Interviews

AMJ had the pleasure of interviewing Gail J Demler–Harrison and Lisa Armitige, two leading experts in infectious diseases. Demler–Harrison raises awareness of congenital cytomegalovirus infections and discusses the importance of fetal and neonatal antiviral therapy. Lisa Armitige speaks about challenges in adult and pediatric tuberculosis, highlighting the need for improved education and prevention strategies globally.

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Q1 First of all, what originally sparked your interest in the field of pediatric viral infections, and cytomegalovirus (CMV) in particular?

As an undergraduate student at the University of Texas in Austin, USA studying pre-med and microbiology, I gravitated towards the virology classes, so from early on I felt comfortable with viruses, in general. Their simplistic elegance fascinated me, and their ability to influence not just the machinery of a single cell, but an entire organism, body, human, was remarkable; and, taking experience from contemporary times and global pandemics, viruses can influence the machinery of an entire country or continent, and that is downright amazing to contemplate.

My specific interest in cytomegalovirus or CMV began when I was a first-year post-doctoral fellow in pediatric infectious diseases at Baylor College of Medicine and Texas Children's Hospital. My mentor was Martha Yow, who was a legendary trailblazer in the field of pediatric infectious diseases, clinical virology, and congenital infections, and the author of a very inspiring book 'Balancing Act: A Memoir of a Southern Woman Doctor'. Early in my fellowship, Yow and I were walking together in the halls of the medical school, and she put her arm around me and said: "I have a new project, a funded grant, on CMV, and I need a fellow to help me do to the work. Would you like to be that fellow?" I immediately said yes, but she immediately said: "Do not ever make such an important personal or professional decision that quickly. Take this grant project home, read it, and see if it is something you want to commit to. If you do, then we can discuss it further tomorrow." That was my first 'mentoring moment' from my mentor Yow, and how I entered the world of CMV. I chose CMV not because it was easy, but because it was hard.

> **CMV is the most common virus most people have never heard of**

In her book, Yow writes something like: "Why did I feel that the study of congenital CMV was so important? Few people had ever heard of it and most doctors didn't understand it, but it was the leading infectious cause of disabilities and deafness. This was a major public health dilemma, and preventive measures were urgently needed."

These words were true when I started my CMV journey. These words are still true today.

Q2 Your research primarily focuses on congenital CMV infections. How common is CMV infection in pregnant women, and are there any warning symptoms during pregnancy?

CMV is the most common virus most people have never heard of, including pregnant people. However, they should know about it. CMV is very common, most of us will be infected with this virus in our lifetime. The prevalence of CMV antibodies, indicating a prior infection with CMV, in individuals of childbearing age is between 45–75% in the USA, depending on a variety of demographics.

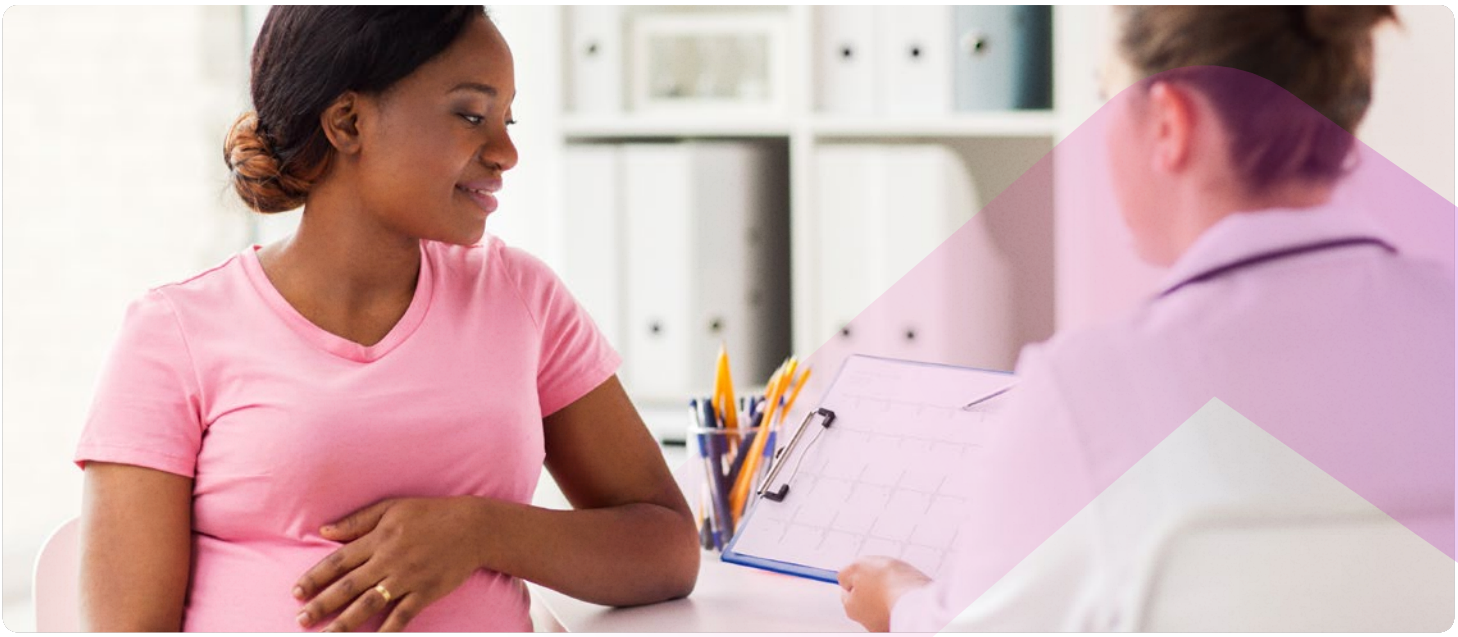
The annual seroconversion rate of CMV antibody-negative individuals who are pregnant is between 1–4%. So, between 1–4 % of pregnant people will contract CMV for the first time during their pregnancy, and about 40% of them will transmit CMV to their fetus after their primary infection. CMV can also cause recurrent infections, through reactivation or re-infection, in individuals who have already been infected with CMV, but the transmission rate to the fetus is much less, probably 1% or so.

Most CMV infections are asymptomatic, making them very difficult to detect and monitor. If CMV had a common rash to go with it, like chicken pox or rubella, it may be easier to follow and study. But it doesn't. Some pregnant people will experience CMV symptoms, such as fever, malaise, hepatitis, sore throat, or mononucleosis-like symptoms. Sometimes, the first indication a pregnant person has had CMV is that the fetal anatomy ultrasound scan may be abnormal, showing poor fetal growth, echogenic bowel, microcephaly, brain malformations, enlarged liver or spleen, fetal ascites, or other anomalies of the fetus.

CMV is not routinely screened or tested for in pregnancy in the USA, so many CMV infections in pregnancy go unnoticed and undiagnosed.

Q3 What are some of the long-term effects of CMV on the growth, development, vision, and hearing of fetuses and newborns?

Most congenital infections with CMV in the fetus and newborn are also asymptomatic, inapparent, or 'silent'. It is a 'stealth virus'. About 90% of live newborns who have congenital CMV diagnosed are asymptomatic at birth with normal exams. The 10% that do have symptoms at birth may have a wide variety of signs and symptoms.



CMV is definitely "protean in its manifestations" as Thomas Weller once said. Babies who have symptomatic congenital CMV infection may have mild symptoms, such as isolated low platelets, growth restriction, mild lab abnormalities of the liver, or mild abnormalities on their brain imaging such as vasculopathy or cysts.

Moderate to severe congenital CMV infection may include severe growth restriction; abnormalities of platelets with low platelet counts, which can cause bleeding; significantly abnormal liver enzymes or cholestasis with elevated bilirubin; sight-threatening ocular eye diseases, such as retinitis or optic nerve atrophy, or even cortical vision impairment if their brain is malformed; hearing loss that is sensorineural (i.e. permanent nerve deafness), bilateral, or unilateral; and brain involvement that may include microcephaly, intra cranial calcifications, ventriculomegaly, or cortical dysplasia such as poly microgyria or lissencephaly.

Long-term effects of congenital CMV include progressive hearing loss, permanent vision loss, growth and developmental disorders, attention deficit disorders, speech and language delays, motor disabilities such as cerebral palsy, and autism has also now been associated with congenital CMV infection. Congenital CMV is a life-long condition, not just a condition for the fetus or newborn or infant. CMV also is a cause of fetal loss, stillbirths, and neonatal death. About 8% of newborns with severe symptomatic congenital CMV will die despite antiviral treatments and neonatal intensive care.

Q4 What are the benefits of fetal and neonatal antiviral therapy for CMV infection?

Antiviral treatment, administered as ganciclovir intravenously or valganciclovir given orally, to newborns with symptomatic congenital CMV, has been shown in multicenter, randomized clinical trials to improve general growth, improve head circumference growth (and therefore likely brain growth), improve hearing outcomes by reducing the risk of hearing loss progressing or later onset hearing loss occurring, and improve neurodevelopmental milestones including speech and language acquisition, in those infants treated with antivirals.

This benefit appears to last at least until at least the age of 2 years, which was the duration of follow-up in these early clinical trials. This is important, because the early years are periods of language acquisition, and if hearing can be preserved during this important period it can be of benefit. However, some studies are showing that antiviral treatment may not benefit long term. In one study we published, we found that when we follow these children longer, up to age 18 years, the hearing benefits do not seem to be enduring through childhood and adolescence, and they continue to lose their hearing after the antiviral is stopped. This antiviral treatment is still not an FDA-approved indication for the treatment of congenital CMV, despite it being in use for decades, but it is a treatment endorsed by expert opinion and consensus guidelines in the USA and Europe.

Fetal treatment is still experimental and emerging. Some studies have shown CMV transmission to the fetus in pregnant people experiencing a primary or first CMV infection can be reduced using oral high-dose valacyclovir during pregnancy. This is an area of active research as well.

Q5 In terms of prevention, what role does professional education and community awareness play in reducing the risk of congenital CMV infections? What strategies have you found to be the most effective

The first step in CMV prevention is awareness. We need to make CMV a household word and we need to 'normalize' CMV, so we are comfortable talking about it. It is still under-appreciated, and knowledge about CMV is limited, both among healthcare workers and the general public. An ounce of CMV awareness plus three simple behavioral precautions may reduce the risk of CMV transmission to the pregnant person. I call this the 'CMV Knowledge Vaccine' or the 'CMV Information Immunization'. For example, toddlers are virtual 'hot zones' for CMV as they actively shed CMV in their saliva and urine for about a year once they acquire it, usually from other toddlers and in daycare or group care settings. So, avoidance of kissing toddlers around the mouth, sharing food or drinks with them, and washing hands well after wiping runny noses, drool, and doing diaper changes are important to reduce transmission.

Q6 Your work also focuses on other neonatal infections, such as herpes simplex virus (HSV), influenza, and respiratory syncytial virus (RSV). Can you tell us more about your work in developing new diagnostic tests and antiviral treatments for these viral infections in newborns?

When I directed the Diagnostic Virology Laboratory at Texas Children's Hospital for 25 years, I helped raise awareness about the importance of viral infections in children and develop rapid diagnostic tests and PCR-based tests to detect viruses in a variety of body fluids to aid rapid and confirmatory diagnosis of a variety of viral illness important to neonates and children. To say "It's just a virus" was never enough for me. I felt then, and I still feel, that it is very important to name the virus causing an illness, so appropriate management decisions can be made for the patient, and also for us to track epidemiologically, viruses by seasons, and how they change over the years.

Most recently, I am working to develop point-of-care tests for CMV detection in urine, saliva, and newborn dried blood spots, to facilitate the accurate and rapid detection of CMV in newborns, and to facilitate universal screening and targeted newborn testing for CMV. Many viruses, such as influenza and RSV, are seasonal; however, many viruses that affect newborns, such as CMV and HSV, are endemic and non-seasonal, and also deserve our attention.

Q7 How do you see the field of antivirals for infants evolving in the next few years, especially in response to emerging/re-emerging viral threats like influenza and RSV?

We need more antivirals, more options for treatment, more creative and equitable approaches, and more approaches that can be globalized, so that all individuals have access to viral diagnosis, viral treatments, and viral preventive measures. We also need more awareness that we can diagnose and treat viruses. Like I said earlier, viruses not only take over and shut down the machinery of a single cell, but they can shut down an entire country or continent if enough individuals get infected. So, they deserve our attention and respect. We should be more proactive rather than reactive, and develop timely strategies for monitoring, diagnosis, treatment, and prevention.

We also need more prevention measures, such as vaccines. The most recent news around newly licensed RSV vaccines for senior adults, pregnant people, and infants is very exciting. It is quite possible we may not see 'RSV seasons' in the future, which currently fill our hospitals and ICUs in the fall and winter months, with infants and adults with bronchiolitis, pneumonia, and other illnesses! More options for influenza vaccines also are very important.

A CMV vaccine is not yet licensed or available, but work has been ongoing since the 1970s on CMV vaccines. In fact, a CMV vaccine, in addition to a better influenza vaccine, was put as a vital vaccine priority for 21st century by the Institute of Medicine in a report published in 2000. Work continues on a CMV vaccine, by many companies around the world in the vaccine industry arena, and Phase III multicenter trials are underway and close to being completed that appear very promising. So, maybe in the near future, congenital CMV will no longer be waiting its turn for prevention by a vaccine.