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Medical scientist Jinal Bhiman says some reagents for testing for RSV have been hard to obtain.

Addressing the data gap

The need to understand respiratory syncytial virus and its effects is crucial — especially in low- and middle-income countries. **By Pratik Pawar**

When the virus SARS-CoV-2 engulfed the world in 2020, respiratory syncytial virus (RSV) infections began to ebb — a silver lining largely resulting from COVID-19 lockdowns. England, for example, reported a 99.6% drop in RSV cases during the 2020–2021 winter compared with previous years[1].

By 2022, when people began to socialize more often, however, RSV bounced back. Canada, Japan and several countries in the European Union reported a sharp rise in RSV cases. The same was probably true in low- and middle-income countries (LMICs) too, where RSV has the biggest affect. It is not known for sure, however, because the systems and infrastructure needed to track the disease in those countries are inadequate, or missing altogether. "Something like 95% of deaths due to RSV take place in low- and middle-income countries," says Maria Zambon, head of respiratory virology at the UK Health Security Agency in London. Barring a few exceptions, RSV data in most LMICs is sparse.

These gaps in surveillance are keeping the global health community in the dark about the affect that RSV has on public health, as well as where and how RSV is spreading. As was seen with SARS-CoV-2, failure to keep track of a highly transmissible virus in one country can have global ramifications. With a flurry of more than 30 potential vaccines and other therapeutics[2], such as monoclonal antibodies, entering the market, the need to understand RSV is clear.

The question is: how do researchers keep track of a virus that often flies under the radar?

Surveillance set-up

Respiratory viruses have often been targets of surveillance because of their pandemic potential. The World Health Organization (WHO), for example, has tracked the influenza virus globally for more than 70 years through its Global Influenza Surveillance and Response System (GISRS). RSV surveillance, however, has always been left to individual countries. The United States, for example, established the National Respiratory and Enteric Virus Surveillance System in the 1980s to monitor several viruses, including RSV. Japan started tracking RSV in 2003. Some LMICs, such as India, have influenza surveillance systems. But, routine, systematized surveillance for other respiratory viruses, including RSV, is rare.

In 2015, the WHO recognized that several potential RSV interventions, such as vaccines, would soon become available. The organization realized that these measures would be best used if we understood the transmission of the virus and which groups are at most risk. So, in 2016, with a grant of US$4.7 million from the Bill & Melinda Gates Foundation, the WHO launched a pilot project to begin tracking RSV around the world[3]. The pilot ran from 2016 to 2018 in Egypt, India, Mozambique and 12 other countries in all 6 WHO regions, and it tested whether the GISRS network could be used to track RSV. The project also aimed to standardize surveillance methods. The WHO earmarked four reference laboratories — in Australia, South Africa, the United Kingdom and the United States — to provide technical guidance and support for the countries included in the pilot. The aim of the pilot was to collect "widespread data on RSV incidents in developing countries as well as some of the developed countries", says Ian Barr, deputy director of the WHO Collaborating Centre for Reference and Research on Influenza at the Peter Doherty Institute for Infection and Immunity in Melbourne, Australia.

In October 2018, the WHO team and independent specialists reviewed the pilot's data. They concluded that the GISRS is well suited to monitor RSV without risking the system's responsibilities to influenza surveillance. The next step, the group decided, was to run a comprehensive project[4] that would build on the pilot. This second phase started in late 2018 and expanded to include Nepal, Philippines, Uganda and eight other countries. This phase had a particular focus on LMICs that were eligible to receive vaccines from Gavi, the Vaccine Alliance, with the hope that once an RSV vaccine became available, there would be enough data to understand where best to deploy it. The extended project was also designed to understand the virus' burden — the number of hospitalizations and deaths caused by RSV — and to differentiate strains of the virus that circulate around the world.

The WHO project focused on the demographic of children under the age of two, because they are disproportionately affected by RSV. In LMICs such as South Africa, most RSV-related deaths occur in that age group, says Jinal Bhiman, a medical scientist at the National Institute for Communicable Diseases in Johannesburg, South Africa.

Phase two was supposed to run from late 2018 to 2021, but the pandemic threw a spanner in those plans. Quickly, existing laboratories that were earmarked for RSV testing were repurposed to test for COVID-19. RSV surveillance fell by the wayside. The pandemic, "resulted in significant disruptions in RSV and influenza surveillance activities", says Siddhivinayak Hirve, a technical officer at the WHO in Geneva, Switzerland, who has worked on influenza surveillance in the past and is now part of the WHO's global RSV surveillance project. Owing to pandemic disruptions, some countries have also had difficulty obtaining reagents to test for RSV, says Bhiman. Despite these setbacks, phase two is still continuing and has been extended to April 2024.

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Children under the age of two are disproportionately affected by respiratory syncytial virus.

Missing clues

The surveillance project is much-needed, but it's far from a perfect solution. "It's not a comprehensive programme by any means," says Barr.

Major disparities remain in surveillance capacities – and the subsequent data collected – between LMICs and high-income countries. At the moment, around 24, mostly wealthy, countries report RSV-related data into their national surveillance bulletins, says Hirve. In most LMICs, little is being done.

Even in countries where there is some surveillance infrastructure, rural areas are not adequately represented. "Most sentinel surveillance hospitals are in urban areas," says Eva Leidman, an epidemiologist at the US Centers for Disease Control and Prevention's National Center for Immunization and Respiratory Diseases in Atlanta, Georgia.

The WHO, for its part, is helping LMICs to develop capacity by supplying laboratory reagents, conducting training webinars, and providing sequencing and bioinformatics training, says Hirve. But improving RSV surveillance capabilities is not going to be a quick fix. "These efforts are relatively new and will take some time to ensure robust surveillance systems are in place," says Leidman.

Pharmaceutical companies are also helping to collate global data on RSV incidence. AstraZeneca, the developer of the RSV monoclonal antibody nirsevimab, for example, has funded an RSV surveillance dashboard run by the non-profit organization ReSViNET, based in the Netherlands, to collect data from 20 countries (see go.nature.com/3y8kkzr). "These companies can then make a case for nations to introduce their vaccines as part of their existing immunization programmes," Barr says. "It's going to be much harder to do that in developing countries."

Even with external help, however, governments will need to foot the bill for qualified personnel and on-ground surveillance, says Barr. Fortuitously, the COVID-19 pandemic has spurred many countries to build-up robust polymerase chain reaction (PCR) testing facilities that can also be used for RSV detection. "It's then a question of how much of that capability in a country is directed towards RSV," says Zambon.

But surveillance is just one part of the puzzle. To truly understand the affects of RSV in a population, countries need to move past mere detection and conduct burden estimation studies. These studies would track the number of hospitalizations caused by the virus and follow how many of people go on to develop severe disease and how many die – but studies such as these can be expensive. "That will then tell us where to use interventions like vaccines and antibodies," says Zambon. What's more, in most countries, health-care providers are not mandated to report RSV-associated deaths to public-health authorities, making it hard to estimate the disease burden.

As the world has learnt from COVID-19, vaccines can induce selective pressure on a virus, leading to the emergence of new variants. The same might happen with RSV. "With large-scale roll-out of RSV vaccines based on the same antigen, we're going to see people developing very similar antibody responses and that's going to push the virus into specific corners," says Bhiman. "If we're not monitoring the virus, we'll never know if our vaccines are being escaped or whether monoclonal antibody therapeutics are going to be effective," she adds.

Globally, there are multi-country networks, which were first established to monitor the effectiveness of influenza vaccines, and then later modified to monitor COVID-19 vaccine efficacy. In the future, such networks can be adapted to track the efficacy of RSV vaccines, once they are deployed, says Leidman. As phase two of the WHO project comes to a close in early 2024, the WHO plans to integrate RSV surveillance into its GISRS network, calling the expanded network GISRS Plus. Over the past seven years, global RSV tracking efforts have made big strides towards improving surveillance capacity in LMICs and collecting crucial impact data around the world. "But having a globally efficient, accurate handle on RSV, we're a long way from that," warns Barr. As the world seeks to move on from the pain caused by the COVID-19 pandemic, keeping the world's focus on RSV will be no small task, but it is key to making sure that we make the most of the new-found vaccines and treatments.

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1. Bardsley, M. *et al. Lancet Infect. Dis.* **23**, 56–66 (2023).
2. Staadegaard, L. *et al. Open Forum Infect. Dis.* **8**, ofab159 (2021).
3. World Health Organization. *WHO Technical Meeting on Piloting RSV Surveillance based on the Global Influenza Surveillance and Response System* (WHO, 2016).
4. World Health Organization. *WHO Strategy for Global Respiratory Syncytial Virus Surveillance Project based on the Influenza Platform* (WHO, 2019).