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Short Communication

Main differences between the first and second waves of COVID-19 in Madrid, Spain

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ABSTRACT

Background: The emergence and rapid global spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) represents a major challenge to health services, and has disrupted social and economic activities worldwide. In Spain, the first pandemic wave started in mid-March 2020 and lasted for 3 months, requiring home confinement and strict lockdown. Following relaxation of the measures during the summer, a second wave commenced in mid-September 2020 and extended until Christmas 2020.
Methods: The two pandemic waves were compared using information collected from rapid diagnostic tests and polymerase chain reaction assays at one university clinic in Madrid, the epicentre of the pandemic in Spain.
Results: In total, 1569 individuals (968 during the first wave and 601 during the second wave) were tested for SARS-CoV-2-specific antibodies using fingerprick capillary blood. In addition, during the second wave, 346 individuals were tested for SARS-CoV-2-specific antigen using either oral swabs or saliva. The overall seroprevalence of first-time-tested individuals was 12.6% during the first wave and 7.7% during the second wave ($P < 0.01$). Seroconversions and seroreversions within 6 months occurred at low rates, both below 5%. During the second wave, 3.5% of tested individuals were SARS-CoV-2 antigen positive, with two cases considered as re-infections. Severe clinical symptoms occurred in a greater proportion of cases during the first wave compared with the second wave (27.8% vs 10.6%, respectively; $P = 0.03$).
Conclusion: The cumulative seroprevalence of SARS-CoV-2 antibodies in Madrid at the end of 2020 was approximately 20%. Seroreversions within 6 months occurred in 4% of cases. Seroconversions and re-infections were clinically less severe during the second wave than during the first wave. Hypothetically, a lower viral inoculum as a result of social distancing, increased use of face masks, promotion of outdoor activities and restrictions on gatherings may have contributed to this lower pathogenicity.

Introduction

The emergence and rapid global spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), from Wuhan, China at the end of 2019 represented an unprecedented phenomenon in medicine. COVID-19 continues to challenge health services and disrupt social and economic activities globally. In Spain, the first wave commenced in mid-March 2020 and lasted for 3 months. It finally abated due to strict lockdown and home confinement. Following relaxation of measures during the summer, a second wave commenced in mid-September 2020 and extended until Christmas 2020.

Although more than half of cases of COVID-19 remain asymptomatic, other individuals experience symptoms ranging from influenza-like episodes (fever, cough, myalgia, etc.) to pneumonia, and occasionally respiratory distress along with thromboembolic complications (severe COVID-19) (Griffin et al., 2021).

Official records indicate total cumulative figures in Spain of 262,814 confirmed cases of SARS-CoV-2 infection during the first wave and 1,254,789 during the second wave (Ministerio de Sanidad, n.d.). COVID-19 was associated with approximately 80,000 excess deaths in Spain in 2020 (Spanish population 47 million) (Instituto Nacional de Estadística, n.d.), representing one

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of the highest COVID-19 mortality rates in Europe (Soriano and Barreiro, 2020; Pastor-Barriuso et al., 2020). Madrid, the country's capital and largest metropolitan region with a population of 6.6 million, was the national epicentre. This article describes the main differences between the first and second waves of COVID-19 in Madrid, examining the clinical and diagnostic records of individuals who attended the university clinic.

Methods

UNIR Medical Centre is a university outpatient clinic in downtown Madrid. Although it mainly serves university personnel and their relatives, medical care is also provided to other citizens when requested in advance.

All consecutive individuals who attended during two trimesters in 2020 were examined retrospectively. The two periods covered the first and second waves of the COVID-19 pandemic, from approximately mid-March 2020 until the end of June 2020, and from mid-September 2020 to Christmas 2020, respectively.

The main epidemiological and clinical features of SARS-CoV-2-positive patients and diagnostic testing procedures used during the 3-month periods of the first and second pandemic waves were compared, using information collected from rapid tests and polymerase chain reaction (PCR) confirmation. All individuals recruited in the study gave informed consent and completed a case report form designed specifically for this research. Recording included information on main demographics and clinical manifestations. The study was approved by UNIR Ethics Committee.

In order to simplify the recording and grading of clinical manifestations, the study population was grouped into two categories: those without symptoms or with minor symptoms lasting $\leq$3 days, and those with mild or severe symptoms. The latter group included fever, cough, headache, shortness of breath, anosmia, ageusia and/or malaise for $\geq$4 days.

SARS-CoV-2-specific antibodies were tested using fingerprick capillary blood (PCL, Seoul, South Korea). SARS-CoV-2-specific antigen testing was only performed during the second wave. Either oral swabs (VivaCheck, Hangzhou, China) or saliva (PCL, Seoul, South Korea) were used. All serological tests had sensitivity and specificity >90–95% (Thompson et al., 2021). SARS-CoV-2-specific PCR testing was performed using a real-time commercial assay that targets S, N and ORF1ab genes on nasopharyngeal swabs. Positivity is reported when at least two genes are amplified with cycle threshold values <35.

Statistical analysis

All results have been presented as absolute numbers and percentages, and as mean values and standard deviations. Rates were compared using Fisher's exact test or Chi–squared test. $P < 0.05$ was considered to indicate significance. All analyses were performed using SPSS Version 21 (IBM Corp., Armonk, NY, USA).

Results

During 2020, 1569 individuals (968 during the first wave and 601 during the second wave) were tested for SARS-CoV-2-specific antibodies using rapid tests at the university clinic. In addition, during the second wave, 346 individuals were tested for SARS-CoV-2-specific antigen. All antigen-positive individuals were confirmed by PCR.

The main demographics of the study population are shown in Table 1. Approximately 55% of tested individuals were female and their mean age was 42 years. Approximately 17% reported positive household contacts. Nearly 40% of cases were university personnel and their relatives. The main reasons for presentation at the university clinic were symptoms potentially associated with COVID-19 or suspicion of close contact with a positive case. Overall, there were no significant difference in cases demographics between the two waves.

The overall seroprevalence of first-time-tested individuals was 12.6% during the first wave and 7.7% during the second wave. Seroconversions and seroreversions within 6 months occurred at rates of 4.9% and 3.8%, respectively. Taking into account the positivity rate during the first wave, and individuals testing positive for antibodies and antigen during the second wave, the estimated cumulative rate of SARS-CoV-2 infection in Madrid was 20% by the end of 2020.

During the second wave, positive SARS-CoV-2 antigen was recognized in 3.5% of tested individuals, all of which were confirmed by PCR. Furthermore, all cases seroconverted for specific antibodies during follow-up. Two cases were considered as re-infections, with intervals between prior and recent episodes of 5 and 6 months, respectively. Interestingly, the first case of re-infection was a 42-year-old male with obesity that suffered pneumonia during the two episodes that required hospitalization. Unfortunately, the authors did not have the opportunity to perform sequence analyses to explore the genetic diversity of SARS-CoV-2.

The proportion of patients with clinical symptoms considered as mild or severe (lasting $\geq$4 days) compared with those without symptoms or with minor symptoms (lasting $\leq$3 days) was significantly higher during the first wave compared with the second wave among antibody/antigen-positive cases (27.8% vs 10.6%, respectively; $P = 0.03$).

Discussion

Spain was one of the European countries worst affected by COVID-19 in 2020. The official estimated figures were nearly

Table 1
Main features of first and second waves of severe acute respiratory syndrome coronavirus-2 infection in Madrid.

Variables	First wave (n = 968)	Second wave (n = 947[a])	P-value
Male gender (n, %)	447 (46.2)	433 (45.7)	n.s.
Mean age (years)	41.7 ± 5.3	43.2 ± 5.7	n.s.
University personnel (n, %)	372 (38.4)	391 (41.3)	n.s.
Positive household contacts (n, %)	158 (16.3)	163 (17.2)	n.s.
Positive antibody test (n, %)			
First time	122 (12.6)	18/601 (7.7)	<0.01
Second time with prior test negative (seroconversion)	–	13/263 (4.9)	–
Second time with prior test positive (seroreversion)	–	4/104 (3.8)	–
Positive antigen test (n, %)	–	12/346 (3.5)	–
Clinical symptoms lasting ≥4 days (mild or severe) in cases who tested positive for antibody or antigen (n, %)	34/122 (27.8)	5/47 (10.6)	0.03

n.s., not significant.
[a] In total, 601 individuals were tested for antibodies and 346 individuals were tested for antigen. A subset of 41 individuals were tested for both antigen and antibodies.

2 million confirmed cases of SARS-CoV-2 infection and 80,000 deaths by the end of 2020 (Ministerio de Sanidad, n.d.; Instituto Nacional de Estadística, n.d.). Madrid was the epicentre of the pandemic and experienced large surges of disease during the two waves.

Given the shortage of diagnostic tests during the first wave, a pilot study was conducted in mid-May 2020 to determine the proportion of asymptomatic individuals and those with symptoms who could not be tested at the peak of the pandemic (Soriano et al., 2020a). Tests with capillary blood identified specific immunoglobulin G (IgG) in 93 of 674 consecutive individuals (seroprevalence 13.8%). A significantly higher rate was found in family households and people living in the community, with seroprevalence rates increasing to 19.2%.

A national seroprevalence study performed during the same period as the first wave (ENE-COVID) examined specific IgG in >61,000 people across Spain (Pollán et al., 2020). The overall seroprevalence rate was 5%, although several hotspot areas were identified, including Madrid with a seroprevalence rate of 11.3%. The study highlighted that a substantial proportion of people with symptoms compatible with COVID-19 did not have a PCR test, and at least one-third of infections determined by serology had been asymptomatic. Clearly, underdiagnosis was common during the first wave of COVID-19 in Spain.

This study found that the cumulative seroprevalence of SARS-CoV-2 antibodies in Madrid at the end of 2020 was 20%. Seroconversion occurred in 4.9% of individuals who tested negative during the first wave. On the contrary, seroreversion occurred within 6 months in 3.8% of individuals who tested positive during the first wave.

Seroconversions during the second wave were clinically less severe than during the first wave. It was hypothesized that high inocula leading to more severe SARS-CoV-2 infection (Guallar et al., 2020) was more common during the first wave than during the second wave. During the second wave, wider use of face masks, promotion of outdoor activities and restrictions on gatherings helped to reduce the viral inoculum. In addition, other variables most likely contributed indirectly to ameliorate disease severity, including wider access to testing (Soriano et al., 2020b), allowing earlier identification and isolation; improvements in medical care, such as earlier use of corticosteroids and antibiotics; and younger average age of infected individuals. The protective role of residual immunity in SARS-CoV-2 re-infections could not be assessed properly in this study given that there were only two cases of suspected re-infection (Babiker et al., 2021). However, one of these cases suffered severe pneumonia in both episodes.

In a serological survey performed by the Spanish Government in December 2020 that included more than 51,000 individuals across the country, the seroconversion rate among those who previously tested negative for SARS-CoV-2 antibodies was 3.8% (Instituto de Salud Carlos III, 2020), which was slightly lower than the rate found in the present study (4.9%). In agreement with the present findings, the national study highlighted that the proportion of symptomatic patients was lower in the second wave compared with the first wave.

This study has several limitations. First, cases of re-infection could not be examined in detail. The authors were not able to perform phylogenetic analyses of viral genomes to confirm whether distinct strains were involved, including the new viral variants that seem to be more transmissible. Second, the determinants of the overall lower virulence of infected cases during the second wave compared with the first wave could not be explored in more detail. The role of distinct medications used in each period could not be assessed properly, including corticoids, hydroxychloroquine, remdesivir, tocilizumbab, etc.

In summary, this study found that approximately 20% of the population in Madrid, a hotspot for COVID-19 in Spain, had been infected by SARS-CoV-2 by the end of 2020. Thus, the benefit of prompt vaccination could be substantial, as current figures are far from the levels required to achieve herd immunity. The clinical severity of SARS-CoV-2 infections declined significantly in the second wave compared with the first wave, most likely reflecting lower viral inocula as a result of social distancing, increased use of face masks, promotion of outdoor activities and restrictions on gatherings.

Conflict of interests

None declared.

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Ethical approval

This study was approved by UNIR Ethics Committee.

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