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Original Article

In 2011, after the end of the 2009 new influenza epidemic, four diseases, Kawasaki disease (KD), hand-foot-and-mouth disease, erythema infectiosum, and aseptic meningitis, occurred simultaneously in Tokyo, but in 2024, after the COVID-19 pandemic ended, the incidence of KD was suppressed by the outbreak of Mycoplasma pneumoniae, resulting in the simultaneous occurrence of three diseases other than KD

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Abbreviations
Kawasaki disease: KD, Hand-foot-and-mouth disease: HFMD, Erythema infectiosum: EI, Aseptic meningitis: AM, Mycoplasma pneumoniae: MP, pollen exposure: PE

Abstract

Following the largest number of seasonal flu cases ever occurred in Tokyo, the new influenza AH1pdm09 pandemic that broke out in Mexico also happened in the summer and fall of 2009 and ended without seasonal flu outbreak in the spring of 2010. The year 2011, after the end of the 2009 new influenza pandemic, was the second highest pollen dispersal year in the history of Tokyo, when the number of cases of Kawasaki disease (KD), hand-foot-and-mouth disease (HFMD), erythema infectiosum (EI), and aseptic meningitis (AM) per sentinel increased simultaneously. The year 2013 was the fourth highest pollen dispersal year in history, followed by an increase in KD, HFMD, and AM, but a decrease in EI. However, in the first half of 2015, EI was very prevalent. In 2018, when the third highest pollen dispersal in history occurred, the number of patients affected by KD was the largest ever and the prevalence of EI was significant, while the extent of HFMD and AM cases was moderate. The COVID-19 pandemic began in early 2020 and the epidemic lasted for several years, with a low point in the 40 weeks of 2023. Ninety percent of the pollen from 2023, the fifth highest pollen dispersal year in history, also flew in 2024, making 2023-2024 the two consecutive year of high pollen counts, when the number of KD patients in week 22, 2024 exceeded the number of patients in 2018. The increase in the number of KD patients in the phase of the annual fall/winter period, which began around October, has been suppressed by the impact of the sudden increase in the number of patients with Mycoplasma pneumonia, which has been sustained and increased. A sudden increase in the number of AM patients occurred in a few weeks during this period. HFMD was also marked by an increase in the number of affected patients along with EI, and unusually began to increase again at week 34 and began to decrease at week 42. EI still continues to increase at week 48. In 2024, after the COVID-19 pandemic ended, the incidence of KD was suppressed by the Mycoplasma epidemic, and three diseases other than KD became prevalent simultaneously, and the simultaneous outbreaks of the four diseases observed in 2011 after the end of the H1N1 influenza did not recur.

Introduction

The COVID-19 pandemic began in Japan at the beginning of 2020 and ended in the early fall of 2023. The number of fixed-point reports of Kawasaki disease in Tokyo before and after the COVID-19 epidemic was reported as 214 in 2018, 150 in 2019, 131 in 2020, 168 in 2021, 93 in 2022, 166 in 2023, and 172 for up to 51 weeks in 2024 [1]. The authors have focused on the association between the dynamics of KD incidence and changes in airborne pollen counts since the 1970s and found a statistically significant correlation between the two at the

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beginning of 2003, which was reported in the same year [2-5]. In parallel with KD, the authors were interested in the dynamics of the incidence of HFMD [6], EI [7], and AM [8], which are considered to be infections caused by summer cold viruses that affect a high percentage of children, by looking at weekly reports of infectious diseases. In September 2017 the author described an editorial in the journal YAKUJINIPPO Pharmaceutical Daily [9] arguing for the significance of conducting a prospective comparative study for about 5 years in which a group of KD sufferers is divided into two groups: one group that implements efforts to prevent pollen exposure as much as possible through daily lifestyle practices such as wearing masks and goggles and installing air purifiers to control and prevent recurrence of the disease, and a group that is exposed to pollen exposure unchecked. In order to discuss the association of pollen exposure with the development of KD, HFMD, EI, and AM, which had already been mentioned in the conference presentation, we had provided the status of the incidence dynamics of these four diseases in Tokyo until 2016 (Figure 1). Since then, the authors have continued with epidemiological reports discussing the possibility that pollen exposure is a triggering factor in the development of designated incurable diseases [10-13] and cancer and malignant tumors [14-17]. In this report, we report the results of our close observation of the trends of these four diseases, as the increase in the number of patients with KD, HFMD, and EI among these four diseases has been conspicuous since around 19 weeks in 2024, and the incidence of AM has been higher than in previous years. Furthermore, we report on the relationship between Mycoplasma pneumonia and the above four diseases (especially the trends in the incidence of KD), given the parallel outbreaks of Mycoplasma pneumonia during this period in 2024. The number of KD cases in the Tokyo Metropolitan Fixed-Point Weekly Report [1] for 2024 tended to be higher than in early spring, and as of week 22, the number of cases was 2 more than the number in Tokyo in week 22 of 2018 (Figure 2), when the number of cases was the largest ever in the national survey of KD [18].

We assumed the possibility of a second peak in the bimodal onset of KD incidence that appears every year in the spring/summer season (March-August) when large amounts of pollen are dispersed, and in the fall/winter season (September-December) when a small amount of cedar pollen is dispersed first [3-4]. If this happens, I feared that the number of patients would exceed that of 2018. We also thought that after the summer of 2024, it is important to practice and maintain lifestyle habits such as wearing masks and goggles on a daily basis and installing air purifiers for family members who have allergic tendencies. Furthermore, the increase in the number of patients with designated incurable diseases and cancers and malignancies was also a concern.

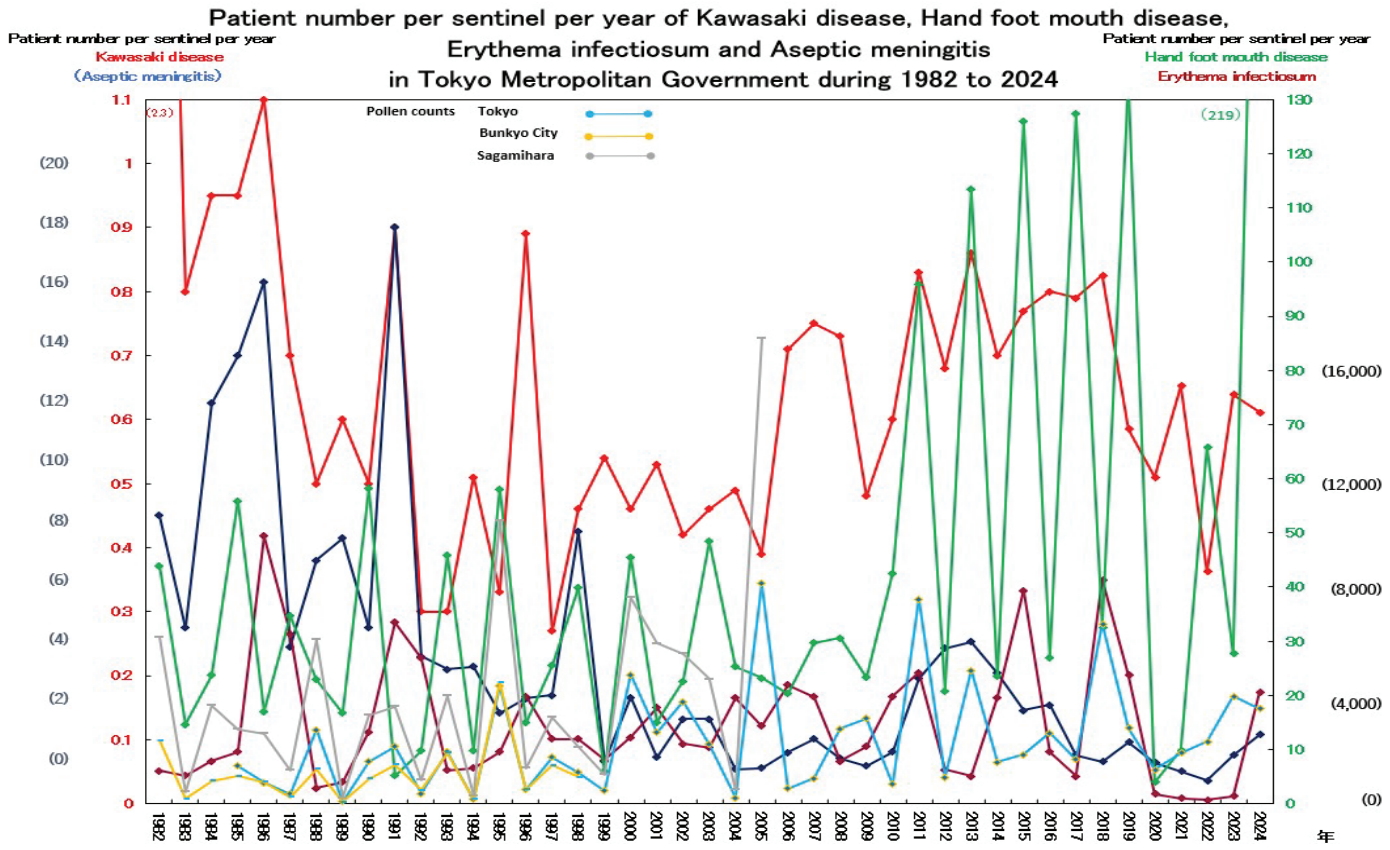

Figure 1. *Patient number per sentinel per year of Kawasaki disease, Hand-foot-and-mouth disease, Erythema infectiosum and Aseptic meningitis in Tokyo Metropolitan Government during 1982 to 2024.*

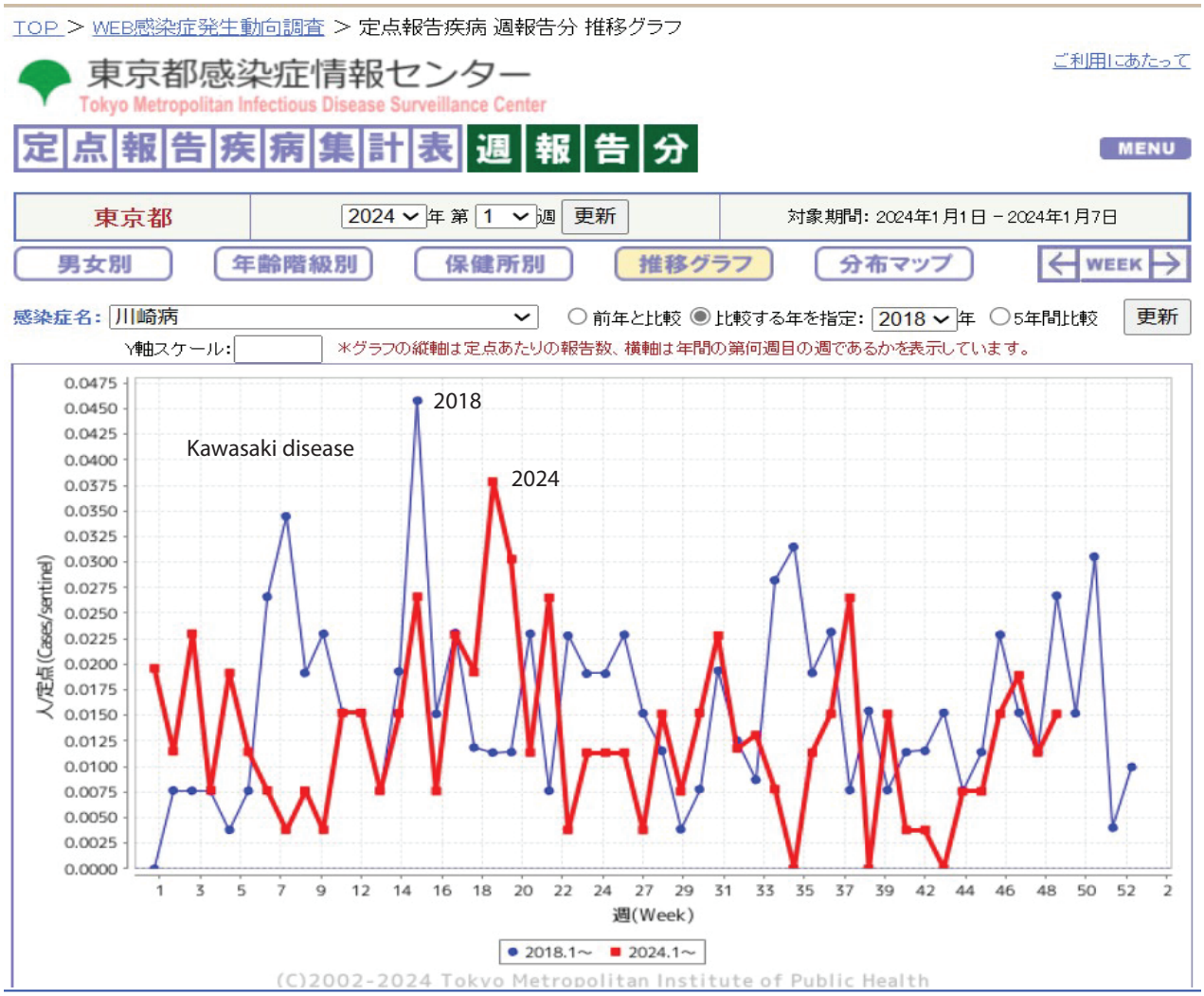

Figure 2. *Patient number per sentinel per week of Kawasaki disease in Tokyo in 2018 and 2024. Dark blue line:2018. Red line:2024.*

Materials & Methods

The authors investigated the latest disease incidence trends based on weekly fixed-point sentinel reports from the Tokyo Metropolitan Infectious Disease Surveillance Center. The number of cases per fixed point for each disease each year, i.e., KD, HFMD, EI (264 sites above), AM, and Mycoplasma pneumoniae (25 sites above), was calculated by multiplying the total number of cases reported annually by 52 or 53(weeks) and dividing by the total number of reports each week. In 2024, the number of incidence cases up to 47 weeks was examined and the incidence dynamics were graphed. The figure plots the pollen counts averaged from the total number of flying pollen at the 12 locations listed in the Tokyo Metropolitan Government's report. Pollen dispersal counts in Bunkyo City, Tokyo and Sagamihara City, Kanagawa, are also shown in the graph for reference. The number of cedar and cypress pollen dispersed each year in Tokyo is shown below (unit: pcs/cm2/season). 2011: 15,112 (second highest in history); 2013: 9851 (fourth highest in history); 2014: 3,077; 2015: 3,637; 2018: 13,260 (third highest history); 2019: 5,572; 2022, 2023: 7,935 (fifth highest in history); 2024: 7,004 (sixth highest in history) [18].

Results

Although 2024 is reported midway through the 49-week period (Figure 2), the results suggest that the second peak of onset after October 2024 to January 2025, which has been observed in previous years for KD, may be suppressed or the peak may shift to the period after the end of 2024 to January or February of 2025. In 2024, unlike the KD incidence trend in 2018, the number of KD patients remained at low level (0,4,1,1,0,2,2 at from 39w to 45w) during the period of KD increase starting in October, and the number of outbreaks at fixed locations finally started to appear around week 46 (Figure 2). Surprisingly, during this period, the number of patients with Mycoplasma pneumonia grew in contrast to KD, although that in 2018 remained low throughout the year (Figure 3). Along with this, there was a noticeable spike in the number of cases of aseptic meningitis from week 35 of 2024, as if one might imagine that it was occurring instead of KD onset, and the spike in week 41 was also remarkable. The incidence of EI continued a sustained trend without a decrease, with a sharp increase afterward from week 34 to week 51. The number of HFMD cases also continued to increase, once declining at week 29, then increasing again at

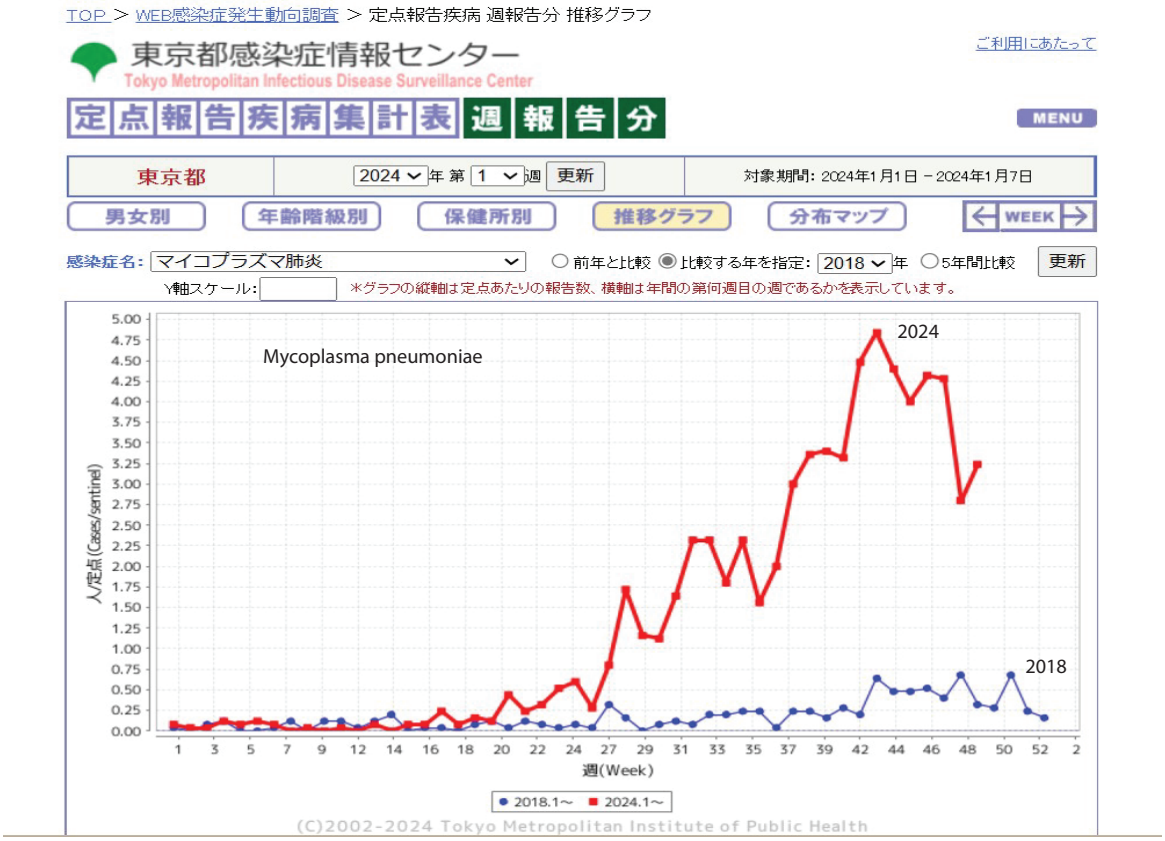

Figure 3. *Patient number per sentinel per week of Mycoplasma pneumoniae in Tokyo in 2018 and 2024. Dark blue line:2018. Red line:2024.*

week 34, and finally declining from week 42. The incidence of KD during the COVID-19 pandemic period from 2020 to early fall 2023 is trending downward from 59.5% to 64.3% according to a national survey [19]. During the COVID-19 pandemic, EI showed little incidence, as did seasonal influenza, while HFMD showed some incidence in summer 2022.

Discussion

Following the seasonal flu pandemic, the new influenza pandemic broke out in Mexico in the summer and fall of 2009 and ended in Tokyo in the spring of 2010. In 2011, after the end of the 2009 new influenza pandemic, the number of cases of four diseases (KD, HFMD, EI, and AM) increased simultaneously, as shown in Figure 1, while the extent of patients with Mycoplasma pneumoniae was moderate. A multiple epidemic of KD, HFMD, and AM occurred in 2013, while a simultaneous epidemic of KD, EI, and AM occurred in 2015.

In 2024, after the COVID-19 pandemic ended, the incidence of KD was suppressed by the Mycoplasma epidemic, and three diseases other than KD became prevalent simultaneously. The authors have argued that KD is assumed to be a type 4 allergic disease caused by pollen exposure with BCG site inflammation [3-5]. The authors have also assumed that AM, HFMD, and EI are diseases that are prevalent during the summer months, when infants and children exposed to pollen become compromised hosts, become easily infected, and catch summer cold viruses. So, I talked about the above hypothesis at the meeting of The Japanese Society of KD, the Japanese Society of Clinical Immunology and Japanese Society of Allergology at the time of 2017, and wrote a related preliminarily discussion, with the first graph in Figure 1 until 2016, in the YAKUJINIPPO Pharmaceutical Daily article [9]. The suppression of the development of KD by an epidemic of Mycoplasma pneumonia may be occurring by a similar mechanism to the phenomenon of seasonal influenza suppressing the development of KD [5]. As the author reported in 2016 [8], seasonal influenza, which is prevalent around February, induces IFN-β, and suppresses the development of KD in children with subclinical infection. We presume that KD development could be also suppressed by the Mycoplasma pneumoniae epidemic by a similar mechanism. In fact, the finding that Mycoplasma induces IFN-β has been reported [20]. It is also possible that aseptic meningitis may be a biological reaction occurring instead of KD. We cannot rule out the possibility that the fall/winter onset of KD is reduced as a result. The trend of simultaneous outbreaks of the three diseases in 2024 after the COVID-19 pandemic needs further investigation to determine whether it is a phenomenon that will continue, a coincidental phenomenon, a phenomenon caused by the suppression of KD due to the newly added Mycoplasma, or an underlying individual difference in pollen exposure responsiveness. Although there have not been many outbreaks of HFMD and EI in the same year in the past, it is desirable to explore new concepts and parameters to determine whether it is safe to assume that in both outbreaks, individuals are only susceptible to infection, without developing severe KD.

The expansion of the Mycoplasma pneumonia epidemic, as well as the seasonal influenza epidemic suppressed the incidence of second peak KD in infants and other children during this year's fall/winter season [5] (Figure 4), and instead increased the number of HFMD, EI, and AM cases (Figure 5).

We have demonstrated, even by statistical analysis [3-4],

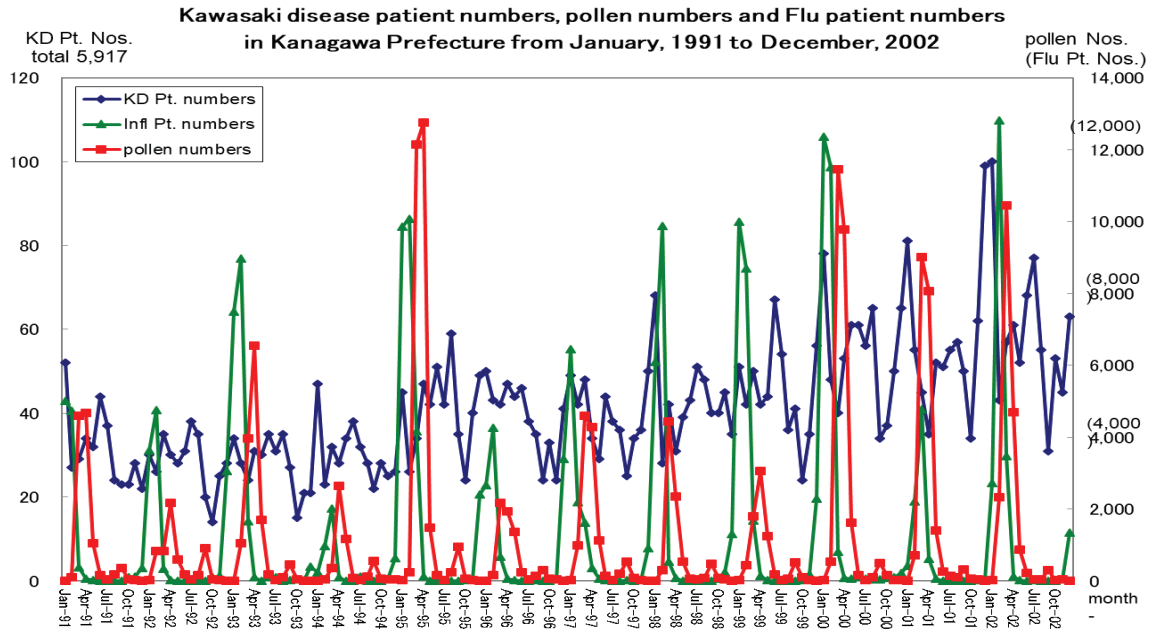

Figure 4. *The number of Kawasaki disease (KD) and influenza patients and pollens in Kanagawa from January 1991 to December 2002. Monthly variations in the number of patients with KD and influenza, and pollens in Kanagawa are shown. The number of KD patients around in February was shown by also analysis to decrease every year.*

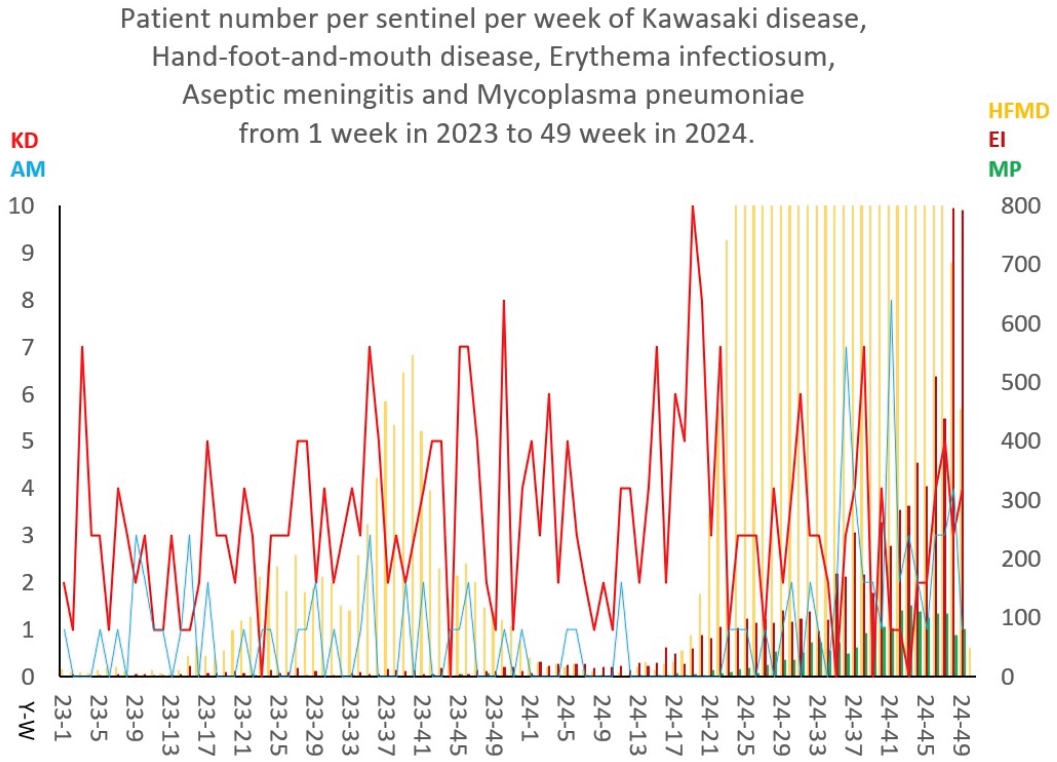

Figure 5. *Patient number per sentinel per week of Kawasaki disease, HFMD, Erythema infectiosum, Aseptic meningitis and Mycoplasma pneumoniae from from 1 week in 2023 to 49 week in 2024.*

Line graph of KD is shown with red. That of Aseptic meningitis (AM) is shown with blue. Bar graph of HFMD is shown with yellow orange. That of EI is shown with dark red. That of Mycoplasma pneumoniae PM is shown with green. The biggest No. of KD was 10 per 264 sentinels at 19 week in 2024. The biggest No. of AM was 8 per 25 sentinels at 41 week in 2024. The biggest No. of HFMD was 4,326 in the former peak at 28 week and that was 3,243 in the latter peak, each per 264 sentinels in 2024. The biggest No. of EI was 801 per 264 sentinels at 51 week in 2024. The biggest No. of MP was 121 per 264 sentinels at 43 week in 2024. On Dec.19 and Dec.26, sentinel data at 50 and 51 week were open to public at 16 hr. Nos of KD:0 and 5, AM:2 and 0, HFMD:277 and 170, EI:749 and 801, MP:63 and 47 were recorded here.

that the annual biphasic peak of KD onset is caused by pollen exposure due to the large amount of pollen dispersal in spring and after a heat wave the small amount of cedar pollen with booster effect that occurs in September to December forerunningly before next spring. We have believed, as described above that infants and children become compromised hosts and are more susceptible to infectious diseases such as HFMD, EI, and AM.

These three diseases generally have a high number of patients in the summer, but unusually for HFMD, there was a second peak in the number of patients in the fall after the summer peak. This is assumed to be the result of a Mycoplasma pneumonia outbreak in which subclinically infected infants escaped developing KD and other diseases, became compromised hosts, and became susceptible to HFMD (Figure 5). It is also assumed that the high number of patients affected in November and December 2024 for EI and AM may also be related to the suppression of KD incidence due to the Mycoplasma pneumonia epidemic (Figure 5).

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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