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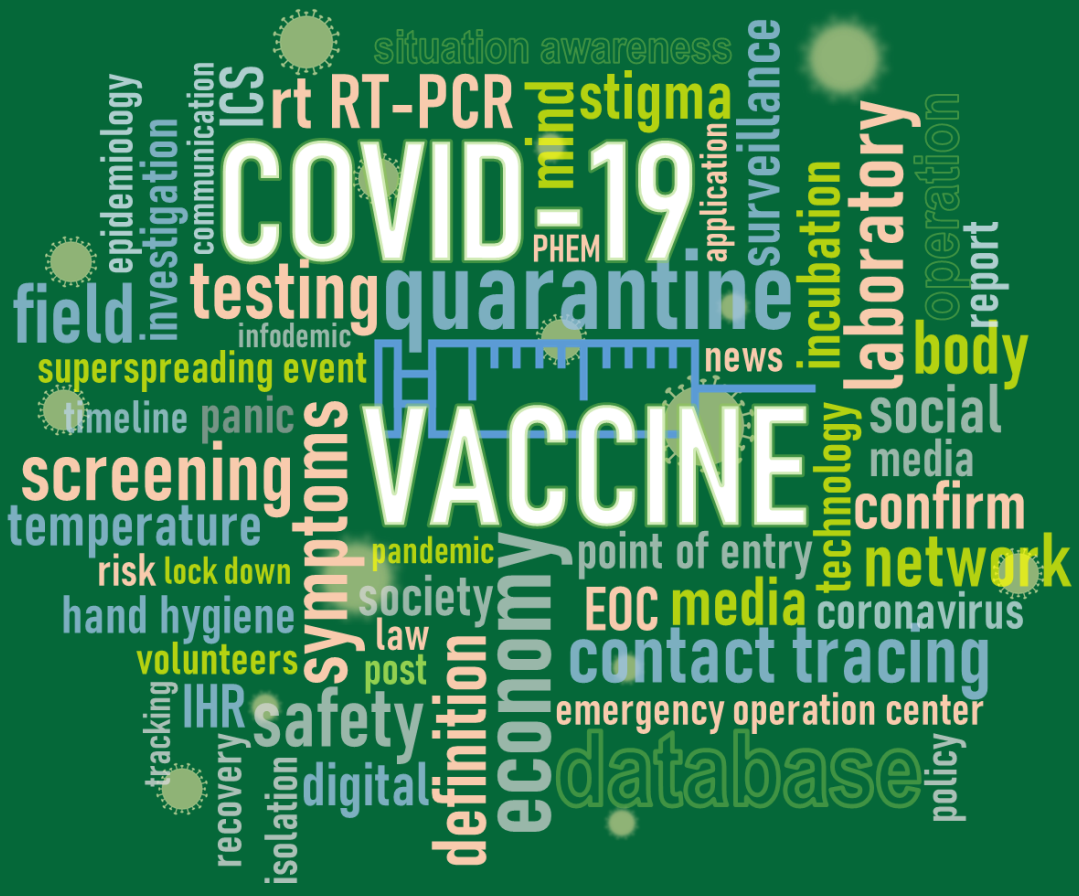

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Field Epidemiology Training Program, Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Tiwanond Road, Talad Kwan Subdistrict, Muang District, Nonthaburi 11000, Thailand

Tel: +662-5901734, Fax: +662-5918581, Email: osireditor@osirjournal.net

Website: <**http://www.osirjournal.net**>

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Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Editorial

What do Field Epidemiologists Do? We Solve Problems by Counting, Comparing, and Communicating.

Alden Henderson, Chief Editor

During my presentation on "Introduction to Field Epidemiology Training Programs", I ask the audience to write down what a field epidemiologist does in ten words or less. I ask this question to find out how much each person's understand what a field epidemiologist does for there is a saying by Albert Einstein: "If you can't explain it simplify, you don't understand it well enough". Most of the responses are over ten words and includes incidence, determinants, and studies. My answer is that field epidemiologists solve problems by counting, comparing, and communicating. I chose these words because they can be understood by epidemiologists and many of the people we need to communicate with: policy makers, media, the public, etc. These are simple words that can be easily understood and has deep meanings.

Counting seems simple but is complicated as demonstrated by the present COVID-19 situation. Just knowing how many COVID-19 cases is challenging and requires lots of resources that are coordinated. Counting becomes more difficult when the definition for a COVID-19 case changes. Demands for real-time reporting adds another level of difficulty. Epidemiologists use case definitions to be sure that we are counting true cases and counting the same thing. Problems occur when the case definition changes, when people have different interpretations of the case definition, and when they apply the case definition differently. Even when we classify the cases correctly, we may not capture all the cases and reporting them accurately and timely.

In the articles in this OSIR issue, the methods section describes what is being counted. In this issue people, cattle and publications are being counted. The counts are further refined by adding inclusion and exclusion criteria, cleaning the data, and categorizing cases or exposures. The article on misdiagnosis of diabetic ketoacidosis instead of COVID-19 is a good example of what happens when we get it wrong. In epidemiology we call this misclassification. This results in Odds Ratios that are closer to the null, showing no difference when there may be a difference – a type II error.

The limitations section communicates to reader assumptions and omissions made and caveats taken. It's the author "letting the reader be aware" of conditions that may bias the data and its interpretation and conclusions.

Now that we are satisfied with our count, we move on to compare them. This is when we transform data into information. We turn lists of numbers into trends, averages, frequencies, rates and odds ratios and confidence intervals to identify susceptible populations, and risk and preventive factors. Seems an easy task but people spend their careers comparing. Many books, university courses and computer programs have information and methods we can use to compare data and produce information: biostatistics, EpiInfo, GPS, etc. People spend their career developing expertise in these topics. One special comparison for field epidemiologists is an epidemic curve as shown in the foot-and-mouth disease article. This curve compares the number of cases (count) by time and provides information on the progress of outbreak, numbers involved, trends, incubation time, transmission, etc.

Part of comparing is interpreting the findings and showing cause and effect. In epidemiology, we often use the Bradford-Hills criteria for causation.

Next, we must communicate our findings. This is where we take results of our comparisons and transform them into a message. Conclusions and recommendations are the most powerful statements coming from our studies. They interpret our information and provide wisdom on what happened, how it happened, and why it happened. Recommendations are how to identify, respond, control, and prevent future incidents. This is often the hardest part to write because we are stepping out of our role as epidemiologists and into the realm of public health professionals. Seek help to write these sections and have others review and comment on what you wrote.

If we do not communicate our findings, we fail our responsibility as epidemiologist. Communication is more than just reporting the information for there must be a message behind our communication and the delivery must be clear. One key element of communicating scientific information is not to confuse the person receiving your message. Simple direct messages work is more easily received that what I call data dumps where lists of numbers are presented. Spend the time to summarize and simplify your message.

So, the next time someone asks you “what do you do?” just say “we solve problems by counting, comparing, and communicating”.

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Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

A Scoping Review on Occupational Exposure of Silica and Asbestos among Industrial Workers in Thailand

Watinee Kunpeuk[1]*, Sataporn Julchoo[1], Mathudara Phaiyarom[1], Jeerapa Sosom[1], Pigunkeaw Sinam[1], Thitiporn Sukaew[1], Nattadhanai Rajatanavin[1], Rapeepong Suphanchaimat[1,2], Panithee Thammawijaya[2], Somkiat Siriruttanapruk[3]

1 International Health Policy Program, Ministry of Public Health, Thailand
2 Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand
3 Division of Occupational and Environmental Diseases, Department of Disease Control, Ministry of Public Health, Thailand

*Corresponding author, email address: watinee@ihpp.thaigov.net

Abstract

Pneumoconiosis is one of the most common occupational lung diseases in Thailand and worldwide. Workplace exposure to asbestos and silica is the main contributor to the prevalence of occupational pneumoconiosis. The aim of this study was to review the prevalence of occupational exposure to asbestos and silica among industrial workers in Thailand. A scoping literature review searched MEDLINE and universities in Thailand. The results from screening 113 were 11 studies selected for further review. Ten studies were cross-sectional and only one study was a retrospective cohort study. Four studies focused on asbestos exposure, whereas seven studies measured silica exposure. From four asbestos exposure studies, three studies showed a higher than standard exposure limit. From seven studies on silica exposure, four studies showed the measured exposure was above the standard level. However, the prevalence of exposure among people working in low-risk areas was not presented. The standard protocol of asbestos and silica exposure measurement was reported. The results showed that the average asbestos and silica exposure exceeded occupational exposure limits stated in either international or national guidelines. The highest level of asbestos exposure was found in a brake pad factory (9.95 fibres/cc). The highest amount of total silica dust was reported in a stone grinding factory (24.3 mg/m^3). Prevention measures and active surveillance programs should be in place for all populations at risk. National surveys on occupational exposure of asbestos and silica are needed to explore current industrial practices and their compliance according to the standard national exposure limit.

Keywords: asbestos, silica, occupational exposure, respiratory, Thailand

Introduction

Pneumoconiosis is one of the most common occupational lung diseases in Thailand and worldwide.[1-3] Exposure to silica asbestos and coal dust can injure lung tissue causing irreversible lung damage.[4,5] Silicosis was the largest specific cause of death from pneumoconiosis, followed by asbestosis and coal workers' pneumoconiosis.[1]

Occupational silica exposure has long been recognized as dangerous to health leading to autoimmune diseases, tuberculosis, lung cancers and other non-malignant respiratory diseases.[6,7] Crystalline silica is considered a human carcinogen by the International Agency for Research on Cancer.[8] Exposure to it has been found in occupations such as construction industries, coal mining, building material industries, glass, and ceramics.[9] It is estimated that silica exposure has been experienced among millions of workers worldwide in a huge number of industries.[9,10] For asbestos, it was widely used in building insulation, roofing shingles, fire blankets, clutches, brake materials and pads for automobiles in many countries during the 19th and 20thcenturies.[11] There are six subtypes of asbestos: chrysotile, crocidolite, amosite, anthophylite, tremolite and actinolite.[12] Asbestos exposure occurs especially from reconstruction and destruction of buildings or

materials, with asbestos contamination, and worn vehicle brakes.[13] Asbestos exposure leads to risk of mesothelioma and cancers in different organs including lungs, larynx, and ovaries.[14,15]

Chrysotile imports in Thailand have resulted in massive benefits to the Thai economy.[16] During 1997 to 2010, the value of chrysotile imports was as large as US$ 0.7 billion. Major exporting countries were Russia, China, Brazil, and Kazakhstan.[16] Due to its hazardous effects, the Thai National Health Assembly banned chrysotile asbestos in 2010. In 2018, 134 asbestosis cases were reported in Thailand in 50 provinces.[17] However, diagnosis of asbestos-related disease remains problematic and maybe underestimated in Thailand, because signs and symptoms of asbestosis are similar to other respiratory diseases. Also, owing to its long latent period patients may have recall bias for occupational asbestos exposure.[18] Although the asbestos ban has been adopted in Thailand, implementation has been delayed by unclear information about use of chrysotile, and external pressure from major chrysotile exporting countries.[16]

The Division of Occupational and Environmental Diseases, Department of Disease Control, Ministry of Public Health of Thailand has been a leading authority in tackling asbestosis and silicosis since 2011. A report by the Department of Primary Industries and Mines of Thailand showed that in 2017 there were 436 registered in quarry factories in Thailand.[19,20] In 2018, silicosis cases nationwide numbered about 240 cases in 31 out of 76 provinces, which is about 25% increase from the figure in recent report in 2017 (195 cases in 28 provinces).[17]

Although there is some knowledge on the number of asbestosis and silicosis cases in Thailand, little is known about exposure of asbestos and silica in industrial workers and populations at risk. We therefore aimed to explore evidence about exposure of asbestos and silica among workers in Thailand through a scoping review approach.

Methods

We used a scoping review approach with a special focus on occupational exposure to silica and asbestos that potentially led to pneumoconiosis. Eligibility criteria for screening studies followed the domains of population, exposure, comparator, outcome (PECO),[21] and study type, with a focus on the Thai context, with details as follows. A scoping review is a useful tool to identify the types and gaps of evidence in a given field, and to explore how the research was conducted.[22] It is different from a systematic review as it aims to confirm current practice or address any variation in a particular research question. Also, it is conducted with a rigorous process on critical appraisal and synthesis. However, in this study, there were no limitations about publication years before 2019.

Scope of the Review

Populations

Industrial workers aged 15 years and over working in both formal and informal employment sectors. Unpaid domestic workers were excluded.

Exposures

Asbestos or silica. There was no limitation concerning periods of exposure. Only objective measurements for occupational exposure were included (such as quantitative sample collection of dust and/or fibre using appropriate technologies). Subjective measurements and self-reporting were excluded.

Comparators

The selected papers could be a descriptive study or analytic study with comparator groups (non-exposure samples).

Outcomes

Prevalence of exposure to asbestos and silicosis and the level of asbestos and silica in working environments.

Study types

Only quantitative research was included. All types of study design were eligible. Qualitative studies, case reports and review papers were excluded. The search was limited to only English or Thai articles.

Information Sources

MEDLINE was used as the main source of searched articles with no restrictions of publication years up to 2019. The search strategy was applied from Mandrioli et al,[5] as presented in Table 1. In addition to the electronic search, we sought gray literature from academic institutes and government authorities. These included master-degree dissertations, doctoral theses, reports, and non-peer review publications. Governmental documents provided by the Division of Occupational and Environmental Diseases, Department of Disease Control, Ministry of Public Health were also included. Furthermore, hand searching from Google Scholar was conducted.

Table 1. Exposure, outcomes, and search terms applied in MEDLINE

Domain	Search terms
Silica and silicosis	(((silica) OR ("Silicon Dioxide"[Mesh] OR "Silica Gel"[Mesh] OR "Silicic Acid"[Mesh])) AND (((((silicosis) OR ("Silicosis"[Mesh])) OR ("Lung Diseases"[Mesh])) OR ("Lung Diseases, Interstitial"[Mesh])) OR ("Anthracosis"[Mesh] OR "Pneumoconiosis"[Mesh]))) AND (Thailand) (16 articles as of 2 June 2020)
Asbestos and asbestosis	(("Asbestos"[Mesh] OR "Asbestos, Amosite"[Mesh] OR "Asbestos, Crocidolite"[Mesh] OR "Asbestos, Amphibole"[Mesh] OR "Asbestos, Serpentine"[Mesh]) AND ((("Asbestosis"[Mesh]) OR ("Lung Diseases"[Mesh] OR "Lung Diseases, Interstitial"[Mesh])) OR ("Caplan Syndrome"[Mesh]))) AND (Thailand) (8 articles as of 2 June 2020)

Study Selection Process

All records from online sources were retrieved by ENDNOTE software. Duplicate publications were removed. Title and abstract screening were independently conducted by three authors (ST, JS, MP) before full-text review of potentially relevant records. When any disagreements arose, another author would help to resolve issues. The stage of study selection and reporting followed the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guideline.[23]

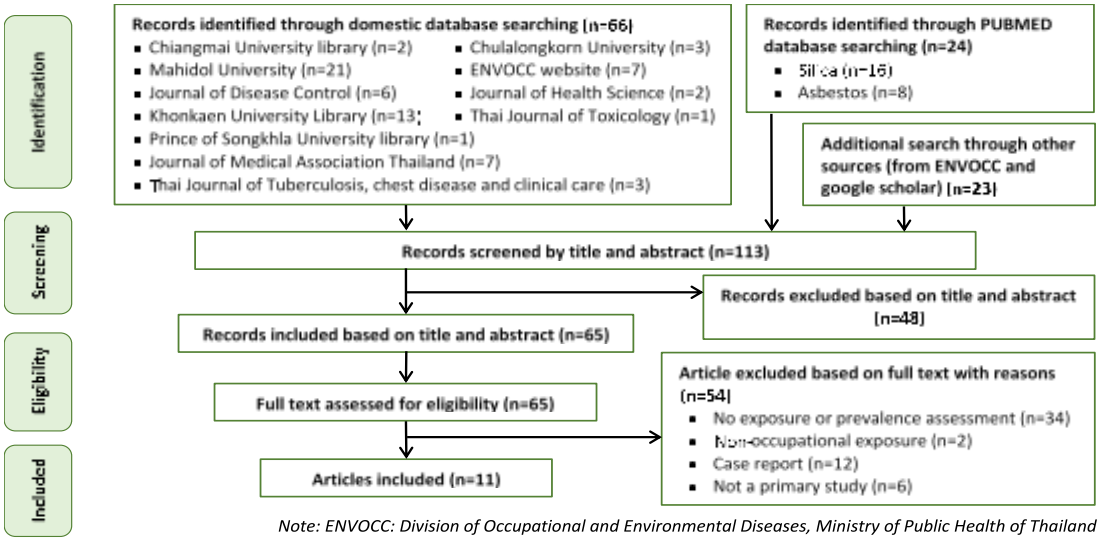
Data Extraction and Analysis

Four authors (SJ, MP, TS, and NR) extracted data from retrieved literature. The extracted data were disaggregated by population characteristics, study design, and industrial or occupation sectors. The proportion of exposed populations to each occupational risk was recorded. Data extraction was conducted using Excel software. We applied framework analysis which was based on the Navigation Guide systematic review methodology.[21] This framework has been applied from the standard Cochrane Collaboration methods for systematic reviews of interventions, and was adapted to the study on occupational and environmental health. The focus of this framework was on hazard identification and risk assessment, which could guide inclusion and exclusion criteria in this study.

Results

Overview of Search Results

A total of 66 articles were selected from domestic websites including Thai universities and government offices, and 24 articles from MEDLINE. Supplementary hand searching identified an additional 23 records. In total, 113 articles were processed for title and abstract screening. Consequently, 48 articles were excluded due to duplication and being non-relevant to the research questions. There were 65 studies eligible for further full-text screening. Finally, we found 11 studies which met inclusion criteria and these entered data extraction process (Figure 1). The excluded data were the articles with no information on asbestos or silica exposure (n=34). Some reported non-occupational exposures (n=2) which were caused by environmental air pollution. Some studies were just a case report (n=12), and were not primary research (n=6). In total, 54 studies were excluded after full-text screening.



Note: ENVOCC: Division of Occupational and Environmental Diseases, Ministry of Public Health of Thailand

Figure 1. Flow diagram of literature search and article selection

Characteristics of Included Studies

Of the eleven studies, year of publication was from 1995 to 2019. Eight studies were peer-review academic articles[24-30] (Table 2 and Supplementary Table 1), one was master-degree thesis,[31] and two were research reports.[32,33] Seven studies focused on silica exposure[19,24,25,29-31,33] while the other four investigated asbestos exposure.[26-28,32]

The central,[28] northern,[32] and southern[27] regions equally had single research about asbestos exposure. Research on silica exposure covered various regions, including two studies in the central region,[24,31] four studies in the northern region,[19,25,30,33] and one in the eastern region.[29] The majority of studies used cross-sectional study design, except Danphaiboon et al,[33] which employed retrospective cohort design.

For asbestos exposure, studies were undertaken in diverse settings (tile factory,[27] cement roof factory,[26] material building factory,[28] and friction material factory).[32] For silica exposure, the majority of studies were conducted in stone mills and stone-related factories,[19,25,30,33] and one study was a sanitary-ware factory.[31] All study participants were identified as 'high risk' as they worked on production sites with direct exposure to asbestos and silica. Mean age of participants varied from 30 to 52 years. The number of participants in most included studies was over 100. Aungkasuvapala et al[24] recruited most participants (n=676). All studies that applied cross-sectional research design presented only descriptive results without analytic findings. Most studies reported 100% high-risk workers exposed to asbestos and silica. It was impossible to estimate asbestos exposure prevalence in a study by Tangtong and Phanprasit[28] as there was no information about participant numbers.

Table 2. Characteristics of the included studies

Author (year)	Type of study record	Study design	Exposure	Location	Characteristics of exposed group	Mean age [years (SD)]	Number of participants (n)	Percentage of exposed workers to total participants involved in the study (%)[40]
Aungkasuvapala et al (1995)[24]	Academic journal	Cross-sectional	Silica in stone grinding factories	Saraburi	High-risk workers at stone-grinding factories	30.7 (9.6)	Exposed=676 Non-exposed =NA	100%
Yingratanasuk et al (2002)[29]	Academic Journal (International)	Cross-sectional	Silica in stone carving company	Eastern region; provinces not specified	Workers at the production site of stone carvers, pestle makers, and mortar makers	33.2 (9.2)	Exposed=97 Non-exposed =NA	100%
Lojananond (2004)[32]	Report	Cross-sectional	Asbestos in break pad (friction materials), tile factory, and cement tube	The lower northern part of Thailand	High risk workers at the production site of break pad (friction materials), tile factory, and cement tube	NA	Exposed=140 Non-exposed =NA	100%
Siriwatananukul (2008)[27]	Academic journal	Cross-sectional	Asbestos in tile factory	Nakhon Si Thammarat	Workers in the tile manufacturing zone and asbestos mixing zone	NA	Exposed=147 Non-exposed =NA	100%
Tangtong and Phanprasit (2008)[28]	Academic journal	Cross-sectional	Asbestos in contained material building	Bangkok	Workers involved in the demolition of building which contained asbestos materials	NA	NA	NA

Table 2. Characteristics of the included studies (Cont.)

Author (year)	Type of study record	Study design	Exposure	Location	Characteristics of exposed group	Mean age [years (SD)]	Number of participants (n)	Percentage of exposed workers to total participants involved in the study (%)[40]
Phanprasit et al.(2009)[26]	Academic journal	Cross sectional	Asbestos in cement roof factory	Four factories; provinces not specified	High risk workers in cement roof factories at the production site	NA	Exposed=19 Non-exposed =NA	100%
Danphaiboon et al. (2012)[25]	Academic journal	Cross-sectional	Silica in stone mill factory	Seven provinces in the northern region of Thailand	Workers at the stone mill production site	NA	Exposed=299 Non-exposed =NA	100%
Danphaiboon (2012)[30]	Academic Journal	Cross-sectional	Silica in stone mill factory	The northern part of Thailand (Chiang Mai, Chiang Rai, Phayao, Phrae, Nan, Lamphun, and Lampang)	Workers in stone mill factory	Overall =40.19 (10.82) Men =40.51 (10.87) Women =35.35 (9.06)	Exposed=272 Non-exposed =NA	100%
Danphaiboon et al (2012)[33]	Report	Retrospective Cohort	Silica in mortar factory	Phayao	Workers in mortar factory	Overall =47.48 (12.08) Men =47.10 (12.10) Women =51.09 (11.84)	Exposed=117 Non-exposed =119	50%
Oopara (2013)[31]	Master's thesis	Cross-sectional	Silica in sanitary ware manufacturer	Saraburi	Workers in the kiln department	36.7 (5.30)	Exposed=168 Non-exposed =NA	100%
Thongtip et al (2019)[19]	Academic journal (International)	Cross-sectional	Silica in stone-mortar factory	Phayao	Stone-mortar workers who had been working there for at least a year	Stone cutters =48 (13) Stone grinders =46 (12) Agricultural workers=47	Exposed=57 Non-exposed =20	74%

NOTE: NA=not described in the paper or not applicable

Exposure Assessment

For asbestos exposure measurement, the standard protocol of the United States National Institute of Occupational Safety and Health (NIOSH), was undertaken to count the number of asbestos fibres. Phanprasit et al[26] and Tangtong and Phanprasit[28] used NIOSH 7400 for reproducible asbestos analysis (Supplementary Table 1). Phanprasit et al[26] conducted both personal and ambient air samplings in wet areas (such as mixing and forming roll areas), and in dusty areas (such as polishing of roof fittings). The number of fibres was counted by a phase contrast microscope. The unit of direct measurement was reported in fibre/cubic centimetre (cc). The unit of

cumulative exposure measurement was fibre-years/cc. Tangtong and Phanprasit[28] also used NIOSH 7400 to assess amounts of ambient asbestos from personal and area samples. Siriwatananukul[27] applied NIOSH 7402 for additional analysis by transmission electron microscopy for counting phase contrast microscopy (PCM) visible asbestos fibres. Lojananond[32] did not report the use of standard exposure measurement, only personal pump with 5-micron polyvinyl-chloride (PVC) filter used for air and personnel sampling. Siriwatanakul[27] reported standard exposure time, although other studies did not.

The occupational exposure limits (OELs) from both international and national standards used the same level (0.1 fibre/cc). Lojananond[32] reported the highest asbestos exposure exceeding international and national OELs in a brake pad factory at 6.22-9.95 fibre/cc. Phanprasit et al[26] reported a high level of asbestos exposure at a roof fitting factory at 0.73 fibre/cc. Tangtong and Phanprasit[28] showed that the average asbestos exposure at a ceiling repairing area containing asbestos was at 0.1-0.4 fibre/cc, exceeding the OELs. Only Siriwatananukul's study[27] reported the level of ambient asbestos lower than the OELs, ranged from 0.002 to 0.0068 fibre/cc. Apart from the direct asbestos exposure measurement, Phanprasit et al[6] also calculated the estimated cumulative exposure for high-risk workers which ranged from 90.13 to 115.65 fibre-years/cc.

Measurements of silica dust levels varied by studies (Supplementary Table 2) (for instance, using only ambient air sampling,[25,30,33] using only personnel sampling,[19,29] and a combination of air and personnel samplings).[24] Three studies[19,25,33] applied NIOSH 7601 to determine crystalline silica in respirable or total dust with spectrophotometry to monitor the complex form of silica. However, this method cannot distinguish the difference between three crystalline polymorphs.[34] Danphaiboon et al[30] applied the NIOSH 7500 with X-RAY powder diffraction. This method improved the performance to detect crystalline polymorphs with elimination of silica interferences by phosphoric acid treatment.[35] Oopara[31] measured silica exposure in the production site of sanitary ware with portable devices and use of a universal sample pump (224 PCXR8).

Aungkasuvapala et al[24] used a personal pump with 5-micron polyvinyl-chloride (PVC) pore filter to collect air for area and personnel sampling. Yingratanasuk et al[29] assessed silica exposure in a stone carving company with personal dust sampling. However, there was no report on direct-reading instruments used for respirable silica dust which is less sensitive to detect relatively low-level concentrations of contaminants.[36] Personnel air sampling is more suitable than ambient air sampling for quantifying chemical exposure in studies targeting high-risk workers.[36] However, three studies[25,30,33] did not indicate clear sampling time. Lack of this information limits comparison of results with OELs, which set 8-hour time weighted average exposure level.[37] The study by Oopara[31] applied only four hours for exposure measurement, then adjusted the time to eight hours in order to comply with the time-weighted average.

Findings suggest that the level of silica in all included studies exceeded the exposure limit, in particular the American Conference of Governmental Industrial Hygienists Threshold Limit Value (ACGIH TLV) for respirable fraction of α-quartz and cristobalite, and the Thailand OELs at 0.025 mg/m^3.[38,39] The highest level of silica dust was found in the study by Aungkasuvapala et al.[24] The average amount of total dust was 24.3 mg/cubic metres (m^3)and respirable silica dust was 2.4 mg/m^3.[24]

The level of silica exposure was considered high in Danphaiboon et al's study.[25] The results showed that silica exposure was approximately 15 mg/m^3 in two factories, and average exposure ranged from 1.10 to 15.91 mg/m^3. Another study by Danphaiboon et al[33] reported high levels of average silica dust at 12.11 mg/m^3, with the maximum at 20.41 mg/m^3 in a Phayao mortar factory.

Apart from stone-related factories, Oopara[31] studied silica level in sanitary ware production. Silica exposure before and after the kiln department site was reported at 4.25 and 4.75 mg/m^3, respectively. Yingratanasuk et al[29] measured the severity of exposure and additional three exposure metrics. They were determined by comparing the current quartz exposure to the value indicated by the Thai permissible exposure limit (PEL), and by the ACGIH TLV. The exposure metrics encompassed three measurements. These included, first, years in trade that accounted for the number of years from the time first hired into stone-carving industry until the study year. The second was exposure-years, which was the summation of the overall exposure time (months per year) that a subject has worked in any stone-working jobs. Third was Jahr's cumulative quartz exposure measurement which was an exposure weighing method for quartz. The results showed that exposure levels in carving and pestle production areas ranged from 0.05 to 0.88 mg/m^3. For severity of exposure, only mortar makers exceeded the PEL and ACGIH TLV limits. Moreover, exposure metrics reported in

arithmetic means showed that exposure-years was 10.87 years, years in trade was 13.32 years, and Jahr's Quartz Exposure was 19.64 mg/m^3–year.

Discussion

Overall, we found an extremely wide range of silica and asbestosis exposures, when assessing against OELs. For example, Lojananond[32] showed 100% prevalence of exposure among workers in areas with high risk of asbestos. Siriwatananukul[27] reported that all workers operated in areas with low level of asbestosis. For silica exposure, three studies conducted by Danphaiboon et al[25,30,33] demonstrated that all workers in mortar or stone grinding factories had been working in areas where silica levels exceeded the OELs.

The search on occupational risk factors for pneumoconiosis including exposures to asbestos and silica in Thailand was small in number. Almost all studies used only a descriptive cross-sectional approach which is a less rigorous research design. The majority of studies lacked a control group of participants who were not working in areas likely to be exposed to asbestos and silica. With lack of 'control' groups at different levels of exposure, it was difficult to draw conclusions on varying risks of hazard of asbestos and silica to pneumoconiosis, because solid evidence on the exposure of these agents was lacking in this population.

The number of studies on asbestos exposure was smaller than silica exposure, and most studies were conducted in limestone-related factories. This industry type was the largest sector reported in mineral production of Thailand during the fiscal years 2014-2015.[20] Findings suggested that most included studies showed excessive exposure limits indicated by both international and national OELs. For silica exposure, most included NIOSH 7601 as the international standard for silica exposure measurement, and all included studies found excessive levels of silica exposure against OELs. Also, those studies measured exposure level at the production site which revealed critical concern for exposed workers. This situation has been pronounced in low- and middle-income countries[40] where proper control measures have not been regularly monitored, and even in high-income countries where incidence of pneumoconiosis is of critical concern.[41]

The study in Australia examined the proportions of short and thin asbestos fibre during work on asbestos containing materials (ACM). Results showed that both types of asbestos fibre exceeded the World Health Organization fibres exposure limits.[42] A study in Italy showed that many construction workers had exposure levels above the exposure limit set by national legislation (0.01 fibre/cc).[43] Findings suggested excessive levels of asbestos exposure in the US and European countries.[44] A study in New Zealand examined the level of respirable crystalline silica in construction workers. Results showed that about half of the personnel crystalline silica samples exceeded the New Zealand Workplace Exposure Standard, and 56% exceeded the more stringent international recommendation (ACGIH TLV).[45] In low- and middle-income countries, an Indian study showed that respirable crystalline silica dust generated during stone crushing operations in one district exceeded the PEL and REL standards.[46] In China, workers in the asbestos products industry were often exposed to high levels of asbestos which frequently exceeded the Chinese official occupational exposure limit.[47,48] These findings highlight the need for effective prevention measures especially in low- and middle-income countries, where there are high demands from the construction industry as part of national infrastructure development.

Limitations

This review is likely to be one of the first studies to explore the level of occupational asbestos and silica exposure in Thailand. However, some limitations remain. First, the majority of industries reported in the included studies were small (1-49 workers) and medium size (50-199 workers). Therefore, the estimated prevalence in large-scale factories is missing. Second, a larger number of articles were from research reports by universities with few from routine monitoring reports by government agencies. These lacked a long-term follow up, and varying degrees of compliance from factories which created difficulties for monitoring process. Moreover, existing laws on environmental health do not give full authority to the Ministry of Public Health to perform monitoring in all factories at risk. These issues cause challenges to assess the trend of hazard exposure over time. Third, monitoring by officials usually focused on high-risk industries. Hence, evidence included might miss those factories that seemed to be low risk. Forth, as this review aimed to map evidence on the occupational exposure, insights of prevention measures and their implementation on mitigating health risks were lacking in the analysis. Fifth, in methodological terms, some of the included papers seemed to be poor quality. They included flaws with a lack of control group, a small number of participants included, and inexplicit information on exposure assessment. Following the routine approach of a scoping review, quality assessment of the included studies might not be

necessary. Moreover, this review did not consider health outcomes of workers. Thus, the causal relationship between pneumoconiosis and its risk factors could not be determined based on this review.

Public Health Recommendations

When considering further public health actions, primary prevention in the workplace should be exercised. Respiratory protective equipment complying with international standards should be strictly and regularly used among workers at risk, and in all factory sizes. All factories should introduce necessary equipment to get rid of the hazards from the beginning, such as installing detectors that can prevent asbestos and silica from contaminating the wider environments. During production activities, preventive measures such as protective equipment for protecting the health of exposed workers in high-risk occupational settings should be in place. In addition, regular monitoring and assessment on the exposure levels to pneumoconiosis risk factors and the health status of the workers at risk should be conducted.

Conclusions

The findings show that most included studies were from the northern region of Thailand with many stone mill factories. A descriptive cross-sectional design was mainly reported, which is considered as less rigorous research design compared with other approaches. The number of participants in most included studies was quite small. More importantly, the lack of information on low levels of silica and asbestos exposure among industrial workers resulted in great difficulties to determine the exact exposure prevalence. NIOSH 7400 and 7402 were the most common methods for assessing asbestos levels. For silica dust, some studies did not present clear methods for exposure assessment. More than half of studies showed that the results of exposure level exceeded OELs, and some studies reported that all high-risk workers functioned in areas where asbestos levels were beyond acceptable standard. Prevention measures and active surveillance programs should be in place for all populations at risk at national level. Current practices of occupational health standards in asbestos- and respirable silica-related factories should be regularly updated. Moreover, analysis of dose-response relationships between asbestos and silica exposure and the effects of respiratory symptoms are of great value and will add academic richness in the field of occupational health in Thailand.

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Department of Disease Control, Ministry of Public Health, Thailand
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Investigation of Foot-and-Mouth Disease Outbreaks in Dairy Cattle from Kageshwari and Shankharapur Municipalities, of Kathmandu, Nepal and Associated Risk Factors from March to April 2020

Manoj K. Shahi[1]*, Khemmapat Boonyo[2], Vilaiporn Wongphruksasoong[2], Mukul Upadhyaya[1], Sujan Rana[1], Surendra Karki[3], Samjhana K. Kafle[1], Sharmila Kafle[4]

1 Department of Livestock Services, Ministry of Agriculture and Livestock Development, Nepal

2 Department of Livestock Development, Ministry of Agriculture and Cooperatives, Thailand

3 Food and Agriculture Organization of the United Nations Representation in Nepal, Nepal

4 Foot and Mouth Disease and Transboundary Animal Disease Laboratory, Ministry of Agriculture and Livestock Development, Nepal

*Corresponding author, email address: avisanu2006@gmail.com

Abstract

Foot and mouth disease (FMD) is endemic in Nepal and significantly impacts the livelihood of farmers, national economy, and trade of Nepal. However, outbreak investigations are not frequently conducted, and there have been limited studies to understand the associated risk factors. A case-control study was performed in dairy cattle farms of Shankharapur and Kageshwari Municipalities, Kathmandu from March to April 2020 to describe the outbreak and identify the risk factors associated with FMD. There were 31 case farms, while 62 farms were selected as control farms (1:2). The information from case and control farms was collected by semi-structured questionnaire survey through field visits and observations. The univariable and multivariable logistic regressions were performed. The farm-level prevalence of FMD was 25.2% (n=31/123). Among the FMD affected farms, the proportion of positive farms in Shankharapur (61.3% (19/31)) was significantly higher than Kageshwori (38.7% (12/31)). The final multivariable logistic regression analysis identified four variables: cattle purchased within 14 days (OR=12.9; CI=2.4-69.5), milk market distance less than two kilometers from the farm (OR=32.7; CI=5.8-186.3), sharing of the bull from other farms for natural insemination (OR=5.7; CI=1.2-26.8), and no vaccination against FMD in the past six months (OR=19.1; CI=2.0-186.2) as significant risk factors for the occurrence of FMD. This study suggests farmers vaccinate their dairy cattle with FMD vaccine as per the vaccination schedule suggested by the veterinarians, practice quarantine measures when new animals are introduced to their farms, practice biosecurity measures in their farms, and do not use bulls from areas where there are ongoing FMD outbreaks.

Keywords: epidemiology, FMD, Kathmandu, outbreak investigation, risk factors

Introduction

Foot and mouth disease (FMD) is a highly contagious and infectious disease that causes substantial economic losses to farmers due to decreased milk production, growth rate and restricted trade.[1,2] The FMD affects cloven-hoofed animals, including cattle, sheep, goats, pigs, and wildlife, and is caused by a RNA virus of the family *Picornaviridae*. FMD disease is characterised by the vesicular eruptions inside the oral cavity, foot and udder.[3] Other symptoms include fever, lameness, salivation, and anorexia.[4] The transmission of the FMD virus occurs from direct contact, fomites, animal products, contaminated surfaces, and sometimes through the air.[4] FMD is endemic in Nepal and has been occurring for many years. Three of the seven FMD virus serotypes (O, A, and Asia1) are circulating in Nepal. The serotype C was historically present in Nepal[5] but has not been detected since 1996.[6] Outbreaks of FMD are reported from all three ecozones of the country: Mountain, Hill, and Terai. Though FMD outbreaks occur throughout the year in Nepal, the higher incidence has been observed during the monsoon and post-monsoon periods.[5]

The strategy for FMD control in Nepal is focused on risk-based ring vaccination surrounding the outbreak area and limited mass vaccination of cattle, buffaloes and pigs in selected areas with a trivalent vaccine, identification and testing of animals, enforcement of quarantine and biosecurity measures.[7] The high prevalence of FMD is a colossal challenge for the livestock sector of Nepal amidst the lack of proper nutrition and veterinary care, and poor herd management leading to low production rates.[8] Nepal has started the National FMD Control Strategies since 2012, which initially targeted the Eastern and Far Western Development Regions and eventually has expanded to cover the entire country.[2] Every year, several outbreaks of FMD occur in different parts of the country. However, very few of these outbreaks have been investigated thoroughly by researchers and government agency. Moreover, there have been limited studies to understand the risk factors associated with these outbreaks. The main objectives of this study were to describe the descriptive epidemiology and identify the risk factors associated with FMD outbreaks reported from March to April 2020 in Kageshwari and Shankharapur Municipalities, Kathmandu, Nepal.

Methods

Study Design

This case-control study was performed from March to April 2020 to describe the situation of FMD outbreak and aimed to evaluate the risk factors associated with the FMD outbreak in the dairy cattle farms of Shankharapur and Kageshwari Municipalities, Kathmandu (Figure 1).

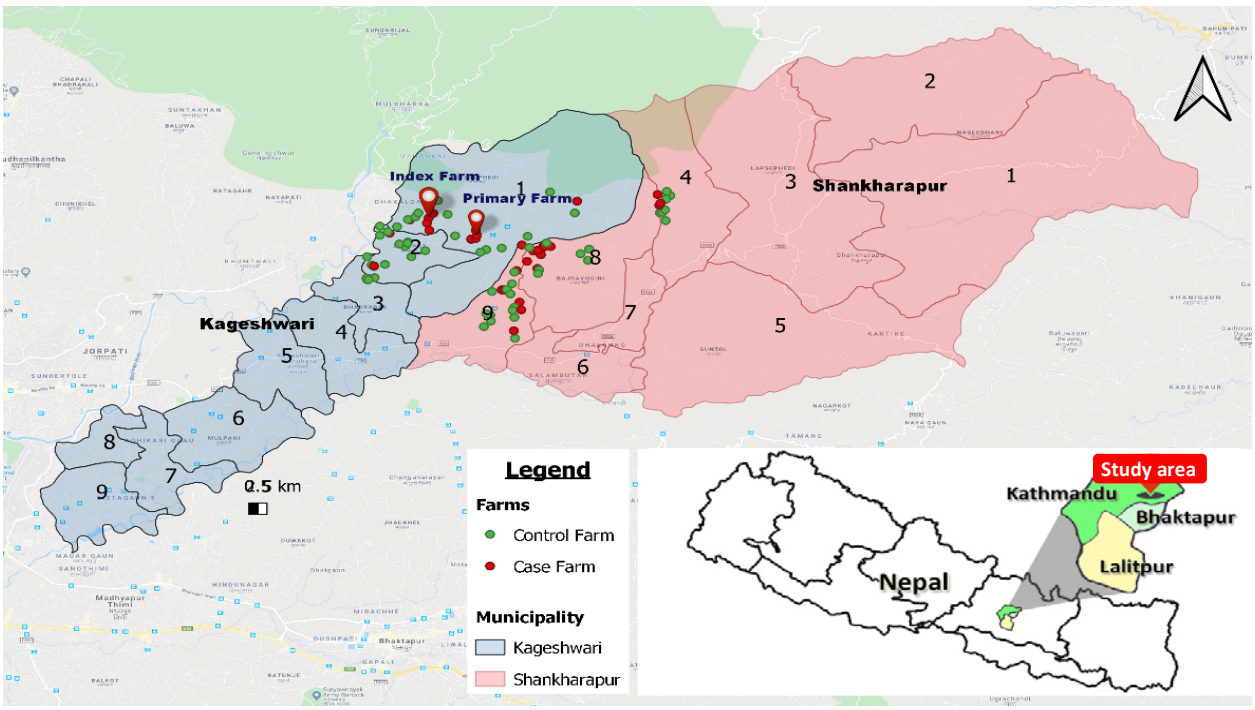

Figure 1. Map of Kageshwari and Shankharapur Municipalities, Kathmandu, Nepal, indicating the case and control farms of FMD outbreak from March to April 2020

Sampling Method

The dairy cattle farms having at least one animal confirmed by polymerase chain reaction (PCR) for FMD or cattle having fever and showing at least one of the signs: drooling of saliva or buccal vesicles or vesicle formation in claws or coronary band observed by the owner and the attending trained veterinary technician of Kageshwari and Shankharapur Municipalities from March to April 2020 were considered as case farms. The cattle farms in which the owner and the attending veterinary technician did not observe clinical signs suggestive of FMD or negative laboratory results by PCR of Kageshwari and Shankharapur Municipalities from March and April 2020 were defined as control farms. Out of the 123 (723 cattle) dairy cattle farms of the study area, the FMD outbreak was reported in 31 cattle farms. All 31 FMD infected farms (228 cattle) were considered as case farms. A total of 62 dairy cattle farms were selected as control farms (case versus control=1:2) from the study area.

Data Collection

The data of case and control farms for the descriptive and analytical study were collected by field visits and observation. In case of incomplete information, follow ups were carried out by subsequent telephone

interviews with the farm owners. The information regarding twelve variables, namely "small farm size", "use of natural-source water", "grazing system", "mixed farming with sheep and goat", "vehicles allowed to enter the farm", "farm to farm distance", "milk market distance", "sharing of the bull for breeding", "sharing of equipment", "cattle purchased within 14 days", "wild deer contact" and "cattle not vaccinated within six months" were collected from fifty-seven semi-structured questions. They were considered as potential risk factors and obtained from the literature review and expert opinion.

Statistical Analysis

Data were entered and processed in Microsoft Excel 2016. The descriptive analysis was done by time, place and animal. The median, mean, range, case fatality rate, morbidity rate and mortality rate were used to describe the situation and demography of FMD farms in the study areas. First, a univariable analysis was performed to measure the association between the individual potential risk factor and the presence of FMD in the farm. The variables that met a cut-off of $p \leq 0.15$ in the univariable analysis were considered for the final multivariable logistic regression model. We checked for multicollinearity using a criterion of the variance of inflation factor (VIF) <4 and a correlation of more than 80% between the variables. The normality of the continuous variable such as "small farm size", "farm to farm distance", and "milk market distance" were tested using Shapiro Wilk test in Stata/S.E. 14. The variables found not to be normally distributed, they were classified as a binary variable using a median cut-off. Odds ratios (OR), their 95% confidence intervals (CI), and corresponding *p*-values were estimated by backward multivariable logistic regression. The Stata 14 software was used to analyse the data. Spatial distribution of the cases was mapped using QGIS 3.4.9.

Results

Descriptive Epidemiology of FMD Outbreak

Out of 123 cattle farms, in the study area, 31 case farms (228 cattle) had FMD outbreaks. This indicated that the farm-level prevalence of FMD was 25.2% (n=31/123). Among the FMD affected farms, in Kageshwari and Shankharapur Municipalities there were 38.7% (12/31) and 61.3 (19/31) farms, respectively. The FMD virus serotype O was confirmed by PCR in two of the case farms. The median farm size with the range of the case and control farms were 6 (3-9) and 5 (2-6), respectively.

The median morbidity and mortality rates (range) of case farms (n=31) were found to be 100.0% (66.7-100.0) and 14.3% (0.0-25.0), respectively. The median case fatality rate (range) in case farms was low in adults (20.0% (0.0-33.3)) in comparison to those in calves (50.0% (0.0-100.0)) of case farms. The index case was reported on 20 Mar 2020, but the first case was traced back to have occurred on 13 Mar 2020. The number of farms affected was increasing until the end of March 2020 and then decreased sharply. The progression of the disease can be seen in the epidemic curve (Figure 2).

The case farms that had not been vaccinated against FMD in the last six months were found to be 96.8%. Up to 67.7% of case farms practiced grazing around the farms or in grazing land, and 51.6% of case farms had chances of contact with wild deer in the common grazing area or through the grass brought from the same area. Similarly, 80.6% of the case farms were located within a distance of 200 meters from another nearest farm.

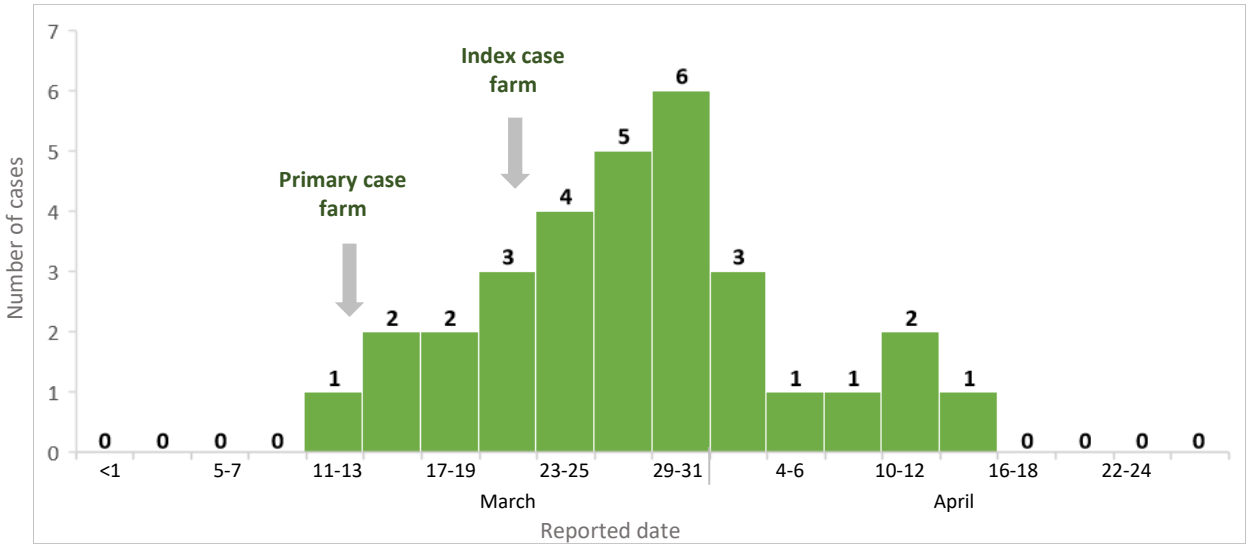

Figure 2. Epidemic curve of case farms (n=31) of Kageshwari and Shankharapur from March to April 2020

Univariable and Multivariable Logistic Regression Analysis

The univariable analyses of risk factors associated with the FMD outbreak in dairy cattle farms in the study area have been presented in Table 1. Among the twelve variables, eight explanatory variables ($p \leq 0.15$) were selected for the multivariable analysis. They included "small farm size", "use natural source water", "grazing system", and "mixed farming". Similarly, they included "milk market distance", "sharing of the bull for breeding", "cattle purchased within 14 days", and "cattle not vaccinated within six months" (Table 1).

Table 1. Result of univariable analysis for risk factors associated with FMD outbreaks (n=93 farms)

Variables	Category	Case (n=31)	Control (n=62)	OR (95% CI)	*p*-value
Farm type					
Small farm size	≤4 cattle	13	43	0.31 (0.11-0.85)	0.011
	>4 cattle	18	19		
Husbandry type	Grazing	21	23	3.56 (1.31-9.94)	0.005
	Stall feeding	10	39		
Farm location					
Farm to farm distance	≤200	25	43	1.84 (0.59-6.35)	0.25
	>200	6	19		
Milk market distance	<2 kilometres	16	9	6.28 (2.08-19.35)	<0.001
	≥2 kilometres	15	53		
Possibility of wild deer contact	Yes	16	29	1.21 (0.46-3.14)	0.65
	No	15	33		
Farm management					
Use natural source water	Natural water	18	46	0.48 (0.17-1.33)	0.11
	Municipality water	13	16		
Mixed farming with sheep and goat	Yes	29	45	5.48 (1.14-51.64)	0.018
	No	2	17		
Sharing bull for breeding	Yes	24	30	3.66 (1.27-11.42)	0.008
	No	7	32		
Sharing of equipment	Yes	19	33	1.39 (0.53-3.71)	0.46
	No	12	29		
Vehicles allowed to enter the farm	Yes	12	23	1.07 (0.39-2.83)	0.87
	No	19	39		
History of vaccination and movement					
Cattle vaccinated within six months	No	30	34	24.70 (3.53-1043.00)	<0.001
	Yes	1	28		
Cattle purchased within 14 days	≤14 days	10	4	6.90 (1.71-32.69)	0.001
	>14 days	21	58		

The multivariable logistic regression yielded four risk factors associated with FMD outbreaks. These included milk market distance less than 2 kilometres (OR=32.74; CI=5.75-186.25), sharing of the bull for breeding (OR=5.71; CI=1.21-26.79), cattle purchased within 14 days (OR=12.85; CI=2.37-69.48) and cattle not vaccinated within six months (OR=19.07; CI=1.95-186.21) which were identified as important risk factors for the occurrence of FMD (Table 2).

Table 2. Result of multivariable logistic analysis for risk factors associated with FMD outbreak (n=93 farms)

Variable	Adjusted OR (95% CI)	*p*-value
Milk market distance less than 2 kilometres	32.74 (5.75-186.25)	<0.001
Sharing bull for breeding	5.71 (1.21-26.79)	0.027
Cattle purchased within 14 days	12.85 (2.37-69.48)	0.003
Cattle not vaccinated within 6 months	19.07 (1.95-186.21)	0.011

Discussion

FMD is an economically significant disease which was observed in 2018 in Kathmandu. The serotype O was confirmed in that outbreak. The serotype O is the most common serotype in Nepal, which was observed in 97% of the samples in the last decade of 2006-2015.[2] This outbreak was confirmed in April 2020, although an earlier study also showed most of the farms reported FMD in December and January and even in the pre-monsoon period (April-May) more than the other times of the year. However, FMD outbreak has been reported throughout the year in Nepal.[2]

The median morbidity of case farms (n=31) was 100.0% which ranged from 66.7-100.0% and the median mortality rates of case farms (n=31) was 14.3% which ranged from 0.0-25.0%. A study in Ethiopia found the morbidity, and mortality rates to be 24.4% and 4.0%, respectively.[9,10] It might be due to the differences in the age composition of herds as the mortality due to the disease is known to be higher in young calves[3] and could also be due to the difference in the pathogenicity of the serotypes found in a different place and type of cattle breed.[9] Up to 97 percent of the case farms were not vaccinated against FMD, which might be the reason for high morbidity. Vaccination against a specific FMD virus serotype does not usually protect animals against other serotypes, and vaccination of FMD carried out every four months (OR=0.06; CI=0.01-0.68) has been found more effective.[11,12] Previous studies have indicated that the timing and number of vaccine rounds are an essential factor against FMD outbreaks and period more than six months between adult vaccination and FMD virus infection resulted in low protection.[13,14] Thus, the time taken to respond to outbreaks through vaccination is critical for the effectiveness of FMD control.[15]

Close distance to the milk markets increased the chances (OR=32.74; CI=5.75-186.25) of disease incursion. The presence of FMD in the milk markets may create problems for all livestock owners who are connected to them. This connection may be geographical or via market chains.[16] The chances of FMD outbreak due to cattle purchased within 14 days (OR=12.85; CI=2.37-69.48) was found higher than the farms that purchased cattle more than 14 days ago which might be due to moving cattle between farms and having contact with potentially infected animals.[17] The farm with no vaccination of the cattle within six months (OR=19.07; CI=1.95-186.21) had a higher risk of an outbreak of FMD than the farms vaccinated against FMD.

Limitations

All cases of FMD considered in this study were not laboratory confirmed. Only 29 cattle in two farms were confirmed by PCR among the 31 case farms with a total of 228 cattle. The role of wild deer, sheep, and goats in FMD spread could not be assessed and verified due to the time limitation.

Conclusions

Our study has provided an insight into risk factors for the recurrence of FMD outbreaks in Kathmandu and found out some recommendations for farmers and policymakers. The descriptive study of this investigation provides valuable insights about the source of transmission, which could even be the wild animal (deer) or silent FMD virus hosts like sheep and goats. This study highlights the importance of continued FMD surveillance in domestic and wild animal populations. Additionally, precautions adopted during the milk marketing, vaccination every six months, and sharing of vaccinated breeding bull need to be improved in farm management practices.

Recommendations

All susceptible animals should be vaccinated for FMD at least every six months, including sheep and goats along with cattle and pigs. There has been limited FMD surveillance carried out in wildlife, so further investigation is needed in wildlife. Farmer awareness about the economic and trade impact, biosecurity measures like movement control, and visitor control would help to reduce the number of outbreaks.

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Investigation Approval

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Department of Disease Control, Ministry of Public Health, Thailand
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Impact of a Missed Diagnosed COVID-19 Patient on Healthcare Workers at a Private Hospital, Bangkok, Thailand, 2020

Patcharaporn Dejburum[1]*, Ratchadaporn Papwijitsil[1], Sirima Thananun[2], Rapeepong Suphanchaimat[1,3]

1 Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand

2 Institute of Urban Disease Control and Prevention, Ministry of Public Health, Thailand

3 International Health Policy Program, Ministry of Public Health, Thailand

*Corresponding author, email address: p.dejburum@gmail.com

Abstract

On 23 Mar 2020, the Situation Awareness Team of the Emergency Operations Center, Department of Disease Control, was notified that a 44-year-old Thai male, who was infected with coronavirus disease 2019 (COVID-19), had died in a private hospital in Bangkok, and there was a suspicion that some healthcare workers were infected with SARS-CoV-2 following his death. A descriptive cross-sectional study was conducted. We reviewed medical records of the index case, interviewed relatives of the index case, and performed contact tracing using a standard questionnaire. We could identify 206 high-risk contacts; they were eight household members, 104 hospital personnel, 30 inpatients and 64 community members. Twenty out of 206 high-risk contacts were then found to be infected with SARS-CoV-2. Fifteen of them were healthcare workers, two of them were current inpatients, and the other three were household contacts. The likely cause of disease spreading was the missed diagnosis of COVID-19 as the index case did not present with upper respiratory tract symptoms at the first visit to the hospital. Meal sharing among healthcare workers and sharing of a portable chest X-ray machine without proper protective equipment potentially served as other causes of COVID-19 spreading.

Keywords: COVID-19, healthcare worker, private hospital

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] As of 23 Mar 2020, globally, 332,930 patients were infected with 14,509 deaths.[3] Thailand is also severely suffering from COVID-19. In February 2020, the cabinet agreed to include SARS-CoV-2 in the list of dangerous communicable disease under the Communicable Diseases Act B.E. 2558.[4]

The situation of COVID-19 among healthcare workers (HCWs) is a concern in many countries. From the Thailand COVID-19 database,[5] as of 15 Mar 2020, a female HCW infected with SARS-CoV-2 from her workplace was notified. She was a nurse that had taken care of a missed diagnosis COVID-19 patient. Her patient was diagnosed with dengue fever, so at that time, she approached that patient without proper protection. She wore gloves but did not wear a mask during the blood sampling. She was considered the first Thai HCW who had COVID-19. Twenty-four hospital staff were quarantined and tested negative for SARS-CoV-2.[6]

On 23 Mar 2020, the Situation Awareness Team of the Emergency Operations Center, Department of Disease Control (DDC), Ministry of Public Health (MOPH), received a notification from a private hospital in Bangkok that there was a 44-year-old Thai male dying from COVID-19 and there were a large number of HCW contacts in the hospital. A joint investigation team consisting of epidemiological staff from the DDC and the Institute of Urban Disease Control and Prevention commenced an investigation on this event from 24 Mar 2020 to 22 Apr 2020. The objectives were to confirm the diagnosis, describe the index case's epidemiological characteristics, perform contact tracing, and provide recommendations for containing further transmission of SARS-CoV-2.

Methods

The investigation comprised three sub-studies: (i) descriptive epidemiological study, (ii) laboratory study, and (iii) environmental survey.

Descriptive Study

A descriptive cross-sectional study was conducted. We reviewed the medical record and interviewed the index case's wife, who was his main caretaker. Then a contact tracing was performed using a standard questionnaire from the DDC. We searched for additional HCWs in the hospital who were patients under investigation (PUIs) by using an online questionnaire. The questionnaire collected information about personal protective equipment (PPE) usage in each activity involved with the COVID-19 case.[7] For the definition of cases and contacts, we followed the DDC guideline (version as of 23 Mar 2020).[8]

For the case definition, the PUI was defined as a person who had a body temperature ≥ 37.5 °C with one of the following respiratory symptoms: cough, runny nose, and sore throat, accompanied with exposure risks within 14 days prior to illness onset. The exposure risks included traveling from COVID-19 affected areas and close contact with people coming from the COVID-19 prone areas.

The confirmed case was defined as a PUI who showed evidence of genetic materials of SARS-CoV-2 by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR). An asymptomatic case is defined as a person showing genetic materials of SARS-CoV-2, but without clinical signs and symptoms.

For the definition of contacts, a high-risk close contact was an individual who lived in the same household as a COVID-19 case, HCW who visited COVID-19 case or handled and processed specimens collected from COVID-19 case without wearing proper PPE, other patients who were hospitalized in the same room and at the same time with the COVID-19 case. A low-risk contact was a healthcare worker, who dealt with a COVID-19 case with proper PPE.

We used median with inter-quartile range (IQR) to present continuous data. For categorical data, we used frequency and percentage. Epi info version 7.2.3.1 was used for all calculations.

Laboratory Study

For all high-risk contacts and HCWs being screened by an online questionnaire, we collected phlegm in a sterile container. For PUIs, a nasopharyngeal swab and a throat swab were conducted. Each sample was delivered to the Department of Medical Sciences, Ministry of Public Health and the Thai Red Cross Emerging Infectious Diseases (TRC-EID), Chulalongkorn Hospital to test for SARS-CoV-2 by RT-PCR. A positive test was confirmed if one of the two reference laboratories reported a positive result.

Environmental Study

We performed a walk-through survey and observation of the behavior of HCWs on 24 Mar and 22 Apr 2020 to explore the hospital's environment, including patients' beds, decontamination equipment, medical devices shared across patients, dining areas, and workstations of HCWs.

Results

Description of the Index Case

The index patient (patient A) was a diabetic 44-year-old male working as a security guard at a famous nightclub in Bangkok. The nightclub was reported to have presented with 17 confirmed COVID-19 cases. On 6 Mar 2020, he started to have dry cough, low-grade fever, and fatigue. On 9 Mar 2020, he started to have dyspnea, anosmia, ageusia, and loss of appetite. He stayed at his home all the time since the symptom started. On 13 Mar 2020, his wife took him to a private hospital due to his high-grade fever and vomiting. His blood sugar was high at the outpatient examination room. The diagnosis at that time was diabetic ketoacidosis (DKA). Then he was transferred without a surgical mask to the emergency room to prepare for admission in the intensive care unit (ICU) (Figure 1).

Patient A was treated in ICU for a day. His clinical symptoms later improved. He was moved to a general inpatient ward (ward 2/7) and was treated there from 14 until 16 Mar 2020. Later, on 16 Mar 2020, the patient's condition got worse. He received nebulization to alleviate breathing difficulty. The doctor intubated and relocated him to a separate room in ICU. Chest radiography showed alveolar infiltration in both lungs. The diagnosis now changed to severe pneumonia. On 17 Mar 2020, his doctor sent a sputum suction sample to Ramathibodi Hospital for SARS-CoV-2 testing. On 19 Mar 2020, the laboratory result showed positive for SARS-CoV-2. The patient received oseltamivir (13 Mar 2020), chloroquine (19 Mar 2020), azithromycin and darunavir (19 Mar 2020), and favipiravir (22 Mar 2020). The patient's condition did not improve after treatment. He later died on 23 Mar 2020 due to severe progressive pneumonia and respiratory failure (Figure 1).

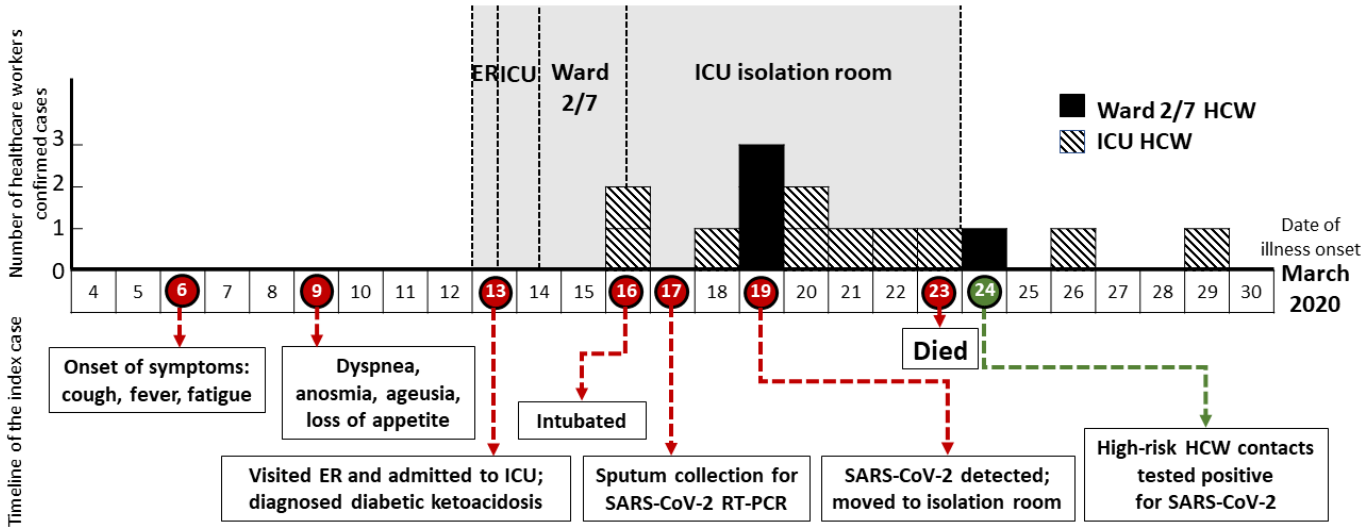
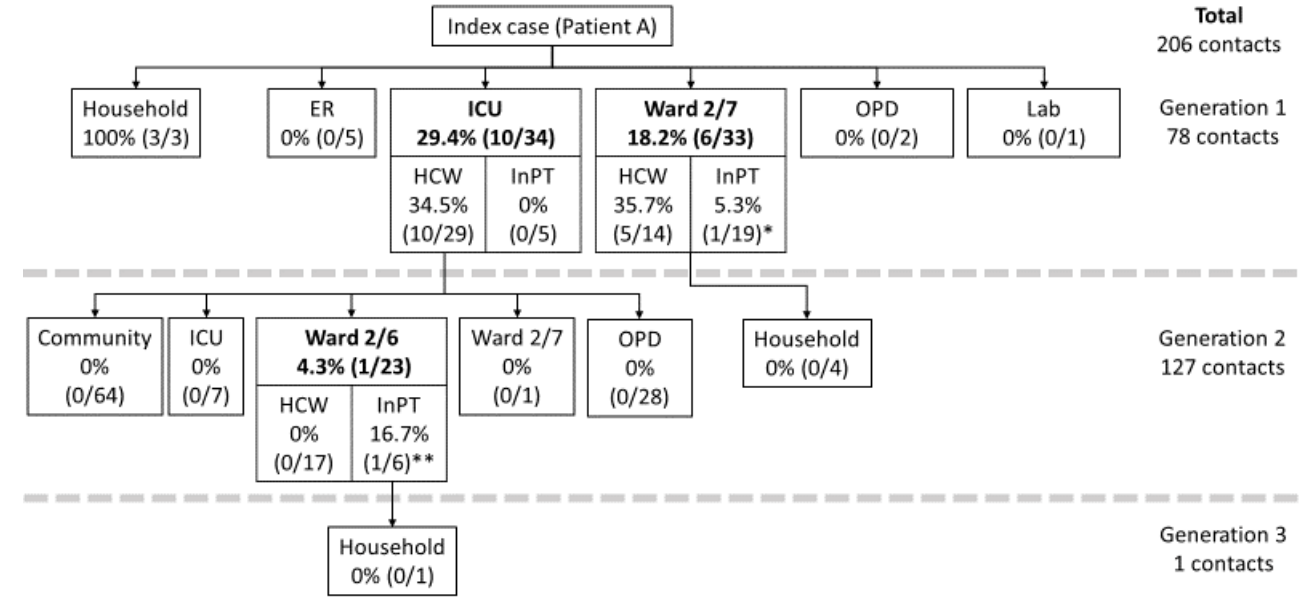


Figure 1. Epidemic curve of healthcare workers infected with SARS-CoV-2 sorted by hospital subunits and timeline of the index patient

Contact Tracing

A total of 206 high-risk contacts were identified from the investigation. Seventy-eight of them had direct contacts with patient A. The attack rate among those with direct contact was 24.4% (19/78). The rest of them were second- and third-generation contacts, with one contact who showed a positive SARS-CoV-2 test (attack rate=0.8% [1/128]). In total, twenty contacts were detected for SARS-CoV-2 (overall attack rate=9.7%). Three of them were his household members, fifteen of them were HCWs who took care of patient A, and two of them were inpatients concurrently admitted in the hospital at the same time with patient A (Figure 2).



*Note: *Patient B, **Patient C*

Figure 2. Number of high-risk contacts of the index case classified by places

Household contacts and contacts at the workplace

Patient A lived with his wife and two children. Laboratory tests detected SARS-CoV-2 in all family members. During the contact period, his wife went to a supermarket while his two children stayed at home. Other than that, they did not go elsewhere. One of the supermarket staff members was identified as a low-risk contact. No additional high-risk contacts were identified at the workplace of the index case.

Contacts at the Outpatient Department (OPD) and Emergency Room (ER)

There were high-risk contacts identified at OPD and ER, including one doctor and six nurses. The RT-PCR results showed negative for SARS-CoV-2 in all of these contacts. All of them reported that they wore surgical masks all the time during working hours.

Contacts in General Ward 2/7

There were 34 high-risk contacts identified in General Ward 2/7 (20 inpatients and 14 HCWs). SARS-CoV-2 was detected in one inpatient and five HCWs. The infected inpatient was a 61-year-old man (patient B). He was admitted to General Ward 2/7 next to the index case (14 to 16 Mar 2020) and was diagnosed with acute right cerebellar hemorrhage. He underwent venous puncture by the same HCW as the index case. Five HCWs were later found positive for SARS-CoV-2. Patient B was discharged on 18 Mar 2020. After he was discharged, he started to develop respiratory symptoms and was re-admitted on 25 Mar 2020, and then was found to be infected with SARS-CoV-2. All of the infected HCWs were nurses who provided care for patient A. The care activities involved mobilizing the patient, cleaning the patient's waste products, performing blood punctures, and accompanying doctors to examine the patient.

Contacts at ICU and General Ward 2/6

There was a total of 64 high-risk contacts in ICU and general ward 2/6 (11 inpatients and 53 HCWs— [48 nurses, two doctors, two cleaning employees, and one X-ray technician]). Laboratory tests detected SARS-CoV-2 in ten ICU HCWs—eight nurses, one physician, and one X-ray technician, contributing to an attack rate of 27.8% among HCWs in ICU (10/36). For inpatients, SARS-CoV-2 was detected in a 53-year-old female (patient C) who was admitted simultaneously with patient A but was in another ward (General Ward 2/6). She was admitted during 10 to 19 Mar 2020 due to urinary tract infection and sepsis, and then she turned to septic shock. She undertook a chest X-ray by the infected X-ray technician—the same person that performed the X-ray for the index case. None of the high-risk contacts from patient C circle were infected with SARS-CoV-2.

History of healthcare worker's illness

The first infected HCW was a nurse who treated patient A. She contacted patient A on 13 Mar 2020. Her duty was to perform blood sugar testing on patient A every 4 hours. She always wore gloves and a surgical mask. Also, she assisted the doctor in intubating patient A. She had meals with her colleagues during working hours. She developed fever and respiratory symptoms on 16 Mar 2020. Then, six additional nurses developed symptoms. All of these nurses were on duty when the symptoms appeared. Then the disease began to spread to General Ward 2/7.

Among the 15 infected HCWs, eight (53.3%) were female. The median age of these patients was 28 years (IQR=31 years). One of them was asymptomatic. The most common symptoms were fever 64.3% (9/14), followed by coughing 50.0% (7/14), and sore throat 42.9% (6/14) (Table 1). Of these 15 infected HCWs, 13 (86.7%) reported that they had worn substandard PPE[8] as they were not aware that the patient was infected. The patient's chart was touched by many ICU nurses including the confirmed COVID-19 HCWs. Two HCWs had a history of meal sharing with other infected staff, and one HCW had a history of talking to patient A's wife while wearing only a loose surgical mask.

Table 1. Demographic characteristics and symptoms among healthcare worker infected with SARS-CoV-2

Characteristic	No (%)
Gender (n=15)	
Male	7 (46.7)
Female	8 (53.3)
Symptoms (n=14)	
Fever	9 (64.3)
Cough	7 (50.0)
Sore throat	6 (42.9)
Muscle aches	4 (28.6)
Sputum	4 (28.6)
Headache	3 (21.4)
Runny nose	3 (21.4)
Difficulty breathing	2 (14.3)
Diarrhea	1 (7.1)

The portable X-ray technician always wore a surgical mask, gloves, and a raincoat for protection. He informed that he took off his gloves and raincoat after finished imaging each patient at the ward and washed hands with alcohol gel, but sometimes he did not wash hands before touching the patient. A plastic sheet was used to cover the X-ray pad and was removed after each use. The X-ray technician then wiped the X-ray pad with alcohol paper. There was only one portable chest X-ray machine in this hospital, which was used in all wards.

Online Questionnaire Screening

According to the online questionnaire on 24 Mar 2020, the total number of respondents was 498 (response rate=60.7%). The results revealed that 149 people (29.9%) had upper respiratory tract symptoms between 5 and 24 Mar 2020, and 22 (4.4%) met the PUI definition. None of these 22 respondents who met the PUI definition showed positive results for SARS-CoV-2 by RT-PCR.

According to the interview, HCWs used appropriate PPE during taking medical histories from patients

62.4% (58/93), followed by venous puncture 41.4% (29/70) and intubation 31.5% (23/73). Activities that showed the least percentage of appropriate PPE were cardiopulmonary resuscitation 23.5% (24/102), cleaning of the patient's secretion 17.8% (18/101), and bed bathing 0.0% (0/81).

Environmental Study

This facility was a 400-bed private hospital with a total of 820 HCWs. All patients were screened for fever before entering the hospital. If fever or respiratory symptoms were detected, the patient would be transferred to either (i) Acute Respiratory Infection (ARI) Clinic (for non-PUI cases); or (ii) PUI clinic (for PUI cases).

In ER, there was a negative pressure room for high-risk patients. The patient beds were separated from each other by a curtain. Nebulization was done in the headboard position. In ICU, there were 11 beds (seven in shared areas and four in isolation rooms) and two washing basins. An alcohol-based hand sanitizer was available at each bedside. General Ward 2/6 and General Ward 2/7 were arranged as a combined unit. Both wards had the same structure. The layout of the room was divided into blocks. Each block contained eight beds with a curtain separating between beds. The dining rooms of the staff were approximately 2x2 meters in size with supplied air-conditioning, causing poor air ventilation. There was a dining table in each room. The distance between seats was less than one meter. The equipment that was circulated in all wards was a portable chest X-ray machine. At the time we observed HCW behaviors, all HCW wore surgical masks, but some HCW pulled the mask down under the chin during the talk. Some nurses were treating patients without gloves and did not wash their hands after touching the patients.

Control Measures

All high-risk contacts were ordered to quarantine themselves at home for 14 days after the last date of exposure with the patients. All were re-tested for SARS-CoV-2 before returning to work. All related wards were temporarily closed and underwent intensive disinfection. We recommended the hospital director to establish a clear policy that required all staff to wear proper PPE and separate the dining times of the staff to avoid over-crowding.

Discussion

One of the key lessons of this outbreak was the misdiagnosis. The index case should have been identified as suspected COVID-19 by the DDC criteria since the first hospital visit. However, in reality, he was diagnosed with DKA without an in-depth investigation of the disease that might aggravate DKA. Thus, he was admitted to a general ward instead of the other wards prepared for COVID-19 cases. Previous studies have suggested an association between COVID-19 and DKA.[10,11]

Another risk of SARS-CoV-2 spreading among HCWs was improper PPE application. This happened because of the unawareness of the disease status of the index case. A prior study in China found a significant positive association between improper PPE wearing and SARS-CoV-2 infection.[12] Furthermore, the portable X-ray equipment might cause disease spreading. The X-ray technician was also infected with SARS-CoV-2. This might be attributed to inadequate PPE application and frequent contacts with the index case. A study about the SARS outbreak in Taiwan in 2003 showed supportive evidence of the relationship between X-ray activity and viral spreading.[13-15] Regarding personal hygiene, some HCWs did not wash their hands every time after touching the patients. An urgent training that emphasizes proper prevention and control against COVID-19 is recommended for all hospital staff. Also, risk communication on COVID-19 prevention and control should be delivered for hospital staff, patients, and caretakers.

A lack of social distancing during mealtimes might also contribute to the disease spreading. According to the interview, some HCWs were seated close to each other during the dining periods. Besides, it is not possible to wear a face mask all the time during mealtimes. This activity thus allowed viral particles to spread without protection.[16] Another potential cause of disease propagation was a failure to quarantine HCWs at risk of COVID-19. Some HCWs still came to work despite the presence of symptoms.

In terms of methodological discussion, this study faced some limitations. First, the investigation took place sometime after the onset of the first case. Hence, memory bias was inevitable. Second, due to time and resource constraints, we neither performed laboratory testing on environmental samples nor whole-genome sequencing from the patients and infected HCWs samples. This undermined the confidence in drawing a conclusion if the wide spreading of COVID-19 in this setting solely originated from within the hospital. Third, not all HCWs in the hospital participated in the online survey. Therefore, the generalization power of the findings was limited. Last was the information bias, as some patients or infected HCWs might not be willing to disclose their entire history of exposure. This phenomenon was possibly caused by a fear of stigmatization and social undesirability.

Recommendations

The hospital director should establish policies that required all hospital staff to wear standard PPE in all areas (Table 2).[7,16] Moreover, regular cleaning of the X-ray machine, and handwashing practice of all staff should be emphasized. A separation of dining time for HCWs was recommended to avoid over-crowding. Lastly, all staff should attend a refreshing course in infection prevention and control to increase awareness of the proper hygiene practice.

Table 2. The minimum requirement of personal protective equipment for disease investigations depending on patient's symptoms and related activities

Personal protective equipment	Patient interview without specimen collection		Collection of respiratory tract specimens	Garbage collection
	Patient has no cough or slight cough	Patient has severe cough		
Head cap	-	+/-	+	+/-
Goggles/face shield	-	+	+	-
Surgical mask	+	-	-	+
N95 respirator or higher	-	+	+	-
Disposable gloves	+/-	+	+	+
Full-length gown/coverall	+	+	+	+
Boots	-	-	-	+

Conclusions

In conclusion, this outbreak was a cluster of confirmed COVID-19 cases in a private hospital. There were three inpatients and 15 infected HCWs from 6 to 29 Mar 2020. The possible causes of disease spreading were a lack of awareness of COVID-19 patients during work and having a meal together among HCWs. Portable X-ray machine is another potential source of the spread of SARS-CoV-2. Policies that require HCWs to adhere to infection and control protocol, such as proper PPE application and frequent hand washing, should be implemented. Some more recommendations included the separation of dining areas and dining periods across wards to avoid over-crowding. Regular and thorough cleaning of the X-ray machine was recommended. A refreshing course to emphasize the prevention of infection in the context of COVID-19 should be urgently implemented to all hospital staff.

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Supplementary Table 1. Case definition of coronavirus disease 2019 (COVID-19) as of 22 Mar 2020

Type	Definition
Patients under investigation (PUIs)	Based on signs/symptoms, along with risk factors as follows: **Scenario 1: Surveillance at Points of Entry Quarantine Stations** A patient has the following signs and symptoms: documented temperature ≥37.5 °C, accompanied by any of the following respiratory symptoms, i.e., cough, runny nose, sore throat, tachypnea, or dyspnea. **Scenario 2: Hospital-based surveillance** A patient has the following signs and symptoms: 2.1. Documented temperature ≥ 37.5 °C, or history of subjective fever during current illness, accompanied by any of the following respiratory symptoms, i.e., cough, runny nose, sore throat, tachypnea, or dyspnea. 2.2. Pneumonia case of unknown etiology. Both 2.1 and 2.2 must be accompanied by one of the following histories of exposure risks within 14 days prior to illness onset: 1) Having a history of travel to or from or living in the areas reported having been affected by ongoing outbreaks of COVID-19. 2) Individuals whose occupation subjected themselves to close contact with travelers from the areas reported having been affected by ongoing outbreaks of COVID-19. 3) Having a history of close contact with or exposure to a probable or confirmed case of COVID-19. 4) Healthcare worker who has contacted with a confirmed case of COVID-19 infection 5) Has been to a place at the same time as a confirmed case of COVID-19 infection Note: Please refer to the areas reported to have been affected by ongoing outbreaks of COVID-19. **Scenario 3: Hospital-based surveillance** A patient has the following signs and symptoms: *Pneumonia case* Scenario 3 must be accompanied by one of the followings: 1) Is a healthcare worker. 2) Unidentified cause or does not improve within 48 hours after treatment. 3) Has severe symptoms or death with unknown cause. 4) Chest radiography compatible with COVID-19 infection. **Scenario 4: Acute severe pneumonia case of unknown etiology or fatal case of severe acute pneumonia of unknown etiology** Clusters of patients or health care workers with acute respiratory tract infections with negative rapid tests or PCR influenza results. *Health Care Workers* More than three health care workers in the same ward during the same week (If the health facility is small, such as a small clinic, use the same criteria - more than three health care workers in the clinic during the same week). *Non-Health Care Workers* More than five people in the same place* during the same week.
Confirmed case	A PUI who has tested positive for genetic materials of SARS-CoV-2 by PCR from one of reference laboratory, by genetic sequencing, or by culture.
Asymptomatic case	A person who has tested positive for genetic materials of SARS-CoV2 by PCR from one of reference laboratory, by genetic sequencing, or by culture, but has shown no signs and symptoms.

*Note: *place is defined as a house, medical or veterinarian facility, sanatorium, or a business facility*

Supplementary Table 2. Classification of close contacts based on different levels of exposure risks

High-risk close contact	Low-risk close contact
Household contacts 1. Family members, relatives, and caregiver of symptomatic COVID-19 case. 2. Individuals who live in the same household as a confirmed case of COVID-19.	
Healthcare-associated contacts 1. Medical and clinical staff, other hospital staff, and those were visiting a hospitalized COVID-19 case without wearing personal protective equipment (PPE) according to standard precautions. 2. Other patients (with other medical conditions) who are/were hospitalized during the same period as, in the same room as, and in the same row as the COVID-19 case and visitors of those patients who visited the patients when the COVID-19 case had yet to be moved to an isolation room. 3. Laboratory staff who did not wear PPE according to standard precautions while handling and processing specimens collected from the COVID-19 case.	Hospital staff or laboratory staff whose job was related to COVID-19 case or visitors of hospitalized PUI, who were wearing PPE according to standard precautions.
Travel-related contacts 1. In case of symptomatic COVID-19 case traveling onboard a commercial flight: • Passengers onboard the same flight as the case; passengers in close proximity to and in the same row as the case, and in the immediate two front and back rows: • All flight attendants in the same section of the plane where the case was sitting. • Co-travelers in the same group as the case, e.g., passengers in the same tour group. 2. In case of symptomatic COVID-19 case traveling on other types of public transportation: • Individuals traveling with the case • Passengers or crew members who were exposed to respiratory secretions, cough, or sneeze from the case. • Passengers who were within 1 m of the case.	All passengers traveling in the same vehicle (except commercial flight) as COVID-19 case do not meet the criteria for high-risk close contacts. Note: In the case of large vehicles such as train, double-decker bus, and passenger ferry, only passengers in the same car or deck as the case will be treated as close contacts.
Close contacts at school, workplace, and community 1. A student or co-worker including a close friend who was mingling with symptomatic COVID-19 case; or who may have been exposed to respiratory secretions, cough, sneeze from COVID-19 case. 2. An individual living in the same community as COVID-19 case or in another community, who has been exposed to respiratory secretions, cough, sneeze of the case.	1. Those who have studied or worked on the same floor/room/department as COVID-19 case, whose symptoms have yet to meet the criteria for high-risk close contact. 2. Individual who lived in the same community as a COVID-19 case, who was found to be within 1 m. of the symptomatic case and do not meet the criteria for high-risk close contact.

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Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Adverse Drug Reactions Associated with Dimenhydrinate, Thailand, 1993-2016

Pakawadee Sriphiromya[1]*, Sareeya Wechwithan[2]

1 Rural and Local Consumer Health Products Promotion Protection Division, Food and Drug Administration, Ministry of Public Health, Thailand
2 Division of Innovative Health Products and Services, Food and Drug Administration, Ministry of Public Health, Thailand

*Corresponding author, email address: pspakawadee@gmail.com

Abstract

In 1984, the Health Product Vigilance Center of Thailand was established and has continuously collected adverse drug reaction (ADR) reports across the country. Severe drug-induced skin reactions with dimenhydrinate can result in death in some cases. All ADRs with dimenhydrinate from 1 Jan 1993 to 31 Dec 2016 were reviewed. Characteristics and system organ class ADRs from 7,282 patients were described. Most patients had no history of allergy (77%) and no underlying disease (83%) and the majority were female (75%). Skin appendage ADRs were the most commonly reported (52%) events and 1,431 reports were severe skin ADRs, including bullous fixed drug eruption (89%) and Stevens-Johnson syndrome (9%). Among patients who received dimenhydrinate and had ADRs, 63% completely recovered and 0.18% died. Multivariate regression analysis revealed that patients aged more than 65 years or having a history of allergy were more likely to have a serious ADR than those in the other groups. Dimenhydrinate must be avoided or used with vigilance when prescribed to the elderly or patients with a history of allergy due to its seriousness.

Keywords: dimenhydrinate, adverse drug reactions, severe drug-induced skin reactions

Introduction

The Thai national adverse drug reactions surveillance center (entitled Health Product Vigilance Center) was established in 1984. The center is responsible for gathering, administering and analyzing individual adverse drug reaction (ADR) case reports, which are submitted from health professionals across the country. Reporting methods are voluntary and spontaneous, involve post marketing studies and intensive monitoring programs. Data were collected in a database called the Thai Vigibase. The information derived from this database was used as baseline data for the Thai Food and Drug Administration (FDA) in regulatory decision-making processes.[1,2]

An ADR is a noxious, unintended response which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. The seriousness of an ADR outcome was measured in four scales: mild, moderate, severe and fatal. The incidence of fatal ADRs is relatively low at around 0.32%.[3-5] Severe drug-induced skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), generalized bullous fixed drug eruption (GBFDE), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) most result in a serious outcome, defined as a severe or fatal ADR.[6,7] SJS and TEN are rare immune-mediated cutaneous adverse reactions and are often drug-induced and mostly result in serious skin reactions.[8] The clinical manifestation of SJS is defined by fever, erosive stomatitis, ocular involvement, purpuric macules on the face and trunk with less than 10% epidermal detachment. TEN symptoms have similar features as SJS but have more than 30% epidermal detachment and high mortality has been reported.[9] Antibacterial sulfonamides, anticonvulsants, non-steroidal anti-inflammatory drugs and allopurinol are the drug or drug groups commonly implicated for serious skin reactions.[10] DRESS is atypical form of drug-induced allergic reactions and developed later, usually 2 to 8 weeks after therapy is started.[11]

Dimenhydrinate is an antihistamine that blocks H1 receptors and is used mainly to prevent motion sickness, to treat nausea and vomiting, and is also used in the treatment of vestibular disorders. The drug may be used alone or combination with other drugs.[12] Antihistamines are not supposed to cause hypersensitivity reactions because they are the keystone of allergy therapy, thus awareness of the problem would reduce its misdiagnosis.[13] Drug-induced events which have resulted in serious skin reactions with dimenhydrinate are rare and unexpected.[14]

The significant drug safety concern would lead to regulatory measures to mitigate the risk in the population. Drug risk management is the current method used to weigh the benefits and risks of treatment with regulatory measures of all drugs through their life cycle. A serious outcome from an adverse drug reaction can result in the utmost regulatory action, such as the withdrawal of a drug from the market.[15] Other actions after marketing, such as a post authorization safety study, are used to gather additional safety monitoring information for planning further risk management.[16]

We describe the adverse drug reactions associated with the use of dimenhydrinate including drug-induced serious skin reaction reports. In addition, we also explore factors associated with serious outcomes in order to identify at-risk subgroups.

Methods

The retrospective ADR case reports associated with dimenhydrinate which were sent to the Health Product Vigilance Center from 1 Jan 1993 to 31 Dec 2016 (study period) were analyzed.

Data Source

The individual ADR reports associated with dimenhydrinate during the study period were retrieved from the Thai Vigibase.

Inclusion Criteria

Reports of at least 1 dimenhydrinate-related ADR either as a suspected, concomitant or interaction with other drugs were included in this study. Adverse drug reaction minimum criteria were: name of patient, name of suspected drug (dimenhydrinate), and adverse drug reaction term(s).

Causality assessment of ADRs is a method used for estimating the strength of relationship between drug exposure and occurrence of an ADR.[17] The causality assessment tool that is widely used in Thailand is Naranjo's algorithm.[18] The causality is classified as "certain", "probable", "possible" or "unlikely". In this study, we included drug-ADR reports assessed by Naranjo's algorithm with "certain", "probable" and "possible" classifications.

Exclusion Criteria

We excluded any report in which the drug-ADR causality assessment was evaluated as "unlikely" and if there was any missing of important patient characteristic (hospital number, patient code, name, age, and gender).

Data Extraction

The date of extraction was 11 May 2017. Patient's demographic characteristics, history of allergy, co-morbidities, drug dosage, dosing regimen, ADR seriousness and outcome information were extracted from the reports.

Data Cleaning

Totally, there were 11,813 reports with complete data. After elimination of duplicate records, 11,058 reports from 7,282 patients remained (Figure 1). Imputation was not applied to the missing data.

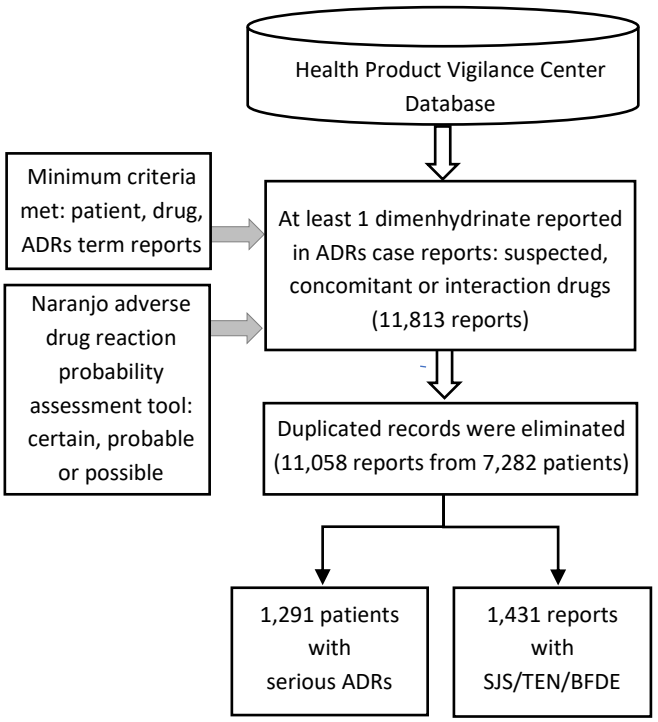

Figure 1. Concept framework diagram for data extraction

Data Analysis

Variables were presented descriptively using means with standard deviations for continuous variables and frequencies with percentages for categorical variables. The units of analyses for patients' characteristics, trend, treatment outcomes, and potential risk factors were patient, and for system organ class and severe drug induced skin reaction were report.

An analytic cross-sectional design is used to explore potential risk factors for seriousness of ADR. A serious ADR is defined as a drug reaction that caused any of the following six conditions to the patient: 1) death, 2) a life-threatening situation, 3) hospitalization, 4) persistent or significant disability/incapacity, 5) congenital anomaly/birth defect, and 6) a medically significant situation. Selection of variables for the multivariate logistic regression analysis was based on the ones which were statistically significant based on the 95% confidence interval (CI) from the univariate analysis.

Results

A total of 11,813 ADRs were reported to the Health Product Vigilance Center during the study period. During data cleaning, 755 duplicated reports were removed, resulting in 11,058 ADRs being reported from 7,282 patients. Trends in the number of patients and reports with dimenhydrinate-related ADRs are presented in Figure 2. From 1993 to 2009, the number of patients and reports with an adverse reaction involving dimenhydrinate gradually increased with a large peak occurring in 1996. From 2009 to 2016, the number of patients and reports gradually decreased.

Females dominated the reports and patients aged 18-65 years were the most common age group (75%). The mean (standard deviation) age of all patients was 48.96 (0.24) years. Most had no underlying disease (83.41%) and no history of allergy (77.01%) as seen in Table 1. Among 6,682 patients who received dimenhydrinate and experienced an ADR, 63.48% recovered, 19.58% recovered with sequelae, 16.75% had not recovered, and 0.18% died (Table 2).

Table 1. Characteristics of patients with dimenhydrinate-related ADRs (n=7,282 patients)

Characteristic	Number (%)
Gender (n=7,248)	
Female	5,411 (74.66)
Male	1,837 (25.34)
Age [years] (n=6,795)	
Mean±SD	48.96±0.24
Age <18 years (n=482)	
Female	264 (54.77)
Male	218 (45.23)
Age 18-65 years (n=4,609)	
Female	3,460 (75.07)
Male	1,149 (24.93)
Age >65 years (n=1,704)	
Female	1,355 (79.52)
Male	349 (20.48)
History of allergies (n=5,821)	
Yes	1,338 (22.99)
No	4,483 (77.01)
Underlying disease (n=6,994)	
Yes	1,160 (16.59)
No	5,834 (83.41)
Serious ADR (n=1,219)	
Age <18 years	73 (5.99)
Age 18-65 years	752 (61.69)
Age >65 years	394 (32.32)
Non-serious (n=5,018)	
Age <18 years	299 (5.96)
Age 18-65 years	3,442 (68.59)
Age >65 years	1,277 (25.45)
Causality assessment (n=7,282)	
Certain	637 (8.75)
Probable	3,959 (54.37)
Possible	2,686 (36.89)

Note: ADR=Adverse drug reaction

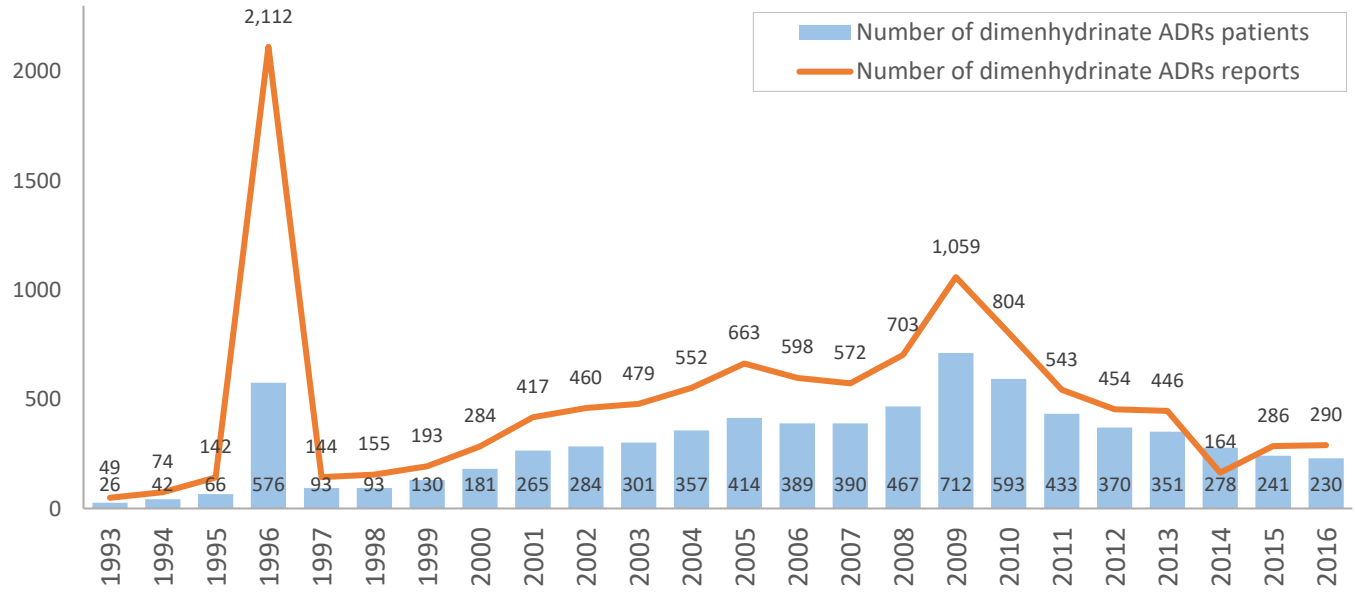

Figure 2. Yearly number of patients and reports with a dimenhydrinate-related ADR, 1993-2016

Table 2. Treatment outcomes of patients with dimenhydrinate-related ADRs (n=6,682 patients)

Outcome	Number (%)
Recovering	127 (1.90)
Recovered without sequelae	4,115 (61.58)
Recovered with sequelae	1,309 (19.58)
Not recovered	1,119 (16.75)
Died	12 (0.18)

Table 3 presents the distribution of ADRs classified by system organ class. Of the 11,059 reports, 51.74% were skin appendage disorders, followed by 23.07% autonomic, central and peripheral nervous system disorders, and 6.35% were gastro-intestinal system disorders.

Table 4 shows the gender-stratified distribution of 1,431 reports of patients who experienced severe dimenhydrinate-induced skin reactions. Bullous fixed drug eruptions were the most commonly reported severe ADR (88.61%), followed by Stevens-Johnson syndrome (9.36%) and toxic epidermal necrolysis (2.03%). The proportion of females (79.59%) with severe dimenhydrinate-induced ADRs was higher than in males (20.41%).

Overall, 1,291 patients with a dimenhydrinate-related ADR (19.33%) had a serious outcome. Table 5 presents the factors associated with serious ADR. Patients aged more than 65 years (Odds ratio (OR)=1.31, 95% CI=1.14-1.52), and with history of allergy (OR=1.41, 95% CI=1.21-1.64) were more likely to experience a serious ADR compared to those aged <65 years and without a history of allergy, respectively.

Table 3. ADRs with dimenhydrinate by system organ class (n=11,058 reports)

System organ class	Number of reports (%)
Skin appendages disorders	5,722 (51.74)
Autonomic, central and peripheral nervous system disorders	2,551 (23.07)
Gastro-intestinal system disorders	702 (6.35)
Body as a whole-general disorders	679 (6.14)
Metabolic and nutritional disorders	445 (4.02)
Respiratory system disorders	324 (2.93)
Urinary system disorders	239 (2.16)
Vision disorders, hearing and vestibular, special sense disorders	149 (1.35)
Psychiatric disorders	88 (0.80)
Musculo-skeletal system disorders	46 (0.42)
Cardiovascular disorders, general	38 (0.34)
Liver and biliary system disorders	30 (0.27)
Reproductive disorders	21 (0.19)
Collagen disorders	8 (0.07)
Blood cell, platelet, bleeding and clotting disorders	8 (0.07)
Others	6 (0.05)
Foetal disorders	2 (0.02)

Table 4. Distribution of patients with severe dimenhydrinate-induced skin reactions (n=1,431 reports)

Severe drug induced skin reactions	Male (%)	Female (%)	Total (%)
Bullous fixed drug eruption	244 (19.24)	1,024 (80.76)	1,268 (88.61)
Stevens-Johnson syndrome	43 (32.09)	91 (67.91)	134 (9.36)
Toxic epidermal necrolysis	5 (17.24)	24 (82.76)	29 (2.03)
Acute generalized exanthematous pustulosis	0	0	0
Total	**292 (20.41)**	**1,139 (79.59)**	**1,431 (100)**

Table 5. Characteristics of patients comparing serious adverse reactions and non-serious reaction related to dimenhydrinate use (n=6,678 patients)

Characteristic	Serious ADR N (%)	Non-serious ADR N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Number of Patients	1,291 (19.33)	5,387 (80.67)		
Sex (n=6,644)	n=1,291	n=5,353		
Male	296 (22.93)	1,197 (22.36)	1.03 (0.89-1.19)	-
Female	995 (77.07)	4,156 (77.64)		
Age (n=6,237)	n=1,219	n=5,018		
Age >65 years	394 (32.32)	1,277 (25.45)	1.39 (1.22-1.61)	1.31 (1.14-1.52)
Age <18-65 years	825 (67.68)	3,741 (74.55)		
History of allergy (n=5,708)	n=1,209	n=4,499		
Yes	342 (28.29)	966 (21.47)	1.44 (1.24-1.67)	1.41 (1.21-1.64)
No	867 (71.71)	3,533 (78.53)		
Underlying disease (n=6,407)	n=1,250	n=5,157		
Yes	251 (20.08)	886 (17.18)	1.21 (1.03-1.42)	1.04 (0.88-1.23)
No	999 (79.92)	4,271 (82.82)		

*Note: *Number of observations included in the multivariate analysis was 5,246.*

Discussion

A study in the United States, concerning post-marketing surveillance of ADRs, found that a spontaneous reporting system could not detect ADRs that occurred from newly marketed drugs. In addition, there was a considerable amount of under-reporting. A spontaneous reporting system needs other ways to collect data concerning exposed and unexposed populations in order to evaluate the incidence of ADRs among patients.[19] Despite its limitations, a spontaneous reporting system is the most effective surveillance system for drugs. It allows rapid detection of potential alarm signals related to drug use. Improvements to the system through linking with the population's database will generate important recommendations related to ADRs such as updating of the product's safety profile or possibly other regulatory actions, including risk communication and other relevant risk minimization measures.

The Adverse Event Reporting System of the US Food and Drug Administration (US FDA) is the world's largest database of voluntary, spontaneous reports of adverse drug reactions. The US FDA established the MEDWATCH program for healthcare professionals to report adverse reactions related to drugs or other products regulated by the FDA. The MEDWATCH program is FDA's post-marketing drugs safety surveillance system, named after the FDA's promotional program to provide safety information to health professionals and encourage reporting of adverse events for drugs and other medical products.[20] The Food and Drug Administration Adverse Event Reporting System (FAERS) database is a database that contains adverse event reports submitted to the US FDA. The database is designed to support the post-marketing drugs safety surveillance program. In Thailand, the monitoring of adverse drug reactions after drug approval is also a voluntary, spontaneous reporting system. Thai Vigibase is the ADR database which gathers all ADR reports submitted from health professionals. The reports are evaluated for potential safety concerns for Thai patients. Unfortunately, both the FAERS database and the Thai Vigibase contain secondary data, therefore there are many missing values.

A study from the United Kingdom (UK) analyzed data collected by the Department of Health from all hospitals during 1998-2005.[21] Although the data was derived from patients admitted in UK hospitals and experienced an ADR within the previous 7 years, the number of ADRs increased by 45%. A French study of 197,580 ADR reports over a 16-year period found a similar increasing trend.[22] All ADR reports came from 31 regional pharmacovigilance centers around the country and were reported by health professionals.

In a study from Thailand, during 2000-2016, the total number of patients with ADRs was 671,774 and they mostly came from hospitals under the Ministry of Health (including outpatients and inpatients).[23] The trend was increasing over time until 2010 and then gradually decreased. Similarly, patients with dimenhydrinate-related ADRs followed the same trend of the total number of ADRs (Figure 3).

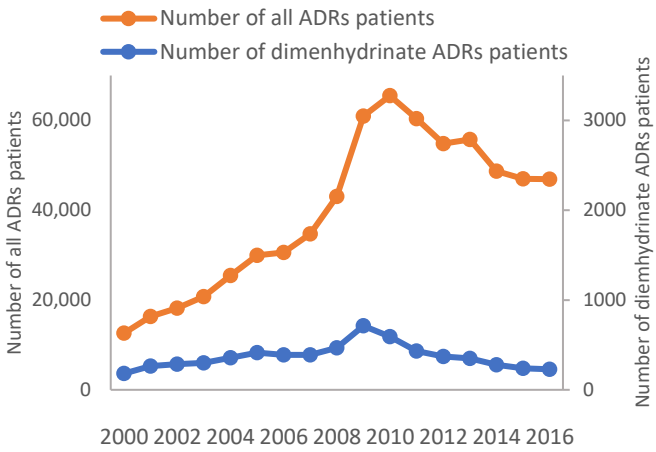

Figure 3. Annual number of patients with a dimenhydrinate-related ADR (blue line) and any ADR (orange line), 2000-2016

A higher number of dimenhydrinate-related ADR reports in 1996 was possibly due to the expanding scope of drug surveillance to other health products under the responsibility of the Thai FDA which included surveillance activities in the National Health Development Plan. In 2009, the Health Product Vigilance Center motivated spontaneous reporting by developing two research projects: Evaluation of the Thai Algorithm Usage for Adverse Drug Reaction Monitoring Project and Signal Detection for Thai Traditional Medicine Project. Those projects may also have enhanced the overall number of other drug-related ADRs in the Thai Vigibase besides dimenhydrinate.[23]

Although the Thai Vigibase has collected many ADR reports, without continuous encouragement, the number of reports would probably decline. In a six-week survey of reporting ADRs in UK hospitals, reporting rates increased after prescribers who reported ADRs received reimbursement and rates declined significantly after reimbursements were stopped.[24]

Adverse drug reactions involving skin appendages were mostly reported among all other system organ classes associated with dimenhydrinate, followed by autonomic central nervous system, which were consistent with previous studies. Moore et al aimed to assess the frequency and cost of drug reactions causing

or prolonging hospitalization in a six-month prospective study. He found that allergic skin reactions were the most ADRs reported and was associated with longer stay in hospital. Orthostatic hypotension (autonomic central nervous system organ class) from using antihypertensive drugs or neuroleptic antidepressants was the second-most common reaction in elderly patients staying in hospital, often due to falls, and resulting in a hip fracture with a fatal outcome.[25]

In this study, among patients who experienced severe drug induced skin reactions with dimenhydrinate, the majority were bullous fixed drug eruption followed by SJS and females predominated. A retrospective analysis evaluated patients with fixed drug eruption in a referral center in Taiwan for period of 11 years and showed no significant difference in the proportion of males and females but a trend in male predominance was noted.[26] Another study found that patients with SJS/TEN had a slight tendency to be female but the association did not reach statistical significance because of the small sample size.[27] Unlike in our study, which included data from a secondary database, most of these studies used retrospective data collected from a single institution.

SJS and TEN are rare, drug-induced skin reactions. There are limited data on the mechanism of action for dimenhydrinate and SJS.[28] H1-antihistamines are probably the most frequently used drugs in allergies, with widely established efficacy, tolerance and safety. However, there is limited information on dimenhydrinate-induced skin reactions with serious outcomes.[28,29]

Our findings indicated that those aged more than 65 years were 31% more likely to have serious adverse reactions after dimenhydrinate use. Another study exploring the incidence and predictors of all and preventable ADRs among frail elderly persons admitted to US hospitals indicated that older age was one of the potential risk factors. Other associated risk factors were multiple medications, severe renal insufficiency, and a prior ADR.[30]

In a prospective multicenter study based on intensive pharmacovigilance in Germany, increasing age correlated with increasing number of ADRs. In patients aged 65-75 years the ADR odds ratio was 2.32 (95% CI=1.54-3.48) which was consistent with our study.[31]

Another significant risk factor of serious ADR from dimenhydrinate in our study was history of allergy. A review of articles published between 1966 and 2010 describing the current evidence-based knowledge of the epidemiology, prevalence, incidence, risk factors and genetic associations of drug allergy found that the true incidence of drug allergy is unknown. The majority of currently available epidemiologic studies have been on ADRs rather than drug allergy specifically. Drug allergies are frequently encountered in patients with HIV infection, particularly to drugs such as cotrimoxazole, abacavir and nevirapine. It is likely that a complex interaction between the host underlying immune status and genetic factors predisposes patients to these allergic drug reactions.[32]

In a prospective cohort study in hospital settings, multiple medication use was identified as a significant ADR risk factor, especially in the elderly. Independent risk factors for all ADRs were number of medications (adjusted hazard ratio=1.07; 95% CI=1.05-1.10 per medication).[30] Unfortunately, data of multiple medications were not available in our study.

Conclusions and recommendations

A higher proportion of adverse reactions associated with dimenhydrinate was found in females. Among the system organ classes, skin appendage disorders were the most commonly reported ADR and one-fifth of patients had severe skin ADRs, including bullous fixed drug eruption and Stevens-Johnson syndrome. Serious or life-threatening outcomes were more likely to occur in older patients and those with a history of allergies. As dimenhydrinate is widely used and may be prescribed with other drugs, it must be used with vigilance when prescribed to the elderly or patients with a history of allergy. Due to the nature of the Thai national adverse drug reactions surveillance system, which is spontaneous, the number of dimenhydrinate-related ADRs are likely to be under-reported. This surveillance system should be periodically evaluated in a systematic way.

Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research and/or publication of this article.

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Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

School Management in Response to Coronavirus Disease 2019

Suwannachai Wattanayingcharoenchai[1], Titiporn Tuangratananon[1], Rapeepong Suphanchaimat[2,3]*

1 Department of Health, Ministry of Public Health, Thailand

2 Department of Disease Control, Ministry of Public Health, Thailand

3 International Health Policy Program, Ministry of Public Health, Thailand

*Corresponding author, email address: rapeepong@ihpp.thaigov.net

Abstract

The coronavirus disease 2019 (COVID-19) outbreak emerged in Thailand in January 2020 with the situation worsening during March-April 2020. The government decided to lockdown most public places, including schools and daycare nurseries even though the proportion of cases in under 15-year-old was small (about 2.8%). Evidence at the global level did not reach consensus on how to manage school openings properly. The Department of Health of the Ministry of Public Health has delivered school guidelines for the prevention and control of COVID-19. The modelling team of the Department of Disease Control demonstrated that the risk of an infective presenting with a long incubation period (more than seven days) was approximately 12%. This figure reduced to only 1% if a fourteen-day cutoff was applied. The infectivity risk did not depend on the incubation period alone, but greatly relied on the ability of a school to detect a case. With a timely and comprehensive detection rate (close to 100%), a seven-day closure policy yielded almost the same infectivity risk as a fourteen-day closure policy. Policy makers should bring the issues of health, education, and the social impact of children to the table and identify the most appropriate measures to control COVID-19 while ensuring the best quality of life of a child.

Keywords: Coronavirus, COVID-19, school, model

School Closure - a Dilemma during COVID-19 Era: International Evidence

Coronavirus disease 2019 (COVID-19) has created a substantial impact on almost all aspects of society. Thailand was the first country outside China to face COVID-19 during March-May 2020. Important clusters of cases at that time emerged mostly from boxing stadiums and nightlife entertainment areas comprising pubs, bars and nightclubs[1]; meaning that the majority of infected cases were in middle adulthood. The Thai Government then endorsed massive lockdown policies intending to curb the epidemic. The policies mostly related to the restrictions of inter-provincial travel, the prohibition of all social gathering events, and the closure of all 'risk' areas and business facilities, including entertainment venues, daycare nurseries, and schools.[2]

Though these policies, *inter alia,* mitigated the epidemic severity, there existed a thorny debate in society about whether 'school closure' is like 'Using a sledgehammer to crack a nut'. This is because, in terms of case volume, children do not account for the lion's share of total cases. Evidence shows that as of 24 Jan 2021, of 13,500 COVID-19 cases in Thailand, the proportion of cases in under 15 year-olds is just 2.8% (379/13,500).[3]

So far, knowledge on the impact of COVID-19 and children has not reached a consensus. A systematic review by Bhuiyan et al demonstrates that nearly half of young COVID-19 cases were asymptomatic and half were in infants.[4] Though it is widely accepted that children and adolescents are less likely to experience severe clinical symptoms than their elders, the fact that most young COVID-19 cases are asymptomatic prompts a concern that children are not risk-free in contracting and transmitting the disease.[5] This notion is coupled with the problem that imposing strict hygienic measures (such as mask-wearing and hand washing) on children is too difficult.[6] Major outbreaks of 260 cases from school settings were observed in Israel, only 10 days following school reopening.[7] A similar situation

occurred in Chile where 52 cases from school clusters were reported within a couple of weeks after notification of the first case in the country.[8]

However, there are contradictory pieces of evidence. Another systematic review by Xu et al suggests that there is limited high-quality evidence available to quantify the extent of COVID-19 transmission in schools, compared with the transmission in community settings.[9] Otte im Kampe et al reveal that outbreaks in schools are always small in terms of the magnitude and severity of the infectees.[10] Lessons from Severe Acute Respiratory Syndrome (SARS) in China, Hong Kong, and Singapore elaborate that school closures contributed to only a trivial effect on COVID-19 mitigation.[11] Besides, the 'collateral damage' from school closure can be enormous. This includes increasing family poverty, food insecurity, child abuse, child neglect, mental health, and enhancing education disparity among disadvantaged children.[12,13] Attention to school lessons and competing daily activities at home are extremely challenging, not only for children but also the parents. The infrastructure supporting home-schooling or distance learning technology is not always available for families in remote areas.[14]

Policies on School Closure and Reopening in Thailand

From these collective pieces of evidence, the decision for school closure or re-opening needs to carefully balance the disease-containment objectives and children's quality of life. The Department of Health has announced preventive measures for school-re-opening since May 2020. Child-care facilities and nurseries are always the first venues for education reopening.

Additionally, the discussion should not be confined to whether the school is allowed to reopen. To manage the disease effectively, all education institutes need to account for behavioral modification amongst all involved parties. Face-masks, temperature scans, and hand-hygiene measures should be stringently implemented. All schools need to restructure the infrastructure and re-orientate classroom design (providing adequate ventilation, reducing the number of students per class and session, avoiding contact activity if necessary, having an acute respiratory section in the school infirmary, and frequent communication on COVID-19 to improve health literacy).[15] Table 1 presents a summary of reorientation measures for schools to respond to COVID-19, recommended by the Department of Health.[15]

Table 1. COVID-19 prevention measures in school

Dimension	Main measures	Supportive measures
Disease prevention and containment	1. Temperature and history screening 2. Students, staffs, and visitors must wear a face mask when being in schools 3. Provide hand washing area and alcohol gel 4. Keep 1-2 meters of physical distancing in class 5. Maintain adequate air ventilation 6. Reduce the number of students in the class to prevent the crowded situation	1. Clean public space surface frequently 2. Keep 1-2 meters of physical distancing in the activity space 3. Encourage the students to use personal utensils 4. Provide isolated nursing room for respiratory disease patients 5. Provide COVID-19 mitigation measure of awareness and knowledge 6. Ensure disease prevention measures in school bus
Social protection	1. Prepare the study plan for students in quarantine or during the school closure period 2. Prepare guidelines to reduce social stigma 3. Provide guidelines to reduce staff stress and anxiety 4. Revalidate risk history of students and staff 5. Disclaim abstinence days of students and staff at risk of COVID-19 infection	1. Communicate with related school members to prevent social stigma 2. In case of COVID-19 infection, students and staffs may be absent without punishment or it being counted as sick leave 3. Quarantine must be applied in contact cases

What does a Modeling Study Suggest on the School Closure Duration?

A recent modeling study conducted by a joint research team of the Division of Epidemiology, Department of Disease Control, and the International Health Policy Program of the Ministry of Public Health demonstrates that a long period of school closure (14 days) may yield similar benefits as a short closing period (7 days) conditional on a 100%-detection rate. In other words, policymakers need to contemplate the ability to detect a suspected case (detection rate) in tandem with the school closure period. The findings were reported to the Strategic and Technical Advisory Group (STAG) under the Emergency Operations Center (EOC) of the Department of Disease Control in June 2020 to aid decision-making.

The study applies the concept of compartmental and system-dynamics models, as demonstrated in Figure 1. Several assumptions are employed: (i) number of susceptible students at the inception=99; (ii) number of infective students at the inception=1 (total students=100); (iii) reproduction number of COVID-19 =2.2;[16] (iv) infectious duration of COVID-19=4.6 days;[17] (v) all children have homogenous random contact with each other; (vi) incubation period follows gamma distribution with mean of 5 days and standard deviation of 3 days;[18] and (vii) the school would be closed (for 7 or 14 days) once a case is detected.

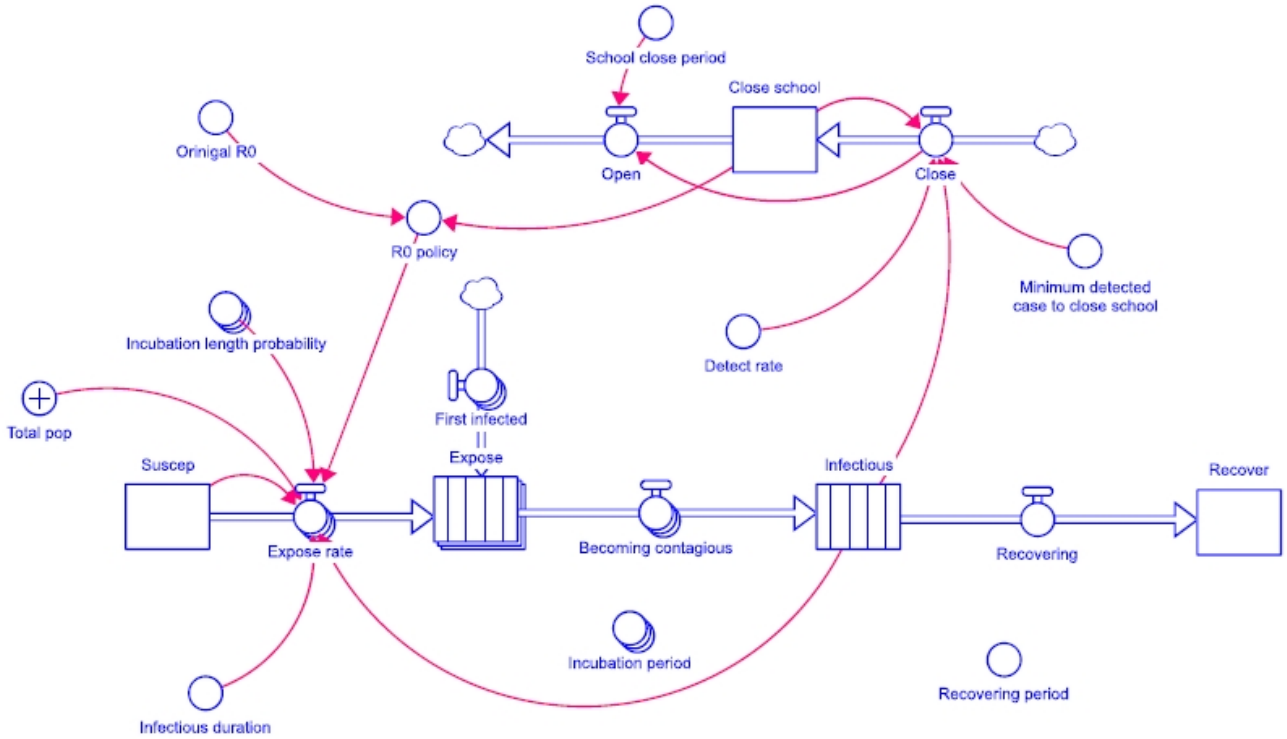

Figure 1. Model framework

The infectivity risk can be estimated from the gamma-distribution characteristic of the incubation period. About 88% of cases have an incubation period of shorter than 7 days while only 1% experience very long incubation periods of 14 days or more. The rest 11% lie between 7 and 14 days.

This means the seven-day closure policy may face a risk of letting the infectives with a higher-end spectrum of incubation period (about 12%) make contact with susceptible students. The fourteen-day closure policy is considered safer in terms of preventing a second wave of cases (with a peak of three cases by approximately day 40) when detection rates are compromised.

From another angle, as mentioned earlier, this situation is not too worrisome if the detection rate is 'sensitive' enough to capture the infectives and seclude them from other students. In this regard, the term 'sensitive' in this case means the extent to which the school officials (or teachers) are able to detect a single infected student. For instance, a 25%-detection rate means that at the time when a single case is detected, there will be (at least) four cases existing in a classroom. This assumption explains why the school closing date differs in different detection scenarios. The findings also point to the case detection measure (such as temperature screening or verbal screening on students with a history of close contacts with other infectives) must not be relaxed. Note that the model focuses only on infection amongst students. The impact on other family members is yet to be explored. Figure 2-3 displays the findings of the model based on the assumption above.

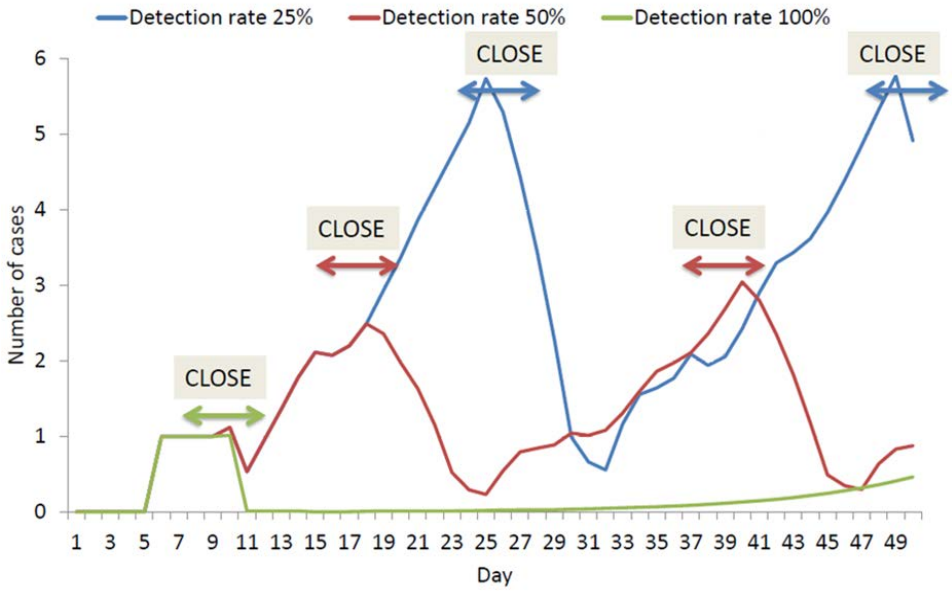

Figure 2. Number of COVID-19 cases based on 7-day school closure policy

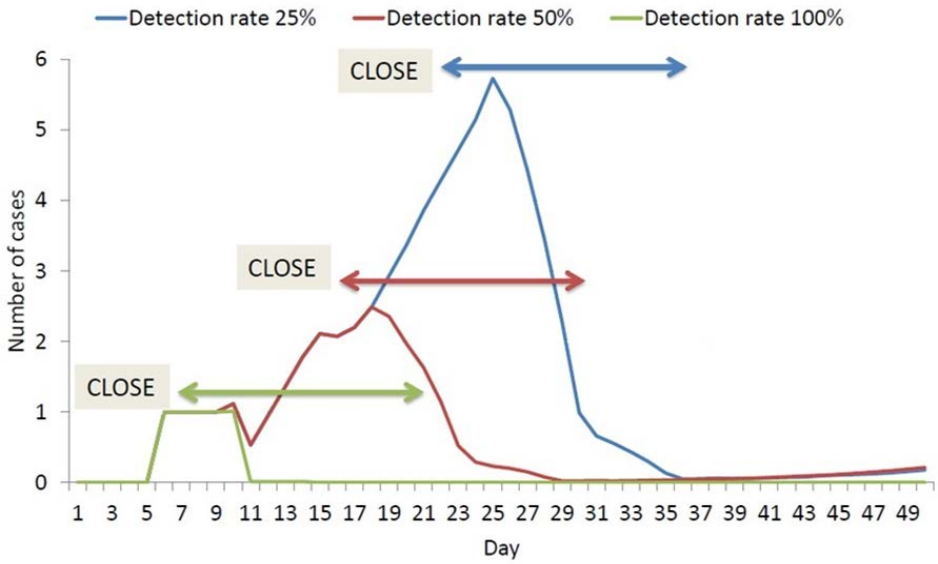

Figure 3. Number of COVID-19 cases based on 14-day school closure policy

The impact on children themselves was mostly related to a higher perception of family stress and instability during the home-school period.[19] The competing responsibilities of parents was also reported as a challenging factor on top of the challenges concerning education access, study motivation, and longer learning outcomes.[20] A survey of 4,342 primary and secondary school children in China revealed a high percentage of anxiety, depression, and stress (24.9%, 19.7%, and 15.2%, respectively). The majority of the children who frequently had discussions with their parents were satisfied with their life.

The Way Forward on School Responses to COVID-19

The COVID-19 pandemic has resulted in unprecedented changes to almost all aspects of human lives, including the well-being of children. Many countries around the world endorse a temporary nationwide and extensive closure of educational institutions in an attempt to contain the spread of the pandemic, while several countries have implemented more localised closures. However, school closure is far from the heart of all measures against COVID-19. The closure policy, which gives priority to 'health', must be balanced with other supporting mechanisms to minimize the detrimental effect on other aspects of the well-being of the children. To find a sound balance of school responses to COVID-19, the government should involve all related parties in the decision-making process. These include not only epidemiological experts and public health specialists but also, educationists, representatives of parent groups, school leaders, and civic groups. While controlling the epidemic is the primary goal of the measures, continuous monitoring of the academic performance and well-being of the students should also be in place.

Suggested Citation

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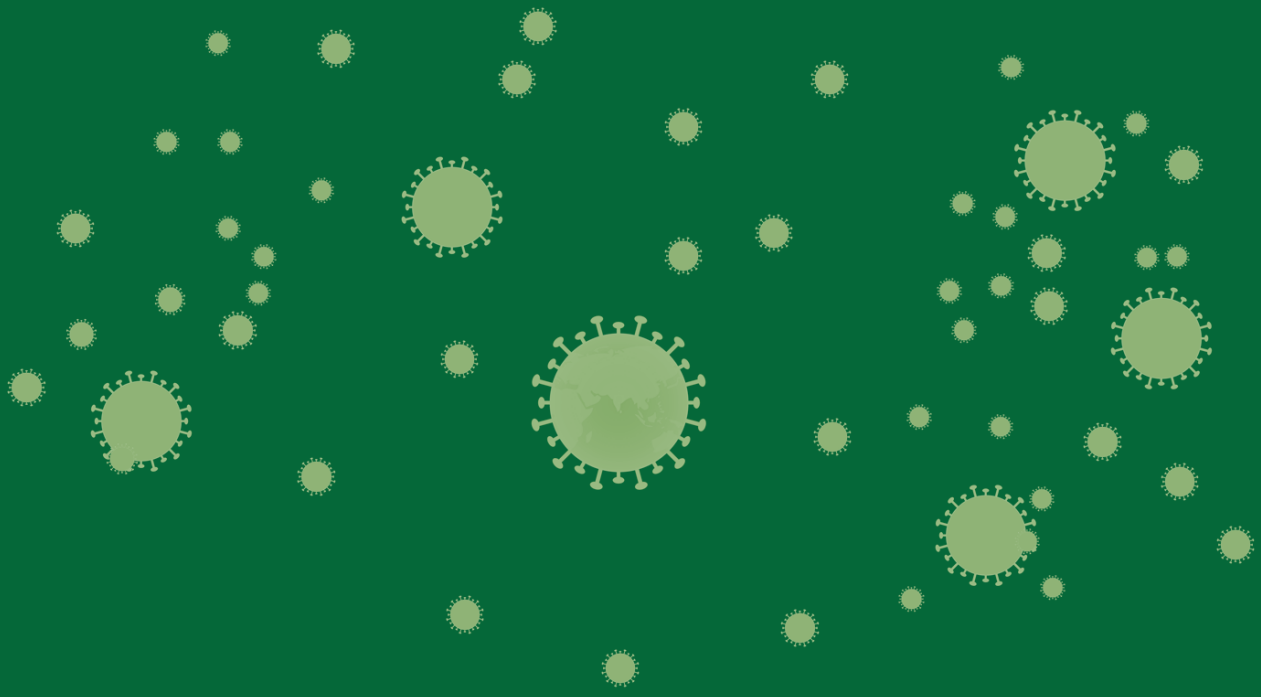

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