Epidemiological Reports


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SUMMARY: Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract illness in infants and young children. In Japan, surveillance for RSV infection started in 2003 based on approximately 3,000 pediatric sentinel sites. In recent years, RSV notifications have increased, but the interpretation of trends has been challenging due to a suspected increase in testing frequency and the expansion of the insurance coverage for RSV testing to include certain outpatients in late 2011. Therefore, we evaluated RSV surveillance data during 2008–2015, considering the number of sites that reported at least one RSV case during a surveillance year and restricting to sites that had continuous reporting status since 2008. While annual RSV notifications had increased, the number of sites reporting also increased. And the same magnitude of increase was not observed when the number of cases reported was restricted to the 1,372 sites that had continuous reporting status since 2008. Additionally, in the year following the insurance expansion, RSV notifications increased more remarkably for clinics than for hospitals. These results suggested that some of the recent increases in notifications might be due to an increase in testing frequency.

INTRODUCTION

Respiratory syncytial virus (RSV) is one of the leading causes of hospitalization in infants (1,2). It is a highly common virus, with nearly 100% of children acquiring a primary infection by the second year of life (3). It can cause serious respiratory illness, such as pneumonia or bronchiolitis, and cause death in high-risk populations such as infants who are immunocompromised or have cardiovascular disorders (4). To reduce such disease burden and mortality, a better understanding of the epidemiology of RSV is needed. Understanding temporal patterns such as annual disease trends and seasonality, for example, can facilitate risk communication and preparedness for clinicians.

To monitor and assess RSV incidence in pediatric populations, Japan initiated surveillance for RSV in 2003, in compliance with the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases (the Infectious Diseases Control Law). As RSV infection is known as a seasonal respiratory illness occurring every year with high frequency among the young, surveillance is sentinel-based. Approximately 3,000 sentinel pediatric hospitals and clinics across Japan report the number of laboratory-confirmed RSV cases (including those positive by rapid test kit results) to local public health centers on a weekly basis (5,6). In recent years, RSV has drawn much attention in Japan with an increasing number of reported cases (Fig. 1). However, it has been difficult to interpret the surveillance data as a measure of incidence to assess temporal trends. One reason is that each year, the number of sentinel sites that have reported at least one RSV case has also been increasing (7). This could indicate a true increase in incidence but also an artefactual increase due to the increasing capability in testing for RSV (resulting in the increased number of reporting sites), as laboratory diagnosis is required for reporting (7). Although only approximately 50% of the sentinel sites had reported an RSV case in 2007 (7), some sites may not have reported at the time because they simply lacked the ability to test for RSV. Another concern is that the national health insurance policy was recently changed—laboratory tests for RSV for certain outpatients (those 24 months of age or younger for whom palivizumab is indicated and those younger than 12 months of age) became covered by national insurance in October 2011 (7). In fact, in 2012, RSV notifications from outpatient clinics increased (7). Thus, these diagnostic and secular aspects—potential surveillance biases—should not be ignored when interpreting RSV surveillance data in Japan. Based on this background, we undertook an epidemiologic assessment of the recent RSV surveillance data, considering the potential increase in the number of sites capable of testing for RSV and the change in the insurance policy.

MATERIALS AND METHODS

We extracted the weekly number of reported RSV cases from sentinel sites from the National Epidemiological Surveillance for Infectious Diseases (NESID) system, the national electronic system for infectious disease surveillance. Data were from 2008 to 2015; while data from 2003 are available, the first 5 years after RSV surveillance began were unstable with limited reporting and were therefore excluded.

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Previously, RSV activity in Japan has been reported to begin in the fall, peaking in winter, and ending in early spring (7). Every year in Japan, comprehensive feedback of national influenza activity starts in week 36 (8), indicating the start of the influenza surveillance year. However, as there is no established starting week for RSV, we first examined the distribution of RSV notifications during the years 2008–2014 and, for each year, determined the week with the lowest number of cases. Among these weeks (range: week 22–28), the median week (week 24) was set as the starting week for the RSV surveillance year, lasting until week 23 of the following year, for a cumulative period of 52 weeks. As 2009 included week 53, the 2009/10 surveillance year was defined as weeks 24–53 in 2009 and weeks 1–22 in 2010.

In order to systematically assess the surveillance data, we applied the standard epidemiologic methods of i) restriction and ii) stratification (9–12). For i), we assessed the annual trends based on a restricted segment of the reporting units, i.e., 1,372 sentinel sites that reported at least one case in the 2008/09 RSV surveillance year and have been registered with continuous reporting status through the 2014/15 RSV surveillance year (hereafter referred to as “continuously reporting sites”). The restriction was performed in order to remove the bias associated with the temporal changes in the ability to conduct RSV testing. As these sites had reported in 2008/09, they should already have had the ability to perform a test for RSV then, and would likely be less affected by such bias; this restricted analysis would not be affected by an increase in the number of sites that become capable of such testing over time. For ii), we stratified the reporting units by the type of facility (hospital or clinic) among these continuously reporting sites—as the insurance coverage for RSV testing expanded to outpatients in late 2011, we assessed if this secular change had any differential influence on hospitals vs. clinics. We presumed a priori that any bias associated with this policy change would affect clinics more than hospitals, as the former only serves outpatients (while the proportion of outpatients among cases reported by hospitals is unknown, outpatients are the majority at clinics). Importantly, as this stratification was restricted to the continuously reporting sites, any increase in reports after the insurance change would be independent of that which could be explained by an increase in sites able to perform RSV testing.

Based on the above restriction and stratification approaches, we described the annual trends based on absolute counts of notifications and also assessed notification trends over time using regression methods. As an additional assessment utilizing a non-surveillance data source, we extracted annual infectious disease-attributed death data from e-Stat (13), the Portal Site of Official Statistics of Japan, to assess the annual number of deaths based on calendar year attributed to RSV infection in Japan. We hypothesized that all else being equal, an increase in ascertainment over time would result in a decrease in the ratio of the number of RSV-associated fatalities to the number of reported RSV cases.

Data were analyzed using Microsoft Excel 2013 and STATA version 10.0.

RESULTS

The number of sentinel sites reporting at least one RSV case during the RSV surveillance year showed an increasing yearly trend, from 1,638 (52%) in 2008/09 to 2,632 (80%) in 2014/15 (Table 1). Excluding the 2009/10 year, the total number of RSV notifications increased steadily every year (Fig. 2A). Among the 1,372 continuously reporting sites (Fig. 2B), the magnitude of yearly increases in notifications was considerably lower than the trend ob-
served for the total number of reported cases (Fig. 2B vs. Fig. 2A). 2014/15 saw a 2.2-fold increase since 2008/09 for the total number of reported cases (Fig. 2A) but a 1.6-fold increase for the continuously reporting sites (Fig. 2B). Based on the generalized linear model (Poisson distributional family and identity link function), we fit a linear regression to both the total number of reported cases and to those from continuously reporting sites, and the respective beta coefficients were 9,409 (95% confidence interval 9,308–9,509) and 3,539 (95% confidence interval 3,452–3,625). Among the continuously reporting sites, the ratio of cases reported from outpatient clinics to hospitals increased over time, from 1.3 in 2008/09 to 1.8 in 2014/15 (Fig. 3).

The 2011/12 surveillance year saw the largest increase in the number of reporting sites relative to the previous year (1.2-fold increase from 1,936 to 2,301 sites) (Table 1). During this period, the total number of RSV notifications also increased 1.2-fold (from 59,177 to 71,422 cases), but for continuously reporting sites, the increase was 1.1-fold, from 45,071 to 50,149 cases. When the distribution of notifications per reporting site for 2011/12 was assessed, we found an increase in the proportion of sites that reported fewer cases. While the overall number of cases reported per sentinel site was 30.6 cases in 2010/11, among sites that began reporting in 2011/12 there were 8.4 cases per sentinel compared to 34.8 cases per sentinel among those that had reported

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<tr>
<td>Sites that reported ≥ one RSV case, N (%)</td>
<td>1,638 (52)</td>
<td>1,834 (56)</td>
<td>1,936 (58)</td>
<td>2,301 (71)</td>
<td>2,521 (77)</td>
<td>2,523 (77)</td>
<td>2,632 (80)</td>
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<td>Total number of registered sentinel sites</td>
<td>3,169</td>
<td>3,232</td>
<td>3,314</td>
<td>3,250</td>
<td>3,281</td>
<td>3,262</td>
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![Fig. 2](image1.png) Notifications of RSV cases by surveillance year based on (A) total number of reported cases, (B) reported number of cases restricted to 1,372 sites that reported at least one case in the 2008/09 RSV surveillance year and have been registered with continuous reporting status thereafter.

![Fig. 3](image2.png) Notifications of RSV cases by surveillance year based on reported number of cases from outpatient clinics (square) and hospitals (triangle) among the 1,372 continuously reporting sites.
cases in the previous year. The proportion of sites which reported fewer than 10 cases per year was 75% (244/325) for sites which began reporting in 2011/12 compared to 32% (625/1,976) for those that had reported cases previously.

In 2012/13, on the other hand, relative to 2011/12, although the increase in the number of reporting sites was smaller (a 1.1-fold increase from 2,301 to 2,525 sites) (Table 1), there was a 1.3-fold increase for both the total number of notifications (from 71,422 to 95,285) and for notifications from continuously reporting sites (from 50,149 to 63,169 cases) (Fig. 2A and 2B). Among continuously reporting sites, the total number of RSV notifications increased in 2012/13 more remarkably for outpatient clinics (1.4-fold from 28,807 to 38,896) than for hospitals (1.1-fold from 21,342 to 24,273) (Fig. 3). Among 325 sites that first began reporting in 2011/12 (previous season), the number of cases per sentinel increased from 8.4 in 2011/12 to 18.0 in 2012/13. The proportion of sites which reported fewer than 10 cases per year decreased from 75% (244/325) to 55% (179/324; 324 as one site dropped out). Since 2012/13, there has also been a notable increase in the number of RSV notifications earlier in the season, beginning around week 35 in September (Fig. 1).

In the 2009/10 year, relative to the previous year, there was a 1.4-fold increase in both the total number of notifications (from 48,269 to 69,004) and in notifications from continuously reporting sites (from 42,335 to 57,845) (Fig. 2A and 2B). Among continuously reporting sites, this increase was observed for both clinics (1.4-fold increase from 24,286 to 34,594) and hospitals (1.3-fold increase from 18,049 to 23,251) (Fig. 3), with the increase occurring unusually late in the season around week 5. The increase observed in 2009/10 was temporary, followed by a decrease in the following year (Fig. 2).

In the most recent 2014/15 year, compared to the previous year, a small 1.1-fold increase was observed in the total number of reports (from 96,234 to 107,036) and for notifications from continuously reporting sites (from 62,379 to 66,701). Among continuously reporting sites, the increase in notifications among clinics (1.1-fold from 38,809 to 42,490) was greater than that among hospitals (1.0-fold from 23,570 to 24,211) (Fig. 3); an unusually sharp peak occurred at week 50 (Fig. 1).

Additionally, we assessed the absolute number of deaths attributed to RSV infection in relation to the total number of reported RSV cases over time. Although RSV notifications increased over time (Fig. 1), the annual number of deaths showed an overall declining trend over time (n = 36, 28, 31, 28, 34, 16, 22, and 19 deaths, from 2008 to 2015, respectively).

Lastly, during the study period, the vast majority of reported cases were those younger than 2 years of age (median = one year; interquartile range = 0 to 2), and the age distribution remained relatively stable, with those younger than 2 years of age remaining predominant (75%, 68%, 72%, 75%, 74%, 74%, and 72%, from 2008/09 to 2014/15, respectively).

**DISCUSSION**

Although Japan initiated RSV surveillance in 2003, it has been difficult to interpret the RSV trend with the reported data as there were important secular factors, such as the likely increase in testing frequency for RSV and changes in insurance policies, which could have affected notifications. Here, in an attempt to evaluate and control for such potential surveillance biases, we assessed the RSV surveillance data accounting for the number of reporting sites and restricting to continuously reporting sites, and further stratified reporting sites by facility type.

First, by restricting to those that had reported in the past, we were able to remove potential bias introduced from any newly gained ability to test for RSV. In doing so, we found that the magnitude of increase from 2008/09 to 2014/15 was considerably less than the total increase (1.6-fold vs. 2.2-fold increase; slope of 3.539 vs. 9.409 based on the fitted linear regression model). The more gradual increase remaining among the continuously reporting sites may reflect i) a true increase in the incidence of RSV infections over time; ii) residual confounding due to the increase in testing capacity (i.e. not in ability but rather in the quantity of tests being performed); or iii) a combination of both. We believe that the remaining increase is largely due to ii), particularly given the large increase observed in 2012/13 and we suspect that testing practices were most affected around the time of the insurance coverage expansion in October 2011. For instance, while the 2011/12 surveillance year saw the largest increase in the number of reporting sites relative to the previous year (Table 1), we found that the majority of new reporting sites reported considerably fewer cases than those that had reported cases in the previous year. We suspected that the change in insurance prompted some sites that had not tested previously to begin testing; in fact, in the following 2012/13 year, these same sites reported more cases (further inspection of sites that newly began to report found that, regardless of the year in which they started to report, there was a large increase in the following year, followed by stabilization of notifications thereafter, indicating that reporting activity, in fact, appears to differ by “experience”). In 2012/13, however, larger increases in both total notifications and notifications among continuously reporting sites were observed. Based on an exploratory analysis, a generalized linear model (Poisson distributional family and identity link function) with a linear increase from 2008/9 through 2011/12, a time-dependent variable for 2012/13, and constant annual notifications thereafter through 2014/15 (model A) was found to better fit the data than the simple linear model (model B), for both the total and restricted data sets, based on the Akaike Information Criterion (AIC) (14,15); the values of AIC for models A and B for the total data set were, respectively, 3,523 and 4,311, and those for the restricted data set were, respectively, 2,944 and 3,740. As the large increase in 2012/13 was observed also in the restricted analysis, either i) or ii) could be possible, but it would be difficult to explain i) given that the level of reporting has been sustained since then (Fig. 2B), with a notable increase in RSV notifications beginning in September every year, possibly due to increased testing from early fall after the insurance expansion.

As additional supporting information for ii), restricted to continuously reporting sites, RSV notifications increased in 2012/13 more remarkably for outpatient clinics than for hospitals—as the insurance coverage expanded to outpatients for the first time, the greater increase in outpatient clinics supports the hypothesis that the increase in
notifications observed may have been the result of this insurance change. Moreover, as this stratification was restricted to the continuously reporting sites, this increase is independent of that which could be explained by an increase in sites able to perform RSV testing. Given the temporality of the increase following insurance expansion, the notable increase particular to outpatient clinics, and high levels of RSV notifications sustained through 2014/15 after the insurance policy change, we believe that the increase since 2012/13 was more likely to be due to the insurance expansion than a true increase in RSV incidence. While the restricted analysis was believed to control for some of the newly acquired ability in testing among the pool of sentinel sites, it was likely unable to control for the willingness to conduct more tests.

Increases in notifications among continuously reporting sites were also observed in 2009/10 and 2014/15. In 2009/10, the increase was particularly remarkable, both for clinics and hospitals, and was followed by a decrease in the following year. The temporary increase may have been due to either a true increase in incidence or a surveillance artifact. Because the influenza H1N1 pandemic occurred in 2009/10, there could have been an increase in healthcare utilization and/or testing practices overall for those with respiratory syndromes. In 2014/15, a small increase was observed among continuously reporting sites (Fig. 2B). An unusually sharp increase occurred around week 50 (Fig. 1), and a similar epidemic curve with a peak in RSV notifications at week 51 was also observed from “RSV online surveillance” (16), a completely separate voluntary pediatric surveillance network (unpublished data). Based on a separate acute encephalitis/encephalopathy notification system, the number of acute encephalitis/encephalopathy cases with detection of RSV, while few, was highest in 2014/15 during this study period. Among acute encephalitis/encephalopathy cases, the number and proportion of RSV detection were 9 cases (1.9%) in 2014/15 relative to 2–5 cases (0.6–1.6%) for the other surveillance years. However, there was no such increase in deaths attributed to RSV infection. Further assessment is necessary to evaluate the reason for the increase in 2014/15.

While there are inherent limitations in this study, such as the lack of testing data, our approach highlights the potential usefulness of restriction to control for possible surveillance bias and stratification to assess where that bias may be most present. Our findings indicated that at least some of the recent increase in RSV notifications, such as during 2011/12 and 2012/13, could be a surveillance artifact. The fact that the ratio of cases reported from outpatient clinics to hospitals has increased over time (Fig. 3) also indicates that the proportion of milder cases being reported has increased. In addition, that the number of reported cases increased but the number of deaths attributed to RSV infection decreased also makes the argument for a true increase in incidence difficult (assuming certain conditions). Notably, although the actual number of tests conducted at sentinel sites is unknown, the number of federally approved RSV diagnostic kits for commercial sale in Japan has been increasing. In fact, at least 12 point-of-care kits for RSV (single or with other viruses) were newly approved during 2009–2014 (1–3 kits newly approved each year). Among them, 4 kits were for detecting multiple viruses, and 2 of them that test for RSV and influenza became available in November 2011 and July 2012 (approval number 22300AMX01248000 and 22400AMX00770000, respectively). It has indeed been reported that with the increase in the number of kits being marketed, the use of kits for RSV has increased in the clinical setting in recent years (17).

Lastly, it would be ideal if the actual number of tests conducted and the proportion testing positive became available, as presented in the U.S. RSV surveillance system (18) and utilized for other infectious disease surveillance systems (19,20). All else being equal, if notifications increased in the context of an increase in the number of tests and a decrease in positivity, it may be a result of enhanced testing. In addition, while patients 24 months or younger became eligible under the new insurance scheme, when we explored the age distribution of the cases in 2011/12 and 2012/13, we found that patients younger than 24 months continued to make up about 75% of all cases (for both the total number of reported cases and those reported from continuously reporting sites), and did not increase disproportionately. In fact, notifications from 2011/12 to 2012/13 increased across all age groups (ranging from a 1.2-fold increase in those aged < one year and ≥ 5 years to 1.5-fold among 2-year-olds), and there may have been an overall increase in RSV testing, including in those not targeted by insurance; evaluating testing data by age group would thus assist in better understanding the situation. It is possible, for example, that clinics may have stocked more rapid test kits since the insurance change and used them regardless of the targeted age group; as rapid test kits that test for both RSV and influenza became available after the insurance change, such changes may also have influenced the increased notifications in older children. As surveillance data are prone to be affected by secular or legal changes, our assessment reminds us of the importance of careful interpretations of such data and the need to systematically address potential surveillance artifacts. In order to improve our assessment of RSV surveillance data over the coming years, continuing to incorporate data from multiple sources would be useful (21).

Knowledge of the epidemiology of RSV has begun to accumulate globally. The World Health Organization has been concerned with the burden of RSV and has initiated RSV surveillance using the Global Influenza Surveillance and Response System platform (22). Such actions are important in obtaining baseline information for evaluating future vaccination programs, and understanding global trends and distributions of RSV. Thus, it is important—not just domestically but also as a contribution to the global knowledge base—that we have a good understanding of our national RSV surveillance data.

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Conflict of interest None to declare.

REFERENCES


