

National Pediatric Cardiology Quality Improvement Collaborative

Research Explained COVID-19 Special Report



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What is RESEARCH EXPLAINED?

Under the umbrella of the NPCQIC Research Committee, the primary goals of the Research Explained Committee are to monitor published research studies that utilize NPCQIC registry data and draft summary pieces to “explain the research”, their purpose and conclusions.

The committee also drafts summary pieces about hypoplastic left heart syndrome (HLHS) and other congenital cardiology research published in medical journals. The criteria considered for selecting research articles includes scientific merit, relevance and impact on medical practice patterns, and widespread family interest.

These “Research Explained” summary pieces are then shared with the families and the community.

Since the emergence of the novel coronavirus, SARS-CoV-2, which causes COVID-19 in late 2019, there has been worldwide spread that WHO has now declared it to be a pandemic. Despite the global impact, there is paucity of data on COVID-19’s clinical and epidemiological patterns, especially on children.

It is in this light that the Research Explained Committee has taken this challenge to find research articles with the most valuable information on COVID-19 to date (there may be more since the release of this report) and expeditiously draft Research Explained summary pieces for the community. It is our hope that this special report will provide some valuable information during this extraordinary time.

THE NPCQIC RESEARCH EXPLAINED COMMITTEE



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Research Explained

Epidemiology of COVID-19 Among Children in China

Yuanyuan Dong, Xi Mo, Yabin Hu, Fang Jiang, Zhongyi Jiang, Shilu Tong

<http://doi.org/10.1542/peds.2020-0702>

Clifford Cua MD (physician) and Richard James (parent)

ABOUT THIS STUDY

This study shows how the new COVID-19 virus affected more than 2,000 children in China. It describes how children of different ages caught the virus, how they were affected differently than adults, how sick they got, and how quickly they recovered.

Why is this study important

It is the first study that includes information about a large group of children infected with COVID-19. It shows that the children who were included in study may not have been as seriously affected as adults with the same virus.

- COVID-19 (2019 novel coronavirus) was first seen in early December 2019 in Wuhan, China.
- Since that report, COVID-19 has become widespread around the world.
- As of 3/26/2020, the Centers of Disease Control (CDC) have reported more than 80,000 possible cases of and more than 1,000 deaths due to COVID-19 in the US.
- Currently, most of the data concerning this virus has been in adults with very little written about children with COVID-19.
- This is the largest study to date which looks at how children are affected by COVID-19.

How was this study performed

- Analysis of records from pediatric patients (defined as less than 18 years old) who had been diagnosed as being infected with COVID-2019, with data obtained from the database at the Chinese CDC.
- Pediatric patients were put into categories of how much risk of infection they had:
 - High risk: child lived with or had direct contact with someone who had COVID-19
 - Medium risk: child lived in an area or community with many COVID-19 cases.
 - Low risk: lived in an area or community with few or no COVID-19 cases.
- Suspected cases were included in the study if a child was in the high-risk category **and** had two of the following conditions:
 - Fever, respiratory symptoms, digestive symptoms (e.g. vomiting, nausea, and diarrhea), or fatigue.
 - Abnormal blood test findings, where white blood cell counts were normal or decreased, or had high counts of a cells that are used to measure inflammation (C-reactive protein or lymphocytes)
 - Abnormal chest X-Rays.
- Suspected cases were defined as confirmed cases if:
 - Nasal or pharyngeal swabs or blood samples tested positive for COVID-19.
- Cases were grouped together by severity. This was defined by clinical symptoms, laboratory testing, and chest imaging findings:
 - Asymptomatic: No symptoms and no test results for infection.
 - Mild: some symptoms such as cough, sore throat, fever.
 - Moderate: fever and cough, wheezing, lung sounds heard with a stethoscope, some signs of infection on a chest X-ray or CT scan.
 - Severe: Fever and cough, shortness of breath and cyanosis, oxygen saturation of 92% or less.
 - Critical: Acute respiratory distress, shock, organ failure.

What were the results of the studies

- By 2/8/2020, 2143 pediatric patients with suspected or definite COVID-19 were reported.
 - The most common age of patients was 7 years old.

- Cases were equally divided between boys and girls.
- About one half of these patients had mild cases (50.9%, a total of 1091 cases)
- Just under 6% of these patients had severe or critical cases (5.9%, a total of 127 cases). This is much lower than the rate of severe or critical cases in adults.
- About 10% of infected children younger than one year old had severe or critical cases.
 - Only 1 death noted, 14 year-old boy (0.05%).

What are the limitations of this study

- The majority of patients were suspected cases of COVID-19, and only about 1/3 of cases were confirmed by laboratory testing. It is possible that some of the suspected cases of COVID-19 were actually due to other viruses such as RSV and influenza.
- Because there was no detailed exposure data, the researchers were unable to estimate the time from exposure to time to illness (incubation period).
- The epidemic is still ongoing and rapidly spreading so changes in overall pediatric data may also change.
- No data on any other underlying medical issues that the children may have had e.g. prematurity, bronchopulmonary dysplasia, congenital heart disease, heart failure, etc. to show if pediatric patients with these conditions are at greater risk from the virus.

What it all means

- Children of all ages can catch COVID-19.
- Children (5.9%) with COVID-19 are usually less sick than adults (18.5%).
- It is not yet known why COVID-19 is less severe in pediatric patients compared to adults.
- Infants (less than 1 year old) seem to be at higher risk for severe/critical illnesses, but there are some problems with the data of that age group, including that more infants counted as having severe or critical illness were not actually confirmed as having the virus through lab tests or X-ray.
- Disease controlling measures are effective in decreasing cases (i.e. social distancing, staying at home, etc.).

- While the US CDC has said that Congenital Heart Disease (CHD) is a risk factor for more severe cases of COVID-19, the Chinese data did not include children with CHD so it is not possible to confirm this from this study.

Tables and Figures

	Asymptomatic	Mild	Moderate	Severe	Critical
Clinical findings	No symptoms	Symptoms of upper respiratory tract infection (fever, fatigue, muscle aches, cough, sore throat, or runny nose) or digestive symptoms (nausea, vomiting, abdominal pain, or diarrhea). Congestion of pharynx and no lung findings	Pneumonia, frequent fever and cough (dry cough followed by productive cough), wheezing, lungs can hear sputum or dry snoring and/or wet snoring.	Fever and cough, may be accompanied by digestive symptoms. Usually progresses around 1 week and shortness of breath with central cyanosis occurs.	Acute respiratory distress syndrome (ARDS), respiratory failure, shock, encephalopathy, heart injury or failure, bleeding/clotting issues, and kidney dysfunction
Laboratory tests	+ COVID-19 test			Saturation less than 92%	
Chest imaging	Normal		Chest CT with lung lesions		

Table 1 Characteristics of Children' COVID-19 Cases in China

Characteristics	All cases	Different Category		
		Confirmed	Suspected	<i>P</i> Value
Median age (Interquartile range)	7.00 (11.0)	10.00(11.0)	6.00(10.0)	<0.001
Age group				
<1	379(17.7)	86(11.8)	293(20.8)	
1-5	493(23.0)	137(18.7)	356(25.2)	
6-10	523(24.4)	171(23.4)	352(24.9)	<0.001
11-15	413(19.3)	180(24.6)	233(16.5)	
>15	335(15.6)	157(21.5)	178(12.6)	
Gender				
Boy	1213(56.6)	420(57.5)	793(56.2)	0.567
Girl	930(43.4)	311(42.5)	619(43.8)	
Severity of illness				
Asymptomatic	94(4.4)	94(12.9)	0(0.0)	
Mild	1091(50.9)	315(43.1)	776(54.9)	
Moderate	831(38.8)	300(41.0)	531(37.6)	
Severe	112(5.2)	18(2.5)	94(6.7)	<0.001
Critical	13(0.6)	3(0.4)	10(0.7)	
Missing	2(0.1)	1(0.1)	1(0.1)	
Days from symptom onset to diagnosis				
Median days (Interquartile range)	2(4.0)	3(4.0)	2(4.0)	<0.001
Range	0-42	0-42	0-36	
Province				
Hubei	984(45.9)	229(31.3)	755(53.5)	
Surrounding areas*	397(18.5)	155(21.2)	242(17.1)	<0.001
Others	762(35.6)	347(47.5)	415(29.4)	
Total	2143	731(34.1)	1412(65.9)	

Data are presented with median (Interquartile range) and n (%).

*Surrounding areas are the provinces and Municipality bordering Hubei, they are Anhui, Henan, Hunan, Jiangxi, Shaanxi and Chongqing.

Age (years)	Percentage of severe and critical cases
Less than 1	10.6% (40/379)
1 – 5	7.3% (36/493)
6 – 10	4.2% (22/521)
11 – 15	4.1% (17/413)
Greater than 16	3.0% (10/335)
Total	5.8% (125/2141)

Table 2 Different Severity of Illness by Age Group

Age group*	Asymptomatic	Mild	Moderate	Severe	Critical	Total
<1	7(7.4)	205(18.8)	127(15.3)	33(29.5)	7(53.8)	379(17.7)
1-5	15(16.0)	245(22.5)	197(23.7)	34(30.4)	2(15.4)	493(23.0)
6-10	30(31.9)	278(25.5)	191(23.0)	22(19.6)	0(0)	521(24.3)
11-15	27(28.7)	199(18.2)	170(20.5)	14(12.5)	3(23.1)	413(19.3)
>15	15(16.0)	164(15.0)	146(17.5)	9(8.0)	1(7.7)	335(15.7)
Total	94	1091	831	112	13	2141(100)

Data were presented with number and percent (%);*Two cases had missing values.

Figure 1. Onset and diagnosis date of 2143 children's COVID-19 cases in China
 (A: onset date, B: diagnosis date)

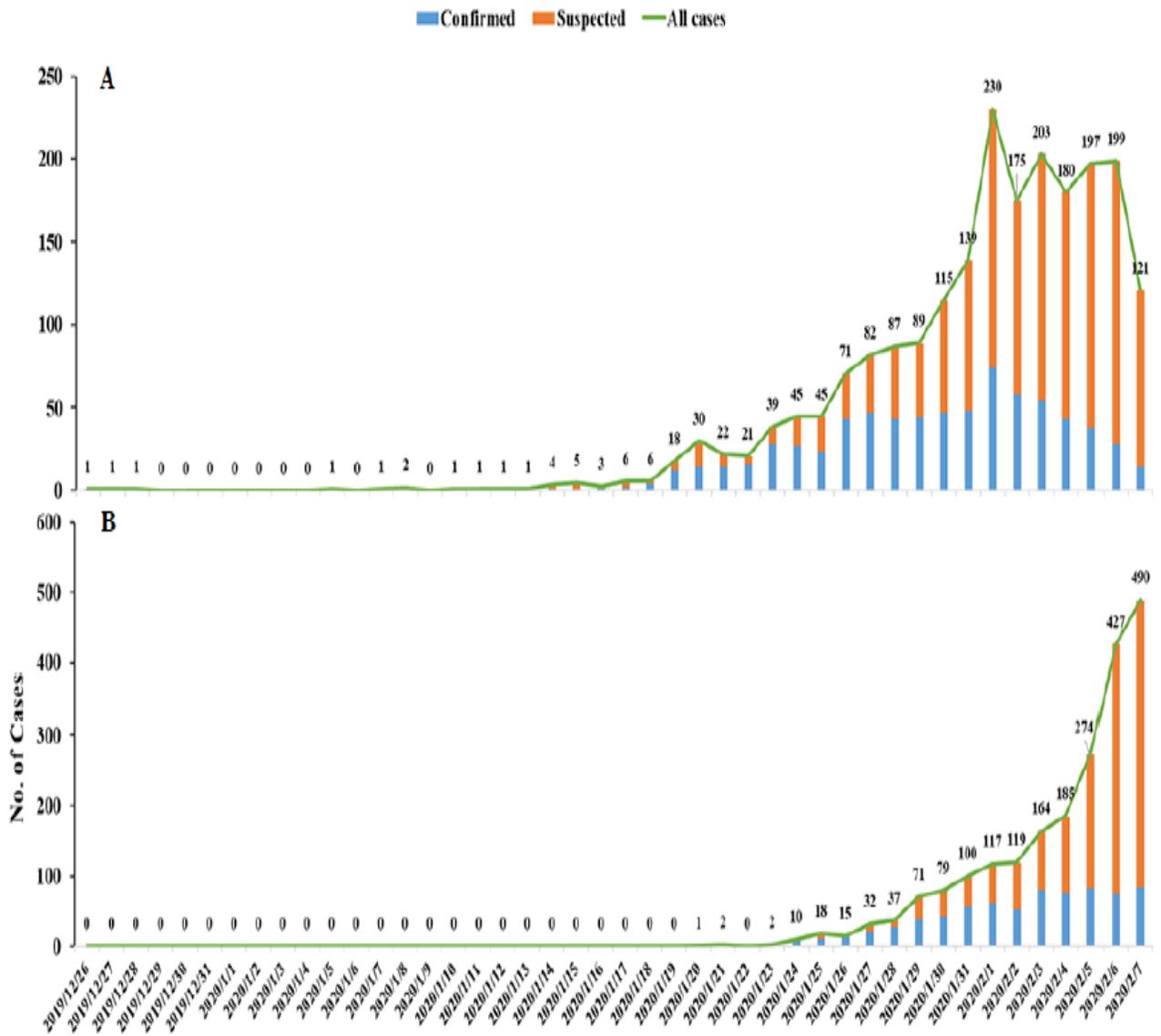


Fig 1 Onset and Diagnosis Date of 2143 children's COVID-19 Cases in China. A: onset date; B: diagnosis date

Figure 4. Relative frequency of days from symptom onset to diagnosis

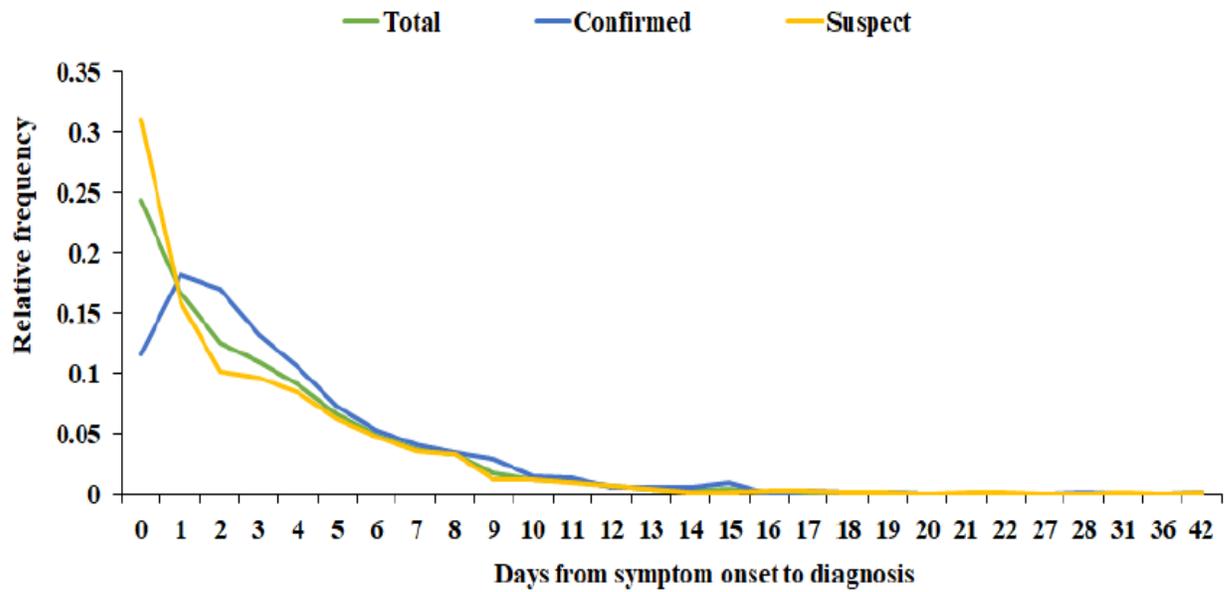


Fig 4 Relative Frequency of Days from Symptom Onset to Diagnosis.



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Research Explained

COVID-19 in Children: Initial Characterization of the Pediatric Disease

Cruz A, Zeichner S

Pre-publication acceptance to *Pediatrics*; 2020
doi:10.1542/peds.2020-0834

Thomas M Zellers MD (physician) and Dawn Mazzanti (parent)

ABOUT THIS STUDY

Why is this study important

- COVID-19 has become a pandemic since its index case in China in December 2019
- There is a significant mortality associated with COVID-19, 4% worldwide but reaching up to 10% in some countries
- Mortality increases in older age groups
- There is a lack of information about the course of COVID-19 in children

How was this study performed

- The most recent studies from China and Norway were read, evaluated and summarized, looking specifically at data on pediatric infections

What were the results of the studies

- Largest study reviewed had 2000 children infected with COVID-19
 - In this study 13% of the children were asymptomatic (this rate is almost certainly higher in reality since many asymptomatic children are unlikely to be tested).

- Among symptomatic children 5% of children developed significant respiratory disease and only 0.6% progressed to respiratory distress syndrome and needed a ventilator
- Preschool-aged children and infants have a higher risk of severe disease
- Children were less likely to become severely ill compared to adults and had a significantly lower death rate
- There are subpopulations of children with higher risk of severe disease, including younger age, underlying lung problems, and immunocompromised conditions
- Available data suggests children may have more upper respiratory infection than lower respiratory infection
- Viral co-infections can occur in patients with COVID-19
- Children may play a role in community spread of the virus because of the higher incidences of upper respiratory involvement and evidence of the virus (not necessarily evidence of infectious virus) in stool for several weeks after diagnosis
- Vertical transmission, from mother to infant during delivery, has not been reported

What are the limitations of the study

- It's a review and summary of other articles
- It's not a controlled study; rather it's a summary of available information and findings for children with confirmed COVID-19 diagnosis.

What it all means

- There is not much data on COVID-19 in children but more is becoming available
- Children are less likely to become infected with COVID-19 and much less likely to die from COVID-19 infection compared to adult patients
- Infants, children with lung disease or in an immunocompromised state like cancer on chemotherapy, or following organ transplant or with diseases like rheumatoid arthritis or inflammatory bowel disease on immunomodulator drugs, have higher rates of significant infections and death, but the rate is still very low compared to adults
- Children may play a role in community spread via a viral shedding from respiratory secretions and stool even when not symptomatic
- Appropriate pandemic modeling needs to include information from children to accurately evaluate the spread of the disease



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Research Explained

SARS-CoV2 Infection in Children

Xiaoxia Lu, M.D., Liqiong Zhang, M.D., Hui Du, M.D.

Published in *The New England Journal of Medicine*, March 18, 2020

Tavener Dibert MD, Jennifer Co-Vu MD (physicians) and Richard James (parent)

ABOUT THIS STUDY

- As of late March 2020, the 2019 novel coronavirus (SARS-CoV2, otherwise known as COVID-19) has caused over half a million infections worldwide and more than 25,000 deaths.
- Prior to this study, there was little information about the signs and symptoms of Covid-19 in children.
- This study looks at children from Wuhan, China who were infected with COVID-19, and describes their ages, prior medical history, symptoms of their infection, and what physicians saw on various types of chest imaging.

Why is this study important

- COVID-19 is a new respiratory virus that has spread rapidly across the world resulting in a pandemic. Parents of children with chronic medical conditions such as Congenital Heart Defects are concerned that their children might be at greater risk because of their existing illness.
- Since this virus was first seen in December 2019, there has been limited time to fully understand the characteristics of this infection, particularly in children.
- This study provides the first evaluation of children infected with COVID-19 and can help parents and medical providers better understand the signs and symptoms of COVID-19 in children as well as their risk for developing severe illness.

How was this study performed

- The study included Children from Wuhan, China who were treated at Wuhan Children's Hospital.
- Children with and without symptoms of COVID-19, and with a history of exposure to sick contacts were included in the study. Sick contacts included people with confirmed COVID-19 infection as well as sick contacts who were suspected to be infected but did not have testing.
- Overall, 1391 children were tested for COVID-19, and of these children, 171 (12%) were found to be positive for the virus. The signs, symptoms, past medical histories and ages of the 171 infected children were then evaluated.

What were the results of the research

- Characteristics of the Children
 - Of the 171 children infected, the ages ranged from 1 day to 15 years
 - It did not seem that any particular age group was infected at a higher rate. Infections were fairly evenly spread amongst the age ranges.
 - More boys were infected than girls (60.8% were male and 39.2% were female)
 - 76% of the children had been exposed to a person with COVID-19 in their family or community, and it was not possible to identify a source of infection in 8.8%.
- Signs and Symptoms
 - 15.8% of the infected children had no symptoms of COVID-19.
 - 19.3% had an upper respiratory tract infection.
 - 64.9% of children had a lung infection (pneumonia)
 - About half of children infected had one or more of the following: a cough, a fever, or redness of the throat (pharyngeal erythema)
 - There were small percentages of patients who had the following symptoms including diarrhea (8.8%), fatigue (7.6%), runny nose (7.6%), vomiting (6.4%) and nasal congestion (5.3%)
- Abnormalities were found on almost 2/3 of chest imaging. Imaging was done using computed tomography (CT) scans.
- Of all the patients studied, only one patient died. This was a 10-month old child with other medical conditions including abnormalities of the intestines.

- Only three children required a breathing tube and mechanical ventilation. All three of these patients had existing medical conditions such as blood cancer or gastrointestinal abnormalities.

What are some limitations of the study

- This was a limited study looking at a small population of children in a single city.
- This study was only able to observe patients over a short period of time (three months at the most).

What it all means

- This study described a variety of illnesses and symptoms among children infected with COVID-19.
- Most infected children had much milder symptoms than what is typically seen in adult patients.
- More children than adults came to the hospital without any signs or symptoms.
- Most frequently seen symptoms included a cough, infection of the lungs, and redness of the throat (pharyngeal erythema). Only about half of the patients had a fever.
- Only 3 children needed mechanical ventilation and all of them had other existing medical conditions.



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Research Explained

Hydroxychloroquine and azithromycin as treatment for COVID-19: results of an open-label non-randomized clinical trial

Gautret, Lagier, Parola, Hoang, Meddeb, Mailhe, Doudier, Courjon, Giordangelo, Vieira, Dupont, Honore, Colson, Chabriere, La Scola, Rolain, Broqui, Raoult

Published in *International Journal of Antimicrobial Agents*, currently in press

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Sarah Plummer MD (physician) and Colleen Melchiorre (parent)

ABOUT THIS STUDY

Why is this study important?

- A new virus came about in December 2019 in China (COVID-19), and is now causing a pandemic, meaning that the disease is present worldwide.
- Based on the Chinese experience, most patients have mild disease - those that die from the virus make up just under 3% of those effected. The virus was particularly hard on people who are older than 70 years old in China.
- We don't have a lot of options to treat this new virus.
- Medications that have worked to treat viral diseases before are being tested to see if they can be used to treat COVID-19. Testing these medicines is a good option because we know how safe they are, what side effects they have, and if they interact with any other drugs.
- A new antiviral drug called remdesivir and an old drug used to treat malaria called chloroquine have been shown to stop/slow COVID-19 grown in lab studies.
- An early clinical trial in COVID-19 Chinese patients showed that chloroquine worked well in terms of clearing the virus and how the patients felt and what complications they had.

- Hydroxychloroquine is similar to chloroquine and has been shown to stop/slow COVID-19 growth in lab studies. It is safer than chloroquine, can be given at higher doses, and interacts with fewer other medications.

How was this study performed?

- Hospitalized patients with at The Mediterranee Infection University Hospital Institute in Marseille, France were included in the study if they were older than 12 years and had tested positive for COVID-19.
- Subjects were left out (excluded from) the study if they had a known allergy to hydroxychloroquine or chloroquine, had another known reason to not take the medicine, were breastfeeding, or were pregnant.
- Every day for 14 total days after the start of taking the drug the patients were examined and had a repeat respiratory test for COVID-19.
- Patients who refused treatment or could not take the drug for various reasons were in the control group (that group that did not receive the drug). The control group also included patients in other hospitals who did not receive hydroxychloroquine.
- The main outcome (end result to see if the medicine worked better than nothing at all) that this study used was whether a repeat respiratory swab for COVID-19 was negative after being on hydroxychloroquine for 6 days.
- Other outcomes that were looked at included a negative test for COVID-19 over time during the 14 days of follow-up, how the patients felt/if they got better, and if there were any medication side effects.

What were the results of the research?

- 42 patients met criteria to be included in the study - 26 patients received hydroxychloroquine and 16 patients did not (control patients).
- 6 of the hydroxychloroquine patients were lost to follow-up. That left 36 patients total: 20 patients who received hydroxychloroquine and 16 patients who did not.
- The hydroxychloroquine and control groups were similar in terms of gender, how sick they were, and how long they had been sick when enrolling in the study. The hydroxychloroquine group was older (average age 51.2 years versus 37.3 years).
- In both groups, 16.7% of patients did not have symptoms, 61.1% had fever or upper respiratory tract symptoms such as cough, and 22.2% had lower respiratory tract symptoms such as pneumonia.

- In the hydroxychloroquine group, 6 patients also received the antibiotic azithromycin to help prevent an additional infection with bacteria.
- There was a real difference seen in the number of patients who had negative respiratory swabs for COVID-19 between the hydroxychloroquine group and the control group that did not get the medicine on days 3-4-5 and 6 of the study.
- On day 6, 70% of the patients who received hydroxychloroquine were negative respiratory swab compared to 12.5% in the control group.
- There was also a real difference seen in the number of patients who had negative respiratory swabs for COVID-19 between the hydroxychloroquine plus azithromycin group, the hydroxychloroquine alone group, and the control group on days 3-4-5 and 6 of the study. On day 6, 100% of the patients who received both hydroxychloroquine and azithromycin and 57.1% of the patients who received hydroxychloroquine alone have negative respiratory swab compared to 12.5% in the control group.

What are the limitations of this study?

- Small number of patients (36 total, only 20 received the medication being studied).
- 6 patients in the hydroxychloroquine group were lost to follow-up.
- Study is not randomized, i.e. it was not random who received hydroxychloroquine versus who did not.
- No follow-up on how the patients did over a longer period of time.
- Adverse effects were not reported.

What it all means

- Hydroxychloroquine may be a good medicine to treat COVID-19, and these early results are really good.
- Hydroxychloroquine plus azithromycin may be even more effective.
- Further studies are needed if these medicines may also be able to be used to prevent transmission of the virus, especially for healthcare workers.
- Additional studies are needed to tell if these medicines truly work to treat the disease.



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Research Explained

Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records.

Huijun Chen, Juanjuan Guo, Chen Wang, Fan Luo, Xuechen Yu, Wei Zhang, Jiafu Li, Dongchi Zhao, Dan Xu, Qing Gong, Jing Liao, Huixia Yang, Wei Hou, Yuanzhen Zhang

Published in *Lancet* 2020. Volume 395, pages 809-815.

Ryan Boggs MD (physician) and Nicole Fenix (parent)

ABOUT THIS STUDY

Why is this study important

- There is a global health emergency due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), otherwise known as 2019 novel coronavirus disease (COVID-19).
- At the time of this article, the understanding of how this virus can be spread as well as how it affects different patient populations was still developing.
- This is the first article reviewing the symptoms of COVID-19 infection in pregnant patients as well as evaluating for **vertical transmission** – the ability for the virus to spread from an infected mother to her fetus/unborn child or during delivery.

How was this study performed

- This was a review of the medical charts of 9 pregnant women with laboratory confirmed COVID-19 pneumonia admitted to Zhongnan Hospital of Wuhan University, Wuhan, China from January 20 to January 31, 2020.

- To evaluate for vertical transmission, samples were taken from multiple different sources of both mother and child soon after delivery and tested for the presence of SARS-CoV-2.
- In addition, the first breastmilk made was also tested for the presence of SARS-CoV-2.
- Vertical transmission was considered to have occurred if any of these samples were positive for the SARS-CoV-2 virus.

What were the results of the research

- All women were in their third trimester at time of admission to the hospital.
- None of the patients had chronic medical conditions such as diabetes, chronic hypertension (high blood pressure), or other unspecified cardiovascular disease. However, one patient had gestational hypertension starting at 27 weeks gestation and a second patient had pre-eclampsia starting at 31 weeks gestation.
- Seven of the nine (78%) patients presented with fever. However, the two patients that did not present with fever ultimately developed fever after delivery. Therefore, 100% of the patients either presented with fever or developed fever soon after delivery.
- While 8 of the 9 (89%) patients had CT evidence for pneumonia, none of the patients developed severe pneumonia requiring mechanical ventilation.
- Four of the nine (44%) patients went into early labor. However, the authors did not believe this was related to their COVID-19 infection. They believed that the causes for pre-term labor were that one had a history of pre-eclampsia, another had a history of irregular contractions, a third had a history of 2 stillbirths, and the fourth had premature rupture of membranes with concern for an intrauterine bacterial infection.
- All 9 (100%) women delivered via caesarian section (C-section). The reasons for C-section included pre-eclampsia, prior C-section, prior stillbirth, premature rupture of membranes, and fetal distress. Due to concern for the risk of vertical transmission during vaginal delivery, two patients were delivered via C-section with no other reason stated.
- None of the infants were found to be sick at time of delivery
- Only 6 of the 9 pregnant mothers had successful samples taken to evaluate for vertical transmission.
- Of these 6 who had samples taken, no sample was found to have SARS-CoV-2 present and thus the authors concluded that vertical transmission had not occurred in any of these 6 patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
Clinical characteristics										
Date of admission	Jan 20	Jan 25	Jan 27	Jan 26	Jan 27	Jan 27	Jan 28	Jan 29	Jan 30	..
Age (years)	33	27	40	26	26	26	29	28	34	..
Gestational age on admission	37 weeks, 2 days	38 weeks, 2 day	36 weeks	36 weeks, 2 days	38 weeks, 1 day	36 weeks, 3 days	36 weeks, 2 days	38 weeks	39 weeks, 4 days	..
Epidemiological history	Yes (exposure to relevant environment)*	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)*	Yes (exposure to relevant environment)*	Yes (contact with infected person)	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)†	9 (100%)
Other family members affected	No	Yes	Yes	No	No	Yes	No	Yes	No	4 (44%)
Onset to delivery (days)	1	6	4	3	1	4	2	2	7	..
Complications	Influenza	None	Gestational hypertension	Pre-eclampsia	Fetal distress	None	PROM	Fetal distress	PROM	..
Signs and symptoms										
Fever on admission	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	7 (78%)
Post-partum fever	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	6 (67%)
Myalgia	No	Yes	No	No	Yes	Yes	No	No	No	3 (33%)
Malaise	No	No	No	No	Yes	Yes	No	No	No	2 (22%)
Rigor	No	No	No	No	No	No	No	No	No	0
Cough	Yes	Yes	Yes	No	No	Yes	No	No	No	4 (44%)
Dyspnoea	No	No	No	Yes	No	No	No	No	No	1 (11%)
Sore throat	No	No	No	No	No	Yes	Yes	No	No	2 (22%)
Diarrhoea	No	No	No	Yes	No	No	No	No	No	1 (11%)
Chest pain	No	No	No	No	No	No	No	No	No	0

Table 1: Maternal Medical History

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
(Continued from previous page)										
CT evidence of pneumonia										
Typical signs of viral infection	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8 (89%)
Delivery										
Method of delivery	C-section	C-section	C-section	C-section	C-section	C-section	C-section	C-section	C-section	..
Indication for C-section	Severely elevated ALT or AST; COVID-19 pneumonia	Mature; COVID-19 pneumonia	History of C-section (x2); COVID-19 pneumonia	Pre-eclampsia; COVID-19 pneumonia	Fetal distress; COVID-19 pneumonia	History of stillbirth (x2); COVID-19 pneumonia	PROM; COVID-19 pneumonia	Fetal distress; COVID-19 pneumonia	PROM; COVID-19 pneumonia	..
Treatment after delivery										
Oxygen support (nasal cannula)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (100%)
Antiviral therapy	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	6 (67%)
Antibiotic therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (100%)
Use of corticosteroid	No	No	No	No	No	No	No	No	No	0

PROM=premature rupture of membrane. NA=not applicable. ALT=alanine transaminase. AST=aspartate transaminase. COVID-19=2019 novel coronavirus disease. C-section=caesarean section. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Exposure to Hankou, the area in Wuhan where the epidemic was first detected. †A university where the patient works, and a gathering of people. ‡Data missing for one patient.

Table 2: Maternal CT findings and delivery characteristics.

What are the limitations of this study

- This is a very small sample size (9 for symptoms/presentation and only 6 for vertical transmission) to be able to confidently apply the results to the general population.
- The time from infection to delivery was less than 7 days in all patients. Therefore, it is unknown if vertical transmission could occur if delivery occurs after 7 days from time of infection.

- All women in the study were in their third trimester. Therefore, it is unknown how the virus can affect a pregnancy as well as the risk for vertical transmission if infection occurs earlier in the pregnancy.

What it all means

- At this time, this article documents symptoms of COVID-19 infection in pregnant mothers are very similar to non-pregnant adults.
- While further studies are needed, there is no evidence for vertical transmission of SARS-CoV-2 based on this article

Addendum:

- Of note, after this article was published, there have been 3 articles published evaluating for vertical transmission:
 - One article (<https://jamanetwork.com/journals/jama/fullarticle/2763854>) evaluated for vertical transmission in 6 pregnant women. They report that none of the infants' blood labs or throat swabs found the presence of SARS-CoV-2. However, 2 (33%) of the infants had antibodies against SARS-CoV-2 that were higher than the normal level, indicating a prior infection. One of the types of antibody that was elevated in these 2 infants is not typically passed from a pregnant mother to her fetus, which would indicate that the fetuses made the antibody in response to themselves being infected before birth.
 - The second article (<https://jamanetwork.com/journals/jama/fullarticle/2763853>) was a case report of a single pregnant woman and her child. They found no presence of SARS-CoV-2 in the infant's nose/throat swabs taken from 2 hours to 16 days of age. However, the infant's antibodies to SARS-CoV-2 were higher than the normal level, indicating a prior infection. One of the types of antibody that was elevated in this infant is not typically passed from a pregnant mother to her fetus, which would indicate that the fetus made the antibody in response to themselves being infected before birth.
 - The third article (<https://jamanetwork.com/journals/jamapediatrics/fullarticle/2763787>) reviewed the charts of 33 infants born to mothers with COVID-19 infection. They report that 3 neonates tested positive for SARS-CoV-2. The first infant developed fever and lethargy on day 2 of life. Their nose/throat and

anal swabs were positive for SARS-CoV-2 on days 2 and 4 of life and negative on day 6. The second infant developed fever, lethargy, and vomiting. Their nose/throat and anal swabs were positive for SARS-CoV-2 on days 2 and 4 of life and negative on day 6. The third infant was born at 31 weeks gestation and was very sick at time of delivery requiring additional resuscitation. They were found to have respiratory distress syndrome and a pneumonia on chest X-Ray as well as a bacterial infection of their blood that resolved with antibiotics. Their nose/throat and anal swabs were positive for SARS-CoV-2 on days 2 and 4 of life and negative on day 6. It is important to note that all 3 of these infants were not tested for SARS-CoV-2 immediately after delivery and, therefore, it is difficult to determine if their SARS-CoV-2 infection occurred from vertical transmission or after they were delivered.

POSITION STATEMENTS

POSITION STATEMENT OF THE ESC COUNCIL ON HYPERTENSION ON ACE-INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS



Based on initial reports from China, and subsequent evidence that arterial hypertension may be associated with increased risk of mortality in hospitalized COVID-19 infected subjects, hypotheses have been put forward to suggest a potential adverse effects of angiotensin converting enzyme inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARBs). It has been suggested, especially on social media sites, that these commonly used drugs may increase both the risk of infection and the severity of SARS-CoV2. The concern arises from the observation that, similar to the coronavirus causing SARS, the COVID-19 virus binds to a specific enzyme called ACE2 to infect cells, and ACE2 levels are increased following treatment with ACE-I and ARBs.

Because of the social media-related amplification, patients taking these drugs for their high blood pressure and their doctors have become increasingly concerned, and, in some cases, have stopped taking their ACE-I or ARB medications. This speculation about the safety of ACE-I or ARB treatment in relation to COVID-19 does not have a sound scientific basis or evidence to support it. Indeed, there is evidence from studies in animals suggesting that these medications might be rather protective against serious lung complications in patients with COVID-19 infection, but to date there is no data in humans.

The Council on Hypertension of the European Society of Cardiology wish to highlight the lack of any evidence supporting harmful effect of ACE-I and ARB in the context of the pandemic COVID-19 outbreak.

The Council on Hypertension strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACE-I or ARBs should be discontinued because of the Covid-19 infection.

Prof. Giovanni de Simone,
Chair, ESC Council on Hypertension
On behalf of the Nucleus Members

HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19



Patients with underlying cardiovascular diseases appear to have an increased risk for adverse outcomes with coronavirus disease 2019 (COVID-19).

Although the clinical manifestations of COVID-19 are dominated by respiratory symptoms, some patients also may have severe cardiovascular damage. Angiotensin converting enzyme 2 (ACE2) receptors have been shown to be the entry point into human cells for SARS-CoV-2, the virus that causes COVID-19. In a few experimental studies with animal models, both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to upregulate ACE2 expression in the heart. Though these have not been shown in human studies, or in the setting of COVID-19, such potential upregulation of ACE2 by ACE inhibitors or ARBs has resulted in a speculation of potential increased risk for COVID-19 infection in patients with background treatment of these medications.



ACE2 is a homolog of angiotensin converting enzyme (ACE). ACE2 negatively regulates the renin angiotensin system by converting Angiotensin II to vasodilatory Angiotensin 1-7, diminishing and opposing the vasoconstrictor effect of angiotensin II. ACE2, ACE, angiotensin II and other renin angiotensin aldosterone system (RAAS) system interactions are quite complex, and at times, paradoxical. Furthermore, tissue expression of ACE2 differ in heart, kidneys and lungs of healthy patients, cardiovascular disease patients, and coronavirus-infected patients, and its role in the setting of COVID-19 infection in patients with cardiovascular disease is unclear. Furthermore, in experimental studies, both ACE inhibitors and ARBs have been shown to reduce severe lung injury in certain viral pneumonias, and it has been speculated that these agents could be beneficial in COVID-19.

Currently there are no experimental or clinical data demonstrating beneficial or adverse outcomes with background use of ACE inhibitors, ARBs or other RAAS antagonists in COVID-19 or among COVID-19 patients with a history of cardiovascular disease treated with such agents. The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease. In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation. Therefore, be advised not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice.

These theoretical concerns and findings of cardiovascular involvement with COVID-19 deserve much more detailed research, and quickly. As further research and developments related to this issue evolve, we will update these recommendations as needed.

Biykem Bozkurt, MD, PhD
President, HFSA

Richard Kovacs, MD, FACC
President, ACC

Bob Harrington, MD, FAHA
President, AHA

COVID-19

Disease caused by the SARS-CoV-2 virus

High blood pressure may increase the risk of complications with COVID-19 infections

Medications to treat high blood pressure include:

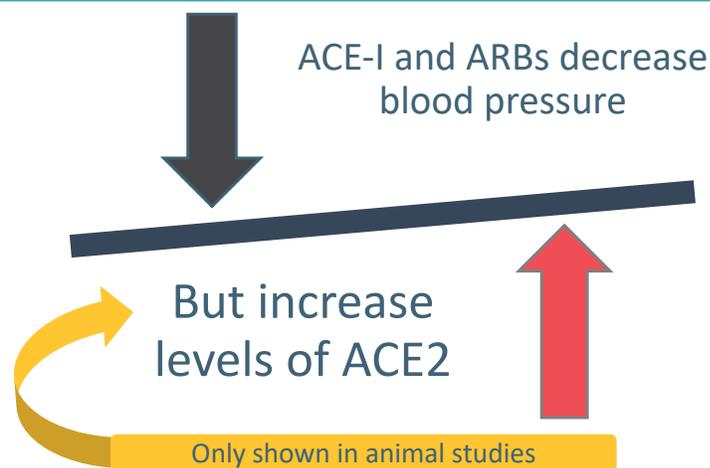
ACE-Is

Lisinopril
Captopril
Enalapril

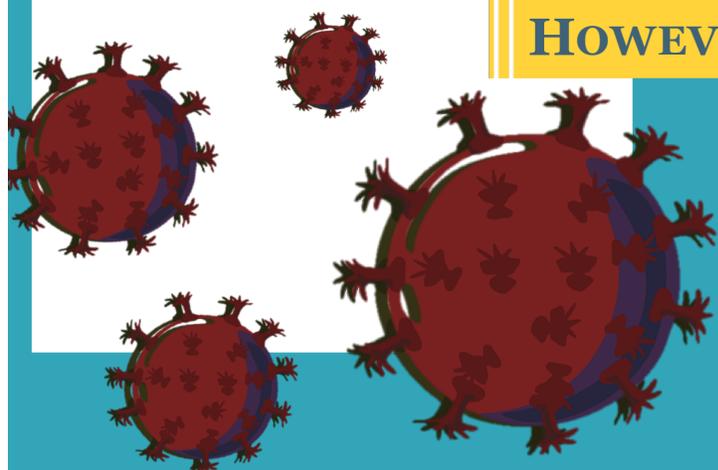
ARBs

Losartan
Valsartan
Olmesartan

ACE-I = Angiotensin converting enzyme inhibitor
ARB = Angiotensin receptor blocker
ACE2 = Angiotensin converting enzyme 2



COVID-19 enters human cells through ACE2 receptors



HOWEVER

For ACE-Is and ARBs:

- There are **no data** that show they are **harmful or beneficial** in COVID-19 patients
- Have been shown to **reduce severe lung injury** in viral pneumonias
- **Reduce your risk of cardiovascular events**, including heart attacks and strokes

• European Society of Cardiology • American Heart Association
• American College of Cardiology • Heart Failure Society of America recommend:

Don't stop your ACE-I or ARB

unless instructed to by your physician

COVID-19

Disease caused by the SARS-CoV-2 virus

Symptomatic Treatment for COVID-19

Symptoms may include:

- Fever
- Muscle Pain

Which are often treated with
OTC NSAIDs such as:

- Ibuprofen
- Naproxen

NSAIDs decrease
inflammation

But can increase
levels of ACE2

COVID-19 enters human cells
through ACE2 receptors

At present, based on currently available information, WHO does not recommend against the use of of ibuprofen.

We are also consulting with physicians treating COVID-19 patients and are not aware of reports of any negative effects of ibuprofen, beyond the usual known side effects that limit its use in certain populations.

WHO is not aware of published clinical or population-based data on this topic.

Could ibuprofen
worsen disease
for people with
COVID-19?



#coronavirus

18 March 2020



There is no clinical data on ibuprofen causing adverse outcomes in patients with COVID-19