

RESEARCH ARTICLE

Post-lockdown respiratory virus epidemiology: a monocentric observational study

Santiago Presti^{1, *}, Manuela Lo Bianco¹, Federico Mollica¹, Sara Manti^{1, 2}, Maria Papale¹, Giuseppe Fabio Parisi¹, Salvatore Leonardi¹

*** Correspondence to:**

santiagopresti@gmail.com/ORCID: <https://orcid.org/0000-0002-4879-5418>

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¹ Pediatric Respiratory Unit, Department of Clinical and Experimental Medicine, San Marco Hospital, University of Catania, Catania, Italy

² Pediatric Unit, Gaetano Barresi Department of Human and Pediatric Pathology, University of Messina, Messina, Italy

ABSTRACT

During the 2020 lockdown and post-lockdown, we assisted in almost zeroing respiratory infections. This study aimed to describe the first epidemic of respiratory viruses after the easing of nonpharmaceutical interventions (NPIs) for the containment of COVID-19 in a pediatric cohort of patients.

All children consecutively hospitalized because of a respiratory infection at our department of Clinical and Experimental Medicine, Pediatric Respiratory and Cystic Fibrosis Unit – San Marco University Hospital in Catania, Italy, from October 1st, 2021, to March 15th, 2022 were tested for respiratory viruses. Among these patients, in the subgroup of children with bronchiolitis, we investigated the following endpoints: the etiology, the mean duration of hospitalization (mean $\pm$ SD), the severity of the disease (Clinical Respiratory Score), and the respiratory support provided (HFNC or Helmet-CPAP). For statistical analysis, SPSS 28.0.1.1 (14) software was used. A 2-tailed t-test for unpaired data was applied to compare the mean duration of hospitalization and need for ventilation, and a chi-square test was applied to relate the severity of viruses.

A total of 138 children were included in the study. The infection of the Respiratory Syncytial virus (RSV) was the most frequently observed (23.2%), followed by Bocavirus (10.87%), Rhinovirus (hRV) (4.38%), Parainfluenza virus (2.9%), Enterovirus (2.17%), endemic Coronavirus (1.45%) and Metapneumovirus (1.45%). 53.6% of patients resulted negative. Of the 138 children, 62 (45%) had a diagnosis of bronchiolitis: in 40% of these children, we isolated RSV, in 8% Bocavirus, in 3.23% Rhinovirus, in 3.3% Parainfluenza virus, 1.61% endemic Coronavirus and Metapneumovirus. In the remaining 42% of patients with bronchiolitis, no viruses were isolated by nasal swabs. The mean duration of hospitalization for RSV-related bronchiolitis (mean 9.48 days $\pm$ SD 3.95) was significantly higher ($p < 0.05$) compared to the non-RSV-related bronchiolitis (mean 7.22 days $\pm$ SD 3.7). According to the clinical respiratory score, RSV-related bronchiolitis resulted in more severe ($p < 0.05$) than non-RSV ones, and consequently, it has been associated with a higher risk ($p < 0.05$) of being subject to ventilation either with helmet CPAP or HFNC.

KEY WORDS

Respiratory syncytial virus (RSV); COVID-19; respiratory viruses; pandemic; epidemic.

During the considered period, RSV was the most widespread respiratory virus, in fact it has been isolated through nasal swab in the 23.2% of the whole study group of 138 patients). RSV was responsible for the most severe bronchiolitis cases, associated with a higher hospitalization length and a more severe disease compared to non-RSV-related bronchiolitis.

ABBREVIATIONS

RSV: respiratory syncytial virus; NPIs: nonpharmaceutical interventions; CRS: clinical respiratory score; HFNC: High Flow Nasal Cannula.

HIGHLIGHTS BOX

What is already known about this topic? During the 2020 lockdown and post-lockdown, we assisted in almost zeroing respiratory infections, probably due to the containment measures adopted (e.g., hand hygiene measures, social distancing, and the use of face masks). **What does this article add to our knowledge?** During the considered period, RSV was the most widespread respiratory virus responsible for the most severe bronchiolitis cases, associated with a higher hospitalization length and a more severe disease compared to non-RSV-related bronchiolitis. **How does this study impact current management guidelines?** It is recommended to particularly monitoring patients with bronchiolitis related to RSV since the disease has a more severe course than bronchiolitis related to other respiratory viruses. Since bronchiolitis related to RSV has a more severe course than bronchiolitis related to other respiratory viruses, it is recommended to strictly monitor especially patients with RSV.

INTRODUCTION

The experience of the COVID-19 pandemic radically changed the epidemiology of respiratory viruses worldwide. A dramatic decrease in respiratory infections has been reported during the epidemic period of 2020, probably due to the containment measures adopted (e.g., hand hygiene measures, social distancing, and the use of face masks) (1-9). Studies reported more than 80% reduction in infant bronchiolitis by reducing hospitalization by comparing the COVID-19 outbreak with the previously reported respiratory viruses' seasonality (10). Van Brusselen *et al.* reported only 20 cases of bronchiolitis due to respiratory syncytial vi-

rus (RSV) in the whole of Belgium, with a reduction of cases by more than 99% compared to the preceding years (11). In Italy, the COVID-19 lockdown for the pandemic started on March 9th, 2020 and lasted until May 19th, 2020. For the whole of 2020 and the beginning of 2021, the restriction measure levels were strict (smart working, quarantine, school in distance learning, etc.). During this period, several Italian hospitals, in line with the rest of the world, reported the same epidemic trend: the absence of peak incidence of respiratory viruses and almost the zeroization of respiratory infections (1, 2, 4, 12). This study aimed to describe, the first epidemic of respiratory viruses after the easing of nonpharmaceutical interventions (NPIs) for the con-

tainment of COVID-19 in a pediatric cohort. During the winter of 2021, restrictions levels in Italy were almost comparable to normality.

METHODS

All children consecutively hospitalized because of a respiratory infection at our department of Clinical and Experimental Medicine, Pediatric Respiratory and Cystic Fibrosis Unit, San Marco Hospital, the University of Catania, from October 1st, 2021 to March 15th, 2022 were tested for respiratory viruses through a nasal swab. The rapid molecular test for testing RSV, Flu-A, and Flu-B (Xpert® Xpress, Cepheid) or the R-GENE® qualitative multiplex real-time RT-PCR (Biomerieux) were used. The study has been conducted in accordance with the declaration of Helsinki. Among these patients, in the subgroup of children with bronchiolitis, diagnosed according to the current guidelines (13), we investigated the following endpoints: the etiology of bronchiolitis, the mean duration of hospitalization, the severity of the disease, and the need for respiratory support. Globally, bronchiolitis is the main cause of lower respiratory tract infection and hospitalization in patients under 1 year of age. It is a viral disease defined by the first episode of respiratory distress associated with use of accessory muscles, presence of crackles and/or wheezing, tachypnea, cyanosis, fever and low O₂ saturation. Normally, symptoms are preceded by rhinorrhea and/or upper respiratory tract infection (13). The severity of bronchiolitis has been defined through the clinical respiratory score (CRS) (14) which includes several predictors of respiratory distress: respiratory rate, auscultation abnormalities, use of accessory muscles, mental status, room air SpO₂, and color of the baby. Based on the overall score, severity has been assessed as mild with a score of ≤3, moderate 4-7, and severe 8-12. Respiratory supports, if used, were High Flow Nasal Cannula (HFNC) or Helmet-CPAP. For statistical analysis, SPSS 28.0.1.1 (14) software was used. A 2-tailed t-test for unpaired data was applied to compare the mean duration of hospitalization and need for ventilation, and a chi-square test was applied to relate the severity of viruses.

RESULTS

Among the 138 patients admitted to our department for respiratory illness, 47.1% (65/138 patients) resulted positive for at least 1 respiratory virus, as shown in **Figure 1**: RSV was the most frequent one (23.2%), followed by Bocavirus (10.87%), Rhinovirus (hRV) (4.3%), Parainfluenza virus (2.9%), Enterovirus (2.17%), endemic Coronavirus (1.45%) and Metapneumovirus (1.45%). 53.6% of patients resulted negative. Among these 138 patients, we considered only those diagnosed with bronchiolitis based on diagnostic criteria (13). We included 62 patients with a distribution of virus-causing bronchiolitis, as shown in **Figure 2**. A total of 40% of bronchiolitis have been caused by RSV, 8% by Bocavirus, 3.23% by hRV, 3.3% by Parainfluenza virus, 1.61% by endemic Coronavirus and 1.61% by Metapneumovirus. Negative patients were 42%. As shown in **Figure 3**, the mean duration of hospitalization for RSV-related bronchiolitis (mean 9.48 days ± SD 3.95) was significantly higher ($p < 0.05$) compared to the non-RSV-related bronchiolitis (mean 7.22 days ± SD 3.7). According to the CRS, RSV-related bronchiolitis was more severe ($p < 0.05$) than non-RSV-related (**Table 1**), and consequently, children with RSV-related bronchiolitis had a higher risk ($p < 0.05$) of being ventilated either with helmet CPAP or HFNC (odds ratio 15.27) (**Figure 4**).

DISCUSSION

The experience of COVID-19 containment measures due to the pandemic almost zeroed the circulation of endemic respiratory viruses leading to new possible epidemiologic trends (1, 2, 4, 10, 11). It has been theorized that the lack of immune stimulation from these pathogens might have conducted to a decline in population immunity with a consequent change in the epidemiology of respiratory viruses after the removal of NPIs for the containment of COVID-19 (15). In our pediatric cohort of patients, during the epidemic season of 2021-2022, RSV was the most widespread virus overall, and it has been confirmed to be responsible for the most severe forms of bronchiolitis. Patients diagnosed with RSV-related bronchiolitis had a significantly longer hospital stay (9.48 days ± SD 3.95 vs. 7.22 days ± SD 3.7) and se-

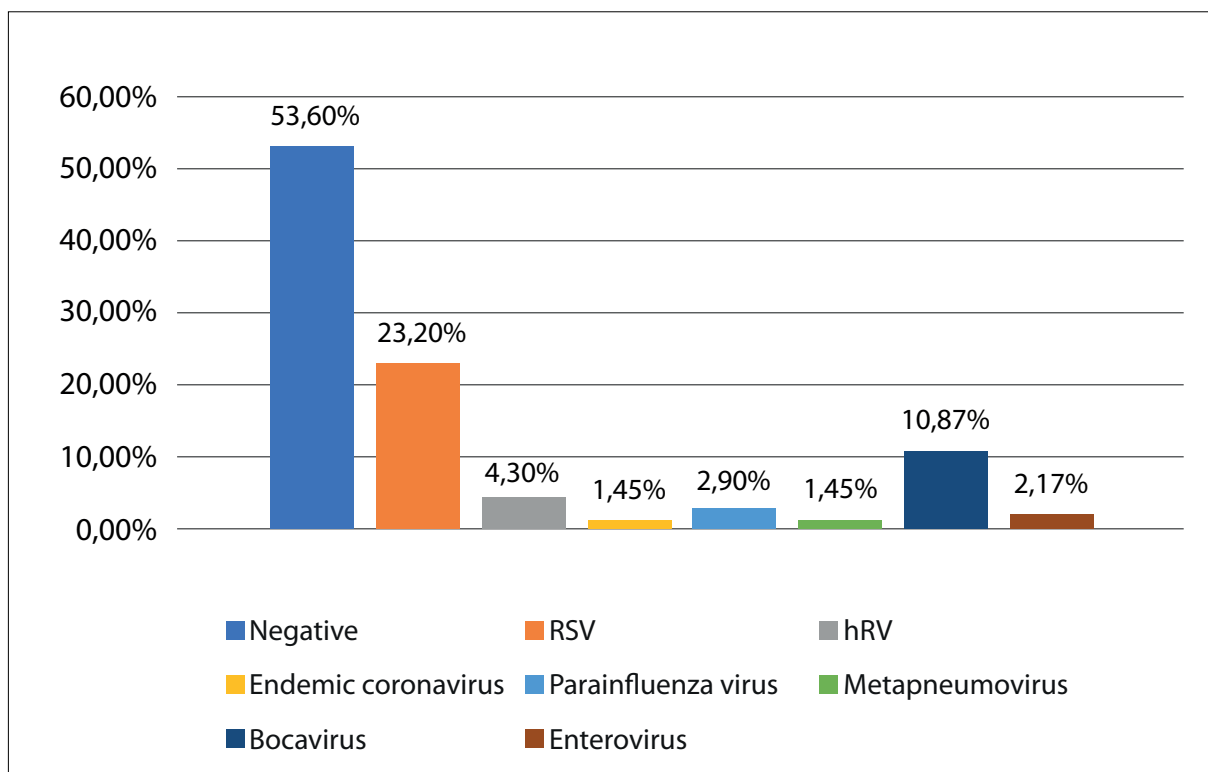


Figure 1. Results of nasal swabs in the whole study group.

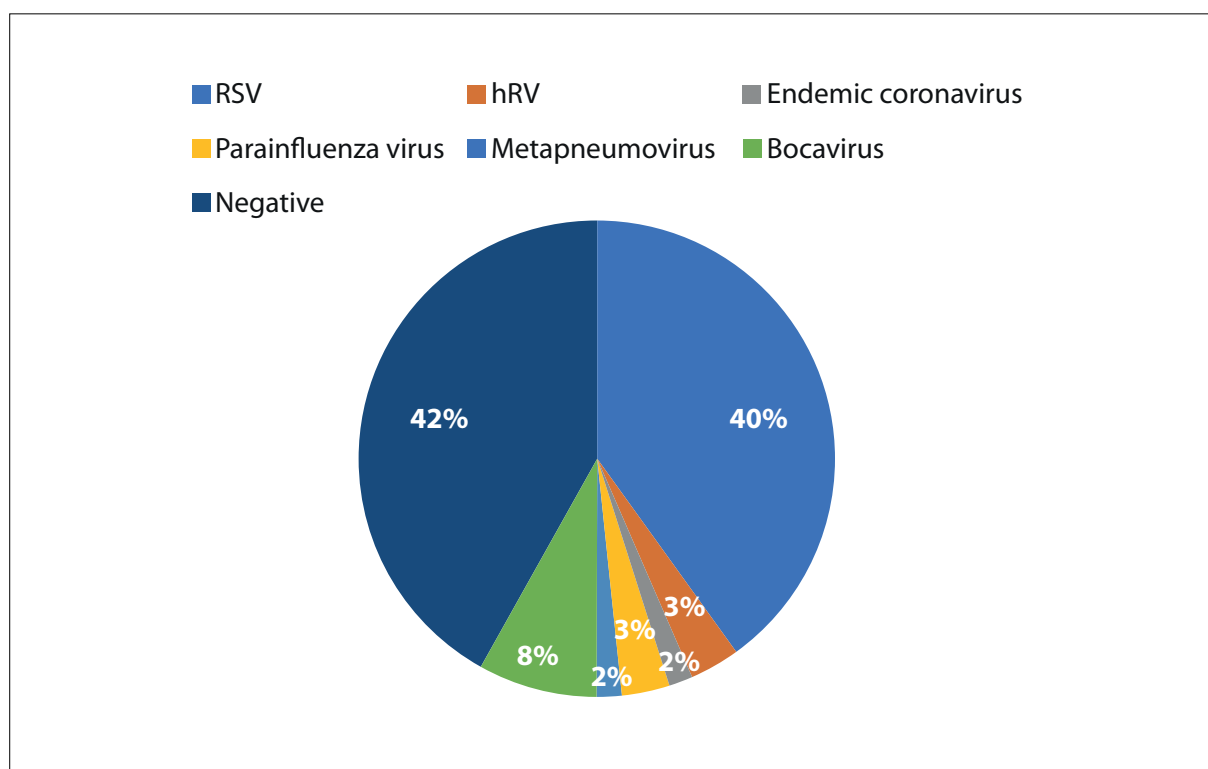


Figure 2. Prevalence of respiratory viruses in patients diagnosed with bronchiolitis.

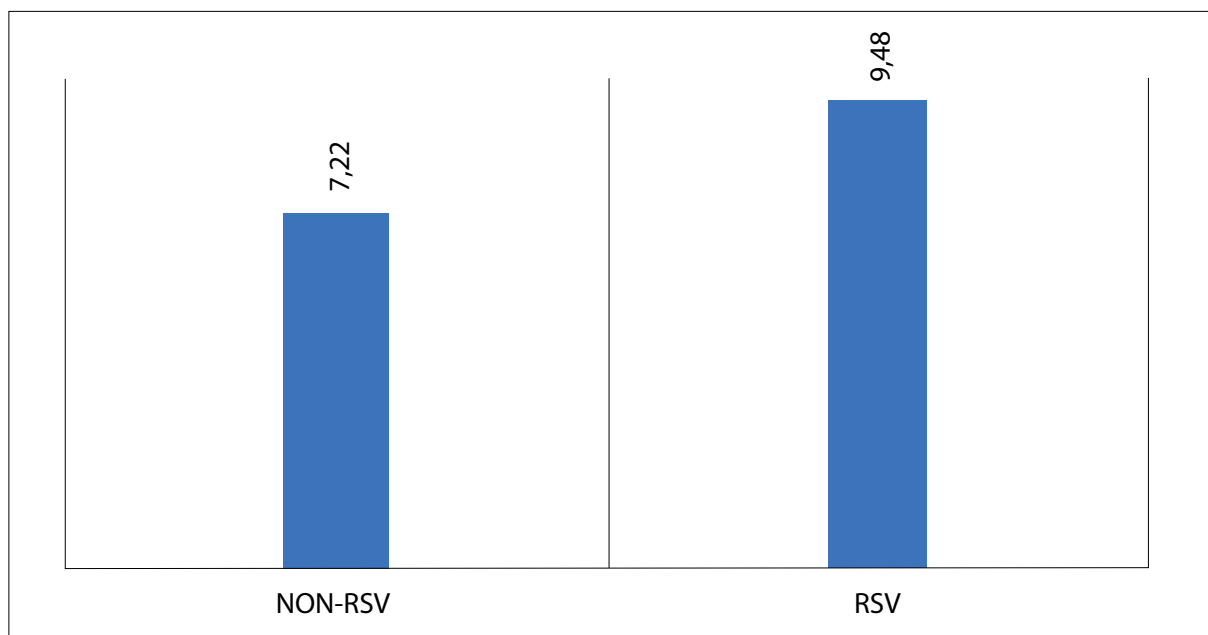


Figure 3. Length of hospitalization in days ($p < 0.05$).

	Mild	Moderate	Severe	p
RSV vs Rhinovirus	36% vs. 100%	44% vs. 0%	20% vs. 0%	0.026
RSV vs. Coronavirus	36% vs. 100%	44% vs. 0%	20% vs. 0%	0.029
RSV vs. Parainfluenza virus	36% vs. 50%	44% vs. 50%	20% vs. 0%	0.027
RSV vs. Metapneumovirus	36% vs. 0%	44% vs. 100%	20% vs. 0%	0.012
RSV vs. Bocavirus	36% vs. 80%	44% vs. 0%	20% vs. 20%	0.024

Table 1. Severity according to Clinical Respiratory Score (CRS).

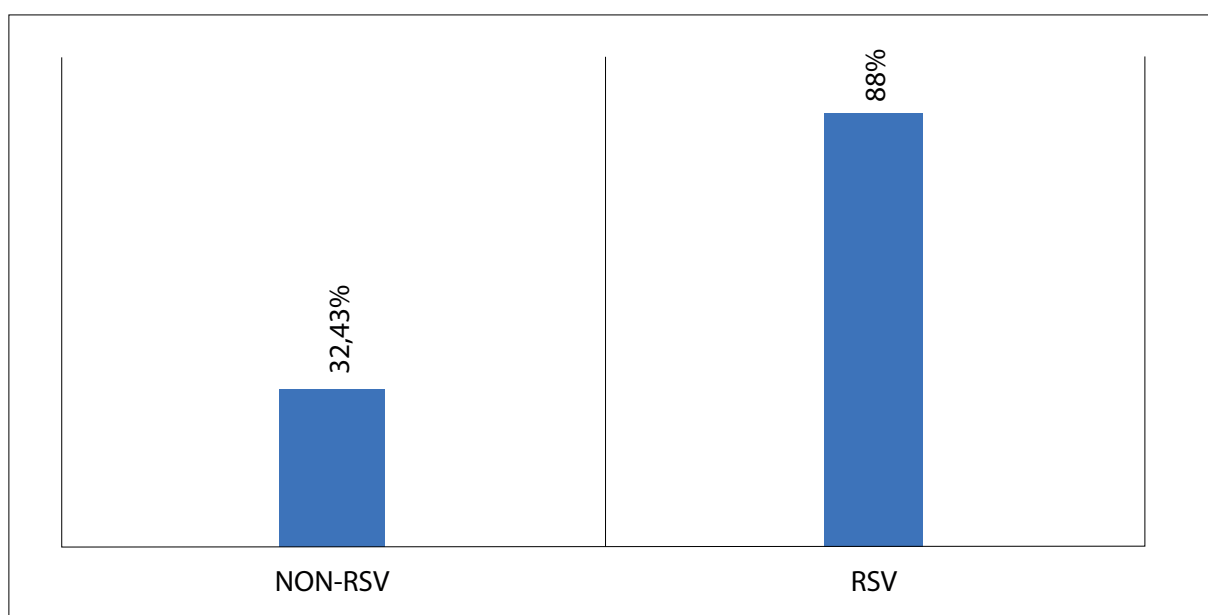


Figure 4. Need for ventilation (CPAP and/or HFNC) $p < 0.05$.

verity of disease: specifically, 88% of RSV bronchiolitis needed ventilation (CPAP and/or HFNC) compared to the 32.43% of non-RSV bronchiolitis ($p < 0.05$). Thus, RSV bronchiolitis has been associated with a more severe score of CRS ($p < 0.05$). Therefore, it is possible to state that during the epidemic season of 2021-2022, RSV has been associated with more severe forms of bronchiolitis than the other respiratory viruses. However, only a few studies compared the severity of RSV-related bronchiolitis to non-RSV; consequently, evidence is not strength (16, 17). Nevertheless, the results highlighted in this study strengthen the hypothesis that RSV-bronchiolitis has a more severe course than non-RSV one. Following the lockdown, unusual epidemiology of RSV and respiratory viruses have been observed in our center: in fact, we reported a resurgence in RSV cases during summer 2021, out of the RSV typical seasonality, despite the hot weather of Sicily. All three hospitalized infants during the summer had severe infections requiring ventilatory support. Tempia *et al.* and Fourgeaud *et al.* also reported a similar phenomenon in South Africa and France: they noted a recurrence in RSV out-of-season, after the easing of containment measures (7, 18). Thus, in this epidemic season, a considerable advance in the peak of incidence of RSV and other respiratory viruses has been observed: the previous peaks of incidence were between January and February while during the last epidemic season the reported peak of incidence was assessed in November. Similar results have been reported by an Italian multi-center study that showed that the hospitalizations curve of RSV bronchiolitis occurred earlier than in the pre-pandemic era, showing an opposite trend with respect to the incidence of SARS-CoV-2 suggesting the hypothesis that SARS-CoV-2 might exhibit a competitive pressure on other respiratory viruses (19). In order to explain this new trend, it has been suggested the possibility of an increased number of susceptible individuals to viral infections due to reduced exposition, limited immunity duration, and reduced antibodies transplacental transfer (15, 20, 21). The next epidemic waves will define whether this new early peak of incidence with sporadic out-of-season cases represents a temporary occurrence or a new epidemic trend of respiratory virus epidemiology. A careful surveillance is currently underway in our department.

CONCLUSIONS

After the about zeroing of respiratory infections during the lockdown and 2020 post-lockdown, a resurgence of respiratory virus diffusion has been registered during the 2021/2022 epidemic season. In the reported population of 138 children, RSV was the most widespread respiratory virus, and was responsible for the most severe bronchiolitis clinical presentation, associated with a higher length of hospitalization and a more severe disease compared to the non-RSV-related bronchiolitis.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interests

The Authors have declared no conflict of interests.

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Authorship

Drs. Santiago Presti, Manuela Lo Bianco, Federico Mollica, Sara Manti, Maria Papale, Giuseppe Fabio Parisi, Salvatore Leonardi.

Author contributions

SP, GFP, SM, and SL: conceptualization, project administration and supervision. FM, MP: data curation and writing - review and editing. SP and MLB: formal analysis and writing - original draft. All authors contributed to the article and approved the submitted version.

Ethical approval

Human studies and subjects

The study has been conducted in accordance with the declaration of Helsinki of 1946.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article can be shared just before a reasonable request to the Corresponding Author.

Publication ethics

Plagiarism

N/A.

Data falsification and fabrication

All the data correspond to the real.

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