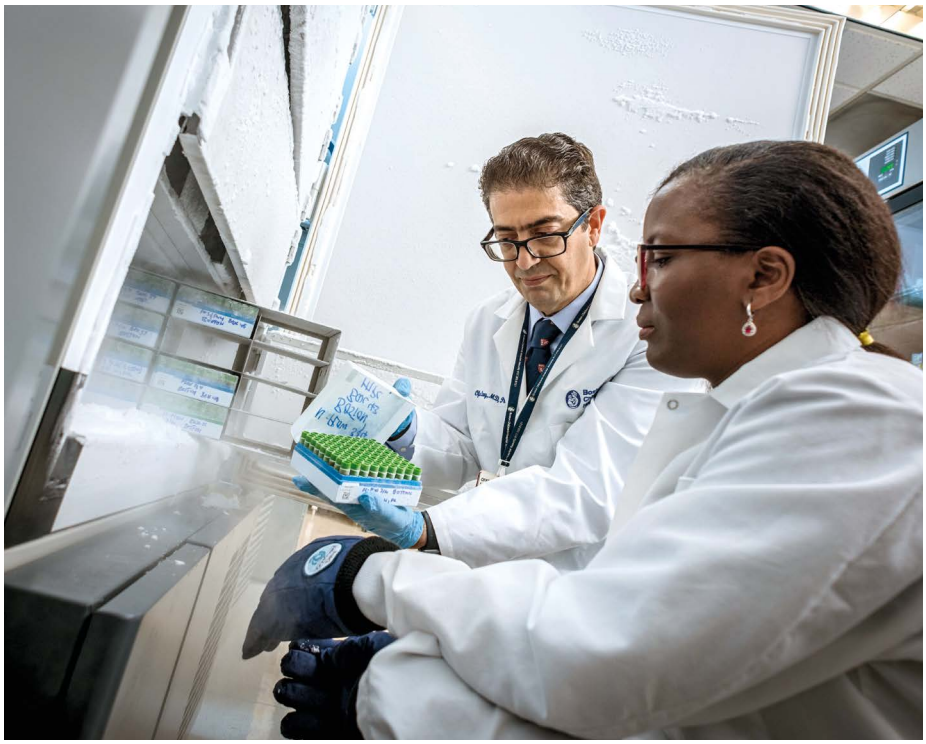

Ofer Levy and his colleague look at biosamples collected from infants in Gambia.

SAM OGDEN

Vaccinating the vulnerable

Researchers are tailoring immunization strategies to improve vaccine responses among newborns and older people. **By Amanda Keener**

In the United States, 70% of people who are hospitalized for influenza are 65 or older. Older people are commonly encouraged to have a flu vaccine each year. But, in what seems like a cruel twist of fate, vaccines against the flu and other respiratory diseases are less effective in older people. Depending on the year, the flu jab typically protects 30–60% of middle-aged recipients; for those aged 65 and over, the protection rate is more like 20–50%.

Infants, particularly newborns, are at a similar disadvantage. Their symptoms are typically worse than those of older children and adults. But again, most vaccines offer less protection to newborns than to adults, and few are recommended before 8 weeks of age. For instance, the vaccine against the bacterium *Haemophilus influenzae*, which can cause meningitis and sepsis, generates a poor immune response in babies under 2 months.

It isn't that those at the far ends of the age spectrum don't respond to vaccines at all, but that they respond differently — and most vaccine testing is done on young and middle-aged adults. "Vaccines have traditionally been developed as one-size-fits-all, but if the immune response is different when you're young and old, that approach leads to lots of failure," says Ofer Levy, who directs the Precisions Vaccine Program, which looks at how variables such as age affect vaccine responses, at Boston Children's Hospital in Massachusetts. This way of developing vaccines is a disservice to the people most in need of protection, says Tobias Kollmann, a vaccinologist at Telethon Kids Institute in Nedlands, Australia. "If you look at the current vaccine schedule, who gets most of the vaccines? The very young and the very old. And yet we don't understand a thing about them."

To better protect vulnerable populations, researchers are investigating how the immune system changes with age. "We want to learn the molecular rules of why vaccines may or may not work in different age groups," Levy says. He and Kollmann are building a biological signature of what a strong vaccine response looks like in newborns. Others are trying to sidestep the unique properties of the newborn immune system by protecting them before birth, through their mothers (see 'Maternal instincts'). And some research groups and companies are tailoring vaccines to boost the responses of older people. Collectively, the aim is to design vaccines and immunization strategies that work for the people most in need.

Early protection

The freezers in Levy's lab are filled with thousands of samples of serum, the liquid component of blood after cells and clotting factors are removed. Most of the samples were taken in the first week of a child's life — some from infants born across the street at Boston Children's Hospital, others from as far away as Papua New Guinea. Together, they hold clues about the newborn immune system that Levy and his collaborators hope will lead to sorely needed improvements in vaccine design.

According to the World Health Organization (WHO), worldwide, 47% of all deaths before the age of five occur during the first four weeks of life, and infections are responsible for 20% of those deaths. Effective vaccines could see more infants through that difficult first month, says Beate Kampmann, an infectious-disease specialist at the London School of Hygiene and Tropical Medicine who directs vaccine research at the UK Medical Research Council unit in Gambia. "There's a myth out there that the baby's immune system doesn't respond to vaccination, and that's not true," she says. Newborns respond well to the bacillus Calmette–Guérin (BCG) vaccine against tuberculosis, the oral polio vaccine and hepatitis B vaccines. The challenge is to work out why those vaccines work, and use that information to create or retool others.

Both hepatitis B and BCG vaccines circumvent the newborn immune system's relative tolerance of foreign organisms. At birth, babies leave the essentially sterile environment of the womb and are bombarded by microorganisms, most of which are beneficial (or at least benign). Because treating all of these organisms as invaders would use so much energy that there would be little left for growth, newborns' immune responses are

blunted. Their innate immune cells — the 'first responders' that detect common patterns on bacteria and viruses — make lower levels of antiviral and antibacterial molecules compared with immune cells in adults. This lack of response is a problem for vaccines, because, in general, more robust activation of the immune system means it remembers the antigens it was exposed to for longer.

Newborn immunity is characterized by rapid flux. Even in the first few days of life, major changes occur in genes and cells related to immunity that researchers are just beginning to identify. Kollmann says that getting a handle on how best to immunize newborns requires a detailed map of those changes. That's where Levy's freezers come in. He and other members of the Expanded Program on Immunization Consortium (EPIC) — an academic group that focuses on vaccination studies in infants — are cataloguing every gene, cell and protein regulated by the immune system that they can find in blood collected during the first week of life. Their study includes samples collected by Kampmann's team in Gambia and by collaborators at another field site in Papua New Guinea.

In a study published earlier this year involving 30 newborn babies, the EPIC team documented marked changes in the quantities of several types of immune cell during the first week of life[1]. These data allowed the researchers to map the common developmental trajectory of the babies' immune systems over that week. Kollmann likens the result to the charts that health professionals use to monitor childhood growth, and suggests this approach could eventually be used to test how potential interventions, such as supporting women so that they can breastfeed for longer, or giving infants probiotics, affect immune health and vaccine responses. The team is adding several hundred more samples to the analysis, so that it can see how an infant's vaccination history affects immune-system development.

Superior shots

The consortium's other major goal is to understand why some infants respond better to vaccines than others. "Now we've got the tools to dissect why things work and why they don't work," Kampmann says. "That is really going to reform the way that we think about the next generation of vaccines." The routine hepatitis B vaccine, for example, is typically given in three parts during a baby's first year or so, but around one-third of infants are fully protected from the virus after just one injection, says Kollmann. Achieving this 'one dose protection' for more vaccines would be a huge win for public health in much of the world, he says. In many low- and middle-income countries, parents must carry their children for kilometres on foot to reach vaccine stations, he explains. It's a trek that they might not be willing or able to make multiple times, so fully protecting children with a single dose could save millions of lives every year, he says.

As part of an ongoing study in Gambia, the EPIC team is trying to identify the immune signatures of children who are fully protected from hepatitis B after one injection, so that vaccines can be designed with one-dose protection in mind. To generate these signatures, the team will carry out the same types of analysis done for their immune-health trajectory study. It will examine blood collected before and at several time points after hepatitis B vaccination, and look at changes in the number of immune cells in the blood, cytokine concentrations and gene expression.

The researchers are also testing the use of another vaccine as an enhancer, or adjuvant, for the hepatitis B vaccine. Researchers have known for decades that infants who receive the BCG vaccine at birth are also less likely to die from a host of other infections. The BCG vaccine is thought to heighten innate immune-cell sensitivity and enhance responses to other vaccines such as pneumococcal and tetanus jabs[2]. Last year, Kollmann, Levy and their collaborators showed that the BCG vaccine boosted the immune response of newborn mice to the hepatitis B vaccine[3]. The researchers hope that a trial in Gambia, due to be completed in 2021, will show whether and how the BCG vaccine might do the same in infants.

Levy's team is also on the hunt for synthetic adjuvants that stimulate the infant immune system as powerfully as the BCG vaccine does. This would allow vaccines to be optimally designed for use in newborns, rather than requiring health professionals to combine multiple

Maternal instincts

The importance and difficulty of protecting infants in the earliest days of life has led to the development of an alternative vaccination strategy for some diseases. The idea is to make use of a natural phenomenon in which antibodies — proteins that help the body to recognize and attack invaders such as viruses and bacteria — are transported across the placenta from mother to developing fetus. After birth, those antibodies act "like a shield that is around the baby for the first three months or so" says Beate Kampmann, an infectious-disease specialist at the London School of Hygiene and Tropical Medicine. Maternal vaccination stimulates the production of antibodies in the mother that are passed to newborns and can protect them from the severe symptoms of infections such as whooping cough and flu before they can receive their first vaccinations at two months.

Questions remain, however, about how best to implement this form of protection. For example, it is unclear how the timing of vaccination or a mother's HIV status affect the number of antibodies that cross the placenta. There is also some concern that maternal vaccination might depress an infant's responsiveness to the same vaccine later on — maternal antibodies might mask the vaccine and prevent the child's immune cells from recognizing it. To clarify this, Kampmann is leading a study in Gambia that will measure responses to the whooping cough vaccine in 600 children whose mothers were vaccinated against the disease during pregnancy.

Kampmann directs the Immunising Pregnant Women and Infants network (IMPRINT), which supports research to advance maternal vaccines. Two infections for which such vaccines are making strides are respiratory syncytial virus (RSV), a common infection that can be serious for infants with other health problems, and group B streptococcus, which babies pick up from their mothers at birth and that caused 90,000 deaths globally in 2015 (ref. 8). Several group B streptococcus vaccine candidates are now being tested, including one that has been tested in a phase II trial in pregnant women in Malawi and South Africa. The maternal vaccine induces antibody responses in infants, but it's not clear yet whether those responses are enough to prevent disease[9]. The most advanced RSV vaccine in development is a maternal vaccine developed by Novavax in Gaithersburg, Maryland. In a phase III trial, the vaccine proved about 40% effective at preventing RSV infection in the first 90 days of life. "That certainly means that we're on the right track," says Justin Ortiz, an epidemiologist at the University of Maryland School of Medicine in Baltimore, who was not involved in the study.

SOFIA BUSK

A health worker gives the BCG vaccine to a newborn baby in Guinea-Bissau.

vaccines that might not always be available.

In 2017, the team reported that synthetic nanoparticles packed with imidazoquinoline molecules can activate a first-responder protein called Toll-like receptor (TLR) 8, as does the BCG vaccine[4]. The group is now developing a vaccine against the bacterium *Bordetella pertussis* – the cause of whooping cough – with a TLR8-activating adjuvant. It plans to test whether TLR-stimulating adjuvants allow the vaccine to provide lifelong protection from birth – something that the current protein-based vaccine, introduced in the 1990s, does not afford.

Ageing immunity

Babies are unprotected against many vaccine-preventable diseases for months until they can have their first set of vaccines, but those at the opposite end of the age spectrum are left susceptible for many years – especially people with declining lung or heart function or those in assisted living communities, where infections can spread quickly. The outcomes of respiratory infections for people over the age of 65 can be even worse than for infants. It's estimated that in the United States, respiratory syncytial virus kills more than 10,000 people over 65 each year, and hospitalizes three times as many older adults as it does children under five. The flu has an even bigger impact. The US Centers for Disease Control estimates that the 2017–18 flu season caused more than 68,000 deaths among the older people. These numbers are likely to increase, says Gregory Poland, an immunologist at the Mayo Clinic in Rochester, Minnesota. By 2050, the global population of people over 60 is expected to be double what it is today. "Most people have ignored the silver tsunami that is coming," Poland says.

Poland says vaccines for older adults will be most successful if they are tailored to the immune characteristics of older people. Along with Kollmann and Levy, he is part of the Human Immunology Project Consortium (HIPC), which is cataloguing the immune signatures of different age groups before and after immunization. In 2017, HIPC researchers reported[5] that several such signatures that could be used to predict responses to vaccines in adults under 35 could not be used for populations of people over 60. That means that the vaccine formulations that work best for older individuals will be unique to that age group.

As people approach 50, Poland says, detrimental changes to the immune system can already be observed. Beyond 60, he says, "virtually everything that we know to look at becomes compromised". Some immune cells, he explains, become "exhausted" from chronic activation, including those that keep the varicella zoster virus – the cause of chicken pox and shingles – in check. That's one reason why researchers think the immunity garnered by a childhood bout of chicken pox often fails to prevent shingles past the age of 50.

Several companies are finding ways to overcome the low responsiveness of the ageing immune system. Some are increasing vaccine potency and the number of doses given to elicit a bigger response. A high-dose flu vaccine for people aged 65 and over produced by Sanofi Pasteur in Lyon, France, for instance, uses four times more influenza antigen than the standard injection. It is 24% more effective than the regular dose at preventing influenza and influenza-related deaths in those 65 and over[6]. Other vaccines such as a flu vaccine produced by Seqirus in Maidenhead, UK, use adjuvants to kick-start the immune response. The vaccine creates a strong immune response in older recipients, but it's not clear yet whether that translates to better protection[7].

"Most people have ignored the silver tsunami that is coming."

The shingles vaccine Shingrix is a prime example of what's possible when vaccines are built with specific populations in mind. Shingrix contains two adjuvants that stimulate the innate immune system, and is more than 90% effective at preventing shingles in adults aged 50 and over. Just two years since its approval, Shingrix has replaced the previous live-virus vaccine as the preferred shingles vaccine in the United States.

Vaccine design is only part of the effort to protect the old and very young from infection. There's general agreement that vaccines already in use could be saving millions more lives if they were better implemented. Improving flu-vaccine coverage – even if a vaccine performs suboptimally in people over 65 – has the potential to save thousands of lives each year, says Justin Ortiz, an epidemiologist at the University of Maryland School of Medicine in Baltimore. "That can be done now," he says. Administering existing vaccines to children – the main transmitters of flu – could also reduce infections in older people.

Kampmann agrees that the development of vaccines and immunization strategies for newborns and older people will only be useful if they are paired with improvements in vaccine coverage and access – particularly in low-resource countries, which carry most of the world's infectious-disease burden. "As much as all the biology is really exciting, we should also use our power and advocacy to make sure that the people who need these vaccines get them," Kampmann says. "We have different fronts to fight."

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