Quando solicitar e como interpretar os testes diagnósticos

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21/05/2020

Webinar - Covid-19 na Hematologia Pediátrica

Declaração de conflito de interesse

- Sem conflito de interesse

Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19

Published by IDSA, 5/6/2020

Table 1. Symptoms Compatible with COVID-19

Symptoms may appear **2-14 days after exposure to the virus.** People with these symptoms or combinations of symptoms may have COVID-19*	*Respiratory symptoms alone* • Cough • Shortness of breath or difficulty breathing *Or at least two of these symptoms* • Fever • Chills • Repeated shaking with chills • Muscle pain • Headache • Sore throat • New loss of taste or smell

Children have similar symptoms to adults and generally have mild illness.

*This list is not all inclusive.

Centers for Disease Control and Prevention. Symptoms of Coronavirus. Available at:
https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents
A Systematic Review

Riccardo Castagnoli, MD; Martina Votto, MD; Amelia Licari, MD; Ilaria Brambilla, MD, PhD; Raffaele Bruno, MD; Stefano Perlini, MD; Francesca Rovida, PhD; Fausto Baldanti, MD; Gian Luigi Marseglia, MD
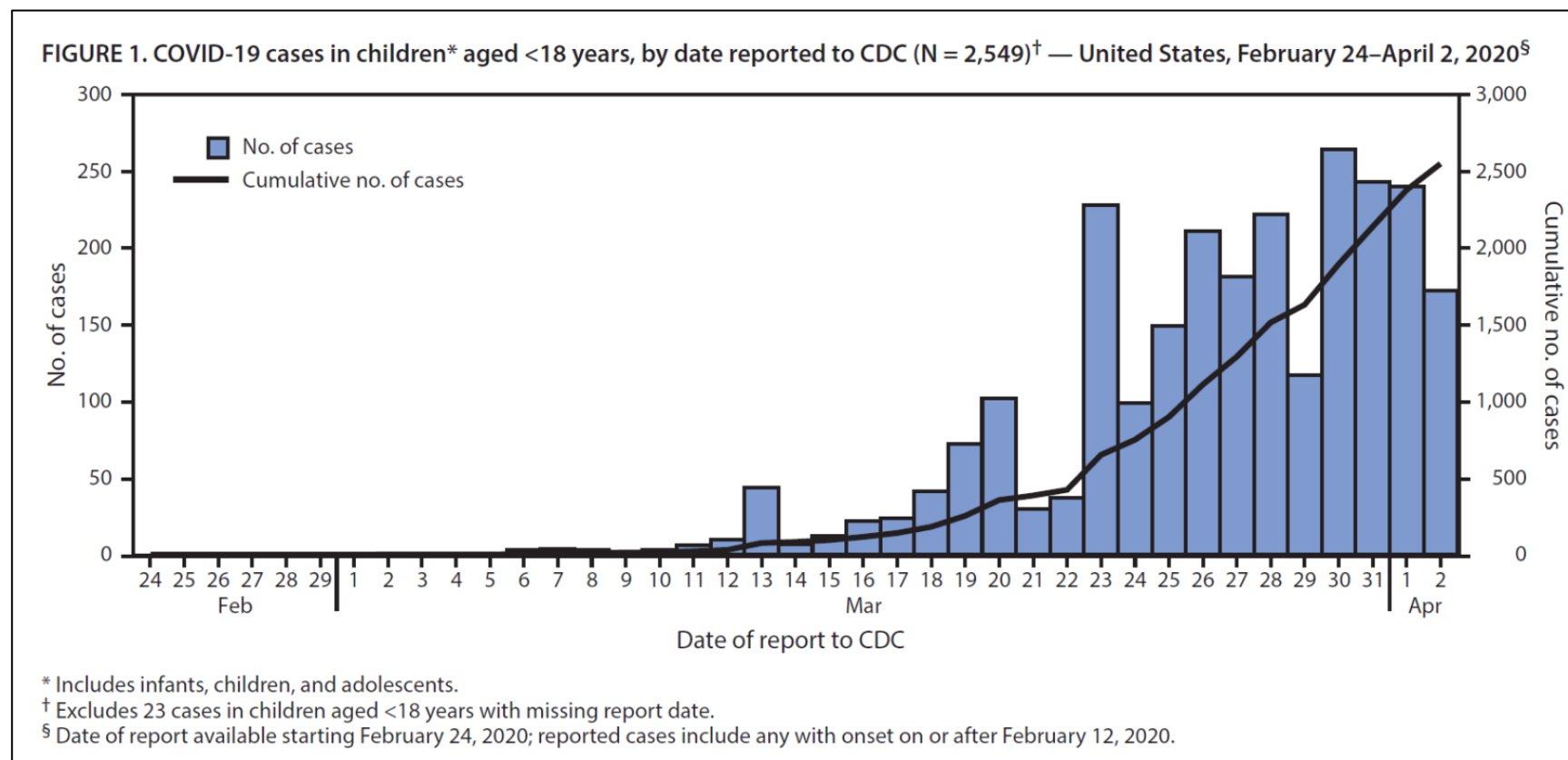
Pesquisa: artigos de 01/12/19 a 03/03/2020

FINDINGS A total of 815 articles were identified. Eighteen studies with 1065 participants (444 patients were younger than 10 years, and 553 were aged 10 to 19 years) with confirmed SARS-CoV-2 infection were included in the final analysis. All articles reflected research performed in China, except for 1 clinical case in Singapore. Children at any age were mostly reported to have mild respiratory symptoms, namely fever, dry cough, and fatigue, or were asymptomatic. Bronchial thickening and ground-glass opacities were the main radiologic features, and these findings were also reported in asymptomatic patients. Among the included articles, there was only 1 case of severe COVID-19 infection, which occurred in a 13-month-old infant. No deaths were reported in children aged 0 to 9 years. Available data about therapies were limited.

Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020

CDC COVID-19 Response Team

EUA – 22% da população tem até 18 anos

Casos de Covid-19: 149.082 – menores de 18 anos: 2.572 (1,7%)

FIGURE 1. COVID-19 cases in children* aged <18 years, by date reported to CDC (N = 2,549)[†] — United States, February 24–April 2, 2020[§]

* Includes infants, children, and adolescents.
[†] Excludes 23 cases in children aged <18 years with missing report date.
[§] Date of report available starting February 24, 2020; reported cases include any with onset on or after February 12, 2020.

TABLE. Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients* with laboratory-confirmed COVID-19 — United States, February 12–April 2, 2020

|	No. (%) with sign/symptom	
Sign/Symptom	Pediatric	Adult
Fever, cough, or shortness of breath[†]	213 (73)	10,167 (93)
Fever[§]	163 (56)	7,794 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Runny nose[¶]	21 (7.2)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain[¶]	17 (5.8)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

* Cases were included in the denominator if they had a known symptom status for fever, cough, shortness of breath, nausea/vomiting, and diarrhea. Total number of patients by age group: <18 years (N = 2,572), 18–64 years (N = 113,985).
[†] Includes all cases with one or more of these symptoms.
[§] Patients were included if they had information for either measured or subjective fever variables and were considered to have a fever if "yes" was indicated for either variable.
[¶] Runny nose and abdominal pain were less frequently completed than other symptoms; therefore, percentages with these symptoms are likely underestimates.

FIGURE 2. COVID-19 cases among children* aged <18 years, among those with known hospitalization status (N = 745),[†] by age group and hospitalization status — United States, February 12–April 2, 2020
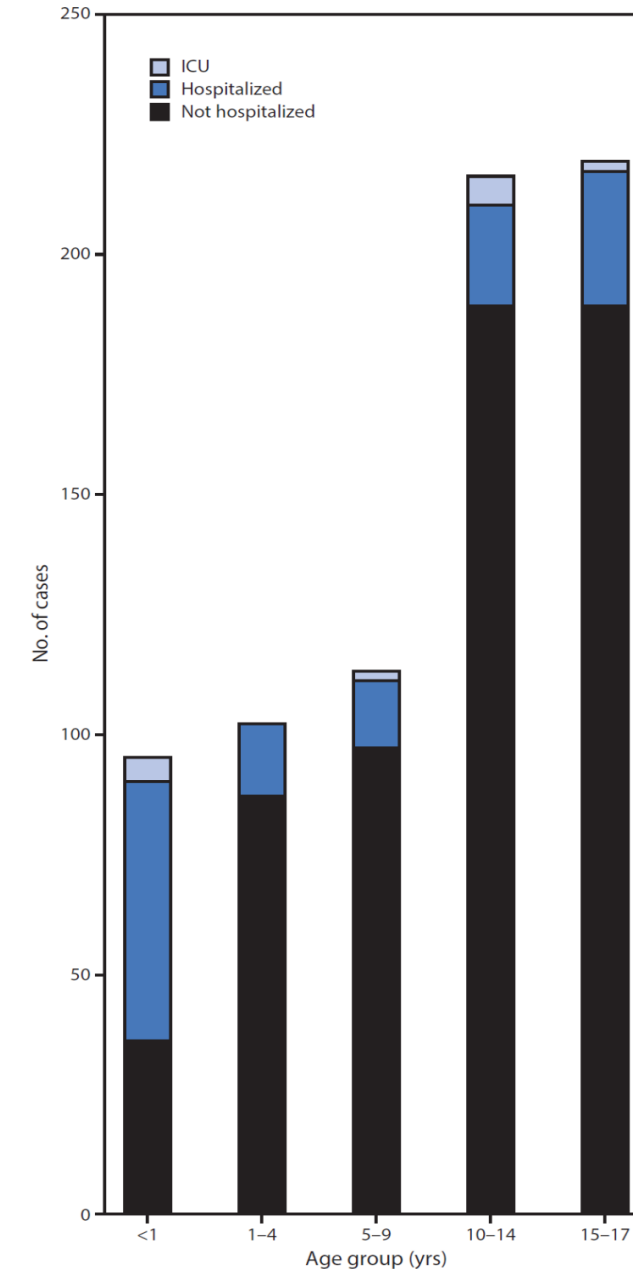
Table 1. Epidemiologic Characteristics, Clinical Features, and Outcomes in the Italian CONFIDENCE Cohort as Compared with Other Cohorts.*

Characteristics	CONFIDENCE Study (N=100)	Lu et al.[3] (N=171)	Dong et al.[4] (N=731)	CDC MMWR[5] (N=2572)†
Median age (range) — yr	3.3 (0–17.5)	6.7 (1 day–15 yr)	7 (NA)	11 (0–17)
Age distribution — no. (%)				
<1 yr	40 (40.0)	31 (18.1)	86 (11.8)	398 (15.5)
1 to <6 yr	15 (15.0)	40 (23.4)	137 (18.7)	NA
6–10 yr	21 (21.0)	58 (33.9)	171 (23.4)	NA
>10 yr	24 (24.0)	42 (24.6)	337 (46.1)	NA
Sex — no./total no. (%)				
Female	43/100 (43.0)	67/171 (39.2)	311/731 (42.5)	1082/2490 (43.4)
Male	57/100 (57.0)	104/171 (60.8)	420/731 (57.5)	1408/2490 (56.5)
Coexisting conditions — no./total no. (%)	27/100 (27.0)	NA	NA	80/345 (23.2)
Exposure to SARS-CoV-2 — no./total no. (%)				
Family cluster	45/100 (45.0)	131/171 (76.6)‡	NA	168/184 (91.3)
Other exposure	48/100 (48.0)	2/171 (1.2)	NA	16/184 (8.7)
Unknown exposure	7/100 (7.0)	15/171 (8.8)	NA	0
Signs and symptoms in patients for whom data were available — no./total no. (%)	100/100 (100.0)	171/171 (100.0)	0	291/2572 (11.3)
Symptomatic on presentation in emergency department — no./total no. (%)	79/100 (79.0)	144/171 (84.0)	637/731 (87.1)	291/2572 (11.3)
Fever, cough, or shortness of breath — no./total no. (%)	28/54 (51.8)	NA	NA	213/291 (73.2)
Fever — no./total no. (%)	54/100 (54.0)	71/171 (41.5)	NA	163/291 (56.0)
Temperature — no./total no. (%)§				
≤37.5°C	46/100 (46.0)	100/171 (58.5)	NA	128/291 (44.0)
37.6–38.0°C	15/100 (15.0)	16/171 (9.4)	NA	NA
38.1–39.0°C	28/100 (28.0)	39/171 (22.8)	NA	NA
>39.0°C	11/100 (11.0)	16/171 (9.4)	NA	NA
Symptoms — no./total no. (%)				
Cough	44/100 (44.0)	83/171 (48.5)	NA	158/291 (54.3)
Shortness of breath	11/100 (11.0)	NA	NA	39/291 (13.4)
No feeding or difficulty feeding	23/100 (23.0)	NA	NA	NA
Rhinorrhea	22/100 (22.0)	13/171 (7.6)	NA	21/291 (7.2)

Table 1. Epidemiologic Characteristics, Clinical Features, and Outcomes in the Italian CONFIDENCE Cohort as Compared with Other Cohorts.*

Characteristics	CONFIDENCE Study (N=100)	Lu et al.[3] (N=171)	Dong et al.[4] (N=731)	CDC MMWR[5] (N=2572)†
Drowsiness	11/100 (11.0)	NA	NA	NA
Nausea or vomiting	10/100 (10.0)	NA	NA	31/291 (10.6)
Fatigue	9/100 (9.0)	13/171 (7.6)	NA	NA
Diarrhea	9/100 (9.0)	15/171 (8.8)	NA	37/291 (12.7)
Dehydration	6/100 (6.0)	NA	NA	NA
Abdominal pain	4/100 (4.0)	NA	NA	17/291 (5.8)
Headache	4/100 (4.0)	NA	NA	81/291 (27.8)
Sore throat	4/100 (4.0)	NA	NA	71/291 (24.4)
Rash	3/100 (3.0)	NA	NA	NA
Cyanosis	1/100 (1.0)	NA	NA	NA
Apnea	1/100 (1.0)	NA	NA	NA
Tachypnea¶	NA	49/171 (28.7)	NA	NA
Tachycardia‖	NA	72/171 (42.1)	NA	NA
Oxygen saturation <92% as measured by pulse oximetry — no./total no. (%)	1/100 (1.0)	4/171 (2.3)	NA	NA
Outcome — no./total no. (%)				
Admitted	67/100 (67.0)	NA	NA	147/2572 (5.7)
Admitted for signs and symptoms	38/100 (38.0)	NA	NA	NA
Admitted and awaiting swab results	4/100 (4.0)	NA	NA	NA
Admitted for isolation	25/100 (25.0)	NA	NA	NA
Survived — no./total no. (%)	100/100 (100.0)	170/171 (99.4)	730/731 (99.9)	2569/2572 (99.9)
Died — no./total no. (%)	0	1/171 (0.6)	1/731 (0.1)	3/2572 (0.1)

Óbitos por faixa etária (NYC)

AGE	Number of Deaths	Share of deaths	With underlying conditions	Without underlying conditions	Unknown if with underlying cond.	Share of deaths of unknown + w/o cond.
0 - 17 years old	9	0.06%	6	3	0	0.02%
18 - 44 years old	601	3.9%	476	17	108	0.8%
45 - 64 years old	3,413	22.4%	2,851	72	490	3.7%
65 - 74 years old	3,788	24.9%	2,801	5	982	6.5%
75+ years old	7,419	48.7%	5,236	2	2,181	14.3%
TOTAL	15,230	100%	11,370 (75%)	99 (0.7%)	1,551 (24.7%)	25.3%

Underlying illnesses include Diabetes, Lung Disease, Cancer, Immunodeficiency, Heart Disease, Hypertension, Asthma, Kidney Disease, and GI/Liver Disease.

Atualizado até 12/05/2020

Letalidade por faixa etária

AGE	DEATH RATE confirmed cases	DEATH RATE all cases
80+ years old	21.9%	14.8%
70-79 years old		8.0%
60-69 years old		3.6%
50-59 years old		1.3%
40-49 years old		0.4%
30-39 years old		0.2%
20-29 years old		0.2%
10-19 years old		0.2%
0-9 years old		no fatalities

Fonte dos dados:
1.The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) - China CCDC, February 17 2020
2.Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Pdf] - World Health Organization, Feb. 28, 2020

https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/#ref-1

An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

	Group 1	Group 2	p value
Time of presentation	Until February, 2020	March–April, 2020	NA
Number of patients	19	10	NA
Age at onset, years	3·0 (2·5)	7·5 (3·5)	0·00035
Incidence	0·3 per month	10 per month	<0·00001
Sex	NA	NA	0·13
Female	12	3	NA
Male	7	7	NA
Incomplete Kawasaki disease	6/19 (31%)	5/10 (50%)	0·43
White cell count, ×10⁹ per L	19·4 (6·4)	10·8 (6·1)	0·0017
Neutrophils	71·9% (17·2)	84·5% (5·7)	0·034
Lymphocytes, ×10⁹ per L	3·0 (1·8)	0·86 (0·4)	0·0012
Haemoglobin, g/dL	10·8 (2·0)	11 (1·2)	0·79
Platelets, ×10⁹ per L	457 (96)	130 (32)	<0·00001

Table 2: Comparison between patients with Kawasaki-like disease presenting before and after the SARS-CoV-2 epidemic

Figure: Incidence of Kawasaki disease in the study period and in the past 5 years
(A) Frequency of Kawasaki disease at the paediatric emergency department of Hospital Papa Giovanni XXIII of Bergamo, Italy, in the past 5 years, by case severity. (B) Number of patients presenting to the paediatric emergency department during the severe acute respiratory syndrome coronavirus 2 epidemic, and date of presentation of ten patients with Kawasaki-like disease (indicated by asterisks).

Hyperinflammatory shock in children during COVID-19 pandemic

- Descrição de oito casos de Choque inflamatório. Um óbito
- Seis crianças eram afro-americanas e cinco meninos.
- Todas as crianças, exceto um, estavam acima do percentil 75 para peso.
- Quatro com exposição familiar à COVID-19
- As apresentações clínicas foram semelhantes:
  - febre (38-40 ° C), erupção cutânea variável, conjuntivite, edema periférico e de extremidades e sintomas gastrointestinais significativos
- Todos progrediram para choque vasoplégico refratário a volume
- A maioria sem alterações respiratórias significativas,
- Sete necessitaram de ventilação mecânica para estabilização cardiovascular.
- Todas tinham resultado negativo para PCR para SARS-CoV-2 em lavado broncoalveolar ou aspirado de nasofaringe
- Todas receberam IVIg no primeiro dia e cobertura antibiótica.
- Duas crianças testaram positivo para SARSCoV-2

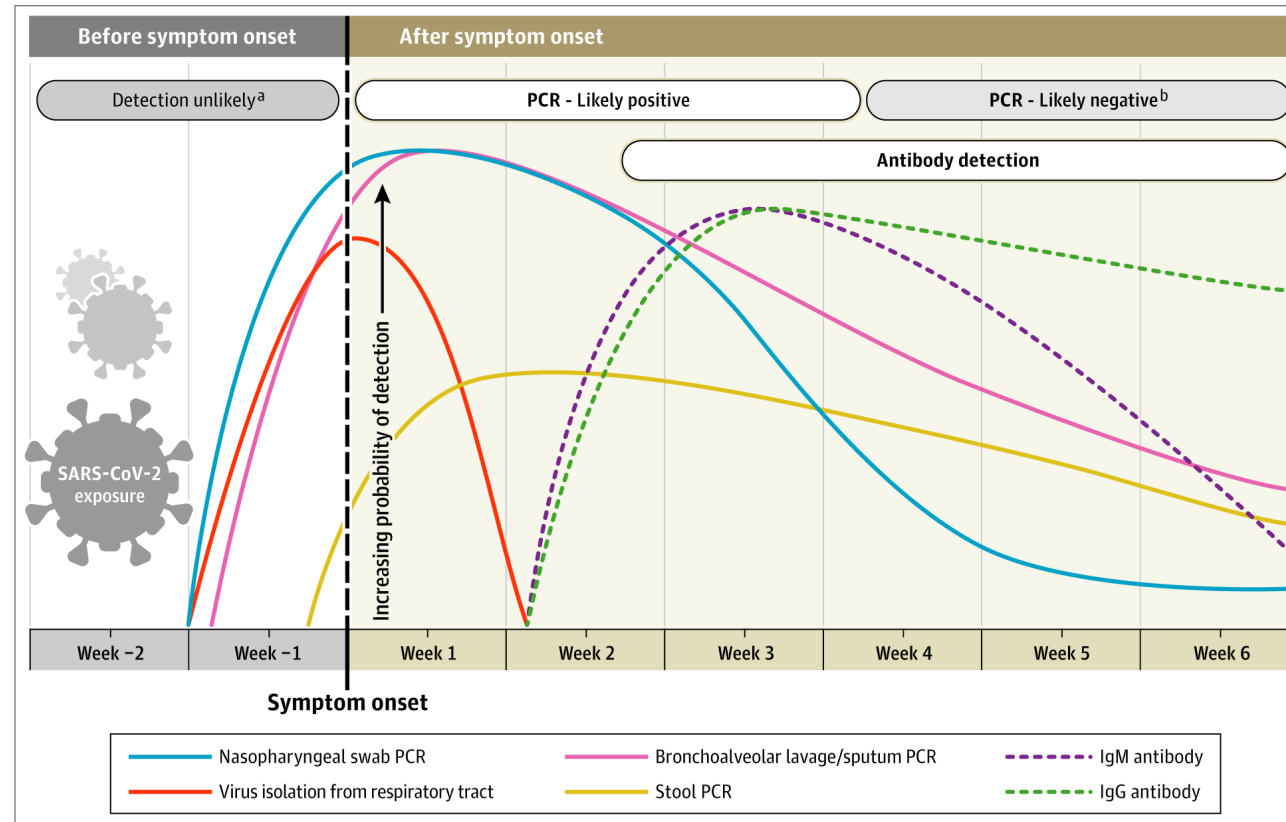*Shelley Riphagen et al. Lancet 2020*

Case definition:

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in Appendix 1). This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).

3. SARS-CoV-2 PCR testing may be positive or negative

Diagnóstico laboratorial

- RT-PCR em tempo real
- Sorologia
- Cultura viral
  - Apenas para pesquisa
- Sequenciamento
  - Monitorar mutações genômicas que possam afetar o desempenho de medidas, incluindo testes de diagnóstico.
  - Também pode informar a epidemiologia molecular estudos.

Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom OnsetEstimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a]Detection only occurs if patients are followed up proactively from the time of exposure.

[b]More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.
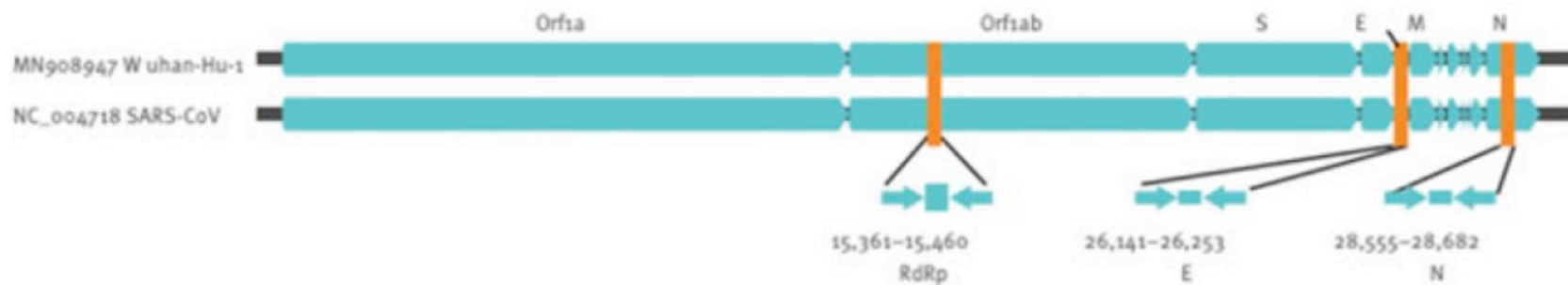
Fig. 9.5 Relative positions of amplicon targets on SARS-CoV-2 genome. *ORF* open reading frame, *RdRp* RNA-dependent RNA polymerase, *E* envelop protein gene, *N* nucleocapsid protein gene, *M* membrane protein gene, *S* spike protein gene

Table 9.2 Currently available protocol

Country	Institute	Gene targets
China	China CDC	ORF 1ab and N
Germany	Charitè	RdRp, E, N
Hong Kong SAR	HKU	ORF 1b-nsp14, N
Japan	National Institute of Infectious Diseases, Department of Virology	Pancorona and multiple targets, spike protein
Thailand	National Institute of Health	N
USA	US CDC	Three targets in N gene
France	Pasteur Institute, Paris	Two targets in RdRp gene

Adapted from WHO (2020e)

PCR falso negativo

Causas:

- Má qualidade da amostra, contendo pouco material do paciente

- Amostra coletada tardiamente ou muito cedo na infecção.

- Amostra não foi manuseada e enviada adequadamente (não manutenção da cadeia fria).

- Razões técnicas inerentes ao teste, por exemplo mutação viral ou inibição de PCR.

- Resultado negativo com alto índice de suspeita
  - Repetir coleta
  - Avaliar possibilidade de amostra de trato respiratório inferior

Table. Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase–Polymerase Chain Reaction

Specimens and values	Bronchoalveolar lavage fluid (n = 15)	Fibrobronchoscope brush biopsy (n = 13)	Sputum (n = 104)	Nasal swabs (n = 8)	Pharyngeal swabs (n = 398)	Feces (n = 153)	Blood (n = 307)	Urine (n = 72)
Positive test result, No. (%)	14 (93)	6 (46)	75 (72)	5 (63)	126 (32)	44 (29)	3 (1)	0
Cycle threshold, mean (SD)	31.1 (3.0)	33.8 (3.9)	31.1 (5.2)	24.3 (8.6)	32.1 (4.2)	31.4 (5.1)	34.6 (0.7)	ND
Range	26.4-36.2	26.9-36.8	18.4-38.8	16.9-38.4	20.8-38.6	22.3-38.4	34.1-35.4	
95% CI	28.9-33.2	29.8-37.9	29.3-33.0	13.7-35.0	31.2-33.1	29.4-33.5	0.0-36.4	

Abbreviation: ND, no data.

Table Title:

Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase–Polymerase Chain Reaction

# Virological assessment of hospitalized patients with COVID-2019
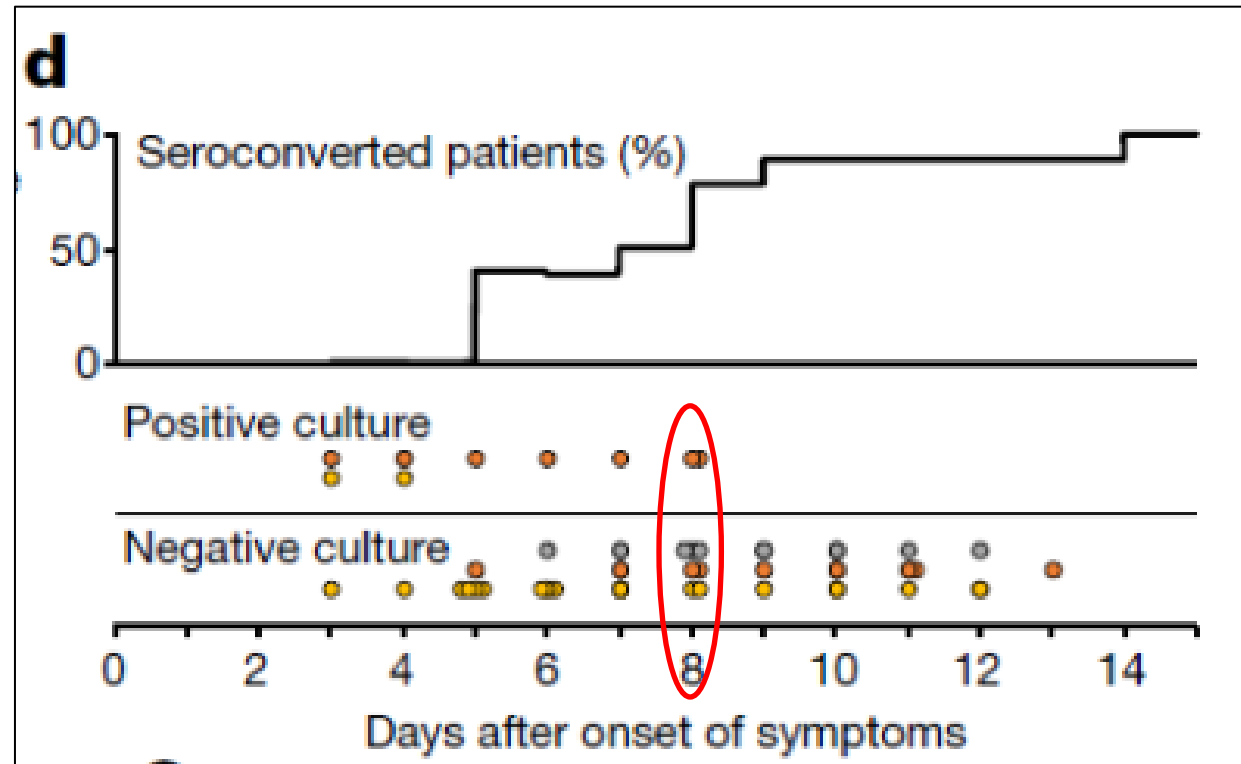
Testes sorológicos

- Normalmente, a maioria dos anticorpos é produzida contra a proteína mais abundante do vírus, que é o NC (nucleocapsídeo) → testes que detectam anticorpos para NC seriam os mais sensíveis.

- A proteína S (RBD-S) é a proteína de fixação do hospedeiro e os anticorpos para o RBD-S seriam mais específicos e espera-se que sejam neutralizantes.

- Os anticorpos podem, no entanto, ter reatividade cruzada com SARS-CoV e possivelmente outros coronavírus.

Testes sorológicos

- Os testes de anticorpos IgM e IgG baseados em ELISA têm > 95% de especificidade

- A coleta pareada de sorologia e PCR inicial, com a segunda amostra após duas semanas aumenta a precisão do diagnóstico.

- 208 samples from 82 confirmed and 58 probable cases (qPCR negative with typical manifestation).

- The median duration of IgM and IgA antibody detection was 5 (IQR, 3–6) days, while IgG was detected 14 (IQR, 10–18) days after symptom onset, with a positive rate of 85.4%, 92.7%, and 77.9%, respectively.

- The positive detection rate is significantly increased (98.6%) when combining IgM ELISA assay with PCR

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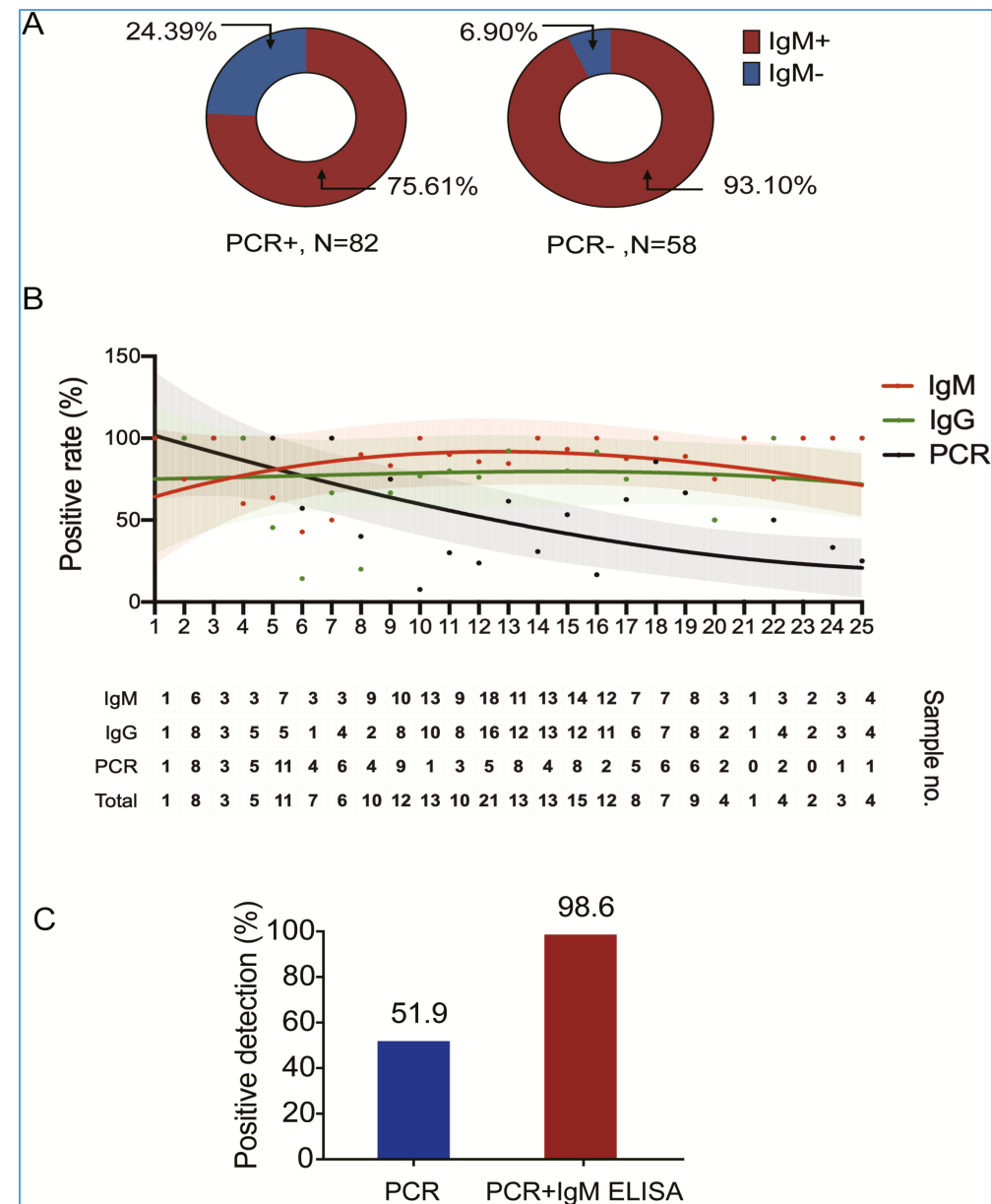
Figure 3. Characteristics of plasma antibodies in patients infected with SARS-CoV-2. A, Time of appearance of IgM, IgA, ...

- The median duration of IgM and IgA antibody detection was 5 (IQR, 3–6) days, while IgG was detected 14 (IQR, 10–18) days after symptom onset, with a positive rate of 85.4%, 92.7%, and 77.9%, respectively.
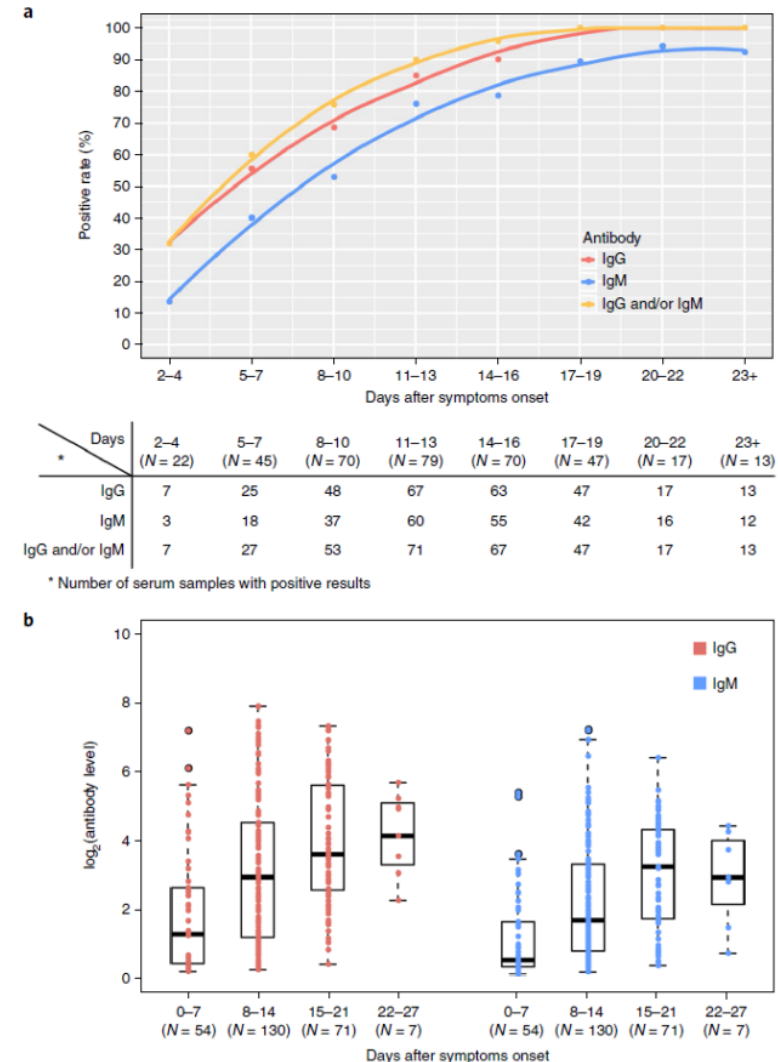
OXFORD
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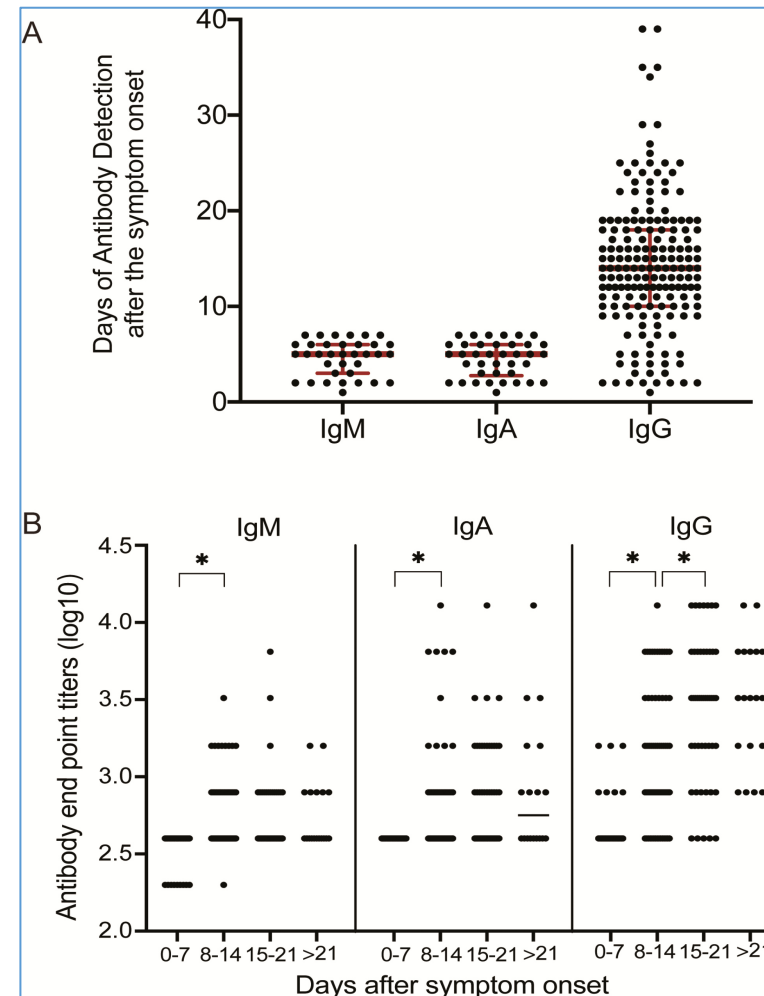
Antibody responses to SARS-CoV-2 in patients with COVID-19

Acute antibody responses to SARS-CoV-2 in 285 patients with COVID-19.

Within 19 days after symptom onset, 100% of patients tested positive for antiviral immunoglobulin-G (IgG). Seroconversion for IgG and IgM occurred simultaneously or sequentially.

and specificity, adds Collignon. That means that testing should turn up only about one false positive and one false negative for every 100 true positive and true negative results.

But some commercial antibody tests have recorded specificities as low as 40% early in the infection. In an analysis[2] of 9 commercial tests available in Denmark, 3 lab-based tests had sensitivities in the range of 67–93% and specificities of 93–100%. In the same study, 5 out of 6 point-of-care tests had sensitivities ranging from 80% to 93%, and 80–100% specificity, but some kits were tested on fewer than 30 people. Testing was suspended for one kit. Overall, the sensitivity of all the tests improved over time, with the highest sensitivity recorded two weeks after symptoms first appeared.

Point-of-care tests are even less reliable than tests being used in labs, adds Smith.

Despite the challenges, when reliable antibody tests are available, they could be important for understanding which groups of people have been infected and how to stop further spread, says Collignon. They could even be used to diagnose active infections when PCR tests fail, adds Smith.

News in focus

Antibody tests have been promoted as a way to get people back to work — but the reliability of their results is unknown.

WILL CORONAVIRUS ANTIBODY TESTS REALLY CHANGE EVERYTHING?

The rapidly developed tests have been touted as society's way out of widespread lockdowns, but scientists say it will be a while before they are as useful as hoped.

By Smriti Mallapaty

British Prime Minister Boris Johnson called them a "game changer". Antibody tests have captured the world's attention for their potential to help life return to normal by revealing who has been exposed, and might now be immune, to the new coronavirus.

Dozens of biotechnology companies and research laboratories have rushed to produce the blood tests. And governments around the world have bought millions of kits, in the hope that they could guide decisions on when to relax social-distancing measures and get people back to work. Some have even suggested that the tests could be used as an 'immunity passport', giving the owner clearance to interact with others again.

Many scientists share this enthusiasm. The immediate goal is a test that can tell healthcare and other essential workers whether they are still at risk of infection, says David Smith, a clinical virologist at the University of Western Australia in Perth. In the future, the tests could assess whether vaccine candidates give people immunity.

But as with most new technologies, there are signs that the promises of COVID-19 antibody tests have been oversold, and their challenges underestimated. Kits have flooded the market, but most aren't accurate enough to confirm whether an individual has been exposed to the virus.

And even if tests are reliable, they can't indicate whether someone is immune to reinfection, say scientists. It will be a while before kits are as useful as hoped, says Smith.

The UK government learnt about this the hard way after it ordered 3.5 million tests from several companies in late March, only to discover later that none of these tests