Evidence-based answers to questions that doctors commonly ask about COVID19.

Dr Rajeev Jayadevan, 26 March 2020

Note:

1. *This is a scientific update written specifically for doctors.* *It is NOT meant for circulation among the general public.* *Those who do not have a medical background and adequate knowledge of statistics SHOULD NOT be reading this, as they will not be able to understand the implications, or derive meaningful conclusions.*
2. *COVID19 is a new virus of only 4 months history. The facts we know today could change with continued research.*
3. *Many of the figures are projections based on known variables, and such projections are essential while we plan for the future.* *Projection should not be confused with prediction.*

1. What is the death rate of COVID19?

Case Fatality Rate (CFR) is defined as the number of people who will die if a hundred people were to get the infection. At this time, in Europe, the case fatality rate is 5.4%.

It is important to note that the case fatality rate has a numerator and a denominator. The denominator is the number of cases diagnosed. The numerator is the number of deaths reported to be due to confirmed COVID19.

One can either decide to test only those with high-risk travel history or contacts (as in India till date), or do large scale testing in the community (as in S. Korea). The latter methodology will also help pick up asymptomatic cases, which can be a substantial number (see below).

Thus, depending on who we decide to test, the denominator can vary. For example, in South Korea, the denominator gets diluted by testing of asymptomatic cases. Since it is a bigger number, the death rate would seem artificially lower than in Italy.

In countries where testing is done only in small numbers on certain segments of the population, both the reported death rate and the prevalence of the disease will be inaccurate. One of the reasons why the reported rates are low from Africa is the absence of adequate testing.

2. What is the death rate in the elderly?

15% is the death rate in the elderly reported in China.

2.3% is the overall death rate reported in China.

3. Is there a sex difference in death risk?

Yes. Italian data indicate that men with COVID19 are 2.4 times more likely to die compared to women. Chinese data also showed similar trends, albeit less marked.

4. How many COVID19 cases require hospitalisation?

Hospitalisation is required in 30% of cases, and ICU admission in 4%.

5. What is the incubation period?

The incubation period is 5 to 6 days, range being 1 to 14 days.

6.When does the viral load peak? (when is the person most infective?)

Unlike SARS and MARS where viral load peaks one week after onset of symptoms, in COVID-19 the viral load peaks at the time of symptoms.

This means that for COVID19, there is viral transmission to other people earlier than in the case of the other two Coronaviruses, that is SARS and MERS.

7.How long does a person carry the virus?

This is still being studied, but it has been documented that a person can carry the viral mRNA for up to 37 days (in the nasopharynx) and more than a month in feces (paediatric cases)

Note that the presence of viral mRNA need not necessarily mean infectivity.

8.Does viral load matter?

Yes, patients with high viral load have more severe illness. Viral load has been seen to be up to 60 times higher among people with severe illness. Older people are known to have increased viral load.

9.What is R-0 of the virus?

R-0 of a virus is defined as the number of people that a single person can transmit the virus to.

In the case of Covid 19, it is 2.7 - 3.25 (Italian data). In China, the number was calculated to be 3.28.

This means that every person has the potential to transfer infection to at least three people.

R-0 can be altered through administrative and community intervention. This is an extremely important fact, and is one of the basics of our present stand of social distancing and lockdown. By increasing the physical separation between individuals, we can reduce R-0.

In other words, R-0 of any virus is not a fixed number. Just like the attack rate of the virus, R-0 also can be modified according to the nature and the behaviour of the target population.

10.Is asymptomatic transmission possible?

Yes. It is conclusively established that people without symptoms are freely spreading the virus. Tapiwa Ganyani et al studied clusters and calculated that in Singapore, 42% of transmission was pre-symptomatic, while 62% was the corresponding number in China.

In the Diamond Princess ship, 48% of those diagnosed with the virus did not have symptoms at that time.

This fact needs to be adequately communicated to the general public, who are under the impression that if someone is looking well, they cannot have COVID19. Such communication will enhance compliance of lockdown.

11.What is the attack rate of the virus? How many people will it infect?

The attack rate is defined as the number of people that will get infected, if a virus is newly introduced into the community.

It is difficult, perhaps even impossible to correctly measure attack rate in a town or village, as we need to test everyone who the virus interacted with, and then see how many of them got sick. We don't know who in the town was exposed to the virus either.

The most reliable estimation of attack rate on record is from the Diamond Princess cruise-ship, where we know that everyone on board would have probably come into contact with the virus, and we also know that 19% of the ship's passengers got the infection in the end. This represents the rare combination of testing the entire community that got exposed, and then seeing exactly how many got the infection.

Obviously, a ship cannot be compared to a country, but the lessons from this ship are the best estimates we have of this new virus's behaviour in a closed community that took maximum precautions.

Being a new virus, there is no natural immunity to COVID19. The attack rate is likely to be high especially in crowded conditions, as the virus gets a free ride by close contact between individuals, without being blocked by people who are immune.

Documented and projected attack rates for COVID19 have varied from 19%, 56%, 68%, and 70%. The implications of these attack rates on a resource-poor country with a large population are significant, to say the least. The population of India is 1300 million or 1.3 crore with a population density of 464/sq km, compared to Italy that has a density of only 206/sq km, and China with just 145/sq km.

The population of Kerala is 34 million with a population density of 860/sq km. Mumbai alone has 22 million people at a density of 30,000/sq km. The projected attack rates and R-0 in such areas will be difficult to predict: it is unlikely to be on the lower side—unless social distancing measures are rigorously maintained.

The California Governor estimates that 56% of California, or 25.5 million people - will be affected by Covid19. Professor Jacob John, retired head of virology from CMC Vellore believes that the data from China is either incomplete or under-reported, as only 80,000 cases have been reported for a population of 1.4 billion. He estimates that about 70% of India will get infected. He has said that we might never hear about the true number of cases in such a large country due to logistical difficulties.

Lourenco et al from Oxford University estimate that 68% of those in the UK could already have been infected by now.

This virus spreads by geometric progression. Geometric progression is a sequence of numbers where the next number is obtained by multiplying the previous number by a fixed number. For instance, 1x2=2, 2x2=4, 4x2=8, 8x2=16, 32, 64, 128, 256, 512, 1024, 2048 is a geometric progression of the number 2.

That COVID19 follows geometric progression is evident from the simple fact that for the first 100,000 cases to be diagnosed it took 67 days, while the next 100,000 took only eleven days, and the third 100,000 took just four days.

This is the reason why initial numbers are always low, and the graph in the earlier days in any country would seem unremarkable.

Assuming the lowest quoted R-0 of 2, as geometric progression progresses, the time taken for 2 cases to become 4 is about the same as that for 10,000 cases to become 20,000, and for 100,000 to become 200,000 as there is no natural immunity.

Prof. Jacob John believes that until at least 70% of the general population develops herd immunity, the pandemic will not slow down naturally.

It is noteworthy that the R-0 for a crowded nation like India in all likelihood will be higher, as the virus spreads rapidly wherever crowds gather. The case in point is the city of Daegu in South Korea, where over 85% of the initial cases were tracked down to the Shincheonji church.

In previously vaccinated populations, taking the case of influenza, the R-0 is lower, as many people do not get infected and therefore do not spread to others. Unfortunately, no one is naturally immune to COVID19 simply because it is a new virus.

12.What are the vulnerable groups?

Men over the age of 70 who have hypertension, cancer, diabetes, heart disease, or respiratory illnesses are the most vulnerable. The reason for increased death rate in this group is not clear, but factors such as frailty, high viral load, greater chance of coexistent silent or overt cardiac or pulmonary disease and severe immunological response are proposed.

Complications from COVID19 are most common in this age group. This group of people is advised to take the most stringent precautions.

13.Should ACE inhibitors or ARB's be stopped or changed?

No. There is a hypothetical concern whether ACE inhibitors or ARB's could make it easier for the virus to enter the body, as the ACE-2 receptor is considered to be a co-receptor for viral entry into the lung cells. There is no recommendation from American and European cardiology societies at this time to change any ongoing treatment based on this concern.

14.How long will immunity last?

This is a big unknown, and is too early to tell. In SARS and MERS (the other two major Corona viruses) immunity was known to last approximately three years.

15. Is there a seasonality, in other words does warm weather or humidity kill the virus? Is India protected?

No. There is no evidence that the temperature or humidity of India will reduce the spread of COVID19. The R-0 of the virus was documented to be elevated in Singapore and Guang-Xi province in China which have comparable temperature and humidity.

16. How long does the virus live on surfaces?

Researchers from national institute of health published in NEJM that the virus can survive for 24 hours and cardboard, 4 hours on copper, two days on steel, three days on plastic and a few hours in droplet form in the air. We must remember that lab conditions are not the same as real world conditions. Besides the virus is known to survive longer in the presence of mucus and other bodily fluids.

On this note, there is no recommendation anywhere in the world that newspapers could spread COVID19. The risk of getting COVID from a newspaper delivered home is considered as insignificant at this time. The UAE has advised against newspapers being placed for public reading where several persons could use the same paper, but has allowed individual subscriptions to continue.

17. Has the COVID19 been actually detected on keyboards and door knobs?

Yes. The virus has been detected on commonly used gadgets such as keyboards, doorknobs, faucets and gloves. However, air samples so far have been negative for the presence of the virus.

18. Is the virus an airborne disease or a droplet disease?

Measles, chickenpox and tuberculosis are airborne spreading infections, which means that these organisms are able to stay afloat in the air and travel over long distances.

COVID19 is not considered to be airborne transmission at this time.

However, the droplets which hang in the air and will eventually settle on the ground, are expected to be at maximum density within a distance of 6 feet, hence the recommendation for maintaining a distance of at least 6 feet.

In contrast, for viruses such as measles, chickenpox, keeping such distances alone does not protect us from getting infected.

19.What is the current status of antiviral medication?

Multiple trials are ongoing. Until we hear from a well-conducted randomised double-blind controlled trial (RDBCT) of sufficient sample size, it is an unknown. In science, we need to acknowledge the presence of unknowns; this is a concept that the general public find particularly hard to digest.

The example I used to explain sample size on CNN this week, is the process of selecting of a player into the Indian cricket team. Just because someone hit a couple of boundaries in school cricket match, that does not mean that he will perform well in the national cricket test team.

The player will need to have consistently performed well in numerous matches in different formats against different oppositions, to get selected.

Similarly, when clinical trials with small numbers of subjects are done, a few patients may be seen to improve with the medication given. This need not necessarily be the effect of the medication, as the disease itself has a spontaneous cure rate of 95%.

The chloroquine study reported from France by Phillippe Gautret et al had inadequate sample size of just 42 patients. It was a non-randomised, open-label study without a control arm (they included those who refused chloroquine in the control arm, which is not acceptable) with a high dropout rate of 6 patients. There was no biological plausibility for adding azithromycin, which itself is not meant to be used with chloroquine due to the danger of cardiotoxicity. Besides, in vitro action of a drug (chloroquine) is not a guarantee for in vivo effect.

Speculation and logic need not always translate into scientific outcomes. For conditions such as Covid 19 where 95% of people will recover without specific medication, the task of demonstrating a reduction in the death rate with a pharmacological intervention can only be done by testing a large number of patients.

If our aim is to demonstrate a reduction in death rate by at least 50%, with a *power* of 80% and a *type 2 error (β error)* of 0.2 (this is the minimum required) a sample size of at least 1812 will need to be tested in an RDBCT.

If we want a beta error of 0.05, 2994 patients will need to be studied. In research, beta error represents the chance of arriving at a false negative conclusion after the study; the lower the better. Technically, *β error or type 2 error* refers to failing to reject the null hypothesis when it is actually false.

Interim analysis however can detect any early major trends, before the full number is reached. While we would like to be optimistic, we must remember that this is science - where such trends can either be positive, null or negative.

Historically, in clinical research, many trials have had to be halted because of unexpected rise in negative outcomes.

As of today 26.3.20, no medication has been approved by the FDA for prevention or treatment of COVID19. Randomised controlled trials to study chloroquine are ongoing, including one from Oxford University as well as from the University of Minnesota. The results of these will be helpful when available.

The so-called *compassionate use* of chloroquine is a topic that needs to be discussed at the highest level. Compassionate use refers to use of an agent in extreme circumstances when nothing else would work.

Compassionate use is not a scientific technique and could have major implications in public health. Once better studies get published chloroquine, the above situation could change.

It is noteworthy that trying out unproven medications on large numbers of people could also result in unexpected outcomes. Theoretically, the treatment arm of a clinical trial could have three possible outcomes: that is either improvement, no improvement or worse outcome.

Individual opinion or hunch does not quality as scientific evidence. This is yet another fact that the general public will not understand. A dangerous outcome of the initial excitement on chloroquine was the tragic death of a man from Arizona who consumed chloroquine on his own to prevent COVID19.

This is the importance of conducting a stringent randomised controlled trial, preferably in multiple centres. An important trial done on Kaletra was published recently in the New England Journal of Medicine, and showed a negative result. This was a combination of Lopinavir and Ritonavir, both of which were HIV medicines and were expected to work for COVID19.

20. What are some of the credible sources of information about COVID19?

WHO, CDC, Ministry of Health and Family Welfare, DHS Kerala are a few of the sources of updated information on COVID19. Following these sites will not only provide useful and relevant information, but help avoid fake news, claims and scams. The WHO has a special WhatsApp based service where they deliver automatic updates upon request. The number is +41 798 931 892.

21. Are healthcare workers at risk?

Yes. Approximately 10% of cases in China and 9% of cases in Italy were healthcare workers. The reason is simple. These are the people who come into direct contact with patients. Healthcare workers will need to be protected with maximum precautions and training of COVID19 protocols. PPE shortages are reported worldwide.

Unlike popular perception, personal protective equipment (PPE) is not the only method of protecting healthcare workers. There has to be administrative and engineering controls, which in fact play a greater role in protecting healthcare workers.

In the Indian setting, protecting them from healthcare-related violence is of paramount importance. The government has been notified by IMA about 1) the urgent need to ramp up production of PPE, 2) 'cohorting' (the process of identifying places to admit patients after existing facilities become full) and 3) to declare hospitals as special zones where armed police aid posts should be present, and there will be zero tolerance of altercations of any kind.

In this extraordinary circumstance, xenophobia against healthcare workers is a potential problem in India, once the disease progresses into the next stage. Xenophobia refers to hatred towards a section of society, by virtue of their race, nationality, occupation or other parameters.

Burnout, fatigue, and guilt or fear of spreading infection are problems that have already affected healthcare workers in other countries, where the demand for medical care is now rapidly overwhelming supply—after an initial period of calm.

22. What can India learn from other countries? What does 'flattening of the curve' mean?

Countries like US, Italy and Iran were apparently in denial in the beginning and perhaps took it too lightly saying that "their numbers are way too low" at the start.

In all countries, the initial numbers will invariably be low because not all the cases are tested, and based on the math of geometric progression described above. This gives a false sense of security and resulting delay in implementing social distancing, quarantine and tracking of contacts. In these countries, after an initial period of calm, the epidemic curve took a steep climb, by which time it got too late to implement strict social distancing.

With a country-wide lockdown, tracking of cases and their contacts and air-travel restrictions, India has taken unprecedented assertive action, and we can only hope that it was early enough along the epidemic curve.

Singapore implemented social distancing and other measures immediately, and the effects are obvious. The epidemic curve of Singapore is already going downward while the graph of UK, Italy and US are going steeply upward.

If a lot of people get sick over a short span of time, even the most modern ICU or hospital will not be able to offer much help. Patients will need to be turned away, as is happening in Europe now.

If people fall sick over a longer period of time, the system will be able to cope better, and mortality rate also will be lower.

The example I use to explain this to lay people is the following:

Imagine an office where twenty people suddenly get a tummy upset and rush to use the toilet all at once. Unfortunately, the building has only one toilet. Only one person is able to use the toilet at a time. This could become the state of our healthcare system, our hospital beds and ICU's and ventilators if we had not taken assertive action.

What we would like to happen is for these twenty people to come *one after the other*, and the toilet can serve each one of them without any problem.

This is the concept of flattening of the curve, which means that people will get sick over a

longer period of time which will make it easier for our health care system to handle the patient flow.

24. How long will the pandemic last? Will it recur?

The truth is, nobody knows. We need to accept that there are things we do not know.

The Spanish flu pandemic of 1918 killed about 3% of the world's population, and India is reported to have lost the highest percentage of its population, among all countries. That epidemic lasted several months, flaring up twice, before finally dying down the following year. Social distancing saved lives wherever it was implemented.

25. On a projected model, how many lives can be saved by enforcing social distancing?

After studying the China epidemic of COVID19, on a travel network-based susceptible-exposed-infectious-removed (SEIR) model, Shengjie Lai et al projected an 18-fold increase in the number of cases if the measures were delayed by 3 weeks, and a 3-fold increase if even a week's delay had occurred.

They also projected that 66% fewer cases would have occurred in China if these measures were taken one week early. Early assertive action saves lives.

In math, a small percentage of a big number is still a big number. Even the smallest change of percentage of patients affected will become an extremely large number in a country like India with limited resource and a population of over 130,000,0000.

We need to be aware that as a community, we have the power to decide the attack rate of the virus.

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Further reading

1. Crowds can rapidly spread the COVID19 virus

https://news.yahoo.com/south-korea-becomes-biggest-coronavirus-centre-outside-china-023510628.html

2. Timing of social distancing saves lives

https://www.medrxiv.org/content/10.1101/2020.03.03.20029843v3

3. Asymptomatic patients transmit virus

https://www.medrxiv.org/content/10.1101/2020.03.05.20031815v1

4. The diamond Princess experience

https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180

5. European CDC Rapid risk assessment Coronavirus 2019 7th update, 25 March 2020

https://www.ecdc.europa.eu/en/novel-coronavirus/event-background-2019

6. California governor projects that 56% of population will get infection.
   https://www.cnbc.com/2020/03/19/coronavirus-california-estimates-25point5-million-residents-56percent-of-the-state-will-get-virus-in-next-8-weeks.html

7. Prof. Jacob John writes in the Hindu about upto 70% of India at risk of being infected eventually
   https://www.thehindu.com/opinion/op-ed/covid-19-and-the-great-chinese-puzzle/article31167412.ece

8. Duration of survival of virus on surfaces and aerosol
   https://www.nejm.org/doi/full/10.1056/NEJMc2004973

9. Oxford University model predicts 68% of UK is already infected with COVID19
   https://www.dropbox.com/s/oxmu2rwsnhi9j9c/Draft-COVID-19-Model%20(13).pdf?dl=0

10. Arizona man dies after taking chloroquine
    https://edition.cnn.com/2020/03/23/health/arizona-coronavirus-chloroquine-death/index.html

11. No need to change antihypertensives to reduce risk for COVID19
    https://jamanetwork.com/journals/jama/fullarticle/2763803

12. No need to stop your newspaper subscription
    https://www.sierraleonetimes.com/news/264382590/united-arab-emirates-puts-temporary-ban-on-paper-circulations

13. WHO on COVID19; mythbusters
    https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters