RISK FACTORS ASSOCIATED TO DIPHTHERIA OUTBREAK IN DEVELOPING COUNTRIES

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FAKTOR-FAKTOR RISIKO YANG BERHUBUNGAN DENGAN KEJADIAN LUAR BIASA DIFTERI DI NEGARA BERKEMBANG

ABSTRACT

Background: Diphtheria is a vaccine preventable disease. In the last 10 years a significant fluctuation of diphtheria incidence led to an outbreak reported in some developing countries. The aim of this study was to review about risk factors in developing countries which are associated with high incidence of diphtheria.
Methods: We conducted systematic search studies using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods based on electronic sources from Pubmed, Proquest, Science Direct, Scopus, and EBSCO for relevant studies. Studies are eligible if the population studies were in developing countries; outcomes were related in risk factors associated to diphtheria outbreak; and design study was observational study.
Results: The 10 selected studies were done in India, Thailand, Lao PDR, Brazil, Dominican Republic, South Africa, and Nigeria. Low vaccination coverage, partially vaccinated or unvaccinated status and poor access to health care services are identified as the main factors that associated directly to diphtheria outbreak in most of the countries. The health care system factors such as availability of Diphtheria anti-toxin and the capability of health personnel in making early diagnosis and prompted treatment also play important roles in controlling Diphtheria outbreak. The study also highlight increasing risk for infection in adult due to waning antibody levels in adulthood.
Conclusion: Low vaccination coverage, poor access to health services, and low income were factors that had led to resurgence of diphtheria in developing countries. The strengthening of surveillance and health care system could give better chance in tackling the diphtheria outbreak.
Keywords: Outbreak, diphtheria, vaccination, risk factors

ABSTRAK

Latar Belakang: Difteri adalah salah satu penyakit yang dapat dicegah oleh vaksin. Namun dalam sepuluh tahun terakhir dilaporkan terjadi peningkatan insiden difteri yang memicu terjadinya kejadian luar biasa di negara berkembang. Penelitian ini bertujuan untuk mengetahui faktor risiko yang berhubungan dengan tingginya insiden difteri di negara berkembang.
Metode: Metode penelitian yang digunakan yaitu Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Literatur yang sesuai ditelusuri dari database elektronik Pubmed, Proquest, Science Direct, Scopus, and EBSCO. Kriteria inklusi yang digunakan yaitu kasus terjadi di negara berkembang, hasil penelitian berhubungan dengan faktor risiko terkait kejadian luar biasa difteri, dan desain studi penelitian adalah studi observasional.
Hasil Penelitian: Diperoleh 10 artikel penelitian yang berlokasi di India, Thailand, Lao PDR, Brazil, Dominican Republic, South Africa, dan Nigeria. Cakupan vaksinasi yang rendah, status vaksinasi tidak lengkap atau tidak di vaksinasi sama sekali serta akses yang buruk ke layanan perawatan kesehatan merupakan faktor utama yang terkait langsung dengan terjadinya kejadian luar biasa difteri di sebagian besar negara. Faktor sistem pelayanan kesehatan seperti ketersediaan anti-toksin Difteri serta kemampuan tenaga kesehatan dalam diagnosis dini dan penanganan segera juga memainkan peran penting dalam mengendalikan kejadian luar biasa Difteri. Hasil studi juga menyoroti peningkatan risiko infeksi pada orang dewasa karena memudarnya tingkat antibodi di masa dewasa.
Kesimpulan: Rendahnya cakupan imunisasi, sulitnya akses pada pelayanan imunisasi, dan rendahnya tingkat pendapatan merupakan faktor yang memicu timbulnya kejadian luar biasa difteri di negara berkembang. Penguatan surveilans dan sistem pelayanan kesehatan sangat diperlukan untuk mengatasi kejadian luar biasa difteri.

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Kata kunci: Kejadian luar biasa, difteri, vaksinasi, faktor risiko

INTRODUCTION

Diphtheria is vaccine preventable disease. Vaccination against diphtheria has reduced the mortality and morbidity of diphtheria dramatically, however diphtheria is still a significant child health problem in countries with poor Expanded Programme on Vaccination (EPI) coverage. Diphtheria is fatal in 5-10% of cases, with a higher mortality rate in young children.[7] Diphtheria is a serious disease, affecting nose, throat and upper respiratory tract. The disease could also lead to death, due to blocked breathing tract and heart failure, particularly in children.[2]

Despite the significant decline in the incidence of vaccine-preventable diseases, there is a considerable number of children with delayed vaccination and a marked heterogeneity in vaccination coverage worldwide,[3] leaving a predictable risk of resurgence of infectious diseases that once are under control, such as Diphtheria. Thus, different vaccination strategies are needed to resolve the issue.

During 2016, about 86% of infants worldwide (116.5 million infants) received 3 doses of diphtheria-tetanus-pertussis (DTP3) vaccine, protecting them against infectious diseases that can cause serious illness and disability or be fatal.[4] While about 130 countries had reached at least 90% coverage of DTP3 vaccine. However, estimated 19.5 million infants worldwide were not reached with routine vaccination services such as DTP3 vaccine. Around 60% of these children live in 10 countries: Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Iraq, Nigeria, Pakistan and South Africa.[5] These children are exposed to risk more than they should. Which ultimately contribute to the occurrence about 7,097 cases of diphtheria around the world in 2016.[4]

In the last 10 years there has been a significant fluctuation in the incidence of diphtheria leading to an outbreak reported in some developing countries.[6] Recent outbreak reported in Indonesia, 591 cases, have been reported from 95 districts in 20 provinces[7] and killed at least 32 people.[8] The majority i.e. 80% of these cases have been reported from seven provinces (Banten, West Java, East Java, Bangka Belitung, Jambi, and Lampung) is attributed to several reasons, including some families rejecting vaccinations, lack of awareness on the benefit of vaccination, and for some areas lack of access to services.[7] Indonesia's high incidence of Diphtheria has been reported since 2011, according to surveillance data there were 3,353 cases reported from 35 among 38 districts in East Java province[9] and in 2012 there are 11 suspected cases have also been reported in Jakarta province.[10]

Diphtheria outbreak also occurred in Lao People's Democratic Republic during 2012-2013, 62 clinical cases of diphtheria and 12 diphtheria related deaths were reported in 7 of 17 provinces. Suboptimal DTP3 coverage likely caused the outbreak.[11] While in India, the world's highest rates of diphtheria, the outbreak also reported in two very remote villages of northern Karnataka in South India in 2011. Ten confirmed cases infected with toxigenic strains of *C. diphtheriae* with 2 people killed, and the majority of confirmed cases were either unimmunized or immune drop-outs.[12]

Several more diphtheria outbreaks have also been reported in some developing countries in other parts of the world occurring over different time spans, who happened to have higher mortality. An outbreak with 27% case fatality rate (CFR) was reported in South Africa in 2015,[13] diphtheria outbreak with 21.4% overall CFR was highest in children aged 0-4 years (42.9%) occurred in Nigeria in 2011,[14] endemic cases of diphtheria that turns out into an outbreak with 11-12% of cases were fatal occurred in Brazil in 2010,[15] and total of 145 diphtheria cases with high CFR (32.5%) was also reported in Dominican Republic in

2004-2005.[16]

Most brief reports on the diphtheria outbreaks above shown interconnectedness between high incidence or outbreak with vaccination coverage, access to health services and anti-toxin availability. The aim of this study is to review in literature about risk factors in developing countries which are associated with vaccination coverage, socioeconomic conditions and health care system characteristics. Vaccination coverage and incidence of diphtheria are also assessed from monitoring and surveillance report from World Health Organization website. The risk factors related to socioeconomic condition and health system characteristic are collected and studied from existing studies/research using literature study design.

METHOD

We conducted systematic search studies using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods based on electronic sources from several online databases. We searched Pubmed, Proquest, Science Direct, Scopus and EBSCO for relevant studies. Systematic literature review methods were used to identify, analyze and synthesize data. Systematic review methods are intended to capture and synthesize the research evidence to answer pre-specified research questions. Journals were searched for using electronic literature databases and targeted internet searches. We developed a search strategy for headings terms and text words of key articles that we identified a priori. This strategy was adapted to each database's search terminology or simplified for a database if it did not support the depth of research. We reviewed the reference lists of all included articles and relevant review articles to identify articles that the database searches might have missed.

First step to search was using advanced search with the following keyword: 'Diphtheria' AND 'Outbreak' NOT 'Pertussis'

NOT 'Tetanus'. The result then filtered by publication year: 2008-2018, filtered by type of articles and free full text. As in the second step, advanced search result studies were selected manually by reviewing the abstract or full text using inclusion criteria: 1) population studies were in developing countries; 2) outcomes were related in risk factors associated to diphtheria outbreak; and 3) design study was observational study such as case report, case series, case-control or cross-sectional. Finally, remaining eligible studies were critically appraisal using Joanna Briggs Institute (JBI) guidelines tools for case report, case series, cross-sectional and case-control.

Two reviewers conducted title scans and abstract reviews and reviewed the full articles to assess eligibility for inclusion for each study. We created standardized forms for data extraction. Data was extracted from the 10 full text articles on the following categories: title, first author, year, country, study design, settings, outcomes and risk factors associated to Diphtheria outbreak. Each article received a double review for data extraction. The second reviewer confirmed the first reviewer's data abstraction for completeness and accuracy.

Extracted risk factors of diphtheria outbreak from the selected articles were categorized and analyzed into following variables:
1. Vaccination coverage (high, low) and vaccination status (fully, partially, unvaccinated)
2. Socioeconomic status (family features, guardians'/parents' knowledge and attitudes, income)
3. Health system characteristics (access to health services, availability and knowledge of health worker, vaccine supplies, availability of anti-toxin)

Because of the limited number of studies for each variable, we did not quantitatively pool the results.

Findings were based on small number of reported confirmed Diphtheria cases may

reduce the power of the study to identify risk factors. Some findings of studies were not statistically significant due to the small number of cases studied. However, the findings are substantially significant based on its directness of evidences, and consistency of the studies. Besides that, many of reported cases were missing vaccination status and it was possible recall bias.

RESULTS

The literature search described in the methods identified 17,754 citations from all databases only using the keyword search. The result then filtered by publication year: 2008-2018, type of articles and free full text resulting of 35 citations in Pubmed, 20 citations in Proquest, 25 citations in Science

Direct, 38 citations in Scopus, and 33 citations in EBSCOHost. For 29 citations were excluded for duplication from this step. The second step were, we selected studies manually for the remaining 122 abstracts using inclusion criteria, resulting on 112 studies were excluded because of the population was not in developing country, outcomes were not related in risk factors associated to diphtheria outbreak, and study design was unmet inclusion criteria. Finally, 10 abstracts were selected for data extraction and critical appraisal as shown in Figure 1. From the articles, we conduct journal critical appraisal using Joanna Briggs Institute (JBI) guidelines tools for case report, case series, cross-sectional and case-control.
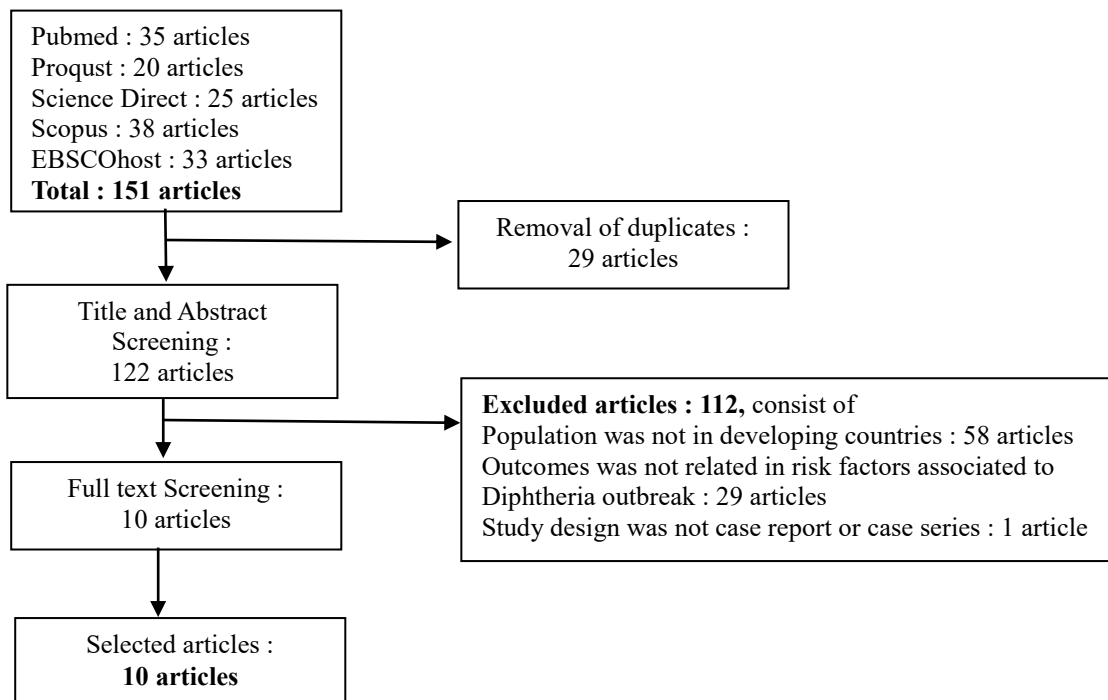

Figure 1.
PRISMA flow diagram of the number search yielded, excluded, and reviewed

The 10 selected studies were done in 7 developing countries mostly in Asia Region (6 studies), some others were in Latin America and Carribean Region (2 studies) and Africa Region (2 Studies). The countries are India, Thailand, Lao PDR, Brazil, Dominican Republic, South Africa and Nigeria. All 7

countries were classified as developing economics countries referring to World Economic Situation and Prospects (WESP) 2018 country classification conducted by United Nation.[17]

Table 1 describes risk factors associated with diphtheria outbreak extracted among

countries. The risk factors are categorized into variables vaccination coverage, sosioeconomic

conditions and health care system.

Tabel 1.
Variables Comparison Among Countries

Variables	Countries						
	India	Lao PDR	Thailand	Brazil	Dominican Republic	Nigeria	South Africa
Vaccination coverage							
60-80%	v		v				v
<50%		v			v	v	
Unvaccinated/Partially Vaccination status	v	v	v	v		v	v
Socioeconomic condition							
Age-related							
Child (<18 years old)	v	v		v	v	v	v
Adult (>18 years old)	v		v				
Religion-related	v						
Sex-related							
Male	v				v		v
Female				v			
Low Income			v		v		
Guardian/Parental's knowledge					v		
Health care System							
Poor access to health care facilities	v	v	v		v	v	v
Lack availibility of Diphtheria anti-toxin	v					v	v
Delayed/ Insufficient early diagnosis and prompt treatment	v			v		v	
Lack availibility of national protocols		v					
Insufficient surveillance system	v						
Other factors							
Level of toxigenicity of bacteria strain	v			v			
Waning antibody levels in adult	v		v				
Overcrowded housing complex with poor ventilation	v						

From result shown in Table 1, low vaccination coverage, vaccination status (partially or unvaccinated) and poor access to health care services were the most cited factors from the studies. These factors are identified as the main factors or problem that associated directly to Diphtheria Outbreak in most of the countries. The findings also highlight that children patient (age below 18 years old) are

the most cases reported in outbreak. Among studies, 5 out of 7 studies showed childhood and adolescent group of ages (<15 years old) at more risk as the majority group of cases. In the other hand, some countries such as Thailand and India showed distinct characteristics where majority cases were adult (>16 years old).

In health care system, poor access to health care services are not the only risk

factors. It is also found that inavailability of Diphtheria anti-toxin, and the capability of health personnel in making early diagnosis and prompted treatment for Diphtheria play important roles in controling Diphtheria outbreak. The study also identified other two health care system factors which are inavailibility of national protocols in Lao PDR and insufficient surveillance system in India.

Other associated factors were identified from studies in India, Thailand and Brazil. The studies reported level of toxigenicity of the *C. Diphtheria* bacteria, overcrowded housing complex with poor ventilation and waning antibody level (seroprotection level of immunity) also associated to outbreak.

Studies in Lao PDR and Northeastern Nigeria proved that Diphtheria outbreak was related in low vaccination coverage. DTP vaccination coverage in Lao PDR is only 59,8% and in Northeastern Nigeria is below 1% which transform the high incidence into Outbreak. While Studies from Dominican Republic, Maranhao Brazil, South Africa, and North Kerala were not mention number of vaccination coverage clearly, but there is information that there were low vaccination coverage level at Dominican Republic, most cases were happened to partially or unvaccinated patient in Maranhao Brazil, South Africa, and North Kerala.

Tabel 2 showed Diphtheria Incidence reported among countries during 2004 to 2016. High national vaccination coverage were showed in some countries as shown in Table 3 and 4. From table 2, India have the most cases compare to other countries. Higher Diphtheria incidence in India were contrast with high National DPT1 and DPT3 Vaccination Coverage Percentage as shown in Table 3 and Table 4. High percentage of National DPT1-DPT3 Vaccination Coverage are not always followed by lower incidence of Diphtheria in India. India's DPT1 vaccination coverage was 85% but yet Diphtheria cases average was still remain high (8,465 cases). In the other hand, Diphtheria cases were not reported properly in Nigeria and South Africa as shown in Table 2. From table 2 we can see Nigeria reported 312 Diphtheria in 2006 cases. However from table 3 we also notice that Nigeria's DPT1 vaccination coverage was quite high (87%) at that time. According to this findings, the question would be were vaccination effective to prevent Diphtheria or there were other risk factors that play a greater role in the high incidence of diphtheria.

Tabel 2.
Comparison of Diphtheria Incidence among countries in 2004-2016

Countries	Diphtheria Incidence (Cases)												
	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004
India	3,380	2,365	6,094	3,133	2,525	4,233	3,434	3,529	3,977	3,812	2,834	5,826	8,465
Lao PDR	3	194	0	20	130	0	34	0	2	2	2	9	11
Thailand	16	19	19	28	63	28	77	12	8	3	2	1	13
Brazil	4	12	5	4	0	5	32	4	85	0	9	27	15
Dominican Republic	3	1	0	0	0	2	4	5	3	4	16	39	122
Nigeria	-	-	-	-	-	0	-	-	-	-	312	-	-
South Africa	0	15	-	-	-	0	-	1	-	-	-	-	0

Compiled from http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html, accessed on May 29th 2018

Tabel 3.
Comparison of National DPT1 Vaccination Coverage Percentage in 2004-2016

Countries	National DPT1 Vaccination Coverage Percentage												
	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004
India	91	90	-	90	89	89	86	84	81	81	81	82	77
Lao Pdr	85	93	94	89	87	83	81	76	73	59	68	68	66
Thailand	-	99	99	99	99	99	99	99	99	99	99	99	99
Brazil	95	97	99	99	99	99	99	99	99	99	99	99	99
Dominican Republic	98	99	99	91	93	91	96	85	86	87	93	92	87
Nigeria	55	55	76	72	67	68	84	82	66	77	87	45	49
South Africa	89	94	96	92	83	89	99	14	99	99	99	99	77

Compiled from http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragedtp1.html, accessed on May 29th 2018

Tabel 4.
Comparison of National DPT3 Vaccination Coverage Percentage in 2004-2016

Countries	DPT3 Vaccination Coverage Percentage												
	2016	**2015**	**2014**	**2013**	**2012**	**2011**	**2010**	**2009**	**2008**	**2007**	**2006**	**2005**	**2004**
India	88	87	-	83	82	82	79	74	70	64	65	65	63
Lao PDR	2	89	88	87	79	78	74	67	61	50	81	49	45
Thailand	99	99	99	99	99	99	99	99	99	98	98	98	98
Brazil	89	96	93	97	95	99	99	99	99	99	99	99	99
Dominican Republic	87	85	91	83	85	84	88	82	82	85	89	87	79
Nigeria	45	45	70	65	57	61	74	71	57	69	72	38	38
South Africa	84	93	95	91	83	87	91	12	98	97	99	97	71

Compiled from http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragedtp3.html, accessed on May 29th 2018

DISCUSSION
Vaccination Coverage

The outbreak or high incidences rates of Diphtheria occur in rural areas of some countries as reported. Low vaccination coverage in certain areas often related to low access of the areas to health services. Vaccine effectiveness can only be achieved with complete vaccination.[18] Pockets of areas with low vaccination rates or some population with unknown vaccination status were increased the risk of Diphtheria resurgence.[14,18] Multiple doses of Diphtheria vaccination should be given in different time of age in order to achieve complete immunity. Missing a dose of Diphtheria vaccination could affect antibody levels and considered to be one of contributing factors to partially vaccination status.[20]

The immunity status also influenced by age factors. Without proper amount of people who had booster vaccination of Diphtheria, adolescent and adult are also at risk of getting the disease. Adolescent and adult without booster vaccination were have low protective antibody level against diphtheria.[19]

Sosioeconomic Factors

Socioeconomic status influence low vaccination coverage. In Dominican Republic, most cases lived in low income urban areas with difficult access to vaccination posts. Education level of parents or guardian became one of risk factors. Low education level of parents or guardian showed greater risks for child not getting vaccinated.[16] Also education level is an aspect that could not be separated from someone's income level. Poverty were the root cause of all risk factors regarding to an outbreak.

The findings also showed sex-related factors where male were at more risk than female. The very high proportion of males getting infected with diphtheria than females may be attributed to the fact that in rural areas, males are more engaged in outdoor activities than females.[21] This suit the fact that Diphtheria is very contagious disease. Diphtheria is transmitted from person to person through respiratory droplets or even in contact with an object that has the bacteria that cause diphtheria on it.[22]

Health Care System

Health system characteristic was related in low vaccination coverage. Lack of access to vaccination services was experienced by Lao PDR, Nigeria, Dominican Republic, and South Africa.[11,13,14,16] In Lao, site with diphtheria outbreak were mountainous. Vaccination services were delivered by mobile outreach unit. They faced difficulties to deliver vaccination services when rainy season because roads to many village was not accessible. It leads to low vaccination coverage in Lao.[11]

Northeastern Nigeria, especially Kimba Village had special cases. Most population at Kimba Village were semi nomadic which were absent for long periods but regularly returns to same home and village. This situation led to low vaccination coverage in Kimba Village, Northeastern Nigeria.[14] Poor access to health care were substantially relevant to the success of the vaccination program.[11,14,16,23]

Resources on health care system were also important aspect in respond to an outbreak. Capability of health personnel in early diagnose and prompt treatment to Diphtheria were reported to be factors associated to case fatality.[16,25] Diphtheria symptoms sometimes were not easily differentiated. Health professionals need to be aware of the possibility of atypical cases of *C. diphtheriae* infection, including pharyngitis without pseudo membrane formation.[15] Therefore delayed clinical diagnosis of Diphtheria that lead to disease severity level increase or even causing the death of patient could be avoided.[14] Lack of access, resources, and not standardized quality of health care system showed health care inequity, resulting

health care capacity disparities among risk areas.[24]

Most of study's findings suggest improvement on surveillance and monitoring system could lead to be better management of outbreak. Availability of national protocols and guidelines on case detection and treatment at all levels of health systems also the key factors for better respond to outbreak.[11,16,26] Information systems also plays important roles in providing better vaccination coverage data, surveillance and monitoring systems. This is also benefitable for decision making process in tackling, detecting and responding to an outbreak timely.[26,27] What crucial about this is when the epidemiological information generated through the surveillance system and how it was utilized in the best way to take evidence-based public health measures.[28,29] Integrated and structured process of collecting, reporting and interpreting information are necessary in order to create sufficient monitoring systems. Absence of mandatory case based reporting, weak laboratory networks, tendency of peripheral staff to under/ non report cases due to fear of action from superiors and weak data analysis at the district level failed to provide a real picture of the disease burden which can generate misinterpreting and misleading in public health status.[26,27] Specifically, the surveillance and monitoring system should be corresponding with the availability of substantial health resources such as anti-toxin serum and primary/booster vaccination in order to tackle deadly outbreak.

Other Factors

Other associated factors to outbreak are level of toxigenicity of bacteria strain, waning antibody levels condition in adult, overcrowded housing complex with poor ventilation. Level of toxigenicity of Diphtheria bacteria could affect bacteria's transmittance ability, by making it more contagious and easier to transmitted from one

person to another as it found from studies in Brazil and India.[28,30] This finding might answer the question why Diphtheria incidence in India remain high and become endemic in Brazil. Further studies are needed to find out more about what possibly cause the difference of toxigenicity level. The other factor is waning antibody level condition in adult as reported in Thailand.[19] Diphtheria antibodies declined with increasing age, making adults are also at risk in getting Diphtheria. It is recommended for adults to have one dose of diphtheria-tetanus toxoid (dT) vaccine once after 20 years of age in order to boost the antibody and revaccinations every 10 years to prevent future outbreaks.[19,22] Waning antibody level condition in adult might not the main risk factor to cause an outbreak, but it need to be monitored in order to have better vigilance to Diphtheria outbreak.[26] Last but not least, overcrowded housing complex with poor ventilation might not be the factor that directly cause Diphtheria outbreak but this condition making Diphtheria easier to spread and harder to resist.[25,31] Such living environment would give greater risk to population who lived there.

CONCLUSION

Developing countries played important roles in keeping vaccination coverage worldwide high. Low vaccination coverage, poor access to health services and low income were factors that had led to resurgence of Diphtheria in developing countries. Children are in greater risk of getting the disease due to incomplete vaccination status. But the trend also shown that adults are increasingly at risk for infection due to waning antibody levels in adulthood. Therefore, different vaccination strategies are needed to resolve the issues. As the driver keys to successful national vaccination program, furthermore studies on vaccines are needed in order to provide less administering doses of diphtheria vaccine but with more protection to increase the vaccination coverage and lower the dropout

rates. The strengthening of surveillance and health care system could give better chance in tackling the diphtheria outbreak.

ACKNOWLEDGMENT

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