



# Chasing the X-factor! Why is the Japanese COVID-19 death rate low?

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What conclusion was drawn from searching, based on the belief that there must be a reason unique to Japanese people?

In *Bungeishunju*, June 2020, Dr. Yamanaka Shinya, Director of the Center for iPS Cell Research and Application (CiRA), Kyoto University, pointed out that there must be some sort of a hidden “X-factor” behind the fact that there are few deaths from COVID-19 among Japanese people, and this was talked about in the news.

I have actually always had the same doubts and searched for possible candidates for an X-factor from public data and the latest papers which are updated daily around the world, and I presented these candidates on the “sendaitribune” blog. My field is developmental neuroscience, which is different from infectious disease medicine and epidemiology. However, with this COVID-19 outbreak, I now respond to infections within the campus as a member of the Tohoku University’s in-house emergency advisory team for COVID-19.

I have also had the opportunity to hear fellow experts speak, including Dr. Oshitani Hitoshi, Professor, Department of Virology, Tohoku University Graduate School of Medicine of the Counter-Cluster Measures Team of the Ministry of Health, Labour and Welfare (MHLW). Something he said piqued my curiosity, and I now research various things as a biological researcher.

There is a saying: “You can’t see the forest for the trees.” In the public health world, I have heard that what is instead required is the idea that, “you can’t see the trees for the forest.” Sure enough, when analyzing wider global trends with regions or countries, you will become unable to take measures if you focus on the details. Despite being in a different field, I was able to understand that it was rational to “look at the forest without seeing the trees” and bundle infection measures together.

However, I am the type of person who looks closely at detailed differences and changes and wonders why things are different. I look at each and every tree and worry about why one tree is being eaten by bugs when the other trees are healthy. As that is who I am, I can’t keep from wondering why things are so different depending on the country and what is different between those who become seriously ill and those who don’t.



Dr. Osumi Noriko

## Why Are There Few Countries that Recommend BCG?

I am a total armchair detective, and I hope that you will understand the limits to my amateur sleuthing. I hope to share the inferences I have made in regards to this mystery.

According to material from The Novel Coronavirus Expert Meeting of the Ministry of Health, Labour and Welfare (dated May 29), important non-biological points related to the low number of infected people and deaths among Japanese people are as follows:

- i) Early detection of infected persons due to easy access to medical care under the national health insurance system, the high quality of medical care even in rural areas, etc.
- ii) The Japanese public's high standard of hygiene, originally different lifestyle habits, and willingness to comply with government requests
- iii) The spread of infection from China (the first wave) and the spread of infection from Europe, etc. (the second wave) were detected early
- iv) Japan's cluster-based approach

I do not have any objections to the fact that efforts in public hygiene have had a large effect, but I look at this from a viewpoint that a biological X-factor exists apart from this.



BCG is a vaccine for preventing tuberculosis. In Japan, inoculations began through the Tuberculosis Control Law (1951), and today, the vaccine is recommended in infants less than one year after birth.

This is because the differences in COVID-19 infections and severe cases is too different among countries. Number of cases is greatly affected by the level of PCR testing, so if we look at the number

of deaths per million in the population in each country, we see that as of June 25, the top eight countries are in Europe, followed by the United States at 373 people, rapidly increasing Brazil at 251, and Russia at 58. [Note: Total deaths, US 236,042, Brazil 162,397, India 127,059, Mexico 95,027, United Kingdom 49,238, Italy 41,750, France 40,665, Spain 38,833, as of Nov. 10 by WHO COVID-19 Dashboard, <https://covid19.who.int/>]

On the other hand, the death rate in Japan is 8 people per million [Note: 14.3 people as of Nov. 9], with South Korea at 5, Thailand at 0.8, Taiwan at 0.3, and no deaths at all in Vietnam (COVID-19 CORONAVIRUS PANDEMIC public data from worldometers website). Not just Japan, but on the whole, there is a trend towards remarkably few infections and deaths in East Asia.

With such differences among countries, there ought to be another factor rather than just efforts in public hygiene. Doing research while thinking this, I arrived at the JSatoNotes blog via Twitter at the end of March, a little before the state of infections reached its peak in Japan. In an article on this blog, it was pointed out that the spread of infections was slow in countries where BCG (Bacillus Calmette–Guérin) vaccine inoculations were given.

Surely there are many who wonder why BCG? As you may know, BCG is a vaccine for preventing tuberculosis. In Japan, inoculations began through the Tuberculosis Control Law (1951), and today, the vaccine is recommended in infants less than one year after birth.

It sounds far-fetched at first that a vaccine for preventing tuberculosis would be effective against COVID-19, and can only be described as an unlikely explanation. However, J Sato later thoroughly researched public data, and pointed out whether BCG had been made compulsory or not, the relationship with the timing of it being made compulsory, and the differences in the effects for each vaccine strain. I had a strong feeling that this was something created through citizen science, with participation from normal citizens who are neither specialists in infections nor doctors.

I checked J Sato's points by looking at materials on my own, and sure enough, countries with many deaths—Spain, Italy, France, and the United States—did not actively implement BCG vaccination. On the other hand, China, South Korea, and Japan are countries that recommend BCG vaccination.

## **The Tokyo and Former Soviet Union Substrains are Potent**

We can see something even more interesting if we look closer at each country.

While most European countries do not have a BCG vaccination program, it was recommended in Poland. The death rate per million in Poland is 37, fewer than the 107 in neighboring Germany.

Spain and Portugal are also neighbors, but when comparing their death rate per million, Portugal is at 151 while Spain is at 606. There is no BCG vaccination program in Spain, but vaccinations have been administered in Portugal.

J Sato further points out that there are differences based on the type of strain of the vaccine.

There are several strains for the BCG vaccine, including the French substrain, the Danish 1331 substrain, the former Soviet Union substrain, the Sweden substrain, and the Tokyo substrain. When a strain diverges from the original vaccine produced at the Pasteur Institute in France, it is labeled as a “substrain,” and it is said that the effects of the vaccine are weakened.

If we look at this in relation to COVID-19, we can see that an incredibly interesting phenomenon is occurring in Germany. In Germany, up until 1998, the former Soviet Union substrain vaccine was used in former East Germany, while the western Europe substrain vaccine was used in former West Germany. As of May 20, the death rate per million in the former West Germany side was 108, while in the former East Germany side it was 46. Of course, it is possible that behind this are the fact that there are many deaths in Berlin and other urban parts and that there may be differences in medical care and immigration issues. The Tokyo substrain used in Japan is actually close to the former Soviet Union substrain and is known to be similar to the original vaccine.

## **An Effect that Strengthens Immunity**

What! But the effects of BCG are only until about age 20, right?

This was my initial thought. Even still, the reason I found this theory interesting was because there was a paper that put forward the novel idea that the BCG vaccine not only had an effect against tuberculous bacilli, but could also strengthen the human immune system as an off-target (separate from the original goal) effect, causing changes on the genetic level with lasting effects.

Before COVID-19 was in the news, the off-target effect that BCG trains natural immunity was known to some researchers. There were also reports that acknowledged its side effects in reducing the risk for adult lung cancer occurrence and controlling the progression of vesical cancer.

Immunity can be broadly classified into two categories: “natural immunity” and “acquired immunity.”

Natural immunity refers to the resistance held by humans from birth. It constantly patrols the body and attacks foreign substances when they enter from outside the body. Macrophages (a type of white blood cells, these immune cells ingest and process foreign invaders and cells that are no longer needed within the body) and natural killer cells are known as the types of cells in charge of this.

On the other hand, acquired immunity refers to immunity acquired after birth through infections, vaccine inoculations, etc., and this is handled by lymphocytes that circulate in our blood. The elite troops of lymphocytes memorize viruses, cells, and other foreign substances (antigens) that have entered the body once and create antibodies, and the antibodies then launch a concentrated attack the next time the same foreign substance enters the body. Originally, the BCG vaccine caused lymphocytes to memorize the tuberculous bacilli by injecting detoxified tuberculous bacilli (antigens) with the aim of having no infection the next time tuberculous bacilli infiltrated the body.

So then how is it possible for the BCG vaccine aimed at tuberculous bacilli to show effects against COVID-19?

A research team from the Netherlands announced that something strange was occurring when they researched the blood of people who had received the BCG vaccination. Immune cells have a switch that prompts enhancement, and they found that this switch was turned on in these people. The switch being continually “ON” means that immunity stays strengthened even when inoculated

as an infant, and it means it is possible that immune strength, used to resist a variety of foreign invaders, is strengthened. (*Cell Host & Microbe*, January 10, 2018 ed.)

The team in the Netherlands named this mechanism “Trained Immunity.” If this theory is true, it means that natural immunity is strengthened in Japan and other BCG vaccination countries as well as many people in countries where tuberculosis infection still spreads, which would allow us to see that infection can be avoided.

## **Effective in Also Preventing Elderly Pneumonia**

While researching trained immunity from BCG vaccination, I found my way to research that indicated that there was a preventative effect with BCG against pneumonia. This research was the “Prevention of elderly pneumonia by BCG vaccination” (Grants-in-aid for Scientific Research Report), carried out in 2003 and 2004 by Dr. Ohrui Takashi, Assistant Professor, Department of Geriatric Pharmacotherapy at Tohoku University (currently Professor for Division of Respiratory Medicine, Tohoku Medical and Pharmaceutical University).

When a tuberculin test was administered to 155 bed-ridden elderly patients placed in a nursing facility, there were 67 who tested positive and 85 who tested negative. (A positive result indicates a medical history of tuberculosis infection or BCG vaccination.) BCG vaccination was then administered to the 85 negative patients, and when looking at the tuberculin test that was re-administered four weeks later, it resulted in 41 patients shifting to testing positive and 44 patients remaining negative.

The pneumonia rate was then tracked for two years.

Looking at the results, an extremely low value is indicated with the pneumonia rate for the group of patients who were initially positive at 13% and the rate of infection for the group of patients who shifted to positive through the vaccine at 15%. At the same time, the results show a high value more than double that with a pneumonia rate of 42% for those that remained negative even after receiving the vaccine.

Pneumonia is a disease that is unrelated to tuberculosis, so it is thought that BCG may have strengthened the elderly patients’ natural immunity. Dr. Ohrui states, “The BCG vaccine lowered the risk of pneumonia for bed-ridden elderly patients whose immune strength was compromised.”

This clinical research was reported as a correspondence in *The Lancet*, a peer-reviewed medical journal. (A correspondence is not a research paper, but is a document publishing a report on clinical research guaranteed by the editor.) It wasn’t large-scale research, and it doesn’t show a long-term off-target effect, but when considering that pneumonia is seen as a characteristic in COVID-19, it is enough of a material to make one want to recommend BCG vaccination as biological X-factor.

As COVID-19 infections spread across the globe, research has begun to determine the effectiveness of BCG vaccination in adults. Clinical research has started in the Netherlands and Australia to inoculate health care workers with BCG and see the preventative effects against COVID-19 infection and progression into serious illness. If it is deemed effective, surely health care workers around the world will receive a BCG vaccination.

There were few advocates as of the end of March in 2020, when I introduced the BCG theory on sendaitribune, but Miyasaka Masayuki, Specially Appointed Professor, the Immunology Frontier Research Center (IFReC) of Osaka University, later presented the idea as a discussion in English and it was mentioned in a document on the Japan Medical Association website by the former President of Osaka University who specializes in immunology.

## **COVID-19 and Thrombosis**

At this point, I began to want to search for other theories. BCG is an acquired factor, but I became curious about whether or not there was a further X-factor as an innate, biological difference.

COVID-19 infections were initially called “novel pneumonia,” and the symptoms of pneumonia attracted attention, but as our detailed understanding grew about the progression of COVID-19 into a serious illness, we learned that generalized organ failure was occurring. The cause of this was thrombosis.

Generally, thrombosis is often talked about as a lifestyle-related disease, and it may be surprising that it is connected to an infection. So why does COVID-19 create blood clots?

The mechanism is like this. Inflammation occurs in cells once infected with COVID-19. Cytokine, a transmitter, is then released from cells, informing the entire body that infection and inflammation have occurred and causing the body to go on the defense. However, when a large amount of cytokine is released at once, a variety of adverse effects occur within the body. This is the “cytokine storm” that has often been talked about in the news lately. It is known that in addition to fever and fatigue, the cytokine storm causes the coagulation of blood. The thrombosis that occurs from COVID-19 is caused by this abnormality in the immune system.

Vitamin K is a nutrient associated with coagulated blood. It has the effect of solidifying blood and when the body is low on this nutrient, it can lead to nose bleeds, intestinal hemorrhage, and more. Conversely, it can also sometimes be the cause of cerebral infarction and cardiac infarction when there is too much vitamin K in the body.

Warfarin is widely known as an anticoagulant to prevent the solidification of blood. This medicine blocks the mechanism of vitamin K and keeps blood from solidifying.

However, it is known that there is a great variance in the required dosage of warfarin depending on the person. While there are some people who only need 0.5 mg per day, there are also some who see their first results after a dose of 10 mg, and so the handling of this drug is difficult. As a side note, it is known that Japanese people are highly sensitive to warfarin and there are many people in Japan who only need a small dose.

This variance in effective dosage is a major issue in the ease of using a drug. A search was undertaken in 2010 to find gene types that influence the dosage of warfarin, and the results were published as a research paper in an authoritative magazine on genetics. (I learned of this research paper from Kitano Hiroaki, Director of the Sony Computer Science Laboratories, Inc.)

[Editor’s note: Prof. Osumi points out that as the prevalence of influenza is related to latitude and seasons (and the corresponding amount of sunlight), amounts of vitamin D, which is assumed to improve “immune strength,” might also have the effect of preventing COVID-19.]

## What Countries in East Asia Have in Common

We know from this research that there are many people of Asian descent who have a gene type that allows warfarin to take effect easily, while there are also many people of African descent who have a gene type that makes it difficult for warfarin to take effect. We also know that among those of Asian descent, warfarin took effect the easiest among those of East Asian descent, which includes Japan, and those of European descent were in the middle between those of Asian descent and those of African descent.

From here we can see a correlation with the state of COVID-19 infections. The correlation is that people from East Asian countries, including Japan, South Korea, and China, where the rate of cases being serious is low, are the most easily affected by the drug, warfarin.

If we make another bold conjecture, we can say that people with a gene type that allows warfarin to take effect easily have a body where blood clots do not form easily, regardless of whether or not the person is taking warfarin, and this may be connected to the prevention of a COVID-19 infection becoming a serious illness. There must be a significant reason behind why the number of deaths in East Asian countries is different by two digits when compared to Europe and the United States. I think that this will be an interesting topic for future research.

There is a theory that says the reason why infections aren't spreading is because the coronavirus was prevalent last year in Japan. If this were true, then this might be another X-factor, but according to the antibody tests presented by the MHLW on June 16, the positivity rate was only 0.10% in Tokyo, 0.17% in Osaka, and even lower at 0.03% in Miyagi. As this is such a low level, the question remains about the possibility of a 2019 epidemic. However, it is also speculated that COVID-19 infections might make it difficult to create antibodies.

From the above, the two biological X-factors that I think are currently important are the "BCG vaccine" and "the gene type related to anticoagulation."

The BCG vaccine is not a get-out-of-jail-free card, of course. I hope it is understood that there is the risk of serious illness even for those Japanese people who were inoculated as children.

The reality is that infections and serious cases of COVID-19 are also related to many social factors, including quality of medical care, living environment, and hygienic and nutritional conditions, as well as work environment, income, and level of education. At the current stage, the differences between country and race are no more than correlations, and the causal relation is not yet known.

With the talk of gene types related to anticoagulation, while I mentioned differences in race, this is nothing more than an indication of a trend, and I hope it is understood that this obviously has nothing to do with superiority or inferiority.

## A Twist Ending in the Search for an X-factor?

At the start, I shared the saying, "You can't see the forest for the trees." Even with this search for an X-factor, which I have become obsessed with, it may actually be that the ending when looking at this talk that only applies to some of the trees is that the most important X-factor is masks after all!

Japanese people naturally wear masks even with a slight cold or with hay fever, but in the West, there are countries where there is resistance to wearing masks, and in those countries, we know that infections are spreading.

Masks, worn to protect oneself, have also proven effective in controlling infections by keeping airborne droplets from spreading to others, and as a result, it is quite possible that this is related to the lower risk of infection within Japan.

Dr. Yamanaka has also offered several non-biological factors as candidates for X-factors, and as it turns out, it is thought that whether or not a person is infected or becomes seriously ill is decided by a combination of multiple factors. I think it will be important to carefully explore this as medical and biological research that is a matter of life and death for people around the world. All of this ought to be helpful in establishing future methods of prevention and treatment.

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Professor Osumi graduated from Tokyo Medical and Dental University, holds a Ph.D. from the same university, and has been a professor at Tohoku University School of Medicine since 1998. She has served as Vice President of Tohoku University since 2018. Her research background is developmental biology, and she has a special interest in brain development, evolution and disease. Recently, she has been working to understand regulatory mechanisms for the transgenerational effects of paternal aging that affect an offspring's behavior. Manipulating embryos and imaging brain cells are areas of expertise in her lab. She has been appointed to various governmental committees concerned with, for example, ethical issues, grant system development, and career paths for young scientists. She was a representative of the CREST project (2005–2010) supported by JST and the Global COE project (2007–2012) supported by MEXT. Currently, she is a leader for Grant-in-Aid for Scientific Research on Innovative Areas (16H06524) “Integrative Research toward Elucidation of Generation of Brain Systems for Individuality”.