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BRIEF REPORT

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Documented vaccination as proof of immunity compared to serology in medical students

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ABSTRACT

We analyzed immunity to vaccine-preventable diseases and the predictive value of documented vaccination *versus* serological results for medical students in Catalonia (Spain). Epidemiological study of antibody seroprevalence and vaccination in medical students at four teaching units of medicine. Blood samples were drawn from participants who completed an epidemiology questionnaire. For seven diseases, we calculated the positive predictive value (PPV) percentages (and 95% CI) reflecting the protection afforded by self-reported vaccination histories compared to serology results. We enrolled 146 medical students (participation 25.7%; 146/569), 79.5% (116/146) women, mean (SD) age 22.6 (1.6) years. Most students (84.2%; 123/146) were fully vaccinated, 18 were unaware of their vaccination status, and 5 students were not vaccinated. Of the six overseas students, only three could document their vaccination status (OR = 6.0; 95% CI: 1.1–31.8). In documented vaccination terms, PPVs for immunological protection were high for varicella (100%), COVID-19 (99.1%), hepatitis A (98.9%), and rubella (94.8%), but was substantially lower for measles (90.0%), mumps (85.9%), and hepatitis B (67.2%). The predictive value of documented vaccination history compared to serology as proof of immunity was above 90% for most vaccines except for measles, mumps, and hepatitis B.

KEY POLICY HIGHLIGHTS

- Documented vaccination as immunity evidence was studied for seven vaccine-preventable diseases.
- Positive predictive values were just 90.0% for measles, 85.9% for mumps, and 67.2% for hepatitis B.
- To administer booster doses as necessary, documented vaccination for measles, mumps, and hepatitis B should be contrasted with serology results.

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Vaccination; medical students; seroprevalence; predictive value

Introduction

The incidence of outbreaks of vaccine-preventable diseases has decreased in recent decades, thanks to widespread vaccination of the populations of most countries.[1] Despite this reduction in incidence, medical students may be exposed to patients with vaccine-preventable diseases during clinical practice.[2] Some studies have suggested that medical students and other healthcare workers are often inadequately vaccinated against diseases such as measles, mumps, and varicella.[2–6] Medical students should therefore be considered a priority group for vaccination campaigns, not only considering their training on hospital wards, but also their future professional roles.[7]

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Healthcare workers' advice plays a key role in shaping patient attitudes to vaccination and in guiding their vaccination decisions. Systematic reviews show that greater trust in healthcare workers, especially general practitioners, is associated with a greater likelihood of accepting vaccines.[7,8] Similarly, it is well established that healthcare workers with little confidence in the benefits and safety of vaccination will be less likely to recommend vaccination for patients, children, and themselves.[8]

For some diseases, booster doses may be required to induce long-term immunity. Some studies indicate that a documented vaccination history is adequate proof of immunity, i.e., serology is not required for confirmation purposes.[9] However, measles and mumps outbreaks may cause vaccinated persons to become infected,[10,11] while hepatitis B vaccine-induced immunity declines over time.[12] For this reason, booster doses are recommended as a means to control transmission.[10–12] In this regard, it is important to explore the reliability and immune protection of documented vaccination history to decide whether a documented vaccination history is sufficient in high-risk situations or whether true immune protection should be confirmed by serology.

In Catalonia (Spain), some current vaccination schedules for vaccine-preventable diseases, such as varicella, were introduced in the last 25 years and were either unavailable to the current adult population at that time or were poorly documented (Supplementary document. Vaccination age in vaccination calendars in Catalonia).

The aim of this study was to analyze immunity to vaccine-preventable diseases and the predictive value of documented vaccination history *versus* serological results in medical students.

Methods

We carried out an epidemiological study of antibody seroprevalence and vaccination against vaccine-preventable diseases among medical students attending teaching units of medicine at four university hospitals in Catalonia (Spain): Hospital Clinic de Barcelona-Universitat de Barcelona, Hospital Universitari de la Vall d'Hebron-Universitat Autónoma de Barcelona, Hospital Universitari Germans Tries i Pujol-Universitat Autónoma de Barcelona, and Hospital Universitari Arnau de Vilanova-Universitat de Lleida.

No sampling was applied; rather, 569 eligible 3rd- to 6th-year medical students (enrolled during the September 2023–June 2024 academic year at any of the four participating teaching units of medicine) were invited to participate, after being provided with comprehensive information on the study, which included aims, the vaccination schedule, the need for a blood sample, questionnaire completion, assurances of anonymity, and informed consent.

Blood samples were drawn from participants, who, earlier in the same consultation, were administered an epidemiology questionnaire regarding their compliance with the Catalan recommended vaccination schedule and the official calendar of the Interterritorial Council of the National Health System of Spain.

In Catalonia, as in Spain, measles, rubella, mumps, and hepatitis B vaccines are recommended and provided free to the general population and healthcare workers. The Catalan recommended schedule, but not those of other Spanish regions, also includes hepatitis A since 2000.[13–15] Two doses of the varicella vaccine were introduced in 2005 for 12-year-old children with no history of the disease. In 2016, the schedule was updated to administer two doses at 15 months and 3 years of age (Supplementary document. Vaccination age in vaccination calendars in Catalonia). Additionally included in our study were COVID-19 and varicella vaccines received outside the schedule (as documented in any official record provided by the participant). Therefore, the present study covers seven vaccine-preventable diseases, but only measles, rubella, mumps, and hepatitis B were considered to assess adherence to the recommended vaccination schedule. Protective antibody analyses for each disease were performed in accordance with the procedures of the participating hospital laboratories. Procedures were established to analyze immune status for the studied diseases, using the chemiluminescence immunoassay (CLIA) technique, as follows: anti-HAV IgG and total antibodies for hepatitis A; antibody titers against the surface antigen (HBsAg) and the core antigen (HBcAc) for hepatitis B; specific IgG for mumps, rubella, measles, and varicella; and anti-spike SARS-CoV-2 IgG for COVID-19 (Supplementary table S1).

We used the European Joint Action on Vaccination (EU-JAV) student survey,[16] adapted to reflect the specific context of Catalan medical students and ensuring both conceptual and semantic equivalence. To

assess clarity and readability, the survey was pilot-tested on 10 medical students and healthcare professionals.

The questionnaire, with 19 items in total (both single- and multiple-choice options), collected information on age, sex, country of origin, future medical specialty (medical, surgical, other), compliance with the recommended vaccination schedule (yes/no), and vaccination against each of the seven studied diseases.

Data were described as percentages with their 95% confidence interval (CI) and as means and standard deviation (SD) for qualitative and quantitative variables, respectively. The statistical analyses were based on the chi-square test or Fisher's exact test, as appropriate, with a p-value <.05. In the bivariate analysis, for reasons of statistical robustness, the 'no' and 'unknown' responses for the 'fully vaccinated, self-reported' variable were grouped into a single variable. The associations between this variable and the other study variables were calculated using the odds ratio (OR) and the 95% CI. We calculated the positive predictive value (PPV) and 95% CI for each disease. The PPV reflected the protection afforded by documented vaccination (self-reported by participants) compared with serological results.[17] The numerator was the number of students with documented vaccination and a positive serology result, and the denominator was the number of students with documented vaccination only, i.e., excluding students with indeterminate serological results and unknown compliance with the recommended vaccination schedule.

Data analysis was performed with the Open Epi program.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committees of the University of Barcelona (CBUB-IRB00003099) and of each participating hospital (*Comitè d'Ètica d'Investigació amb medicaments* -CEIm- Hospital Universitari Vall d'Hebron: EOM(AG)034/2023; CEIm Hospital Universitari Arnau de Vilanova: CEIC-2884; CEIm Hospital Clínic de Barcelona: HCB/2023/1154; and CEIm Hospital Universitari Germans Trias i Pujol: PI-23–237). All subjects included in the study received detailed information on the study and its aims and granted their consent to participate.

Results

Of the 569 medical students invited to participate, 28.1% (160/569) responded, 69.6% of whom were women (67.5% to 71.1% depending on the center). Once 14 responses were excluded due to incomplete questionnaires, 146 participants were enrolled in the study (participation 25.7%; 146/569), with women accounting for 79.5% (116/146) (Figure 1). Mean (SD) age was 22.6 (1.6) years. All but six students were born in Spain (95.5%; 140/146), the majority were in 5th year (69.2%; 101/146), and most had a preference for medical specialties (51.4%; 75/146) (Table 1).

A high proportion of participants (84.2%; 123/146) self-reported being fully vaccinated in accordance with the Catalan recommended vaccination schedule, 12.3% (18/146) were unaware of their vaccination status, and 3.4% (5/146) reported not being fully vaccinated.

As for students' opinions and beliefs, over 99% fully/quite agreed that vaccines were both safe and effective (Table 1).

Documented vaccination for the vaccination schedule diseases was high for both sexes, all age groups, all included degree years, and all future medical specialties, and also in relation to opinions and beliefs regarding vaccine safety and effectiveness (Table 2). The only variable associated with lower documented vaccination was country of origin: just 3 of the 6 students from a country other than Spain had a correctly documented vaccination history.

For each of the seven diseases, when documented vaccination was compared with serological results, the PPV reflecting immunological protection according to documented vaccination was above 90% for varicella (100%), COVID-19 (99.1%), hepatitis A (98.9%), and rubella (94.8%). However, PPVs of documented vaccination were at or below 90% for three of the seven studied diseases: measles (90.0%), mumps (85.9%), and hepatitis B (67.2%) (Table 3 and Supplementary Table S3).

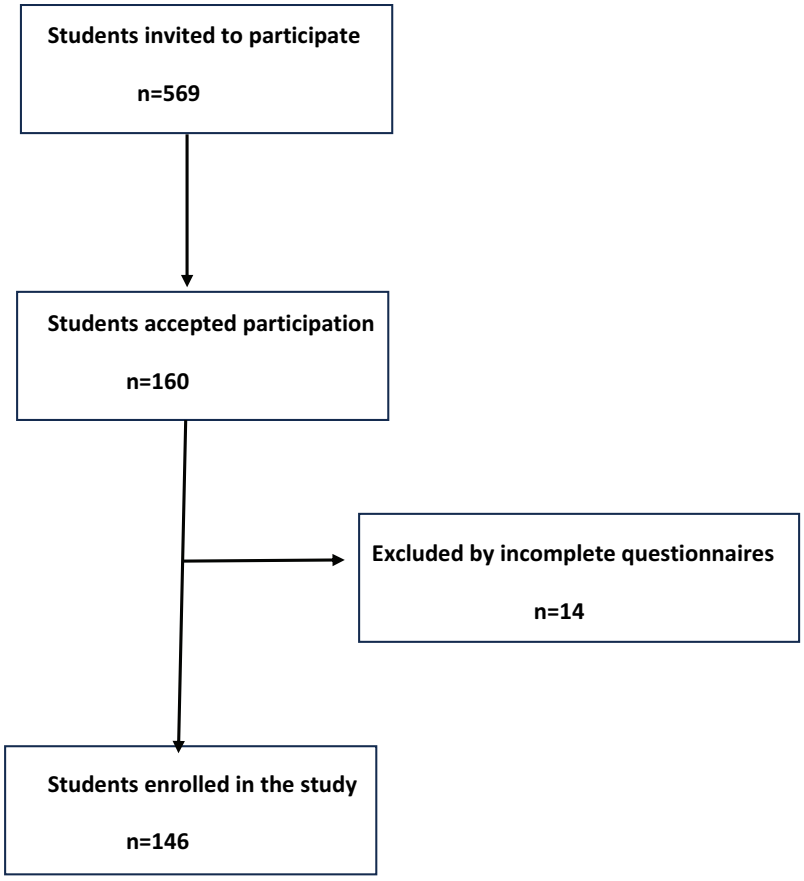

Figure 1. Flow diagram of recruitment and participation in the study.

Discussion

Most of the participants in our study self-reported full adherence to the recommended vaccination schedule. However, highlighting potential gaps in vaccination awareness among medical students was the fact that 15% were either unaware of the vaccines they had received or reported not being vaccinated.

Vaccine safety and effectiveness were both rated highly by the students and were compatible with their beliefs. The high opinions on vaccine safety and effectiveness of vaccines, which corroborate the findings of another study conducted in Spain,[18] would indicate that students are well trained and trust the recommendations of health authorities.

The only variable associated with lower vaccination coverage was origin in a country other than Spain, but non-Spanish subgroup findings are exploratory due to small sample size. While this lower vaccination coverage for students originating abroad corroborates observations by other authors,[19] the number of overseas students in our study was too small to be able to draw conclusions or make generalizations.

Documented vaccination history prevalence, at 85%, was similar to the 87% observed in the Baer et al.[2] study of 170 medical students in Switzerland. While this prevalence may be considered high, it is not only insufficient for regions with measles and rubella elimination programs, but is especially so for healthcare workers and medical students, whose infection risk has been reported to be around 13 times higher than for the general population.[20]

While we observed high PPV of documented vaccination as proof of immunity for most of the vaccine-preventable diseases, PPVs were 90% or lower for three of the seven studied diseases: measles (90.0%), mumps (85.9%), and hepatitis B (67.2%). These relatively low PPV, especially for a potentially severe disease (hepatitis B) and for a disease focused on by an elimination program (measles), would indicate the need for serology testing and booster vaccination for certain risk situations.[10,11]

Only 67.24% of our hepatitis B-vaccinated students had protective titers greater than 10 IU/mL. Other authors have indicated that primary vaccination for hepatitis B may not provide lifelong immunity and that

Table 1. Characteristics of the participating medical students and their compliance with the recommended vaccination schedule.

Variable	*N* = 146	%
Country of birth		
Spain	140/146	95.9
Other	6/146	4.1
Sex		
Male	30/146	20.5
Female	116/146	79.5
Age group (years)		
19–24	135/146	92.5
25–31	11/146	7.5
Medical degree year		
3rd	8/146	5.5
4th	20/146	13.7
5th	101/146	69.2
6th	17/146	11.6
Future specialty		
Medical	67/146	45.9
Surgical or medical-surgical	69/146	47.3
Family/community medicine	7/146	4.8
Preventive medicine/Other/Don't know	3/146	2.1
Fully vaccinated, self-reported		
No	5/146	3.4
Yes	123/146	84.2
Unknown	18/146	12.3
Vaccines are safe		
Fully/quite agree	145/146	99.3
Fully/strongly disagree/don't know	1/146	0.7
Vaccines are effective		
Fully/quite agree	146/146	100
Fully/strongly disagree/don't know	0/146	0.0
Vaccines are compatible with my beliefs		
Fully/quite agree	146/146	100
Fully/strongly disagree/don't know	0/146	0.0

Table 2. Bivariate analysis of factors associated with self-reported adherence to the recommended vaccination schedule.

	Self-reported adherence to recommended vaccination schedule*			
Variables	Yes, *N* (%)	No*, *N* (%)	OR (95% CI)	*P* value
Country of birth				
Spain	120 (85.7)	20 (14.3)	–	–
Other	3 (50.0)	3 (50.3)	–	
Sex				
Male	25 (83.3)	5 (16.7)	0.9 (0.3–2.7)	.877
Female	98 (84.5)	18 (15.5)	1.0	
Age group (years)				
19–24	113 (83.7)	22 (16.3)	0.5 (0.1–4.2)	.528
25–31	10 (90.9)	1 (9.1)		
Medical degree year				
3rd	6 (75.0)	2 (25.0)	1.0	–
4th	15 (75.0)	5 (25.0)	1.0 (0.1–6.6)	.978
5th	86 (85.1)	15 (14.8)	1.9 (0.3–10.7)	.446
6th	16 (94.1)	1 (5.9)	5.3 (0.4–70.2)	.255
Future specialty				
Medical	64 (83.1)	13 (16.9)	0.8 (0.3–2.0)	.702
Surgical or medical-surgical	59 (85.5)	10 (14.5)	1.0	
Vaccines are safe				
Fully/quite agree	123 (84.8)	22 (15.2)	–	–
Fully/strongly disagree/don't know	0 (0.0)	1 (100.0)		
Vaccines are effective				
Fully/quite agree	123 (84.2)	23 (100)	–	–
Fully/strongly disagree/don't know	0 (0.0)	0.0		
Vaccines are compatible with my beliefs				
Fully/quite agree	123 (84.2)	23 (100)	–	–
Fully/strongly disagree/don't know	0 (0.0)	0.0		

*No, includes No and Unknown. OR, odds ratio; CI, confidence interval.

*The study covered seven vaccine-preventable diseases, but only measles, rubella, mumps, and hepatitis B were considered to assess adherence to the recommended vaccination schedule.

Table 3. Predictive value of documented vaccination versus serological results*.

	Serological results			
Compliance with recommended vaccination schedule	Positive	Negative	Predictive value	95% CI
Hepatitis A				
Yes	91 (97.8%)	1 (3.3%)	98.91%	(94.1, 99.81)
No	2 (2.2%)	29 (96.7%)	93.55%	(79.28, 98.21)
Hepatitis B**				
Yes	78 (67.2%)	38 (37.8%)	67.24%	(58.27, 75.11)
No	1 (100%)	–	0.01%	(0.0, 79.35)
COVID-19				
Yes	111 (99.1%)	1 (0.9%)	99.11%	(95.12, 99.84)
No	1 (100%)	–	0.01%	(0.0, 79.35)
Rubella				
Yes	109 (94.8%)	6 (5.2%)	94.78%	(89.08, 97.59)
No	8 (80.0%)	2 (20.0%)	20%	(5.67, 50.98)
Measles				
Yes	99 (92.9%)	11 (10.0%)	90.00%	(82.98, 94.32)
No	8 (88.2%)	1 (11.8%)	11.11%	(1.99, 43.5)
Mumps				
Yes	104 (85.9%)	17 (14.1%)	85.95%	(78.65, 91.04)
No	8 (72.7%)	3 (27.3%)	27.27%	(9.75, 56.57)
Varicella**				
Yes	19 (100%)	–	100%	(83.18, 100)
No	101 (99.0%)	1 (1.0%)	0.98%	(0.17, 5.35)

*Students with indeterminate serological results and unknown compliance with the recommended vaccination schedule for the specific disease are excluded from the analysis. (See Supplementary Table S2).
** Hepatitis B PPV calculation excludes 12 unknown vaccination status and 17 indeterminate serological results of participants.
** Varicella denominators exclude 3 unknown vaccination status and 22 indeterminate serological results.
CI, confidence interval.

booster doses may be necessary.[12] Dawson et al.[21] reported that only 33% of undergraduate nursing students at a US university had HBsAc >10 IU/mL, and Alshehri et al.[22] similarly reported that 81.7% of a sample of Saudi Arabian medical students had insufficient hepatitis B antibody levels. Phattraprayoon et al.,[12] for a study in Thailand, reported an annual overall surface antigen antibody decline of 42.39 mIU/mL, concluding that primary vaccination may not provide lifelong protection since hepatitis B immunity declines over time. In Spain, the hepatitis B vaccine is administered at the ages of 2, 4, and 11 months; hence, the fact most of the medical students in our study would have received the vaccine more than 20 years ago may explain why some had antibody levels below the seroprotective threshold.

The PPV of measles vaccination was 90%, insufficient in a region with a measles elimination program, and especially for healthcare workers and medical students, who run a greater risk of measles than the general population.[20] As one example, 13 of 14 cases of measles in a nosocomial outbreak in public hospitals in Marseille (France) occurred in healthcare workers aged under 30 years.[11] Some studies have documented even lower antibody prevalences:[4,19]. In their study of 1,467 Italian medical students, Coppeta et al.[19] reported protective antibody prevalence of 66.7% overall and 44.4% for overseas students, and warned of the importance of checking the protective antibody levels of students before they started clinical practice. In Spain, since measles-mumps-rubella (MMR) vaccines are administered at 12 months and 3–4 years, most of the medical students in our study may be experiencing waning immunity. Furthermore, a drastic reduction in recent years in the circulation of the measles and mumps viruses in the Spanish population means that our students have had few natural boosters from exposure.

Measles is highly transmissible, and because response to one and two vaccine doses is 90%–95% and 97%, respectively,[23] two doses are needed to sustain control and elimination. Given the risk of occupational exposure, Coppeta et al.[19] indicate that the ideal immunity rate for healthcare workers should be 100% in order to avoid nosocomial spread of a virus. For diseases, like measles, which are the focus of elimination programs, low serological levels would indicate the need for individual serology testing and booster vaccination.

Only 85.95% of vaccinated participants had protective antibodies against mumps, i.e., the PPV of a documented vaccination history was the lowest of the three diseases covered by the MMR vaccine. Since 2000, the incidence and number of outbreaks of mumps have increased, and most outbreaks have occurred in young adults who had been vaccinated twice.[3,10] Mumps outbreaks in vaccinated populations

point to a need to study possible interventions, such as a third MMR dose (MMR3) for persons considered at increased risk by public health authorities, and irrespective of documented age-appropriate vaccination. A recent large effectiveness study of MMR3-vaccinated University of Iowa students reported that the mumps attack rate was lower in students who had received three compared to two MMR doses (6.7 vs 14.5 cases per 1000 population).[10] Furthermore, administration of a third dose of a mumps-containing vaccine in specific situations is supported by a recent position paper on mumps vaccination.[24]

Several factors may contribute to observed post-vaccination seroprevalence differences, despite MMR vaccine administration, between the three viruses. According to clinical data from the Summary of Product Characteristics (Priorix, GlaxoSmithKline), rubella shows a slightly higher initial seroconversion rate (100%) than measles (98.1%) and mumps (94.4%) following a single dose. While these differences are small, they may partly contribute to the higher long-term seropositivity observed for rubella. Additionally, the rubella component is known to induce a more durable immune response, possibly due to its slower antigenic evolution and lower waning rate.[25]

Regarding study limitations, the request for documentary evidence of their vaccination status may have acted as a disincentive for candidate participants, nor can we rule out the possibility of error in the vaccinations administered. The small subgroup of non-Spanish students ($n = 6$) precluded meaningful statistical comparison; findings should be interpreted as exploratory. The representativeness of the study is limited by the low participation rate and the high percentage of women among the participants. Nonetheless, the gender balance of the sample (79.5% women) reflects the current men/women distribution of medical students at the four participating Catalan teaching units of medicine. Since our study relied on voluntary participation, self-selection bias was possible, making the sample unrepresentative of all medical students. Furthermore, social desirability bias may have resulted in some survey questions (especially those related to vaccine safety and effectiveness) being answered according to perceptions of social acceptability, although the guarantees of anonymity and confidentiality should have mitigated this possible bias. Some responses may also have been influenced by the immune status of the students, although since the survey was completed before blood sample analysis, the students would not have known their serological results. Individuals who are seronegative after vaccination may still retain cellular immune memory (T-cell responses) that can provide protection or mitigate disease severity. Therefore, the observed lack of protection may partly reflect methodological limitations rather than true susceptibility.

As for strengths, the study was based on an anonymous and confidential questionnaire, vaccination was confirmed by health documentation to avoid recall error, and opinions on vaccine safety and effectiveness were collected before serological results were known.

Conclusions

Documented vaccination in relation to the recommended vaccination schedule is high and is consistent with medical students' opinions on vaccine safety and effectiveness. The PPV of documented vaccination compared to serological as proof of immunity is above 90% for most vaccines, except for measles and mumps, and most especially for hepatitis B. Our findings for those three diseases suggest that documented vaccination should be contrasted with serological results for medical students so that booster doses are administered if necessary. For measles and mumps, targeted serology and boosters may be necessary. Given the low PPV (67.2%) for hepatitis B, routine serological screening and booster doses for medical students should be considered, irrespective of documented vaccination history. In addition, immunization records should be a condition of admission to medical studies, and optionally, serological testing could be a requirement for elimination and control program diseases, such as measles and hepatitis B.

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Angela Domínguez (AD) contributed to study conceptualization and design, Pere Godoy (PG), Diana Toledo (DT), and AD contributed to formal data analysis, data interpretation, and writing of the first draft. Irma Casas (IC), Karen Colmenares (KC), Anna Vilella (AV), Andreu Prat (AP), Saray Mormeneo-Bayo (SM), Rosa Bartolomé (RB), and

Mercè Ibarz (MI) have access to the dataset, contributed to data collection, data analysis, and data interpretation, and critically reviewed the manuscript. All co-authors had access to and verified the data reported in the study. All authors have read and agreed to the published version of the manuscript.

Author contributions

CRediT: **Pere Godoy:** Formal analysis, Investigation, Methodology, Validation, Writing – original draft; **Diana Toledo:** Data curation, Formal analysis, Writing – review & editing; **Irma Casas:** Data curation, Investigation, Writing – review & editing; **Karen Colmenares:** Data curation, Investigation, Writing – review & editing; **Anna Vilella:** Data curation, Investigation, Writing – review & editing; **Andreu Prat:** Data curation, Investigation, Writing – review & editing; **Saray Mormeneo-Bayo:** Data curation, Investigation, Writing – review & editing; **Rosa Bartolomé:** Data curation, Investigation, Writing – review & editing; **Mercè Ibarz:** Data curation, Investigation, Writing – review & editing; **Angela Domínguez:** Data curation, Investigation, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

De-identified data available from corresponding author under data-sharing agreement.

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