

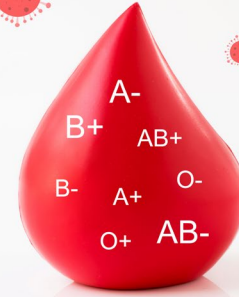
Is There a Relationship Between Blood Type and Risk of Contracting COVID-19?

by

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Part I – Blood Type Background

Introduction

“Hey, Tina! How are you holding up with all of the sudden changes?” Jim asked as he lowered the window of his Jeep.

“I’m okay, I guess. I really don’t think they needed to cancel school though. Now I’m stuck at home and my parents think I should be spending a lot more time helping out around the farm. They just don’t understand that our professors still expect us to continue with our studies online. It doesn’t help that one of my professors is especially demanding.”

“Oh, that’s tough. Probably feels like you’re being asked to work two jobs at the same time,” Jim said. “That’s probably even more difficult than having to maintain our three-foot distance from others at all time.”

“That’s exactly right” said Tina. “I certainly didn’t sign up for this workload at the beginning of the semester,” Tina sighed. “I think if I could just get out for a bit and see my friends or even others in my community I’d feel better. I miss all of the social interactions.”

“Have you thought about volunteering or helping by donating blood?” asked Jim.

Tina replied, “Nah, I do enough here. Besides, I don’t even know my blood type. They might not even want my blood.”

Jim replied, “You don’t even know what blood type you have?! Even more of a reason to donate blood. They always inform you of your blood type after donating and since there’s really only two blood types it’s not hard to remember. Plus, with the pandemic going on, the need for blood donations is at an all-time high.”

“What does the pandemic have to do with the need for blood around here? There are so few cases here in rural areas since nobody ever travels far from home. Plus, I thought COVID-19 was a lung disease not a blood disease,” replied Tina.

“True,” said Jim. “But those being treated for sickle cell anemia and some cancers require blood. Furthermore, blood is needed for victims who have been in accidents. I once heard that every day in the U.S. 36,000 units of red blood cells are needed. And just because we live in the middle of the country doesn’t mean we aren’t impacted. I heard on a cable news station that Kansas was a state in particularly bad shape when it came to blood donations and supply levels.”

“Kansas?” exclaimed Tina. “I didn’t know we ever made the national news! Ok, ok, I’m convinced, but how do I know where to sign up? And will there be other people around? I’m so tired of being in some self-imposed quarantine when I feel perfectly fine. I’m pretty sure if I had the coronavirus I would know it. I need to get out and talk to other people! But, social distancing is still being enforced so can I go without getting in trouble?”

Jim sighed and patiently said, “There will be other people there, but the American Red Cross can safely mitigate the risks of spreading the virus. Plus, you’re young so you can’t really get the virus anyway. I’ll send you the website.”

That afternoon Tina received an email with a link to a webpage, “What to know about the Coronavirus and blood donation,” hosted by the American Red Cross: <<https://www.redcrossblood.org/donate-blood/dlp/coronavirus--covid-19--and-blood-donation.html>>. After reading the information on the page she decided to give blood. It was at the donation center that she learned she had blood type A+.

Activity 1 – Identify Misconceptions

Given the dialogue and information in the link above, can you find any misconceptions that Tina and Jim might have? Jot these down in the space below. You will come back and add to this as you move through the case study so leave yourself extra room. Please be sure to check with your instructor that you have caught all of the misconceptions; it is very important that you identify all of the misconceptions between Tina and Jim that are included in this case study because these are misconceptions that may be seen on social media and even sometimes in national media sources.

<i>Tina</i>	<i>Jim</i>

Blood Components and Type

Blood is a type of connective tissue and like all other connective tissues, blood contains cells that are suspended in an extracellular matrix. For example, osteocytes (bone cells) are surrounded by an extracellular matrix of ossified bone. Chondrocytes (cartilage cells) are surrounded by an extracellular matrix comprised of collagen, elastin, and water, which is held together by proteoglycans. Blood cells are also surrounded by an extracellular matrix called plasma. This arrangement of cells suspended in a matrix distinguishes blood and all other connective tissues from the primary tissue types (nervous, epithelial, and muscle).

Unique to blood is the fact that its main components can be easily separated and examined. This is possible because blood is a fluid containing formed elements such as red blood cells (erythrocytes), leukocytes (white blood cells), and thrombocytes (platelets). Formed elements are more dense than the fluid in which they are suspended.

As shown in Figure 1, a sample of blood that is centrifuged for about ten minutes segregates itself into easily identifiable components by density. Percentages provided are a general estimate for a healthy adult although these values do vary a little between men and women. Details of these main components are given on the next page.

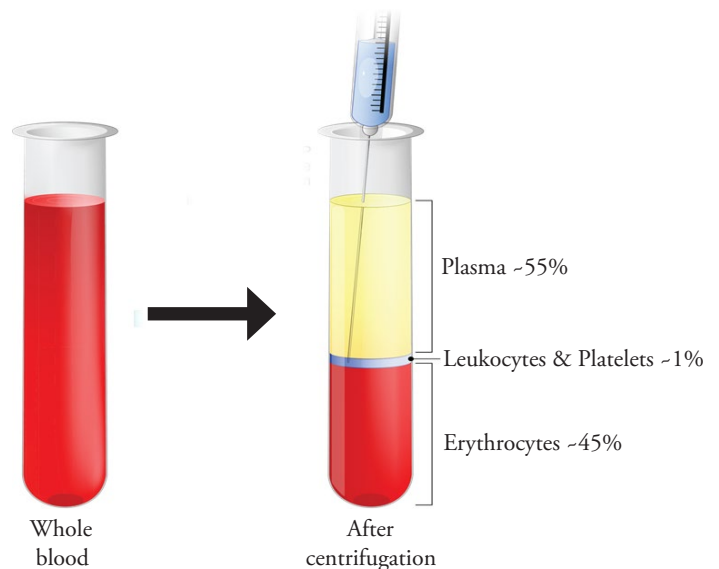


Figure 1. Results of centrifugation, which separates whole blood into different fractions by density. Credit: © Designua | Dreamstime.com, ID 137533295.

Plasma: Ground Substance/Extracellular Matrix of Blood

Plasma suspends and carries blood components; this is possible because plasma is 92% water by volume. Plasma also contains components that are crucial for regulating and powering cellular processes as well as buffering blood pH. Below is a list of the main components found in plasma (besides water).

- *Albumin*: Regulates oncotic (also called colloid osmotic) pressure (think osmolality) of blood helping with fluid volume of interstitial fluid areas.
- *Carrier proteins*: Transport ions and hormones in more stable form; aids solubility and helps prevent them from being excreted.
- *Protein cascade precursors*: Includes complement and blood clotting factors.
- *Antibodies*: Protect against foreign antigens.
- *Hormones*: Chemical messengers that allow communication.
- *Nutrients, cellular waste*: Plasma provides transportation for these solutes.

Leukocytes: White Blood Cells

Representing the cellular part of the immune system, leukocytes only make up about 1% of blood but have a significant impact on health. Their numbers can increase quickly and substantially. CBC (complete blood count) results can provide clues about infections by analyzing various leukocyte parameters.

- *Monocytes*: Long lifespan, help break down bacteria; circulate as monocytes and then become macrophages as they enter the tissue.
- *Lymphocytes*: Provide cellular immunity and create antibodies to defend against bacteria, viruses, and invaders; main types are T and B cells.
- *Dendritic cells*: Continuously sample environment, capture and process foreign antigens then present the information to T cells.
- *Natural killer cells*: Help limit spread of tumors and microbial infections; assist in killing virally infected cells.
- *Basophils*: Small cells that alert other cells when pathogens have invaded, secrete histamine.
- *Eosinophils*: Attack and kill parasites, help destroy cancer cells, participate in allergic responses.
- *Neutrophils*: Provide first line of defense after bacterial, fungal, or viral infection; constitute first and most abundant cell population reaching sites of infections where they phagocytize pathogens and reduce viral replication.
- *Macrophage*: Large phagocytic cells that have the ability to engulf and destroy whole cells such as bacteria, foreign tissue cells or even virally infected cells. Macrophages can phagocytize cells without being activated by other cells of the immune system but can also recognize constant regions of antibody molecules, making them a link between innate (non-specific) and acquired (specific) immunity. These cells also trigger the majority of the inflammatory response to infection.

Erythrocytes: Mature Red Blood Cells

The function of erythrocytes is to transport blood gasses. Red blood cells have a lifespan between 90–120 days and form via a process called erythropoiesis where progenitor cells differentiate through three developmental stages to form erythrocytes. These are described below.

- *Normoblasts*: Nucleated precursors of red blood cells in bone marrow; presence of normoblasts in blood is abnormal.
- *Reticulocytes*: Direct precursors to mature red blood cells, anucleated but still possess large amounts of RNA so translation can continue; these cells are released into the blood and account for about 1% of total circulating RBCs.
- *Erythrocytes*: Mature red blood cells, biconcave, flattened, anucleated, no RNA, no mitochondria, and are exclusively reliant upon glycolysis for ATP production.

Although erythrocytes are unique in some ways, they still share similarities with other cells. For example, the plasma membranes of erythrocytes, like those of all mammalian cells, consist of a lipid bilayer in which are embedded highly specific glycoproteins. These glycoproteins extend into the extracellular fluid and serve as antigens. Typically antigens by definition are anything the body perceives as foreign such as bacteria, toxins, *viruses and viral proteins made by cells*, and even cancer cells. The immune system produces antibodies against foreign antigens, including those found on erythrocytes not produced by the body (such as in donated yet mismatched blood). The immune system does not produce antibodies against its own erythrocyte antigens. The reason for this is, regardless of the cause, foreign antigens are perceived as a threat and trigger an immune response, which leads to the production of antibodies by lymphocytes.

Antibodies to foreign blood type antigens form naturally at an early age, usually in response to encountering antigens in foods or micro-organisms. Interestingly, both food and micro-organisms present antigens that the body perceives as identical, or at least similar to, erythrocyte antigens. Thus, all people have some antibodies against certain foreign erythrocyte antigens in circulation. However, antibody production against foreign erythrocyte antigens can increase exponentially after an initial exposure to the wrong blood type as could occur in a transfusion if blood types are not carefully labeled at clinics. For example, if a person with type A blood receives a transfusion of type B blood, the antigens on the surface of the erythrocytes within the type B blood will be perceived as foreign because they do not match those on the recipient's own erythrocytes. As a result, the introduced erythrocytes would have antigens on their cell surfaces that would cause the recipient's immune system to perceive them as foreign invaders, leading to agglutination (clumping). Because the "foreign invaders" in this case are cells, the antibodies produced against the erythrocyte antigens are called "opsonins" because they induce macrophages to phagocytize the cells and break them down with enzymes in the cytoplasm of the macrophage.

Activity 2 – Items Associated with an Erythrocyte and Plasma

1. Label the glycoproteins (antigens) in Figure 2.
2. Label the antibodies in Figure 2.
3. In a centrifuged sample, what fraction would contain erythrocyte antigens?
4. In a centrifuged sample, what fraction would contain antibodies?
5. In a centrifuged sample, where would cells that produce antibodies be found?

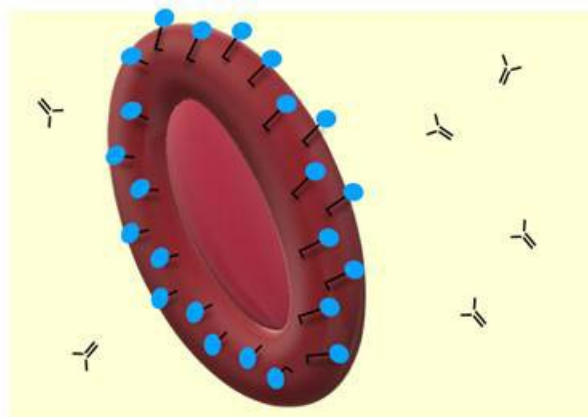


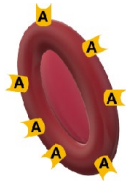
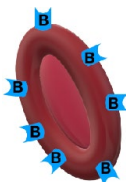
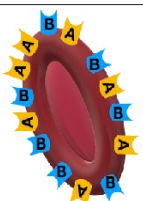

Figure 2. Erythrocyte.

Hopefully at this point you are beginning to see why it's a good idea to understand the ABO blood groups and to know your blood type (which you can easily find out by donating blood). Interestingly, human erythrocytes can express over 100 different antigens but the ABO system of antigens captures the most common. The information on the following pages explains the basics of the ABO blood system, also known as immunophenotyping.

Activity 3 – ABO Blood Group System and Immunophenotyping

ABO blood groups are based on the presence or absence of two erythrocyte glycoproteins (antigens): A and B. Depending on which of these are expressed on a person’s erythrocytes, his or her ABO blood group will be one of the following: A, B, AB, or O. People with blood type A have erythrocytes that express only A antigens on their surface. Those with blood type B have erythrocytes that express B antigens on their surface. People with blood type AB have erythrocytes that express both A and B antigens on their surface. And finally, people with blood type O have erythrocytes that do not have any antigens on their surface. For this reason, the O blood type is considered the universal donor. The absence of antigens on their surface means they are far less likely to trigger an immune response, regardless of the recipient’s blood type. On the other hand, people with blood type O can only receive O blood as introduction of other blood types would initiate an immune response due to the introduction of foreign antigens.

Complete the chart below to illustrate the differences described above regarding ABO blood types. The first one has been done for you.

<i>Blood Group</i>	<i>Erythrocyte Antigens</i>	<i>Antibodies in Circulation</i>	<i>Blood that can be Received</i>
A 	A	B	A, O
B 			
AB 			
O 			

Activity 4 – Rh Blood Group System

In addition to the A or B antigens expressed on erythrocyte surfaces, antigens known as the Rhesus factor can also be expressed on the surface. These antigens are proteins produced from genes that are also found in a similar form within rhesus monkeys. A person with erythrocytes that express Rhesus protein antigens is considered to have Rh+ blood. If a person’s erythrocytes lack Rhesus antigens, they are considered to have Rh- blood. Usually, the presence of the Rhesus antigen is just attached to the end of the blood type such that a person with blood type A who also expresses the Rhesus antigen is said to be A+. A person with blood type O who does not express Rhesus antigens would be type O- and so on. Currently, the Rhesus factor blood group system consists of 50 defined blood cell antigens. Antigen D, however, is one of the most common. In fact, the terms Rh+ and Rh- *only* refer to the presence or absence of antigen D on erythrocytes.

If a person is Rh+, their bodies would not produce any antibodies against antigen D if they received blood from another person, whether that person is Rh+ or Rh-. However, if a person is Rh- their bodies do produce antibodies against antigen D if they receive blood from an Rh+ person. As with the ABO blood group system, the need to know a person's Rhesus factor is important before they are given any blood. Luckily, though, a mismatched Rhesus factor doesn't cause the massive and spontaneous immune response as would be seen with a mismatch in the ABO blood system. In fact, a mismatch of the Rhesus factor very rarely causes spontaneous clumping. Fortunately there are also drugs that can be given to prevent the person's immune system from recognizing and mounting an immune response to antigen D, which is particularly important for pregnant women who are Rh- carrying an Rh+ fetus.

Complete the table below to illustrate the differences described above regarding the Rhesus factor (antigen D).

<i>Blood Type</i>	<i>Erythrocyte Antigens</i>	<i>Antibodies in Plasma</i>
Rh+		
Rh-		

- List all possible antigens (the common ones) that can be expressed on mature human erythrocytes.
- If given the wrong blood type during a transfusion, which leukocyte would be responsible for producing antibodies against the foreign antigens found on the donated erythrocytes? Which leukocyte would be responsible for removing the foreign erythrocytes?
- Given what you've learned about antigen expression on erythrocytes, do you think other cells in the body express glycoproteins on their surface that help identify them as "self"? Why or why not?

Serological tests use blood serum to detect if a person has been exposed to a certain virus, such as the coronavirus. Blood serum and blood plasma are both descriptions of the fluid portion of blood but they are not the same thing. If whole blood is treated with a chemical to prevent clotting (an anticoagulant) and then centrifuged, the fluid portion will be plasma because it will still contain the clotting factor proteins. If the blood sample is first allowed to clot, the clotting factor proteins will have been removed and the resulting fluid portion after centrifugation is serum. Thus, serum is defined as plasma minus the clotting factors and a few other proteins. Serum is often preferred for testing many blood components because the clotting process can cause cells to release certain factors into the extracellular fluid, such as potassium ions or lactase dehydrogenase enzymes.

Even though the virus isn't typically present in the blood, an infection or even previous exposure to the virus causes leukocytes to quickly recognize specific protein antigens from the virus and mount an immune response. This immune response is often in the form of T cells that recognize virally infected cells (infected cells usually have viral proteins in their cell membranes) and kill them. In addition, B cells make antibodies that bind to virus particles and prevent them from infecting cells, or flag and help destroy cells infected with the virus. These antibodies circulate in the fluid portion of the blood, which is why the tests for them are called "serological" tests. Once virally infected cells are detected by T cells or antibodies, other leukocytes produce inflammatory factors that result in dramatically increased blood flow to the area that often results in edema (excess fluid) within the infected tissue. This is why SARS-CoV-2 infection often results in such severe pneumonia (a condition of the alveoli within the lungs being filled with fluid or pus).

- Describe how you could isolate the serum portion of blood from other blood components for analysis if you were given a whole blood sample from a patient. Why does that method work?

And the Story Continues...

“Hey Jim, I did it! I donated blood!” exclaimed Tina when she saw Jim the next day. This time she was careful to stand six feet away from Jim, who was sitting in his Jeep.

“That’s great! What blood type do you have?” he inquired.

Tina replied, “I have blood type A+, how about you?”

“I have blood type O- so I try to donate frequently,” said Jim.

“Why? Is there something unique about your blood?” asked Tina.

“I think if I have blood type O- it means I can’t get the coronavirus so it’s safer for me to be out in public and they can use my red blood cells to help protect others who may have the virus since red blood cells make antibodies against the virus,” said Jim. “I saw a report about blood type and coronavirus susceptibility on *Fox News*. I’ll text you the link... hang on.”

Tina looked at her phone, saw the following, and began reading immediately:

- *Anon.* March 18, 2020. People with blood type A might be more susceptible to coronavirus, study finds. *Fox News*. <<https://www.foxnews.com/health/people-blood-type-a-might-susceptible-coronavirus-study-finds>>
People with blood type A might be more vulnerable to the coronavirus, while those with type O blood could be more resistant, according to a new preliminary study from China.
Researchers studying COVID-19 in its outbreak epicenter, Wuhan, and the city of Shenzhen found the proportion of Type-A patients both infected and killed by the disease to be “significantly” higher than those with the same blood type in the general public.
Type O patients, meanwhile, made up a smaller proportion of both those infected and killed by the virus ...

“Whaaaat???” exclaimed Tina. People with blood type A might be more susceptible? But I got the flu shot! That’s got to count for something, right?



Remember to add any misconceptions in the dialogue above to the chart on page 2.

Part II – Is Blood Type Related to COVID-19 Risk?

Activity 5 – Risk Factors

To date different risk factors have been identified regarding the likelihood of contracting COVID-19 (coronavirus disease discovered in 2019), the disease caused by the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2; the SARS outbreak in 2003 was also from a coronavirus, SARS-CoV(1)). For example, there is a lower risk of contracting COVID-19 if you are in the same area as someone who is confirmed to have the disease if you remain six feet away from them. The risk becomes much greater if you are in close contact with someone who has been infected with the virus because the virus is known to be carried on particles expelled from the respiratory system of the infected person, and can remain viable on surfaces for up to several days. And yet, some who are exposed to people infected with the virus do not seem to be as susceptible to getting COVID-19 as others. Why is this?

To help guide your thinking, consider the following video and answer the questions found below:

- *A Virus Attacks a Cell*. Produced by Vaccine Makers Project, 2017. Running time: 1:42 min. <<https://youtu.be/jkNxmTrrZSk>>.

1. What did the virus use on the host cell in order to make contact with and gain access to the cell?
2. Given the information in Part I of this case study, hypothesize what could differ between people that might impact their susceptibility to being infected with a virus.

It is possible that natural differences in host cells influence the risk of contracting a disease post-exposure; evidence from different authors exists. For example, it has been shown that some viruses like the hepatitis C virus and the norovirus exploit differences in blood group antigens expressed on host cell surfaces. These differences can have interesting consequences regarding susceptibility to contracting a disease as opposed to simply being exposed to it. In regards to the norovirus, it is likely that it uses specific intestinal cell antigens, which are the same as the blood group antigens found on erythrocytes, as receptors, allowing the virus to latch on and gain access to the body. This might help explain why norovirus outbreaks that occur on cruise ships may spare some people on board; they might not possess antigens conducive to norovirus binding despite exposure.

The idea that antigens expressed by host cells influence disease susceptibility has also been associated with blood type. This is likely because blood antigens such as A, B, and Rh, which can be expressed by many of the body's cells, are known to act as receptors for infectious agents. In other words, antigens found on erythrocytes are also found on cells comprising the lungs or on the outer (apical) surface of cells lining the intestines (Cooling, 2015). Thus, a person's blood type may be associated with certain disease susceptibility even if that disease does not directly impact erythrocytes. For example, according to Ewald and Sumner (2017) it is possible that people with blood type AB may have cell-surface antigens that make them more susceptible to contracting smallpox, *E. coli*, and salmonella, while people with blood type B might be more susceptible to contracting gonorrhea, tuberculosis, and *S. pneumoniae*. Additionally, people who are Rh+ have been found to potentially be more susceptible to viral infections such as that caused by Chikungunya virus which is transmitted by mosquitos (Kumar *et al.*, 2010). It is also possible that having a certain blood type could provide protection or a natural resistance to infectious diseases if antibodies such as those made against antigens A or B that are already in circulation also work against invading pathogens (Skripal, 1996).

In a preprint of a study that was released by Zhao *et al.* (2020), the authors described a potential relationship between blood type and risk of being hospitalized with COVID-19. The authors of the study were quick to point out that their research has not been peer reviewed. Peer-reviewed journal articles are those which are first sent to the journal editor, who then assigns expert reviewers in that particular field. These reviewers point out any flaws in the design of the study, its methods or results, and the reviewers often also correct imprecise language or improper wording of conclusions or

hypotheses. Thus a preprint is an article that has not yet been examined by other experts in the field and therefore may contain issues normally found by reviewers as described. It is very rare that the peer-review process finds no errors or issues in a submitted manuscript.

In addition to being a preprint, the Zhao *et al.* (2020) article only takes into account data collected from people in certain regions of China who were known to be infected. It does, however, raise an interesting question; is there a relationship between blood types and risk of contracting COVID-19?

Activity 6 – Hypothesize and Design a Study

3. What is the difference between being infected with a virus such as SARS-CoV-2 and contracting a disease such as COVID-19?

Given the information presented thus far in this case study about antigens, antibodies, and potential relationships to disease susceptibility, generate a basic list of factors that could influence a person’s susceptibility to contracting a disease after being infected with a virus:

<i>Factors Related to Antigens and Antibodies</i>	<i>Potential Relationship to Disease Susceptibility</i>

Next, using your list above, formulate a testable hypothesis and a null hypothesis that could be used to investigate one of the factors and its relationship to disease susceptibility. Remember, a solid, testable hypothesis is one that cannot be answered with a simple yes or no; thus, the question you ask needs to be carefully crafted. It is often helpful if hypotheses have directional predictions (e.g., variable x will increase/decrease variable y).

<i>Testable Hypothesis</i>	<i>Null Hypothesis</i>

One way to help make sure your testable hypothesis is logical is to think about ways in which you could go about investigating your question. Be realistic and consider issues related to time, cost, and utility of your findings. For example, saying you're going to test the entire human population and have results in one month is not feasible. After completing this activity, you might need to redo or adjust your hypotheses and that is fine. It's all part of the scientific method.

<i>Study Components or Design</i>	<i>Participants or Samples Required</i>

Activity 7 – Analysis of Preprint by Zhao et al. (2020)

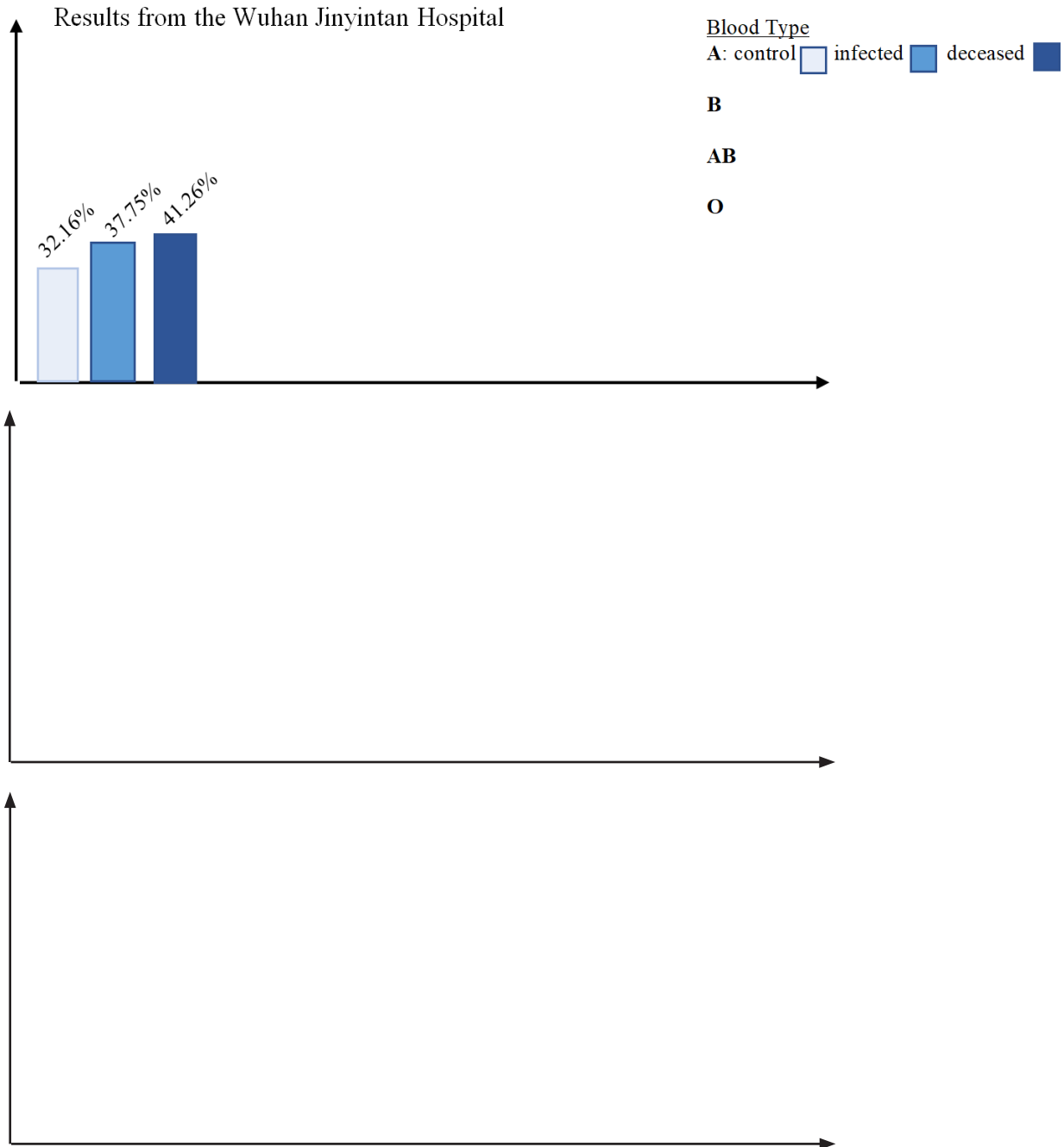
In this next section of the case study, we will take a look at specific information extracted from the original preprint released by Zhao *et al.* (2020), and which was the version picked up by media outlets and widely disseminated. We will dissect their results by graphing and analyzing their numbers, examine limitations, and think about additional questions that could be asked given the data. If you prefer to read the preprint in its original form it can be found here:

Zhao, J., Y. Yang, H. Huang, D. Li, D. Gu, *et al.* 2020. Relationship between the ABO blood group and the COVID-19 susceptibility. *MedRxiv*. <<https://doi.org/10.1101/2020.03.11.20031096>>.

- *Objective:* To investigate the relationship between the ABO blood group and the COVID-19 susceptibility.
 - *Design:* The study was conducted by comparing the blood group distribution in 2,173 patients with COVID-19 confirmed by SARS-CoV-2 test from three hospitals in Wuhan and Shenzhen, China with that in normal people from the corresponding regions. Data were analyzed using one-way ANOVA and two-tailed χ^2 and a meta-analysis was performed by random effects models.
 - *Setting:* Three tertiary hospitals in Wuhan and Shenzhen, China.
 - *Participants:* A total of 1,775 patients with COVID-19, including 206 dead cases, from Wuhan Jinyintan Hospital, Wuhan, China were recruited. Another 113 and 285 patients with COVID-19 were respectively recruited from Renmin Hospital of Wuhan University, Wuhan and Shenzhen Third People's Hospital, Shenzhen, China.
 - *Main Outcome Measures:* Detection of ABO blood groups, infection occurrence of SARS-CoV-2, and patient death.
 - *Results:* See Table 1 in the original article.
 - *Conclusion:* People with blood group A have a significantly higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O has a significantly lower risk for the infection compared with non-O blood groups.
4. Many people who have COVID-19 are asymptomatic meaning they do not show any signs of the disease and thus are unlikely to seek out medical help. Do you think this study by Zhao *et al.* (2020) represents or captures data from asymptomatic people? In other words, did the authors actually test or examine what they claim to have examined given their stated objective? Why or why not?
 5. In regards to the question above, how could the preprint by Zhao *et al.* (2020) be improved to make it more accurate? For example, would you alter the design to include more people or perhaps people that fall into additional categories? Could you alter the objective to make it more specific? Explain your answer.

- Provide an example of a testable hypothesis that more accurately captures this study’s design, participants, and main outcome measures.

Data presented in tables like Table 1 above can be difficult to interpret sometimes because there is so much information. Often the data become easier to understand if they are converted to a more visual form, and this is particularly true when relationships between different groups are more important than the actual numbers. Construct a well-designed bar graph with the information provided in Table 1 for each of the three hospitals’ data showing blood group (blood type) percentages for controls and COVID-19 patients. On your graphs make sure you include: Labels for the X and Y axes, metrics or units where appropriate, a title and figure legend. An example has been started below for the Wuhan Jinyintan Hospital but you will need to finish it.



7. Look at your charts representing data from all three hospitals. Do you think the conclusions by Zhao *et al.* hold true for all populations sampled in this study in that people with blood type A have a significantly higher risk for contracting COVID-19? What variations or anomalies exist?

8. Given the information about possible antigens expressed on the surface of erythrocytes as well as other body cells, what antigen discussed in the pre-class component of this case study was not reported as part of this study by Zhao *et al.* (2020)?

9. In regards to factors known to increase a person's risk for contracting COVID-19, what else should Zhao *et al.* (2020) have considered before drawing conclusions that blood type alone increases susceptibility to the disease?

10. Compared to data from the Wuhan Jinyintan Hospital, some data are missing from the Remnin Hospital of Wuhan University and the Shenzhen Third People's Hospital. What are these missing data and how does this impact the accuracy of the Main Outcomes Measured in the study by Zhao *et al.* (2020)?

11. Given the data reported by Zhao *et al.* (2020) in Table 1, what additional questions could be asked or alternative hypotheses explored?

12. Do you think Jim is justified in thinking he has protection against contracting COVID-19 given the data by Zhao *et al.* (2020)? Is there danger in presenting "raw" data like that presented in Table 1 to the public? Why or why not?

Is There an Ending to This Story?

Several days after Tina and Jim last chatted, Jim dropped by to visit Tina on her family's farm and offered to help with her chores, thinking he was immune from social distancing requirements given his blood type.

"Hey Jim!" Tina greeted him while trying to keep her distance. "I've been reading up on the article from *Fox News* that you texted me... Something just didn't seem right. I don't think one study that isn't even reviewed by other scientists is very trustworthy yet. In fact, I found an article and meant to text it to you earlier."

- Anon. 2020. Coronavirus: are people with blood group A really at higher risk of catching COVID-19? *The Conversation*, March 23, 2020. <<https://theconversation.com/coronavirus-are-people-with-blood-group-a-really-at-higher-risk-of-catching-covid-19-134181>>.

Jim began reading the article immediately on his phone and looked startled. "Well, good thing I'm taking other precautions like being outside and helping you with these farm animals. I mean, there's nothing risky about that, right?"

"Uh, yeah, about that..." Tina hesitated. "Turns out living in a rural area might not be the safeguard against exposure to SARS-CoV-2 that I had thought. Check this out too."

- Stevens, C. 2020. The origins of SARS-CoV-2: part 1. Emergence of a new species. [Webpage]. *Benhur Lee Lab*. <<https://leelabvirus.host/covid19/origins-part1>>

After giving Jim some time to read the article she'd sent him, Tina said, "Jim, I like hanging out with you and I'm sorry you've lost your job but we need to flatten the curve."

"What does that even mean?" asked Jim.

"It means that humans need to avoid contact with other humans for a while. We need to be very careful about going out in public, and when we do things like going to the grocery store we need to be sure and not touch our faces until we can thoroughly wash our hands afterwards, because the virus can't very well get through our skin but it enters mostly through openings like the mouth, nose and eyes. We also need to be more careful about washing fruit and avoiding setting things that have been exposed to the public on the same counters where we prepare our food, and things like that. We need to dramatically slow down the rate of new infections in order to avoid overwhelming our medical capabilities, and to give us time to develop countermeasures like vaccines."

"I've heard about that," said Jim. "What if we gave susceptible people blood plasma from people who have been infected and either recovered or didn't have COVID-19 symptoms? Would that work?"

"That's a great question, Jim! From what I've been reading that could provide passive immunity for some people because antibodies are present in the plasma, which is really the same as blood serum except it still contains the clotting factors. It's passive immunity, though, because it only protects for as long as those antibodies are present. What we really need is active immunity, which is when the person's own immune system mounts a response to the virus. I think that involves using a part of the virus that is modified to prevent infection but recognizable by the immune system so that memory T and B cells are formed, and can respond quickly if confronted with the actual virus."

"Wow, Tina, you've really been doing a lot of reading. I'm going to practice social distancing now and go read up on all of this myself. Knowledge is power! See ya later!"

