JOHNS HOPKINS UNIVERSITY

CENTER FOR BRIDGING INFECTIOUS DISEASE, GENOMICS, AND SOCIETY (BRIDGES)

Case Study 1 – COVID-19/SARS-CoV-2

[primarily infectious (communicable) → partially genetic]

Introduction

The novel disease COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in nearly 530 million confirmed cases and more than 6 million deaths worldwide.[1] As of May 2022, more than 80 million Americans have tested positive for SARS-CoV-2 and over 1 million have died from COVID-19, with the United States (US) reporting the highest number of both cases and deaths.[1] Owing to its severity and rapid spread, the Director-General of the World Health Organization (WHO) declared SARS-CoV-2 to be a Public Health Emergency of International Concern on January 30, 2020.[2] The following day, the Secretary of the US Department of Health and Human Services declared the COVID-19 outbreak a federal public health emergency (PHE),[3] and shortly thereafter, every US state followed suit. These PHE declarations triggered additional powers and resources to aid in emergency preparedness and response, including the authority to reallocate funds to the emergency; use of out-of-state volunteer health professionals; activation of waiver of liability protection for first responders; and suspension and waiver of certain provisions of state and federal health programs, insurance rules, and privacy protections.

COVID-19 Exposure, Transmission, & Severity

SARS-CoV-2 is transmitted through the air and is associated with a wide variability in severity of symptoms, from asymptomatic presentations to respiratory failure, multi-organ system dysfunction, and death. About 10% of patients recover from the acute illness but continue to experience ongoing symptoms and disabilities, which has been colloquially named "Long COVID." Recent studies have also suggested that many children may develop long COVID, but more research is needed regarding the effect of long COVID on children.[4] In addition, new variants of SARS-CoV-2 have emerged throughout the past 2 years, resulting in somewhat different courses of disease and level of severity in many patients, though study of new variants is ongoing. To date, the Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages) variants have been classified as "Variants of Concern (VOC)" by both the CDC and WHO.[5] There remain many questions about the impact of these new variants, and of course, additional variants will emerge over time.

SARS-CoV-2 does affect individuals and groups differently through mechanisms that are not yet fully understood. Nearly three-quarters of the deaths due to COVID-19 have been among individuals who are 65 years and older.[6] Men appear more likely to suffer a serious disease course than women, and children are more likely to have a mild course of COVID-19 illness and

seem less likely to transmit disease. These differences may be explained in part by scientific factors. However, groups who have been historically marginalized in the US have been disproportionately affected in many ways by the pandemic due to structural racism and high levels of health disparities in the country. Black Americans are 2.5 times more at risk of hospitalization due to COVID-19 than White, Non-Hispanic Americans while Native and Hispanic/Latinx Americans are at 3.2 time and 2.4 times at risk, respectively.[7] Black and Hispanic/Latinx Americans account for 13.7% and 16.7% (respectively) of COVID-19 deaths in the US despite constituting only 12.4% and 18.7% of the entire US population.[8] There are several structural factors responsible for why historically marginalized groups are disproportionately impacted by the pandemic and why they face increased exposure to SARS-CoV-2.

COVID-19 Treatment

The preventive measures, increasingly effective therapies, and vaccines have all altered the course of the pandemic. Prior to vaccination, the preventive measures mainly consisted of physical distancing, masking, handwashing, contact tracing, and isolation. Care and treatment of COVID-19 patients have evolved substantially over the course of the pandemic, with clinical care improving with experience, and evidence for interventions increasingly available. In fact, many early interventions thought to be useful (e.g., hydroxychloroquine) have largely been abandoned. In October 2020, the US Food and Drug Administration (FDA) re-issued its emergency use authorization (EUA) for the antiviral drug Remdesivir, for the treatment of hospitalized patients with COVID-19.[9,10] In November 2020, an EUA was issued for the monoclonal antibody cocktail comprised of casirivimab and imdevimab, for the treatment of mild to moderate COVID-19.

COVID-19 Vaccination

Currently, there are 3 approved COVID-19 vaccines in the US: Pfizer-BioNTech, Moderna, and Johnson & Johnson's Janssen (J&J).[11] The Pfizer and Moderna vaccines use a novel approach to vaccination. Rather than delivering to our cells pieces of an inactivated virus so that our bodies can mount an immune response, these vaccines deliver the instructions [in the form of messenger RNA (mRNA)] needed to enable our cells to build SARS-CoV-2 spike proteins, against which our bodies then mount an immune response, protecting us from future infection. Both vaccines require ultra-cold storage, involve a two-dose regimen, and are ~95% effective against COVID-19.[12,13] The third vaccine developed by Johnson & Johnson is a one-dose vaccine that can be stored at standard refrigerator temperature. In the fall of 2021, booster shots of the COVID-19 vaccines were approved for all adults who have been fully vaccinated for 5 to 6 months.

As of May 2022, more than 583 million doses of vaccine have been administered throughout the country, 220.8 million Americans have been fully vaccinated, and 102.6 million have received a booster dose.[14] Globally, over 11.4 billion vaccines doses have been administered with about 67.4% of the world population (i.e., more than 5.17 billion people) partially vaccinated (i.e., receiving at least one dose of the COVID-19 vaccine).[1,15] Countries that report high rates of vaccination have seen significant declines in the rate of hospitalizations and mortality from COVID-19.[16] However, the new SARS-CoV-2 variants that continue to be identified behave somewhat differently than the original strain, for example, having increased transmissibility.[17] It is as yet unclear if currently authorized vaccines will protect against all of these new variants and

reduce susceptibility. However, there is evidence that receiving all three doses of the mRNA COVID-19 vaccines were effective in preventing moderately severe and severe COVID-19 during the Delta and Omicron surges.[18]

There have also been a series of mandatory vaccine policies across the US and around the globe. Since the arrival of the Delta variant in July 2021, major private employers announced the requirement of COVID-19 vaccination for all employees and many US schools and universities also issued mandatory vaccination policy.[19,20] In September 2021, the Biden administration issued executive orders directing all federal agencies to mandate the COVID-19 vaccination.[21] The Occupational Safety and Health Administration (OSHA) also released an Emergency Temporary Standard (ETS) requiring vaccination, masking, and testing policies by large employers to protect their employees.[22,23] This mandate was predicted to lead to the vaccination of an additional 84 million American workers.[24] However, there has been tremendous pushback against these vaccine mandate policies. The Supreme Court blocked the OSHA ETS in January 2022 and this court ruling is expected to have significant negative impact on the country's COVID-19 rates.[24,25] Even prior to COVID-19, a substantial proportion of the American public has been vaccine hesitant. While a range of reasons exist for vaccine hesitancy in the US, a recent study found that dissent and distrust were significant predictors of an individual rejecting COVID-19 vaccination.[26] The authors also noted that the uniquely politicized nature of the COVID-19 pandemic in the US has contributed to the widespread vaccine hesitancy.[26]

COVID-19 Host Genomics

Since the beginning of the pandemic, ongoing research has been directed at host genomic factors associated with COVID-19 severity and outcomes, with the aim of guiding the development of therapeutics. There have been several genome-wide association studies (GWAS) published that are led by both publicly funded research groups and commercial entities, such as 23&Me.[27,28]

Recent GWAS studies have identified and replicated the finding of several genetic variants in a gene cluster on chromosome 3 that are associated with COVID-19 hospitalization and/or severity.[29-31] There is also some evidence that COVID-19 severity is associated with differences in the ABO gene on chromosome 9, but the associations has been much weaker than the chromosome 3 findings.[29,30] Other genes that have been implicated in COVID-19 critical illness (different from mild or moderate illness even among hospitalized patients) include interferon receptor (IFNAR2), antiviral restriction enzyme activators (OAS1, OAS2, OAS3), tyrosine kinase 2 (TYK2), dipeptidyl peptidase 9 (DPP9) and chemotactic receptor (CCR2).[30,32,33] Of note, variants in the IFNAR2 gene have previously been linked to severity in many other viral diseases.[34] Another recent study also found that in hospitalized patients, expression of prenylated OAS1 was associated with protection from severe COVID-19 and the authors also noted a geographical variation in the frequency of alleles encoding prenylated OAS1.[33] Currently, most of these studies do not account for comorbidities nor, critically, exposure to SARS-CoV-2, and all studies are primarily focused on individuals of European descent. Vaccinomics research suggests that host genetic polymorphisms could both lead to variability in the immune response among individuals receiving the same vaccine[35] and may be associated with serious adverse events related to COVID-19 vaccines.[36] In addition to host genomics, the microbiome may also play a role in COVID-19 severity. A study by Hong Kong researchers found that gut microbiome composition was significantly different among COVID-19 patients and non-COVID-19

individuals, suggesting that the gut microbiota influences COVID-19 severity by modulating host immune responses.[37]

Global Context

The pandemic of SARS-CoV-2 has prompted comparison with many other global disease outbreaks, most notably the influenza pandemic of 1918-19. On the one hand, historical analogies were drawn with the potential role of non-pharmaceutical interventions to reduce transmission,[38,39] the anticipated backlash to mitigation measures,[40] and the implications of extremely rapid global spread.[41] On the other hand, such comparisons tended to gloss over epidemiological differences between the two viruses,[42] and it was notable that historical analyses of influenza had been relatively unconcerned with racial, ethnic and class inequalities in exposure and access to care.[43]

Of course, the 1918-19 influenza pandemic occurred before the responsible virus was known (or even observed by the human eye) and before dense global networks of scientific knowledge exchange were commonplace. In contrast, the early months of the COVID-19 pandemic witnessed multiple global host-genomic research projects, designed to uncover the host genetic variants associated with human responses to SARS-CoV-2, particularly with regard to disease severity. Several global efforts to identify host genomic factors have emerged, including the COVID-19 Host Genetics Initiative and the COVID Human Genetic Effort.[44,45] There have also been efforts to enable an international system of data sharing through the WHO's International Health Regulations (IHR), but the IHR have not been updated since 2005 and do not fully address the sharing of host genomic data during an emergency.[46-48] As such, the United Nations has been working towards the creation of a new international pandemic treaty that would aid with pandemic preparedness and response.[49]

Structural Racism & COVID-19 in the US

It is important, however, to keep attention on the historical, structural, and political choices that have led to the disproportionate impact of the pandemic on historically marginalized populations. Black and brown people in the US are more likely to live in crowded housing situations, in neighborhoods with poor infrastructure, and in multigenerational households. They are more likely to hold low-paying jobs seen as essential during the pandemic (e.g., package and food delivery). As such, black and brown people in the US are more likely to be exposed to SARS-CoV-2 and to subsequently expose others in their families and communities, resulting in the disproportionate impact of COVID-19 mortality and hospitalization among these groups. Further, these circumstances (i.e., social determinants of health) and the structural racism that drove them can have biologic effects of their own, that can increase vulnerability to disease.[50]

Similarly, decisions about immigration, border crossing, and travel in general related to infectious disease have a long history in policy and law, as do considerations about genetics, and "genetic fitness." As we investigate, discuss, and respond to host genomic research regarding COVID-19 disease, it is important not to disaggregate the genetic data from social determinants of health and the historical context that helps explain current conditions.[51] Historically, such care has not always been taken, leading to racialized characterizations of behavior and health.[51] For example, and relevant to a respiratory illness like COVID-19, there is a well-documented history of racialized understandings of differences in lung function.[52] Racialized conceptions of disease

and disease causation have then been used to justify hegemonic racial orders including slavery and segregation.[53-55]

One notable feature of the public discourse surrounding COVID-19 is a sustained insistence that racial inequities in morbidity and mortality are not due to innate differences between groups, but to underlying social inequalities. Mass protests for racial justice in the spring of 2020 led to discussions in the public health community of racism and COVID-19 as intersecting public health crises.[56-58] At the same time, approaches to COVID-19 increased the potential to reinforce racial hierarchies, whether in President Trump's insistence on naming it the "Chinese virus" and the upswell in hate crimes against Asian-Americans, or in efforts to find biological explanations for racial differences in susceptibility. Thus, it remains to be seen whether the response to COVID-19 will ultimately reiterate or challenge the history of infectious disease responses that reinforce systemic racism.[53,59]

All that said, as noted above, despite the disproportionate impact of the pandemic on black and brown people, most of the research on host genomics has been focused on individuals of European descent.

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CENTER FOR BRIDGING INFECTIOUS DISEASE, GENOMICS, AND SOCIETY (BRIDGES)

Case Study 2 – Cancers/HPV

[primarily non-communicable or genetic → infectious]

Introduction

In recent decades, we have come to understand the important role of viruses and microbes in the development of a number of cancers – some of which, like colorectal cancer, have a strong genetic contribution. We have decided to focus this case on our emerging understanding of the role of human papillomavirus (HPV) in the development of cancers. HPV is a common DNA virus that infects up to 14 million Americans every year.[1] HPV is a sexually transmitted infection (STI) and an estimated 85% of all sexually-active persons are infected with HPV at some point in their lifetime.[1] While HPV infections and most HPV-associated conditions are not nationally notifiable for public health purposes, many cancers, including most of those attributable to HPV, are reportable to central cancer registries.[1] The prevalence of HPV is primarily understood through cancer registries – the National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology & End Results (SEER) – and is used to assess vaccine impact[2] (more on this below).

HPV Persistence

In most cases, HPV-infected individuals are asymptomatic and clear the virus spontaneously within 1-2 years of exposure.[3] In addition, while there are more than 100 types of HPV, studies have identified only 13 HPV types that are oncogenic.[4] Although millions of individuals are infected with HPV each year, only 10-20% of infections persist latently and only 1% of women with cervical HPV develop cervical cancer.[5] Persistent infection with an oncogenic strain of HPV is associated with increased risk for – but not certainty of developing – cervical cancer.[6, 7]

An additional factor associated with HPV persistence or clearance appears to be the microbiome. While there is little literature on the role of the microbiome in HPV-associated cancers of the head and neck[8], studies of vaginal microbiome composition in individuals with HPV infection and cervical cancer suggest that the microbiome may mediate the interaction between the virus and the host.[8-13] For example, the presence of certain species of *Lactobacillus* have been shown to be associated with HPV clearance[9-11, 13], and there is evidence that *Gardnerella* is associated with progression to precancer.[11] While not definitive, work to date suggests that the microbiome may be important in the development of cancer secondary to HPV infection, and that it may be both a marker of risk and a potential therapeutic target.

HPV-Associated Cancers

Persistent HPV infection causes more cancers than any other viral infection and is the primary causal factor for 91% of all cervical cancers.[3, 14, 15] An average of 45,300 new cases of HPV-associated cancers are detected each year in the United States. The cancer sites include cervix, vagina, vulva, penis, anus, and oropharynx. Of the new cases, 56% (25,405 cases) are detected in females while 44% (19,925 cases) are detected in males.[16] Although research is ongoing to better understand the extent of HPV's role in causing non-cervical cancers, 90% of anal and cervical cancer, 70% of vaginal and vulvar cancers, 60% of penile cancers, and around 60-70% of oropharyngeal cancers are linked to HPV.[16] In the US, 4000 women die each year from cervical cancer.[1] Each year, 14,000 people are diagnosed with head and neck cancers caused by HPV, more than 80% of which afflict men.[16] Historically, head and neck cancers were associated with smoking and alcohol consumption, and were largely HPV-negative.[17] However, between 1988 and 2004, the prevalence of HPV- negative oropharyngeal cancers in the US decreased by 50% due to declines in smoking rates, while the prevalence of HPV-positive cancers increased by 225%.[17] This increase included incidence in young children, leading researchers to question the designation of HPV as solely a STI.[18]

Global Impact of HPV

Globally, 4.5% of cancers diagnosed each year are linked to HPV, representing 8.6% (570,000) of cancer diagnoses in women and only 0.8% (60,000) in men.[19] In addition to cervical cancer, 8,500 HPV-attributable vulvar cancers, 12,000 vaginal cancers, 35,000 anal cancers (50% in men), 13,000 penile cancers, and 38,000 head and neck cancers are diagnosed annually worldwide.[19] While 70% of global cervical cancer cases are diagnosed in less developed countries, 73% of the head and neck cancers are in more developed countries.[19]

Globally, cervical cancer is the 4th most common cancer found in women with around 570,000 new cases and 311,000 deaths due to cervical cancer in 2018.[20] Around 90% of these deaths occurred in low- and middle-income countries (LMICs) due to limited access to vaccines (more on this below), cervical cancer screening, and other preventive measures.[19] Currently, all preventive measures are targeted primarily towards girls and women worldwide with the WHO's 90-70-90 targets: 90% of girls fully vaccinated against HPV by age 15, 70% of women screened by 35 and 45 years of age, and 90% of women with cervical disease receive treatment.[19]

HPV Vaccination

Fortunately, HPV infections and deaths due to cervical cancer have been dramatically reduced in recent years due to the development of HPV prophylactic vaccines and cervical cancer screening programs and early detection.[1] The HPV vaccine provides protection against most common types of HPV, and in the US is approved for the prevention of HPV-associated anogenital, oropharyngeal, and other head and neck cancers.[21] The CDC has recommended HPV vaccination for everyone aged 11 through 26 years, and for some adults between 27 and 45 years of age.[22] In the US in 2018, almost 60% of women aged 18-26 received one or more doses of the HPV vaccine while less than 30% of men aged 18-26 received the vaccine.[23]

However, as of 2017, 95% of the 100 million girls who received at least one dose of the HPV vaccine were in high-income countries (HICs).[24] As of 2020, HPV vaccine has been introduced into the national immunization schedule in 85% of HICs, but less than 30% of LMICs have done the same, and there is a similar breakdown for cervical cancer screening programs.[24] "High

vaccine prices coupled with recent supply challenges have significantly constrained the ability of many countries to introduce the HPV vaccine into national immunization programmes and to ensure sustainability of current programmes."[24] It has been estimated that the elimination of cervical cancer would cost US $10.5 billion; 59% of those dollars would go towards vaccination efforts while the rest would fund cervical cancer screening and management.[24]

Currently, there are no treatments for HPV infection, but clinical studies are testing potential therapeutic vaccines.[25] Therapeutic vaccines are designed to stimulate the immune system to treat—rather than prevent—certain kinds of diseases, such as cancer, infectious disease, and autoimmune disorders. For example, such vaccines are being designed to fight HPV infection through immunotherapy, by bolstering HPV T-cell adaptive immunity.[25]

HPV Host Genomics

Host genomics (meaning genetic variation in the genome of the infected human) may play a role in determining who is at higher risk of developing cancer due to persistent HPV infection. Current research is focused on identifying host genetic susceptibilities that increase risk of HPV persistence and progression of cervical lesions to carcinoma.[26] Data suggest that both genetic and environmental/social determinants can significantly increase the likelihood of developing persistent infection, though host genetic factors appear to be the major determinant.[25, 26] Several studies have shown that the heritability of cervical cancer, as measured across different studies and with different methods, can range from 22% to 64%. This means that 22-64% of the variation that we see in persistent HPV infection and subsequent development of cervical cancer can be attributed to differences in the human genome. Furthermore, certain HLA alleles are associated with both persistent HPV-infection and development of cervical cancer.[5, 6] A genome-wide association study (GWAS) found strong associations between HLA Class II haplotypes and both increased and reduced risk of HPV- associated cervical cancers.[5] A study by Leo *et al*. identified three haplotypes that increased the risk for cervical neoplasia.[5, 27] GWAS have also identified HLA Class II alleles with protective effects against HPV- positive head and neck cancers versus HPV-negative cancers, raising further questions about the role of host genomic factors vis-à-vis HPV-positive cancers.[28]

Historical Context

From the nineteenth century onwards, sexual intercourse, childbirth, the susceptibility of female reproductive organs, and hereditary factors were all considered influences in the development of gynecological cancer.[29] As early as the 1840s, cervical cancer was associated with women's sexual activity, when one physician's study of deaths between 1760–1839 noted "a high frequency of cervical cancer in married women, widows and prostitutes, but their rare occurrence in virgins and nuns."[30, 31] Untreated cervical tears were thought to become inflamed and infected, leading to cancer.[29]

The end of the nineteenth century notion that cancer might be infectious was short-lived, when experiments on rats and mice could not demonstrate that inoculation and transplantation of cancer between and within species was routinely possible. In the early twentieth century, researchers took an interest in the different rates of cancers in different populations, and some argued that different races had different hereditary susceptibilities. For example, scholars debated whether low rates of cervical cancer in Jewish populations were due to cultural factors

or "racial immunity."[32] This discussion was revived around the time of the Human Genome Project, with one 2003 paper concluding "it seems that there may indeed be something in race."[33]

Initially, the HPV vaccine was approved only for use in girls and women, with the CDC's Advisory Committee on Immunization Practices (ACIP) recommending the shot for girls at 11 or 12 years of age, as vaccination is most effective prior to the start of sexual activity; the vaccine was not initially approved for use in boys.[34] Even before FDA approval, debates had begun about mandatory vaccination and the moral implications of vaccinating young children against a sexually transmitted disease, with some expressing concern that vaccination would undermine abstinence-based sexual education.[35] Controversy also surrounded the decision to include (or not) boys and men in vaccine approval and mandates – FDA approval was not extended to include use of the HPV vaccine in boys and men until 2009.[35] Boys and men can, of course, carry and transmit HPV to sexual partners; HPV can also cause genital warts and certain cancers in men.

The controversy surrounding the vaccine has frustrated public health efforts to implement state-level mandates, leading to relatively low HPV vaccination rates.[36]

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