

# Urgency of conducting serological studies for COVID-19

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# Introduction:

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- A little over four months after the first report of COVID-19, the disease became the world's first and utmost health priority.
- It has had a deep and vast impact globally;
- It is not a hazard for human health only, but its effects on the economy in micro and macro-levels, security, social solidarity, politics and international relationships are also considerable

# Introduction:

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- The researchers found that  $R_0$  ranged from 1.4 to 6.49 in China. (The  $R_0$  for novel influenza A (H1N1) has recently been estimated to be between 1.4 and 1.6.)
- The reported  $R_0$  indicate the rapid spread of the disease in all parts of the world.

# Total number of cases

2020-01-14

Per country over time



+

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# Total number of cases

2020-01-29

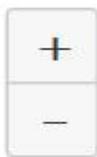
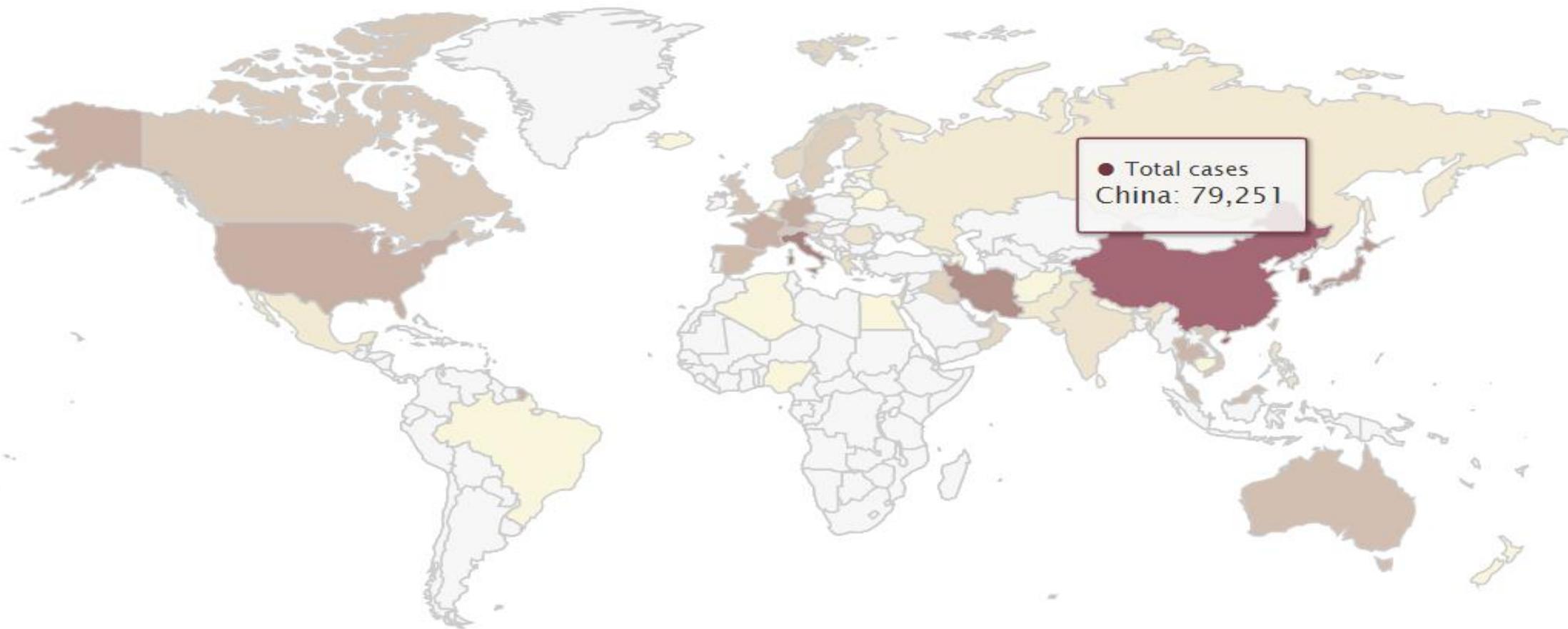
Per country over time



2020-02-28

# Total number of cases

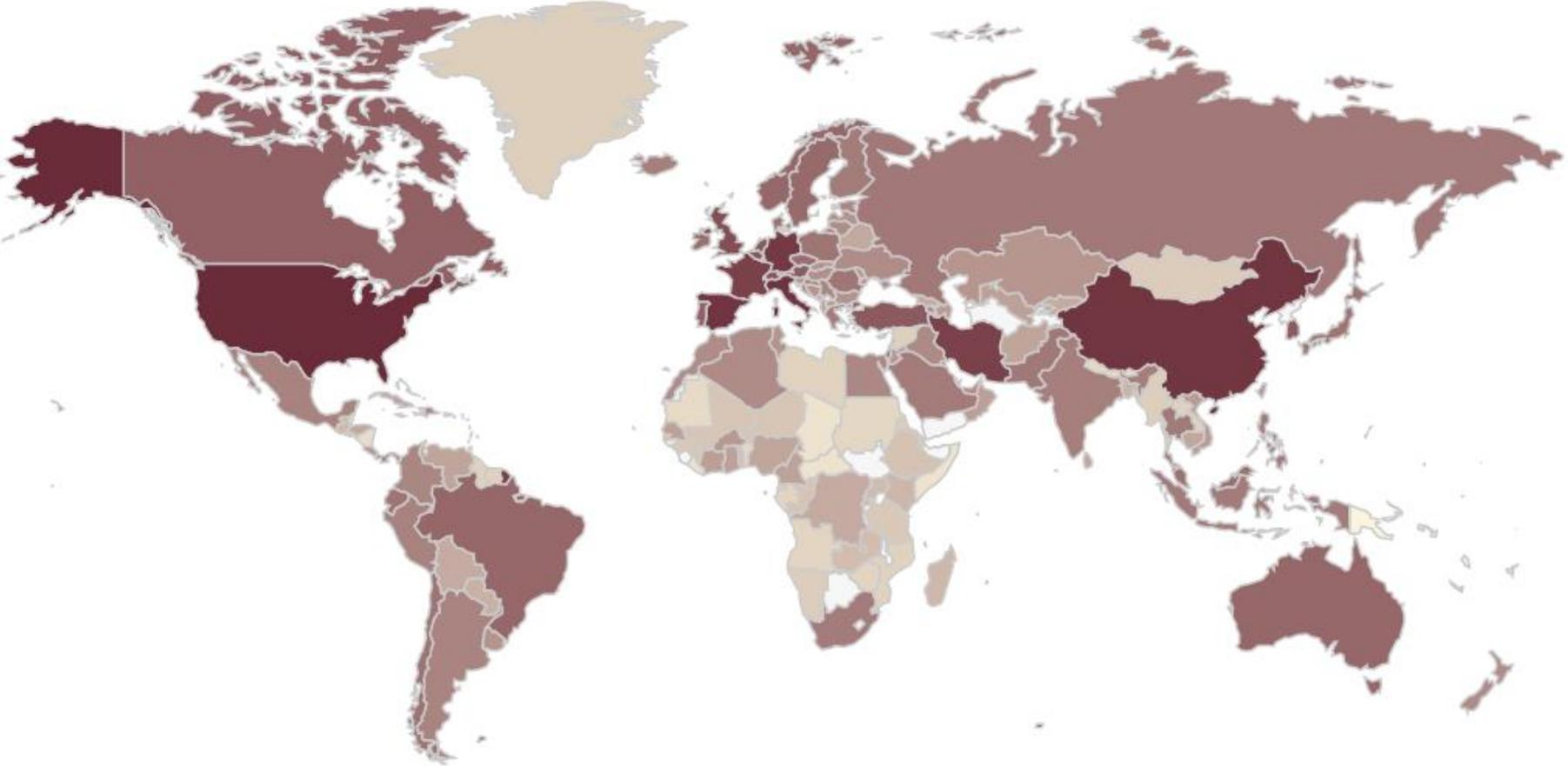
Per country over time



# Total number of cases

2020-03-29

Per country over time

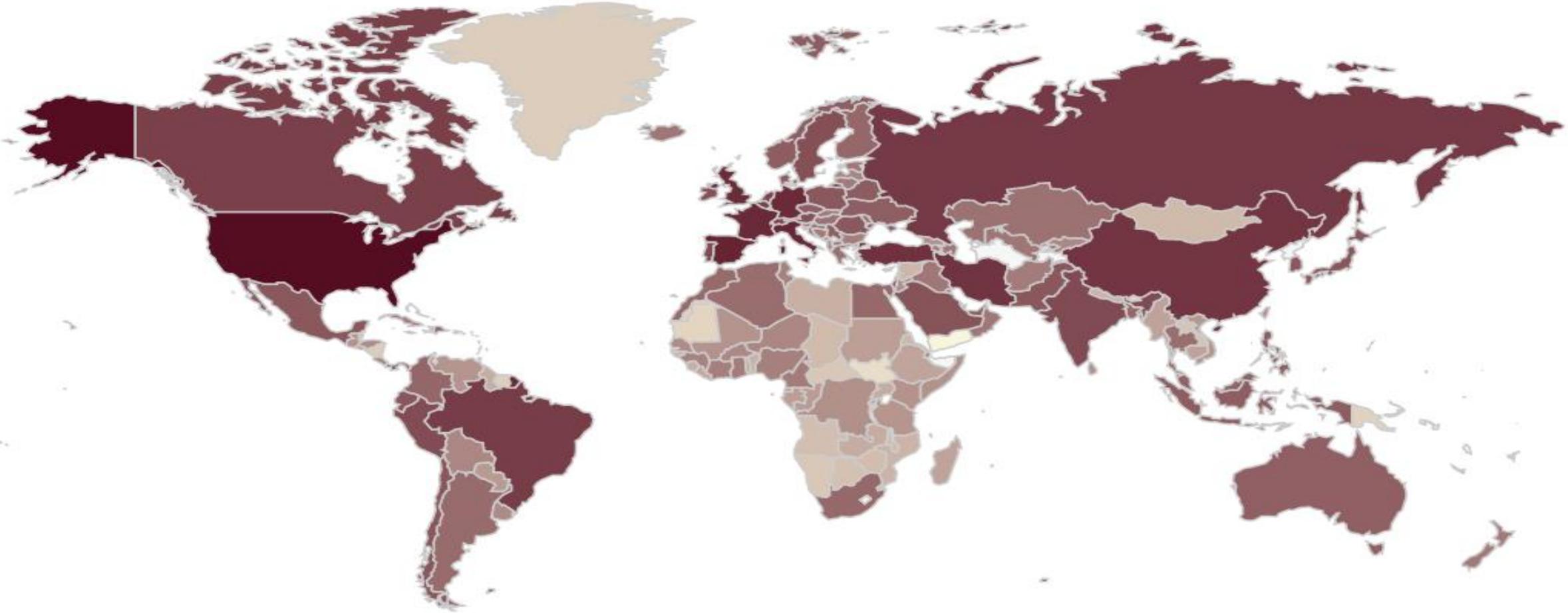


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# Total number of cases

2020-04-23

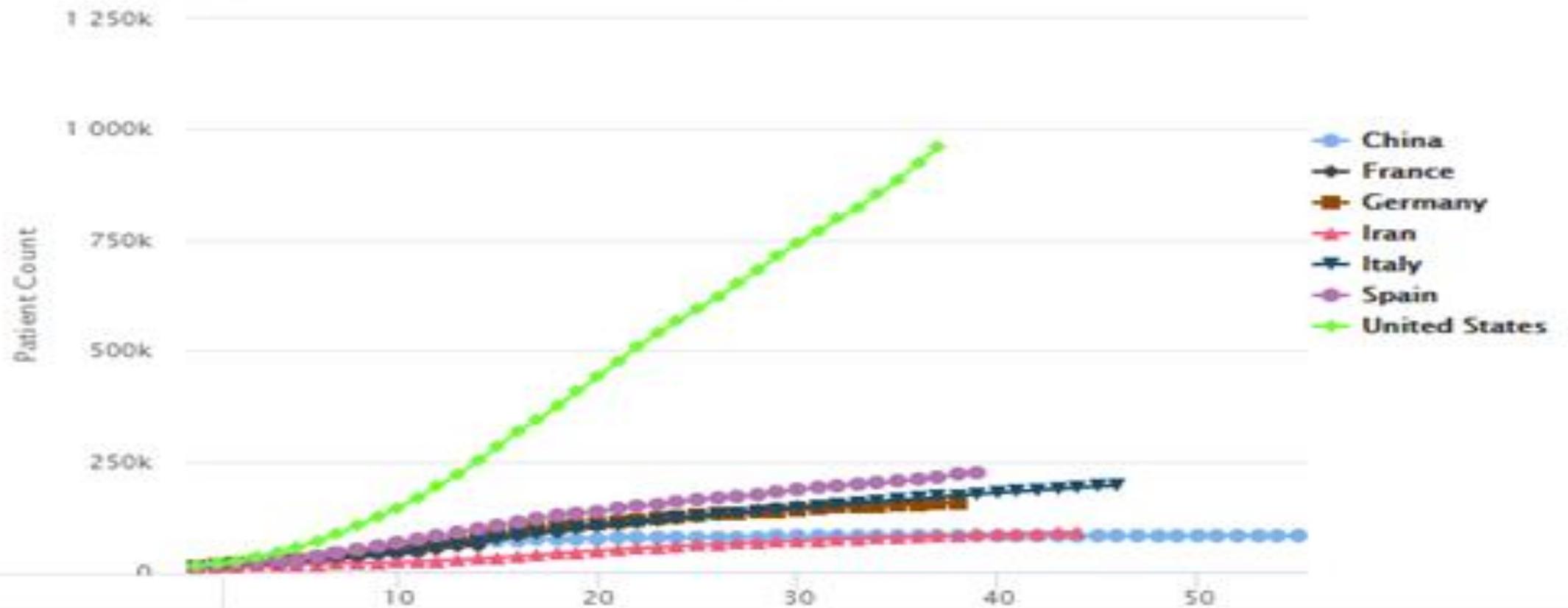
Per country over time



+  
-

# Cumulative number of cases (by number of days since 10,000 cases)

Cumulative number of cases, by number of days since 10,000 cases



Coronavirus Cases:

**2,907,971**

[view by country.](#)

Deaths:

**202,489**

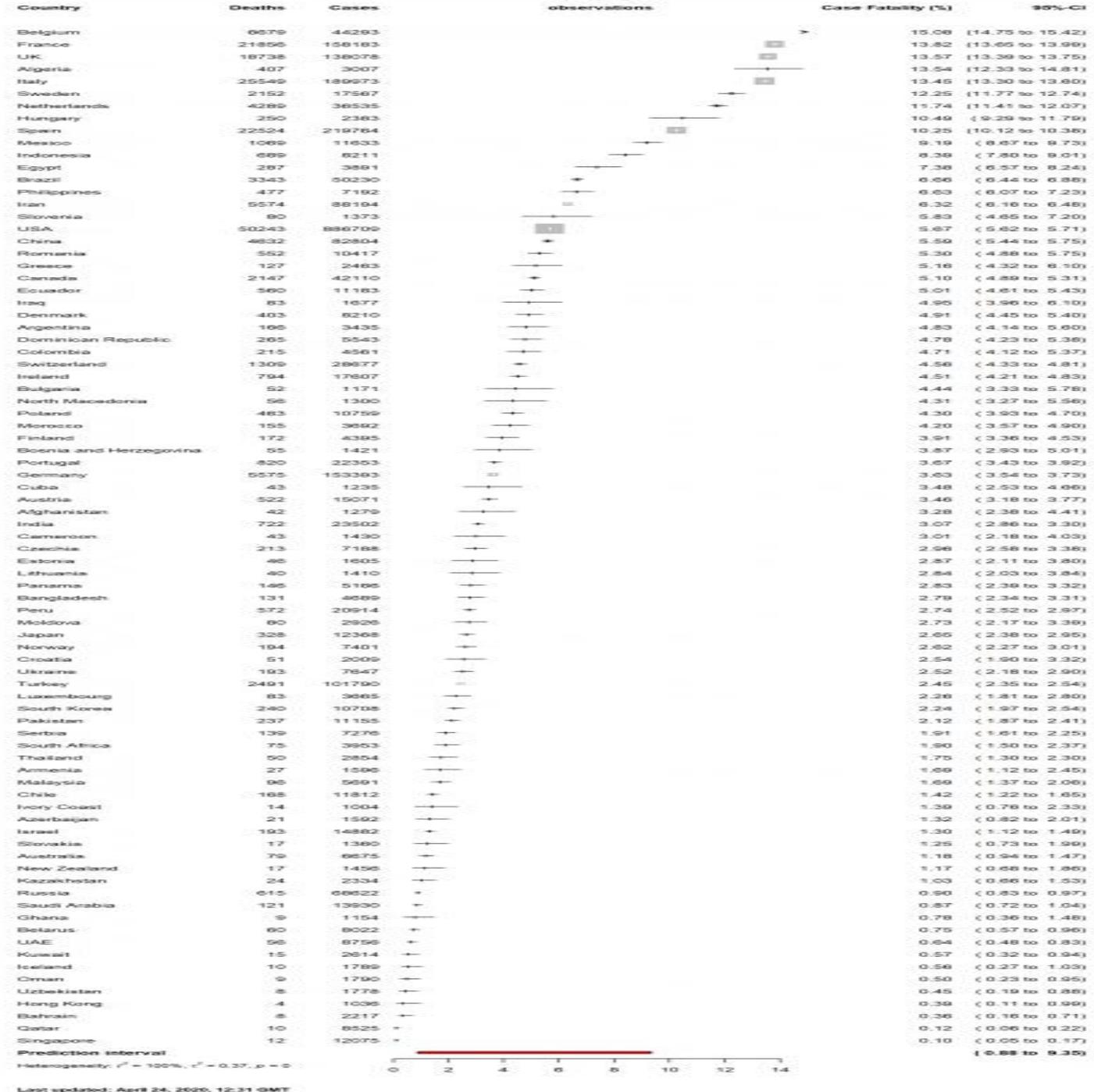
Recovered:

**832,211**

# Introduction: What did we learn?

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- The actual number of patients in communities is much higher than the officially reported number of cases.
- The proportion of asymptomatic cases is estimated to be 10% to 90% of all affected people
- The actual number of patients in communities is much higher than the officially reported number of cases
- That children and young adults can be asymptomatic



Reference:  
<https://www.cdc.gov/media/releases/2020/s0423-covid-19-fatality.html>

CFR different  
 between 0.1% - 15%

Setting	Proportion	Comment
<a href="#">Diamond Princess</a> <a href="#">cruise ship</a> , Yokohama, Japan (n=-634 tested positive). [1]	<b>18%</b> (95% credible interval 16%-20%).	Most infections occurred before the quarantine start.
Vo'Euganeo, 50 km west of Venice, <a href="#">Italian village</a> [2]	<b>50% to 75%</b> —were asymptomatic	In an open letter to the authorities in the Tuscany region
<a href="#">MERS-CoV</a> [3]	Increased from <b>0% to 29%</b> over time	As the MERS-CoV progressed over time there was more identification of asymptomatic individuals due to increased surveillance and contacts testing.
<a href="#">328 adults</a> in Shanghai [4]	13 ( <b>4%</b> ) patients were asymptomatic	

<p><a href="#">Japanese nationals</a> evacuated from Wuhan (n=565) [5]</p>	<p><b>31%</b> (95% CI: 7.7% to 54%)</p>	<p>Based on temperature screening before disembarkation, interviews on symptoms including fever, cough, and non-specific symptoms</p>
<p>23 Residents of a <a href="#">Long-Term Care Nursing Facility</a> King County, Washington[6]</p>	<p>10 (43%) had symptoms, and <b>13 (57%)</b> were asymptomatic.  Seven days after testing, 10 of 13 asymptomatics developed symptoms</p>	<p>Symptom-based screening could fail to identify approximately half of nursing home residents with COVID-19.</p>
<p><a href="#">Airport screening</a> of travellers [7]</p>	<p><b>17%</b> undetectable by typical screening procedures</p>	<p>Based on: A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: Lancet.</p>

<p><a href="#">Hospitalised in Beijing, China</a> (n=262)[8]</p>	<p><b>13 (5.0%)</b> asymptomatic cases</p>	
<p>391 cases including 48 <a href="#">family index cases in Zhejiang Province</a> [9]</p>	<p><b>54 (14%)</b> asymptomatic</p>	<p>higher family secondary attack rate, the secondary attack rate of spouses is higher than other family members.</p>
<p><a href="#">Chinese perspective</a> [10]</p>	<p>Over the past few days, asymptomatic patients were found in many Chinese cities.</p>	<p>Whether asymptomatic people can transmit SARS-CoV-2 to others is unclear.</p> <p>Another uncertainty is whether those who are asymptomatic can cause large-scale infections.</p>
<p><a href="#">36 children, Zhejiang, China</a> [11]</p>	<p>Asymptomatics, <b>10 (28%)</b></p>	<p>7 had acute upper respiratory symptoms (19%)</p>

<p>People's Hospital of Daofu county. Tibetan population (n=83) [16]</p>	<p>Asymptomatic carriers <b>22%</b></p>	<p>median age of asymptomatic carriers was 31 years and 1/3rd were students, aged &lt;20 years.</p>
<p><u>WHO Q&amp;A:</u> Similarities and differences – COVID-19 and influenza [17]</p>	<p>suggest that <b>80%</b> of infections are mild or asymptomatic,</p>	
<p><u>Iceland</u> [18]</p>	<p><b>50%</b> of the people who tested positive had no symptoms."</p>	<p>See also: <u>First results of the voluntary screening in Iceland</u>[19]</p>
<p>CDC [20]</p>	<p>A significant number of individuals that are infected actually remain asymptomatic. That may be as many as <b>25%</b>.</p>	

[Interim Clinical Guidance](#) for Management of Patients with Confirmed Coronavirus Disease [21]

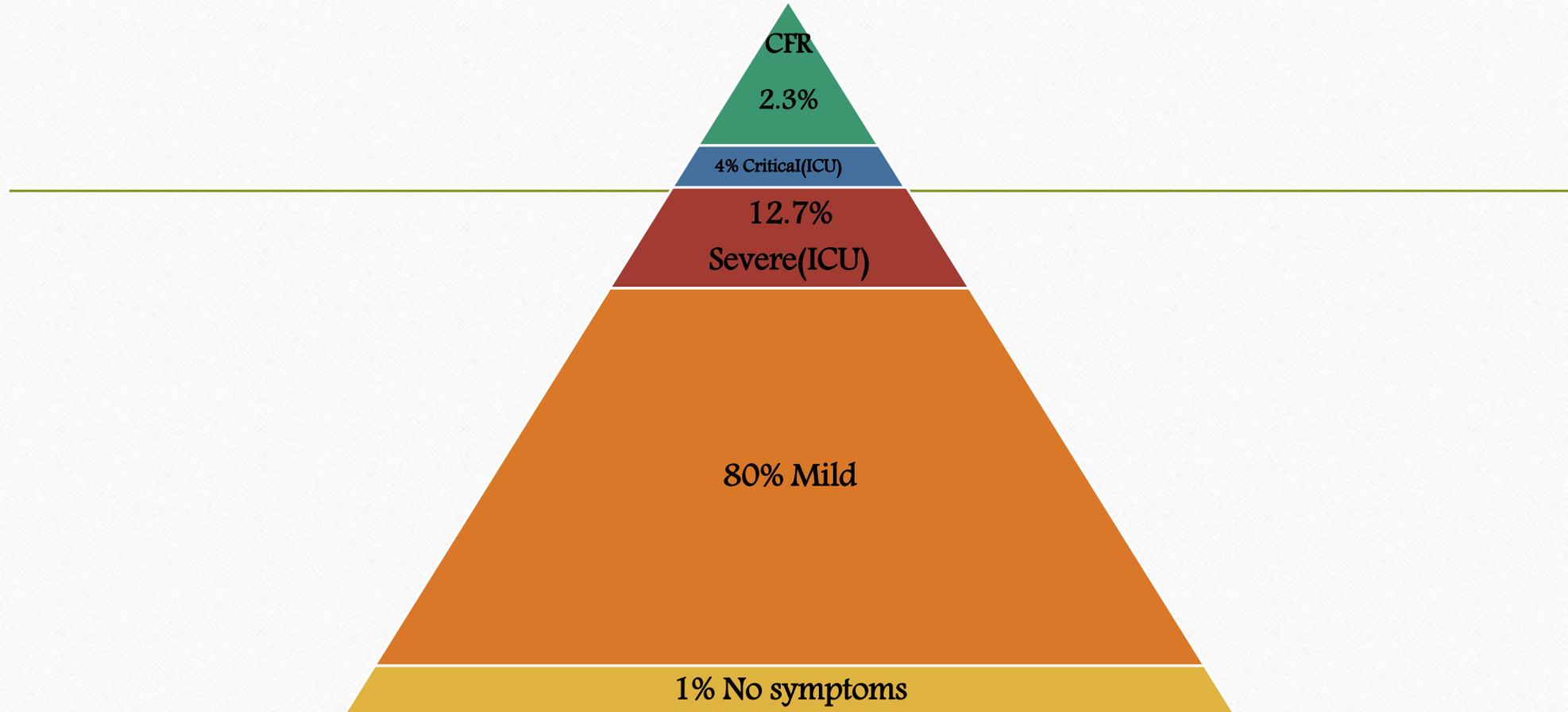
Among children in China, illness severity was lower with **94%** having asymptomatic, mild or moderate disease,

[Northern Italy](#), 60 volunteer blood donors [22]

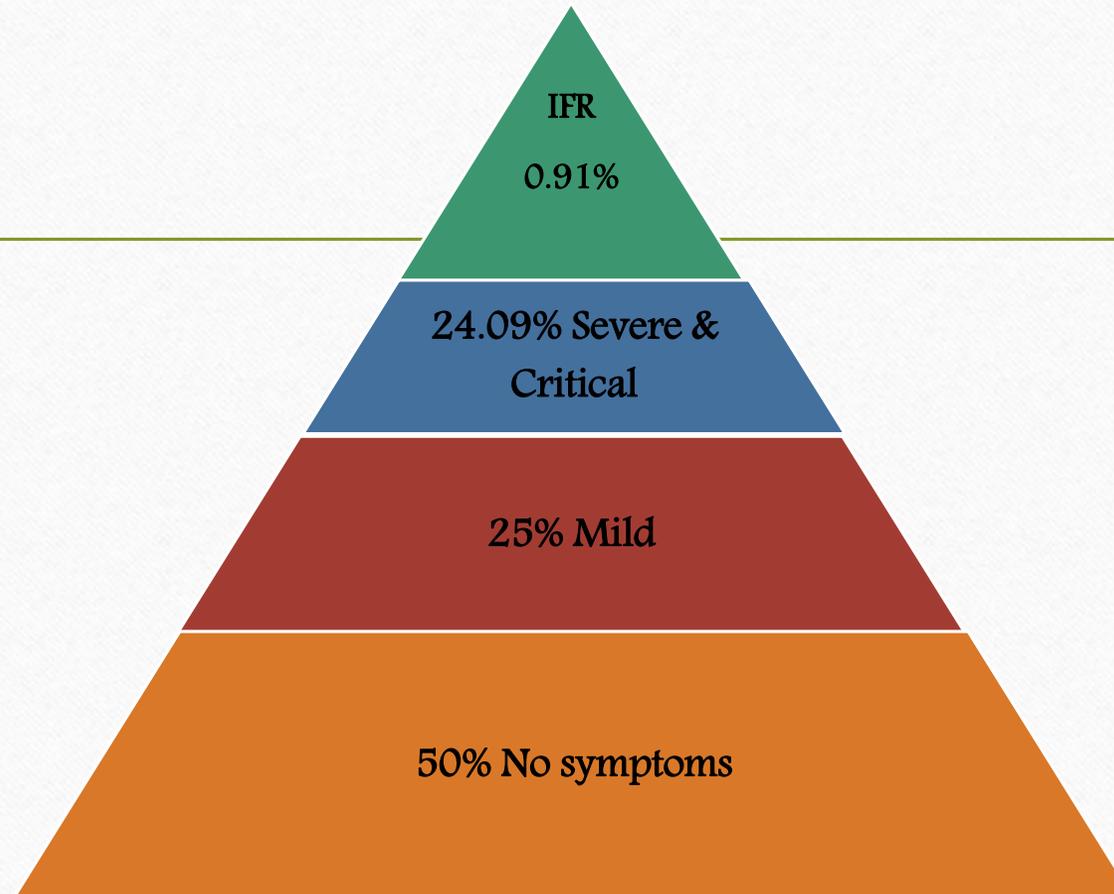
**40 (67%)** tested positive

Sir Basil's "fog" is continuing to cover the topic and prevent us from seeing what lies on the other side of the hill

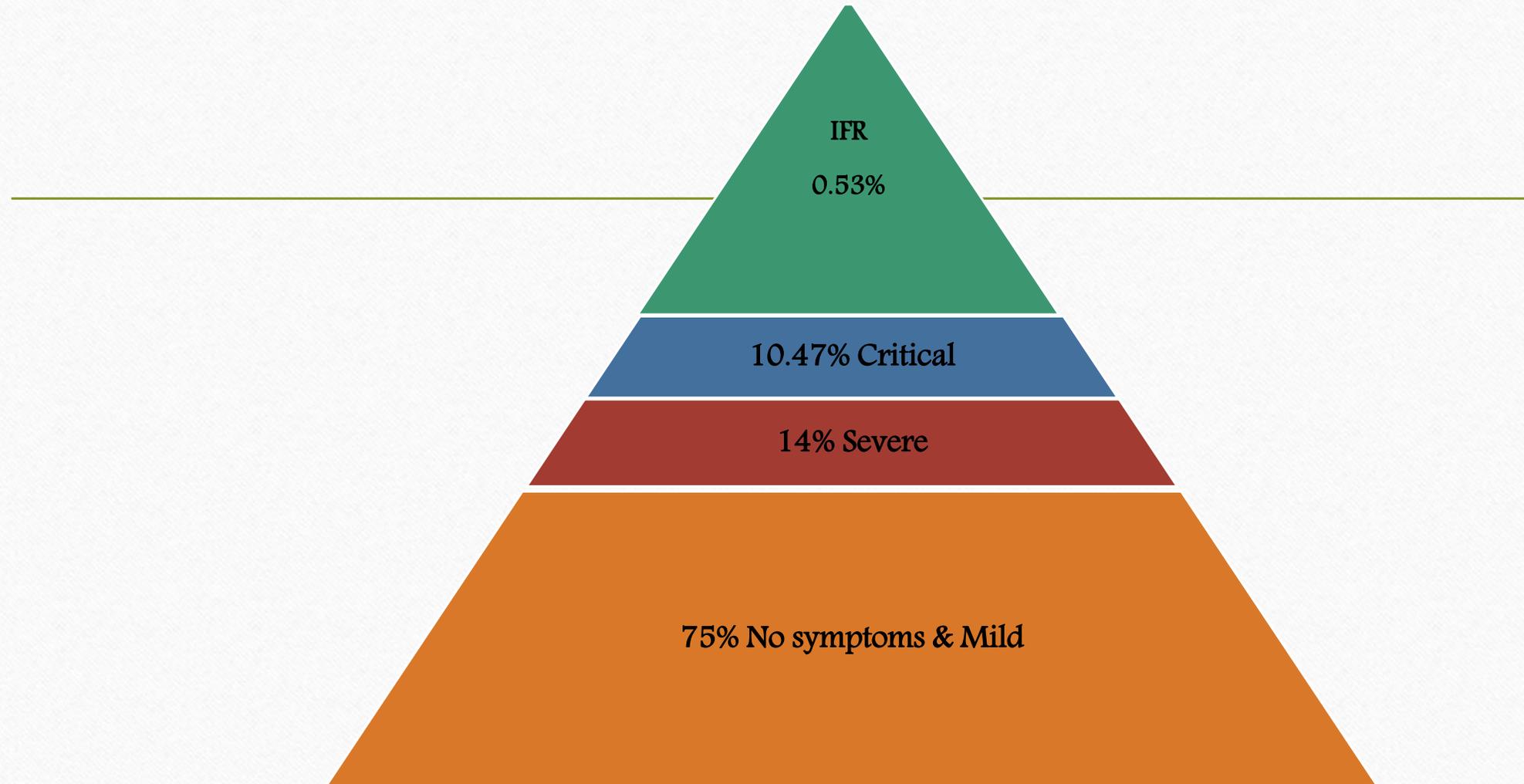
# Which scenario is correct?



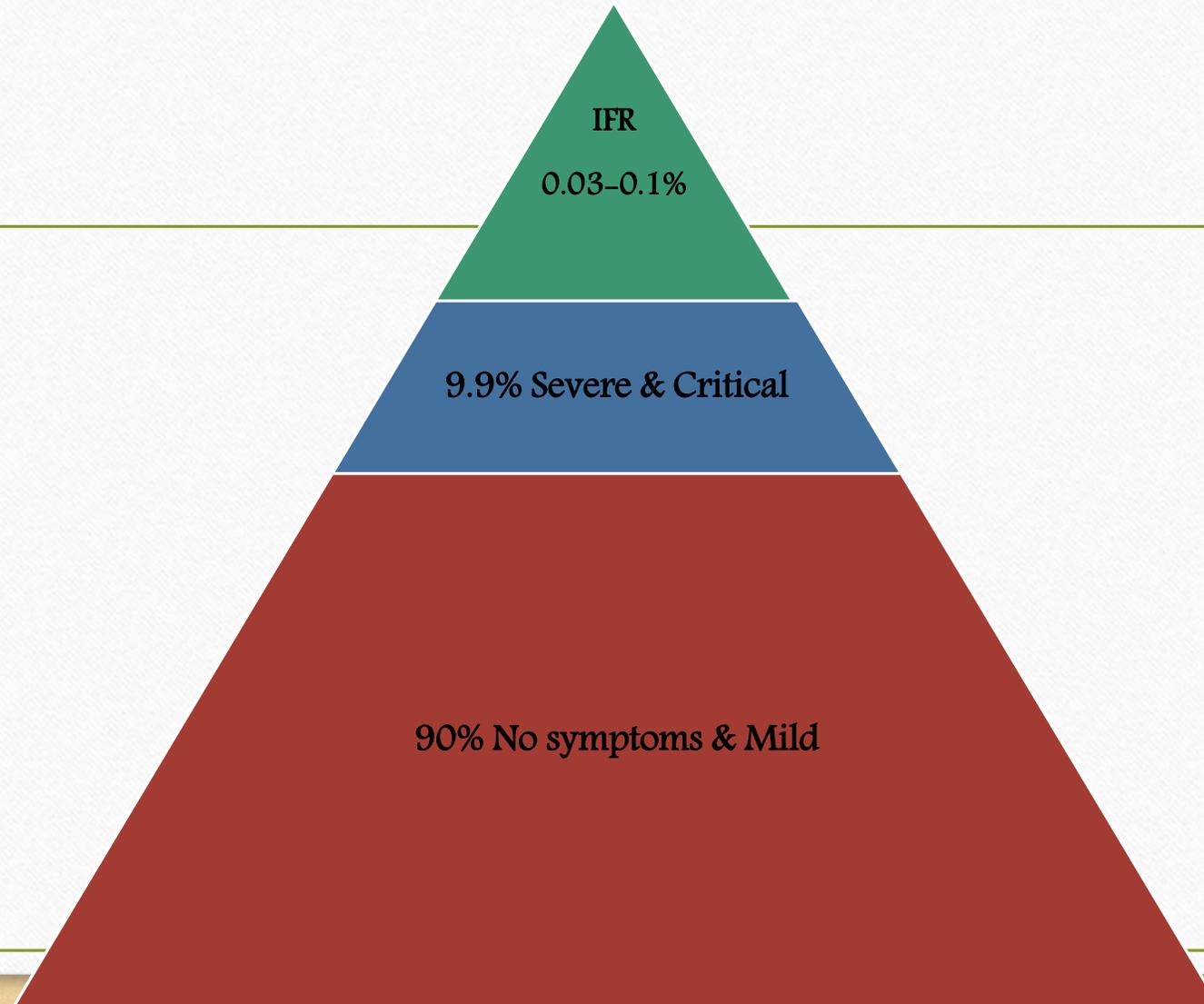
# Which scenario is correct?



# Which scenario is correct?



# Which scenario is correct?



# What things we need?

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- We need the natural history of the diseases.
- We need to know more about diseases.
- Quarantine and Lockdowns can not continue untie .....
- We don't know that what time we can have vaccination?
- We don't know that what time we can have treatment?

# What things we need?

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- Information for decision

# Why urgency of conducting serological studies for COVID-19 ?

- The researchers taking a gamble with antibody tests for coronavirus
- Despite uncertainties, some scientists are betting that blood tests will help end lockdowns and get people back to work.

nature



NEWS · 21 APRIL 2020

## The researchers taking a gamble with antibody tests for coronavirus

Despite uncertainties, some scientists are betting that blood tests will help end lockdowns and get people back to work.

Amy Maxmen



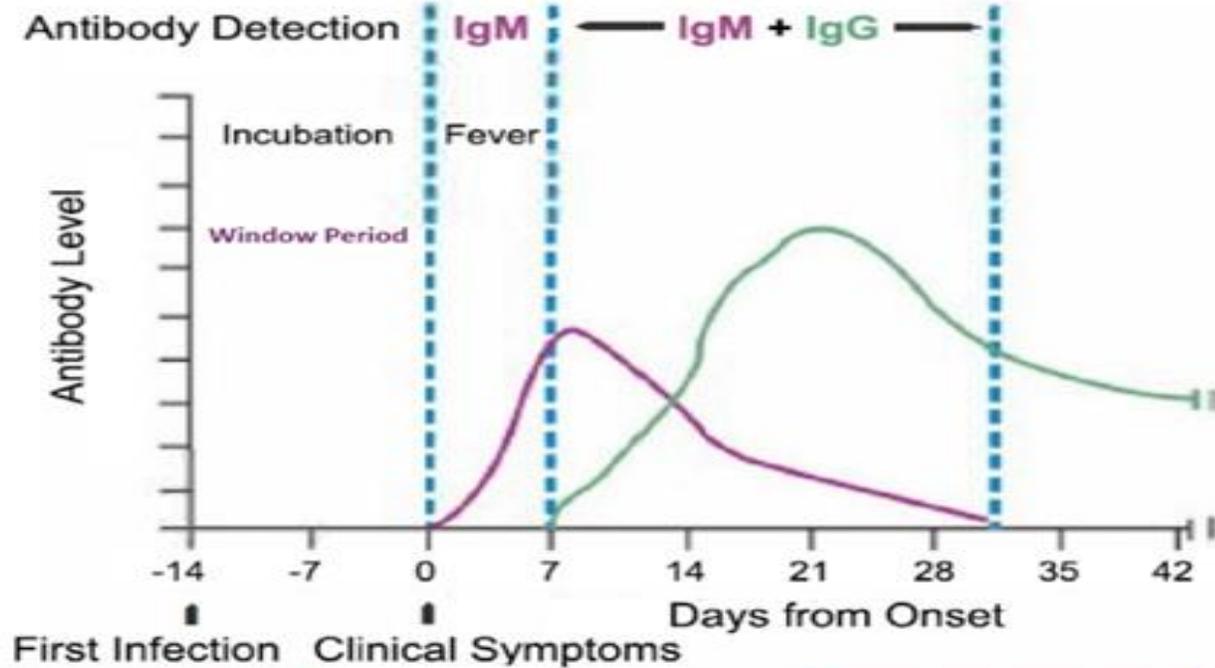
# Antibody study suggests coronavirus may be far more widespread than previously thought

**Non-peer reviewed study from Stanford found virus may be 50 to 85 times more common than official figures indicate**

- [Coronavirus - live US updates](#)
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# The natural history of COVID-19 in terms of appearance of symptoms, the diagnostic and immunological markers



# IgG & IgM

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- The level of IgM antibody begins to rise one week after the initial infection
- while IgG appears later (usually within 14 days following the emergence of the first signs of infection).
- The detection of these antibodies can be conducive to diagnosing patients in the acute phase as well as those with acquired immunity after the recovery

# The status of and changes in IgM, IgG, PCR, and natural history of the disease.

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- Antibodies may not be detected in the early days of infection with the emergence of immune responses.
- This limits the effectiveness of COVID-19 diagnostic tests, hence the fact that these tests should not be considered as the sole basis for diagnosing COVID-19.
- Most of studies show that people who have recovered from infection have antibodies to the virus. However, some of these people have very low levels of neutralizing antibodies in their blood,

# Limitation:( WHO)

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- The asymptomatic or mildly symptomatic patients may show low-titer antibodies, that may affect the sensitivity of the serological tests.
- It is estimated that about 30% of people show very low antibody titers, and around 5% may have undetectable antibody titers.
- Serological tests may also cross-react with other pathogens, including other human coronaviruses, and give false positive results

# Limitation (WHO)

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- It is indicated that the time of antibody production and the strength of antibody response depends on several factors, including
  - age,
  - nutritional status,
  - the severity of the disease,
  - and certain medications or infections like HIV that suppress the immune system
- For this reason, some affected people may show negative test results (false negative).
- Detection of those who were highly exposed to the virus without any symptoms and raise of antibody can help to explore the level of susceptibility of subjects and its determinants.

# Limitation:

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- However, before these tests can be recommended, ***they must be validated in the appropriate populations and settings.***
- *Inadequate tests may miss patients with active infection or falsely categorize patients as having the disease when they do not,* further hampering disease control efforts
- At present, based on current evidence, WHO recommends the use of these new point-of-care immunodiagnostic tests only in research settings.
- ***They should not be used in any other setting, including for clinical decision-making,*** until evidence supporting use for specific indications is available.

# Why immunodiagnostic tests only in research settings?

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- Studies suggest that the majority of patients develop antibody response only in the second week after onset of symptoms
- This means that a diagnosis of COVID-19 infection based on antibody response will often only be possible in the recovery phase, when many of the opportunities for clinical intervention or interruption of disease transmission have already passed.
- Lastly, there has been discussion about whether RDTs detecting antibodies could predict whether an individual was immune to reinfection with the COVID-19 virus. There is no evidence to date to support this.

# Why immunodiagnostic tests only in research settings?

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- WHO does not recommend the use of antibody-detecting rapid diagnostic tests for patient care but encourages the continuation of work to establish their usefulness in disease surveillance and epidemiologic research.
- Laboratory tests that detect antibodies to SARS-CoV-2 in people, including rapid immunodiagnostic tests, need further validation to determine their accuracy and reliability.
- Inaccurate immunodiagnostic tests may falsely categorize people in two ways. The first is that they may falsely label people who have been infected as negative, and the second is that people who have not been infected are falsely labelled as positive. Both errors have serious consequences and will affect control efforts

# Advantages and why urgency?

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- Tests to detect antibody responses to COVID-19 in the population will be:
  - critical to support the development of vaccines,
  - and to add to our understanding of the extent of infection among people who are not identified through active case finding
  - and surveillance efforts,
  - the attack rate in the population,
  - and the infection fatality rate.

# Advantages and why urgency?

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- For clinical diagnosis, however, such tests have limited utility because they cannot quickly diagnose acute infection to inform actions needed to determine the course of treatment.
- Some clinicians have used these tests for antibody responses to make a presumptive diagnosis of recent COVID-19 disease in cases where molecular testing was negative but where there was a strong epidemiological link to COVID-19 infection and paired blood samples (acute and convalescent) showing rising antibody levels.

# Advantages and why urgency?

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- In order to adjust the observed percentage of positive results for the sensitivity and specificity of results, a few formula can be used to estimate the positive percentage of the cases in a community

# Advantages and why urgency?

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- Serological tests can be advantageous in sero-epidemiological studies and epidemic investigations in special contexts.
- Late raise of antibodies and even undetectable level of antibodies are main barriers to recommend these tests as an alternative method for screening in normal population and case detection for care and treatment (Figure 2).

# Applications of serological tests to study various aspects of COVID-19

## Not recommended because of

1. Cannot detect cases in the early stage
2. Does not show strong association with the clinical progress of the diseases

Care and treatment

**Serological tests to detect the level of antibody**

Sero-epidemiological studies

Screening in normal populations

## Recommended because of

1. Easy to implement
2. Address to specific questions such as the level of reaction of the immunity system

Epidemic investigation in special contexts

## Recommended because of

1. Easy to implement
2. May adjust the results based on the sensitivity and specificity of the tests

## Not recommended because of

1. Considerable false negative rate
2. Cannot detect case in the early stage

# Advantages and why urgency?

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- A quick and extensive serological study on targeted groups can be conducive to gaining access to valuable information in affected communities.
- The results of such studies can facilitate the implementation of interventions tailored to each group, and to determine the most optimal time to reopen businesses, schools and universities.
- Conducting these studies at different frequencies helps obtain a better picture of the disease.

# Advantages and why urgency?

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- These tests can also be useful for public health professionals and clinicians to estimate the cumulative incidence rate to personalize the risk of developing the disease over the time.
- In case of limited access to antibody kits, a high priority should be given to studying high-risk groups susceptible to infection, including health care workers and family members of infected people.

# Advantages and why urgency?

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- In seroepidemiological studies where IgM is detected in the studied population, the results can also be used as a screening method because the disease may still be in the active phase in these positive cases.
- Identifying IgM positive cases and performing PCR to confirm their current disease can be a strategy to find some new cases.
- As the world is currently focusing on vaccine production as an effective approach to controlling the disease, it is also possible to evaluate the effectiveness of vaccines through measuring the level of antibodies in vaccinated people.

# Advantages and why urgency?

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- In seroepidemiological studies, specifying the ratio of those with positive IgM or IgG alone or both can help determine the epidemic status of COVID-19 in recent days and weeks.
- Normally, as the duration of IgM positivity is shorter than IgG, and duration of both of them to be positive is shorter, so if the incidence rate is uniform, the lowest positive percentage should be reached for the concurrence of both IgM and then IgG, then positive for IgM and then positive for IgG.

# Advantages and why urgency?

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- A high ratio of people with positive IgM can indicate that the virus and disease are active in the community; however, a high proportion of people with positive IgG can be indicative of an epidemic in the later stages of the disease.
- On the other hand, the high concurrence of positive IgG and IgM can contribute to interpreting the status of the epidemic in a community.

# Advantages and why urgency?

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- In addition, the serological tests can be used to explore and investigate the epidemics in special locations such as harpists, prisons and so on.
- Seroepidemiological studies can be further utilized to make decisions about bringing employees back to work.
- People who have acquired enough **immunity can receive a health certificate to return to work with a higher level of assurance.**

# Advantages and why urgency?

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- A significant proportion of people may be infected with the asymptomatic form of the disease; therefore, acquiring information concerning the immunity of different groups of people at high risks of occupational exposure, such as health care workers, can help the infected individuals to continue their work more confidently.

# Advantages and why urgency?

## "Immunity passports" in the context of COVID-19

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- WHO has published guidance on adjusting public health and social measures for the next phase of the COVID-19 response.
  - Some governments have suggested that the detection of antibodies to the SARS-CoV-2, the virus that causes COVID-19, could serve as the basis for an "immunity passport" or "risk-free certificate" that would enable individuals to travel or to return to work assuming that they are protected against re-infection.
  - There is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection.

# Other considerations

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- At this point in the pandemic, there is not enough evidence about the effectiveness of antibody-mediated immunity to guarantee the accuracy of an “immunity passport” or “risk-free certificate.”
- People who assume that they are immune to a second infection because they have received a positive test result may ignore public health advice. The use of such certificates may therefore increase the risks of continued transmission.

# Conclusion

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- It is necessary to urgently obtain up-to-date information about the disease in order to be able to tackle it. The cumulative incidence rate of the disease is one of the most important factors for specifying its status. If this indicator is set correctly in a community, more targeted and appropriate interventions can be designed and the results can be evaluated more accurately. Lack of access to valid kits is one of the limitations hindering the studies of such ilk.
- Given the importance of such studies, all affected countries should promptly provide the necessary support for the production of serological kits with high sensitivity and specificity. Immunologists and molecular biologists can help human communities via conducting research on the natural history of the disease, determining the time of antibody production, and identifying its diagnostic and immunological markers.

# Special thanks

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- Dr Ehsan Mostafavi
- Dr Aliakbar Hghdoost

Thank you for your attention  
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## Antibody study suggests coronavirus may be far more widespread than previously thought

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