"For more than 20 years, researchers have been talking about pregnancy-associated death and homicide of women," says Phyllis Sharps, a nurse-scientist at the Johns Hopkins School of Nursing in Baltimore, Maryland. The consensus, she says, is that this is happening in large part because of violence by intimate partners.

'An age and race story'

To arrive at a national snapshot, reproductive epidemiologist Maeve Wallace at Tulane University in New Orleans, Louisiana, and her co-authors analysed data for deaths in all 50 US states from 2018 and 2019, using information in the National Center for Health Statistics database, which is hosted by the US Centers for Disease Control and Prevention (CDC).

In 2003, the United States began requiring that death certificates indicate whether a person had died while pregnant, or within either 42 days or one year of the end of a pregnancy. By 2010, about 37 states included such an option on their certificates; by 2018, all 50 states required this information. This year, Wallace and her co-workers analysed the resulting records. According to their count, across 2018 and 2019, a total of 273 women died by homicide either while pregnant or within a year of the end of their pregnancy. (*Nature* recognizes that transgender men and non-binary people can become pregnant. 'Women' is used in this story to reflect language from the study, which is based on death certificate identification.)

When tracking deaths among pregnant women in the United States, the CDC doesn't classify homicide, accidents or suicides as causes of 'maternal mortality'. Wallace and others say homicides should be counted, because there is indeed a connection between homicide and pregnancy.

The overall rate of maternal mortality in the United States is on the rise. And it is particularly high for a wealthy country. Contributing factors include inadequate access to health care, and sub-par care given to Black women because of racism in clinical practice.

On the basis of years of study, specialists in intimate-partner violence expect women who are already in abusive relationships to be at increased risk of homicide if they become pregnant. Wallace and her co-authors say that about two-thirds of the homicides recorded in their data occurred in the person's home, suggesting that the woman was killed by her partner. It's not a perfect indicator, Wallace says, "but it's all we've got in these data".

The team found that Black women in the United States who are pregnant or were recently pregnant have a nearly threefold higher risk of dying by homicide than have those who are not pregnant — the highest increase reported among any racial or ethnic group. (The team reported rates only among Black, Hispanic and white women, because the sample sizes for other groups — such as Asian American women or Native American women — were too small to publish.)

Black women are similarly at heightened risk of death from obstetric causes. Overall, Black women who are pregnant or were recently pregnant die of pregnancy-related causes 2.5 times as often as non-Hispanic white women, according to the CDC.

Age is also a factor in pregnancy-related homicide, the team found: young women between the ages of 10 and 24 are at higher risk of homicide while pregnant than are those who are older, according to the study. "It's an age and race story," Wallace says.

What Wallace and co-workers "have done with the data available gives more confidence to the scope of the problem and the work that came before", says Aaron Kivisto, a clinical psychologist at the University of Indianapolis in Indiana who studies domestic violence and suicide prevention.

Sharps says part of the reason that Black women are at higher risk could be that experiences of racism have led them to be more distrustful of law-enforcement agencies and less likely to bring forward complaints about domestic violence.

Studies such as Wallace's could be used by policymakers or hospital administrators to improve monitoring of pregnant people and those who have recently given birth, Singh says. It could also build public understanding of harms and risks during pregnancy. "There's an idea in our society that pregnancy is a happy time," Sharps says. "But for a lot of women, that's just not true, and a lot of women are just not safe in their homes."

DO CHILDHOOD COLDS HELP THE BODY RESPOND TO COVID?

Immune imprinting helps some to people fight off the flu, but its impact on coronaviruses is still unclear.

By Rachel Brazil

Some people are better at fighting off seasonal flu when the strain of influenza virus is similar to the first one they encountered in childhood — a phenomenon evocatively dubbed original antigenic sin, or OAS. Now, there is increasing evidence that people's immune responses to COVID-19 could be shaped in a similar way by previous infections with common-cold coronaviruses.

The effect could have implications for the design of future COVID-19 vaccines. However, to what extent it affects people with COVID-19 — and whether it provides enhanced protection or, in fact, hampers the immune response — is still unclear. "The debate is quite polarized at the moment," says Craig Thompson, a virologist at the University of Oxford, UK.

OAS — also called immune imprinting — was first characterized in 1960 by US epidemiologist Thomas Francis Jr, who noticed that the immune system seemed to be permanently programmed to produce antibodies against the first strain of a flu virus that it encountered[1]. Immune cells reactivate when the body is infected by a flu virus that shares regions, or 'epitopes', with that first strain.

For SARS-CoV-2, there is growing evidence that exposure to other coronaviruses — including those that cause colds and other respiratory illnesses — plays a part in people's immune responses. "Much like flu, most of us are infected with these common coronaviruses by the age of five or six," says Scott Hensley, a microbiologist at the University of Pennsylvania in Philadelphia. His group discovered that blood serum samples taken from people before the pandemic contained antibodies against a common-cold coronavirus called OC43 that could bind to the SARS-CoV-2 spike protein[2].

Using samples taken before and after infection, Hensley and his colleagues were able to show that catching SARS-CoV-2 boosted the production of OC43-binding antibodies. Their study, published in February, found that these antibodies bind to the S2 subunit of the SARS-CoV-2 spike protein — which has a similar structure to that in OC43. But the OC43 antibodies did not bind to the S1 region of the SARS-CoV-2 spike and were unable to stop the virus entering cells.

Effects of imprinting

In some cases, imprinting is known to have a positive effect on immunity. Hensley and his colleagues studied the effects of imprinting during the 2009 H1N1 flu pandemic and found that exposure to some historical flu strains provided protection against H1N1 infection[3].

GETTY

Exposure to other coronaviruses affects how the immune system responds to SARS-CoV-2.

"There were some epitopes in that virus that were conserved with past seasonal influenza strains," Hensley says. "The recall of antibody responses against those epitopes was actually beneficial."

But OAS also has potential downsides. Sometimes, antibodies produced as a result of imprinting are not a very good match to the virus causing an infection, but their production suppresses the activation of naive B cells that would otherwise produce more-protective antibodies. "You get a response that may be skewed towards conserved antigens versus the new antigens," says Adolfo García-Sastre, director of the Global Health and Emerging Pathogens Institute at the Icahn School of Medicine at Mount Sinai in New York City. This can diminish the immune system's ability to fight the new infection.

García-Sastre looked at the early immune responses of people hospitalized with COVID-19 in Spain, and observed increased levels of antibodies against both OC43 and another betacoronavirus, called HKU1, that share epitopes with SARS-CoV-2 (ref. 4). "We looked for a correlation between people mounting higher [levels of] antibodies against these conserved epitopes versus having less protective immunity against SARS-CoV-2, and there was a slight correlation," says García-Sastre.

Signs of OAS negatively affecting people with COVID-19 were also seen by Thompson and his colleagues, in a preprint posted earlier this year[5]. The analysis was based on samples taken in 2020 from people in the United Kingdom who had asymptomatic infections, and from people who were admitted to hospital with severe COVID-19, half of whom subsequently died. The researchers found that people who died produced fewer antibodies against the SARS-CoV-2 spike protein than did people who survived, but produced the same amount of antibodies to another protein found in the virus — the nucleocapsid protein.

Thompson says these results indicate that imprinted memories of the spike protein from a different coronavirus could be preventing a more effective immune response in those who did not survive. "This is a fingerprint of OAS," he says. But he adds that it is too early to conclude this definitively.

It is difficult to tell from such early results whether OAS is beneficial or detrimental to the immune response against SARS-CoV-2, and the results of preliminary studies are open to interpretation. Hensley warns that just measuring antibody levels does not provide a full picture of a complex immune response. He also thinks the presence of OC43 antibodies in people with COVID-19 could indicate that a recent OC43 infection is helping the immune system to fight the virus. In July, a study of samples from health-care workers showed that individuals with signs of recent OC43 exposure recovered from a SARS-CoV-2 infection faster[6] than did those without such signs. Other research has shown similar protective effects.

"Most of the evidence points to a positive overall contribution, not a negative one."

In a study published in December 2020, George Kassiotis, an immunologist at the Francis Crick Institute in London, also found that pre-existing OC43 antibodies showed reactivity to SARS-CoV-2 (ref. 7). At the time, he wasn't sure of the implications, but after reviewing studies published since, he says, "most of the evidence points to a positive overall contribution, not a negative one".

García-Sastre suggests that even if they are not able to stop SARS-CoV-2 entering cells, OC43 antibodies might trigger the immune system to kill infected cells.

Vaccine updates

A key question is whether these observations can help to inform future COVID-19 vaccination strategies. For now, vaccines based on the original version of the coronavirus — first reported in Wuhan, China, in late 2019 — protect against all known variants, says Kassiotis.

Imprinting sometimes reduces the effectiveness of flu vaccines, according to Sarah Cobey, an evolutionary biologist and flu researcher at the University of Chicago in Illinois. The flu vaccine is updated each year to protect against those strains that researchers think are the most likely to be prevalent. Some people's immune systems are still not seeing the update, says Cobey, and still target parts of the virus that are familiar to them. "It looks like they're not really mounting a response to the thing that we carefully updated the vaccine for." It is possible that future COVID-19 vaccines tailored to new variants could have similar problems.

Hensley does not think this is likely, however. In a study published as a preprint last month, he and his colleagues reported that people do not produce as many OC43 antibodies after receiving a messenger RNA vaccine as they do when infected with SARS-CoV-2 itself[8]. This could be because the mRNA vaccines establish such an efficient immune response that they can bypass any immune-imprinting effect. "Maybe in the context of mRNA vaccines there's not really going to be as much of a biasing towards conserved epitopes. That's the hope," says Hensley.

Thompson says that the problem could also be circumvented in updated COVID-19 vaccines by removing the shared epitopes: "You could easily just chop the S2 domain off … or make a vaccine just targeting the receptor binding domain of the most recent circulating strain," he says. "But this is really hypothetical."

"There likely is a very complicated interplay between seasonal coronavirus infection and disease outcome upon SARS-CoV-2 infection," says Hensley. "I don't think anything should be pitched as complete fact at this point."

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