE 80 vector (Figure 7).

Figure 8. Sequencing result of PQE EP2PD1 (1) using Sanger method, comparation of sequence was using PD-1 full gene.
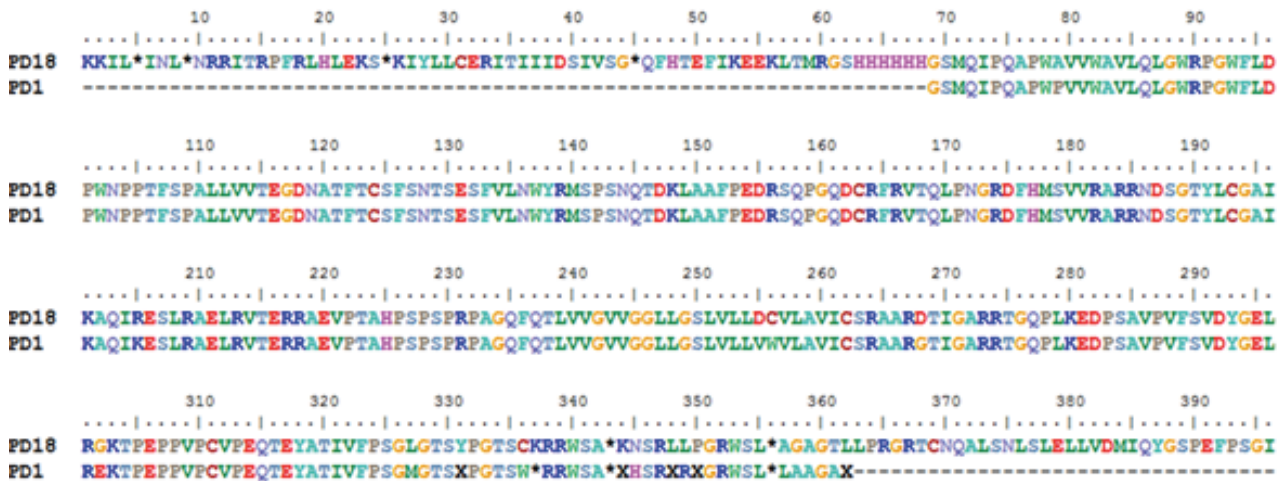

Figure 9. Sequencing result of PQE PD-1 (8) using Sanger method, comparation of sequence was using PD-1 full gene.

From sequencing result in Figure 9, we found that there is no mutation at recombinant PQE PD-1 (8). It means that this two clone a can be a candidate for antibody monoclonal development.

DISCUSSION

In this study, we have proved to be successful in constructing PD-1 human sequence and EP2PD1 sequence into prokaryote expression system PQE80. The purpose of his study is to make recombinant of PQE PD-1 which is going to be use for development of antibody monoclonal PD1. According to Xu research.[6] not all part of PD1 are easily to express specially domain region but other studies showed that the extracellular domain of PD-1 could be express. One study was carried out to express a human PD-

1-GST fusion protein and it was also found that the fusion protein was completely in inclusion bodies.[6] EP2PD1 is located at 145-217 amino acid which is an extra cellular domain according to software https://protein-sol.manchester.ac.uk (data not showed). Since this epitope is protrude it is possible to make this epitope as tools for detect efficiency of antibody monoclonal PD-1 or as DNA vaccine which combine with other immunogenic factor.

This sequence were optimized to B cell because B cells expressing high-affinity antibodies differentiate into antibody-secreting plasma cells and memory B cells that mediate humoral immunity against pathogens[7] but in spite of advance in B- cell epitope mapping , it is important to note that antibodies raise against peptides often lack the ability to bind native proteins due to unstructured nature of the peptide.[9] In

this study we check the antigenicity of peptide using Kolaskar and Tongaankar method with threshold value 1,007. At the score value not all epitopes have the highest score only four of them the rest is below the threshold. For constructing EP2PD1 we choose epitope position from 145- 217 which have threshold value higher than 1,007. This might be the meaning that this epitope doesn't have proper activity to interact with circulating tumour reactive CD8+, these finding suggest that there is other factor to be added to modulate activity of epitope EP2PD1 like IL 12.[10]

E. *coli* was select in this study as expression system because this system have many advantages, it has doubling time is about 20 min[11], it means that a culture with a 1/100 dilution of starter culture may reach stationary phase in a few hour, this make E.coli a robust system to amplified DNA and highly density cultures are easily to achieved.[12] In this study we use PQE 80 (Qiagen) as vector plasmid because this vector have properties of 6x His tag at the N-Terminal of the protein, make it the insert if ligated in framed easily to purified[13] and also the PQE series from Qiagen was provide with termination codons it means that the 3' end of the insert does not need to determined accurately.

In conclusion, construction of recombinant PQE PD-1 and PQE EP2PD1 are constructed without any mutation in the sequence. It is means that this recombinant can be used in the next study for protein expression of PQE PD-1 and PQE EP2PD1, which will be proceed to development of monoclonal antibodies.

Acknowledgements

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Laboratory-based Acute Flaccid Paralysis surveillance pre-polio free certification: Indonesia experience, 2003-2013

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Abstrak

Latar belakang: *Virus Polio Liar dapat menyebabkan kelumpuhan dan dapat dicegah dengan imunisasi. Untuk memonitor transmisi virus polio liar dilakukan surveilans Acute Flaccid Paralysis (AFP) dan investigasi laboratorium yang telah dimulai sejak tahun 1995 di Indonesia. Virus polio liar Indigenous terakhir ditemukan di Indonesia tahun 1995. Indonesia masih memiliki ancaman importasi virus polio liar dari negara endemis dan mutasi virus polio dari vaksin yang menyebakan kelumpuhan yang sama seperti virus polio liar. Artikel ini bertujuan untuk memberikan gambaran mengenai surveilans AFP berbasis laboratorium di Indonesia pada tahun 2003-2013 sehingga mengantarkan Indonesia sebagai negara bebas polio pada tahun 2014.*

Metode: *Data yang dianalisis adalah data kasus AFP seluruh Indonesia periode tahun 2003-2013. Data didapat dari laboratorium jejaring laboratorium Polio di Jakarta, Bandung, Surabaya dan Sub Direktorat Surveilans, Direktorat Surveilans dan Karantina Kesehatan, Direktorat Jenderal Pencegahan dan Pengendalian Penyakit. Data di analisis menggunakan program Microsoft Excel.*

Hasil: *Sebanyak 305 kasus AFP yang disebabkan oleh infeksi virus polio liar tipe 1 impor ditemukan pada tahun 2005 dan 2006. Terdapat 39 kasus AFP yang disebabkan cVDPV tipe 1 ditemukan di Pulau Madura pada tahun 2005. Virus polio liar tipe 1 hanya ditemukan di pulau Sumatera dan Jawa. Penyebaran Virus polio berhasil dihentikan pada tahun 2006 dan sudah tidak ditemukan lagi hingga tahun 2013.*

Kesimpulan: *Surveilans AFP berbasis laboratorium yang baik berhasil memantau dan mendeteksi sirkulasi virus polio. Peningkatan kinerja surveillance AFP diperlukan untuk membuktikan terhentinya transmisi virus polio sehingga eradikasi polio secara global dapat diraih. (**Health Science Journal of Indonesia 2019;10(1):8-14**)*

Kata kunci: *surveilans, laboratorium polio, Acute Flaccid Paralysis*

Abstract

Background: Wild Poliovirus can cause flaccid paralysis and can be prevented by immunization. To monitor wild polio virus transmission, Acute Flaccid Paralysis (AFP) surveillance and laboratory investigations was initiated in 1995 in Indonesia. The last indigenous wild poliovirus found at 1995 in Indonesia. Indonesia still has the threat of imported wild polio viruses from endemic countries and poliovirus mutation from vaccine that can cause paralytic as well as wild poliovirus. The aim of this article is to describe the laboratory-based AFP surveillance in Indonesia from 2003-2013 so that it had led the Indonesia certified for polio free in 2014.

Methods: Data analysis performed on AFP cases data from all provinces in Indonesia period of 2013-2014. Data were collected from polio laboratories network in Jakarta, Bandung, Surabaya and the Sub Directorate of Surveillance, Directorate of Surveillance and Health Quarantine, Directorate General of Disease Prevention and Control. Data were analyzed using Microsoft Excel program.

Results: 305 paralysis cases were caused by imported type 1 wild poliovirus infection were found in 2005 and 2006. 39 paralysis cases caused by type 1 cVDPV infection were also found on Madura Island in 2005. Type 1 wild polioviruses only found on the Sumatra and Java island. The wild poliovirus transmission was stopped in 2006 and was no longer found until 2013.

Conclusion: Good laboratory-based AFP surveillance has been successfully monitoring and detecting the circulation of the poliovirus. Improved AFP surveillance performance is needed to prove cessation of poliovirus transmission so that eradication of poliovirus can be achieved globally. ***(Health Science Journal of Indonesia 2019;10(1):8-14)***

Keywords: surveillance, polio laboratory, Acute Flaccid Paralysis

Poliovirus can cause poliomyelitis in humans, mainly affects children who have no immunity to the poliovirus. Poliomyelitis can be prevented by immunization which through Expanded Program on Immunization (EPI) started in 1988, the poliovirus transmission has been interrupted. The number of poliomyelitis cases due to wild poliovirus reduced to more than 99% in over 125 countries globally with only 3 endemic countries left nowadays; Afghanistan, Nigeria, and Pakistan. Wild poliovirus type 2 has not been found since 1999 globally while the last case of type 3 wild poliovirus reported in 2012 in Nigeria. Global Polio eradication can be achieved if this condition can be maintained.[1-6]

World Health Organization has implemented four strategies since the eradication program began in 1988, including strategy to increase immunization coverage as well as acute flaccid paralysis (AFP) surveillance and laboratory investigations. The AFP surveillance and laboratory investigation play an important role to ensure the cessation of wild poliovirus transmission. As paralysis was only shown in 0.1- 1% of children infected with the poliovirus, acute flaccid paralysis (AFP) surveillance followed by confirmation with virological laboratory examination needed to assure that there is no paralytic cases caused by poliovirus. AFP surveillance activities which including laboratory confirmation activities were carried out on children under 15 years old through surveillance officers at the District and Provinces Health Service Offices. In Indonesia, this programme have been implemented in Indonesia since 1995.[7-9]

In Indonesia, indigenous wild poliovirus circulation has not been found any more after 1995. However, Indonesia still faces threat of the wild poliovirus importation from polio-endemic countries as the last previous outbreak in 2005. Moreover polio immunization program in Indonesia utilize Oral Polio Vaccine containing live attenuated vaccines which might become another threat because the vaccine polio virus may experience mutations in the human body (Vaccine Derived Polio Virus/ VDPV) and cause symptoms such as wild polio virus infections.[1,7,10]

The sensitive and active surveillance in finding AFP cases and laboratory quality is crucial role in ensuring that poliovirus transmission has been interrupted and immunization programme has worked. Documentation of the cessation of the poliovirus transmission is needed in the certification of polio eradication globally. The data collected may provide evidence of the elimination of the poliovirus and can also be used as a guideline in making plans to prevent and eradicate polio infections. This study provides epidemiological and virological information on AFP cases in Indonesia from 2003-2013 which further gives an overview of polio eradication program in Indonesia before the certification of polio free is obtained. Furthermore, through the data obtained during the period 2003 – 2013, it can be seen the development of the surveillance system in Indonesia in detecting the circulation of wild polio viruses in Indonesia as experiences and a lesson learnt of laboratory networking to prevent poliovirus transmission and achieving polio-free certification including response to the poliovirus outbreak.

METHODS

Study Design

Indonesia has 34 provinces which spread over 5 major islands and thousands of small islands. The health system is managed by the central government in collaboration with local governments with tiered tasks and responsibilities given. This article analyzes AFP surveillance data reported and sent by specimens to the polio laboratory network for the period 2003-2013 before Indonesia was declared polio-free by the World Health Organization. Data analysis covered surveillance activities in finding AFP cases, retrieval and condition of stool specimens.

Acute Flaccyd Paralysis surveillance activity

AFP surveillance implements hospital-based and community-based surveillance systems in finding AFP cases. AFP surveillance in Indonesia was performed by Vaccine Preventable Diseases surveillance department Directorate General of Center for Disease Prevention and Control (CDPC) involved all relevant health workers in health facilities to actively find and report acute paralysis cases found in hospitals and health centers and also involved other leaders in the community to capture cases in communities. Specimens should be collected from the AFP cases with at least 2 stool specimens are obtained in 24 hours apart within 14 days after onset and then sent to laboratory accredited by WHO. The specimens should be received in a laboratory with good condition. Acute Flaccid Paralysis surveillance officers in districts will send reports to CDPC Indonesia every month.

Laboratory Investigation

The collected specimens were sent to three polio network laboratories, namely the Center for Biomedical and Basic Health Technology, National Institute of Health Research and Development Laboratory in Jakarta which examined samples from the all the provinces in Sumatera Island region, Kalimantan Island region, Banten Province and DKI Jakarta Province; Biofarma Laboratory in Bandung which examined samples from West Java Province, Central Java Province and D.I.Yogyakarta Province and; Balai Besar Laboratorium Kesehatan (BBLK) Surabaya Laboratory which examined specimens from Sulawesi Island, East Java, Bali, Nusa Tenggara, Moluccas, and Papua Island region. The specimens were examined in the laboratories using procedures established by WHO and results were reported to the Expanded Program on Immunization data in Sub Directorate Surveillance, Directorat Surveillance and Health Quarantine, DG CDPC as well as to the provincial health offices.[9]

Data Analysis

The data from AFP cases were analyzed combining laboratories and epidemiology data from CDPC which collected between 2003-2013. The data which used in this study is analysed with microsoft excel programme including year, number of AFP cases, number of AFP specimens, the condition of the specimens.

RESULTS

The AFP cases were found by surveillance officers and reported to CDPC and followed by specimens

collection and sent them to the polio laboratory network according to their coverage working area. Figure 1 shows the number of AFP cases reported and specimens collected and sent to the laboratory. The AFP cases reported in 2003 and 2004 were still relatively few, which then begun to increase in 2005, almost reaching twice number of case discoveries in the previous year. The number of cases since 2005 was then relatively consistent until 2013. From the figure it was also seen that less than 10% of cases were reported without specimens sent to the laboratory.

Table 1 shows AFP surveillance performance with the number of specimens received in the laboratory and the condition of the specimen. It appears that specimens in adequate conditions range from 78-90% of all cases found and reported to central surveillance. Table 1 also illustrates the increase in Non Polio AFP rates. Non-polio AFP rate is really the incidence of AFP caused by diseases other than poliomyelitis. Before 2005 there were still around 1/100,000 population of children, whereas in 2005 to 2013 Non Polio AFP Rate increased to >2/100,000 population of children.
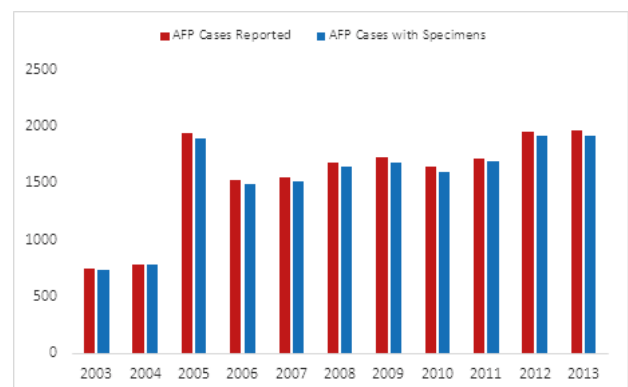
Figure 1. AFP cases trend in 2003 - 2013

Table 1. AFP Surveillance Performance Based on Adequate Specimens and Non Polio AFP Rate

Year	No. of AFP cases Reported	No. of Sample Sent to The Lab	Adequate Specimens		In Adequate Specimens					Non Polio AFP Rate
			Total	%	Total	1 spc	Without Specimens	Bad Condition	Collection >14 days	
2003	749	737	660	88%	89	1	12	31	45	1,22
2004	782	779	705	90%	77	4	3	25	45	1,25
2005	1939	1900	1521	78%	418	37	39	88	254	2,45
2006	1527	1497	1209	79%	318	13	30	101	174	2,46
2007	1557	1516	1263	84%	253	11	41	49	152	2,54
2008	1684	1641	1403	83%	281	16	43	15	207	2,75
2009	1724	1685	1477	86%	247	26	39	13	169	2,81
2010	1641	1601	1385	84%	256	13	40	11	192	2,63
2011	1720	1692	1540	90%	180	6	28	3	143	2,76
2012	1951	1922	1749	90%	202	15	29	7	151	2,77
2013	1963	1922	1722	88%	241	12	41	5	183	2,74

The laboratory tests are virus culture by inoculating specimens to both RD and L20B cell lines followed by identification of Poliovirus using the Probe and Hibridization (2003-2008) and Polymerase Chain Reaction method (since 2009). Table 2 describes the results of viral culture and identification of polio virus in stool specimens from AFP cases. The wild poliovirus were found in Indonesia both in 2005 and 2006. The Vaccine Derived Poliovirus (VDPV) type also detected in 2005 while vaccine Poliovirus were detected every year with the highest was in 2005.

VDPV was originated from vaccine poliovirus and mutated during over time.[10] Vaccine poliovirus type 3 was the most frequently detected amongst the others.

In 2005, there was an outbreak of wild poliovirus in Indonesia. First case of wild poliovirus found in Cidahu district, West Java province in March 2005, which then spread to eight other provinces in Java and Sumatera. Distribution of wild type 1 polio cases in Indonesia in 2005-2006 was shown in figure 2.

Table 2. Laboratory Result of AFP Specimens

Year	Number of Specimen	Vaccine Poliovirus			Wild Poliovirus			VDPV		
		P1	P2	P3	P1	P2	P3	P1	P2	P3
2003	737	1	1	3	0	0	0	0	0	0
2004	779	0	0	1	0	0	0	0	0	0
2005	1900	41	42	58	303	0	0	39	0	0
2006	1497	24	9	13	2	0	0	0	0	0
2007	1516	7	5	9	0	0	0	0	0	0
2008	1641	6	8	4	0	0	0	0	0	0
2009	1685	3	3	5	0	0	0	0	0	0
2010	1601	4	2	6	0	0	0	0	0	0
2011	1692	5	6	20	0	0	0	0	0	0
2012	1922	4	6	11	0	0	0	0	0	0
2013	1922	0	6	9	0	0	0	0	0	0

Figure 2. Mapping of Wild Poliovirus Cases in Indonesia in 2005-2006

DISCUSSION

This paper discusses laboratory-based AFP surveillance activities in Indonesia for the period 2003 - 2013 that represent the period before the discovery of paralysis cases due to imported wild polio virus infection in 2005 until Indonesian polio-free certification was achieved in 2014. AFP cases reported in 2003-2004 were less than the number of cases in the previous year. The highest number of AFP cases was reported in 2005 due to an outbreak of imported type 1 poliovirus which was first

discovered on Cidahu, Sukabumi, West Java. The increased number of AFP cases detected which more than two times from the previous year was due to avoid a paralytic case that escaped from monitoring. All cases of acute paralysis including paralysis of more than 2 months were investigated and reported, followed by collection of stool specimens to expand the possibility of finding paralytic cases due to poliovirus. This strategy was followed with the increase of cases with inadequate specimens in 2005-2006. The number of case findings after 2005

was constant until 2013 may due to an increase in non-Polio AFP rates that followed the rules for finding cases in endemic areas. An increase in cases is needed to prove that there are no more paralyzed cases caused by wild poliovirus as evidenced by the results of laboratory tests. [9,13-16]

As shown in figure 1 and table 1, not all reported and investigated AFP cases had specimens. There are several reasons of the incompleteness AFP such as the AFP case location was difficult to reach by the health officers (far geographically difficult and lack of transportation), the difficulties of AFP patients for defection. The otherreason of incomplete AFP investigation was because the AFP cases detected after 2 months of paralysis symptoms onset, which made the collection of specimens no longer needed. In addition to incomplete specimens collection, more than 65% of the specimens categorized as non-adequate. Inadequate specimens can be caused by specimens collection more than 14 days from paralysis, specimens were not collected, or just collecting and sending one specimen, and the condition of the specimens at arrival in the laboratory were not adequate. Adequate specimens must be above 80% in every single year and this condition cannot be achieved in 2005 and 2006.[8] The delay in the collection of the AFP specimens might be due to the delays in case finding. The poliovirus was still excreted in 66% -100% in 2 weeks after the onset and the viruses excretion decreases to 15% at the fifth and sixth weeks. Stool can still be collected until the eighth week to catch the possibility of the virus still being excreted. WHO does not recommend to collect AFP specimens after 2 months of paralysis, although the research was conducted in children in China found that the poliovirus was still detected in the stool from AFP cases after the twelfth week.[11-12]

Inadequacy of the specimens was also due to collection of only one specimens instead of two. Collecting a pair of specimens is very important because if only 65% of AFP cases showed positive poliovirus detection in both stools, the sensitivity of the poliovirus was reduced in 7% of AFP cases.[17] In addition, around 15% of the specimens which sent to the laboratory were received inappropriate conditions that were not cold or insufficient volume. The main causes of this problem were because the not enough ice packs, the ice pack is not replaced when melted before reach the laboratory. The specimens temperature affects the stability of the virus. The high temperature for a long period causes the viral titre decreases,and will affect the results of laboratory

tests. The poliovirus is stable for 72 hours at 2-8ºC until they arrive at the laboratory. Type 1 poliovirus is most affected by increasing temperature. Virus titre decreased by 20% if stored at 22ºC for 14 days and 50% if stored at 36ºC for 14 days.[18]

The risk of occurrence of AFP cases due to importation of poliovirus is very high. Global data for the period of 2003-2014 showed the spread of wild poliovirus cases because of the imported polioviruses were very significant of 53% in 2005, 85% in 2010 and 62% in 2013.[20-22]

The AFP surveillance system has successfully monitored the wild poliovirus circulation with a finding of 305 cases of AFP caused by type 1 wild polio virus infections in Indonesia in 2005.[19] This poliovirus originated from an African country which transmitted through Indonesian citizens who visit the Middle East.[9] The poliovirus was first detected in Cidahu West Java and then spread to Banten and quickly spread to the some provinces in Java and Sumatra Island. The immunization response to epidemics through the supplementary Immunization Activity and National Immunization Days in areas affected by outbreaks and areas affected by the outbreak successfully stopped the transmission of wild polio viruses. The last case was found in 2006. Cases are generally found in children living in the vicinity of rivers, areas with high population mobility, low immunization coverage, high population density, poor sanitation. Active and sensitive surveillance can cause cases to be found in certain areas and in large numbers. [7]

Along with the AFP cases due to wild poliovirus, AFP cases due to type 1 VDPV were found in Madura, East Java in 2005. This finding was different from other countries in the world as the type of poliovirus that mutates and becomes VDPV generally is type 2 polio virus.[5] One of the causes of emergence of VDPV is the low number of children who have immunity to poliovirus.[7,25] Low immunization coverage was found in 64% of VDPV cases and 50% of cases have never been immunized against poliovirus. VDPV transmission had occurred before the 2005 VDPV outbreak and no cases could be found due to AFP surveillance being relatively less active in the area. Based on 2003 and 2004 data, it was found that AFP surveillance targets before 2005 in that area were still below the WHO recommended target. In addition to Non Polio AFP rates in that year were <1 / 100,000 population (0.4 and 0.7) and adequate specimens were also below 80%. In addition, cold chains that

are not properly managed also cause the stability of the virus to be disrupted during delivery to the laboratory so that the virus were no longer viable and were not detected by laboratory test.[7,23-26] Based on the specific results of poliovirus isolates in VDPV cases, mutation nucleotide differences between 1.1-1.2% found occurred for 2 years.

The vaccine poliovirus was also found in the stool from AFP cases. Indonesia is still using OPV (Oral Poliovirus) for routine vaccination. Vaccine poliovirus replicates in the human intestine and is excreted through stool. Outbreak Response Immunization (ORI) in outbreak area causes the poliovirus vaccine to be found in the stool of children who have just received immunization in the last 3 months.[15-16]. Data of AFP cases from 2003-2013 shows that vaccine poliovirus type 3 was the most frequently found even though some literatures showed that vaccine poliovirus type 2 was most frequently found because of its characteristics that longer circulated and transmitted.[27-29] Based on Troy et al study in Mexico, shows that vaccine poliovirus type 3 found in 60% in children who recently received OPV. It showed that after direct vaccination, poliovirus type 3 most frequently detected in stool compared to vaccine poliovirus type 1 and 2.[29] The vaccine poliovirus can turn into virulent in the human body and causes the same paralysis as wild poliovirus (vaccine asosiated poliovirus /VaPP). Further investigation is carried out to decide whether the vaccine virus that enters the child's body changes its nature to become virulent and causes paralysis.[29]

In conclusion, good quality AFP surveillance helps government programmes in detecting the transmission of wild poliovirus and ensuring that wild poliovirus can be stopped transmitting through laboratory evidence. This evidence can be used as a document to achieve polio-free certification and program legacy in maintaining Indonesia free of wild poliovirus. Improved sensitive AFP surveillance performance is needed to provide more quality evidence so that eradication of poliovirus can be achieved globally.

Acknowledgements

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Characteristics of Acute Transfusion Reactions and its related factors in Cipto Mangunkusumo Hospital Jakarta, Indonesia

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Abstrak

Latar belakang: *Reaksi transfusi akut (RTA) merupakan sekelompok kejadian yang tidak diinginkan akibat pemberian transfusi darah. Manifestasi dari RTA bervariasi dari yang ringan hingga mengancam nyawa. Saat ini, data mengenai reaksi transfusi di Indonesia masih sangat terbatas. Dalam studi ini, kami bertujuan untuk memberikan gambaran mengenai karakteristik RTA dan faktor-faktor yang mempengaruhinya.*

Metode: *Studi ini merupakan studi retrospektif yang melibatkan 288 subyek dengan RTA. Studi dilakukan di Rumah Sakit Dr. Cipto Mangunkusumo, dimulai sejak Januari hingga Desember 2017. RTA dikelompokkan berdasarkan sistem tubuh yang mengalami manifestasi, serta derajat manifestasinya.*

Hasil: *Sel darah merah merupakan produk darah utama yang ditransfusikan ke subyek, diikuti dengan konsentrat trombosit, plasma segar beku, dan kriopresipitat. Lima gejala utama dari RTA adalah gatal, demam/kenaikan suhu tubuh, menggigil, urtikaria, dan angioedema. Berdasarkan sistem tubuh yang terkena, umumnya RTA bermanifestasi sebagai gejala pada kulit (56.6%). Berdasarkan derajat manifestasinya, RTA umumnya dikategorikan dalam derajat ringan (55.9%). Anak-anak cenderung mengalami manifestasi yang ringan (64.8%) dan utamanya bermanifestasi pada kulit (65.4%). Riwayat transfusi mempengaruhi derajat RTA secara signifikan. RTA derajat sedang dan gejala konstitusional lebih banyak ditemukan pada subyek yang mendapat PRC dibanding produk darah lainnya.*

Kesimpulan: *Umumnya RTA bermanifestasi sebagai gejala dermatologi. Hanya sedikit kasus RTA yang disebabkan oleh reaksi inkompatibilitas. Manifestasi dan derajat RTA juga dipengaruhi oleh umur, riwayat transfusi, dan jenis komponen darah.* **(Health Science Journal of Indonesia 2019;10(1):15-20)**

Kata kunci: *Transfusi darah, reaksi transfusi akut, riwayat transfuse, usia*

Abstract

Background: Acute transfusion reactions (ATRs) are a group of adverse events caused by blood transfusions. Manifestations of ATRs vary from mild to life threatening. At present, data about transfusion reactions in Indonesia are still limited. In this study, we aim to determine the characteristics of ATRs and its related factors.

Methods: This was a retrospective study of 288 subjects with ATRs. The study was conducted in Cipto Mangunkusumo Hospital, started from January to December 2017. ATRs were categorized based on the body systems affected and degree of manifestations.

Results: Packed red cells (PRC) was the predominant blood product (51.4%) which was transfused to subjects, followed by thrombocyte concentrate (TC), fresh frozen plasma (FFP), and cryoprecipitate. Five most common predominant symptoms of ATRs were pruritus/itch, febrile/increased temperature, chills, transient urticaria, and angioedema. Based on the affected body systems, the majority of ATRs manifested as dermatologic symptoms (56.6%). Based on the degree of manifestations, the majority of ATRs were categorized as mild degree (55.9%). Children tended to have milder symptoms (64.8%), which mostly manifested as dermatologic symptoms (65.4%). History of transfusion affected the degree of ATR significantly. Moderate degree of ATRs and constitutional symptoms were found more common in subjects who received PRC than other blood products.

Conclusion: Most of ATRs manifest as dermatologic symptoms, which represent allergic reactions. Only a small portion of ATRs are caused by incompatibility reactions. The manifestation and degree of ATRs are also affected by age, history of transfusion, and type of blood components. **(Health Science Journal of Indonesia 2019;10(1):15-20)**

Keyword: Blood transfusion, acute transfusion reaction, transfusion history, age

Acute transfusion reactions (ATRs) are a group of adverse events which occur within 24 hours after starting blood transfusion. Transfusion reactions are the most common side effects related to blood products administration. Previous studies reported various incidence rate of transfusion reactions, started from 0.4% to 1.1%.[1,2] In the mild form, the most common manifestation was feeling discomfort, which was found in 0.16% patients.[2] Around 0.14% of transfusion reactions manifested as breathing problems, which is life-threatening and need immediate treatments.[2,3]

Transfusion reactions are divided into two main groups: non-hemolytic transfusion reactions and hemolytic transfusion reactions. Acute non-hemolytic transfusion reactions vary from mild pruritus, transient urticaria, febrile non-hemolytic transfusion reaction (FNHTR) to most fatal form like transfusion-related acute lung injury (TRALI). Acute hemolytic transfusion reactions are usually the result of incompatibility of red blood cell donor with patient's antibody. The symptoms are various, including sudden onset of febrile or chills, hypotension, dyspnea, hemoglobinuria, disseminated intravascular coagulation, and acute renal failure.[4]

Hemovigilance is a set of systematic procedures to detect any adverse events and incidences in the whole transfusion chain, from the collection of blood, processing blood products, until follow up of its recipients. Hemovigilance is very important to prevent any adverse events related to blood product transfusion.[5]

Understanding the characteristics of transfusion reaction and its contributing factors are important to construct plan in facing transfusion reactions. At present, there are limited data about transfusion reactions in Indonesia. Therefore, in this study, we aim to determine the characteristics of acute transfusion reactions and its relations with other contributing factors.

METHODS

This was a retrospective descriptive study conducted at Cipto Mangunkusumo Hospital, an Indonesian national referral hospital. The data of transfusion reactions were obtained from inpatients and outpatients from all unit/department in the hospital. This study started from January to December 2017. Total sampling was preferred to produce more reliable results.

In our center, transfusion reactions were categorized into three different degree: 1) mild (e.g. localized erythema, pruritus, mild rash, transient urticaria/flushing); 2) moderate (e.g. unexplained febrile ≥ 39°C, temperature rise ≥ 2°C, chills, rigors, multiple rash, nausea, vomiting, myalgia, angioedema/wheezing/persistent urticaria without signs of circulatory problems); 3) severe (e.g. hypotension, any signs of shock, dyspnea, severe stridor, angioedema, anaphylaxis, chest pain, headache, bleeding, and hemoglobinuria).

Meanwhile, based on the affected body systems, transfusion reactions were grouped into dermatologic (e.g. edema, erythema, pruritus, flushing), respiratory (e.g. dyspnea, wheezing), constitutional (e.g. chills, febrile, rigors, diaphoresis, pain), neurological (e.g. seizure, dizziness, lethargy, agitation, twitching), and circulatory symptoms (hypotension, tachycardia).

The experiment used archive materials which do not have link with patient information.

RESULTS

Transfusion reactions were occurred in 288 subjects (0.5%) from a total of 57.227 patients received blood transfusion. Table 1 showed that the number of children subjects (56.6%) were greater than adults (43.4%). No significant difference was observed between the number of male and female subjects. Packed red cells/PRC (51.4%) was the predominant blood product which caused transfusion reactions, followed by thrombocyte concentrate/TC (43.4%), fresh frozen plasma/FFP (4.2%), and cryoprecipitate (1.0%). A total of 51.4% of subjects had past transfusion history.

There were many manifestations of acute transfusion reactions (Table 1). Five most common predominant symptoms of ATRs were pruritus/itch (27.4%), febrile/increased temperature (19.1%), chills (14.2%), transient urticaria (9.7%), and angioedema (7.7%).

ATRs could be classified by several indicators. Based on the affected body system, the majority of subjects had dermatologic (56.6%) and constitutional symptoms (34.4%). Based on the degree of transfusion reaction, most of subjects had mild (55.9%) and moderate (33.0%) manifestations (Table 2).

Table 1. Characteristic of subjects

Characteristics	n (%)
Age	
≤ 18 years	163 (56.6)
> 18 years	125 (43.4)
Gender	
Male	136 (47.2)
Female	152 (52.8)
Blood products	
PRC	148 (51.4)
TC	125 (43.4)
FFP	12 (4.2)
Cryoprecipitate	3 (1.0)
Past transfusion history	
Yes	148 (51.4)
No	140 (48.6)
Predominant symptoms	
Pruritus/itch	79 (27.4)
Febrile or temperature rise	55 (19.1)
Chills	41 (14.2)
Transient urticaria	28 (9.7)
Angioedema	22 (7.7)
Flushing	20 (6.9)
Dyspnea	18 (6.2)
Rash	14 (4.9)
Hypotension	6 (2.1)
Nausea	3 (1.1)
Seizure	2 (0.7)

Table 2. Classification of transfusion reactions.

Transfusion reaction categories	n (%)
Systems involved	
Dermatologic symptoms	163 (56.6)
Constitutional symptoms	99 (34.4)
Respiratory symptoms	18 (6.3)
Circulatory symptoms	6 (2.1)
Neurological symptoms	2 (0.7)
Degree of transfusion reactions	
Mild	161 (55.9)
Moderate	95 (33.0)
Severe	32 (11.1)

Due to some limitations, we proceeded further evaluation in only 64 subjects or 50.4% of total subjects with moderate and severe manifestations. Table 3 showed that no incompatibility was found in 70.3% of the evaluations. Major incompatibility was found in two subjects with manifestation of febrile and chills. Minor incompatibility with positive donor HLA antibody was detected in one subject, which presented with TRALI. Antibodies in the rest of minor incompatibility results were undefined.

Table 3. Detection of incompatibility

Type of incompatibility	n (%)	Manifestation
Major incompatibility		
anti-E	1 (1.6)	Febrile and chills
anti-E and anti-c	1 (1.6)	Febrile and chills
Minor incompatibility		
anti-HLA antibody	1 (1.6)	TRALI
Undefined antibody	16 (25)	variative
No incompatibilty	45 (70.2)	

Most of children subjects had dermatologic symptoms (65.4%), while manifestations in adult subjects were dominated by dermatologic and constitutional symptoms (42.2%). Age of the subject affected the manifestation significantly (p=0.001). History of past transfusion did not affect the manifestation significantly (p=0.109). Mostly, subjects who got TC, FFP, and cryoprecipitate showed dermatologic symptoms (72.8%, 83.3%, and 100%, respectively). Interestingly, constitutional symptoms were the most common manifestations in patients who got PRC (Table 4).

Age of the subject also affected the degree of transfusion reactions significantly (p=0.001). Most of children subjects showed mild manifestations, while adult subjects showed mild and moderate manifestations. Past transfusion history also affected the degree of manifestations (p=0.022). Severe manifestations were found more common in patients without transfusion history (15.7%) than patients with transfusion history (6.7%). The majority of patients who got TC, FFP, and cryoprecipitate had mild manifestations. Meanwhile, patients who got PRC transfusion commonly had moderate (43.2%) and mild (42.6%) manifestations (Table 5).

DISCUSSIONS

In our study, we found PRC was the blood component that contributes the most acute transfusion reactions, followed by TC, FFP, and cryoprecipitate. The main explanation for this is the fact that the most common blood components being transfused in order are PRC, TC, FFP, and cryoprecipitate. Other studies also found similar results. Study in Japan revealed that the incidence of transfusion reaction per transfusion unit was higher in TC (3.8%), compared to FFP (1.3%), and PRC (0.6%).[6] Meanwhile, another study in India revealed that the highest incidence of transfusion reactions was occurred in patients receiving PRC (1.4%) and FFP (0.6%), but transfusion reactions never occurred in patients receiving TC.[7] These discrepancies may be explained by the fact that the transfusion reactions are affected by several factors, including ethnicity and clinical diagnosis.[8,9]

Table 4. Factors affecting predominant symptoms of transfusion reactions

	Symptoms, n(%)					p value
	Dermatologic	Constitutional	Respiratory	Circulation	Neurological	
Age						
≤ 18 years	117 (65.4)	53 (29.6)	6 (3.4)	2 (1.1)	1 (0.6)	0.001
> 18 years	46 (42.2)	46 (42.2)	12 (11.0)	4 (3.7)	1 (0.9)	
Past transfusion history						
Yes	94 (63.5)	45 (30.4)	8 (5.4)	0 (0)	1 (0.7)	0.109
No	69 (49.3)	54 (38.6)	10 (7.1)	6 (4.3)	1 (0.7)	
Type of blood products						
PRC	59 (39.9)	70 (47.3)	12 (8.1)	5 (3.4)	2 (1.4)	
TC	91 (72.8)	27 (21.6)	6 (4.8)	1 (0.8)	0 (0)	
FFP	10 (83.3)	2 (16.7)	0 (0)	0 (0)	0 (0)	N/A
Cryoprecipitate	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	

Table 5. Factors affecting the degree of transfusion reaction

	Category, n(%)			p value
	Mild	Moderate	Severe	
Age				
≤ 18 years	116 (64.8)	52 (29.1)	11 (6.1)	0.001
> 18 years	45 (41.3)	43 (39.4)	21 (19.3)	
Past transfusion history				
Yes	92 (62.2)	46 (31.1)	10 (6.7)	0.022
No	69 (49.3)	49 (35.0)	22 (15.7)	
Type of blood products				
PRC	63 (42.6)	64 (43.2)	21 (14.2)	
TC	85 (68.0)	29 (23.2)	11 (8.8)	N/A
FFP	10 (83.3)	2 (16.7)	0 (0)	
Cryoprecipitate	3 (100)	0 (0)	0 (0)	

In total, allergic reactions (pruritus/itch, transient urticaria, rash, etc) and febrile were the most common manifestations of ATR. This result was consistent with Bassi R study, which found that the most common clinical features of transfusion reactions were FNHTR and allergic reaction.[10] Allergic reactions are caused by reaction of recipient's IgE with allergen from donor, leading to release of mediators from mast cells. Several allergens that has been documented are donor's plasma protein (IgA and haptoglobin), chemical allergens (methylene blue in FFP preparation), and food allergen. Allergic reactions are also caused by passive transfer of antibodies and passive sensitization, when IgA and IgE-specific antibodies are infused from donor to patient.[11] Other studies found that allergic transfusion reactions might occur without allergen involvement, especially in platelet transfusions. Stored platelet concentrates contain accumulated inflammatory cytokines and chemokines, which directly bind to receptors in mast cells and basophils, called biological response modifiers (BRMs), including vascular endothelial growth factor, sCD40 ligand, and transforming growth factor-β1.[12,13]

Anaphylactic reactions (hypotension, bronchospasm, angioedema, etc) are the severe form of allergic reactions. It is caused by interaction of recipient's antibody with donor's plasma protein including IgA, haptoglobin, complement, and ethylene dioxide [11]. In case of anaphylaxis, IgG mediated mechanisms plays an important role, beside Ig-E mediated mechanisms. IgG specific allergen binds to FcγRs and causes subsequent release of platelet-activating factor (PAF) from basophil. In this mechanism, PAF is the major mediator for systemic anaphylaxis, rather than histamine.[12]

Febrile, rise in temperature, and chills are caused by interaction of WBC antigen – antibody and consequent cytokines release. Some cytokines that has been identified as the primary cause of febrile related transfusion are interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor α, which are released from leukocytes by acute hemolytic process (febrile hemolytic transfusion reaction/FHTR) or during storage (FNHTR).[11,14-16]

In our study, we found two cases of major incompatibility of rhesus antigen. One subject had anti-E, while the other had anti-E and anti-c, both in pre-transfusion and post-transfusion blood samples.

Interestingly, manifestations that appeared in both subject were only fever and chills. Other symptoms of acute hemolytic transfusion reactions (e.g. flank pain and hemoglobinuria), which usually appear in major incompatibility transfusion reaction cases, did not appear.[17] The symptoms resolved after transfusion was stopped and administration of acetaminophen and antihistamine IV. Goodell PP study demonstrated that 85.7% of patients with positive non-ABO incompatibility did not show any symptoms of transfusion reactions [18]. Besides, rhesus antigen C, c, E, and e are less immunogenic than antigen D.[16] The patient had underwent crossmatch analysis before transfusion, but the result was negative. Therefore, antibody screening before transfusion was conducted in our center since mid 2017.

One subject showed signs and symptoms of TRALI during administration of PRC. Further examination proved that the subject had minor incompatibility, and HLA antibody was detected in blood donor. Antibodies of a quarter of subjects with incompatibility could not be determined. They had various manifestations, including febrile, chills, urticaria, and angioedema. National Blood Bank plays an important role to assure that the donor with HLA antibody is excluded for further donation of any blood products.[11] In this study, we found that children tended to have milder ATRs than adults. Dermatologic symptoms, which represent allergic reaction, were found more common in children. The same results were also found by Oakley FD study, which demonstrated the incidence of allergic transfusion reaction between children and adults were 2.7/1000 and 1.1/1000.[19]

In this present study, we observed that from the total subjects who experienced transfusion reactions, the number of subjects with past transfusion history was almost equal to the number of subjects who never got transfusions. Moreover, subjects with transfusion history tended to have milder symptoms and mostly manifested as allergic reactions. This result can be explained by Kato H study which showed that first transfusion incidences of allergic reactions are higher than on subsequent transfusions.[20] On the contrary, Gwaram BA study showed previous transfusion history increased the risk of getting transfusion reactions.[21] Pedrosa AKKV study found that previous history of transfusion was not significantly associated with the type of transfusion reactions.[22] These discrepancies may be explained because the study population characteristics (including race) and type of blood being used in the practice are different from one study to others.

Most of subjects with PRC transfusion had constitutional symptoms, while subjects who received other blood products transfusion had dermatologic symptoms. Similar result was also found in Cho J study, which observed that the most common cause of FNHTR was RBC transfusion.[23] This can be explained by the fact that PRC has the greatest number of leukocytes, followed by TC, FFP, and cryoprecipitate.[24] Previous study proved that the prevalence of FNHTRs was reduced in the pre-storage leukocyte-reduced RBC transfusion and the prevalence of allergic reactions was reduced in the pre-storage leukocyte-reduced platelets transfusion.[15] It is hardly to determine whether allergic reactions following platelet transfusion are caused by plasma proteins or BRMs, but there is general agreement that the decreased amounts of plasma protein will reduce the risk of allergic reactions.[12]

Limitation of this study is not all subjects with moderate or severe transfusion reactions can be proceeded into further examinations. Other limitations are lack of data about leuco-filtration status for each blood component and the occurrence time of each transfusion reaction. Therefore, further studies with adding these variables are needed to fully comprehend the characteristics of transfusion reaction and its related factors, especially in Indonesian population.

In conclusion, PRC is the most common blood product received by subjects with transfusion reaction. ATRs predominantly manifest as dermatologic symptoms, which represent allergic reactions. Only a small portion of the ATRs are caused by incompatibility reactions. ATRs of PRC usually manifest as constitutional symptoms. ATRs of other blood components mostly manifest as allergic reactions. Children usually have milder ATRs, which are frequently presented as dermatologic symptoms. History of transfusion also affects the degree of ATRs.

From this study, we suggest for every blood transfusion practitioner to obtain full transfusion and adverse reactions history prior to transfusion. It is mandatory to closely monitor any adverse reactions related to transfusion, from the mildest to the most severe one. For patients receiving PRC, medical team members must be ready if any constitutional symptoms appeared, while for patients receiving other blood components, medical team members must be ready encounter allergic reactions.

Acknowledgements

Conflict of interest

There is nothing to declare.

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Screening of *Legionella pneumophila* from water sources in the hospitals in Jakarta

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Abstrak

Latar belakang: *Pneumonia akibat bakteri Legionella masih menjadi masalah di berbagai tempat di dunia; menjadi penyebab 2-15 % dari pneumonia yang perlu di rawat di Rumah Sakit. Kasus legionellosis di Indonesia dilaporkan terjadi di Bali pada tahun 1996 dan di Tangerang tahun 1999. Keberadaan Legionella di fasilitas Pelayanan Kesehatan berpotensi sebagai penyebab infeksi nosokomial. Bakteri Legionella hidup di lingkungan perairan hangat dan lembab, juga ditemukan diberbagai sumber air seperti, sumber air sistem pendingin ruangan, kolam renang, tempat penampungan air di rumah sakit, perkantoran, hotel, dan perumahan sehingga turut berkontribusi dalam terjadinya community acquired dan pneumonia nosokomial.*

Metode: *Penelitian ini merupakan penelitian deskriptif yang bertujuan untuk penapisan keberadaan Legionella pneumophila diberbagai sumber dan penampungan air di Rumah Sakit (RS) di Jakarta dengan menggunakan medium Legionella Charcoal Yeast Extract (CYE) dan dengan berbagai suplemen. Tujuh belas sampel air yang berasal dari berbagai sumber air di dua RS yang berlokasi diJakarta Utara dan Barat telah diteliti.*

Hasil: *Dua puluh satu koloni yang ditemukan memiliki karakterisitik L. pneumophila dari semua varian medium, namun pada tes agglutinasi latex tidak memberikan reaksi positif.*

Kesimpulan: *L. pneumophila tidak ditemukan diberbagai sumber air dari dua RS ini. Penggunaan metode yang lebih sensitif dan spesifik perlu dilakukan untuk memastikan ditemukannya L. pneumophila. **(Health Science Journal of Indonesia 2019;10(1):21-6)***

Kata kunci: *Legionellosis, Legionella pneumophila, medium BCYE*

Abstract

Background: Pneumonia due to Legionella bacteria is still a problem in various places in the world, causes 2-15% of pneumonia that need hospitalization. In Indonesia, legionellosis cases have been reported in Bali in 1996 and Tangerang in 1999. The existence of Legionella in healthcare facilities is potential to cause nosocomial infections. Legionella bacteria live in warm and humid waters, and are also commonly found in various water sources, such as water cooling systems, swimming pools, water reservoirs in hospitals, offices, hotels and housing. These bacteria contribute to the occurrence of community-acquired and nosocomial pneumonia.

Methods: This study was a descriptive research, and aimed to screen water sources and reservoirs in the hospitals in Jakarta for the existence of *Legionella pneumophilla* using Legionella Charcoal Yeast Extract (CYE) medium with various supplements. A total of 17 water samples from 2 hospitals located in West and North Jakarta have been examined.

Results: The results showed a total of 21 colonies with characteristics as of *L. pneumophila* were obtained from those water samples, however, none showed positive results in the latex agglutination test.

Conclusion: *L. pneumophila* was not found thus far in the water sources in these two hospitals. A more sensitive and specific approaches might be used to enable the findings of *L. pneumophila*. ***(Health Science Journal of Indonesia 2019;10(1):21-6)***

Keywords: Legionellosis, *Legionella pneumophila,* BCYE medium

Legionella is a rod or cocobacilli, aerobic, fastidious Gram-negative bacteria. These bacteria live in water, attach to biofilms and multiply intrinsically in amoeba.[1] Legionella habitats are warm and humid aquatic environments, and commonly found in various water sources such as water reservoirs, air conditioning systems (cooling tower)[2], swimming pool[3], hospital shelters[4,5,6], offices and hotels[6,7], and housing. *Legionella pneumophila* contributes to the occurrence of Community Acquired Pneumonia (CAP) and Health Care Associated Pneumonia (HAP).[6,8,9]

The incidence of Legionnaire disease globally remains uncertain. Legionellosis occurs when humans breathe aerosols or aspirate water containing *L. pneumophila* serogroup 1 and 6, and/or some other Legionella species; WHO in 2007 stated that legionellosis is a collection of various respiratory diseases caused by infection with *L. pneumophila* and several bacteria in the family Legionellaceae.[2] Seventy percents of cases of legionellosis are caused by *L. pneumophila* sero group 1, 20-30% of cases caused by other serogroups, and only 5-10% due to infection with other non-pneumophilla Legionella species such as *L. micdadei* (60%), *L. bozemanii* (15%), *L. dumoffii* (10%), *L. longbeachae* (5%), and the remaining 10% are *L. gormanii, L. wadsworthii, L. jordan, L. feeleii, L. oakridgensis*.[1,2,3,6]

ELDSNet, 2012 reported that in Europe, the cases of Legionnaire disease were from 1 to 30 cases per million cases and it was estimated that unreported cases were as much as 20 times.[8] The study by Phin et al, 2014 showed that the largest contributor to the case of Legionnaire disease was men and the world population was above 50 years old.[4] In the United States, there has been an increase in the crude incidence of Legionnaire disease from 2000 to 2009 which was associated with increased temperature and humidity.[4] In Iran, Yaslianifard et al, 2012 stated that the mortality rate from hospital-acquired Legionellosis was 80%, especially in patients with immunosuppression who were not treated with antibiotics. Visca et al, 1999[9] reported 30% of HAP was caused by Legionella in which *Legionella pneumophila* (*L. pneumophila*) serogroup 6 was found in a hospital heated-water systems. In Indonesia, legionellosis has been reported in Bali in 1996 and Tangerang in 1999.[10] Yasmon et al., 2010 using duplex-PCR method found Legionella sp. in 6 samples, and 1 positive sample of *L. pneumophilla* from a total of 9 samples from water reservoirs in offices towers in Jakarta.[6] Also, in Surabaya, Aksono

et al., 2017, found *L. pneumophila* in 1 out of 10 samples of swimming pool water.[3]

Feeley et al, 1978[11] and Feeley J. C. et al, 1979[12] developed a medium specifically for Legionella i.e. Buffered Charcoal Yeast Extract (BCYE), which then was further modified by Edelstein, 1981[13] and Edelstein, 1982[14] and was used as a selective medium for Legionella species. BCYE contains amino acid L-cysteine which is specifically needed by Legionella bacteria for its growth when cultured from environmental samples and clinical specimens; supplements containing antibiotics i.e. Cefamandole, Polymyxin and Anisomycin are also needed to inhibit many other bacteria found in water and specimens originating from the human body so that *L. pneumophila* can thrive. Various studies on Legionella have been carried out, however, information whether water sources in health facilities (hospitals) in Jakarta has been contaminated by *L. pneumophila* is not available thus far. This study aimed to screen the presence of *L. pneumophila* in various water sources and reservoirs in hospitals in Jakarta using BCYE variants medium.

METHODS

Study design

This research was a descriptive study with a cross-sectional design.

Place, population and time of study

The study was carried out in the Microbiology Laboratory of Department Microbiology Faculty of Medicine and Health Sciences Atma Jaya Catholic University of Indonesia from March 2018 to October 2018 (Research contract: No. 0419/III/LPPM.10.01/ 04/2018), ethical clearance No. 21/12/KEP-FKUAJ/2018. Two private hospitals located in North and West Jakarta Jakarta participated in this study. Water samples of each 200 mL were collected aseptically from several sources i.e. central air conditioning, storage water, tap water and hot water (pipe systems were either galvanised iron, PVC and polyethylene), and were put into sterile bottles and stored in boxes at room temperature for only a short time or less than an hour.[14,15] Samples were immediately sent to the Microbiology laboratory for processing. Samplings were conducted once on each sources.

The collection of environmental samples is in accordance to the regulation from Indonesia Health Ministry No.1538/MENKES/SK/XI/2003 concerning Standard Management of Legionella Specimens.

Bacterial Cultivation and Identification

Water samples, each of 10 ml, were centrifuged at 5500 rpm for 15 minutes, supernatant was discarded, and the sediment was pipetted on to selective media and streaked using Koch method. Incubation was carried out at 37^0C for 3-10 days in anaerobic jar contained 5%-10% CO_2.[15] Bacterial colonies were observed on day 3, 7 and 10. Morphology characteristics of the colony of *L. pneumophila* are as follow: gray in colour, shiny, convex, circular, smooth edge, and darker at center with 3-4 mm diameter.

Four variants of selective medium were used as follow:

Variant 1: Charcoal Yeast Extract (CYE) agar base medium (Oxoid™) contained activated charcoal, yeast extract with addition of BCYE (Oxoid™) supplements containing potassium hydroxide, ferric pyrophosphate, cysteine and ketoglutarate.

Variant 2: CYE agar base medium with addition of BCYE supplement that did not contain cysteine (Oxoid™)

Variant 3: The same as variant 1, plus supplement BMPA-α (Oxoid™) which contains antibiotics cefamadole, polymyxcin and anisomycin[14]

Variant 4: The same as variant 2 with addition of BMPA-α supplement[14]

The suspected colonies were picked up and stained with Gram stain, and further tested for their properties of oxidase and catalase. The oxidase test was conducted using oxidase strip (Oxoid™), and the catalase test was carried using H_2O_2 3%; *L. pneumophila* showed variable results with oxidase test and positive with catalase test. Finally, latex agglutination test was performed using Legionella (M45) from Microgen®, in which individual *L. pneumophila* serogroups 1, 2-15 and non *L. pneumophila* latex and positive control were included in the kit separately. The test permits the identification of *L. pneumophila* serogroups 1, 2-15, and non *L. pneumophila* species. The principle of the method is that the latex particles are coated with purified polyvalent serum against *L. pneumophila* serogroups. The test is positive when suspension of *L. pneumophila* mixed with the reagent and show aggregation of latex particles. *L. pneumophila* ATCC 225493 is used as a positive control bacteria.

RESULTS

Cultivation of control bacteria, *L. pneumophila* ATCC 22549, was carried out using variant 3 and 4 media following the procedures mentioned above. On day 3, the control bacteria grew and appeared thriving in both media as shown in Figure 1. Morphology of the colonies grew in both variants were as described above, they showed the same morphology characteristics.

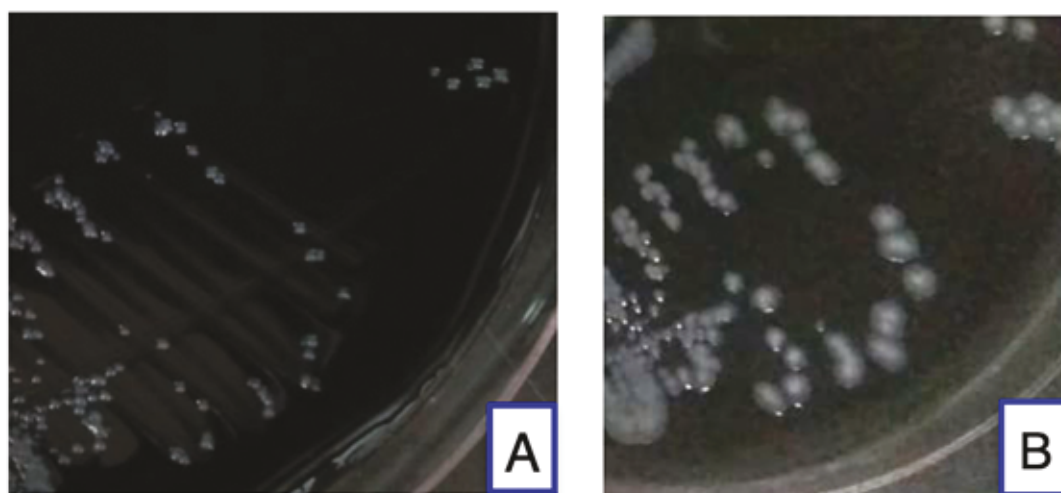*Figure 1. Colonies of L. pneumophila ATCC 225493 cultivated on CYE medium with addition of BCYE and BMPA-α supplements (variant 3) dan BCYE without cysteine and BMPA-α supplement (varian 4)*
This figure showed colonies of *L. pneumophila* ATCC 225493 grew on variant 3 medium (A) and on variant 4 medium (B). These colonies showed similar morphology characteristics on both media.

A total of 17 water samples were collected from 17 different sources, in which 10 samples were obtained from the hospital in North Jakarta (A), and 7 samples from the one in West Jakarta (B) (see Table 1). Water samples were all cultivated in all four variants media as described in the Methods section. The cultivated media were taken out from the incubator on day 3, 7 and 10 for observation of the growth and the presence of colonies that were in accordance with the characteristics of Legionella. Eight out of 17 water samples showed bacterial colony morphology with characteristics as of *L. pneumophila* (Table 1). Sixty percents (6/10) water samples from hospital A showed suspected *L. pneumophila* colonies, while those from hospital B showed only *29% (*2/7). The growth of the colonies suspected as *L. pneumophila* in variant 1 medium was shown in Figure 2. All suspected colonies showed no diffferences in their morphology regardless the medium used. The colony that showed characteristics of *L. pneumophila* was then picked and Gram stained and tested for catalase and oxidase. The result of Gram staining of the suspected colony was shown in Figure 3.
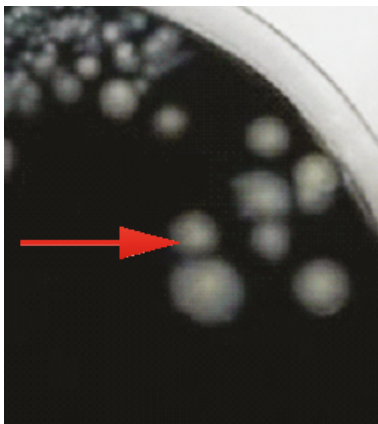

Figure 2. Appearance of bacterial colonies cultivated from water sample on CYE agar base medium contained BCYE supplement (variant 1 medium) Cultivation of water sample from water reservoir on variant 1 medium showed bacterial colonies with morphology characteristic in accordance of *L. pneumophila.*

A total of 21 colonies with morphology, catalase and oxidase characteristics in accordance to *L. pneumophila* were obtained (Table 1). Confirmation test using latex agglutination as described in the Method section was performed on these bacterial colonies and no agglutination showed up. None of the *L. pneumophila* serogroups 2-15 latex gave agglutination with all of the colonies tested.
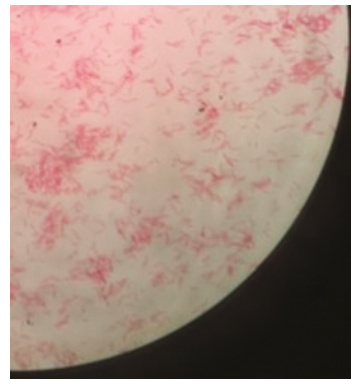
Figure 3. Gram stained of the bacteria colony with characteristic in accordance to L. pneumophila Gram staining of the suspected bacteria colony grew on variant 1 medium contained CYE (Oxoid™) agar base medium with addition of BCYE (Oxoid™) supplement showed rod bacilli Gram-negative.

DISCUSSION

Many studies reported that Legionella bacteria grew better in the present of L-cysteine amino acid.[11,12,13] On the contrary, however, this study showed that bacteria with characteristics such as *L. pneumophila* grew more on variant 2 medium in which supplement BCYE did not contain L-cysteine i.e. 5 water samples (sample number 3, 5, 8, 9 and 14), and only 2 water samples (no. 2 and 7) showed bacterial colonies suspected as *L. pneumophila* in variant 1 and 3 media which contained L-cysteine, which indicating that the growing colonies needed an amino acid L-cysteine. One water sample (no. 17) grew colonies suspected as *L. pneumophila* in variant 1 and 4 media, and seemed these bacteria could grow in either conditions i.e. with or without of L-cysteine.

Variant 3 medium contained L-cysteine and antibiotics, it was a highly selective medium and has been reported to be an enriched medium and could suppress the growth of other Gram negative bacteria found in water.[13,14] In this study, 5 water samples (no. 5, 7, 8, 9 and 14) showed colony growth with characteristics of *L. pneumophila* in variant 3 medium but also many other colonies that were not with the characteristics. Seemed many other bacteria also presence in the water sources that were not killed by the antibiotics in BMPA-α supplement. It was worth noted that 1 water sample i.e. no. 7 grew bacterial colonies only in variant 3 medium, indicating that the bacteria needed the present of amino acid L-cysteine and the growth was not inhibited by antibiotics. This colony was highly suited with the characteristics of *L. pneumophila*.

Table 1. Sources of water samples and the results of cultivation on Legionella CYE agar base medium with various supplements

No	Hospitals	Sources	Culture medium			
			Variant 1	Variant 2	Variant 3	Variant 4
1	A	Tap water (Staff room)	-	-	-	-
2		Water reservoir	+	-	-	-
3		Tap water (ICU)	+	+	-	+
4		AC (Pharmacy in operating theatre)	-	-	-	-
5		AC (Operating theatre 3)	-	+	+	+
6		AC (Operating theatre 2)	-	-	-	-
7		Tap Water (NICU)	-	-	+	-
8		AC (Operating theatre 1)	+	+	+	+
9		AC (Recovery room)	-	+	+	+
10		Tap water (Haemodialysis room)	-	-	-	-
11	B	Water reservoir (1st floor)	-	-	-	-
12		AC (ICU room 1)	-	-	-	-
13		AC (Operating theatre 1)	-	-	-	-
14		AHU (3rd floor)	+	+	+	+
15		AHU (4th floor)	-	-	-	-
16		Hot water (Operating theatre 3)	-	-	-	-
17		Water reservoir (2nd floor)	+	-	-	+

Note:
A: represented the hospital in North Jakarta; B represented the hospital in West Jakarta
+: Bacterial colonies showed morphology characteristics of *L. pneumophila*, catalase test positive, oxidase test variable
 -: None showed characteristics of *L. pneumophila*
Variants 1, 2, 3 and 4: culture medium used as described in the Methods section
AC: Air conditioner; AHU: Air handling unit; ICU: Intensive care unit; NICU: Neonate intensive care unit.

In variant 4 medium, which did not contain L-cysteine but contained antibiotics, 6 water samples showed positive bacterial colonies in accordance with *L. pneumophila* characteristics; this variant medium showed the highest number of growth of suspected *L. pneumophila* colonies, though none of them showed positive reaction in the latex agglutination test.

Latex agglutination used in this study is specific for *L. pneumophila* serogroups 2-15 which are found in many water sources, but has a relatively low virulence compared to *L. pneumophila* serogroup 1. In this study none of the colonies with the characteristics of *L. pneumophila* showed agglutination, not even the one of colony from sample no.17 which was highly suspected. Serology tests such as latex slide agglutination are commonly used in the diagnostic laboratory because they are simple, rapid and widely available. However, the sensitivity and specificity of the agglutination test needs to be considered. Previous study reported the sensitivity of latex agglutination was 85.7% compared to 16S rRNA PCR-DNA methods, and also showed some cross reactivity.[16] Further, up to recently 42 Legionella species with 64 serogroups has been identified, in which *L. pneumophila* constituted 91.5% of the isolates. Serogroup 1 was the predominant (84.2%), and serogroups 2–13 (7.4%) accounted for the remaining serogroups.[17] CDC reported only less than 5% of cases of was caused by Legionella non-pneumophila species.[18]

Conventional methods somehow are more applicable to be used in the middle income country such as Indonesia since the practice does not require highly skilled personnels and expensive machineries. The use of specific medium with various supplements for the cultivation of Legionella in the present study showed some colonies with characteristics of *L. pneumophila*. Nonetheless, the confirmation test using latex agglutination was not successful to identify *L. pneumophila*. This might be due to the existence of many species of Legionella and serogroups of *L. pneumophila*. Therefore, more specific and sensitive methods such as PCR-DNA sequencing of 16S rRNA might be needed to enable the findings this microorganism.

In conclusion, screening of Legionella bacteria from many water sources collected from two private hospitals in Jakarta using four variants media specific for Legionella showed some growth of bacterial colonies with morphology, catalase and oxidase characteristics in accordance to *L. pneumophila*.

Nonetheless, the confirmatory test using latex agglutination was not successful to identify *L. pneumophila*. A more sensitive and specific approach such as 16S rRNA PCR and sequencing may be used in the up coming investigation to ensure the findings of *L. pneumophila.*

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Evaluation of claim submission and returning for BPJS inpatient services: a case study of hospital X in 2017

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Abstrak

Latar belakang: *Keterlambatan dan ketidaklengkapan pengajuan klaim menyebabkan keterlambatan pembayaran klaim yang akan berdampak pada arus kas rumah sakit (RS). Artikel ini bertujuan untuk menilai pengajuan dan pengembalian klaim pada pelayanan rawat inap pasien BPJS.*

Metode: *Penelitian potong lintang dengan desain studi kasus. Sumber data menggunakan data pengajuan dan pengembalian klaim rawat inap pasien BPJS periode Januari-Juni 2017. Data dianalisis secara deskriptif.*

Hasil: *frekuensi pengajuan klaim rawat inap terbanyak 17 kali dan terendah 13 kali dalam sebulan, yang berarti RS mengajukan klaim ke BPJS hampir setiap 2-3 hari sekali.Dari 11,945 berkas klaim, sebanyak 3,013 (25,2%) berkas klaim dikembalikan ke RS oleh BPJS. Nilai klaim yang diajukan untuk 11,945 berkas adalah Rp. 146,967,494,700, sedangkan nilai klaim dari berkas yang dikembalikan sebesar Rp. 45,150,888,100-. Alasan berkas dikembaliakn antara lain masalah administrasi, ketidaklengkapan resume medis, pemeriksaan penunjang, konfirmasi koding, tidak layak, pinjam status, dan TXT yang tidak terbaca. Penyebab paling banyak berkas dikembalikan adalah konfirmasi koding (42,4%) dan ketidaklengkapan resume medis (30,3%).*

Kesimpulan: *tampaknya RS tidak pernah mengalami keterlambatan dalam pengajuan klaim, namun berkas klaim yang dikembalikan BPJS masih banyak, yang utamanya disebabkan oleh permasalahan koding dan ketidaklengkapan resume medis.* ***(Health Science Journal of Indonesia 2019;10(1):27-31)***

Kata kunci: *Penilaian, klaim, pengajuan, pengembalian.*

Abstract

Background: incomplete and late claim submission may result in the delay of claim payment. The impact of late payment will certainly disrupt the cash flow of the hospital. This study aims to evaluate the claim submission and returning for BPJS inpatient services.

Methods: this was cross sectional study with a case study design approach. The source of data used was submission and returned claim data from hospital financing department during the period of January to June 2017. The data were analyzed descriptively.

Results: the highest frequency for inpatients claim submission was 17 times and the lowest was 13 times. The hospital submit the claim file almost every 2-3 days. Of the 11.945 inpatient claims, as many as 3.013 claim files were returned by BPJS. The total claim amounts of 11,945 files was Rp. 146.967.494.700,- and, the total amount of returned claim was Rp. 45.150.888.100,-. The reasons of claim returned including administrative completeness, incomplete summary discharge , confirmation of coding, inappropriate files, unreadable TXT in BPJS application and supporting examination. The most common causes of claim files returned was confirmation of coding (42.4%) and incompleteness of discharge summary (30.3%)

Conclusion: the hospital was never late in submitting claim documents but the claim returned by BPJS were still high. The most common causes of claim returned to the hospital was coding confirmation and incompleteness of discharge summary. ***(Health Science Journal of Indonesia 2019;10(1):27-31)***

Keywords: Evaluation, claim, submission, returning

In the Jaminan Kesehatan Nasional (JKN) era, most of the hospital patients (80-90%) are the JKN participants.[1,2] This has caused the health insurance claims become the main income for hospital in Indonesia.[3] Incomplete and late claim submission may result in the delay of claim payment by Badan Penyelenggaraan Jaminan Sosial (BPJS). Therefore the claim file submitted must be complete in accordance with the requirements determined by the BPJS.[4] Claim management is a process since the claim is accepted by BPJS until the claim is verified, recorded and paid. Badan Penyelenggaraan Jaminan Sosial must pay the hospital claim no later than 15 days after the claim is verified.[2] If the document is complete, the claim payment process will be faster.[4] Conversely, the incomplete document will extend the claim settlement process.[4]

Badan Penyelenggaraan Jaminan Sosial will returns the claim file to the hospital when the file is incomplete or need to be revised after the verification process has been finished.[5] Revising and returning claim documents to BPJS can take time up to six months.[6] BPJS will postpone the payment for returned claim until the hospital resubmitted the claims. The impact of late payment will certainly disrupt the cash flow of the hospital, especially if 90% of hospital patients are JKN participants.[1] The hospitals in collaboration with BPJS depend on the income from BPJS for operational funding.[6] There are several problems faced by hospitals as a result of late claim payments such as the disruption of drug availability or lack the stock of medicines and consumables, poor maintenance of medical equipments as well as decrease in doctor's performance because of the delay in salary and incentive payment.[2,7]

BPJS targets all claims to be paid within one month after the claim document is submitted. However, the target has only been met as much as 60%. There is a tendency to delay claim settlement since November 2017.[2] Timely and appropriate claim reimbursement are very important to ensure provider satisfaction, fiscal stability, and compliance with regulations.[8] According to USAID report, in 2015 a total of pending claims for type B hospitals in Indonesia there are around 589 million USD or Rp. 8 trillion (the rupiah exchange rate in 2015: Rp. 13,726, -). Several studies on the BPJS claims previously found that pending claims are caused by disagreement of coding diagnosis or medical procedure between hospital coder and BPJS. The diagnosis code used is sometimes not approved by BPJS. In addition to coding problems, pending claims are also caused by

incomplete claim documents, incomplete medical resumes, surgery report, and supporting examination documents.[6,9,10] After 4 years the implementations of JKN, the hospital X still faces the problem of pending claim payments from BPJS due to returning of claim file for inpatient services. This study aims to evaluate the claim submission and returning for BPJS inpatient services.

METHODS

This was a cross sectional study with a case study design approach. It was carried out at one type A government hospital in Jakarta, from July to Desember 2017. The data was collected from hospital financing department. The source of the data in this study was obtained from all claim data of submission and returning for hospitalization of BPJS patients during the period of January to June 2017 (first semester).

Claim submission is regarded since the patients discharge from the hospital until the claim is accepted by BPJS. Based on the guidance of health care facilities claim administration from the BPJS, the health facilities must submit claims every month, no later than the 10th of the following month regularly. Claim will be returned if BPJS does not approve the claim file after verification process. The data collected were the frequency of claim submission (times in a month), the number of claim submission, total amount of claim submission, number of returned claim, total amount of returned claim, and the causes of returned claim.

The data were analyzed descriptively. Ethical approval was obtained from Ethics Committee, Faculty of Public Health, University of Indonesia with letter number: 564/UN2.F10/PPM.00.02/2017.

RESULTS

This study used the inpatient claim submission and returning data from January to Juni in 2017 which consisted of 11.945 individual claims.

This following pie chart illustrates that during January, hospital had submitted the claim for BPJS inpatients as many as 17 times, followed by 13 times in February, 15 times in March and so on. During the first semester, the highest frequency for claim submission was 17 times and the lowest was 13 times. The hospital delivered the file claims to BPJS almost every 2-3 days.
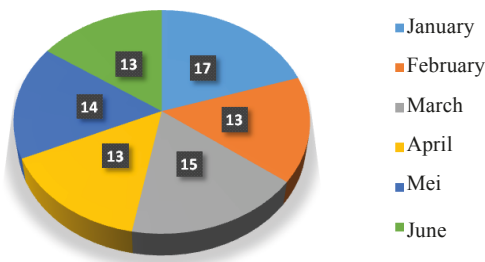
Figure 1. frequency of inpatient claim submission (times a month)

Tabel 1 shows that the average of BPJS inpatients is about 2000 patients per month. In term of claim submission during the first semester, there are 11,945 individual claims files submitted to BPJS which the total claim amounted to Rp. 146,967,494,700, -. Of the

11,945 filing claims, there are 3,013 file claims or as many as 25.2% were returned by BPJS. Meanwhile the total claim value of returned claims is Rp. 45,150,888,100 - for this period.

The pie chart on figure 2 demonstrates return of claim files from January to June 2017 by BPJS verifiers. There are several reasons including administrative revision, denied claims, incomplete discharge summary, confirmation of coding, borrowing documents in medical records by BPJS, unreadable TXT file and incomplete supporting examinations. The most common cause of claim files returned is confirmation of coding, which has 42.4%, following by incomplete discharge summary 30.3%, incomplete supporting examination 11.1% and administrative revision 9.8%.

Table 1. Condition of claim submission and returned for BPJS inpatient

Month	Submission (n)	Claim amount (IDR)	Returned		Claim amount (IDR)
			(n)	%	
January	2047	25,552,561,200	650	31.8	10,260,426,000
February	1839	22,883,642,800	584	31.8	8,985,010,200
March	2208	27,276,245,000	262	11.9	3,844,762,800
April	1924	23,434,893,500	454	23.6	6,305,600,000
May	2073	24,355,891,200	573	27.6	8,594,112,500
June	1854	23,464,261,000	490	26.4	7,160,976,600
Total	11945	146,967,494,700	3013	25.2	45,150,888,100
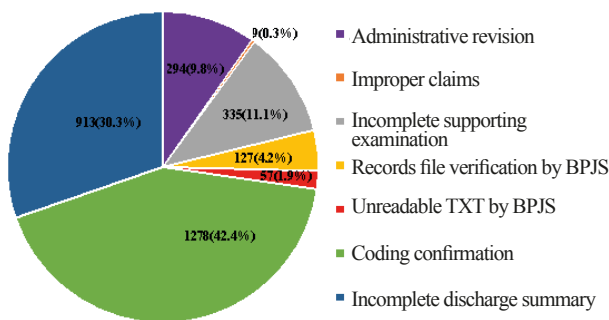
Figure 2. causes of returned claims for BPJS inpatients

DISCUSSION

This study has limitation. Among others, there was an absence of claim payment data and conformity of claim submission and claim payment by BPJS, interviews with financing department staff were not conducted to sharpen the result of the study.

This study found the frequency of claims submission to BPJS office around 13 to 17 times per month or in other word the claims was submitted more or less

every 2-3 days per month. According to the practical guideline for BPJS administration claims, hospitals should submit claim documents that are complete no later than the 10th of the following month.[11] In this case, the hospital is quite good in submitting the claims because after the patients discharge from the hospital, the claim was submitted in the same month. Even for the patients discharge at the end of the month, the claim file can be delivered faster than the time set by the BPJS. In contrast, Sophia et al. found the claims in 2015 at the Mintoharjo public hospital were billed in 2016. Mintohardjo public hospital had not been able to carry out the claim submission according to the time set. Claims were carried out 2 to 3 times per month of service because of the problems in the hospital.[12]

Of the total claims submitted, there were 25.2% of claim documents returned by BPJS during the first semester of 2017. In other words, BPJS postponed the claim payments by 25.2% or worth Rp.45.150.888.100,- until the hospital revise the claim documents in accordance with BPJS

verification results and re-submitted these claims. Similarly with this study, Park Y et al reported the claim returned to the providers was 25% and 24% for tertiary and general hospital respectively, where the claim returned was higher in inpatient groups in South Korea.[13] Compared to study done by Andi, the percentage of pending claims in this study was still higher, in Pontianak public hospital the pending claims was 6.98%.[14] Likewise, the study conducted by Ervita at the Muhammadiyah Malang General Hospital found that from the total inpatient claims submitted to BPJS, as many as 5.3% had been returned by BPJS.[9] The difference of the result may be due to the hospital X was a type A hospital which was set as a national referral hospital. Likely, the hospital treated the diseases or medical condition with severity level 3 which the diseases was more severe or complex.

The greatest percentage of claims returned by BPJS was coding confirmation, following by incompleteness of discharge summary and supporting examination. This issues will be coordinated by medical record department with the medical staff groups. Meanwhile the administrative revision, improper claims and unreadable TXT file will be handled by patient receivables management unit. The previous study done by Irmawati also reported similar causes for pending claims such as incomplete administration files, discharge summary, lack of supporting file and incompatibility of diagnosis made by physicians.[5] Other previous study done by Malonda et al found that many physicians did not write diagnosis and procedures code based on the ICD in the discharge summary.[15] Dhakal S revealed that coding errors in the discharge inpatients data as one of the major issues found in health information management department at Happy Valley Medical Center Hospital, Southern California.[16] However Cheng P suggested that accurate and complete clinical documentation is an important precondition for accurate clinical coding.[17]

In conclusion, the hospital was never late in submitting inpatients claim file but the returned claims by BPJS were still high. The most common causes of returned claims was coding confirmation and incompleteness of discharge summary.

The hospital management should coordinates with medical record department, medical staff groups and receivables management unit to address the issues.

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Correlation of overweight and academic achievement at grade 1-3 pupil at school of highscope Indonesia 2018

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Abstrak

Latar belakang: Berdasarkan data WHO pada tahun 2011 menunjukkan 1 dari 10 anak di dunia mengalami obesitas (WHO, 2011). Data status gizi pada anak usia 5-12 tahun di DKI Jakarta menunjukkan underweight 14,0% dan overweight 6,8%. Data secara spesifik untuk wilayah Jakarta Selatan adalah underweight 7,4% dan overweight 7,3%. Permasalahan gizi merupakan salah satu faktor penting yang berpengaruh terhadap prestasi akademik siswa. Tujuan dari penelitian: mengetahui pengaruh status gizi terhadap prestasi akademik siswa kelas 1-3 sekolah dasar.

Metode: desain yang digunakan adalah cohort restrospective dengan melihat hubungan antara hasil School Wide Assessment (SWA) dengan status gizi anak pada 9 bulan sebelumnya. Populasi dalam penelitian ini adalah siswa kelas 1-3 sekolah dasar di Sekolah HighScope Indonesia dengan total sampling yaitu berjumlah 480 anak.

Hasil: Hasil penelitian ini menunjukkan bahwa terdapat hubungan signifikan antara variabel status gizi terhadap prestasi akademik 6:29 RR (95% CI 3,82-10,35). Dalam analisis regresi cox menunjukkan status gizi yang baik memiliki RR pada 3,17 (95% CI 2,404 hingga 4,204) dan signifikan pada nilai p-value 0,000. Artinya, siswa yang memiliki kelebihan berat badan memiliki risiko kinerja akademik yang buruk. Sedangkan variabel lainnya menunjukkan bahwa tidak ada hubungan yang signifikan dengan risiko memiliki kinerja akademik yang buruk. Pada model akhir analisis regresi cox pada variabel status gizi pada prestasi juga menunjukkan nilai RR sebesar 3,09 (95% CI 2,365 hingga 4,053) p-value 0,000.

Kesimpulan: Anak-anak dengan kelebihan berat badan berisiko untuk memiliki prestasi akademik yang buruk sebesar 6.3 kali. (Health Science Journal of Indonesia 2019;10(1):32-40)

Kata kunci: Status gizi, prestasi belajar, faktor risiko, cohort retrospective

Abstract

Background: Based on WHO data in 2011, 1 in 10 children in the world are obese (WHO, 2011). Nutritional status data in children aged 5-12 years in DKI Jakarta shows 14.0% underweight and overweight 6.8%. Data specifically for the South Jakarta region is 7.4% underweight and 7.3% overweight. Nutritional problems are one of the important factors that influence student academic achievement. The purpose of the study: to determine the effect of nutritional status on academic achievement of students in grades 1-3 in elementary school.

Methods: the design used was a retrospective cohort by looking at the relationship between the School Wide Assessment (SWA) score and the nutritional status of children in the previous 9 months. The population in this study were students in grades 1-3 at HighScope Indonesia School with a total sampling of 480 children.

Results: The results of this study indicate that there is a significant relationship between variables of nutritional status on academic achievement 6:29 RR (95% CI 3.82-10.35). In the cox regression analysis showed good nutritional status had RR at 3.17 (95% CI 2.404 to 4.204) and was significant at p-value 0.000. While other variables indicate that there is no significant relationship with the risk of having poor academic performance. In the final model cox regression analysis on variable nutritional status on achievement also showed RR values of 3.09 (95% CI 2.365 to 4,053) p-value 0,000.

Conclusion: Children who are overweight are at risk for having bad academic achievement of 6.3 times. *(Health Science Journal of Indonesia 2019;10(1):32-40)*

Keywords: Nutritional status, academic achievement, risk factors, retrospective cohort

Nutritional status for children measuring by body mass index that calculate with weight and height of children.[1, 2] The definition of obesity according to the World Health Organization (WHO) is the abnormal accumulation of body fat that will increased healthy risks,[1,2] in 2007 reported that there were 95.2 million children, or approximately 14.3% having prevalence of underweight in children's nutritional status in the world[3], While based on data from the WHO in 2011 stated that 1 in 10 children in the world are overweight. Research of Bier (2007) also showed that more than 9 million children aged 6 years and over are overweight[12], In fact, since 1970, obesity problems in children tends to increase. These numbers tend to be doubled at children aged 2-5 year in 2007, and threefold in children aged 16-11 years.[11, 12]

The nutritional status in Indonesia, according to Riskesdas data 2013 on children aged 5-12 years, the prevalence of underweight is 11.2%, consisting of 4% of severe and malnutrition status 7.2%[4], and also showed that obesity problems in children in Indonesia were quite high, with prevalence of 18.8% comprising 10.8% obese and very obese (obesity) as much as 8.8%. Likewise for stunting prevalence is as much as 30.7%, which is composed of 12.3% malnutrition and 18.4% severe nutrition status.[4]

The nutritional status of school children aged 5-12 years in Jakarta shows 3.2% is a very thin, 6.1%, underweight, 4.0% stunting and 10.0% wasting[4]. While in DKI Jakarta the nutrition data showed that 14.0% underweight, 22.7% stunting, 9.9% wasting and 6.8%. In South Jakarta showed 7.4% underweight, 17.8% stunting, 6.3% wasting and 7.3% overweight. These data showed of the nutritional problems that occurred in Jakarta.[4]

The nutritional status of children will be having impacts on improving the quality of human resources. Chronic malnutrition or stunting is closely linked to getting lower in academic achievement school.[5,6] Nutritional problems also have an impact on child development. Nutrition is one of important factor in contributing to the quality of education achievements[7]. However, the nutritional problems actually just not only malnutrition but children who are overweight actually also having nutritional problems.[11, 13] The prevalence of stunting, underweight and wasting were 27.5% (95% CI 23.2–31.9%), 20.4% (95% CI 16.5–24.3%) and 8.7% (95% CI 6.2–11.5%),

correspondingly. Previous studies conducted in different areas have shown that under nutrition is common among school-age children; it was reported in the form of stunting range from 11 to 48.7% and underweight from 7.2 to 59.7%.[12] A study conducted in eastern Ethiopia reported that the prevalence of stunting was 8.9%, of which, 2% had severe stunted among school-aged children.[12] Though evidence about the prevalence of malnutrition is well studied in Ethiopia, there is insufficient evidence regarding nutritional status allied with academic performance among school-age children.[12]

The low level of educational performance was significantly higher ($p < 0.05$) among the stunted, underweight and wasted children than that of the normal children. In multivariable logistic regression, age of the child (Adjusted Odds Ratio (AOR) = 0.177, 95% CI 0.07, 0.4), monthly income less < 1000.00 birr (AOR = 0.05, 95% Cl 0.02, 0.15), stunted children (AOR = 0.21, 95% CI 0.10, 0.43) and under-weight (AOR = 0.63, 95% CI 0.26, 0.84) were associated with academic performance. This study revealed that indicators of undernutrition were prevalent among school-age children. Thus, collaboration between the health and education sectors is required to alleviate the problem.[11,12]

The purpose of this study is to determine the relationship of nutritional status with the cumulative academic achievement in grades 1-3 elementary school students in the HighScope Indonesia in 2018.

METHODS

This is a quantitative research with a retrospective cohort study aimed to look at the relationship between nutritional status and academic achievement. The data consist of dependent and independent variables. Taken from secondary data obtained from the recapitulation of the evaluation of student learning examination called School Wide Assessment (SWA) on the 3rd quarter of 2017/2018 school year its mean at March 2018. While the nutritional status data obtained from the health monitoring conducted by the school clinic at 9 months earlier, at June 2017.

This is how these restropective study conducting :
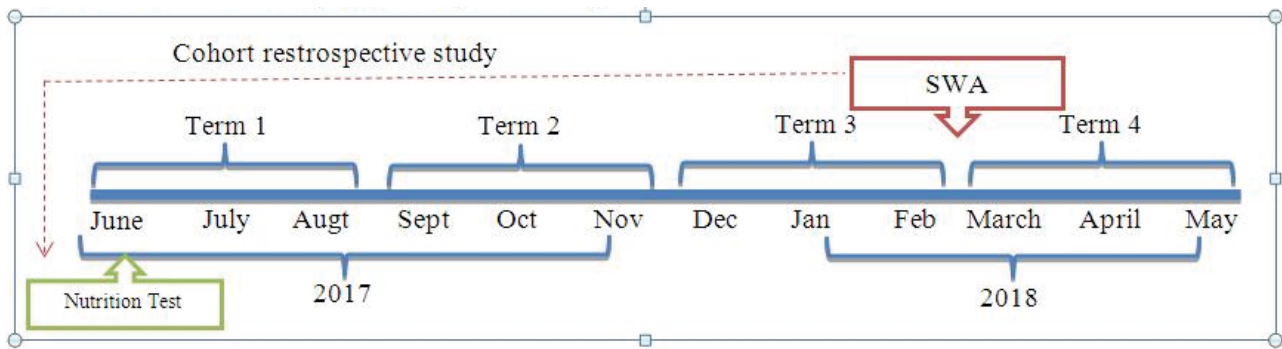
So, this research comparing between the SWA score and the nutritional status of the students for the past 9 months. It means that, th-is research is determining the relationship between the students' academic achievement with their nutritional status in the past(9 months earlier).

The study population is grade 1 until 3 primary school students in HighScope Indonesia with total 480 students. The inclusion criteria were boys and girls, age between 7-9 years who are elementary school students grades 1-3 in HighScope Indonesia who were at least already 1 year went enrolment; having normal child development, not experience physical disability and obtain written permission from parents (informed concent) to participate in the study. While the exclusion criteria were if respondents refused to participate in the research process, HighScope special needs students that have a neurological problems which is including autism, ADHD, learning disability, down syndrome, cerebral palsy, intellectual disablility, low vision or others.

The study was conducted at the HighScope Indonesia in South Jakarta. The research using Kelsey formula to determinate the sampling and base on that these research will need 341 students as a minimal sampling. So, the researcher determined that all of the grades 1-3 be used as total sampling. Data collection tools are questionnaire to determine the nutritional status and students academic achievement.

The number of samples is calculated by the minimum number of samples using the Kelsey formula for retrospective cohort studies, here are the results of the calculation:

$$N = \frac{(Z\frac{\alpha}{2} + Z\beta)^2 \times \rho \times (1 - \rho) \times (r + 1)}{(d*)^2 r}$$

N = Minimum sample size
P1 = Proportion of outcomes for those at risk
P2 = Proportion of outcomes for those who are not at risk
P = Average P1 and P2 or (P1 + P2) / 2

Based on academic achievement of HighScope Indonesia students in 2016 where the number of students who have a bellows level is 33.3% with RR is 1.5, the results of the calculation are as follows:
P1 = (RR) P2 = 1.5 (0.333) = 0.499
p   = (p1 + p2)/2 = (0.585 +0.39)/2 = 0.416
d * = p1-p2 = 0.585-0.39 = 0.166
Kelsey Sample Calculation Formula

$$= \frac{7.849 \times 0{,}416 \times 0{,}584 \times 2}{(0{,}166)^2 \times 1}$$

$$= \frac{3{,}813}{0{,}027}$$

= 141.24 "rounded up to 142, this is the number of 1 group. So that if 2 groups become = 142x 2 = 284. To anticipate a lost to follow-up or incomplete data, 20% is added to become = 341 samples.

The data was analyzed for statistical correlation and conducted with SPSS 24 serial to determine the relationship between the dependent and independent variables and also used logistic regression to determine the greatest affect between the variabels. Undernutrition in young children is often determined through measurement of height, weight, skin-fold thickness and age. The commonly derived indices from these measurements are: stunting - low height for age (HAZ), wasting - low weight for height (WHZ), underweight - low weight for age (WAZ) and BMI-for-age z-score.

Stunting is an indicator of chronic undernutrition, the result of prolonged food deprivation and/ or disease or illness; wasting is an indicator of acute undernutrition, the result of more recent food deprivation or illness; underweight is used as a composite indicator to reflect both acute and chronic undernutrition although it cannot distinguish between them.

These indices are compared against an international reference population developed from anthropometric

data collected in the United States by the National Center for Health Statistics (NCHS). Children whose measurements fall below –2 z-scores of the reference population median are considered undernourished, i.e. to have stunting, wasting or to be under-weight. Those children with measurements below –3 z-scores are considered to be severely undernourished.

Ethical Declaration

This study has been approved by Universitas Indonesia Public Health Ethics Committe with 420/UN2.F10/PPM.00.02/2018 as ethical number registered.

RESULTS

Respondents characteristics

Table 1. The Distribution Respondents Characteristics

Respondent's characteristics		n	%
Age	7 years	163	34.9
	8 years	165	34.4
	9 years	152	31.7
	Total	480	100
Number of siblings	≤ 2	336	70.0
	> 2	114	30.0
	Total	480	100
Order in family	elder	254	52.9
	second	215	44.8
	third	8	1.7
	fourth	3	0.6
	Total	480	100
Gender	Man	240	50.0
	woman	240	50.0
	Total	480	100
birth weight	Low`	16	3.3
	Normal	464	96.7
	Total	480	100
Birth termination	preterm	14	2.9
	aterm	466	97.1
	Total	480	100
Mother's education	S1	192	40.0
	S2	224	46.7
	S3	64	13.3
	Total	480	100
Father's education	S1	64	13.3
	S2	272	56.7
	S3	144	30.0
	Total	480	100

Respondents in this study were 480 students with aged 7 years are 163 children (34.9%), aged 8 years

are 165 children (34.4%) and aged 9 years old are 152 children (31.7%). There were 16 (3.3%) subjects had a history of low birth weight and 14 (2.9%) of the children had a history of premature birth. The nutritional status of underweight are 12 (2.5%), and children who having overweight categori are 112 (23.3%) and obese children are 131 (27.3%) children.

Nutritional Status of Respondents

Based on height, weight and age data of the respondents conducted by the school clinic in June 2017, the researcher calculating nutritional status using WHO Anthro-plus applications:

Calculating WAZ, HAZ and BAZ using data of the height, weight and age of the respondents. The result are:

Table 2. WAZ, HAZ and BAZ

Variables	mean	Std. Error	Std. deviation	Min	Max
WAZ	0.29	0,026	.570	-1.88	2.39
HAZ	0.30	0,019	.463	-0.76	1.88
BAZ	0.73	0,027	0,597	-2.71	2,66

After calculating the value of WAZ, HAZ and BAZ then the next step is referring to the Z-Score as shown in Table 1.2, so we will get the nutritional status of respondents into five categories as follows:

Then the nutritional status of respondents categorized into 3 categories: (1) Normal, (2) Underweight, (3) Overweight. The results were as follows:

Table 3. Nutritional Status 3 Category

Variables	Category	Frequency (n)	Percentage (%)
Nutritional status	Normal	354	47.3
	Underweight	2	2.5
	Overweight	124	50.2
Total		480	100

Counting and categorizing nutritional status is conducted in order to do bivariate and multivariate analysis to determine the influence of nutritional status on academic achievement.

Cumulative academic achievement based on school test's scores using the School Wide Assessment (SWA) are 69.05 as the average value and the lowest score on the math and English are 56. While 95 is the highest score in English and Bahasa Indonesia.

Respondents Academic Achievement

Table 4. Cumulative Academic Achievement

Variables	mean	Std.Error	Std. deviation	Min	Max
English	73.23	0.49	1.07	56	95
Indonesian	73.27	0.43	9.425	60	95
Mathematics	74.62	0.433	9.50	56	91
Science	72.01	0.39	8.54	60	90
Cumulative Academic Achievement	69.05	0.41	8.98	56	95

Formulation to calculating into cumulative academic achievement is as follows:

Cumulative Academic Performance Score = (Bahasa Indonesia x 35%) + (English x 35%) + (Mathematics x 15%) + (Science x 15%). After that will be defined into 3 categories : (1) Proficiency if the score are 80-100, (2) Progressing if the score are 60-79 and (3) Bellow level if the score are under 30-59.

So based on the formulation of the results obtained cumulative value of academic achievement as follows:

Table 4. Cumulative Frequency Distribution of Academic Achievement

Academic achievement	n	(%)
Cumulative Academic Achievement		
Proficiency	128	26.7
Progressing	141	29.4
bellow level	211	44.0

The frequency distribution of cumulative academic achievement in grade 1-3 are 128 students (26.7%) reach the proficiency level of, 141 students (29.4) is still progressing and 211 students (44.0%) is still on bellows levels.

Factors that Influence Nutritional Status

Nutritional status is the primary independent variable in this study, and would be analyze the effect of nutritional status on achievement is cumulative and will also be seen in greater depth effect on achievement in each subject. Due to the nutritional status of respondents divided into four categories: underweight, normal, overweight and obese then to the category bivariate analysis performed by dividing into two groups: good nutrition category and malnutrition. Good nutrition category contains respondents who have underweight and normal nutritional status. Category skinny inserted into good nutrition category because the respondents have a nutritional status at the level which is approaching the upper limit of normal category. While nutrition overweight and obese categories into malnutritional groups.

Next will be the analysis of the effect of nutritional status on cumulative academic achievement which is a cumulative value of the four subjects above. Here are the results:

Table 5. Relationship of Nutritional Status and Achievement Cumulative

Variables	Category	Good Nutrition		Malnutrition		Total		RR	95% CI	p-value
		n	%	n	%	n	%			
Nutritional status	Good Nutrition	253	71.0	103	29.0	356	100	1	The reference	The reference
	overweight	14	11.3	110	88.7	124	100	6:29	3.82-10.35	0000

On a cumulative academic achievement category, there were 253 children (71%) who are on good nutrition group, who has good academic achievement, and there were 103 children (29%) who had no good academic achievement. While the respondents have overweight there are 14 children (11.3%) who have a good academic achievement and 110 children (88.7%) who had no good academic achievement. Statistical analysis showed that the nutritional status of the respondents have a significant effect on student

achievement with value RR of 6.29 (95% CI 3.82 to 10.35) and p value of 0.000. From the table we can see that children with better nutritional status have a greater risk up to 6.3 times to having poor academic performance.

Based on the analysis above it can be concluded that nutritional status has a significant effect on cumulative academic achievement even statistically proven to have a greater impact if compared with achievement in each subject.

Multivariate analysis

Multivariate analysis were performed to examine the relationship of dependent variables (nutrition status) and the independent variables together with covariate variables that can be estimated relationship between independent variables and the dependent variable after being controlled by other covariates. The results of the multivariate analysis between academics achievement and the nutritional status are mentioned in table 6. In Cox regression analysis showed good nutritional status has a RR at 3.17 (95% CI 2.404 to 4.204) and significant at p value = 0.000. Its mean that the students who have overweight having a risk for poor academic performance. While the other variables showed that no significant relationship to the risk of having poor academic performance.

The result of confounding variables test, found that there is no confounder of father's education, mother's education, gender, number of siblings, birth weight status, prematurity or pre-term birth, extracurricular and age. The final model of the analysis mentioned at table 7.

Table 6. Cox Regression Analysis Between Nutritional Status and Other Variables Cumulative Against Academic Achievement

Variable	RR	95% CI	P-value
Nutritional status			
Good nutrition	(Ref)		
Overweight	3.17	2.404 to 4.204	0,000
What order are you in the family			
Child to 1	(Ref)		
2nd child	1.10	0.327 to 3.736	.871
3rd child	1.13	0.328 to 3.904	0,844
All 4 Kids	1.35	0.291 to 6.273	0,700
Number of siblings			
≤ 2	(Ref)		
> 2	1.08	0.779 to 1.517	0,624
Gender			
Man	(Ref)		
Woman	0.95	0.694 to 1.320	.790
LBW			
Normal	(Ref)		
Low	0.93	0.556 to 1.569	0.797
Type of preterm birth			
Normal	(Ref)		
premature	0.90	0.170 to 4.869	0.911
Education level of mother			
S1	(Ref)		
S2	1.04	0.665 to 1.644	0,848
S3	0.93	0.588 to 1.483	.770
Education level of father			
S1	(Ref)		
S2	1.14	0.679 to 1.917	.620
S3	1.11	0.742 to 1.676	0.599
extracurricular			
Mixed	(Ref)		
Physical	1.16	0.433 to 3.147	.760
Art	1.33	0.611 to 2.905	.471
IQ			
Superior	(Ref)		
Normal Birght	0.75	0.468 to 1.205	0.236
Average	1.01	0.666 to 1.537	0.955

Table 7. Results of Final Model Assessment of Nutritional Status Among the confounding Influence on Academic Achievement

Variable	RR	95% CI	P-value
Nutritional status			
good nutrition	(Ref)		
overweight	3.09	2.365 to 4.053	0,000

In the final model of the cox regression analysis on the nutritional status variables on achievement also demonstrates the value of RR of 3.09 (95% CI 2.365 to 4.053) p-value 0.000 so that it can be concluded that the nutritional status are variables that can have an influence on the risk of achievement poor academic in students.

DISCUSSION

The prevalence of nutrional status in this research are 2.5% underweight, and children who having overweight categori are 23.3% and obese children are 27.3%. In contrast, this finding of overweight children was higher as compared to other previous studies conducted in Brazil was found (14.9% stunted and 9.7% wasted)[12], in Kenya (24% stunted, 14.9% underweight, 9.7% wasted)[17], in Nicaragua (5% wasted).[18,19] The reason for this observed discrepancy might be due to sociodemographic characteristics, area of sampling and study period.

Our analysis found a significant relationship between nutritional status and cumulative academic achievement. Children with overweight are at risk in not good cumulative academic achievement at 6.2 times when compared with children who are well-nourished. After multivariate analysis using cox regression to the variables studied are obtained variables that had a significant influence are nutrition status.

Previous study revealed that age and income were significant factors for academic performance among primary school children. This finding was consistent with a systematic review and meta-analysis showed that there is a strong association between academic performance and socio-economic status including age.[20] Compromised socio-economic status of a family was statistically associated with poor academic performance in children.[21] Similarly, other studies done in Southeast Ethiopia[22] and in Malaysia[23] reported that minimum wealth indexed score of the family were a positive association with poor academic performance. This might be due to a balanced nutritional intake for adequate biological functioning lead to the cognitive processes and the outcome of academic performance.[23,14]

Research limitations

The limitations of this study are: (1) Potentially the lack of validity of secondary data is used both data about PSG and SWA. (2) Tend potential for the occurrence of selection bias and information bias due to the use of secondary data. (3) Limitations in the analysis of the other factors that influence academic achievement possible. (4) The result was a relative risk. (5) The sample used may be less representative of the population.

Data Quality

This study took a secondary data is data regarding school health monitoring are routinely conducted by the school clinic. The nutritional status periodicly conducted by schools every two months, however, the research only used nutritional data on June 2017. Secondary data related to nutritional status is mainly about their weight and height measurements made by nurses served in the school clinic so that in this case the validity of the data on weight and height can be properly accounted for. However, researchers did not perform the calibration of the equipment and tools used to measure weight and height, so it is possible the potential for misclassification bias.

While the data on academic achievement is taken from the data tabulation of the value of the School Wide Assessment (SWA) where it is the form of the exam schools for students who are exclusively designed by Teacher & Research Department (TRD) to measure the achievement of teaching and learning activities as well as one component used by schools to evaluate the education system applied in Indonesia HighScope school. Validity of School Wide Assessment (SWA) which is compiled by the Teaching and Research Department (TRD) though drafted by a team that is also responsible for the development of educational curriculum in schools HighScope Indonesia but have never tested the validity and reliability test. One of the things that can lessen its validity by researchers is that form of matter from the School Wide Assessment (SWA) is based on a paper and pencil test, while the system of teaching and learning in schools HighScope Indonesia using active learning and also Project Based Learning (PBL). It is possible there is a student's academic potential that may not be measured with a model question paper and pencil test. Nevertheless indeed

the School Wide Assessment (SWA) has been implemented by the School HighScope since 2014 with development efforts are continued until 2018. pencil test, while the system of teaching and learning in schools HighScope Indonesia using active learning and also Project Based Learning (PBL). It is possible there is a student's academic potential that may not be measured with a model question paper and pencil test. Nevertheless indeed the School Wide Assessment (SWA) has been implemented by the School HighScope since 2014 with development efforts are continued until 2018. pencil test, while the system of teaching and learning in schools HighScope Indonesia using active learning and also Project Based Learning (PBL). It is possible there is a student's academic potential that may not be measured with a model question paper and pencil test. Nevertheless indeed the School Wide Assessment (SWA) has been implemented by the School HighScope since 2014 with development efforts are continued until 2018.

The use of secondary data in this study is made of the limited data obtained by researchers because it is based only on data available to other factors which may affect the nutritional status can not be identified with more depth, while the primary data conducted by researchers only be complementary if No respondents have data that is incomplete, for example in terms of birth history data, birth weight and other data.

Respondents were used in this study was grade 1-3 elementary school, although the total sampling was taken and no respondents were lost to follow-up and yet there is still potential for selection bias because it can not represent the entire elementary school students from grades 1-6 where possible have different characteristics primarily related to age and nutritional status wherein the multivariate analysis both variables are variables that give large influence on achievement.

Validity Research

Exclusion and inclusion criteria set out in the sample selection is expected to minimize selection bias. The use of total sampling as a technique of sampling is also an effort to anticipate the existence of selection bias. However, the direct election of the site and the respondents used in this study could potentially lead to selection bias because it may not represent the general population of elementary school students in grade 1-3.

Outcome and risk factors in this study have also been the case in the past however, a lack of accuracy the validity of the measurement may still be occurs namely in terms of the measurement of nutritional status, the researchers do not know exactly the measurement process and the use of the measuring instrument, but due to the measurements performed by professional nurses, the potential for misclassification bias can be minimized. While in terms of the outcome measurement tools namely School Wide Assessment (SWA), made possible bias which has never done any test the validity of the test forms or types of questions used in the School Wide Assessment (SWA) is. Although determining the location and sample directly, but the number of samples used in this study have exceeded the minimum sample size, this study can be generalized to the general population. If the population have different types of schools with the School HighScope Indonesia.

In conclusion, the results of this research is nutritional status in the 1-3 grade elementary school students in the HighScope Indonesia Elementary School in 2018 divided into three categories: underweight, normal and overweight. There is a significant relationship between the variables of nutritional status on cumulative academic achievement. children with overweight were at risk in poor cumulative academic achievement compared to children who are well-nutritioned. Better nutritional status or children with overweight have a greater risk up to 6.3 times to having poor academic performance. Base on cox regression analysis, this study finded that the nutritional status are variables that can have an influence on the risk of achievement poor academic in students.

Educational activities to parents with effective communication which contains information about the importance of nutritional status of children, especially awareness of nutritional problems both nutrition and undernourishment. So that not only the child, thin and very thin are considered to have nutritional problems, but also on overweight should also get attention too. The parents also need to be aware of the influence of nutritional status and age to academic achievement so it would be more wise in choosing the food intake and type of school or training appropriate to the child's age.

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The evaluation of Nusantara Sehat program using Nusantara Sehat Public Health Index

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Abstrak

Latar Belakang: *Faktor geografi Indonesia yang berupa daratan, lautan, pegunungan, dan pulau-pulau yang tersebar menyebabkan distribusi tenaga kesehatan dan akses pelayanan kesehatan yang tidak optimal. Berdasarkan Peraturan menteri kesehatan yang telah ditetapkan, pemerintah berupaya mendayagunakan secara khusus sumber daya manusia kesehatan dalam kurun waktu tertentu dengan jumlah dan jenis tertentu, agar meningkatkan akses dan mutu pelayanan kesehatan pada fasilitas pelayanan kesehatan khususnya di wilayah Daerah Tertinggal, Perbatasan, dan Kepulauan (DTPK) dan Daerah Bermasalah Kesehatan (DBK) melalui Program Nusantara Sehat (NS).*

Metode: *Tahun 2015 telah ditugaskan Tim NS Batch 1 dan 2 pada 120 Puskesmas di DTPK dan DBK selama 2 tahun. Kemudian pada tahun 2017 setelah masa tugas berakhir, diadakan evaluasi program yang bertujuan untuk mengetahui dampak program NS terhadap indeks kesehatan masyarakat dengan menggunakan desain Pre and Post-Test Intervention with Control. Evaluasi dilakukan di 15 provinsi, 27 kabupaten, dan 60 Puskesmas pada bulan Februari - Desember 2017.*

Hasil: *Hasil evaluasi program menunjukkan bahwa pada tahun 2017 terjadi perubahan rata-rata indeks kesehatan masyarakat dibandingkan dengan tahun 2015, baik pada Puskesmas intervensi maupun kontrol (p=0,000). Kemudian hasil uji independen t-test terhadap delta perubahan indeks menunjukkan bahwa peningkatan indeks kesehatan masyarakat pada Puskesmas intervensi lebih besar dibandingkan dengan Puskesmas kontrol (p=0,046).*

Kesimpulan: *penugasan Tim NS pada Puskesmas telah membawa perbaikan indeks kesehatan masyarakat yang lebih baik. Diperlukan pengamatan lebih jauh terkait sustainabilitas Program NS dan analisis biaya manfaat (cost benefit analysis) terhadap Program NS.* **(Health Science Journal of Indonesia 2019;10(1):41-50)**

Kata Kunci: *Evaluasi program, Nusantara Sehat, Indeks Kesehatan Masyarakat, Indonesia.*

Abstract

Backgrounds: Indonesia's geographical factors in the form of land, oceans, mountains, and scattered islands have caused the distribution of health workforce and access to health services are not optimal. Based on the Minister of Health regulation, the government seeks to utilize health human resources specifically for a certain period, with certain number and types, in order to improve access and quality of health service to health service facilities, especially in remote area through the Nusantara Sehat Program (*Health Indonesia Program*-NS).

Methods: In 2015, NS Team Batch 1 and 2 were assigned to 120 primary health care center (Puskesmas) in remote areas for 2 years. Then in 2017 after the term ends, NS program evaluation were conducted in 15 provinces, 27 districts, and 60 Puskesmas from Feb to Dec 2017.

Results: This evaluation aims to analyze the impact of NS program on public health index using Pre and Post-Test Intervention with Control Design. The results of program evaluation showed that in 2017 there was a change in the average public health index compared to 2015, both in intervention and control Puskesmas (p = 0,000). The independent t-test result on the delta of index change indicated that public health index improvement at intervention Puskesmas is greater than the control (p = 0,046).

Conclusions: The assignment of NS Team at the Puskesmas has brought improvement of public health index. Further observations are needed regarding the sustainability and the cost benefit analysis of NS Program. **(Health Science Journal of Indonesia 2019;10(1):41-50)**

Keywords: Program evaluation, Nusantara Sehat, Public Health Index, Indonesia.

The health workforce has an important role in the health system where contributions, quantity, and distribution of the health workforce can improve the access and quality of health services, thereby affecting the health status of the community.[1] The more health workforce available in an area, the wider chance to access the health services in the region.[2,3] The World Health Organization (WHO) report states that there is a meaningful relationship between the number and quality of health workforce with immunization coverage, coverage of primary health services, child and infant health services and maternal survival, all of which are health indicators.[4]

One of the causes of the uneven spread of the health workforce in a region is the geographical condition.[5] Indonesia is an archipelago country which has geographical factors of land, sea, mountains, and scattered islands. This condition causes access to health services for the underdeveloped areas, border area, and the islands (*Daerah Tertinggal, Perbatasan, dan Kepulauan* - DTPK) very difficult to reach. In addition to DTPK, the same conditions exist in areas with health problems (*Daerah Bermasalah Kesehatan* - DBK). There are still many health service facilities in DTPK and DBK provided by the government which do not have health workforce. This causes health services in the area can not be implemented optimally.[6] In the era of *Universal Health Coverage* (JKN), policies to ensure access to health services in remote areas are a must. Without the access, universal coverage cannot be achieved. The issues of Human Resources (HR) in health sector is the biggest inhibiting factor in developing access to health services in difficult areas.[1,7] The main problem faced today is the lack of availability of health workforce, especially doctors, in the DTPK area. The distribution of health workforce is uneven because most work in densely populated areas, mainly in Java.

Provision of resources in health care facilities is the responsibility of the government, including among others health workforce. In the 2015-2019 RPJMN (*Indonesia's Medium Term Development Plan*) in Health, fulfillment the needs of health workforce are one of the main targets.[8] In this case the government is required to issue a policy on the model of placement of health workforce in health care facilities that are adjusted to regional characteristics and not to generalize the policy for the entire territory of Indonesia. One way to health personnel provision in Indonesia is carried out through Team Based Special Assignments in support of the Nusantara Sehat Program (*Health Indonesia Program* - NS).[9]

Team Based Special Assignment is a government breakthrough that is expected to be able to implement an integrated program and can provide optimal health services at the level of basic services, especially in the DTPK and DBK.[10] The ultimate goal of this program is the fulfillment of health workforce in the Puskesmas (*primary health care center*), implementation of Puskesmas management, increasing efforts in basic health services in the Puskesmas work area, and achieving the target coverage of the Puskesmas program. In its implementation, this program was carried out through the placement of Team NS with the priority of very remote Puskesmas in DTPK and DBK which experienced a lack of health workforce. Each team consists of eight health workforce from various professions, namely doctors, midwives, nurses, environmental health workforce, nutritionist, medical laboratory technology experts, pharmacy personnel, and public health workforce. Team assignments at DTPK were carried out for 2 years. The program began in 2015, in June Batch 1 was sent to 20 Puskesmas and Batch 2 in December was sent to 100 other Puskesmas.[11]

National Institute of Health Research and Development (*Badan Penelitian dan Pengembangan Kesehatan* - NIHRD) of Indonesia is in charge of escorting the monitoring and evaluation of NS Team placement. Evaluation of the NS Team placement was carried out at pre-, mid-, and post-term. At the time before the team was placed, basic Puskesmas data (pre-term) was taken along with the health status of the community. After a year of placement, mid-term data is retrieved to see the results of the activities. Furthermore, at the end of the placement period (post-term), the last basic data and the health status of the community are retrieved to be compared with the pre-term data.[11]

Year 2017 is the final year of the NS Batch 1 and 2 from year 2015 teams in carrying out their duties. Evaluation research of the team post placement conducted this year aims to assess the impact of the placement of the NS Team on the achievement of the Puskesmas health program, the performance of the Puskesmas, the range of services, improvement of services, and providing benefits to the community. Regarding that matters, baseline data collection was carried out in 120 Puskesmas with the placement of NS Batch 1 Team to collect data on community health status in 30 Puskesmas locations for NS Team placement as Puskesmas intervention and 30 Puskesmas which were not the location of NS Team as Puskesmas control.

The existence of Puskesmas control as a comparison is to test whether the changes that occur in the Puskesmas are properly affected by the presence of the NS Team or the performance is mature. To assess

the health status of the community, it was carried out through a rapid survey. In this quick survey, comparing the health status of the community before and after the placement of the NS team whether in the Puskesmas interventions and the Puskesmas controls has the effect of the placement of the NS team on the health status of the community. The Nusantara Sehat Public Health Index (*Indeks Kesehatan Masyarakat Nusantara Sehat - IKM NS*) was created to assess the success of the NS program in the Puskesmas that were placed by the NS team. The index is a composite of 12 indicators which are almost entirely adopted from the indicator of the Healthy Indonesia Program with Family Approach (*Program Indonesia Sehat dengan Pendekatan Keluarga* - PIS PK). This evaluation aims to analyze the impact of NS program on public health index using Pre and Post-Test Intervention with Control Design.

METHODS

This research is part of the three-year study that had been conducted in 2015 (pre), 2016 (mid) and 2017 (post). The selection of 120 Puskesmas (obtain the NS team) was carried out using a two-stage sample design and conducted at the time of pre in 2015. Then for this study was selected 30 Puskesmas from 120 Puskesmas in purposive method. 30 Puskesmas that obtain the NS team is called by the Puskesmas Intervention, whereas the puskesmas that is not obtain the NS team (but similar in geographical category and needs) is called a control, so there 60 Puskesmas were selected purposively from the available list of NS Program Batch 1 and 2 in 2015 covering 15 provinces, 27 districts. The time of research was conducted in February-December 2017.

This research is a program evaluation using a cross sectional research design with quantitative and qualitative methods which taken concurrently where scoring is emphasized on quantitative methods and qualitative methods as supporting data (Concurent Embedded Mixed Method). Quantitative research uses the Pre- and Post-Test Intervention design with Control Design.

The population is all households in the working area of the Puskesmas Intervention and Puskesmas Control. Samples were selected households located in the working area of the Puskesmas Intervention and Puskesmas Control. The unit of this study is an individual who is willing to be the subject of research (signing Informed Consent). Quantitative data were taken using questionnaire research instruments and anthropometric measurement tools. Qualitative data is taken through in-depth interviews by researchers according to the guidelines that have been designed, assisted with notes and, sound recording devices (recorders).

The sample selection was carried out using a two-stage sample design, which was purposively selected 30 Puskesmas Intervention and 30 Puskesmas Control from from the available list of NS Program Batch 1 and 2 in 2015. Then choose 30 clusters (*Rukun Tetangga* = Neighborhood Association) from each Puskesmas working area and choose households per cluster with systematic random. Data analysis included univariate and bivariate analysis with an independent t-test to compare pre- and post- conditions in the Puskesmas intervention and Puskesmas control if the data were normally distributed, and a dependent t-test to compare the conditions of the Puskesmas intervened in 2015 with 2017 and compare the conditions of Puskesmas control in 2015 with 2017.

Table 1. Summary of Research Methods

No.	Objectives	Type	Data Collection	Analysis Data
1	Measuring the variables included in the compiler indicators of IKM-NS year 2015 and 2017 on each Puskesmas intervention and Puskesmas control	Primary data	Structured interview with questionnaire.	Descriptive (univariat)
2	Analyze the compiler indicators of IKM-NS	Primary data	Measurement, literature review, and statistical analysis	Descriptive (Univariat: data transformation)
3	Analyze the conditions of the compiler indicators of IKM-NS year 2015 and 2017 on Puskesmas intervention	Primary data	Measurement, literature review, and statistical analysis	Analytical (independent t-test)
4	Analyze the conditions of the compiler indicators of IKM-NS year 2015 and 2017 on Puskesmas control	Primary data	Measurement, literature review, and statistical analysis	Analytical (independent t-test)
5	Analyze the changes in averages NS index year 2015 and 2017 on Puskesmas intervention	Primary data	Measurement, literature review, and statistical analysis	Analytical (independent t-test)
6	Analyze the changes in averages NS index year 2015 and 2017 on Puskesmas control	Primary data	Measurement, literature review, and statistical analysis	Analytical (independent t-test)
7	Analyze the significance of differences (delta changes) between the average index of Puskesmas interventions and Puskesmas control	Primary data	Measurement, literature review, and statistical analysis	Analytical (independent t-test)
8	Collecting qualitative data	Secondary data	In-depth interview	Reduction, display, conclusion/ verification

Then an independent t-test was conducted to see the significance of the difference between the Puskesmas intervention and the Puskesmas control. This research obtained ethical approval from the Ethics Comission of Health Reasearch - NIHRD Indonesia on March 15, 2017 Number LB.02.01/5.2/KE.080/2017.

RESULTS

The details and operational definitions on how to calculate indicators can be seen in Table 2 as follows:

Table 2. Indicator of the Nusantara Sehat Public Health Index Compiler

No	Indicator	Operational Definition
1	The mothers follow family planning program (*Keluarga Berencana* - KB)	The mothers are married and use family planning program then divided by the number of currently married mothers who use and not using family planning.
2	Ideal ANC	Pregnant mothers who had checked herself on Trimester I (1x), Trimester II (1x), dan Trimester III (2x) divided by all mothers who did pregnancy check-up at health facilities (ideally and not ideal)
3	Labor at health facilities	The numbers of mothers who had labor in health facilities for the past 3 years divided by numbers of mothers who had labor in health facilities and not
4	Complete immunization	The numbers of toddlers who had complete immunization divided by the total numbers of toddlers
5	Exclusive breastfeeding	Infants from 0 – 6 months old who had breastfeeding and still had only breastfeeding during the last 24 hours divided by the total numbers of infants from 0 – 6 months old
6	Children under 5 years growth and development	The children under 5 years who had been taking weight measurement 6 times a year and get vitamin A divided by the total numbers of children under 5 years.
7	TB patients get the treatment	The numbers of TB patients who had the treatment divided by total numbers of TB patients
8	Regular check-up for hypertension patient	The number of hypertension patient who had regular check-up divided by the total numbers of hypertension patients
9	Smoking behavior	Respondents ≥ 18 year-old who SMOKE [code: (1) Yes, smoking everyday. (2) Yes, sometimes. (3) No, but was smoking everyday. (4) No, but was smoking, divided by total respondents ≥ 18 year-old
10	Universal health coverage (*Jaminan Kesehatan Nasional* – JKN) membership (BPJS/KIS, Jamkesda, private insurance)	The numbers of respondents who has national health coverage (BPJS/KIS, Jamkesda, or private insurance) divided by the total respondents who has it and not
11	Access to clean water	Households who have water source which meet the KS indicator and the physical quality fulfill the health requirement divided by households who has water source
12	Family toilet	Households who has its own toilet with the right type according to KS indicator divided by total households who has their own toilet or not

The formulation of Nusantara Sehat Public Health Index was conducted based on Indonesia's Public Health Development Index (*Indeks Pembangunan Kesehatan Masyarakat* - IPKM) calculation. IPKM compiled and formulated by NIHRD Indonesia in 2007 based on Basic Health Reserch (Riskesdas) 2007, National Social Economic Survey (Susenas) 2007, and Survey of Village Potential (2008). Calculation of IPKM obtained copyrights from Indonesia Ministry of Justice and Human Right on July 8, 2011.[12]

Referring to the preparation of IPKM, in the preparation of the IKM-NS, the 12 indicators were scored based on the "Absolute", "Important", and "Necessary" category. Indicators categorized into

"Absolute" groups are given a score of 5, "Important" given a score of 4, and "Necessary" to be given a score of 3. It is categorized "Absolute" if the indicator directly affects the incidence of mortality. It is categorized as "Important" if the indicator does not directly affect the incidence of mortality but affects morbidity and its impact can lead to a wider incidence of morbidity and/or mortality. Whereas it is said "Necessary" if the indicator does not directly cause mortality and morbidity, but in general it will affect the health status of the community. Based on the discussion among the research team, the categorization of the 12 indicators was determined as follows:

Table 3. Category of Nusantara Sehat Public Health Indicator Compiler

No	Indicator	Category	Weight	Type
1	The mothers follow family planning program (*Keluarga Berencana* - KB)	Necessary	3	Favorable
2	Ideal ANC	Absolute	5	Favorable
3	Labor at health facilities	Absolute	5	Favorable
4	Complete immunization	Absolute	5	Favorable
5	Exclusive breastfeeding	Important	4	Favorable
6	Children under 5 years growth and development	Important	4	Favorable
7	TB patients get the treatment	Absolute	5	Non-favorable
8	Regular check-up for hypertension patient	Absolute	5	Non-favorable
9	Smoking behavior	Necessary	3	Favorable
10	Universal health coverage (*Jaminan Kesehatan Nasional* – JKN) membership (BPJS/KIS, Jamkesda, private insurance)	Necessary	3	Favorable
11	Access to clean water	Absolute	5	Favorable
12	Family toilet	Necessary	3	Favorable

In the preparation of IKM-NS, the scope of indicators for each Puskesmas (both Puskesmas intervention and Puskesmas control) was assessed based on community-based surveys. Each indicator has a value between 0-100. Each of favourable indicators (in percent) were multiplied by the weight of each indicator (see Table 3), each of non-favourable indicators were converted into positive value (100 minus proportion percentage of non-favourable indicators), which lead to equal positive value between favourable and non-favourable indicators.

It also determined the maximum value which may be obtained by the Puskesmas for each indicator. Due to the possibility that Puskesmas coverage for each indicator is between 0-100, the maximum value is: 100 x INDICATOR WEIGHT and the minimum value is: 0 x INDICATOR WEIGHT. The following is a simulation of value calculation for complete immunization indicators and smoking behavior. This assessment was then carried out for all intervention and control Puskesmas (60 Puskesmas) and for all selected indicators (12 indicators).

Table 4. Simulation of Complete Immunization Indicator Value and Smoking Behavior Calculation

No.	Puskesmas	Complete Immunization Coverage	Smoking Behavior	
			Proportion	Conversion value (100 – proportion)
1	Adaut	86,4	33,6	66,4
2	Badau	90,6	37,4	62,6
3	Balai Karangan	86,1	45,9	54,1
4	Bere-Bere	68,6	45,5	54,5
5	Bupul	71,0	49,8	51,2
6	Dorehkar	52,6	52,5	47,5
7	Enggano	75,7	52,0	48
8	Gemeh	82,8	46,5	53,5
9	Ilwaki	70,8	37,1	62,9
	Indicator Classification	Absolute (Weight 5)		Necessary (Weight 3)
	Maximum value	500		300
	Minimum value	0		0

Indicator Value (Value x Score)

No.	Puskesmas	Complete Immunization Coverage Score	Smoking Behavior Score
1	Adaut	432,0	199,2
2	Badau	453,0	187,8
3	Balai Karangan	430,5	162,3
4	Bere-Bere	343,0	163,5
5	Bupul	355,0	150,6
6	Dorehkar	263,0	142,5
7	Enggano	378,5	144,0
8	Gemeh	414,0	160,5
9	Ilwaki	354	188,7

Table 5. Theoritical Minimum and Maximum Value of Indicator of the Nusantara Sehat Public Health Index Compiler

No	Indicator	Weight	Theoritical Minimum Value	Theoritical Maximum Value
1	The mothers follow family planning program (*Keluarga Berencana* - KB)	3	0	300
2	Ideal ANC	5	0	500
3	Labor at health facilities	5	0	500
4	Complete immunization	5	0	500
5	Exclusive breastfeeding	4	0	400
6	Children under 5 years growth and development	4	0	400
7	TB patients get the treatment	5	0	500
8	Regular check-up for hypertension patient	5	0	500
9	Smoking behavior	3	0	300
10	Universal health coverage (*Jaminan Kesehatan Nasional –* JKN) membership (BPJS/KIS, Jamkesda, private insurance)	3	0	300
11	Access to clean water	5	0	500
12	Family toilet	3	0	300
	Total Score		0	5000

Furthermore, the calculation of the maximum value and minimum in theoretical and empirical values are carried out. Theoretical value is a value that is theoretically possible to occur (0 or 100). Empirical value is the value achieved by each Puskesmas (0-100).

Calculation of empirical values using the same calculation method, but using real coverage obtained based on the results of community surveys, as exemplified in Table 6. Calculations in the same way were carried out on all Puskesmas both in the intervention and control Puskesmas.

Determination of the index value is done by dividing the maximum empirical total value with the maximum theoretical total value, so that the IKM-NS obtained for each Puskesmas is intervention and control both at pre- (year 2015) and post- (year 2017). The complete calculation results can be seen in Table 7.

From the results in Table 7, it can be seen that there is an increase in the average index in 2017 both in the Puskesmas intervention and control when compared to the conditions in 2015. At first glance it is seen that changes in the index of the Puskesmas intervention are greater than the changes in the index at the Puskesmas control. These results are confirmed from calculations using SPSS software.

Table 6. Empirical Minimum and Maximum Value of Indicator of the Nusantara Sehat Public Health Index Compiler in Puskesmas Adaut, Badau, dan Balai Karangan

No	Indicator	Adaut	Badau	Balai Karangan
1	The mothers follow family planning program (*Keluarga Berencana* - KB)	121,3	203,2	185,4
2	Ideal ANC	285,7	450,0	411,8
3	Labor at health facilities	222,0	409,0	147,0
4	Complete immunization	432,0	453,0	430
5	Exclusive breastfeeding	200,0	0,0	0,0
6	Toddler growth and development	255,2	266,7	257,1
7	TB patients get the treatment	400,0	500,0	166,7
8	Regular check-up for hypertension patient	451,2	421,6	373,0
9	Smoking behavior	199,2	187,8	162,3
10	Universal health coverage (*Jaminan Kesehatan Nasional –* JKN) membership (BPJS/KIS, Jamkesda, private insurance)	170,7	123,0	213,0
11	Access to clean water	478,6	255,4	301,9
12	Family toilet	211,4	252,5	254,7
	Total Score	3427,311	3522,175	2903,427

Table 7. Nusantara Sehat Public Health Value Index in Puskesmas Intervention dan Puskesmas Control Year 2015 and 2017

Puskesmas Intervention	Year		Puskesmas Control	Year	
	2015	2017		2015	2017
Adaut	0,5214	0,6854	Ainiba	0,5133	0,6855
Badau	0,5048	0,7044	Bandar Khalifah	0,5349	0,5998
Balai Karangan	0,4787	0,5806	Daruba	0,6052	0,7110
Bere-Bere	0,4034	0,5782	Essang	0,4824	0,5373
Bupul	0,5269	0,6771	Galing	0,4918	0,5126
Dorehkar	0,4139	0,4095	Halilulik	0,5705	0,6634
Enggano	0,5350	0,5694	Hulu Gurung	0,5816	0,6414
Gemeh	0,4712	0,5773	Kanarilang	0,5485	0,6729
Ilwaki	0,4491	0,5509	Kelong	0,5540	0,6147
Kendahe	0,6342	0,7472	Kembayan	0,4739	0,6767
Lelang	0,3621	0,3808	Kuma	0,6727	0,7445
Long Ampung	0,4483	0,5708	Laulalang	0,4380	0,5156
Long Nawang	0,5198	0,6183	Long Loreh	0,4813	0,6799
Maritaing	0,4412	0,5931	Lorulun	0,5549	0,6189
Namfalus	0,4607	0,7380	Mahaleta	0,3501	0,3690
Ndao	0,4723	0,6407	Muting	0,4730	0,4813
Ogodeide	0,5053	0,5680	Pembeliangan	0,4831	0,5208
Rupat Utara	0,5211	0,5125	Rupat	0,5316	0,6298
Sabarmiokre	0,5538	0,6132	Serasan	0,5915	0,7334
Sajingan Besar	0,3800	0,4940	Simeulue	0,5312	0,5991
Sei Menggaris	0,4370	0,7288	Soenimanu	0,4474	0,5298
Serasan Timur	0,5417	0,6612	Sungai Boh	0,5286	0,6721
Silawan	0,5946	0,7036	Tanah Merah	0,4173	0,4990
Simeulue Cut	0,4470	0,6456	Tanjung Harapan	0,5549	0,6242
Skouw Mabo	0,5750	0,6256	Tounwawan	0,3734	0,3455
Sungai Guntung	0,3877	0,5278	Ujoh Bilang	0,4727	0,5866
Tambelan	0,6448	0,7927	Waygama	0,3895	0,5480
Tanjung Beringin	0,5099	0,7127	Weowe	0,5194	0,6407
Tiong Ohang	0,4181	0,4913	Yenggarbun	0,4900	0,6536
Wedomu	0,6149	0,7459	Yoka	0,6821	0,6684
Average Intervention Index	0,4925	0,6148	Average Control Index	0,5113	0,5992

Changes in the average index at the Puskesmas intervention and control:

Table 8. The Result of Paired Samples Statistic

Puskesmas	Year	Mean	N	Std.Deviation	Std.Error Mean
Control	2015	.51	30	.077	.014
	2017	.60	30	.097	.018
Intervention	2015	.49	30	.074	.013
	2017	.61	30	.100	.018

The results of the dependent t-test showed that changes that occurred both in the Puskesmas intervention and control were statistically significant with p = 0.000.

Results of the Puskesmas intervention and control dependent t-test:

Table 9. The Result of Paired Samples Test

Puskesmas	Paired Differences					t	df	Sig.(2-tailed)
	Mean	Std. Deviation	Std.Error Mean	95% Confidence Interval of the Difference				
				lower	Upper			
Kontrol 2015 – 2017	-.088	.059	.011	-.110	-.066	-8.214	29	.000
Intervensi 2015 – 2017	-.122	.071	.013	-.149	-.095	-9.349	29	.000

Then the independent t-test was tested to see the significance of differences (delta changes) between the Puskesmas intervention and control. The results showed that there was a statistically significant difference in the changes that occurred in the intervention Puskesmas compared to the control Puskesmas (p = 0.046).

The results of the Shapiro-Wilk data normality test showed that the data were normally distributed (p = 0.493).

Table 10. The Result of Test of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Delta	.054	60	.200*	.981	60	.493

a. Lilliefors Significance Correction
*. This is a lower bound of the true significance

The results of the independent t-test on the delta of the Puskesmas intervention were compared to the Puskesmas control:

Table 11. The Result of Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std.Error Difference	95% Confidence Interval of the Difference		
								Lower	Upper	
Delta	Equal variances assumed	.513	.477	2.043	58	.046	.034	.010	.000	.068
	Equal variances not assumed			2.043	55.77	.046	.034	.016	.000	.068

DISCUSSION

Indonesia is an archipelago that has more than 13,000 islands, stretching from Sabang to Merauke and from Miangas to Rote Island. This natural condition has implications for the distribution of health human resources and the difficulty of access the health services, especially in DTPK and DBK. To overcome this, the government seeks to specifically utilize health human resources within a certain period of time with a certain number and category, in order to improve access and quality of health services in health care facilities in these areas through the NS Program in accordance with the Minister of Health Regulation Republic of Indonesia No. 16 year 2017 concerning the Assignment of Health Personnel in the Nusantara Sehat Program, as well as the Permenkes No. 23 year 2015 concerning the special assignment of team-based health workforce (Team Based in supporting the Nusantara Sehat Program)[10,13]. As a embodiment of the Minister of Health Republic of Indonesia Regulation, the assignment of NS Batch 1 and 2 Team was conducted in 2015 in 120 DTPK and DBK Puskesmas. The assignment period of the NS Batch 1 and 2 from 2015 Team has ended in 2017, so the post-term evaluation is carried out, where the results will be compared with the pre-term results that have been carried out before the assignment of Team NS Batch 1 and 2 begins.

The evaluation results of the NS Batch 1 and 2 programs that have been conducted show that in 2017 there was a change in the average public health index compared to 2015, both in the Puskesmas intervention and control (p = 0,000). Then the independent t-test results of on delta index changes showed that the increase in the public health index in the Puskesmas intervention was greater than Puskesmas control (p = 0.046). It said the assignment of the NS Team to the Puskesmas has brought a better improvement in the public health index. The number of qualified human resources for health that fulfilled on an area can overcome and prevent disease or factors that threaten the health of high-risk groups.[14] The fulfillment of quality human resources for health is part of the strategy to achieve the goals in the

Sustainable Development Goals (SDGs) in reducing child mortality and improving maternal health.[14,15]

The Puskesmas control was chosen based on the similarity of characteristics with the Puskesmas intervention, such as the similarity of the Puskesmas working area conditions, the number of networks, service facilities, and the condition of available the health human resources. Based on the results of this study, it should be noted that the Puskesmas control that did not get the NS Team intervention also experienced an improvement in the public health index naturally, although the improvement in the index was not as large as the index improvement in the Puskesmas intervention, but statistically significant.

According to the researchers during preparation, monitoring and evaluation of the NS program, the implementation of the NS Batch 1 and 2 programs in the field was very diverse. This relates to the priority of health problems that vary from each placement area so it affects the innovation that is prioritized by each NS Team (qualitative results with the chair of the NS Team Batch 1 and 2). For example, Puskesmas in areas with high rainfall have initial data on health indicators related to improved access to clean water and NS teams in the area have more potential to conduct public health interventions regarding clean water, compared to Puskesmas in areas that tends to be dry and arid. Another example, in a Puskesmas with topography having preliminary data on health indicators related to delivery carried out in health care facilities, it tends to be better than Puskesmas with topographic waters or islands. Due to vehicle options that can be used to reach health care facilities through the mainland more than the waters or islands that have periodic or sudden high-wave challenges.

In measuring the population health needed a constituent factor that clearly measured, there was comparability of indicators, and the use of appropriate statistical models to analyze.[16,17,18,19] The public health index in this study was adopted and compiled from the determinants of basic health in accordance with the Health Goals that we have and is a composite of 12 indicators adopted from the PIS-PK Program indicators. Therefore, this study has been able to describe temporarily how the impact of the Team NS Batch 1 and 2 assignments on the public health index in the Puskesmas work area was selected in 2017. However, this research still needs to be developed and associated with other research related to the NS program, more factors can be explained to help improve and improve the public health index.

In conclusion, from From this study, it can be concluded that the public health status in 2017 experienced a statistically significant improvement compared to 2015, both in the Puskesmas intervention and Puskesmas controls. If it is viewed from the comparison of delta changes or the significance of differences at the end of the observation, the improvement of the public health index in the Puskesmas intervention is greater than Puskesmas control. That is, the presence of the NS Team in the Puskesmas intervened could bring a greater improvement in the public health index compared to the Puskesmas control.

Suggestion

Based on these conclusions, it is recommended that further observations be made regarding the sustainability of the NS Program and the need for cost benefit analysis of the NS Program.

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Residential area, hygiene behaviour, and pre-cervical lesions of women aged 25-64 years in Indonesia

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Abstrak

Latar belakang: *Kanker serviks merupakan penyakit kanker dengan prevalensi tertinggi di Indonesia. Penelitian ini bertujuan untuk mengidentifikasi hubungan antara wilayah tempat tinggal, perilaku kebersihan diri, dan lesi prakanker serviks pada wanita pernah kawin umur 25-64 tahun di Indonesia.*

Metode: *Studi ini menggunakan data Riset Penyakit Tidak Menular tahun 2016 di daerah perkotaan di 34 provinsi Indonesia. Populasi dan sampel adalah wanita pernah kawin berusia 25-64 tahun yang diwawancara dan dilakukan pengambilan apus serviks menggunakan metode Inspeksi Visual Asetat (IVA) untuk mengetahui indikasi prevalensi lesi prakanker serviks. Analisis hubungan menggunakan regresi logistik dengan metode enter, dengan total sampel yang dianalisis 37.456 responden.*

Hasil: *Hasil analisis menemukan proporsi 7% wanita dengan hasil tes IVA positif. Wanita yang tinggal di sekitar lokasi industri berisiko 1,2 kali (Adjusted OR= 1,2; 95% CI= 1,1-1,4) positif terhadap hasil periksa IVA daripada mereka yang tidak tinggal di wilayah tersebut. Sedangkan perilaku hygiene perorangan seperti membersihkan alat kelamin setelah selesai berhubungan seksual tidak bermakna secara signifikan terhadap hasil IVA positif.*

Kesimpulan: *Ada hubungan antara tinggal di lingkungan industri dengan hasil IVA positif pada wanita usia 25-64 tahun menunjukkan pentingnya penapisan dini secara teratur pada wanita terutama yang tinggal daerah industri. **(Health Science Journal of Indonesia 2019;10(1):51-7)***

Kata kunci: *Lesi prakanker, serviks, IVA, lingkungan, industri*

Abstract

Background: Cervical cancer is a cancer with the highest prevalence in Indonesia. This study aims to identify the relationship between residential area, personal hygiene behavior, and precancerous cervical lesions in ever-married women aged 25-64 years in Indonesia.

Method: This study uses data on the 2016 Non-Communicable Disease Research in urban areas in 34 Indonesian provinces. The population and sample were ever-married women aged 25-64 years who were interviewed and also performed cervical smear extraction using the Visual Inspection with Acetic Acid (VIA) method to determine indications of the prevalence of cervical precancerous lesions. Relationship analysis using logistic regression with enter method, with a total sample analyzed by 37,456 respondents.

Results: The results of the analysis found a proportion of 7% of women with positive VIA test results. Women living in the vicinity of industrial sites were 1.2 times at risk (Adjusted OR = 1.2; 95% CI = 1.1-1.4) positive for VIA results than those who did not live in the area. While individual hygiene behaviors such as cleaning genitals after completing sexual intercourse did not significantly affect the positive VIA results.

Conclusion: There is a relationship between living in an industrial environment with positive VIA results in women aged 25-64 years showing the importance of regular early screening among women, especially those who live in industrial areas. ***(Health Science Journal of Indonesia 2019;10(1):51-7)***

 Keywords: Precancerous lesions, cervix, VIA, environment, industry

Government of Indonesia launched a national program for the Prevention and Initial Detection of Cancer in Indonesian Women in 2015-2019 at the Nanggulan Community Health Center (Puskesmas) Kulonprogo Regency, Yogyakarta Special Region to coincide with the commemoration of Kartini Day on May 21, 2015. Indonesia is one of the countries with the high cancer rates. Data from the Ministry of Health shows that in 2015, on average every hour the number of cervical cancer patients increased by 2.5 people and the death victim was 1.1 people.[1]

Cancer is one of the main causes of morbidity and mortality worldwide, with around 14 million new cases in 2012. The number of new cases is expected to increase by around 70% over the next 2 decades. Cancer is the second leading cause of global death, and is responsible for 8.8 million deaths in 2015. Globally, almost 1 in 6 deaths are caused by cancer.[2]

About 70% of cancer deaths occur in developing countries, where around one third of cancer deaths are due to behavior and diet. Tobacco use is the most important risk factor for cancer which contributes to around 22% of cancer deaths.[3] Infection can also cause cancer, such as hepatitis and human papilloma virus (HPV), which are responsible for up to 25% of cancer cases in developing countries.[4]

In Indonesia alone, cancer is the second leading cause of death after cardiovascular disease. At the 2013 Basic Health Research (RISKESDAS), the prevalence of cancer in Indonesia was 1.4 per mile (‰) or an estimated 347,792 people.[5] Cancer of the cervix and breast was the highest prevalence of cancer in Indonesia in 2013, cervical cancer is 0.8 ‰ and breast cancer is 0.5 ‰.[6] Meanwhile, data from the WHO Information Center on HPV and Cervical Cancer show that 2 out of 10,000 women in Indonesia suffer from cervical cancer and an estimated 26 women die from cervical cancer everyday.[7]

The national program for the Initial Women's Cancer Prevention Movement in Indonesian actually exists, but now it is more focused on effort to invite the public, especially members of the Family Welfare Empowerment (PKK), to be more active in prevent cancer. Last year the cost of cancer treatment has become the highest disease cost reaching 1 trillion rupiah. Therefore there must be a movement to reduce mortality and morbidity due to cancer by encouraging patients to get early treatment. The national program for prevention of cervical cancer that has been implemented at this time is by early detection of cervical cancer using the visual inspection of cervix with acetic acid (VIA) method.

Prevention of cervical cancer will be more effective if combined with carrying out specific protection efforts by providing immunization for Human Papilloma Virus (HPV) which becomes a new vaccine into the national immunization program.[7] In developed countries, a pre-cancerous lesions screening program is identified at an early stage so that women can be easily treated up to 80%. In developing countries, access to effective screening services is limited, so the disease is often not quickly identified. In addition, the prospect of treatment for diseases is low, so the mortality rate from cervical cancer in these countries is higher.[8]

In addition to prevent cervical cancer with initially detection, other efforts must also be taken to reduce deaths and morbidity due to cervical cancer. Several studies have shown that lifestyle and environment play a role in increasing the development of HPV infection into cervical cancer.[9-12] Environmental factors, sanitation and personal hygiene such as the use of sanitary napkins and maintaining cleanliness during menstruation, the use of cleaning substance with fragrances and washing sensitive area after sexual intercourse is thought to have a relationship with reproductive tract infections and also cervical cancer.[13–17] Control of cancer-causing infections and lifestyle-related carcinogens have played a significant role in prevention, but environmental and occupational contributions are frequently lessen addressed.

Although until now experts have not found a definite cause of cancer, some studies have suggested an association between environmental factors and cancer, as found in positive cases of VIA in women in the diamond mining in Cempaka District, Banjarbaru City. The study aims to determine the results of VIA examinations of women in mining areas. The study sample of 30 people according to the inclusion criteria was selected by purposive sampling technique. The results showed that 7 women (23.3%) were examined for VIA with positive results. Based on interview questionnaire research, all respondents used mining water for their daily needs. Diamond mining activities can produce follow-up materials in the form of sand and gold if the mining process uses mercury which is one of the most dangerous heavy metals that can cause damage to many organs. Continuous use of mercury will pollute the waters of the area, so that if waters exposed to mercury waste will trigger the formation of reactive oxygen species (ROS) which results in damage to cell DNA and trigger a carcinogenic process if it enters the body.[18] Handling of mercury waste and securing the environment around diamond mining by making

settling ponds can reduce the risk of water pollution in the mining environment.[19]

In this study, writer wish to identify the relationship between environmental factors, personal hygiene behavior, characteristics, and precancerous cervical lesions in ever-married women aged 25-64 years in 34 provinces in Indonesian urban areas.

METHODS

Sources of data is the 2016 Non-Communicable Disease (NCD) Research, which has been carried out by The National Institute of Health Research and Development, the Ministry of Health. Data collection was carried out in 76 districts / cities selected in 34 provinces in 2016. The population and samples were ever married women aged 25-64 years who lived in Indonesian urban areas on the selected census block in selected households. Sampling was carried out independently for each province through several stages.

Sampling is done independently for each province with the following withdrawal stages: first selecting a number of sub-districts in urban areas, followed by selecting a number of urban census blocks, then selecting 50 census buildings in the census block systematically, and finally selecting households that have been randomly updated in selected census buildings. Eligible women according to criteria are selected using the Kish table method. The cross-sectional study design was used to see the relationship between environmental factors, personal hygiene behavior and characteristics with pre-cervical cancer lesions at the same time.

To see the relationship between environmental factors and the characteristics of women with the results of VIA examination, the variables chosen according to data availability are living in a mining and industrial location marked by the respondent's acknowledgment whether she has lived in a mining or industrial environment, age, education level, employment status, economic status, knowledge related to cervical cancer, smoking behavior, and personal hygiene behavior. Personal hygiene behavior is assessed by the respondent's acknowledgment whether cleaning the genitals after each sexual encounter. Pre-cancerous cervical lesions are the presence of white patches (*acetowhite epithelium*) on the cervix that are assessed by inspection of Visual Acetic Acid (VIA). This examination is one method used to detect the presence of precancerous lesions. VIA is carried out by trained midwives / doctors. VIA is an examination by observing the cervix using the naked eye. The cervix is diluted with runny acetic / vinegar (a concentration of 3─5%). If there are precancerous lesions, after waiting for approximately one minute there will be white spots called *acetowhite epithelium*. White patches indicate changes in cells (dysplasia) on the cervix. This sign concludes the positive VIA test.[20]

The sub-district sampling frame, census block and selected households were obtained from the SP2010 results conducted by the Central Bureau of Statistics (CBS). The instrument used was the 2016 NCD Research questionnaire, both household and individual questionnaires.

Data processing starts from data cleaning, checks the completeness and consistency of the contents of each variable, followed by re-coding variables according to operational definitions. Statistical analysis uses SPSS version 17.0 software. The analysis was carried out in several stages, namely univariate, bivariate and multivariate analysis. In final model, multivariate analysis using logistic regression was conducted to see the relationship between environmental factors, hygiene behaviour and characteristics with the results of the VIA test and to find out which variable was the most important. In the analysis of this study using p-value <0.05 was interpreted as statistically significant.

The writing of this article does not use ethical permission but rather a Data Usage License from the Data Management Laboratory, because the source of the data is secondary data (Non-Communicable Disease Research) that have been collected by the research team of the National Institute of Health Research and Development (NIHRD) in 2016.

RESULTS

The results showed that of the total sample of 43,948 women aged 25-64 years who were successfully interviewed, only 37,456 people could be analyzed according to inclusive criteria and the willingness of women to come to the puskesmas and be examined. Of these, visual inspection of cervix with acetic acid (VIA) results showed that 7% were tested positive for pre-cancerous cervical lesions.

In the table below illustrates the behaviour of samples related to VIA examination. Most women are non-smokers and passive smokers. Almost all women claim to always clean the genitals after having sex, where most say cleaning it only with water or even with ordinary water and soap.

Table 1. Several sociodemographic characteristics, household environment variables, personal hygiene behaviour and VIA test result

Variables	VIA test result				Crude odds ratio	95% confidence interval	P
	Negative (n=34836)		Positive (n= 2619)				
	n	%	n	%			
Age group (years)							
< average (<43 y.o)	17631	91.8	1573	8.2	1.00	Reference	
Average & above (>=43 y.o)	17205	94.3	1046	5.7	0.68	0.63-0.74	0.000
Formal education							
Junior high school or higher	23014	92.7	1804	7.3	1.00	Reference	
Illitery-elementary school	11822	93.6	815	6.4	0.88	0.81-0.96	0.003
Work status							
Not work	22182	92.9	1696	7.1	1.00	Reference	
Work	12654	93.2	923	6.8	0.95	0.88-1.04	0.267
Economical status							
Rich	19357	93.2	1404	6.8	1.00	Reference	
Poor	15479	92.7	1215	7.3	1.08	0.99-1.17	0.052
Ever live in mining area							
Never	34286	93.0	2592	7.0	1.00	Reference	
Yes	550	95.3	27	4.7	0.65	0.44-0.96	0.028
Living in industry area							
Never	30602	93.2	2234	6.8	1.00	Reference	
Yes	4233	91.7	385	8.3	1.25	1.11-1.39	0.000
Smoking behaviour							
Never	32379	93.0	2450	7.0	1.00	Reference	
Yes/ever smoking	2457	93.6	169	6.4	0.91	0.77-1.07	0.246
Cleaning genital after sex							
Yes	33540	93.0	2540	7.0	1.00	Reference	
No	1293	94.4	77	5.6	0.79	0.62-0.99	0.043

Table 2. Relationship between age, personal hygiene, living in mining and industry area and VIA test result

Variables	VIA test result				Adjusted odds ratio	95% confidence interval	P
	Negative (n=34836)		Positive (n=2619)				
	n	%	n	%			
Age group (years)							
<43 y.o	17631	91.8	1573	8.2	1.00	Reference	
>=43 y.o	17205	94.3	1046	5.7	0.68	0.63-0.74	0.000
Formal education							
Junior high school or higher	23014	92.7	1804	7.3	1.00	Reference	
Illitery-elementary school	11822	93.6	815	6.4	1.01	0.91-1.09	0.990
Work status							
Not work	22182	92.9	1696	7.1	1.00	Reference	
Work	12654	93.2	923	6.8	0.96	0.88-1.04	0.327
Economical status							
Rich	19357	93.2	1404	6.8	1.00	Reference	
Poor	15479	92.7	1215	7.3	1.07	0.99-1.16	0.104
Smoking behaviour							
Never	32379	93.0	2450	7.0	1.00	Reference	
Yes/ever smoking	2457	93.6	169	6.4	0.91	0.78-1.07	0.262
Cleaning genital after sex							
Yes, water+soap	21819	93.1	1608	6.9	1.00	Reference	
Yes, only water	11721	92.6	932	7.4	1.09	1.01-1.19	0.044
None	1293	94.4	77	5.6	0.83	0.66-1.05	0.125
Ever live in mining area							
No	34286	93.0	2592	7.0	1.00	Reference	
Yes	550	95.3	27	4.7	0.64	0.44-0.95	0.027
Living in industry area							
No	30602	93.2	2234	6.8	1.00	Reference	
Yes	4233	91.7	385	8.3	1.23	1.10-1.38	0.000

Of the women examined VIA, there is more positive VIA result in young women (below average age 43 years old), has completed secondary education (SMP-SMA), not working, from poor families, claiming clean genitals after having sex with a partner, ex-smoker and also passive smoking, and once lived in an industrial area.

Logistic regression analysis has indicated some variables which have significantly associated with VIA positive results. The risk factors which are significantly associated with positive cervical precancerous lesions are living in industry area (Adjusted OR=1.23; 95%CI=1.10-1.38). While ever live in mining area variable as a protective factor (Adjusted OR=0.64; 95%CI=0.44-0.95). Cleaning genital after sexual intercourse has no association with positive VIA result (p-value>0.05).

DISCUSSIONS

The results of the study show that women living in industrial areas have a greater risk of getting positive VIA test results compared to those who do not live in industrial areas. This, if associated with living in the tobacco industry area, makes a lot of sense. Ratnasari et al (2018) reported the results of a study stating that exposure to substances found in cigarettes in women working in the cigarette industry, especially in a long time, was associated with positive VIA results.[21]

In addition to the cigarette industry, other studies have also reported a link between the use of solid fuels, which is commonly used in industry, and cervical cancer. Air pollution, especially through burning fossil fuels such as coal, wood and straw, has been linked to lung cancer. During burning of those, carbon monoxide, particulates, sulfur and nitrogen oxide, and polycyclic aromatic hydrocarbon (PAH) mixtures are released; most PAHs have been classified by the World Health Organization as likely to be carcinogenic to humans. In this study, OR was 3.67 among women with 25-34 years of exposure to wood smoke and 6.35 among women exposed to ≥35 years. The association was even stronger among women infected with HPV. This fact strongly indicates that exposure to wood smoke is that there may be a biological effect. Current data show that the use of wood for cooking is a strong risk factor, especially among women with HPV infection. The latter shows that the effect depends on HPV, may support tumor development once HPV has created the conditions needed for the carcinogenic process to occur.[22] However, the possibility that the association of living in industry area and cervical cancer is in fact due to other factors cannot be excluded. Although not conclusive, the present evidence, is important enough to warrant further investigation

While protective results are found in women who have lived in mining areas. This is not equivalent to the findings of McCormack (2012) who stated that exposure to mining and plantations can increase the contribution to cancer.[23] This protective result can be assumed because respondents only claimed to have lived in a mining area where it was possible for a short period of time. This variable should be controlled with the length of stay to be able to obtain the right measurement results.

The results were not significantly indicated by the variables of personal hygiene behaviour measured by the habit of cleaning the pubic area after every intercourse. There was no significant difference in the group of women who did not clean the vagina, or just cleaned it with soap or water to the incidence of precancerous cervical lesions. This finding contradicts the results of the Dianti et al (2016) study which found that there was a relationship between personal hygiene in treating genitals and cervical cancer. For example cleaning genitals using antiseptics is a risk for cervical cancer.[13] This is also in accordance with Sukaca et al. (2009), because the use of antiseptics that too often will cause irritation in the vagina that triggers cancer.[24] This is also in accordance with the theory put forward. The study results of Diananda (2007) state that washing the vagina with antiseptic drugs or deodorants will cause irritation to the cervix which stimulates cancer.[25]

On the other hand, from the results of the analysis, older age shows protective results, where mothers who are young (below the average of 43 years old) tend to be more at risk of positive results of the VIA test. This can be interpreted as a cervical cancer tends to occur more in young women. This finding is in line with several research published in several countries such as England and Finland. The results of those studies reported that age has a relationship with the incidence of cervical cancer, where the risk of cervical cancer increases at a young age compared to old age. This is possible related to the cervical cancer screening service policy. If the coverage of screening in the age group of 20-25 years decreases, then it will increase the number of cervical cancer incidence at a young age.[26,27] However, these results contradict the study reported by Benard et al (2012) which states that cervical cancer cases at a young age are very rare in USA.[28]

In conclusion, this study confirms the relationship between living in an industrial environment with positive VIA results and demonstrates the importance of health promotion as a way to develop healthy lifestyles in populations in industrial and mining environments.

Regular early screening (VIA or Pap smear) is believed to be essential as a preventive measure. Reducing exposure to carcinogens in industrial sites through the use of protective equipment for female workers in the industry is also important. Management of industrial waste so as not to pollute the environment is also included as crucial things that must be done to reduce the risk of cervical precancerous.

Acknowledments

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How to control the sexually transmitted diseases in Benjina?: qualitative studies on the practice of prostitution

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Abstrak

Latar Belakang: *Prostitusi yang muncul bersamaan dengan industri besar menimbulkan masalah kesehatan, masalah sosial ekonomi, dan budaya. Artikel ini dimaksudkan untuk mengeksplorasi faktor-faktor yang berkaitan dengan praktik prostitusi di Benjina dan mengeksplorasi potensi untuk mengendalikan dampak penyakit penularan melalui hubungan seks.*

Metode: *Penelitian kualitatif ini dilakukan dengan pendekatan etnografi. Wawancara mendalam dan observasi partisipatif dilakukan terhadap 30 informan yang terkait langsung dengan praktik prostitusi di Benjina.*

Hasil: *Tidak ditemukan lokalisasi di Benjina. Praktik pelacuran ditemukan sebagai hal yang biasa di tempat yang disebut rumah karaoke yang menyediakan peralatan menyanyi sederhana, minuman keras, dan layanan seksual. Ada 46 pekerja seks perempuan yang bekerja di 12 rumah karaoke. Faktor ekonomi ditemukan sebagai faktor dominan yang mendorong para pelaku pelacuran, di samping balas dendam. Ada beberapa kendala dalam menggunakan kondom dalam praktik pelacuran ini. Di antara mereka adalah bentuk fisiologi penis yang mengalami modifikasi, dan hubungan pekerja seks khusus dengan kekasih mereka. Ada potensi Sasi yang dapat digunakan sebagai upaya untuk mengendalikan penyakit penularan melalui hubungan seks.*

Kesimpulan: *Sasi sebagai hukum adat berpotensi menjadi hukum positif untuk menerapkan kondomisasi secara keseluruhan di Benjina.* ***(Health Science Journal of Indonesia 2019;10(1):58-66)***

Kata kunci: *Penyakit menular seksual, pelacuran, hukum adat, Sasi, adat istiadat.*

Abstract

Background: Prostitution that appears together with massive industry raises health problems, socio-economic problems, and culture. This article was intended to explore factors related to prostitution practices in Benjina and explore the potential for controlling the impact of sex transmission disease.

Methods: This qualitative study was carried out with an ethnographic approach. In-depth interviews and participatory observation were carried out on 30 informants who were directly related to the practice of prostitution in Benjina.

Results: No localization was found at Benjina. The practice of prostitution was found to be commonplace in a place called karaoke houses that provided simple singing equipment, liquor, and sexual services. There were 46 female sex workers who worked in 12 karaoke houses. Economic factors were found to be the dominant factor driving the perpetrators of prostitution, in addition to revenge. There are some obstacles to using condoms in this practice. Among them were the forms of penile physiology that experience modification, and the relationship of special sex workers with their lovers. There was a *Sasi* potential that can be used as an effort to control sex transmission disease.

Conclusion: *Sasi* as a customary law has the potential to be a positive law to implement condomization as a whole in Benjina. ***(Health Science Journal of Indonesia 2019;10(1):58-66)***

Keywords: sexually transmitted disease, prostitution, customary law, *Sasi*, traditional customs.

Benjina is one of the names of villages located in Aru Tengah District, Aru Islands Regency, Mollucas. The Aru Islands Regency is ranked as the 394th Public Health Development Index in 2007[1] and dropped to rank 426th in 2013. The ranking is one of the lowest ranks in Mollucas Province after the Eastern Seram District was ranked 434th.[2]

Benjina became a byword at around the beginning of 2015 and even became an international issue because of cases of slavery of foreign workers who were accused of an economic wheel control company there. The existence of a company, foreign labor, rich natural resources, and rapid money circulation, has become an economic potential that attracts migrants from various corners of the archipelago. In Benjina the history of prostitution began when there was an industry entering Benjina, followed by massive migrants seeking better livelihoods, and the opening of land rulers and customary rulers to the migrants. Beyond this openness, of course, there is a big stimulant from the industrial sector itself, which is a business that makes a lot of money. The money circulation involves people who are not only involved in the business of prostitution (in this case, including customers) but also people who directly or indirectly depend on their economic resources for the existence of the business.[3]

One of the effects of all the things mentioned earlier is the emergence of health problems and socio-economic and cultural problems. Emerging migrants who work as female sex workers are associated with the rise of HIV / AIDS cases in Benjina. There is also a prostitution business that promises high income and involves several parties at Benjina. There is an interesting thing here, HIV / AIDS is so feared but not with its prostitution business.[3]

Based on data obtained from the Aru Islands District Health Office, the number of people examined for HIV / AIDS in the Aru Islands in 2014 was 1,602 people. Blood samples for VCT examinations were taken by officers in all karaoke houses operating in Benjina. Unfortunately, the blood sampling has not been able to reach sex workers who are outside the karaoke house and foreign crew members who also have the potential to contract the virus or even as spreaders of the virus.[3] Based on this background, this article is intended to explore factors related to the practice of prostitution in the Benjina and explore the potential for controlling the impact of the sexually transmitted disease.

This research was part of Health Ethnography Research in 2015. The research was carried out by the National Institute of Health Research and Development, Ministry of Health, the Republic of Indonesia.

METHODS

We used a qualitative design with an ethnographic method approach for this study. Ethnographic methods were useful when the purpose of the research was to understand the point of view of a community, its relationship to life, and to get its views on its world.[4,5] Qualitative in-depth interviews were very useful for the purpose of examining informants' opinions and personal experiences.[6,7] The study was conducted in 2015 in Benjina District, Moluccas, Indonesia.

The researcher consisted of two people from different backgrounds. The first researcher was an anthropologist. The second researcher was a person with a public health background. This combination was useful for understanding the context and phenomena that occur in the research area. Data collection was done by using the method of in-depth interviews and participatory observation. The process of data collecting was done by researchers lived in with the research subject. These must be done in research with the ethnographic design so that researchers could see and understood problems according to their original context.[4,5] We have developed interview guides and observation forms based on literature and preliminary knowledge of research subjects based on previous preliminary research. Data triangulation was done to ensure data validity.[8,9] Triangulation was done by confirmation based on two different data collection methods and the collection of the same information in several different informants.[10]

The Informants

At the initial stage, key informants were determined based on their role in the practice of prostitution at Benjina (purposive). Furthermore, the informant was selected based on information from the key informant (snowball).

In ethnographic research, the context was left as natural as possible in accordance with the original[4], as well as informants and key informants, for which researchers take informants in accordance with the substance of the research objectives, only key

information from actors and people who are directly related to the practice of prostitution in Benjina, including the female sex worker itself. In detail, the characteristics of the informants could be seen in Table 1.

The informants taken included various roles in the practice of prostitution at Benjina. From the user side, it was found with backgrounds from various ethnicities. Including users from several neighboring countries.

Data analysis

Interviews were conducted with the help of a recording device, and the results were transcribed verbatim. Every time the interview was over, researchers reflected on what was recorded in the diary. With thematic analysis, the results of reflection were then developed into themes in accordance with the context of the field.[4,5] Furthermore, the results of recording and verbatim transcription were coded according to these themes.

Ethic and Consent

This research had an ethical clearance that was approved by the national ethical committee (ethic number: LB.02.01/5.2/KE.194/2015). Informed consent was used during data collection, which was considered aspects of the data collection procedure, voluntary, and confidentiality.

Table 1. Characteristics of informants

Informant	Total
Gender	**30**
Male	10
Female	20
Profession	**30**
Female Sex Worker	10
Fisherman	5
Ex- Female Sex Worker	4
Religious leaders	2
Landlord	1
Other professions (police, teenage boy affected by prostitution, midwife, doctor, traders)	8
Role	**30**
Female Sex Worker	10
User	7 (2 foreign people)
Ex- Female Sex Worker	4
Pimp	4
Landlord	1
Religious leaders	2
Productive age (15-50 years old)	**29**
Male	10
Female	19
Religious affiliation	**30**
Moslem	25
Christian	3
Buddhist	2
Ethnicity	**30**
Javanese	23
Bugis	1
Burmese (foreign people)	1
Thai (foreign people)	2
Arunese	3
Language	**30**
Javanese	23
Bugis	1
Burmese (foreign people)	1
Thai (foreign people)	2
Arunese	3

Source: primary data

RESULTS

There is no official localization in the Benjina area. People are more familiar with the complex that provides sexual services as a karaoke house. The karaoke house provides simple equipment such as television and song CDs for singing. Besides that, it also provides liquor, and of course sex services.

There are 12 karaoke houses spread across Benjina. Of all the karaoke houses that have been recorded, there are 46 female sex workers who work, 36 of them are from East Java, and the rest come from Central Java (3 people), South Sulawesi (2 people), Southeast Sulawesi (2 people), Central Kalimantan (1 person), Mollucas (1 person), and Riau Islands (1 person).

The female sex workers: economic factors and revenge

Why must there be female sex workers? What reasons encourage someone to choose to work as a sex worker? Is it based solely on economic reasons? Are they proud of their work? Or vice versa, feeling pressured and forced? There are many things that affect an individual to decide something important in his life. Related to the problem of prostitution, there could be factors from outside the individual and from within the individual. External factors can be related to the environment and socio-economic conditions of the individual. Internal factors may be psychological pressures that originate from past traumatic experiences, are obsessed with sex, etc.

> "I can't possibly go back to the village in a broken heart. So just let me be here. I can play my heart's as much as I like..."
> (AM, female sex worker, 33 years old)

Economic factors are the dominant factors encountered at Benjina. Poverty and the narrowness of employment in the village of origin are not balanced with economic needs that are getting heavier every day. Coupled with a low level of education and skills that are limited to domestic work (household) only, making the burden of life increasingly heavy. Another factor that was found was the story of the destruction of the household or the runoff of a love relationship which eventually triggered a sense of hurt and resentment towards men.

> "I want men to kneel in my vagina!"
> (IY, female sex worker, 32 years old)

Another factor that has a strong economic motive is an obsession to fulfill a luxurious lifestyle in his hometown. When the measure of success in wanderings is judged by the amount of material obtained and significant changes in the ownership of goods or luxury homes, the economic motives remain the biggest driving factor.

> "I have not returned to Banyuwangi for 3 years. Anyway, I'm not going to go home to my house in the village has been made. If the house is not yet finished, I already go home, I'm embarrassed, it's the same as my parents and neighbors. The problem is later when you go home, the savings for building a house are used up for fare to Miss. How come the old wanderer isn't successful too, right hehe... "
> (BM, female sex worker, 38 years old)

Economic motives also apply to pimps, most of whom are also nomads. Then what did they tell about their work at Benjina? How honest are they telling their work to relatives in their hometown? It turned out that most of them hid the status of sex workers and the pimp from family. Many of them claim to be factory employees, food stall owners, or rental house owners in Benjina. They argue that if they say honestly about the work they are doing in Benjina, then they will hurt and humiliate their families in the area of origin.

Even so, there are a small number who tell if their families (especially parents) know the work they are doing at Benjina and do not object. The reason for the sense of irregularity is because parents understand the economic urges of the family, and the interesting reason is that the work is considered normal in their neighborhood.

> "My parents understand. My mother understands but yes (they) are not angry. The problem is that nowadays it is hard to find money, so I have been looking for money. In my village there are also people who work like this, it's okay because of a lot too..."
> (BM, female sex worker, 38 years old)

The user: 'squid' penis, 'marbles' penis, and condom use

The main customers who are highly expected by female sex workers are Thai fishermen, although the female sex workers also serve customers from fishermen from other South East Asia countries, including from Myanmar, Burma, and Cambodia,

including local people who want their services. The choice of Thai fishermen because according to the female sex worker they are among the most anticipated and potential customers. This is, of course, related to the amount of money they will get. A condom is not a 'good' choice when dealing with these potential customers. Thai fishermen who are Buddhist do not experience the circumcision process on their penis, so the skin at the tip of the penis is still thick. The skin at the end is then divided into several parts. When the penis has an erection, the part of the penis that has been split into several parts expands like squid tentacles.

> "But if you get (users) who are drunk, rude, play long, use 'marbles', or use 'squid', that's already it ... Yaa Allaaaah I cry, Miss. Sometimes I already screamed and said that he was even sicker like his horse. Not to mention that 'the item' (penis) is as big as an aqua bottle. Yes, it hurts ... sometimes until this (vagina) bleeding."
> (IE, female sex worker, 45 years old)

Another customer modified his penis by inserting marbles into the shaft of his penis. Visually this treatment will enlarge the penis shaft. Marbles are like accessories and boost the confidence and masculinity of men. Another modification found was injecting 'something' to increase the size of the shaft of the penis. The output is a penis with an equivalent diameter of 600ml of bottled mineral water.

> "That's the size of my goodness, sis... similar to the middle-sized bottle of mineral water. How do I not get sick, I feel it. The marbles are ... the pain. So if the stuff goes in and out and goes in and out, right, the marbles automatically hit my vagina, right, sis. It's been so rough playing, I want to cry, Miss. He said it was injected using something like that... so it became big like that. If I don't remember looking for money that's hard, I don't want to... "
> (NI, female sex worker, 32 years old)

The use of condoms on the modified penis found various obstacles. Jumbo-sized penises are difficult to find the appropriate condom size. While penis modification is facing another obstacle. The unusual shape of the penis with a protruding and jagged surface is not able to make a condom survive. Condoms used in the intercourse process are more often torn, so they are not functioning properly. Moreover, copulation often takes place in a long time.

> "I have seen those people before intercourse with me, taking pills like that, I don't know. But there are many who said before intercourse taking pills first. It's been more than an hour, it can't stop, too, until it hurts a lot, sis... "
> (AT, female sex worker, 39 years old)

Constraints on using other condoms are found in sex workers who have lovers or contract husbands. In this type of relationship, a condom is considered a barrier. According to him sex based on love should not be limited by condoms.

The health services: interrupted program

The Aru Islands District Health Office has a free blood sampling and condom program throughout the karaoke houses in Benjina. This was done to monitor the spread of high sexually transmitted diseases in Benjina. At first, the program was funded by funds from the Global Fund, so that it could be carried out routinely. But when the Global Fund is no longer helping, the program is stalled because of the limited allocation of funds.

> "In the past when there was donor assistance, all programs could work. But when donors stopped giving help, the program was also forced to stop. That's what we regretted. Even though we had to carry out routine checks, we were short of funds."
> (MSF, doctor, 37 years old)

Puskesmas Benjina (Health Center) itself has a monthly program in the form of Pap smear conducted by one midwife who oversees the field of HIV / AIDS, which is carried out to all sex workers in every karaoke house in Benjina. Sex workers who are checked for hygiene of their genitals are charged between Rp 50,000 - Rp 100,000. There are pros and cons about these costs. Some questioned why the price set could be different between one sex worker and another sex worker, why the checks carried out were not like what was done at the clinic in Dobo (the capital of the Aru Islands), and some questioned why they had to pay?

Unfortunately, the program was stopped because the midwife who is usually in charge of running the program was undergoing further education in Makassar. Previously, midwives who did the assignment had never received special training to do Pap smear. The midwife indirectly also acts as a counselor for sexually transmitted diseases

problems, especially HIV / AIDS for sex workers, and the midwife guarantees the confidentiality of the identity of sex workers who have tested positive for HIV / AIDS.

> " I have to go to school again in Makassar, it makes me rather difficult to monitor the condition of the karaoke house again. No one can replace me."
> (N, midwife, 29 years old)

Sasi of condomization, is it possible?

For the Aru tribe community, traditional customs and the government are considered to be on equal footing, there are even some people who say that traditional customs have a higher position than the government. So from that traditional customary law is often obeyed when compared with state or government law. Aru tribe as a native tribe of Benjina has local wisdom in the form of *Sasi*. *Sasi* is found in almost all regions in Mollucas to date. *Sasi* is a form of prohibition or taboo aimed at protecting certain natural resources. *Sasi* applies if there is already a threat of over-exploitation or irresponsibility from a party, to natural resources that are considered to be almost gone or almost extinct.

Over time, resources that are protected are not only natural resources but also human resources. Sanctions given if the sentence is violated is sanctioned by traditional and social customs. Sanctions can be in the form of agreed traditional customs fines, sanctions for exclusion, sanctions in the form of assets or money, and the most feared is sanctions from God or ancestors that can be in the form of pain and curses.

The application of *Sasi* in Benjina has not experienced significant changes in meaning. In fact, the *Sasi* tradition was adopted by the Christian church of Benjina to carry out several interventions to certain parties who felt they wanted to threaten the preservation of natural resources in Benjina. So the collaboration between traditional customs and the church can be done, and this shows that there is no significant distance between traditional customs and religion in Benjina. *Sasi* carried out in Benjina has been done more often to protect natural resources from excessive exploitation from irresponsible parties.

In the context of a pluralistic Benjina community, *Sasi* is carried out by ethnic groups that are still part of Mollucas. The Tepa, Kei, Tanimbar, Ternate, Tidore, Ambon ethnic groups are ethnic groups who

are also still obedient to the existence of *Sasi*. The number of ethnic groups who are of Moluccan blood in Benjina is as large as the number of immigrant ethnic groups that are not of Moluccan origin. So it can be said that half of the Benjina community has the potential to adhere to the provisions of the *Sasi*. Even a small number of Javanese tribes do ritual *Sasi* and obey their provisions.

DISCUSSION

The results of the 2014 VCT examination which only received 28 positive HIV / AIDS is not the actual number. The iceberg phenomenon applies to this case. Often the reality of the numbers is far greater. This can be because the person being examined is not as a whole, it can also be because it is still in the window period, so it is too late to be known.[11-14] Moreover, the practice of prostitution in Benjina which involves several fishermen from abroad (South East Asia) as the main customers, thus expanding the impact of the spread of infectious sexually transmitted diseases, and increasingly complicating efforts to control them.[15-17].

A study with the subject of sexual transmission disease recommends interventions that focus on sex workers. Sex workers are recommended by researchers as the target of interventions because they prove to be more cost-effective than interventions that focus on other subjects.[18] Treating sex workers humanely is also highly recommended because it is proven to be better in controlling sexual transmission disease.[19] Efforts to criminalize and intolerance attitudes towards sex workers will actually hinder efforts to prevent sex transmission disease.[20,21] In addition, the use of condoms as a policy to prevent and control sexual transmission disease is also believed to be the most effective and inexpensive intervention.[16,22,23]

The intervention that will be given cannot only be focused on sex workers.[24] Attention also needs to be given to the community and health workers. The public perception on the practice of prostitution which tends to be permissive needs to be straightened out again. Change in perception is needed as a prevention effort from the impact of the practice of prostitution.[25,26]

The government (Health Office) in addition to the need to pay attention to the availability of health workers, also needs an understanding that health workers cannot be separated from the influence of

health belief.[27] Health workers are also part of the community, which cannot be separated from the local cultural context in which he lives.[28,29]

Sex transmission disease intervention policy in a country as wide and as diverse as Indonesia, in addition to evidence-based[30-32], should have been done by paying attention to regional locality. Intervention programs and policies must adopt the local context in setting priorities if they want an effective and sustainable program.[33, 30, 34, 35]

Boundary law as policy based on local context

In South African Universities since 2015, studies have begun on customary law. The process was preceded by student protests that demanded the government to end colonial legal domination and the practice of apartheid in South Africa. Finally, a strategic step was taken by exploring the potential of customary law as a source of positive law in the black continent.[36] This step was taken in an effort to demand the return of community resource rights.[37]

In the Indonesian context, one of the uses of customary law as positive law is the implementation of Islamic law in Aceh Province. Aceh as an autonomous region adopted Islamic law which was considered in accordance with the traditional customs of the Acehnese people. This decision was taken as a consensus from all stakeholders in Aceh.[38] Another study of the use of customary law in Indonesia was found in the Atoin Meto tribe in the West Timor region. The study found a positive contribution from the customary law to reduce the vulnerability of livelihoods in the region through community forest resource management and maintenance of members' rights to access agricultural land and natural resources.[39]

The Government of Aru Islands Regency can learn from the cases of Aceh and West Timor by implementing *Sasi* condomization in Benjina. Although the implementation must involve stakeholders who truly understand traditional customs. Because of the failure of the implementation of customary law often results from involving outsiders who do not understand local traditions.[40]

In conclusion, *Sasi* as a potential local culture and wisdom needs to be used as a fighting tool that regulates, controls, and most importantly requires that individuals or communities obey a positive regulation. Because of the consideration of the potential *Sasi* to be obeyed, the *Sasi* is very potent as a solution to the problem of non-compliance with condom use. Condomization by setting it into *Sasi* is a recommendation that is worth considering. If successful, there will be big and positive implications for efforts to prevent sexually transmitted diseases.

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Conflict of Interest

No potential conflict of interest was reported by the authors. The authors alone are responsible for the views expressed in this publication, and they do not necessarily represent the views, decisions or policies of their institutions.

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Policy options to integrate HIV services into Social Health Insurance (JKN) in Indonesia

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Abstrak

Latar Belakang: *Setelah sekian tahun bergantung pada sumber pendaaan luar negeri, pembiayaan Program HIV AIDS di Indonesia diharapkan menggunakan sumber pendanaan dalam negeri. Skema Jaminan Kesehatan Semesta atau Jaminan Kesehatan Nasional (JKN) yang dimulai tahun 2014 menanggung pengobatan termasuk infeksi oportunistik. Pertanyaan penelitian apakah paket manfaatnya dapat mencakup intervensi kesehatan masyarakat seperti HIV tanpa menghambat penyediaan pelayanan? Implementasi untuk Program HIV yang selama ini disubsidi Pemerintah memerlukan kehati-hatian. Studi ini bertujuan untuk menganalisis skenario terkait biaya dan utilisasi pada pelayanan HIV guna mendukung kebijakan yang potensial untuk mengintegrasikan intervensi HIV ke dalam paket manfaat JKN.*

Metode: *Penelitian ini menganalisis paket manfaat dan mekanisme pembiayaan terkait pelayanan HIV, keanggotaan JKN, target populasi kunci, serta estimasi premi untuk pelayanan HIV hingga tahun 2019. Studi observasional ini menghasilkan data biaya dan utilisasi dari tingkat nasional dan daerah sebagai data dasar. Peneliti membangun model dan menganalisis skenario proyeksi biaya dan utilisasi dari beragam program aktivitas HIV serta konsekuensinya.*

Hasil: *Skenario dikembangkan berdasarkan kelengkapan paket manfaat dan komponen mana yang bisa dijamin dalam JKN.Pelayanan yang terkait HIV saat ini sebagian besar dijamin oleh pemerintah mulai dari Konseling dan Tes HIV Sukarela (KTS) hingga pengobatan Infeksi Oportunistik. Pengobatan dan perawatan kemungkinan dapat dijamin oleh JKN, dengan bantuan pemerintah untuk pencegahan dan pelayanan ART.*

Kesimpulan: *Skenario dengan paket manfaat dasar akan membutuhkan biaya medis yang rasional per pasien per bulan, tergantung pada kelengkapan paket manfaat. Sebuah peta jalan yang jelas perlu disusun t untuk memastikan seluruh pelayanan terjangkau dan berkualitas baik.* ***(Health Science Journal of Indonesia 2019;10(1):67-76)***

Kata Kunci: *Jaminan kesehatan semesta, pelayanan HIV, dan Opsi Kebijakan*

Abstract

Background: HIV and AIDS program in Indonesia is planned to be financed by domestic sources after depending on external sources for many years. Indonesia has started its Social Health Insurance scheme so called Jaminan Kesehatan Nasional (JKN) program in 2014, that covers HIV treatment including opportunistic infection. Research question is whether JKN could expand its benefit package to public health interventions without hampering service provision. Converting HIV program that has been subsidizied by the Government needs careful considerations. The study aimed to assess scenarios on cost and utilization to support decision on integration of HIV interventions into the JKN benefit package.

Methods: The study assessed the current coverage and funding mechanisms for HIV-related services, JKN membership, key target populations, and estimated premium for HIV services up to 2019. We captured cost and utilization from national and subnational levels as the baseline through an observational study. Researchers developed model and scenarios on the projection of cost and utilization of various HIV program activities and its consequences.

Results: We developed scnearios based on benefit covered by JKN. current services mostly covered by government. The Care and treatment could be possibly covered by the JKN, with support from government for prevention and ART.

Conclusion: The scenarios show that provision of HIV services within the basic benefits package of JKN would require a reasonable cost per member per month, depending on the comprehensiveness of the benefit. A clear roadmap should be developed to ensure all services provided are affordable and in good quality. ***(Health Science Journal of Indonesia 2019;10(1):67-76)***

Keywords: Universal Health Coverage, HIV AIDS, Policy Option

Indonesia has significant number of people living with HIV (PLHIV). The Ministry of Health (MoH) [1] reported the number of new HIV cases in 2014 was 32,711 or increased 12.6% compared with 2013's cases; while the new AIDS cases was 5,494, relievely decrease about 45.9% from the previous year. The National Strategy and Plan mentioned that this country confronts two very distinct epidemics namely a concentrated epidemic among injecting drug users, sex workers, and men-having-sex-with-men outside of Papua, and a low-level generalized epidemic, with transmission among both vulnerable groups and the general population in the provinces of Tanah Papua[2]. From financing point of view, the annual spending for HIV response in Indonesia has increased from USD25 million in 2003 to USD60 million in 2009 to USD87 million in 2012. The trend in 2013 and 2014 also showed increasing spending from USD98 million in 2013 to USD107 million in 2014 [3-4]. In 2006, public funds were contributed only 25% of national spending but the trend is increasing annually up to 40% in 2012 while funding support from the international donor showed a decreasing trend. The latest data on spending for HIV response in the country showed that government contribution has increased to 52% in 2013 and 57% in 2014 [4].

Indonesia should participate and set the target of "ending the AIDS epidemic" by 2030 with three possible sub-targets related to a) reducing new adult HIV infections and eliminating new infections among children; b) reducing stigma and discrimination faced by people living with HIV and key populations; and c) reducing AIDS-related deaths[2]. The World Health Organization (WHO) stated that HIV program have opportunities to be integrated with other priority health areas, in addition to their core business of HIV prevention, diagnosis, treatment and care, and its distinct integration with maternal and child health and tuberculosis [5]. Lesson learned from othercountries shows that Universal Health Coverage (UHC) conceptis effectively ensure that all individual have access to use the promotive, curative, rehabilitative and palliative healthcare services they need, of sufficient quality to be effective, without suffering financial hardship[5-9].

Indonesia has already developed its Social Health Insurance (SHI) scheme called "Jaminan Kesehatan Nasional or JKN" since 2014 with short term goal to achieve Universal health Coverage (UHC) in 2019 [9]. Benefit package of the JKN include mainly treatment for sick people who has membership of the scheme. Typically a public health program such as HIV intervention received high subsidy from central government. Drugs, medical equipment, technical assistance are among support from central government, as well as other support that come from the Global Fund under MOH's coordination. Local government provides support for operational and maintenance of the program to its people, while the JKN scheme covers few components such as incentive for healthcare facility staffs. Currently, initiative to improve effectiveness and eficiency of the service provision has been started by identifying potential integration of financing and provision of services, including for priority programs that have been funded by government and JKN. Substantial increased of HIV AIDS cases, limited domestic resources as well as the need to improve efficiency by integrating sources of fund has lead the need to conduct this study. The policy question on financing part is whether it is possible to inlcude care provision and outlay a vertical program such as HIV and listed as benefit package of the JKN? At least four aspects need to be considered a) coverage of both targeted population and services; b) basic benefit package and the cost calculation; c) the payment methods, and d) the performance measurement. This paper discuss the Indonesian context of the potential integration of HIV program into the JKN scheme, with particular emphasize on cost implication and utilization of services.

This study drew policy options for possible integration of HIV and AIDS intervention into JKN. The objectives of the study were 1. to develop a model based on list of HIV services to be provided and options of the scenarios in the model 2. to calculate costs and its trend based on increased need and demand for HIV services for each option, and 3. to provide recommendation on proposed benefit package option of HIV intervention including per member per month additional premium for its inclusion into the JKN scheme and what would be the role of the Ministry of Health (MOH).

METHODS

We developed a simulation model to analyze options of integrating HIV program components into benefit package under JKN scheme. The model was derived based on evidence from national level and selected samples from four provinces. Sampling frame was drawn purposively based on coverage and substantial contribution from local government (based on National AIDS Spending Assessment

data, 2015). Three public hospitals from Bali, West Java and Batam as well as two private hospitals from Batam and West Java, were selected to capture program and costs from hospital perspective. In addition, to capture primary care perspective we also collected data from eight primary health centers and two clinics in West Java and Jakarta. Data collection was done for during November-December 2014. Secondary data were analyzed to project coverage and resources used (costs). Future costs were projected based on the estimated epidemic trajectories until the next five years using 2014 data as the baseline. Cost analysis was done to capture baseline costs of current program coverage and cost of additional HIV services inclusion into the existing benefit package. The analysis was done during January-March 2015, followed by serial discussion with stakeholders to verify and confirm the model.

Analysis on the prevention category included Sexual Transmission Infection (STI) services, HIV Counseling and Testing, Harm Reduction, and Prevention of Mother-to-Child Transmission of HIV (PMTCT). Meanwhile, the treatment and care services covered elements such as screening test namely ARV eligibility, prophylaxis drugs, ARV; monitoring test namely CD4 & Viral Load (VL) testing, Opportunistic Infection Hospitalization, OI Drugs, Condoms, and consultation. Cost for each service was determined and analyzed by component, and verification of component to be covered by the JKN or from Government subsidy was conducted.

The study results were discussed in a workshop held by the National AIDS Commission involving various stakeholders involving informants officials from BPJS and program manager and staffs from MOH as well as selected hospital and health centers, and resulted a final model that derived for two scenarios. A model to calculate cost of integration of HIV services into JKN basic benefit package. After reviewing the existing benefit package and the nature of provision of HIV program intervention, several options were set up. Various data sources were used for the cost calculation including a rapid survey on HIV services unit cost, utilization and claims data from the JKN program, and HIV epidemic data from MOH. Estimate of coverage and its future trend were derived from analysis using Key Affected Population (KAP) and People Living with HIV (PLHIV) population data from the Ministry of Health. Membership data were estimated from JKN in order to estimate the cost per member per month, and projection analysis was carried out using the

Asian Epidemic Model (AEM). Thus, epidemiology and economic scenario model were systematically analyzed and incorporated in the model to show future utilization and cost for each option application.

We consider that ethics approval was not required for this study or "not applicable" because this study used secondary data and not included any detailed, individual patient information.

RESULTS

Mobilization of domestic resources has increased to sustain HIV program funding after external funding support graduation from Indonesia. In 2014 the Government started the Strategic Use of Anti RetroViral (SUFA) program to gradually scale up ART to all PLHIV regardless of how advanced their HIV infection. [10] It is expected that treating more PLHIV will help reducing new infections. At the same time, the Government has initiated the Comprehensive Continuum of Care (CoC) or *Layanan Komprehensif Berkesinambungan* in several sites, and which will be rolled out to more districts. Under the SUFA, HIV treatment has been expanded and the country has made substantial progress in scaling up ART coverage. MOH has developed a roadmap with clear strategies and implementation plan for (i) expanding HIV diagnostics, (ii) promoting effective enrollment and retention in HIV care, and (iii) building on the LKB. Current coverage and funding mechanism for HIV interventions were available under a mix funding scheme. Some of components, typically the treatment and care services are already paid using money received by healthcare facility through the JKN payment i.e through capitation for health center, while some prevention program activities remain reliant on donor funding. Detail description of coverage scheme of each service can be seen in Annex 1.

Proposed Basic Benefit Package (BBP)

The proposed options of basic benefit package that includes HIV services are developed based on three considerations (i) the funding source, (ii) who will be managing the fund, and (iii) what service components to be included in the BBP.

Option 1 - Comprehensive Coverage

The first BBP model covers all HIV-related services including counseling and condoms, screening tests (pre-ARV, other basic laboratory tests), ARV treatment, STI screening tests and treatment, Prevention of Mother to Child Transmission services,

HIV (OI) services at ambulatory care and inpatient setting. This option excludes outreach activities, public/mass social behavior change activities and community prevention programs.

This option has two financing scenarios :

- Scenario A: The whole cost of above mentioned services is included (actuarially calculated) in the premium; and paid by all members. For government-assisted recipients (i.e. the poor) premium contribution will be paid by the Government.

- Scenario B: The whole cost paid by the Government.

Option 2 – Basic HIV Services Coverage

The following options describe HIV-related services to be included in the JKN benefit package:

- Option 2 a – Current Basic Benefit Package coverage plus ARV treatment and screening tests.

- Option 2 b – Similar to option 2a but exclude ARV treatment. ARV remains provided through Government vertical channeling mechanism. This option has a slight expansion of the existing package.

Financing scheme for this option will be from premium contributions and government subsidy for ARV. Other HIV-related services will continue to be financed by public (domestic) and external financing that is under the ongoing service provision mechanism.

This option is a potential start for an incremental BBP expansion; over time BBP can be expanded to include more services.

Cost of HIV-related services

As the baseline data for analysis, data on cost from selected providers were analyzed by component to describe how much cost is actually needed to provide certain benefit package. The baseline data is shown in Table 1.

Utilization Rate of HIV Services in BBP

The study used the Asian Epidemic Model (AEM) to estimate Key Affected Population (KAP) and PLHIV population. The model estimates 8.5 million KAP in 2014 and will be increased to 9.1 million KAP in 2019. Meanwhile, the number of PLHIV was estimated 272,000 people in 2014 and will be increased to 331,000 people in 2019 (see Annex. 2).

Table 1. Unit Cost of HIV Services

Components	Benefit Packages	Unit Cost (Rp)
Counseling	Pre-Counseling	28,834
	Post-Counseling	48,944
HIV Test	Screening test	64,336
	Confirmation test	67,719
STI Lab Test	Vaginal Discharge	45,712
	Urethral Discharge	45,712
	Genital Ulcers	39,466
	Pelvic Inflammatory disease	45,712
	Inguinal Bubo	45,712
	Genital vegetation / genital warts	191,500
	Scrotum swelling	45,712
STI Treatment	Drugs	140,922
Pre-ARV Test	Rontgen	16,679
	Blood Test	13,872
	SGOT/SGPT	15,002
	Creatinin	14,629
	CD4	199,389
	Urine Test	46,000
	Viral Load	1,064,125
	HbsAg	136,000
	Sputum	18,937
ARV	ARV 1st Line	379,260
	ARV 2nd Line	1,389,981
Side Effect Treatment	ARV 1st Line	22,561
Prophylaxis Therapy	Cotrimoxazol	13,937
	INH	30,861
Opportunistic Infection Treatment	Inpatient (Severity I)	3,689,640
	Inpatient (Severity II)	5,693,836
	Inpatient (Severity III)	9,265,506
	Outpatient	278,178

Cost Projection and Per Member Per Month (PMPM) Cost Estimate

All costs for HIV services which was calculated then multiplied with the number of KAP and this generates the total cost estimate for HIV and AIDS services. Based on this estimate, the cost per member per month is defined. The 2014 per member per month data for the option 2 as the baseline showed that with additional HIV comprehensive services the additional charge per member was approximately IDR466,6 per month or IDR5.599,2 per year (approximately equivalent to USD 0.5 where USD 1 is equivalent with IDR 10,271.64) as seen in the Table 2. Meanwhile, PMPM premium of benefit package of option 1 can be seen in Annex 3. The cost was estimated to cover comprehensive service including counseling, HIV testing, STI laboratory test, STI treatment, diagnostic test for pre-ARV, ARV treatment, side effect treatment, and PMTCT.

Table 2. Summary of the PMPM Cost in 2014

		Unit Cost	Utilization	PMPM		
			Scenario 1	Scenario 1	Scenario 2	Scenario 3
		(Rp)	(/1000)	(Rp)	(Rp)	(Rp)
Counseling	Pre counceling	28,834	8.095	19.45	21.40	17.51
	Post counceling	48,944	8.047	32.82	36.10	29.54
	Condom	96,000	8.047	64.38	70.81	57.94
HIV test	Screening test	64,336	8.070	43.27	47.59	38.94
	Confirmation test	67,719	0.241	1.36	1.50	1.22
STI Lab test	vaginal discharge	45,712	0.488	1.86	2.04	1.67
	urethral discharge	45,712	0.075	0.29	0.32	0.26
	Genital ulcers	39,466	0.015	0.05	0.05	0.04
	Pelvic Inflammatory disease	45,712	0.019	0.07	0.08	0.07
	Inguinal Bubo	45,712	0.002	0.01	0.01	0.01
	genital vegetation/ genital warts	191,500	0.027	0.42	0.47	0.38
	Scrotum swelling	45,712	0.003	0.01	0.01	0.01
STI treatment	Drugs	140,922	1.918	22.52	24.78	20.27
Pre ARV test	Rontgen	16,679	0.877	1.22	1.34	1.10
	Blood test	13,872	2.954	3.42	3.76	3.07
	SGOT/SGPT	15,002	3.647	4.56	5.02	4.10
	Creatinin	14,629	1.569	1.91	2.10	1.72
	CD4	199,389	1.569	26.08	28.69	23.47
	Urinalisa	46,000	0.877	3.36	3.70	3.03
	Viral load	1,064,125	0.877	77.78	85.55	70.00
	HBsAg	136,000	0.877	9.94	10.93	8.95
	sputum	18,937	0.877	1.38	1.52	1.25
ARV	ARV 1st line	379,260	4.350	137.47	151.21	123.72
	ARV 2nd line	1,389,981	0.107	12.44	13.68	11.19
Side effect treatmentt	ARV 1st line	22,561	0.098	0.18	0.20	0.17
Prophilaxis therapy	Cotrimoxazole (CTX)	13,973	0.100	0.12	0.13	0.11
	INH	30,861	0.100	0.26	0.28	0.23
	Total PMPM - Basic 2 A			466.6	513.3	420.0
	Total PMPM - Basic 2 B (excluding ARV)			316.7	348.4	285.0

The cost projection between 2015 – 2019 was using inflation rate at 4% and trend of utilization rate was generated after several consultation meetings with HIV-UHC Working Group. The meeting with the working group was aimed to identify factors influencing the use of services after implementation of the national strategic responses, such as expansion of ARV (SUFA) and comprehensive continuum of care (LKB).

The projection illustrates high cost to be covered by the JKN in the next 5 years and potentially will be doubled in 2019, option 1 projection can be seen in Annex 4. The analysis shows an increasing trend not only because of thecosts and increasing utilization,

but also increasing number of people joining the JKN. As it was claim in 2014 claims, when UHC had just started, people accessing the healthcare facility were double compared to 2012. Future trend shows that premium (IDR730-1,000 PMPM, depending on chosen scenario) in 2019 will be 2 times higher than in 2014. This higher rate gives idea to the government to expand VCT service which also cover condom provision. Overall premium PMPM in 2019 will be higher in comparison with 2014 premium. The premium will be 3 times higher if condom and counseling service are included in the benefit package and will be 4 times higher if screening for HIV test is included in the benefit package. Other components demonstrate mild effect indicating a slight increased over the years.

Table 3. Summary of PMPM Cost, 2015-2019 (IDR)

Option	Scenario/Model	2014	2015	2016	2017	2018	2019
Basic Package 2A	Baseline	467	625	711	798	902	1.000
	Upper Bound 10%	513	687	782	878	992	1.100
	Lower Bound 10%	420	562	640	718	812	900
Basic Package 2B	Baseline	317	468	535	615	714	811
	Upper Bound 10%	348	515	588	676	786	892
	Lower Bound 10%	285	421	481	533	643	730

DISCUSSIONS

The subsidy for HIV and AIDS program was mostly for providing ARV and implementing prevention program. However, financing for other program components remain depend on external support. In the past, spending for HIV response in Indonesia is dominated by three donors – the GFATM, AusAID, and USAID – that together accounted for more than 90% of total international spending in 2011/12 or 58% of total HIV expenditures of US$50.2 million. In 2012, the Global Fund alone funded 28.6% of total national HIV response (or ~ 0.4% of public expenditure on health) in the country. Indonesia will no longer obtain funding support from the Global Fund by 2020 [3]. The national HIV program achievement which substantially influenced by the work of NGOs and other stakeholders' need to be sustained. In fact, increasing funding support from domestic sources is needed, both from public and private sources. From public funding point of view, it is expected that role of central and local government shall be improved, as well as other potential sources for JKN scheme. This study revealed certain option for the JKN scheme to support its inclusion of HIV–related services with careful considerations.

The current situation on provider payment for community health center as primary healthcare provider revealed that capitation payment is one the main source of fund to support public health interventions. However, depending solely on the JKN to support such a vertical or integrated program remain a challenge. Giving a more flexibility to the health center to manage its fund will aid the program to strategically use its multiple sources of fund in implementing planned activities.

The option 2 was proposed with some reasons. Integration of HIV-related services into JKN, requires some efforts and considerations. First, continuum of care of HIV intervention includes prevention, care and treatment also all others should be covered. Procurement and accountability become a challenge

the JKN payer. Second, one important issue is financial burden for HIVAIDS in the future can only avoided with a good prevention program, hence the outreach program should be continued to ensure prevention such as condom use and STDs lab and treatment are successfully achieved, which clearly have been funded and managed under Government's source of fund. Nevertheless, dealing with stigma around people, health workers in facilities in particular should be carefully managed. Third, the capacity and quality of health provision should be upgraded in many settings [10]. The next important one is a strict and transparent monitoring mechanism to ensure professionalism of the implementation (particularly for treatment care) and the Ministry of Health (particularly for prevention care) to avoid fragmentation of interventions. Besides, universal coverage context proponents should reforms partnership between government and the public communities as the effort of strengthening community systems to extend services to marginalized and stigmatized populations[10].

In addition, vertical program integration to also include HIV and AIDS issues into social health insurance will impact not only to more services that should be covered, but also to consider all matters related to health system pillars in all levels. In the aspect of human resources among others are (i) increasing work-load of health facility workforce, (ii) preparing the supportive and complementary services for HIV patients, (iii) adding more activities to control the treatment cascade for specific target population groups, (iv) ensuring that services or benefit packages are equal in every region, and (v) other region-based problems, such as fragmented services that discourage patients in getting certain services, for example, diagnostic tests in primary health care while ARV services in many regions only exist in hospital[11-13].

The researchers acknowledged study limitation that mostly because of limited number of samples and rapid changing of policy during the implementation in the country. The sample selection was not intended to represent Indonesia. The difference

between local government capacity was not ideally captured. However, as a vertical program, role of central government is critical and this situation was captured for the model developed. The scenarios and projection of the cost, utilization, and cost per member per month could be seen as input for further steps for strategic purchasing, by carefully looking at the need and demand in the future and stakeholders' acceptance. This challenge to integrate this program into JKN need further careful assessment, especially considering the trend of raising claims for treatment.

Experience from other countries showed that HIV services could possibly be managed by insurance, such as in Thailand and Vietnam[14-17]. Under tax-based system, insurer/payer could play a central role for managing payment and ensuring access for PLHIV, such as Thailand where National Health Security Office (NHSO) is the payer for national HIV program intervention and responsible for procurement and monitoring[14-15]. In other developing countries such as in Zimbabwe, increased funding from other options was suggested, such as increased ''sin taxes''that could decrease HIV related risk behaviours[18]. It was also proposed to seek potential support from social health insurance that could help attract further household resources[18].

This study revealed that the Basic Package would be possibly implemented, where all program components that included in the current package/subsidy remain available. If it is accepted, the government would remain support ART service. In the context of Indonesia, early detection is considered as part of government's role, where VCT services may best be scaled up in community-based clinics[19]. The increasing number of new HIV cases requires increasing demand for ART for adults and children with HIV. In 2009, a million extra people received ART, but 5.5 million of 9.5 million people in need of treatment worldwide did not receive ART [17]. Furthermore, because the WHO guideline recommend earlier initiation of ART, the number of people classified as in need of treatment will increase by almost half [21-22]. Financial constraints were reported to be the most significant barrier to antiretroviral adherence in patients living with HIV and AIDS in Botswana and other countries in sub-saharan Africa prior to the introduction of free treatment[21-23].

In the case of Indonesia, to ensure ART is provided timely at reasonable price is part of the underlying consideration why option 2 is more favorable. In addition, prophylaxis and side effect treatment should be included in option of basic package. Under most reasonable option, the government should seek more fund to support the program.

In conclusion, 1. Although burden of current HIV and AIDS services claims under the SHI scheme is only 1% compared to total claims, without a systematic case prevention the government will be facing potential increase of financial burden to cover treatment in the future. This means the JKN should also take part in prevention. However, this does not mean all tasks will be shifted to JKN. Some of the services are potentially managed under UHC and program that related to public health and outreach programs should remain as government responsibility.

2. Some HIV services integration into the JKN would help improve provision of treatment and care more efficient while it can be done at affordable cost. Choosing option 2 or Basic Benefit Package will increase the premium up to only 2% while Option 1 will increase 3% of the premium.

3. A clear and realistic roadmap for integration of HIV services into the JKN should be developed if it is to be done in an incremental manner in changing the funding mechanism. In addition, monitoring and evaluation plan development and other efforts should be taken into consideration such as handling the sensitive issues due to social stigmatization of PLHIV and targeted population.

4. The integration of HIV services into the JKN should be considered as a part of the efforts to develop the country's transition plan from donor dependency to ensure financial and programmatic sustainability of the National HIV response. The Ministry of Health is responsible for HIV prevention and care program, ARV provision as well as ensuring its availability and accessibility for those who need it.

Acknowledgments

Conflict of Interest

We declare that we have no conflict of interest

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Annex

Annex 1. Current Coverage and Funding Mechanism for HIV Services

Interventions	Service Component	Service elements	Current Coverage/Funding mechanism
Prevention	STI services	Diagnostic : STI tests	**JKN** and Public Financing
		Drugs	**JKN** and Public Financing
		Condom and lubricant	Public - Domestic and External
		IEC materials	Public - Domestic and External
		Consultation (Medical and Lab Technician fee)	**JKN** and Public Financing
	HIV Counseling and Testing	Diagnostic tests	Public financing - Central & Sub National
		Condoms	Public - Domestic and External
		Consultation (Medical and LabTechnician fee)	**JKN** and Public Financing
	Harm Reduction	NSP	Public - Domestic and External
		MMT	Public financing
		Condoms	Public – Domestic and External
		Consultation (Medical and Lab Technician fee)	Public Financing
	PMTCT	Diagnostic tests	Public financing - Central &Sub National
		Condoms	Public - Domestic and External
		ARV	Public - Domestic and External
		C-section	Public - Domestic and External
		IEC materials	Public - Domestic and External
		Consultation (Medical and Lab Technician fee)	**JKN** and Public Financing
Treatment and Care	Treatment and Care	Screening tests: ARV eligibility	Public financing - Central & Sub National
		Prophylaxis drugs	Public - Domestic and External
		ARV	Public - Domestic and External
		Monitoring tests : CD4 & VL	Public - Domestic and External
		OI Hospitalization	**JKN**
		OI Drugs	**JKN** and Public Financing
		Condoms	Public - Domestic and External
		Consultation (Medical& Lab fee)	**JKN** and Public Financing

Annex 2. Key Affected Population Size Estimates - Targeted beneficieries (IDR)

	2014	2015	2016	2017	2018	2019	2020
Total Population (all)	252,073,120	255,461,700	265,499,840	275,537,980	285,576,120	295,614,260	305,652,400
JKN Members (Roadmap Target)	15%	39%	60%	83%	90%	100%	100%
JKN Members (Current & Projection)	135,700,000			228,696,523	257,018,508	295,614,260	305,652,400
Key Affected Population (15+)							
KAP Total	8,577,964	8,694,356	8,809,579	8,924,000	9,037,279	9,148,556	9,257,543
Total Population (15+)	184,131,232	186,583,955	189,037,263	191,482,978	193,902,756	196,280,239	198,609,853
PLHIV Population							
Total KAP PLHIV	272,153	282,353	293,170	304,853	317,522	331,195	345,842
Total PLHIV	649,884	679,736	708,048	735,297	761,786	787,795	

Annex 3. Summary of the Premium PMPM 2014 for Option 1 (IDR)

Benefit	PMPM 2014 (baseline)
Counseling	117,03
HIV Test	44,63
STI lab test	6,84
STI treatment	25,44
Pre ARV test	175,41
ARV	187,34
Prophylaxis and treatment	1,41
Total PMPM	558,13

Annex 4. Summary of Cost Projection Option 1, 2015-2019 (IDR)

Basic	2014	2015	2016	2017	2018	2019
	558	747	850	954	1.079	1.196