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Hepatitis A epidemics in Japan, France, and Thailand from 2007 to 2021, highlighting a post-COVID-19 decline

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Hepatitis A infection is an acute hepatitis disease transmitted through contaminated water, food, and sexual contact, especially among men who have sex with men (MSM). This retrospective cohort study analyzed trends in hepatitis A infection in Japan, France, and Thailand from 2007 to 2021 to investigate varied epidemic trends including the MSM pandemic and the COVID-19 pandemic under different public health conditions. We analyzed annual and monthly number of cases using the national surveillance databases of Japan, France, and Thailand. We statistically evaluated the decrease in hepatitis A after the COVID pandemic. Hepatitis A average incidence in Japan, France, and Thailand was 0.21, 1.79, and 0.75, respectively. Outbreaks were recorded in 2010, 2014, and 2018 for Japan, 2009 and 2017 for France, and 2012 and 2017 for Thailand. In 2012, a hepatitis A outbreak was recorded at an ice manufacturing factory in Thailand. In Japan, in 2014, 80.5% of cases were transmitted by contaminated seafood or water. Hepatitis A increased during 2017–2018 (324% in 2018 Japan, 489% in 2017 France, 166% in Thailand), possibly linked to the global MSM pandemic. After the COVID-19 pandemic, the cases significantly decreased in all three countries ($p < 0.001$). The characteristics of hepatitis A epidemic may reflect the activities of people, including high-risk groups.

Keywords Hepatitis A COVID-19, Pandemic

Hepatitis A is an acute viral hepatitis caused by the hepatitis A virus (HAV). The virus is transmitted primarily via the fecal-oral route through contaminated water or food or through sexual contact[1]. HAV is mainly prevalent in low-income and underdeveloped countries with low-quality water supply. In contrast, the major transmission route in developed countries is sexual contact; food or waterborne infection is rare due to the well-equipped water supply and sewage systems[2]. HAV is not endemic to developed countries; therefore, adults are more susceptible to HAV infections due to a lack of seropositivity, leading to sexually transmitted hepatitis A outbreaks among adults[3]. Globally, epidemics of HAV were reported among men who have sex with men (MSM) in 2016 to 2018 in countries such as Taiwan, the United States, and European countries[4,5].

Since 2020, the coronavirus disease 2019 (COVID-19) pandemic has had major medical and social impacts. The COVID-19 preventive measures, such as wearing masks, washing hands, and lockdowns, affected the prevalence of other infections. Intestinal infection and sexually transmitted infection (STI) cases decreased after the COVID-19 pandemic. However, both types of the infections reportedly resurged after 2021[6]. The epidemic routes of hepatitis A are diverse, including gastrointestinal and sexual infections.

Each country has had different COVID-19 pandemic situations and adopted different preventive measures. In Japan, the government declared a state of emergency from April 4 to May 31, 2020, and from January 8 to March 21, 2021, along with a more moderate protocol called "Quasi-emergency measures" that was created and declared multiple times during the years 2020 and 2021. During the state of emergency and quasi-emergency measures in Japan, store opening hours were restricted, maximum capacities of amusement parks and stadiums were decreased, and residents were asked to stay at home except for essential tasks such as grocery shopping[7].

In France, strict lockdown measures were taken, starting on March 17, 2020, including mandating residents to stay at home except for groceries and minimal physical activities for their health. Those who did not carry

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a justification document for their presence outside were fined[8]. In total, three lockdowns were conducted with gradual lifting of curfews and restrictions, ultimately ending in June 21, 2021 [9].

In Thailand, the government successfully contained the initial outbreak from March 2020 to June 1, 2021, through various preventive measures[10]. However, with new waves emerging after July, more strict lockdown policies were imposed in high-risk areas of Greater Bangkok until further notice[11,12].

We investigated the epidemiological characteristics of the hepatitis A trends under varying baseline conditions to track the global spread of hepatitis A in concordance with the MSM pandemic which started in Europe then to Asia, and how their trends have transitioned into the COVID-19 era in Japan, France, and Thailand. Very few studies have examined how the hepatitis A epidemic has changed amid the different COVID-19 pandemic situations and prevention methods in multiple countries. The three countries were selected based on their diverse public health statuses; France experiences marked seasonal characteristics and leads the MSM-related outbreak originating in Europe; Thailand is historically known for high prevalence of sexually transmitted diseases[13], and Japan having high standards of food sanitation and infectious disease prevention measures[14].

Methods

This retrospective, cohort study used data obtained from national surveillance databases in Japan, France, and Thailand. Data sources were; The National Epidemiological Surveillance of Infectious Diseases (NESID) under the coordination of the National Institute of Infectious Diseases (NIID) for Japan[15], the European Centre for Disease Prevention and Control (ECDC) surveillance database for France[16], and the database provided by theMinistry of Public Health and the Department of Disease Control in Thailand[17] from January 1, 2007, to December 31, 2021. We examined the annual number of cases, and age-grouped cases for each country, with incidence calculated using annual population data from World Bank Open Data[18]. In addition, we examined the number of cases for each prefecture for Japan. We included patients of all ages and genders reported from these national databases that employs notifiable disease surveillance system, and there were no exclusion criteria for this study (Figs. 1 and 2).

We calculated reduction percentages by dividing the number of cases in 2020 and 2021 by the mean number of cases of 2018 and 2019. Geographic heatmaps of reported cases per population 100,000 by prefecture were created by using Excel version 2304 (Microsoft Corporation, Redmond, WA).

Statistical analysis included calculating means and standard deviations using an independent t-test. We used monthly reports of new hepatitis A cases from Thailand, Japan, and France databases. We compared the characteristics between two phases: phase 1, from January 2018 to December 2019 (before COVID-19), and phase 2, from January 2020 to December 2021 (during the COVID-19 pandemic). Statistical significance was

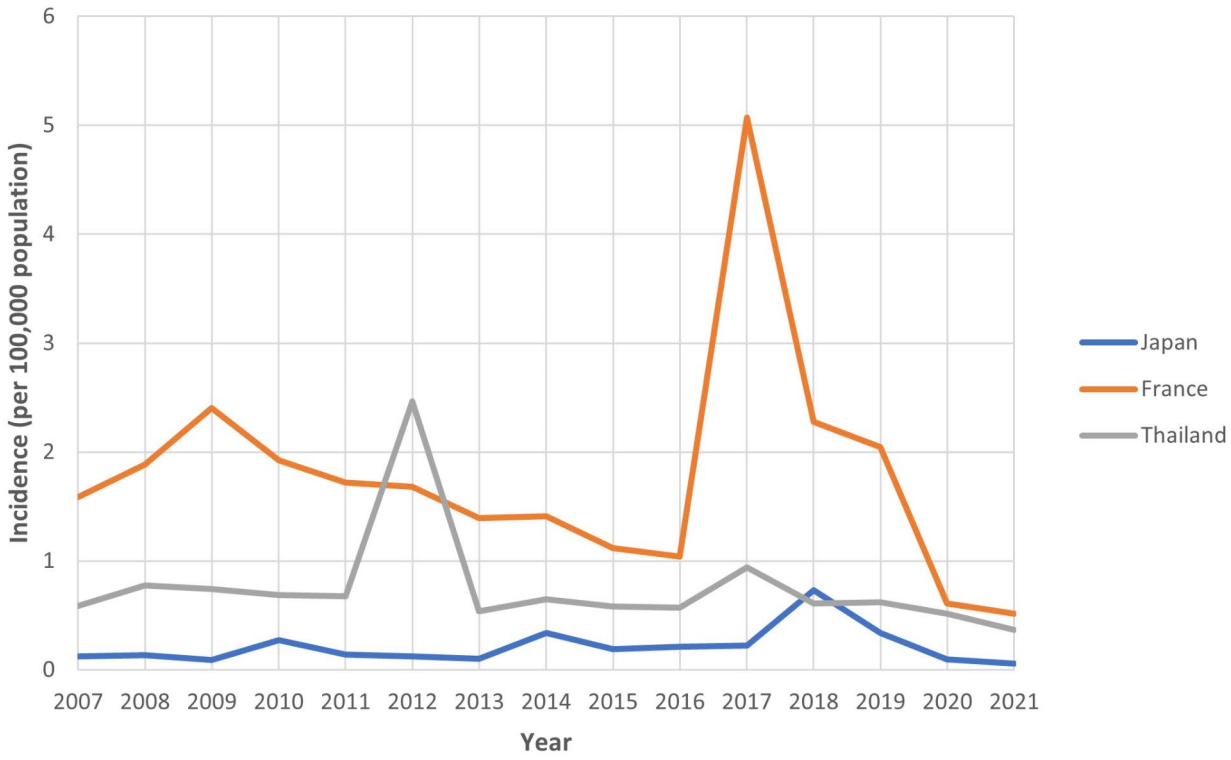

Fig. 1. Incidences of hepatitis A cases in Japan, France, and Thailand from 2007 to 2021. The vertical axis shows the incidence, and the horizontal axis shows the year.

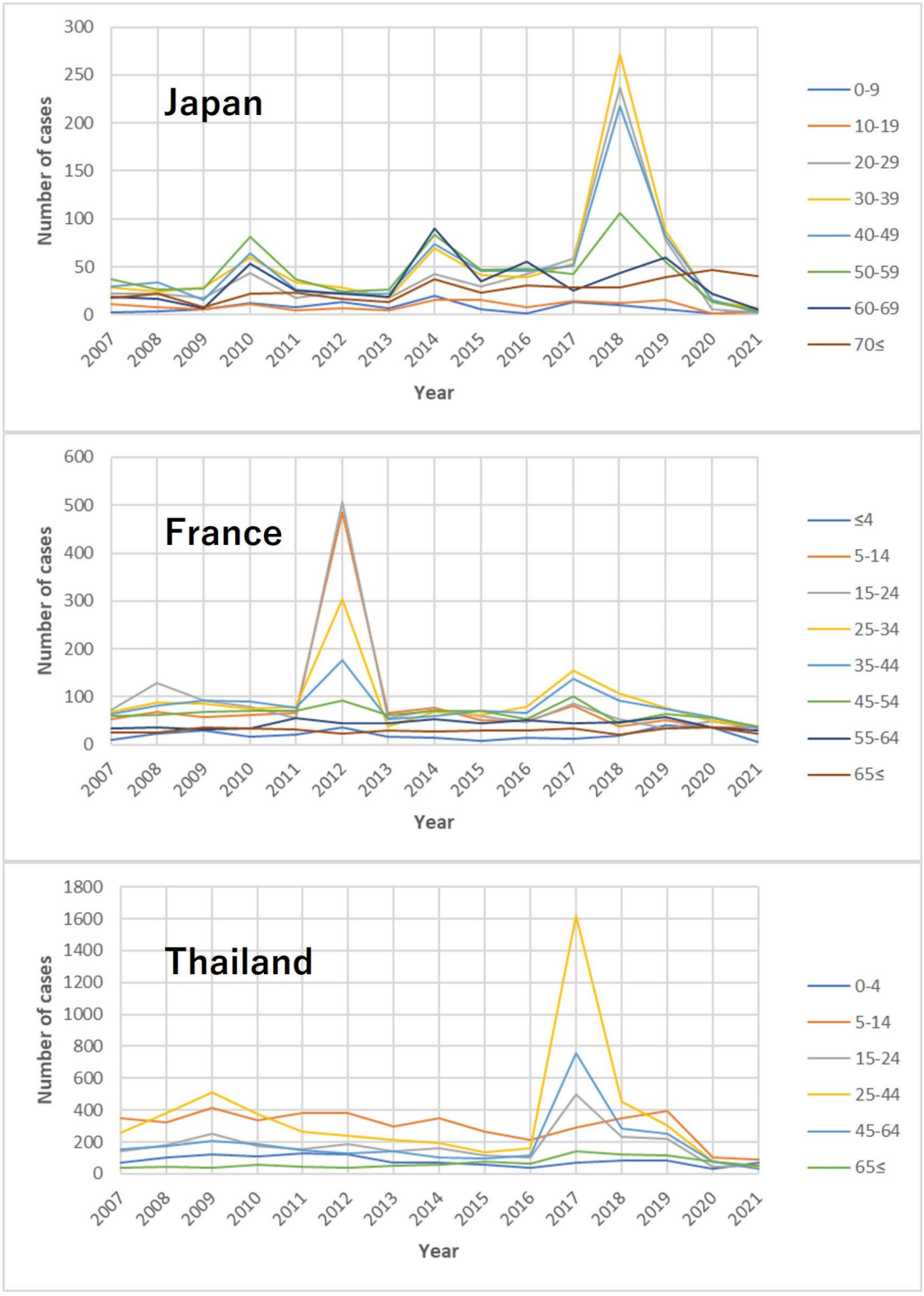

Fig. 2. Number of cases of hepatitis A by age group in Japan, France, and Thailand from 2007 to 2021. The vertical axis shows the number of hepatitis A cases, and the horizontal axis shows the year.

defined as a two-sided P-value < 0.05. All statistical analyses were performed using SPSS for macOS version 29.0.2.0 (20) (IBM Corp., Armonk, NY).

Results

Table 1 shows the number of hepatitis A cases in Japan, France and Thailand from 2018 to 2021 and the reduction percentages for 2020 and 2021. Reduction rate by 2020 was 82.3%, 71.7%, 16.3% respectively, and for 2021 they

Country	2018	2019	2020	2021	Reduction rate by 2020	Reduction rate by 2021
Japan	926	425	120	71	82.3%	89.5%
France	1525	1375	411	337	71.7%	76.8%
Thailand	423	432	358	241	16.3%	43.6%

Table 1. Number of hepatitis A cases in Japan, France, and Thailand from 2018 to 2021 and reduction percentages by 2020 and 2021.

were 89.5%, 76.8%, and 43.6%, respectively.Thailand experienced a decrease in 2021. The decrease in monthly cases after 2021 for Thailand can also be seen in the monthly trends of hepatitis A cases in Fig. 3.

Table 2 shows that the number of newly reported hepatitis A cases significantly decreased in phase 2 compared to phase 1 across all three countries. In Thailand, the mean number of cases significantly decreased from phase 1 to phase 2 (35.63 vs. 24.96, $P<0.001$), as did the numbers for France (120.83 vs. 31.17, $P<0.001$) and Japan (51.96 vs. 6.42, $P<0.001$).

Figure 1 shows hepatitis A cases and incidences in Japan, France, and Thailand. The average hepatitis A incidence per 100,000 population per year from 2007 to 2021 was 0.21 in Japan, 1.79 in France, and 0.75 in Thailand. Epidemic peaks occurred in 2010, 2014, and 2018 in Japan; in 2009 and 2017 in France; and in 2012 and 2017 in Thailand.

Figure 2 shows the age-grouped annual trends of hepatitis A cases for Japan, France, and Thailand. In Japan, individuals aged 20 years or older accounted for the 92.5% of infections in average, with increases in 2010, 2014, and 2018. In France, 28.8% of the total cases were children aged 5 to 14 years, and 8.3% were aged 0 to 4 years and 7.2% were 65 years and older. In Thailand, people aged 5 to 54 years contributed to 79.1% of the infections, with 5 to 24 year age group accounting for 59.5% of the cases in 2012. In Japan, cases increased by 20.5% among those aged 70 years and older in 2020, in contrast to the decrease observed in all age groups in France in the same year. In Thailand, a decrease across all age groups was seen in 2021.

Figure 3 shows the monthly trends of hepatitis A cases and COVID-19 cases from the year 2018 to 2020 for Japan, France, and Thailand. Monthly hepatitis A cases decreased at a time when COVID-19 cases decreased. An increase in the monthly cases were seen throughout 2018 in Japan. The seasonal outbreaks of hepatitis A in France were reported, with the maximum monthly number of cases occurring in September of 2018 and 2019.

All three countries also experienced increases in the number of cases in 2017 or 2018. In Japan, the number of cases among individuals aged 20 to 69 years increased in 2018 by 381% (Fig. 2), accompanied by an increase in monthly cases (Fig. 3). In France, the number of cases among those aged 15 to 64 years increased by 531% in 2017. In Thailand, cases among individuals aged 25 to 54 years increased by 192% in 2017 (Fig. 2).

Hepatitis A prevalence was distributed throughout Japan in 2016 and 2017. In 2018, number of hepatitis A cases per 100,000 population increased by 657% in Tokyo. By 2020 and 2021, average cases per 100,000 population were 0.046 and 0.039, respectively (Fig. 4).

Discussion

This study investigated the hepatitis A trends influenced by food-borne outbreaks and the global MSM pandemic, followed by the impact of the COVID-19 pandemic in Japan, France, and Thailand. Hepatitis A cases significantly decreased in all three countries after the COVID-19 pandemic. In the previous report, the preventive measures during the pandemic, including wearing masks, washing hands, restricting large gatherings or lockdowns, and quarantines were reported to decrease other gastrointestinal infections and STIs worldwide[6,19,20], supporting our results.

The case reduction percentage for Japan was 89.5% by 2021, and was the highest of all three countries, possibly reflecting the high awareness of the pandemic and self-imposed closure and suspension of restaurants and public places without an apparent lockdown during that time (Table 1). While all-age hepatitis A cases in Japan significantly decreased during the COVID-19 pandemic, the incidence for individuals aged 70 years and older remained largely unchanged, while cases in younger groups dropped sharply (Fig. 2). In 2020 and 2021, the older age group accounted for 39.1% and 56.3% of all reported cases, respectively. Further analysis revealed that these older-age cases were clustered in a non-urban prefecture for both years. This relative rise in older adults may appear counterintuitive, given that there is high anti-HAV seroprevalence in older populations due to past exposures[21]. Lockdown measures likely had a stronger effect in densely populated areas[22,23], and considering that all the 7 cases in Toyama prefecture, which had the highest cases for patients aged 70 years or older in 2020, were reported within a specific week[24], we suspect that these relative increases in cases compared to the normal population during 2020 and 2021 may be unrelated to the COVID-19 pandemic.

Between 2016 and 2019 in Japan, hepatitis A infection was predominantly seen in metropolitan Tokyo and some seaside prefectures, likely reflecting high seafood consumption. In 2018, during the MSM-related increase, Tokyo experienced a marked surge in cases. In 2020 and 2021, however, COVID-19 had a strong suppressive effect on infections in metropolitan areas, as well as in most other prefectures, which likely contributed to the overall decrease (Fig. 4).

France recorded the highest average incidence of hepatitis A, an unexpected finding given that developed countries generally show lower incidence due to better hygiene and public health measures. Unique monthly trends of cases peaking in September in both 2018 and 2019 can be seen. One explanation may lie in the Schengen Agreement, which allows European Union residents to travel among EU countries without border checks, leading to a great increase in the number of tourists going in and out of France[25]. Along with France's

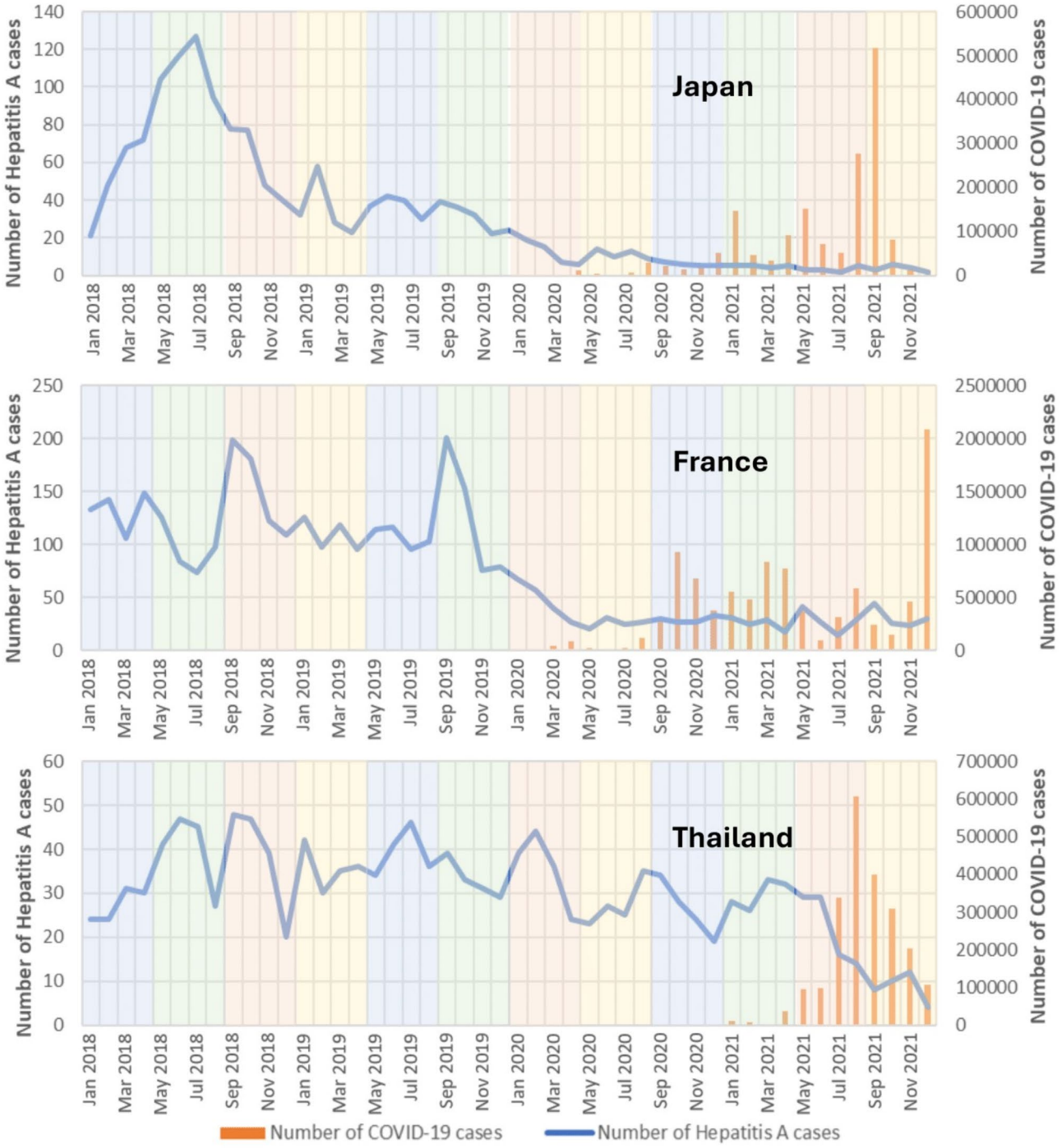

Fig. 3. Monthly trends in the number of hepatitis A and COVID-19 cases in Japan, France, and Thailand from 2018 to 2021. The line graph shows the monthly trend of hepatitis A cases, and the bar graph shows the monthly number of COVID-19 cases. The horizontal axis shows the year.

relatively long legislated annual leave[26], families may have visited regions with higher hepatitis A prevalence in the summer breaks, and then spread the infection in schools or workplaces upon returning in September (Fig. 3).

Sporadic foodborne outbreaks have been documented worldwide over the past two decades. In Japan, a sudden rise in 2010 led to 236 reported cases, including 58 linked to contaminated oysters from Hiroshima, a major oyster-harvesting region[27,28]. Another outbreak in 2014 involved 421 cases, primarily affecting individuals aged 30–69, with 275 out of the 342 cases (80.5%) reported by week 22 related to contaminated seafood or water[29]. That same year, a single case of Guillain-Barré following hepatitis A was documented in a 44-year-old woman in coastal Hiroshima[30]. In France, a smaller outbreak in 2009 affected 59 cases, traced to semi-dried tomatoes imported from Turkey, representing a rare example of imported non-seafood foodborne hepatitis A[31].

Country	Phase 1 Mean (SD)	Phase 2 Mean (SD)	*p*-value	95% Confidence interval
Japan	51.96 (31.07)	6.42 (4.43)	< 0.001	[33.18, 57.90]
France	120.83 (35.56)	31.17 (11.74)	< 0.001	[74.28, 105.05]
Thailand	35.63 (8.02)	24.96 (10.20)	< 0.001	[5.335, 15.998]

Table 2. Mean and SD of hepatitis A cases in phase 1 (before COVID-19), phase 2 (after COVID-19) and the comparison by each phase.

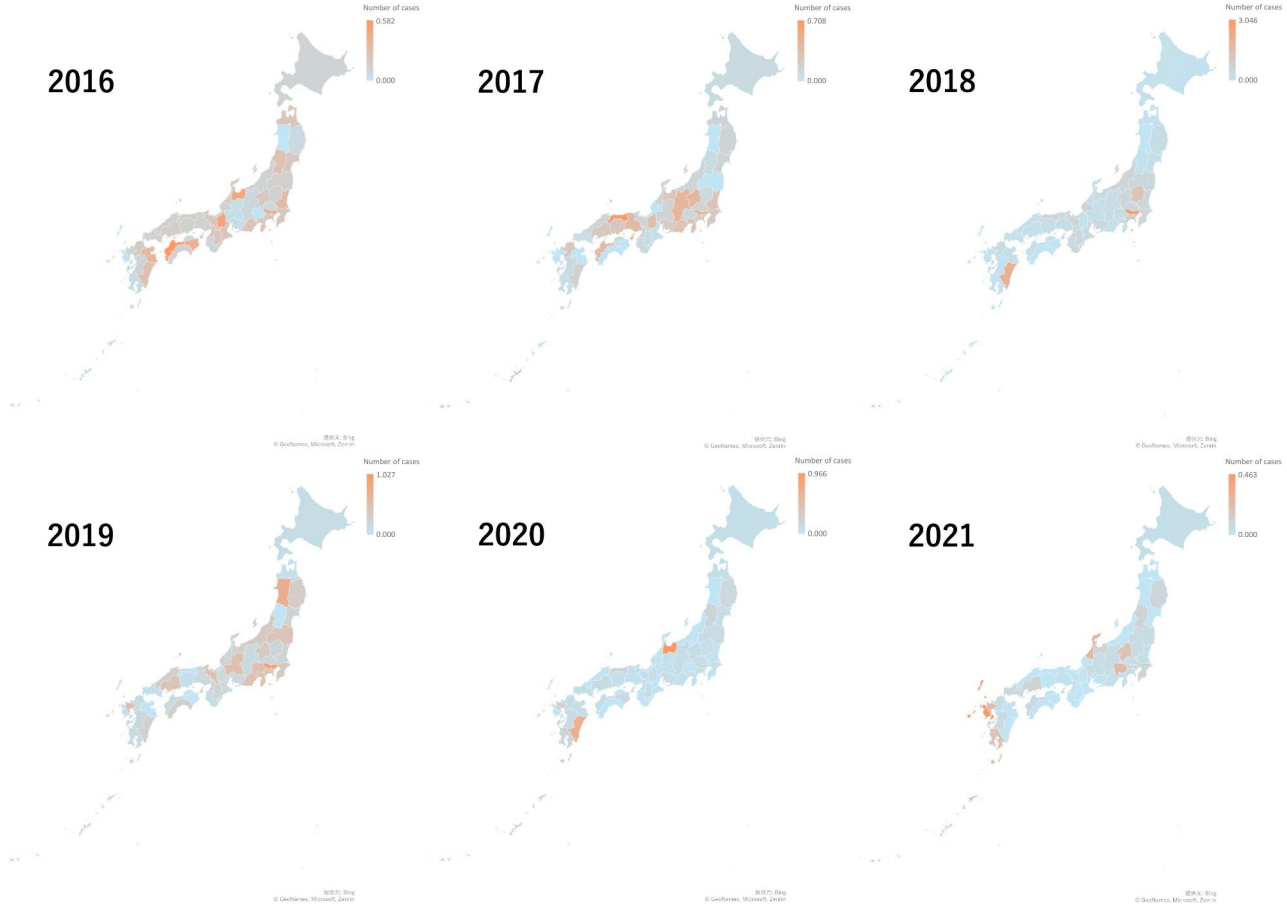

Fig. 4. Heatmap of hepatitis A cases per 100,000 population for each prefecture in Japan from 2016 to 2021.

Thailand experienced an unique outbreak in 2012 when a contaminated ice factory in Bueng-Kan Province resulted in 1,619 cases, predominantly among children and adolescents[32].

A recent global surge of hepatitis A among Men who have Sex with Men (MSM) also affected Japan, France, and Thailand (Fig. 1). In 2017, a hepatitis A pandemic swept through European countries, originating from an outbreak in the Netherlands, during the EuroPride festival in Amsterdam in August 2016. A subsequent surge in hepatitis A cases was seen in nearby European countries such as the United Kingdom, Germany, and Italy[33,34]. In addition, another lesbian, gay, bisexual, and transgender (LGBT) festival was held in Madrid, Spain in June 2017, which also have exacerbated the ongoing spread[35].

In Japan, the proportion of sexually transmitted cases increased sharply from 4 to 53% in 2018, while food-borne transmission dropped from 74 to 38%. Genomic analysis showed that within the 1 A strain, which accounted for 98% of the cases in 2018, 90% cases matched the EuroPride strain (RIVM-HAV16-090), indicating a clear strong link with the European Outbreak[36]. Historically, multiple outbreaks of hepatitis A in the MSM population had been reported around the world, whereas Japan had only a single MSM-related outbreak in 1999, underscoring how the 2018 event signifies a new high-risk pattern[37], and Tokyo metropolitan area saw an pronounced increase in cases (Fig. 4), suggesting an MSM outbreak in the metropolitan and dense areas where many people gather frequently. Similarly, France recorded a five-fold increase in 2017 (Fig. 1), with approximately half of the 885 analyzed cases linked to the Spanish MSM outbreak (56%) and the remainder to the EuroPride strain (41%). An outbreak report regarding hepatitis A outbreak in the HIV-infected MSM population further supports the linkage[38]. In Thailand, cases nearly doubled in 2017 (Fig. 1). In Bangkok, Thailand, a high prevalence of hepatitis

A infection was observed among MSM, with a history of hepatitis A reported as an independent predictor of HIV infection, indicating a link between hepatitis A and sexual activity in this population[39,40]. Between March and May 2017, five acute hepatitis A cases were identified among participants in a hepatitis A cohort among men with history of HIV infection, and serological analysis showed concurrence with the Netherlands strain[32].

Limitations

The present study has some limitations. First, the present study was based on data from national databases, and there were different age groupings among the different databases. Since the difference was about 5 years, it would not have had a major impact on the analysis. Second, it was not possible to obtain in-depth information on the hepatitis A vaccination percentage for each country, although it greatly affects the epidemiology of the infection. Third, the geographic data analysis was available only in Japan, not in Thailand and France; thus, the geographic characteristics in Thailand and France are not clear. Fourth, there were no concrete data on the extent to which hepatitis A testing is possible in each country. In each country, local medical institutions may not be conducting sufficient evaluations.

Conclusion

There were aspects of both gastrointestinal infections and STIs in the baseline, with the MSM pandemic heavily affecting the trends in 2017–2018. France had the highest average incidence of hepatitis A, showing that a developed country can have a higher incidence of hepatitis A infection. The location of outbreaks differed depending on the route of transmission in Japan, with STIs more prevalent in urban areas and intestinal infections in coastal areas. Lastly, the number of cases for all three countries have significantly decreased during the COVID-19 pandemic. These findings suggest the overall correlation of hepatitis A with population activity, and underline the importance of targeted interventions for high-risk populations. Further research is needed to understand and predict future global hepatitis A epidemics.

KM conceived of and designed this study, interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. HM conceived and designed this study, interpreted the data, and revised the manuscript for important intellectual content. DK and DR conducted the statistical analysis. AM, RP, SV and YH conceived this study and revised the manuscript for important intellectual content. TN conceived this study and revised the manuscript for important intellectual content. All authors contributed to the acquisition of data, and reviewed, discussed, and approved the final manuscript.

Data availability

The datasets generated and/or analyzed during the current study are available. https://www.niid.go.jp/niid/ja/idwr.html, http://doe.moph.go.th/surdata/disease.php? dcontent=old&ds=11, https://atlas.ecdc.europa.eu/public/index.aspx? Dataset=27&HealthTopic=25.

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Author contributions

"KM conceived of and designed this study, interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. HM conceived and designed this study, interpreted the data, and revised the manuscript for important intellectual content. DK and DR conducted the statistical analysis. AM, RP, SV and YH conceived this study and revised the manuscript for important intellectual content. TN conceived this study and revised the manuscript for important intellectual content. All authors contributed to the acquisition of data, and reviewed, discussed, and approved the final manuscript."

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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