






Determination of respiratory syncytial virus epidemic seasons by using 95% confidence interval of positivity rates, 2011–2021, Germany

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Abstract

Based on our national outpatient sentinel surveillance, we have developed a novel approach to determine respiratory syncytial virus (RSV) epidemic seasons in Germany by using RSV positivity rate and its lower limit of 95% confidence interval. This method was evaluated retrospectively on nine RSV seasons, and it is also well-suited to describe off-season circulation of RSV in near real time as observed for seasons 2020/21 and 2021/22 during the COVID-19 pandemic. Prospective application is of crucial importance to enable timely actions for health service delivery and prevention.

KEYWORDS

acute respiratory infection, confidence interval, epidemic season, respiratory syncytial virus, surveillance

1 | INTRODUCTION

Respiratory syncytial virus (RSV) is the major cause of acute lower respiratory tract infection (ALRI) in children.¹ Globally, 33.1 million episodes of ALRI were caused by RSV infection which resulted in estimated 3.2 million hospital admissions, and 59,600 in-hospital deaths in children younger than 5 years in 2015.² To date, no approved vaccine against RSV exists.³ In order to prevent severe ALRI due to RSV, passive immunoprophylaxis with palivizumab can be carried out in infants at high risk.⁴

RSV causes seasonal epidemics worldwide.⁵ In Europe, an average RSV season starts in the beginning of December, peaks in early February, and continues until early April.⁶ So far, there is no accepted

method for defining start and end of RSV epidemic seasons, although few methods have been recently recommended.⁷

In Germany, RSV activities were commonly investigated within our national outpatient sentinel surveillance, and RSV epidemic seasons have been determined retrospectively.^{8,9} This study aimed to establish a prospective, sensitive, and sustainable method to determine the start and end of RSV epidemic seasons on population level.

2 | RSV DETECTIONS

Specimens (nasal or throat swabs, and nasopharyngeal swabs) from outpatients of five age groups (0–4, 5–14, 15–34, 35–59, and

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>60 years old) with acute respiratory infection (ARI) were collected year-round by physicians participating in the national sentinel surveillance and sent to the Robert Koch Institute (RKI, Berlin, Germany) where they were prospectively tested for RSV by real-time reverse transcription PCR.¹⁰

From 2011/12 to 2019/20, a total of 33,351 RSV positives were detected within calendar weeks 40 to 20, the time of regular RSV activity in Germany. Although RSV detections were observed in all age groups, median positivity rates (PR) were highest among young children aged 0 to 4 years (Figure 1). Further, median RSV PR in young children were 2.6-fold higher compared with median PR in all ages (nonparametric Mann-Whitney *U* test, $P = .0003$, Stata[®] version 17). Because robust and reliable RSV surveillance data are of crucial importance, RSV PR among 0 to 4 years old children was selected for the determination of RSV epidemic season solely.

3 | DETERMINATION OF RSV SEASONALITY

Among children aged 0 to 4 years, the number of RSV positive and negative tested cases were sorted by season and calendar week (collection date, if not available then received date). For each calendar week, the

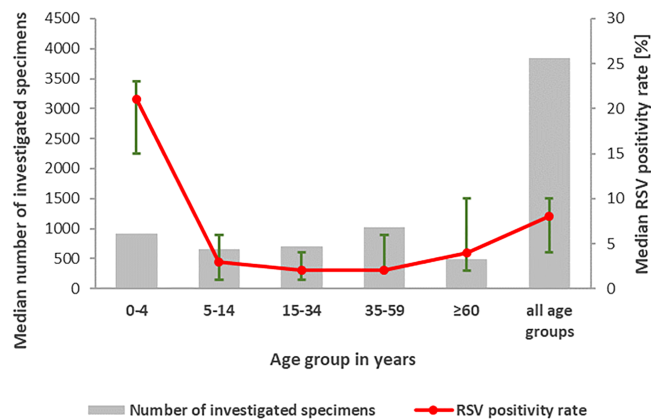


FIGURE 1 Median number of investigated specimens (gray bars) and median RSV positivity rate (red line) with range (green error indicators) in different age groups, calendar weeks 40 to 20 in seasons 2011/12 to 2019/20

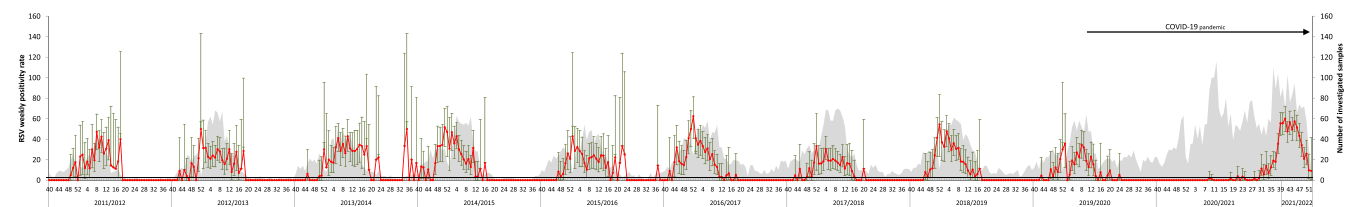


FIGURE 2 RSV weekly positivity rates (red) with 95% confidence interval (green error bars) for age group 0–4 years by calendar week from season 2011/12 to 2021/22. A season was defined from calendar week 40 up to week 39 of the following year. Gray shadows represent number of investigated samples with the corresponding scale on secondary axis. The black line marks the threshold (5%, lower limit of 95% confidence interval of the RSV positivity rate). Black arrow displays the course of COVID-19 pandemic

PR and the associated 95% confidence interval (95% CI) were calculated with Stata[®] version 17. Both RSV PR and the corresponding 95% CI were plotted against the calendar week of the seasons 2011/12 to 2021/22 (Figure 2). A high PR can be associated with a low number of investigated (received) samples and single RSV positive detections and will moreover result in a less precise estimate of the 95% CI with probably reduced lower limit of 95% CI (Figure 2). To circumvent such unlikely high RSV PRs, the lower limit of the 95% CI was used herein to determine the RSV epidemic season. Within an iterative process, manually different thresholds were thoroughly evaluated to determine the cut off for the start and end of retrospective RSV epidemic seasons. Then, the start of the RSV epidemic season was defined as the first of two consecutive weeks in which the lower limit of 95% CI of the RSV PR exceeds 5% among 0 to 4 years old children. The RSV epidemic season ends by the week that precedes first of two consecutive weeks, in which the lower limit of 95% CI of the RSV PR drops below 5%. One gap week below the threshold was allowed.

Among 0 to 4 years old children, an RSV epidemic season could be retrospectively assigned to each season from 2011/12 to 2019/20 (Figures 2 and 3). The median start of RSV epidemic seasons was in calendar week 50 (range: 45–3), peaked in median in calendar week 8 (range: 51–10), and ended in median in week 12 (range: 10–18). The median length of the RSV season was 15 weeks (range: 13–18).

In contrast, during the COVID-19 pandemic starting in calendar week 11 in 2019/20,¹¹ there was almost no RSV detected within the time of RSV epidemics as observed for the seasons 2011/12 to 2019/20 (median weeks 50–12) among 0 to 4 years old children. Between calendar weeks 9 and 30 in 2020/21, only sporadic RSV cases occurred. The number of RSV cases and the corresponding RSV PR increased in calendar week 31. According to our definition of the timing of an RSV epidemic season, in 2020/21, the RSV season began in calendar week 35 (PR: 13%, 95% CI: 5.2–24.1) and continued until calendar week 50 (PR: 26%, 95% CI: 15.3–39.0) in season 2021/22 (Figures 2 and 3).

4 | ETHICAL STATEMENT

The German national ARI sentinel surveillance has been approved by the Charité-Universitätsmedizin in Berlin Ethical Board (Reference EA2/126/11).

AUTHOR CONTRIBUTIONS

Wei Cai: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; visualization.

Ralf Dürrwald: Conceptualization; investigation; resources; supervision. **Barbara Biere:** Data curation; investigation; methodology.

Brunhilde Schweiger: Conceptualization; investigation; resources; supervision. **Walter Haas:** Resources; supervision. **Thorsten Wolff:**

Conceptualization; resources; supervision. **Silke Buda:** Conceptualization; investigation; methodology; project administration; resources; supervision; validation. **Janine Reiche:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization.

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How to cite this article: Cai W, Dürrwald R, Biere B, et al. Determination of respiratory syncytial virus epidemic seasons by using 95% confidence interval of positivity rates, 2011–2021, Germany. *Influenza Other Respi Viruses*. 2022;16(5):854-857. doi:10.1111/irv.12996