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Latent tuberculosis infection one year after exposure among hospital laboratory workers

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Abstract

Health workers are at high risk of tuberculosis (TB) infection through occupational exposure to tuberculosis, and medical laboratory personnel are a high-risk group for getting TB at work. The infection can be caused by their work process and/or be contracted from co-workers. Latent tuberculosis infection (LTBI) detection and controls are thus needed to prevent the spread of TB in the workplace. The current study aimed to determine the proportion and characteristics of laboratory personnel infected with tuberculosis. All medical laboratory workers 75 individuals employed in the medical laboratories in a hospital in northeastern Thailand with high or medium prioritized contact with TB index cases in the workplace between September 2019 to October 2020 were included in the study. Post-exposure TB surveillance data were obtained from the Occupational Health and Safety Office, and laboratory work processes and work environment data were collected through workflow studies and interviews. After a one-year follow-up, the proportion of LTBI among medical laboratory workers was 13.3% (ten persons). The bivariate conditional logistic regression analysis showed that older age (>55 years) (odds ratios (OR) = 6.57, 95% confidence intervals (CI): 1.43,29.93, $p = 0.063$), and workers with high-prioritized contact (OR = 3.986, 95%CI 1.595, 8.974, $p = 0.030$) had a statistically significant association with the occurrence of LTBI. LTBI in the workplace among medical laboratory workers was probably caused by prolonged, cumulative, close contact with infected co-workers in daily life activities rather than work-related procedures.

Keywords: Latent tuberculosis infection, TB, Health care worker, Medical laboratory worker

1. Introduction

Tuberculosis (TB) is an infectious disease, a significant cause of ill health, and one of the top ten causes of death worldwide (estimated 1.5 million deaths in 2020) [1]. According to the WHO, Thailand ranks 30th for TB burden and 30th for TB/HIV burden [2]. Health workers (HWs), particularly doctors and nurses, are at high risk of TB infection through occupational exposure to patients with active TB [3]. Other HWs, especially laboratory personnel, are a high-risk group for getting TB at work [4-6], both from work process (e.g., TB culture) and drug resistance testing. TB can be aerosolized, thereby increasing the risk of contracting TB at work [7], and it can be contracted from close contact with a co-worker with active TB [8]. Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB. Although individuals with LTBI do not have active TB disease, they may yet develop the disease [9]. The World Health Organization (WHO) requires the management of LTBI to halt the global TB epidemic (WHO End TB Strategy) [10]. The prevalence of active TB among HWs ranges between two and six times higher than that of the general population [11]. In Thailand, 53.1% of health personnel have a latent TB infection, according to tuberculin skin testing (TST) [12,13]. Factors commonly associated with TB transmission in healthcare settings include delayed diagnosis and isolation, infection from drug-resistant strains, and failure to isolate untreated patients in areas with appropriate engineering controls (e.g., negative pressure room and high-efficiency particulate air filtration (HEPA) systems) [14-17]. Detection of LTBI for diagnosis and treatment is necessary to prevent the spread of TB in the workplace [10]. Medical laboratory workers in our hospital, who are at high risk for TB infection, had never been screened for LTBI and during the past two years, several cases of tuberculosis have been diagnosed in medical laboratory workers. Post-exposure TB surveillance among exposed medical laboratory workers was done to prevent the spread of TB in the workplace. The current study was thus designed to detect post-exposure TB infection among medical laboratory workers (i.e., by searching for LTBI and TB cases) and aimed to determine the proportion and characteristics of LTBI among laboratory workers after one-year exposure to TB from hospital co-workers. Disease investigations for disease control was the source of information.

2. Materials and methods

2.1 Study design, population, and sample

This was a descriptive study. All the medical laboratory personnel at the medical laboratories of a hospital in northeastern Thailand were enrolled in the study. The personnel were exposed to TB index cases in the workplace between September 2019 and October 2020. The laboratory workers categorized their exposure risk according to the characteristics of the respective index case as high, medium, or low. The workers 50 persons in the low-risk group were excluded from the study. In addition, persons with a history of tuberculosis, latent tuberculosis infection, or a history of positive TST or interferon-γ release assays (IGRAs) were excluded from this study. After applying the inclusion and exclusion criteria, 75 medical laboratory workers were identified as the study population.

2.2 Study tool and data collection

The study used data from two sources:

1) Existing TB post-exposure surveillance data for the medical laboratory workers from the Occupational Health and Safety Office, Faculty of Medicine, Khon Kaen University; (A) forms for collecting the existing data were developed, (B) the existing TB post-exposure surveillance data collected consisted of factors associated with LTBI, including personal biodata, work practice, contact characteristics with index case, duration of exposure, size of the workroom, workroom environment data, and air change rate (ACR) data, and (C) results of the investigation (including IGRA and chest X-ray (CXR)) were recorded on this form. IGRA indicates the use of the QuantiFERON®-TB Gold In-Tube test (QFT-GIT).

2) Laboratory work processes were collected from an interview with the supervisor of the medical laboratory and a workflow study.

2.3 Operational definition

2.3.1 Priority of contact

The priority of contact with TB, assigned by a contact investigation, was determined according to the characteristics of the index case: susceptibility and vulnerability of contacts, and the circumstances of the exposure(s). In summary, the priority of a TB contact was classified as ‘high’ if it was with a patient definitively diagnosed by a positive CXR or sputum acid-fast bacilli (AFB), or a patient suspected (by positive CXR) of having a weak immune system, or the contact was via a procedure (viz., bronchoscopy, sputum induction, or autopsy). If none of the aforementioned were relevant, the duration of contact exposure and ventilation system of the room where the contact occurred were taken into account. The definition of a high of priority contact was fulfilled when: (1) the cumulative exposure of a HWs to the index case was ≥8 h in a small room with poor ventilation; (2) the cumulative exposure of a HW to an index case was ≥16 h in a small room with good ventilation; (3) the cumulative exposure of a HW to an index case was ≥24 h in a standard classroom size; or, (4) the cumulative exposure of a HW to an index case was ≥24 h in an open-air setting. The definition of a medium priority was fulfilled when an HW was exposed to an index case if no AGPs took place. To be assigned a medium priority, only the duration of exposure and room ventilation were considered (viz., cumulative exposure ≥4 h in a small room, ≥8 h in a standard size classroom, or ≥50 h in open-air). Any contact not classified as high, or medium was classified as a low priority.

2.3.2 Index case

TB index cases numbered three patients in this laboratory. The index cases were divided into two groups, according to the likelihood of spreading the infection as per the patient's symptoms from the post-exposure TB guidelines set out by the Occupational Health and Safety Office. The index cases had the following clinical symptoms:

Group I Index A and B: Patients with active TB

Index A did not have any symptoms; however, the CXR revealed signs of tuberculosis, and the sputum PCR (Xpert MTB/RIFassay) confirmed a TB positive result.

Index B had a cough, weight loss, and the CXR revealed signs of tuberculosis, and the sputum AFB and sputum PCR were positive for TB.

Group II Index C: Patient with suspected active TB

Index C did not have any symptoms. The CXR did not show signs of tuberculosis, but the sputum AFB and PCR were positive for TB.

2.3.3 Medical laboratories characteristics

A medical laboratory is a controlled facility where tests are conducted on clinical specimens to obtain a patient's health information. Such facilities are categorized according to the type of testing and services provided (Figure 1). Laboratory work processes include specimen examination, but these are usually now automated machines not requiring direct specimen handling (i.e., clinical chemistry and immunology). Some sub-departments, however, directly handle specimens-viz., Clinical Microbiology, Diagnostic Molecular Biology, and Diagnostic Microscopy. Unit processes and services include the following:

1. Phlebotomy and Specimen Collection Unit

Medical technologists (MT) draw blood and collect specimens from patients while laboratory workers prepare equipment and collect specimens.

2.Specimen Center Unit

Medical technicians and assistants receive and process specimens and prepare them for sending to other laboratories for analysis.

3.Diagnostic Microscopic Unit

MT, scientists, and technician assistants conduct microscopic examination specimens (i.e., blood, urine, and stool). The MT summarizes, analyzes, and certifies the results. Assistant scientists and laboratory personnel receive the specimens and prepare and clean equipment.

4.Clinical Microbiology Unit

MT and technician assistants analyze bacterial culture, test bacterial susceptibility to anti-bacterials, conduct direct-smear TB microscopy, handle TB cultures, and conduct TB drug susceptibility testing. Assistant scientists and laboratory workers receive specimens, prepare, and clean equipment.

5.Diagnostic Molecular Biology Unit

MT, scientists, and assistant technicians analyze blood and sputum for pathogen genetic material using DNA and RNA analysis methods. Assistant scientists and laboratory workers receive specimens, prepare and clean equipment.

6.Clinical Chemistry and Immunology Unit

MT and technician assistants conduct chemical and immunological testing of specimens using automatic machines. Assistant scientists and laboratory workers receive specimens, prepare and clean equipment.

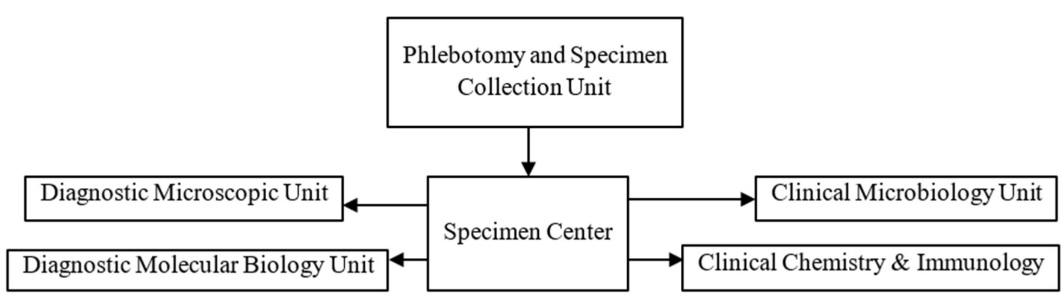

Figure 1 Medical laboratories organization.

2.4 Data analysis

Data analyses were performed using SPSS, Version 26. Data were analyzed and reported as descriptive statistics. The characteristics of the subjects were summarized using descriptive statistics. Means with standard deviations and medians with ranges (minima and maxima) were used for continuous variables according to normal distribution variables. Frequency counts and percentages were used for categorical variables. The proportion of LTBI in laboratory workers was reported. A crude analysis was performed to determine the association of factors with LTBI. The crude odds ratios (crude OR) and 95% confidence intervals (CI) were computed using bivariate conditional logistic regression.

3. Results

3.1 Medical laboratory workers' characteristics

According to the study, workers exposed to the three laboratory workers who had active TB, 75 presented with general characteristics (Table 1). Fifty-five percent were female. The median age of workers was 34 years (interquartile range (IQR) 22-59). Most (65.3%) had a bachelor's degree, 14.4% had a higher degree, and 19.2% had a diploma certificate. The majority (86.7%) denied having any underlying disease(s). Workers having underlying diseases being at risk of becoming infected with TB included human immunodeficiency virus (HIV) infection (n=1), diabetes (n=2), and breast cancer (CA breast) (n=2). Nearly all (96%) the laboratory workers had had the Bacillus Calmette-Guérin (BCG) vaccine. Job titles included: (a) professional-level-60% medical technologists and 4.8% medical laboratory scientists, and (b) operational-level staff-15.2% medical technician assistants and 14.4% assistant scientific officer/laboratory administrative (Table 1). The medical laboratories' staff worked in 6 sub-departments: most (32%) in the Immunology and Clinical Chemistry Unit, followed by the Diagnostic Microscopy Unit (23.2%), and the Clinical Microbiology Unit (17.6%) (Table 1).

Table 1 Characteristics of participants (n=75).

Characteristic	(%)
Sex	
Male	20 (26.6)
Female	55 (73.3)
Age (year)	
Median (IQR)	34 (22-59)
Underlying diseases	
No	65 (86.7)
Yes	10 (13.3)
Disease-associated TB	
HIV	1 (1.3)
Diabetic Mellitus	2 (2.7)
Breast cancer	2 (2.7)
Disease not associated with TB	9 (12.0)
BCG vaccination status	
Yes	72 (96)
No	3 (4)
Education level	
Technical certification	16 (21.3)
Bachelor degree	49 (65.3)
Master degree	10 (13.3)
Work division	
Clinical chemistry and immunology	15 (20.0)
Diagnostic microscopic unit	13 (17.3)
Clinical microbiology unit	18 (24.0)
Phlebotomy unit	12 (16.0)
Specimen center	10 (13.3)
Diagnostic molecular biology unit	3 (4.0)
Administrative unit	4 (5.3)
Job title	
Professional level	
Medical technologist	34 (45.3)
Medical laboratory scientist/scientist	6 (8.0)
Operation level	
Medical technician assistant	12 (16.0)
Assistant scientific officer/Laboratory admin	19 (25.3)
Administrative personnel	
General service officer	4 (5.3)

3.2. Characteristics of TB exposure in medical laboratory workers

According to the study, a workplace where medical laboratory workers shared the same area with co-workers with undiagnosed active TB presented a greater risk of exposure for workers who worked in the same type of environment-viz., a medium-sized room with standard ventilation air exchange rate > 12 times/h. All TB exposed workers thus had characteristic prolonged exposure to index cases-usually through cumulative exposure during work activities. The workforce exposure duration ranged between 8 and 480 h of exposure to index cases. In addition, there were (a) 32 high-prioritized cases of exposure with index cases (i.e., speaking within 1.5 -m proximity with index cases without a surgical mask more than three times/week, eating together 3-5 times/week, and prolonged cumulative exposure with index cases in a medium-sized room before the index cases were diagnosed), and (b) 43 medium-prioritized cases of exposure with index cases (i.e., prolonged cumulative exposure < 8 contact h).

3.3. Proportion of LTBI in medical laboratory workers

Based on the follow-up, the proportion of laboratory workers with LTBI after exposure to index cases was 13.3% (n=10). At the one-year follow-up, none of the workers had active TB despite having had LTBI after exposure to the index case. The proportion of workers with LTBI is presented in Table 2. Within three months of worker exposure to index cases, eight (6.4%) had LTBI. By comparison, it was 1.5% at the six-month follow-up and again 1.5% at the one-year follow-up (Table 2).

Table 2 Proportion of LTBI in medical laboratory workers at the one-year follow-up.

Diagnosis	Follow-up period (proportion)			Number of LTBI in a 1-year period (proportion)
	3 months n=75	6 months n=67	1 year n=66	
LTBI	8 (6.4%)	1 (1.5%)	1 (1.5%)	10 (13.3%)
LTBI to Active TB	0	0	0	0

3.4. Characteristics of LTBI workers

Among the ten laboratory workers who developed LTBI, eight were women, and two were men. The median age was 47 years (IQR 33-59 years). Eight of the workers with LTBI did not have underlying diseases, while two had CA breast. All had had BCG vaccine. All those with LTBI denied having any TB exposure from other sources except work. The job titles of workers with LTBI included medical technologist (n=3), medical technician assistant (n=3), laboratory admin (n=3), and medical laboratory scientist (n=1). Subsidiary departments where laboratory workers work include the Clinical Microbiology Unit (n=3), the Diagnostic Microscopy Unit (n=2), the Specimen Center (n=2), the Clinical Immunology Section (n=1), Clinical Chemistry Section (n=1), and the Blood Collection Room (n=1). Workers with LTBI had an average length of service of 25 years: most (n=9) had a length service of more than ten years. They all had undergone training and review of laboratory safe work practices and functioned accordingly. As per work activities, 3 LTBI workers were exposed to tuberculosis specimens through low- and/or high-risk laboratory activities (direct sputum microscopy or culture manipulation for identification and drug resistance testing, respectively). Notwithstanding, all processes were performed in biosafety cabinets (Table 3).

All LTBI-positive workers worked in the same type of environment-a medium-sized room with a standard air exchange rate > 12 times/h), all had a history of tuberculosis from colleagues at work. A respective No. 4, No.5, and No. 1 LTBI workers had been in contact with index cases A, B, and C. All LTBI-positive workers that had been in contact with index case A were prioritized as having had a high-risk contact. A respective No. 3 and No. 2 of the workers exposed to index case B were classified as having had a high- and medium-risk contact. One worker exposed to index case C was classified as having had a high-risk contact. The exposure characteristics with an index case by LTBI workers included talking within 1.5 m of an index case without respiratory protection, eating together, and prolonged cumulative exposure in a medium-sized room before the index case had been diagnosed, and duration of exposure between 8 and 480 h. Four LTBI-positive workers were categorized as having had a high-risk exposure, and the characteristics of their exposure were talking within 1.5 m of an index case without respiratory protection more than 3 times/week, eating together 3-5 times/week, and prolonged cumulative working exposure with an index case in a medium-sized room before the index case had been diagnosed (Table 3).

Table 3 Characteristics of LTBI workers.

Characteristics of LTBI workers					TB infection risk level by job					TB infection risk level by the characteristic of exposure with TB co-worker			
No.	Age	Sex	Underlying disease	Time of IGRAs positive (mth)	Duration in the current (yr)	Job title	Department	Working process with TB laboratory procedure	Risk level	Index case	Characteristic of contact with index case	Contact (h)	Risk level
1	56	Female	CA breast	3	34	Medical technician assistant	Clinical microbiology	Direct sputum-smear microscopy, culture, and identification.	Low	A	Talking 1-2 h/wk, working in the same room.	360	High
2	54	Female	No	3	31	Medical technician assistant	Clinical microbiology	Direct sputum-smear microscopy, culture, and identification.	Low	A	Talking 5 h/wk, eating together 3-5 times/week, working in the same room.	360	High
3	34	Female	No	3	12	Medical Scientist.	Diagnostic microscopy	No	Low	B	Talking 1-2 h/week, working in the same room.	108	High
4	59	Male	No	3	34	Laboratory administrator	Clinical chemistry	No	Low	B	Working in the same room 1-2/month.	8	Medium
5	47	Male	No	3	22	Laboratory administrator	Specimen center	No	Low	B	Talking 5 h/wk, eating together 3-5 times/wk, cumulative exposure in the same room.	480	High
6	46	Female	No	3	22	Medical technician assistant	Diagnostic microscopy	No	Low	B	Talking 1-2 h/wk, working in the same room.	108	High
7	57	Female	No	3	35	Laboratory administrator	Specimen center	No	Low	C	Working in the same room 3-5 times/month.	36	Medium
8	33	Female	No	3	9	Medical technologist	Phlebotomy unit	No	Low	B	Talking 2-3 h/month.	8	Medium
9	55	Female	CA breast	6	33	Medical technologist	Immunology	No	Low	A	Talking 5 h/wk, eating together 3-5 times/wk.	48	High
10	35	Female	No	12	6	Medical technologist	Clinical microbiology	Direct sputum-smear microscopy, culture, and identification.	Low	A	Talking 5 h/wk, eating together 3-5 times/wk, cumulative exposure in the same room.	360	High

3.5 Association between risk factors and positive IGRAs result

A bivariate conditional logistic regression was used to analyze the factors associated with the occurrence of LTBI, and the results are presented in Table 4. The statistically significant factors related to the occurrence of LTBI include medical laboratory workers over 55 years of age (crude OR = 6.57, 95% CI: 1.43, 29.93, *p* = 0.063), and prolonged cumulative exposure contact (high-prioritized contact) (crude OR 3.98, 95%CI 1.59, 8.974, *p* = 0.030).

Table 4 Association between risk factors for the occurrence of LTBI and a positive IGRAs result.

Factor	IGRAs				
	Positive (n=10)	Negative (n=65)	Crude OR	95%CI	*p*-value
Age					
<55	4	6	1		
≥55	6	59	6.56	1.436, 29.93	0.015
BCG status					
Present	10	62	1		
Absent	0	3	0.97	0.045, 20.79	0.830
Priority of contact					
Medium	3	40	1		
High	7	25	3.73	1.595, 8.974	0.030
Working in Clinical Microbiology Unit					
No	7	53	1		
Yes	3	12	1.89	0.426, 8.424	0.401

4. Discussion

The study results are based on a follow-up on the proportion of laboratory workers with persistent LTBI after exposure to index cases using an IGRA test every three months. Within the first three months, 8 persons (6.4%) had LTBI. The diagnosis of LTBI was based on the cellular immune response to mycobacterial antigens, which develop 2-10 weeks after infection with M. tuberculosis, identified using TST or IGRA results [18-20]. The estimated interval between infection and detectable test reactivity is 2-12 weeks [21]. In the current study, the highest proportion of LTBI was found in the first three months, probably due to close and prolonged unprotected exposure to index cases (co-workers with un-diagnosed active TB). Factors associated with TB infection include susceptibility or immune status of the exposed host, the infectiousness of the person with TB, proximity, frequency of exposure, duration of exposure, and environmental factors affecting the concentration of TB organisms [22]. Based on our results, the median age of laboratory workers with LTBI was 50.5 years (IQR 33-59). Another research also reported that the older a person (55 and above), the more likely the occurrence of LTBI [23-25]. In our study, persons over 55 years of age had a higher risk for LTBI (OR 6.56, 95%CI 1.436, 29.93, *p*= 0.015).

We also found that host immune status was a significant factor-two cases had breast cancer as an underlying disease. Having an underlying disease and/or chronic disease are risk factors of LTBI. It is consistent with research conducted in 2019 that having an underlying disease including HIV, various types of immune deficiency, and taking immunosuppressants are related to an increased risk of contracting tuberculosis [24].

The current study revealed one LTBI-positive worker at the 6-month post-exposure follow-up for TB, and the contributing infection factor was breast cancer. The presence of an underlying disease weakens immunity [24]. The key contributing factor was cumulative exposure to TB-infected co-workers, despite working in different departments. There was a 48-h exposure period, but there were daily activities with the index case-i.e., talking 5 h/wk, and eating together 3-5 times/wk.

At the one-year follow-up, one worker was diagnosed with LTBI, and she had no underlying disease. She had worked in the clinical microbiology department as a medical technologist for six years and was exposed to tuberculosis during work processes. High-risk TB laboratory procedure exposures included culture inoculation and drug resistance testing (direct DST). [7,25-26] In a follow-up study, one year after exposure to tuberculosis, three workers in the clinical microbiology departments were found at risk of TB exposure: one medical technologist and two medical technician assistants. During work, they were directly exposed to tuberculosis as the medical procedure for TB examination can produce aerosols (AGP) (e.g., culture inoculation, drug resistance testing (direct DST) [25-26].

One study reported that tuberculosis among laboratory workers is 3 to 9 times higher than the general population [27]. Previous studies conducted among health workers in high LTBI burden countries like Thailand reported that microbiology laboratory work was a risk for LTBI (OR: 5.65, 95% CI: 1.74;18.36) [28-30], but it was not a statistically significant factor in the current study. This was probably because although laboratory workers managed active specimens, they operated using closed biosafety cabinet hoods. It has been found that work-related tuberculosis is more likely from contact with contagious co-workers.[24] In the current study, we confirmed tuberculosis from the workforce was due to close, prolonged contact with infectious TB-infected co-workers (i.e., between 8 and 480 h). Despite good ventilation, there is a high risk of contracting TB for workers conversing within 1.5 m with an index case without respiratory protection, eating together with the index cases, or having prolonged cumulative exposure with the index case in the same room (range, 48-480 h). Prolonged cumulative contact with index case resulted in a higher risk for LTBI (OR 3.73, 95%CI 1.595 - 8.974, p=0.030).

The current study results reveal that the proportion of LTBI among laboratory workers, after monitoring of exposure to index cases for one year, was ten persons (13.3%). A similar 2015 study on LTBI among laboratory workers in Thailand using IGRAs revealed that the prevalence of LTBI among laboratory workers was 9.5%, [29] which is similar to the current study. In addition, studies in Saudi Arabia, Korea, and China on the proportion of LTBI among laboratory workers using IGRA testing reported the proportion ranging between 19.4% and 43.4%, and the respective prevalence of latent tuberculosis infection among laboratory workers was 19.4%, 23.4%, and 43.4% [23,26,31].

5. Conclusion

Based on the current study, the likely cause of TB transmission among laboratory workers occurs between and among the laboratory workers. Appropriate ventilation and airflow systems [7] could reduce the spread of tuberculosis. Tuberculosis infection in the workplace is probably caused by close contact with co-workers, activities performed together (i.e., dining and/or conversing together for several hours every workday). Early detection of LTBI and active TB by screening of laboratory workers with IGRA, CXR and symptom questionnaire would help decrease the spread of TB infections among co-workers.

6. Ethical approval

The Khon Kaen University Ethics Committee for Human Research reviewed and approved the study protocol (Reference Nos. HE631339 and IRB00001189) on June 16, 2020.

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