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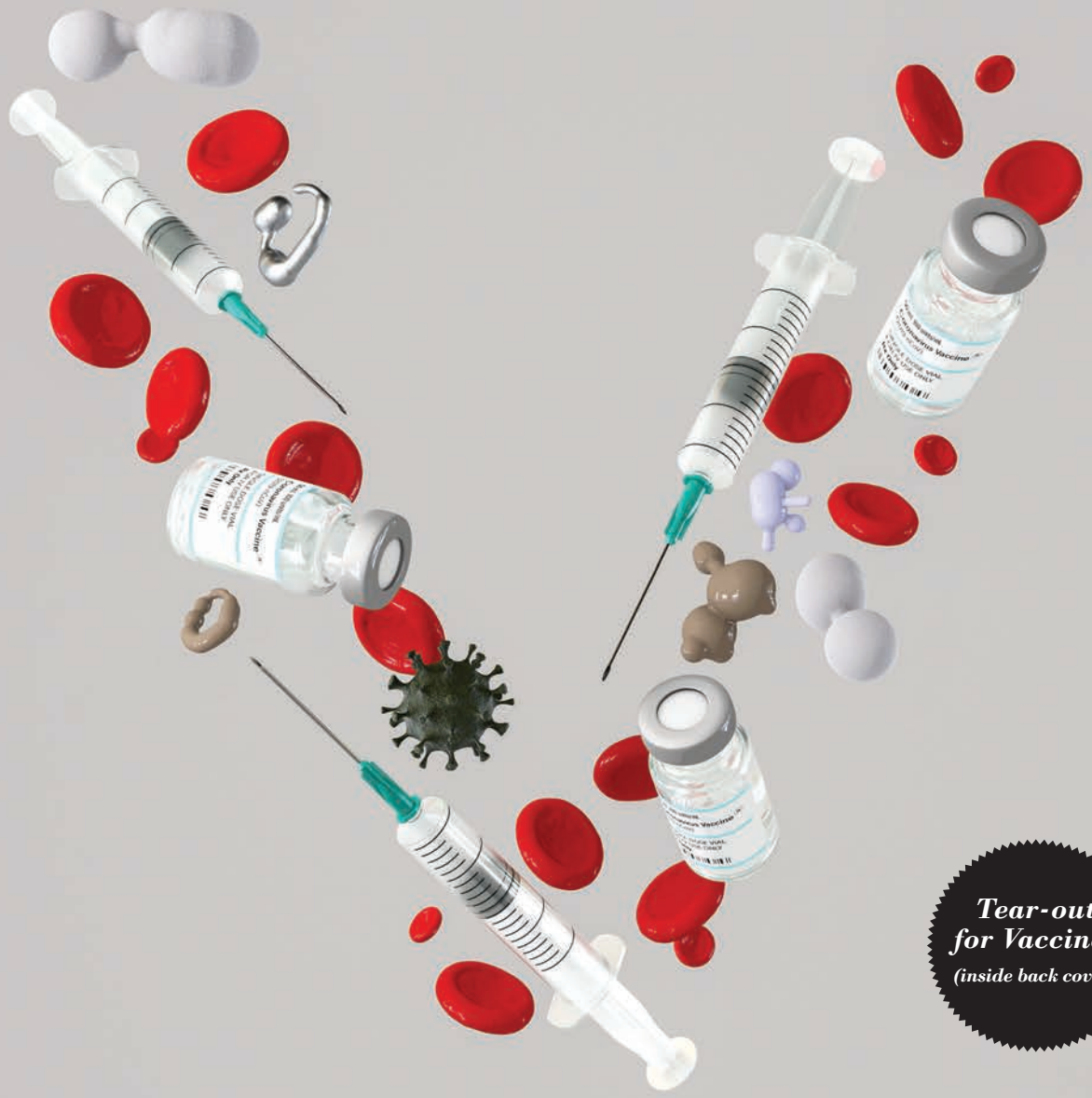

Tear-out for Vaccines
(inside back cover)

INS & OUTS OF VACCINES

REBUILDING TRUST WITHIN UNDERREPRESENTED POPULATIONS

CAN CLINICAL TRIALS BE IMPROVED?

AMERICAN SOCIETY FOR MICROBIOLOGY

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From the editor

STANLEY MALOY, PH.D., EDITOR IN CHIEF

PANDEMICS, PEOPLE AND POSSIBILITIES

Although the COVID-19 pandemic is recent, pandemics have plagued humans throughout history, decimating communities. Pandemics of plague, smallpox, measles, chickenpox, mumps, whooping cough, influenza, typhoid fever, cholera and many other microbial pathogens have had profound impacts on humanity, and some continue to impact many people around the world.

Once an airborne infectious disease becomes a pandemic, it rarely disappears. Like seasonal influenza, the pathogen returns over and over again, infecting many people with each visit, rather than generating herd immunity. For example, devastating outbreaks of bubonic plague recurred in England every two to five years from 1361-1480.

Containment can reduce the transmission of airborne diseases and save lives by flattening the curve, but does not eliminate the risk of another round of infection once the containment measures are no longer in place. With the efficiency of international flights, it is possible to acquire an infection and travel to another corner of the globe before symptoms appear, potentially reinfecting a community that seemed to have eradicated transmission.

A JOURNEY THROUGH VACCINE HISTORY

Widespread use of variolation techniques date as far back as the year 1000. Since that time, groundbreaking contributions in the field of vaccine research have revolutionized modern medicine, saved countless lives, led to the eradication of a significant human pathogen and had remarkable impact on pandemic diseases throughout history. Presently, the uncontrolled spread of SARS-CoV-2, a novel pandemic pathogen against which no prior immunity existed, continues to pose a significant threat to public health and further emphasize the power and utility of vaccination. To highlight these important contributions and ongoing needs, we present a timeline of vaccine research, development and use in the bottom border of this issue of *Microcosm*.

The most effective way to break this cycle is development of an effective vaccine. The impact of vaccines on pandemic diseases is nicely illustrated in the Vaccine Timeline printed along the lower border of this issue of *Microcosm*.

An effective vaccine will provide protection for the individual, but for a vaccine to prevent ongoing disease in the community, a sufficient proportion of the population must be vaccinated such that the transmission of the pathogen is effectively stopped – that is – enough people must be vaccinated to safely achieve herd immunity. And that means that the vaccine has to be widely accepted.

Wide acceptance of a vaccine requires that the vaccine has proven to be safe and effective. Demonstrating the safety and efficacy of vaccines relies on carefully controlled clinical trials. When we are in the middle of a pandemic like COVID-19, there is a tremendous desire to rush the clinical trials to get a vaccine to market as quickly as possible. But how can clinical trials be done faster and still be trustworthy? The article "*Can Clinical Trials Be Improved?*" provides thoughtful perspectives on this question.

Two other articles in this issue address the continuing search for effective vaccines that could save many lives and thwart pandemic threats: an HIV vaccine and a universal influenza vaccine. Despite tremendous scientific efforts and innovative approaches, these vaccines have been elusive so far. These two articles describe the challenges faced in developing these vaccines and optimism for future success.

Nevertheless, having a safe and effective vaccine is not enough. Even when the science is thorough and the data is solid, the population has to trust that the vaccine will not harm themselves or their families.

The article "*Rebuilding Trust for Underrepresented Populations*" discusses the challenges of regaining the confidence of vulnerable communities that had previous negative experiences with the medical system. Rebuilding this trust is crucial for reducing health disparities in marginalized populations. In contrast to the experiences of marginalized populations, vaccine deniers doubt the safety of vaccines based upon misinformation and misunderstanding. The fold-out in this issue of *Microcosm* provides concise, actionable recommendations for how you can effectively communicate the seriousness of COVID-19 and the crucial role of vaccines to friends, neighbors and colleagues. This one-page synopsis is meant to be "torn out" and used as a resource.

Overcoming these infectious disease challenges is crucial for human health, but microbiology is continuing to make important discoveries in many other areas as well. Some recent microbiology publications that we thought were particularly cool are highlighted in the "What's Hot" feature. A broad, robust basic research portfolio continues to be the essential pipeline for new applications. As highlighted by the recent Nobel Prize awarded to Emmanuelle Charpentier and Jennifer Doudna for CRISPR-Cas9, important scientific applications often come from areas of research that couldn't be predicted from the outset.

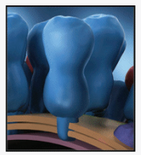
Even when the science is thorough and the data is solid, the population has to trust that the vaccine will not harm themselves or their families.

~1000 The variolation technique is used. This approach involves inoculation of children and adults with dried scab material recovered from smallpox patients. Variations of variolation are developed in China, Africa, the Middle East and Europe. [Note: Some people are protected, while some die from the disease].

1796 Edward Jenner, an English physician, creates the world's first vaccine by testing the observation that dairymaids and other persons afflicted with the mild disease called cowpox are subsequently protected from infection by smallpox. Using material taken from cowpox lesions on the hands of a milkmaid, Jenner is able to deliver the first successful smallpox immunization to an 8-year-old boy. The term "vaccination" is derived from the Latin *vacca*, or cow.

1880 Louis Pasteur discovers a new method of attenuating a virulent pathogen (*Pasteurella multocida*, the bacterium that causes chicken cholera) that could immunize chickens without causing disease. Thanks to this conceptual break-through, it is now possible to establish protection against disease through inoculation of a weakened strain of the causative agent. Pasteur uses the word "attenuated" to mean "weakened" and credits Jenner's success with smallpox as his inspiration.

1881 Louis Pasteur and his associates develop an attenuated derivative of *Bacillus anthracis* by exposing bacteria to oxygen, and demonstrate its efficacy in a public experiment at Pouilly-le-Fort. 48 animals are injected with live *Bacillus anthracis* cultures; 1/2 of them had been previously inoculated with the vaccine, and those animals all survive. All the others die.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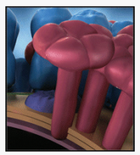
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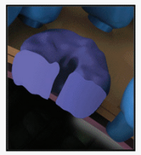
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A Universal Influenza Vaccine: How Close Are We?

BY ***ANGEL CORONA, PH.D.***

Seasonal influenza vaccinations currently provide narrow protection against select strains of the virus, but several "universal" flu vaccine candidates, designed to deliver broader and longer-lasting influenza protection, are now in Phase 2 and Phase 3 clinical trials. While much progress has been made to develop these vaccines, researchers still have several hurdles to clear to improve vaccine efficacy.

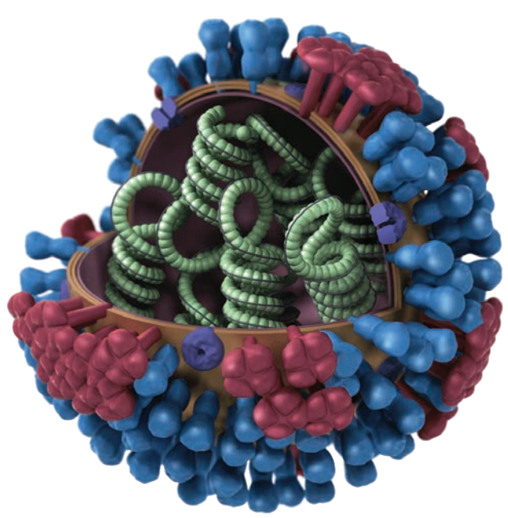


figure 1: The viral membrane contains several membrane proteins, such as hemagglutinin (HA) and neuraminidase (NA).

The flu is primarily caused by influenza A and B viruses (IAV and IBV). Both are enveloped RNA viruses that have hemagglutinin (HA)[1] and neuraminidase (NA)[2] surface proteins bound to their membranes. These are important for the entry and release of the virus (respectively) from infected cells. Immune responses to influenza viruses are usually strain-specific because most neutralizing antibodies generated by infection or vaccination target the globular head of HA.[3] As shown in the graphic to the left, HA and NA are the more numerous and more accessible[4] antibody targets on the viral envelope.

WHY SEASONAL INFLUENZA VACCINATION IS NECESSARY

1. STRAINS OF INFLUENZA CHANGE ANNUALLY

One reason we need yearly flu vaccinations is the propensity of HA to experience sequence changes. A person exposed to one strain of IAV will develop neutralizing antibodies[5] specific to the HA globular head of that strain. Random mutations, known as antigenic drift, in IAV make the globular head of HA highly variable over time. Antibodies that recognize a previous strain will no longer protect against the new variant. Another mechanism of immune evasion is antigenic shift, or recombination. In the same host, recombination of two different strains of viruses can yield a completely new HA that has never been seen by the host's immune system. Antigenic shifts have caused pandemic strains of influenza, such as the 2009 H1N1 outbreak.[6] This is why the U.S. Centers for Disease Control and Prevention (CDC) analyzes circulating strains to predict which ones will be common and should be vaccinated against in the coming year. The predictive nature of vaccine design is a primary reason why vaccine efficacy varies widely from year to year.

2. FLU VACCINE EFFICACY IS NARROW AND SHORT-LIVED

Additionally, the antibody response to current flu vaccines is frustratingly fleeting. A recent systemic review and meta-analysis[7] of various influenza vaccination studies suggested a fading immune response within six months of flu vaccination. Most influenza vaccinations have narrow protection and short-lived efficacy.[8] In this scenario, efficacy refers to broad protection against multiple strains of influenza.

STRATEGIES FOR A HEMAGGLUTININ (HA)-BASED UNIVERSAL VACCINE

The search for more conserved HA epitopes across multiple influenza strains is underway. If vaccines can help the immune system target viral regions that undergo less mutation, there is a greater probability of conferred protection.

The stalk, or domain of HA that anchors the globular head to the membrane of the virus, is relatively similar across IAV strains. Conserved regions of the genome typically correspond to preserved enzymatic activity[9] that cannot be easily changed without deleterious effects, making the HA stalk a reasonable target of universal vaccine candidates. One strategy involves a recombinant HA protein that lacks the globular head and contains only the stalk domain.[10] To date, most vaccines using this approach remain in preclinical trial.

STRATEGIES FOR A HEMAGGLUTININ (HA)-BASED UNIVERSAL VACCINE

STRATEGY	PROS	CONS
Recombinant stalk-specific HA	Straightforward approach. Generates antibodies against a conserved IV region.	Deletion of globular head changes HA structure. Deletion of globular head generates antibodies against naturally inaccessible epitopes.
Chimeric recombinant HA	Maintains native HA structure. May provide protection against future pandemic strains. Can be used in any vaccine platform.	Does not enrich for stalk-specific antibodies.
Recombinant M2	Conserved IV structure. M2's ion channel function makes it less likely to mutate.	Less accessible to antibodies compared to HA or NA.

An alternative strategy uses reverse genetics to make viruses that express recombinant, chimeric HA proteins. These constructs typically consist of a stalk from the H1 clade of widely circulating IAV strains[11] fused with the globular head of non-human IAV strains. Sequential vaccine doses against chimeric HAs aim to generate stalk-specific antibodies that provide universal protection against IAV.

1981 Maurice Hilleman and colleagues develop a vaccine for hepatitis B using treated and filtered blood serum. This treatment is used until 1986, when Pablo DT Valenzuela develops a process for preparing the vaccine using yeast cells instead.

1988 The World Health Organization (WHO), CDC, Rotary International and United Nations Children's Fund (UNICEF) establish the Global Polio Eradication Initiative (GPEI), and as a result of concerted vaccination efforts, the Americas are declared polio-free in 1994.

1998 The first vaccine against rotavirus infection, RotaShield, is licensed for use in the U.S. The following year, safer vaccines, made from attenuated live virus, are developed: Rotarix and Rota Teq.

2000 National Institute of Allergy and Infectious Diseases (NIAID) forms the HIV Vaccine Trials Network (HVTN), a network of more than 25 clinical sites in the U.S., Africa, Asia, South America and the Caribbean dedicated to developing a preventive HIV vaccine.

Because the use of non-human influenza HA globular heads encourages the immune system to generate strain-specific antibodies against the head, along with the conserved stalk domain, this approach also has the potential to protect against novel pandemic IAV strains if the same HA is ever expressed. Unfortunately, vaccine-generated stalk-specific antibodies may target regions that are inaccessible during actual infection. Epitope mapping of the most immunogenic sites of HA stalk[12] can help determine availability during infection and aid in vaccine design.

There are many HA-based vaccines in various stages of development and clinical trial. Candidates to watch include GlaxoSmithKline (GSK), Novavax's Nanoflu, Vaxart, Inc.'s VXA-A.1 and Altimmune's NasoVax. VXA-A.1 is a proof-of-concept vaccine for the use of an oral tablet-based vaccine versus the standard intramuscular injection. NasoVax is a nasal spray-administered vaccine composed of a replication-deficient adenovirus vector expressing an H1N1 HA.[13] Evidence suggesting reduced efficacy of FluMist, an approved nasal influenza vaccine, has caused some trepidation about nasal sprays as delivery systems.[14] NasoVax must clear that trepidation if it is to establish credibility.

Another proof-of-concept vaccine, a quadrivalent HA virus-like particle (VLP) vaccine from Medicago, Inc., uses plant-based VLP technology to manufacture recombinant virus-like particles. These particles can be engineered to express HA proteins from influenza or spike (S) proteins from coronaviruses, such as SARS-CoV-2.

RECOMBINANT M2 AND OTHER NON-HA VACCINE STRATEGIES

The exposed surface domain of M2 structural protein is another conserved region of IAV that's under investigation; however, it is less often targeted for flu vaccine development because it is a less accessible antigen, and HA- and NA-specific antibodies are more common than M2-specific antibodies in natural infections.

It is noteworthy that non-HA vaccine candidates include FLU-v, a synthetic peptide-based vaccine created by Imutex that was designed to promote cellular (T-cell) immune responses[15] over humoral (antibody) immunity and has demonstrated successful protection against intranasal challenge with H1N1.[16]

BiondVax's M-001 was created using a bioinformatics analysis of conserved peptides across IAV strains and is undergoing clinical trials. Osivax's OVX836 induced CD4 and CD8 T-cell NP-specific responses in mice[17] during preclinical studies, and similar results are expected from clinical human trials. Vaccitech's MVA-NP+M1 combines NP and M1 from IAV in an adenoviral[18] vectorplatform.

HOW "UNIVERSAL" ARE UNIVERSAL INFLUENZA VACCINES?

Many of the above strategies target a variety of IAV and some IBV strains, but researchers don't yet know how protective they will be in people. Dosage effects of chimeric HA vaccines differ in mice compared to preliminary results[19] from human trials, and there is uncertainty about the length of protection that will be conferred by a universal vaccine.

Ultimately, this is not an exhaustive list of current vaccine candidates or strategies. There are numerous ongoing Phase 1 trials and several promising pre-clinical strategies[20] being investigated. While influenza continues to strike each year, promising work on broadly effective vaccines may ultimately break our never-ending cycle of annual influenza vaccinations.

CURRENT UNIVERSAL INFLUENZA VACCINE CANDIDATES IN LATE CLINICAL TRIALS

NAME	DATE COMPLETED	VIRUS TARGETED	ANTIGEN TARGETED	VACCINE
FLU-v	11/6/2019	IAV/IBV	M2/NP/M1	Synthetic
Multimeric-001	2/17/2020	IAV/IBV	NP/M1/HA2	Recombinant Peptide
MVA-NP+M1	1/27/2020	IAV	NP/M1	Viral Vector
NanoFlu	Ongoing	IAV	HA stalk/head	Recombinant Protein
NasoVAX	4/11/2019	IAV	HA	Viral Vector
OVX836	9/19/2019	IAV	NP	Nanoparticles
QVLP	6/11/2020	IAV/IBV	HA	VLP
VXA-A1.1	7/26/2018	IAV	HA	Viral Vector

[1] Smart S.T. and Lorieau J.L. Membrane Fusion and Infection of the Influenza Hemagglutinin. *Adv Exp Med Biol.* 2017.

[2] Yang J. *et al.* A new role of neuraminidase (NA) in the influenza virus life cycle: implication for developing NA inhibitors with novel mechanism of action. *Rev Med Virol.* July 2016.

[3] Sedeyn K and Saelens X. New antibody-based prevention and treatment options for influenza. *Antiviral Res.* Oct. 2019.

[4] Padilla-Quirarte HO. *et al.* Protective Antibodies Against Influenza Proteins. *Front Immunol.* July 18, 2019.

[5] Corti D. *et al.* Tackling influenza with broadly neutralizing antibodies. *Curr Opin Virol.* May 18, 2017.

[6] Jilani T.N. *et al.* H1N1 Influenza. 2020 Jul 20. In: StatPearls [Internet]. Jan. 2020.

[7] Young B. *et al.* Duration of Influenza Vaccine Effectiveness: A Systematic Review, Meta-analysis, and Meta-regression of Test-Negative Design Case-Control Studies. *J Infect Dis.* Feb. 14, 2018.

[8] Radin J.M. *et al.* Influenza vaccine effectiveness: Maintained protection throughout the duration of influenza seasons 2010-2011 through 2013-2014. *Vaccine.* July 19, 2016.

[9] Heiny, A.T. *et al.* Evolutionarily conserved protein sequences of influenza a viruses, avian and human, as vaccine targets. *PloS one*, 2(11), e1190. https://doi.org/10.1371/journal.pone.0001190.

[10] Sagawa H. *et al.* The immunological activity of a deletion mutant of influenza virus haemagglutinin lacking the globular region. *J Gen Virol.* July 1996.

[11] Xiangjie Sun. *et al.* N-Linked Glycosylation of the Hemagglutinin Protein Influences Virulence and Antigenicity of the 1918 Pandemic and Seasonal H1N1 Influenza A Viruses. *Journal of Virology.* July 2013.

[12] Adachi Y. *et al.* Exposure of an occluded hemagglutinin epitope drives selection of a class of cross-protective influenza antibodies. *Nat Commun.* 2019. https://doi.org/10.1038/s41467-019-11821-6.

[13] Tasker S. *et al.* 2554. Safety and Immunogenicity of NasoVAX, a Novel Intranasal Influenza Vaccine. *Open Forum Infectious Diseases.* https://doi.org/10.1093/ofid/ofy209.162.

[14] Piedra P.A. Live Attenuated Influenza Vaccine: Will the Phoenix Rise Again? *Pediatrics.* Feb. 2019.

[15] Pleguezuelos O. *et al.* A Synthetic Influenza Virus Vaccine Induces a Cellular Immune Response that Correlates with Reduction in Symptomatology and Virus Shedding in a Randomized Phase Ib Live-Virus Challenge in Humans. *Clin Vaccine Immunol.* July 2015.

[16] Pleguezuelos O. *et al.* Efficacy of FLU-v, a broad-spectrum influenza vaccine, in a randomized phase IIb human influenza challenge study. *npj Vaccines.* 2020. https://doi.org/10.1038/s41541-020-0174-9.

[17] Del Campo J. *et al.* OVX836 a recombinant nucleoprotein vaccine inducing cellular responses and protective efficacy against multiple influenza A subtypes. *npj Vaccines.* 2019. https://doi.org/10.1038/s41541-019-0098-4.

[18] Fukuyama H, *et al.* Influenza vaccination strategies targeting the hemagglutinin stem region. *Immunol Rev.* July 2020.

[19] Margine I, *et al.* H3N2 influenza virus infection induces broadly reactive hemagglutinin stalk antibodies in humans and mice. *J Virol.* Apr. 2013.

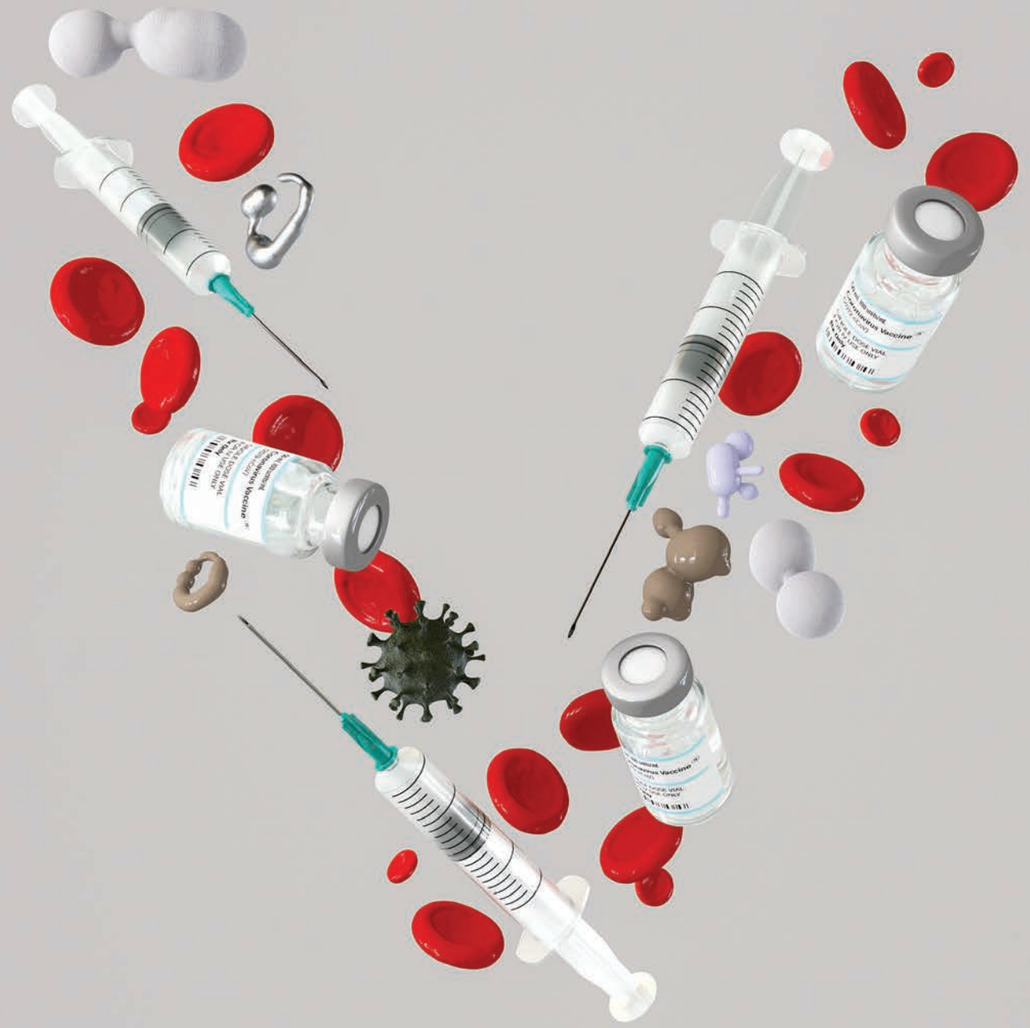
[20] Thrane S, *et al.* A Vaccine Displaying a Trimeric Influenza-A HA Stem Protein on Capsid-Like Particles Elicits Potent and Long-Lasting Protection in Mice. *Vaccines* (Basel). July 15, 2020.

1885 Louis Pasteur develops a rabies vaccine using dried spinal cords from rabbits that had been experimentally infected with the rabies virus.

1886 Theobald Smith and D. E. Salmon inject heat-killed whole-cell vaccine of *Salmonella enterica* into pigeons and demonstrate immunity upon subsequent exposure to a live culture of the bacteria. Although they were trying to develop a vaccine to hog cholera, which is caused by a virus, the disease is commonly associated with a secondary Salmonella infection.

1890 Emil Behring and Shibasabro Kitasato develop antitoxin, or serum therapy, against both tetanus and diphtheria by using iodine trichloride to modify the corresponding toxins and showing that they could provide short-term protection of infected animals.

1896 Wilhelm Kolle develops a heat-killed cholera vaccine using *Vibrio cholerae* grown on agar and resuspended in saline. This type of vaccine is used for many years.



Rebuilding Trust Within Underrepresented Populations: A Necessary Step for the COVID-19 Vaccine

A long history of medical abuses and injustice against underrepresented/ historically excluded groups complicates efforts to get vaccines to the communities at highest risk. During a pandemic, the stakes are life or death.

BY ***STEPHEN ORNES***

Everyone is at risk for COVID-19, but the disease doesn't affect every community equally. Data on hospitalizations and deaths from COVID-19 in the U.S., reported by the Centers for Disease Control and Prevention (CDC), have revealed stark racial disparities. African Americans/ Blacks, Native Americans and people of Hispanic/Latinx ethnicity are about five times as likely as non-Hispanic/ Latinx whites to be hospitalized for their symptoms. In many areas, people in underrepresented communities are dying at twice the rate — or more — as that of non-Hispanic/Latinx whites.[1]

People in underrepresented populations face higher risks because of a multitude of social factors: They're more likely to have front-line jobs — like in health care facilities or grocery stores — and lack access to personal protective equipment. They're also less likely to have health insurance, less likely to be working from home and have less sick leave from their jobs. Historically excluded communities have higher rates of health conditions like diabetes and obesity that have been linked to worse outcomes in COVID-19.[2]

"Disproportionate numbers of underrepresented populations have suffered from COVID, relative to others," said health policy expert Esther Krofah during a recent briefing held by the Alliance for Health Policy, a nonprofit organization focused on clarifying health issues for policymakers.[3] Krofah leads the Faster Cures program at the Milken Institute in Washington, D.C., which promotes ways to include the experience of patients in medical research. "It's important that we ensure [people from underrepresented groups] are included in clinical trials" of both vaccines and treatments, she said.

A safe and effective COVID-19 vaccine can save lives, but only if it reaches all vulnerable populations.[4] However, existing research suggests that recruiting individuals from underrepresented populations for clinical trials and getting the vaccines to the communities who can most benefit from them may be a challenge — not because of a lack of access (although that could play a role), but because of vaccine hesitancy, which is the term that public health experts and the World Health Organization use to talk about communities of people who delay or refuse vaccines when they're available.[5]

Consider influenza, which according to the CDC killed 22,000 people in the U.S. during the 2019-2020 season and about 80,000 people the year before.[6] A flu shot can lower a person's risk of getting sick, but every year, U.S. vaccination rates fall far short of the 70% target set by the Healthy People 2030 program.[7] Last year, fewer than half of people over six months old got the shot, and most of them were children. The rates skew lower among individuals from underrepresented populations. Last year, only about 41% of African American/Black adults and 38% of Hispanic/Latinx adults received a flu shot.[8]

last year, fewer than

1/2

of people over 6 months old got the flu shot

Researchers have proposed and investigated myriad reasons for vaccine hesitancy. Some groups refuse because of religious beliefs or because of misinformation about the side effects or ingredients of immunizations, for example. But among underrepresented communities, there's likely another, even more significant factor at play: centuries of medical abuse and injustices.

Among historically excluded communities who are most vulnerable to COVID-19, understanding the reasons behind vaccine hesitancy has become a matter of life or death. Ongoing investigations by the University of Maryland's Center for Health Equity in Baltimore, among others, have found over and over again that the central issue at the heart of vaccine hesitancy in these communities is trust.

Between 2012 and 2014, researchers from the center interviewed people from different racial backgrounds and opinions on vaccines and found that white people were more likely to trust the government on medical matters, while African Americans/Blacks were more likely to be skeptical. And whether or not a person trusted the government clearly shaped their thoughts on an FDA-approved, CDC-recommended vaccine.

"You don't trust a government vaccine!" one of the participants told the researchers.

Sandra Crouse Quinn, Ph.D., who studies vaccine hesitancy and is involved in community efforts to raise vaccination rates in historically excluded communities in Baltimore, led that study, which was published in *Social Science and Medicine* in January 2019.[9] She said that although many forces likely fuel mistrust of government vaccines, one of the strongest — and most unavoidable — is the past.

"There's a well-known history of medical research abuses against people from underrepresented communities," she said. "And we have to recognize that that still has resonance for many people."

Amelia Jamison, M.P.H., who recently began pursuing a Ph.D. in health, behavior and society at Johns Hopkins University, worked with Dr. Crouse on the study in Baltimore. She recalled that when she asked one group about the flu vaccine, one woman spoke up immediately.

"We can't even have this discussion," the participant said, "without talking about Tuskegee."

TUSKEGEE'S SHADOW

Tuskegee, Ala., is the county seat of Macon County. It was also home, for a full four decades, to an unethical and abusive experiment conducted by the U.S. Public Health Service on African American/Black men. By 1932, when the experiment began, scientists had a solid understanding of the causes, symptoms and effects of syphilis. They knew that the pathogen behind the disease was a bacterium called *Treponema pallidum*, and that it spread through sexual contact.

Standard treatment for syphilis at the time included injections of arsenic and mercury over the course of a year. The cocktail was expensive and toxic, but it kept the disease under control. In Tuskegee, where rates of syphilis infection were high, government researchers set out to study the natural course of the disease, untreated, by recruiting about 400 uneducated male sharecroppers with syphilis and 200 men who didn't have the disease.[10]

Participants were told they had "bad blood," but they weren't informed that the infection could spread to sexual partners. As compensation, participants received free meals, medical exams and burial insurance — but not treatment. Although the men consented to participate in the trial, later investigations revealed that they were not told the purpose or extent of the experiment.

"There's a well-known history of medical research abuses against [people from underrepresented communities] ... we have to recognize that it still has resonance for many people."

The first reports from the experiment began to appear in 1934. By 1943, doctors in the U.S. had begun treating syphilis patients with penicillin, an antibiotic, and by 1947 it had become the standard treatment for the disease[11] — but not in Tuskegee: Despite the availability of a cure, the men in the experiment didn't receive it, and they weren't given the opportunity to quit the study.

In the late 1960s, an investigator in the U.S. Public Health Service named Peter Buxtun, then in San Francisco, heard about the Tuskegee experiment and raised concerns. The Centers for Disease Control and Prevention decided, in 1969, to continue the study anyway. It continued for another three years, until the publication of a scathing 1972 Associated Press exposé effectively ended the research.[12]

Today, "Tuskegee" has become shorthand for medical abuses against African Americans/Blacks — but it has not been the only one. In January 1951, a 31-year-old African Americans/Black woman named Henrietta Lacks was treated for vaginal bleeding at Johns Hopkins Hospital in Baltimore. She was diagnosed with cervical cancer, and during treatment doctors removed cancerous cells from her cervix without her consent. Lacks died in October that year, but her cancerous cells divided so quickly that they doubled in number every day. Since then, researchers have used HeLa cell lines for tens of thousands of experiments, but Lacks's five children remained unaware for decades that their mother's cells were being used in research.

"There's a long history of poor treatment of certain populations, which has led to mistrust in research motivations," said Brenda Huneycutt, Ph.D., M.P.H., who oversees Faster Cures' online tracker of vaccines and treatments.

Other events have similarly cast a long shadow on today's mistrust of government health programs. Between 1973 and 1976, for example, more than 3,000 Native American women were involuntarily sterilized as part of a program run by the Indian Health Service. "If public health experts want to get vaccines — including one for COVID-19, when it's ready — to vulnerable underrepresented communities in the future," Dr. Crouse said, "then they need to reckon with the past."

YESTERDAY'S LESSONS, TOMORROW'S OUTREACH

Dr. Crouse said that distrust in the medical system doesn't only affect vaccination rates; it likely fuels other well-documented disparities that persist as well. A 2002 report by the National Academy of Medicine — then called the Institute of Medicine — detailed a wide range of examples from published literature. Individuals from historically excluded communities are less likely to receive kidney dialysis or transplants, for example, and less likely to be prescribed appropriate medicines for cardiac problems.

1897 Waldemar Haffkine uses killed organisms to produce an anti-plague vaccine, the prototype of which he tests on himself.

1897 Almwroth Wright and David Sample develop an effective vaccine with killed cells of *Salmonella typhi* to prevent typhoid fever.

1914 Typhoid vaccine is licensed for use in the United States.

1924 Albert Calmette and Camille Guerin introduce a living non-virulent strain of tuberculosis (BCG) to immunize against the disease. This is the result of work begun in 1906 to attenuate a strain of bacterium that causes bovine tuberculosis. More than 200 subcultures are grown before the resulting non-virulent strain is tested.

They're also less likely to receive appropriate cancer care and sophisticated treatments for infection by HIV.

Among the hardest hit are African American/Black men, who have the worst health outcomes among all racial and demographic groups in the U.S. At age 45, the average life expectancy of African American/Black men is five years less than for African American/Black women, and three years less than for white men.[13]

In a study published in February 2018 in the *Quarterly Journal of Economics*, researchers blamed Tuskegee. They estimated that the 1972 disclosure of the experiment accounted for 35% of the life expectancy gap between African American/Black men and white men in 1980.[14]

African American/Black men are more likely than white men to be diagnosed with prostate cancer and twice as likely to die from the disease, according to research published in December 2018 in *JAMA*.[15] However, African American/Black men are underrepresented in clinical trials for new treatments and less likely to trust their physicians. This isn't a new problem: Studies have shown that African American/Black men are more likely than white men to think that their doctors are exposing them to unnecessary risks.

Knowledge of these disparities — and past abuses — have helped shape efforts to recruit participants from historically excluded communities in clinical trials of COVID-19 vaccines, said Krofah. "The FDA has made it clear to product sponsors that underrepresented populations be included in clinical trials, and all of these [vaccine] companies have made very specific efforts to enroll [underrepresented] populations," she said.

RACIAL DISPARITIES AND COVID-19 VACCINES

Vaccine manufacturers have been mostly transparent about the racial makeup of clinical trial populations. In late July 2020, American biotechnology company Moderna, Inc. launched the first phase III clinical trial of a COVID-19 vaccine in the U.S. At the end of August, the company reported that only 18% of the 13,000 enrolled participants were African American/Black, Hispanic/Latinx, Native American or Alaskan Native individuals. By early November, the study had grown, and so had the number of participants from communities of color. Moderna reported that 37% of the 30,000 enrolled participants were from communities that have been historically underrepresented in clinical research.[16] As of November, this ratio is close to the diversity of the U.S. at large, but remains below the rate at which underrepresented populations are being hospitalized and dying from the coronavirus.

Part of the problem in recruiting, Dr. Crouse said, is that trial organizers don't reach out to underrepresented communities. "We know that researchers often do not ask," she said. "They have preconceived notions that [historically excluded populations] won't participate [in] or won't be compliant with the protocol. There's a lot of work to be done on the side of researchers on how to reach out and build partnerships and build trust."

That may seem particularly daunting right now, she said, because issues around COVID-19 have become highly politicized and augmented by growing racial tensions. "Many African American/Black communities have experienced being devalued and marginalized over [the] past few years," she said. "We have to fight an uphill battle for recruitment and trials."

The battle might be uphill, but it's not impossible, she said. In many cities, from Baltimore to Boston to Nashville, Tenn., physicians and leaders from underrepresented communities have publicly joined COVID-19 vaccine clinical trials to build trust and try to reach vulnerable populations. Public health advocates are reaching out to people in churches, barbershops, community centers and clinics.

"There are multiple methods of getting out and talking to people," Dr. Crouse said. "We have to be ready when the person says to you, 'I'm not going to be a guinea pig because of Tuskegee.'"

VACCINE STATUS

As of November 19, the FDA has not approved any vaccines for preventing infection by the SARS-CoV-2 virus. That's not surprising, as vaccines usually take years of development and testing before they become available to the public. In order to be approved, the FDA announced in June that a vaccine would have to protect at least half of the people who receive it.

Since the pandemic began, researchers have investigated more than 200 different possible immunizations. Some use genetic material like DNA or RNA from the virus itself. Vaccines like the one developed by Moderna, Inc., for example, use messenger RNA from the coronavirus to teach the immune system how to recognize the spike proteins on coronavirus particles.

The first phase I clinical trials, which look at safety and dosage, began in March; as of mid-November, 54 clinical trials have been launched to study vaccine candidates. Thirteen of those are phase III trials, which enroll thousands of people to test the efficacy on a large population.

As of November 16, two mRNA vaccine candidates are at the forefront of COVID-19 vaccine development and have announced that they intend to seek Emergency Use Authorization (EUA) from the FDA in the upcoming weeks.

→ *For the latest information about COVID-19 vaccine status, visit* ***asm.org****.*

[1] CDC. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. 2020.

[2] Medicine I of 2002. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care.*

[3] Part I Briefing: COVID-19 Vaccine Deployment – Alliance for Health Policy FasterCures | Milken Institute.

[4] Jaklevic M.C. "Researchers Strive to Recruit Hard-Hit Minorities into COVID-19 Vaccine Trials." *JAMA* 324:826. 2020.

[5] WHO | Improving vaccination demand and addressing hesitancy. WHO. World Health Organization.

[6] Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths in the United States — 2019–2020 Influenza Season | CDC. 2020.

[7] Increase the proportion of people who get the flu vaccine every year — IID-09 - Healthy People 2030 | health.gov.

[8] Table 6. Flu Vaccination Coverage, United States, 2019–20 Influenza Season | FluVaxView | Seasonal Influenza (Flu) | CDC. 2020. https://www.cdc.gov/flu/fluvaxview/coverage-1920estimates.htm.

[9] Jamison A.M., Quinn S.C., and Freimuth V.S. "You don't trust a government vaccine": Narratives of institutional trust and influenza vaccination among African American and white adults. *Social Science & Medicine* 221:87–94. 2019.

[10] Jones J.H. Bad blood: the Tuskegee syphilis experiment. Free Press; Collier Macmillan Publishers, New York; London. 1982.

[11] Tuskegee Study - Timeline - CDC – NCHHSTP. 2020.

[12] "Henrietta Lacks: Science must right a historical wrong." 7823. *Nature* 585:7–7. 2020.

[13] Table 15. Life expectancy at birth, at age 65, and at age 75, by sex, race and Hispanic origin: United States, selected years 1900–2016. 2017.

[14] Alsan M. and Wanamaker M. "Tuskegee and the Health of Black Men." *Q J Econ* 133:407–455. 2018.

[15] Mahal B.A. *et al.* "Racial Disparities in Prostate Cancer — Specific Mortality in Men with Low-Risk Prostate Cancer." *Clinical Genitourinary Cancer* 12:e189–e195. 2014.

[16] COVE Study: Participate to Make a World of Difference | Moderna, Inc. https://www.modernatx.com/cove-study.

**Historically excluded and underrepresented:*

These terms are recommended by the ASM Diversity, Equity and Inclusion (DEI) Task Force. These terms are used interchangeably throughout the document. As defined by the ASM DEI Task Force, both terms describe individuals or groups that have been subjected to bias, discrimination and unequal treatment. Such groups include, but are not limited to women, Blacks/African Americans, Asians, Native Americans, Native Alaskans, Latinx/Hispanic Americans, Native Pacific Islanders, persons with disabilities, lesbian, gay, bisexual, transgender, queer, intersex, and asexual (LGBTQIA) people, and people at all career stages who were first-generation undergraduates.

1925 Gaston Ramon discovers that inflammation at the injection site produces a stronger immune response, leading to the development of "adjuvents" that increase the efficacy of a wide variety of vaccines.

1936 Between 1936 and 1943, Pearl Kendrick carries out several pertussis vaccine trials by inactivating freshly isolated *Bordetella pertussis* with thimerosal and precipitating the vaccine with alum. She and Grace Eldering develop a method to standardize vaccine production and test its potency by conducting an intracerebral challenge of mice.

1938 Field tests of Max Theiler's yellow fever vaccine, based on a mouse-passaged virus, prove successful. The Rockefeller Foundation manufactures more than 28 million doses by 1947. In 1951, Theiler is awarded the Nobel Prize in Medicine or Physiology for this achievement.

1940 Thomas Francis and Jonas Salk developed an inactivated Influenza vaccine with support from the U.S. Army. This vaccine uses virus grown in fertilized chicken eggs. This vaccine only recognized one type of influenza virus, but a bivalent vaccine that recognizes both Type A and Type B influenza is produced in 1942. The inactivated influenza vaccine is licensed in 1945.

Quest for an HIV Vaccine: Some Progress Despite Major Challenges

BY ***DAVID C. HOLZMAN***

"HIV remains one of the defining epidemics of our generation," according to Dr. Dan H. Barouch, M.D., Ph.D., in the ASM podcast "Meet the Microbiologist: HIV Vaccines with Dan Barouch." Currently, more than 36 million people are infected, and nearly 2 million new infections occur annually. "Vaccines are historically the way viral epidemics are definitively ended," said Dr. Barouch, who is a professor of medicine at Harvard Medical School and director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center.

Despite the ample number of researchers developing HIV vaccines, results have been disheartening, with the best protection hovering around 30%. The challenges of developing an HIV vaccine are among the toughest in biomedical research.

One challenge is the lack of a proof of concept. There is no example of a patient's immune response having cleared HIV that investigators could use to model a vaccine.

A second challenge involves the speed with which HIV viruses can integrate themselves into the genomes of cells they infect, and the dormant, or latent, state they assume once so integrated.

Latent viruses may later re-emerge to infect other cells, but they are immune to antiretroviral therapy, and as of yet, no one has figured out how to expunge them.

Viruses become latent within the first few days after exposure to HIV. To prevent latency, a vaccine would have to generate an immune response still faster than that. Existing vaccines do not act that quickly.

A third challenge is the HIV virus's diversity. Replication of HIV is error-prone, and the mutation rate is high, especially in recently infected individuals, where it is 30 times higher than in chronically infected patients, according to an article in ASM's *Journal of Virology*.[1] The virus exists not as a single sequence, but as numerous different sequences both within the individual and throughout the world.

Thus, an HIV vaccine would need to induce an immune response to a diversity of viral sequences. One promising concept to address this diversity is a "mosaic vaccine." Mosaic vaccines combine pieces from a wide variety of HIV viruses to provide maximum coverage of the viruses' global diversity.

more than

2M

new infections occur annually

The data — from both animals and humans — suggests that the resulting immune response can target multiple regions of multiple viruses, using both T-cell and antibody responses.

Data published in July 2018 from a phase 1/2A (safety) study of a mosaic antigen vaccine in nearly 400 individuals in the U.S., East Africa, South Africa and Thailand showed that the vaccine was safe and induced an immune response.[2]

The magnitude, the kinetics, the phenotype, and other properties of immune responses the vaccine raised in humans strongly resembled the immune responses it induced in animal models, which the investigators were able to test — successfully — for protective effect. (So far, there is no human data on whether that immune response will prove protective against HIV in humans.)

A larger study, a phase 2/B safety and efficacy study of this technology, commenced in sub-Saharan Africa late in 2018, with a goal of enrolling 2,600 individuals. Enrollment was completed in May 2019, and the researchers announced the completion of vaccinations at AIDS 2020.[3]

The study is a blinded, randomized and placebo-controlled trial. Subjects were educated on risk-reduction strategies and advised that they should not expect that the vaccine will work until new data show otherwise.

The rationale for the location is that it has the highest HIV prevalence in the world and thus would likely generate the most robust results.

During the podcast, the question arose as to what level of protection by vaccine could be considered a success. Dr. Barouch responded that a vaccine that had conferred a 31% level of protection had "led to many insights that have substantially impacted the research field and allowed [the] development of improved versions...."

As for what level of efficacy would be considered successful, "I think the answer will change over time, and is also dependent on the degree to which the infection is still [at] epidemic levels," said Dr. Barouch. "The degree of protection needed to have a major public health impact in sub-Saharan Africa might be very different from the efficacy needed for a major public health impact in the Western world."

"Vaccines are historically the way viral epidemics are definitively ended...."

[1] Maldarelli F. *et al.* "HIV Populations Are Large and Accumulate High Genetic Diversity in a Nonlinear Fashion." *J. Virol.* Sept. 2013.

[2] Barouch D.H. *et al.* "Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19)." *The Lancet.* July 6, 2018.

[3] Johnson & Johnson and Its Partners Mark a Milestone in the Quest for a Global Preventive HIV Vaccine With the Imbokodo Study (News Release, July 7, 2020).

1976 Hilary Koprowski and colleagues adapt rabies virus to human diploid cell cultures, leading to a new and highly immunogenic rabies vaccine for humans.

1977 Clinical trials supervised by Robert Austrian result in the licensing of a 14-type polysaccharide pneumococcal vaccine.

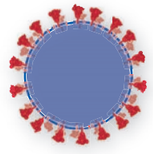
1977 Smallpox is eradicated from the human population, a result of widespread vaccination promoted by the World Health Organization in 1967. During the first year of the program, 44 countries, 31 of which had endemic smallpox, reported 217,218 cases.

1980 An improved rabies vaccine, developed by Maurice Hilleman, Tadeusz Wiktor and Stanley Plotkin in the 1960s, is licensed for use in the U.S.

Vaccine Platforms

BY ***GEOFFREY HUNT, PH.D.***

Ever since Edward Jenner first formalized the vaccination process in the late 18th century, scientists have been experimenting with different approaches for developing effective vaccines. In 2020, existing vaccine technologies utilize a wide variety of related, sometimes overlapping, methods, each of which comes with benefits and costs. Will the vaccines of the future coalesce around a perfected platform?

	WHOLE-PATHOGEN VACCINES		VIRAL VECTORS		SUBUNIT VACCINES				NUCLEIC ACIDS	
										
	ATTENUATED	INACTIVATED	REPLICATING	NON-REPLICATING	PROTEIN SUBUNIT	POLYSACCHARIDE/ CONJUGATE	TOXOID	VIRUS-LIKE PARTICLES	RNA	DNA	
DESCRIPTION	Living pathogen that has been weakened (but not killed) in the laboratory	Whole pathogen killed by heat, chemicals or radiation	A carrier virus that is able to infect human cells (such as an adenovirus) is introduced carrying genetic material that codes for the specific viral antigen in order to elicit the immune response.	A carrier virus (such as an adenovirus) that is able to infect human cells ***but cannot replicate*** is introduced carrying genetic material that codes for the specific viral antigen in order to elicit the immune response.	Purified viral antigens	Surface polysaccharide antigens, primarily from bacterial pathogens	Chemically inactivated toxins from pathogen	Particles that contain virus surface proteins that can elicit an immune response, but lack viral genetic material (so cannot replicate)	mRNA injected directly into muscle tissue and translated into specific pathogen protein antigens by host cellular machinery.	Plasmid containing pathogen DNA that encodes for specific antigens, injected directly into cellular tissue.	DESCRIPTION
EXAMPLES	MMR vaccine	Polio vaccine, Rabies vaccine, Typhoid vaccine	Animal vaccines such as for Rift Valley fever virus, avian influenza	Animal vaccines such as for Rift Valley fever virus, avian influenza	Candidate Zika vaccine	Candidate vaccines for SARS, Bird flu (H5N1, H1N1), Zika	Diphtheria vaccine, Tetanus vaccine	Human papillomavirus vaccine	Candidate Zika vaccine	Candidate vaccines for SARS, Bird flu (H5N1, H1N1), Zika	EXAMPLES
PROS	Elicits strong immune response	Contains actual pathogen so will direct proper immune response	Efficient delivery of genetic material into host cells and tissues	Efficient delivery of genetic material into host cells and tissues	No chance of infection by pathogen	No chance of infection by pathogen	Raise direct immune response to pathogenic component	Easy access into cells	Directs the expression of viral antigens without threat of viral infection or need for integration into host DNA	Directs the expression of viral antigens without threat of viral infection	PROS
CONS	Slight potential for microbe reactivation	May require an adjuvant to stimulate complete immune response	May be suppressed by existing host immune response	May be suppressed by existing host immune response	Requires efficient delivery mechanism that protects against degradation	May require an adjuvant to stimulate complete immune response	May require an adjuvant to stimulate complete immune response	May be suppressed by existing host immune response	Difficult delivery into cells	Difficult delivery into cells	CONS

Can Clinical Trials Be Improved?

BY ***GEOFFREY HUNT, PH.D.***

1 in 10

prospective treatments is approved by the FDA

10 years and $1 billion. That's how long[1] and how expensive[2] the average clinical trial in the U.S. is. Even then, only one in 10 prospective treatments is ultimately approved for use by the Food and Drug Administration (FDA).[3] Under normal circumstances, these conditions are daunting; during an emergency, they are lethal.

Stakeholders have long pushed for improvements to be made to the clinical trial process,[4] hoping for faster results, cheaper cures and broader participation by both patients and clinicians. The COVID-19 pandemic has brought a renewed urgency to these calls, forcing a reevaluation of what changes could (and should) be made, not just for the current crisis but also for future trials.

HOW CLINICAL TRIALS WORK

In the U.S., the development of disease treatments such as drugs and vaccines occurs through a rigid, stepwise clinical trial process that is overseen by the FDA (see image). This rigorous approach has methodically evolved over the past several decades, adapting to advances in medicine, technology and societal perspectives.[5]

PHASES OF A CLINICAL TRIAL

PRECLINICAL

LABORATORY STUDIES

DURATION: SEVERAL YEARS

- Provide Information on dosing and toxicity levels

PHASE 1

SAFETY

DURATION: SEVERAL MONTHS

- Evaluate safety
- Gather information about how a drug interacts with the human body

PHASE 2

SAFETY & DOSING

DURATION: SEVERAL MONTHS

- Future evaluate safety
- Monitor side effects
- Check which dose works best
- Check effectiveness

PHASE 3

SAFETY & EFFICACY

DURATION: SEVERAL YEARS

- Confirm effectiveness
- Monitor Safety

FDA APPROVAL

PHASE 4

POST MARKETING SAFETY & EFFICACY

DURATION: SEVERAL YEARS

- Gather information on the drug's effects in various populations and any side effects associated with long-term use

figure 1: Steps of the clinical trial process (Adapated from Dr. Stacey Schultz-Cherry)

1945 Colin MacLeod, Richard Hodges, Michael Heidelberger and William Bernard show that an isolated capsular polysaccharide can immunize against *Nesseria meningtitis*. The vaccine is finally approved in 1977 after extensive international testing.

1954 Jonas Salk begins preliminary testing of a polio vaccine. The vaccine is composed of three types of killed virus.

1960 The oral polio vaccine developed by Albert Sabin is approved for use in the U.S. after trials are conducted abroad on more than 100 million people.

1960 John Enders and colleagues develop a live attenuated vaccine against measles virus, and the vaccine is licensed in the U.S. in 1963. Prior to this vaccine, nearly all children got measles by the time they were 15 years old, with approximately 3-4 million people infected each year in the U.S.

In 2011, the Institute of Medicine (IOM; now the National Academy of Medicine) convened a collection of stakeholders to identify and address deficiencies in the U.S.'s clinical trial enterprise. The resulting workshop report enumerated several major recommendations that the authors envisioned as being implemented by 2020.[4]

WHERE ARE WE NOW?

Looking back nine years later, "from where we were, we've made progress," asserts workshop chair Dr. Jeffrey Drazen, M.D., editor-in-chief of the *New England Journal of Medicine*. He points to better utilization of technology, enhanced methods of patient data collection, and more flexible use of nontraditional approaches such as so-called basket and umbrella clinical trials as major areas of improvement. "But," Dr. Drazen cautions, "progress occurs slowly."

Indeed, several issues identified in the IOM report remain unresolved. The most troubling for Dr. Drazen is the continued difficulty of enrolling patients in trials, particularly individuals from underserved communities. Stacey Schultz-Cherry, Ph.D., co-director of St. Jude Hospital's Center of Excellence for Influenza Research and Surveillance, agrees. "We can do a better job with enrollment," she says. To do so means "building trust with communities, so that when trials happen you have a population of people who trust what you're doing and why you're doing it."

"We can do a better job with enrollment. To do so means building trust with communities, so that when trials happen you have a population of people who trust what you're doing and why you're doing it."

Lack of trust has manifested itself in other ways, especially with respect to risk perception about clinical trials. Americans, by nature, "are risk averse," points out Dr. Schultz-Cherry. Instead of effectively communicating to patients the risks and benefits of proposed clinical trial approaches in order to come to a common understanding, clinicians and researchers have often fallen back upon low-risk approaches that have better odds of working but tend to have lower impact. "We really haven't come up with easy ways to get around that yet," acknowledges Dr. Drazen.

Beyond the need for improved communication between patients and clinical trial operators, experts have also urged better coordination between laboratory researchers and clinicians. As an example, the IOM report noted that "the majority of clinical guidelines for cardiovascular care are based merely on expert opinion or low-quality data."[4] This depressingly common disconnect between the lab and the clinic bogs down the entire process by increasing clinical trial length and costs, while also introducing confusion over terminology and interpretation of results.

Shoddy coordination also tends to result in individual trials being started from scratch, instead of building upon prior knowledge and utilizing existing platform technologies.[6] Eliminating these redundancies would make trials faster and cheaper by reducing the resources needed for the scientific and clinical research components, as well as lessening the burdensome regulatory process by relying on pre-approved methods. "Lower cost," declares Dr. Schultz-Cherry, "doesn't have to mean slower."

A BETTER TOMORROW

There are reasons to be optimistic about the progress being made with how clinical trials operate. Dr. Drazen sees the current pandemic as instilling a new sense of urgency within the broader public for the need to fight infectious diseases, which he feels could lead to more robust participation in trials. For Dr. Schultz-Cherry, examples such as the National Institute of Allergy and Infectious Disease's Collaborative Influenza Vaccine Innovation Centers, which are working together to develop a more robust influenza vaccine,[7] showcase how clinical trials could ideally be run from start to finish.

Ultimately, improving the clinical trial process will take a holistic response in which scientists, health professionals, regulators, legislators and the public at large all work together in a coordinated, symbiotic way. "It's a fuzzy problem," admits Dr. Drazen.

ASM members (and others within the scientific community) have particularly important roles to play. Obviously, continuing to deliver top-notch laboratory and clinical research is the primary mechanism. But there are also crucial opportunities beyond the bench, whether it's communicating and engaging with public audiences, serving as advocates for science with local and federal legislators to promote policies that support the research and clinical enterprises, or by acting as sources of knowledge and information within local communities *(see tear-out)*. "Don't be afraid to engage," Dr. Schultz-Cherry encourages her fellow scientists. "It's our responsibility [to do so]." It could also save lives.

"Don't be afraid to engage. It's our responsibility to do so. It could also save lives."

[1] Van Norman G.A. "Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs." JACC: *Basic to Translational Science*, 1(3): p. 170-179. 2016.

[2] Wouters O.J., McKee M. and Luyten J. "Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018." *JAMA*, 323(9): p. 844-853. 2020.

[3] Huss R. "The High Price of Failed Clinical Trials: Time to Rethink the Model." *Clinical Leader*. 2016.

[4] Medicine, I.o., Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020: Workshop Summary, eds. Weisfeld N., English R.A. and Claiborne A.B. Washington, DC: The National Academies Press. 248. 2012.

[5] Junod S.W. "FDA and Clinical Drug Trials: A Short History," in *A Quick Guide to Clinical Trials*, eds. Davies M. and Kerimani F. Food and Drug Administration. p. 25-55. 2008,

[6] Adalja A.A. *et al., Vaccine Platforms: State of the Field and Looming Challenges*. 2019.

[7] NIAID. Collaborative Influenza Vaccine Innovation Centers (CIVICs). 2020. https://www.niaidcivics.org/.

1963 Baruch Blumberg describes the "Australia Antigen" (hepatitis B antigen) that is found in the blood of viral hepatitis sufferers. Together with Irving Millman, Blumberg develops a vaccine against the virus. Some consider it to be the first vaccine against cancer because of the strong association of hepatitis B with liver cancer. Blumberg, together with Daniel Carelton Gadjusek, is awarded the Nobel Prize in Medicine or Physiology in 1976.

1965 Harry Meyer, Paul Parkman and colleagues at the National Institutes of Health develop a vaccine for rubella (German measles). Another rubella vaccine developed by Stanley Plotkin at the Wistar Institute is released in 1969. In 2005 the Centers for Disease Control and Prevention declares the disease eradicated in the United States.

1967 Maurice Hilleman develops a vaccine for mumps, based on material taken from throat swabs from his daughter Jeryl Lynn. Current vaccines are still made from the Jeryl Lynn strain of the mumps virus.

1971 Maurice Hilleman develops a single vaccine that combines existing vaccines against measles, mumps and rubella. The vaccine is commonly known as MMR.

ASM's Accomplishments During the COVID-19 Pandemic

BY ***VICTOR DIRITA, PH.D., ASM PRESIDENT***

While 2020 has been a difficult year for all of us, the ASM commitment to our mission of advancing microbial sciences has never been stronger and our work never more urgent and visible. In the face of disruption caused by the COVID-19 pandemic, ASM turned obstacles into opportunities to do more and seek new and innovative ways to respond to the biggest challenges of our time.

On behalf of ASM leadership, thank you for your support during this unprecedented year. Your membership commitment enabled ASM to provide much-needed support to scientists around the world. With your help, we advocated, educated, and created new ways to bring our community together.

Here are just some of the highlights of what we accomplished together in 2020:

KEEPING YOU AND THE PUBLIC INFORMED ABOUT COVID-19

In January, ASM launched a comprehensive COVID-19 resource page, providing evidence-based, up-to-date information about SARS-COV-2. In late March, the ASM Council on Microbial Sciences convened nearly 100 experts from around the world to discuss questions surrounding diagnostics, vaccines and treatments for SARS-CoV-2. Just a few days following the summit, ASM leaders published a paper in mBio summarizing diagnostics for COVID-19.

Building on recommendations from the Summit, we launched the ASM COVID-19 Research Registry, with the goal of bringing researchers top-ranked, expert-curated COVID-19 research articles. We also host in-depth monthly, virtual journal clubs to give you an opportunity to participate in expert-led discussions of recent articles published in the COVID-19 Research Registry. The Registry continues to grow, with new articles added as soon as they are available, and it has become an invaluable and trusted resource for the global scientific community.

STANDING UP FOR SCIENCE WHEN IT MATTERED MOST

ASM worked closely with policymakers, the Food and Drug Administration, the White House Coronavirus Task Force and the Centers for Disease Control and Prevention to advocate for science-based approaches to address the COVID-19 pandemic. We educated and advocated to increase access to testing and PPE, increase transparency around allocation and availability of COVID-19 lab testing supplies, and provide equitable access to future COVID-19 vaccines. We also urged appropriate oversight and enforcement of diagnostic and antibody tests that come to market. Additionally, ASM members had an opportunity to meet directly with congressional lawmakers and provide expert testimonies on the need for scientific funding and research during the ASM Hill Day.

ENSURING THAT CONCERNS OF CLINICAL MICROBIOLOGISTS ARE HEARD

Clinical microbiologists have been on the front lines during the pandemic, and we made it our priority to identify the roadblocks impeding their work with testing. In May, ASM hosted a Serology Testing Webinar for COVID-19 that was attended by nearly 800 experts from around the world, making it abundantly clear that the demand for knowledge about this topic was high. We provided an in-depth look at the principles of serology testing: protocols, platforms, authorization guidelines, interpretation of results, accuracy concerns, and overcoming roadblocks to success.

ASM also worked with IDSA to develop guidelines for RNA testing for SARS-CoV-2, followed by a second set of guidelines on serologic testing. Most recently, we developed a data-collection tool to identify the status of supplies for COVID-19 tests, as well as other microbiological tests, in order to highlight and help alleviate the debilitating supply-chain issues the U.S. has been facing.

MAKING HIGH-IMPACT, PEER-REVIEWED RESEARCH AVAILABLE—FAST

In 2020, ASM journals received a record number of submissions. Toward the goal of sharing rapidly evolving science with the community, we expedited the review and publishing process. Additionally, we opened access to hundreds of COVID-19 related articles published in ASM journals. This special collection continues to include new articles, making it possible for researchers around the world to freely and quickly access the latest in COVID-19 research.

We will continue to build on these achievements to advance your science, your network, your career and your community in 2021. But we need your support. Please renew your 2021 ASM membership to continue receiving your benefits, and to support the microbial sciences and your community. Please visit asm.org/membership.

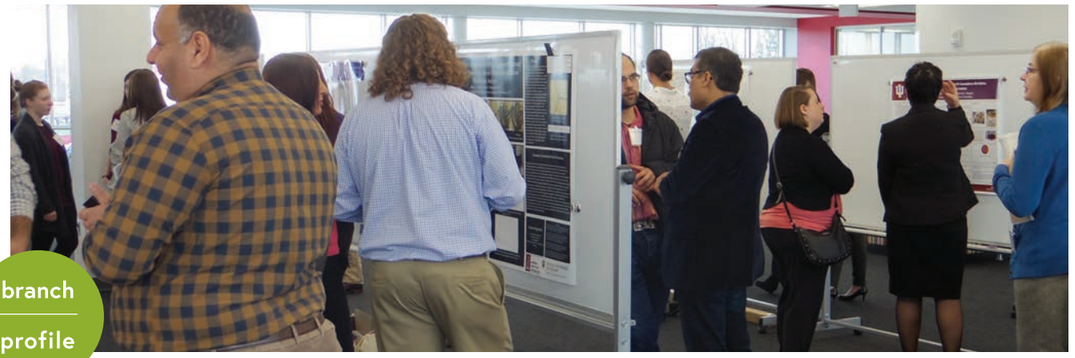
2005 *Meningococcal conjugate* vaccine (MenACWY-D; Menactra) is approved by the FDA and becomes available for public use to treat bacterial meningitis.

2005 The CDC's Advisory Committee on Immunization Practices recommends that adults from 19 to 64 years of age be vaccinated with a newly licensed adult booster tetanus, diphtheria and pertussis (whooping cough) vaccine (Tdap).

2006 The FDA approves the first preventive HPV vaccine, marketed by Merck & Co. under the trade name Gardasil, recommended as a prevention for cervical cancer in women 25 years old or younger.

2009 Gardasil is approved by the FDA for use in males aged 9 to 26 for prevention of genital warts and anal cancer.

Indiana Branch



branch profile

The Indiana Branch of the ASM (IBASM) was founded in 1935 by W.A. Jamieson (president) from the Biological Research Laboratories at Eli Lily & Co., L. Wade (vice president), M.S.A. Campbell (secretary/treasurer) and H.M. Powell (councilor). IBASM has a rich history, as does Indiana microbiology in general. Notable Indiana microbiologists include former ASM presidents S.E. Luria in 1967-68 and W.A. Wood in 1980-81. Several more Indiana microbiologists have been awarded membership in the prestigious National Academy of Sciences, including I.C. Gunsalus, S.E. Luria, N.R. Pace, J.R. Preer, F.W. Putnam, R.Y. Stanier, E.H. Umbarger and J.D. Watson. Other well-respected Indiana microbiologists include T.D. Brock, H. Gest, A.L. Koch, E.D. Weinberg and L.Y. Mazzini.

The IBASM currently has 70 members, including a large number of undergraduate, master's and doctoral students. Each spring, the Branch hosts an annual meeting with support from ASM and typically draws participants from 13 universities across Indiana and eastern Illinois, industry and state health labs, and municipal water quality labs. Locations for the annual meeting vary from year to year and include universities, hotels and state parks in different parts of the state. This meeting provides members with the opportunity to connect and honor colleagues through teaching and research awards, as well as to engage and reward students presenting their research. Meetings generally include a presentation by an ASM Distinguished Lecturer, student presentations, a poster session and invited speakers. To educate its large student population on career opportunities outside of academia, IBASM invites representatives from industry and state health labs to participate in its meetings.

IBASM will partner with 15 other Indiana academies to hold a virtual meeting, "Beyond Borders," April 9-10, 2021. The meeting will feature high-caliber, nationally renowned invited speakers, scientific sessions including a Branch-sponsored session on "Diet, Health and the Human Microbiome," poster sessions, student talks, cross-disciplinary discussions and opportunities for interactions between societies.

→ *For more information about the Indiana Branch of ASM, please visit* ***https://indianaibasm.weebly.com/****.*

2011 An advisory panel for the CDC recommends the HPV vaccine for boys ages 11–12 to prevent genital warts and anal cancers in males, and possibly prevent head and neck cancer. The CDC also recommends vaccination for males 13-21 who have not been vaccinated previously or who have not completed the three-dose series. For those under the age of 27 who have not been fully vaccinated, the CDC recommends vaccination.

2017 NIAID and partners begin a phase 2 proof-of-concept study, known as HVTN 705/HPX2008 or Imbokodo, to test the safety and efficacy of a "mosaic" antigen vaccine against a variety of HIV strains.

AMBASSADOR PROFILE

VISHAL CHHETRI, ***ASM'S YOUNG AMBASSADOR FOR BHUTAN***

Vishal Chhetri is the senior laboratory officer of the Food and Nutrition Laboratory at the Royal Center for Disease Control Department of Public Health, MoH in the Royal Government of Bhutan. He has been an ASM member since 2015 and was appointed as the ASM Young Ambassador for Bhutan in February 2019.

Describe your experience working on the front lines in Bhutan during the COVID-19 pandemic.

Being on the front lines in the battle against this pandemic is very rewarding, though the risk of contracting the virus is always a concern. Bhutan recorded its first COVID-19 case on March 6, 2020, and had a total of 298 confirmed COVID-19 cases as of May 10, 2020. I have been actively engaged in sample collection for PCR tests and antibody testing. Moreover, being the team lead gives me additional responsibility to assess the proper use of PPE by my colleagues.

Tell us more about your research in parasitology, microbiology and transfusion medicine.

My love for conducting scientific research has been my core interest. As a field worker in the southern belt of Bhutan, where the cases of hemo-parasite (malaria) were a major concern, I had the opportunity to work with the Vector Borne Disease Control Program and conducted a few studies on malaria that were published in *Malaria Journal* and in the *International Journal of Innovative Research in Medical Science*.

As a laboratory manager, I managed a blood bank. I had the opportunity to conduct data research at the Gelephu Centre Regional Referral Hospital (CRRH) on the frequency distribution of abo and rh blood groups among blood donors.

My passion for microbiology pushed me to obtain my Masters of Science in food microbiology. In my graduate research, we investigated and isolated halophilic bacteria in salt-fermented foods with active inhibitory effect against *Staphylococcus aureus*.

Why did you become an ASM YA, and what has been your most rewarding experience thus far?

ASM connects microbiologists across the globe in a single platform. Bhutan has a handful of microbiologists, thus I joined ASM to gain more scientific knowledge and share experiences. I have been very fortunate to be selected as the YA for Bhutan for this prestigious forum, and my most rewarding experience so far has been presenting at the Bhutan ASM forum.

What are your plans and future goals as an ASM YA?

As an ASM YA, I hope to introduce and present about ASM to universities in Bhutan. Although I have not been able to promote ASM actively, I have had the opportunity to discuss ASM's goals and mission to my colleagues and students who attend my laboratory. Moreover, I plan to continue encouraging microbiology research and publishing it through ASM. I think we can strengthen ASM globally by providing publication fee waivers for ASM members in developing countries.

2018 AAP Committee on Infectious Diseases (COID) recommends annual influenza vaccination for everyone six months and older. Inactivated influenza vaccine (IIV3/4) is the primary choice for all children because the intranasal live attenuated influenza vaccine is less effective, although the intranasal vaccine may be offered for children who would not otherwise receive an influenza vaccine.

2018 The FDA approves a new hexavalent vaccine, DTaP5-HB-IPV- Hib (Vaxelis, Merck), for primary and booster vaccination in infants and toddlers against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive disease caused by *Haemophilus influenzae* type b.

ASM Members Speak Up for Science During Hill Day

Illustrated by ASM Member, Callie Rodgers Chappell

On Sept. 10, 2020, ASM hosted a Capitol Hill Day with over 30 early-career scientists and members of the Public and Scientific Affairs Committee (PSAC). Without setting foot in Washington, D.C., participants met with members of Congress and their staff through online platforms. Together, they completed 55 meetings representing 20 states and 29 congressional districts. Their connection may have been virtual, but the impact was real. ASM member advocates stressed the importance of adequately funding the sciences and gave first-hand accounts of how COVID-19 has affected their labs and research. Their stories provide a deeper reason for legislators to support the RISE Act, a bill designed to compensate for the damage done to scientific progress this year.

"As microbiologists, we have an obligation to work with policymakers so they understand the impact of their decisions on the work that we do. I'm so inspired by the scientists who participated in Hill Day and encourage everyone — regardless of career stage — to play a role in ASM's advocacy efforts," said Dr. Stacey Schultz-Cherry, PSAC chair. During Hill Day, ASM advocates established the foundation of a relationship of trust and open communication that will allow them to work with their legislators to make better scientific policies.

Representative Diana DeGette (D-Colo.) was one of five members of Congress to address the group, driving home the importance of scientists playing a role in advocacy. "I think all of our public policy needs to be based on science," she said. "The people who are the very best to explain that to their elected officials are scientists. You're coming from a position of knowledge and science, and that's so important." However, advocacy is not a one-time commitment, and ASM is consistently offering new ways to get involved.

→ *If you're interested in being part of ASM's advocacy activities, visit* ***asm.org/advocacy***.

Agar Art Contest Update for 2020

Agar Art is one of our favorite activities here at the ASM. Using only microbes grown on agar, contest participants have created an amazing variety of artworks.

This year, we changed things up a bit by allowing participants to use any type of artwork (like a painting or a video) to create their submission. The only requirement was that the work promote the theme, "Microbes are Beautiful."

Ultimately, we received 189 total submissions from 29 countries around the world. As expected, the submissions we got were stunning in their creativity and technique.

"A Tribute to Chadwick Boseman" by Parasmita Das Choudhury, Dina Raja and Lakshyasri Baishya from Gauhati Medical College and Hospital in Guwahati, India

To see this year's winners, visit www.asm.org/agarart.

ASM Sponsors Black in Microbiology Week

Black in Microbiology, a "Vibrant Celebration of Black Microbiologists," was held from Sept. 28-Oct. 4, 2020. As a Gold Member Sponsor, ASM supported Black in Microbiology through content creation and collaboration, connections to speakers and communicators, social media amplification, sponsorship for annual programming, branding and leadership. Featuring eminent Black microbiologists, virologists, parasitologists, mycologists, microbiome researchers, women and early-career microbial scientists, Black in Microbiology seeks to showcase, celebrate and amplify the contributions of Black microbial scientists.

Led by early-career scientists, the virtual platform connected talented scientists, facilitated dialogue, and supported collective work to address disparities and racism in academia, business and government.

→ *For more information, visit* ***asm.org/articles/ASM-sponsors-black-in-microbiology***.

2019 Dengvaxia becomes the first dengue vaccine approved by the FDA for children aged 9-16 years who live in endemic areas and have a history of prior dengue infection. This vaccine is shown to effectively prevent all 4 serotypes.

2019 Ervebo becomes the first FDA-approved vaccine for the prevention of Ebola virus disease (EVD) caused by Zaire ebolavirus in individuals 18 years of age and older. This virus is a recombinant vesicular stomatitis virus that expresses a glycoprotein from the Ebola virus and produces a neutralizing immune response to Ebola.

2020 Nigeria is removed from the list of countries with endemic wild poliovirus, leaving only two countries, Afghanistan and Pakistan, with WPV1. However, eradication efforts must continue because, in addition to these wild cases, outbreaks of vaccine-derived poliovirus persist in West Africa and Ethiopia.

2020 Preclinical and clinical trials of SARS-CoV-2 vaccine candidates begin. The U.S. government develops Operation Warp Speed, a public/private partnership to facilitate and accelerate the development, manufacturing and distribution of COVID-19 vaccines, therapeutics and diagnostics. As of Oct. 2020, approximately 320 vaccine candidates are being evaluated worldwide.

What's Hot
in the microbial sciences

BY ***STANLEY MALOY, PH.D. & ASHLEY HAGEN, M.S.***

1

COVID-19

Since the novel coronavirus emerged in late 2019, a major question has been whether people infected with SARS-CoV-2 acquire long-term immunity to this virus. An outbreak of COVID-19 in a group of 122 people aboard a fishing vessel provided a unique opportunity to answer this question because pre-departure screening, RT-PCR and serology data were available for a majority of the crewmembers both before and after the outbreak. Initially, no crewmembers tested positive for SARS-CoV-2 by RT-PCR, but six tested positive for SARS-CoV-2 antibodies. In the weeks following the outbreak, 101 crewmembers tested positive for SARS-CoV-2 via RT-PCR or seroconversion during the follow-up period, and 21 crewmembers tested negative. Of the six crewmembers who initially tested seropositive, three had neutralizing activity against SARS-CoV-2 spike particles. None of the crew members who had neutralizing antibodies prior to departure were infected in the subsequent outbreak. The overall rate of infection among individuals with neutralizing antibodies was zero of three, while the rate of infection among individuals without neutralizing antibodies was 103 of 117. These results, published in the *Journal of Clinical Microbiology*, provided the first direct evidence that anti-SARS-CoV-2 neutralizing antibodies are protective against SARS-CoV-2 infection in humans and have important implications for vaccine development.

A review published in *Future Virology* indicates that the viral load in nasopharyngeal swabs from asymptomatic carriers is sufficiently high for effective transmission. Until widespread SARS-CoV-2 testing is available, asymptomatic carriers provide an insidious source for the spread of COVID-19. Determining what proportion of people who had an asymptomatic infection develop an effective, long-lasting immune response will have important public health implications.

ANTIBIOTIC RESISTANCE AND TARGETING

Antimicrobial resistance (AMR) is the source of an estimated 2.8 million infections and over 35,000 deaths in the U.S. each year and remains one of the most pressing public health concerns of our time. Most antibiotics are derived from naturally occurring products and are therefore susceptible to coevolution of microbial resistance. A study published in *Nature* described a synthetic approach to combating AMR. Using recent advances in chemistry, *in vitro* analysis and high-resolution cryo-electron microscopy, scientists created seven molecular building blocks and pieced them together like LEGOs to design novel analogues of streptogramin antibiotics that were optimized to overcome *Virginiamycin acetyltransferase* resistance. These results suggest that the redesign of available antibiotics to overcome specific bacterial-resistance mechanisms may moderate the need to continually develop new classes of antibiotics as resistance to existing antibiotics evolves and new vaccines are developed.

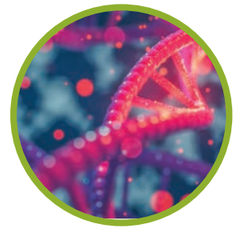
2

Another problem with many current antibiotics is that they disrupt the microbiome, often resulting in dysbiosis, which is a growing health concern. Disruptions in commensal bacteria may allow opportunistic pathogens such as *Clostridoides difficile* and *Candida aurius* to colonize and cause secondary infection. An *mSystems* study used mass spectrometry informatics and three-dimensional whole-organism data-visualization to analyze the acute and delayed effects of a single dose of vancomycin or ampicillin on the metabolome and microbiome of mice. Data showed that a single antibiotic dosage altered host chemistry in a variety of organs, with the most significant impact occurring the day after the antibiotic was administered. The microbiome throughout the gut was impacted in a non-uniform manner. For example, ampicillin had the greatest effect on the microbiota of the lower gastrointestinal tract. Understanding how antibiotics spatiotemporally impact the gut microbiota and influence the host's body chemistry may help guide the design of new antimicrobials and influence health care practices.

3

CRISPR

With applications ranging from cancer to sickle cell anemia to improving crops, Emmanuelle Charpentier's and Jennifer Doudna's work on the unusual "clustered regularly interspaced short palindromic repeats" in bacteria (CRISPR) was recently recognized with a 2020 Nobel Prize. An example of a novel application of CRISPR technology to address current and future pandemics is described in a recent paper in *Cell*. Selle *et al.* used a CRISPR-Cas-13-based strategy known as PAC-MAN (prophylactic antiviral CRISPR in human cells) to target and degrade SARS-CoV-2 RNA and influenza A virus in human epithelial cells. By defining highly conserved regions of the SARS-CoV-2 genome, a group of cRNAs were identified that can target all sequenced coronaviruses. The CRISPR-Cas13d system targeted and degraded SARS-CoV-2 RNA *in vitro*, and was also successful against live influenza A virus. However, several technical limitations must be overcome



ARTICLE 1 Addetia A. *et al.* "Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with high attack rate." *Journal of Clinical Microbiology*. Aug. 21, 2020. https://jcm.asm.org/content/early/2020/08/21/JCM.02107-20.

Tan J. *et al.* "Transmission and clinical characteristics of asymptomatic patients with SARS-CoV-2 infection." *Future Virology*. June 12, 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7291769/.

ARTICLE 2 Li Q. *et al.* "Synthetic group A streptogramin antibiotics that overcome Vat resistance." *Nature*. Sept. 23, 2020. https://www.nature.com/articles/s41586-020-2761-3.

ARTICLE 2 Vrbanac A. *et al.* "Evaluating Organism-Wide Changes in the Metabolome and Microbiome following a Single Dose of Antibiotic." *mSystems*. Oct. 6, 2020. https://msystems.asm.org/content/msys/5/5/e00340-20.full.pdf.

ARTICLE 3 Selle K. *et al.* "*In Vivo* Targeting of *Clostridioides difficile* Using Phage-Delivered CRISPR-Cas3 Antimicrobials." *mBio*. March 10, 2020. https://mbio.asm.org/content/11/2/e00019-20.

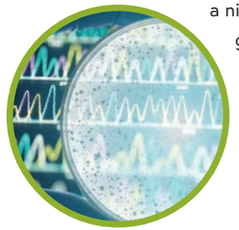
Abbott T.R. *et al.* "Development of CRISPR as an Antiviral Strategy to Combat SARS-CoV-2 and Influenza." *Cell*. May 14, 2020. https://www.cell.com/cell/pdf/S0092-8674(20)30483-9.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420304839%3Fshowall%3Dtrue.

before this tool can be used in a clinical setting, and an *in vivo* delivery method that effectively introduces CRISPR-Cas13d to human respiratory tract cells is not yet available.

CRISPR is also being used to design targeted antimicrobials. Self-targeting CRISPR-Cas systems can redirect endogenous activity against bacterial chromosomes and may offer a viable strategy for the treatment of recalcitrant and multidrug-resistant pathogens. An *mBio* study demonstrated that a CRISPR-Cas system could be repurposed as an antimicrobial specific for *Clostridioides difficile*. Efficient targeting and killing of *C. difficile* was observed in both *in vitro* and *in vivo* experiments. The potency was further enhanced by engineering the phage delivery system to reduce lysogeny and promote lysis. This targeted antimicrobial approach may overcome problems associated with the disruption of the microbiome. A wide variety of other applications for CRISPR are under investigation.

4 TANDEM REPEATS ARE COMMON IN BACTERIAL GENOMES — BUT WHY?

In addition to CRISPR, there are many other types of repeated DNA sequences that play a variety of roles in bacteria, including serving as genetic hot spots for genome rearrangements. Nevertheless, unlike CRISPR, where we understand a tremendous amount about the biological role of the repeated sequences, we know very little about many of the tandemly repeated genomic sequences. The most comprehensive characterization of bacterial satellites to date has identified over 121,000 of these repeated sequences from 12,233 fully sequenced and assembled bacterial genomes. The study, published in the *Journal of Bacteriology,* revealed that 85 genomes had very large numbers of repeats with similar sizes despite a lack of sequence conservation. Understanding the roles of bacterial satellites may provide insights into the organization and folding of bacterial genomes or lead to new genome-editing applications — an enticing genetic playground!



5 ANTICIPATING THE NEXT PANDEMIC: ZOONOTIC DISEASES AND ONE HEALTH

Zoonoses are often the cause of outbreaks and pandemics in humans, as emphasized by the emergence of SARS-CoV-2, a novel coronavirus with bat origins. The CDC estimates that three of every four emerging infectious diseases in humans came from a zoonotic source. This is due, in part, to human interventions that facilitate zoonotic disease transmission.
A study published in *Nature* analyzed more than 6,800 ecological assemblages and 376 host species worldwide and determined that land use changes, such as the conversion of natural habitats to urban or agricultural ecosystems, have global and systemic effects on local wildlife populations. Human-managed habitats (in comparison to nearby undisturbed ones) were more heavily populated by ecological generalists, animals that are small, abundant and resourceful *(e.g.*, rodents, bats and raccoons), and less heavily populated by ecological specialists, which are animals that depend on a niche environment or diet to survive. Ecological generalists are much more likely to transmit diseases to humans, suggesting that land development promotes hazardous interfaces among people, livestock and wildlife reservoirs, thereby increasing the risk of zoonotic disease transmission.

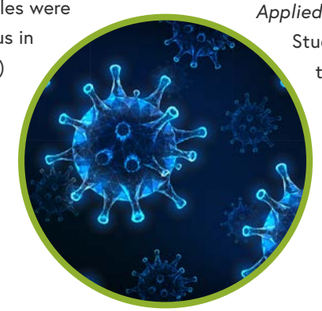
Livestock (*e.g.*, pigs, cows, sheep and chickens) may also serve as significant sources of zoonotic disease. A recent *Journal of Virology* article used

extensive surveillance and genetic sequence analysis to understand the transmission dynamics of the influenza A virus (IAV) in swine exhibited at agricultural events. By characterizing the hemagglutinin and full genotypic diversity of IAV early in the season, and monitoring its dissemination at subsequent agricultural fairs, it was possible to identify a time point that was critical to transmission of H1δ-2, the virus associated with the majority of zoonotic infections during the 2018 season.

"One Health" emphasizes the relationship between environmental, animal and human health. These examples demonstrate the role of environmental disruption and agricultural practices in the transmission of infectious diseases. Understanding the ecological pressures and dynamics that drive transmission can inform targeted mitigation strategies to prevent spillover of zoonotic disease.

6 THE MICROBIOME AND TRANSMISSION OF VIRUSES

An *mSystems* study indicates that the respiratory tract microbiome plays an important role in the airborne transmission of Influenza A virus (IAV). Direct interactions between IAV and bacteria with capsules were shown to increase stability of the virus in the environment (desiccation survival) and increase its transmission. While antibiotic treatment, which reduced respiratory flora, was shown to reduce the transmission of IAV, coinfection with *Streptococcus pneumoniae* in antibiotic-treated ferrets restored IAV infectivity. These data expanded scientific understanding of how bacteria influence viral transmission and pathogenesis, and may provide useful clues as to how disease transmission of IAV and other airborne respiratory viruses can be reduced by modulating the respiratory tract microbiome.



7 OXYGEN LIMITATION, METABOLISM AND SURVIVAL

Microorganisms are persistent and resourceful. A paper in *Nature Communications* provided evidence that aerobic microbial life persists in toxic marine sediment deposited over 100 million years ago. Aerobic microbes obtained from the sediment were able to readily incorporate carbon and nitrate substrates and reproduce in the laboratory. Within 68 days of incubation, total cell numbers had increased by four orders of magnitude. These observations suggested that there was sufficient oxygen to support the low-level metabolism required for survival in an environment that was previously thought to be inhospitable, providing some of the first direct evidence that microbes can survive in energy-poor buried communities, and raising questions about the possibility of microbial survival in other "inhospitable" places.

An interesting trick some bacteria use for survival was described in a paper from *Applied and Environmental Microbiology*. Studies on *Vibrio natriegens* (which has the fastest known bacterial doubling time) elucidated an extracellular electron transport (EET) system that enhances its anaerobic survival. The EET pathway is a hybrid of pathways used by other bacteria, such as *Shewanella* and *Aeromonas*, and may be common to other *Vibrio* species as well.

ARTICLE 4 Subirana J.A. *et al.* "Unique Features of Tandem Repeats in Bacteria." *Journal of Bacteriology.* Aug. 24, 2020. https://jb.asm.org/content/202/21/e00229-20.abstract.

ARTICLE 5 Gibb R. *et al.* "Zoonotic host diversity increases in human-dominated ecosystems." *Nature.* Aug. 5, 2020. https://www.nature.com/articles/s41586-020-2562-8.

Nelson M.I. *et al.* "A heterogenous swine show circuit drives zoonotic transmission of influenza A viruses in the United States." *Journal of Virology.* Sept. 24, 2020. https://jvi.asm.org/content/early/2020/09/24/JVI.01453-20. DOI: 10.1128/JVI.01453-20.

ARTICLE 6 Rowe H.M. *et al.* "Respiratory Bacteria Stabilize and Promote Airborne Transmission of Influenza A Virus." *mSystems.* Aug-Sept 2020. https://msystems.asm.org/content/5/5/e00762-20.

ARTICLE 7 Morono Y. *et al.* "Aerobic microbial life persists in oxic marine sediment as old as 101.5 million years." *Nature Communications.* July 28, 2020. https://www.nature.com/articles/s41467-020-17330-1. DOI: 10.1038/s41467-020-17330-1.

Conley B. *et al.* "A Hybrid Extracellular Electron Transfer Pathway Enhances the Survival of *Vibrio natriegens*." *Applied and Environmental Microbiology.* July 28, 2020. https://aem.asm.org/content/86/19/e01253-20. DOI: 10.1128/AEM.01253-20.

ASM Media Highlights for 2020

Since SARS-CoV-2 was first identified, ASM has worked on multiple fronts to share factual, timely information on the novel coronavirus and advocate for expedited and widespread SARS-CoV-2 testing. Here are the most listened-to podcasts and top news stories on the pandemic and other topics.

THE BEST OF ASM NEWS

Forbes: Researchers Just Found that Antibody Levels Decline Soon After Coronavirus Symptoms End

This week in *mBio*, a team of researchers report that SARS-CoV-2 antibody levels in the blood of COVID-19 patients plummet quickly after symptoms disappear.

U.S. News & World Report: Study Sheds Light on Why COVID-19 Hits Elderly Hardest

An age-related difference in immune response may partially explain why older COVID-19 patients have more severe illness, according to a study published in the journal *mBio*.

Bloomberg News: U.S. Medical Supply Shortage Plaguing More than Just Tests for COVID-19

Shortages of key supplies for COVID-19 testing are also limiting testing for other illnesses. What's running low can change as often as daily, adding to the strain of managing supplies, said Robin Patel, past president of ASM.

CNN: Could an Everyday Childhood Vaccine Help Against Coronavirus?

In a letter published in the journal *mBio*, researchers say the everyday vaccine for MMR could help prevent the worst effects of coronavirus infection.

The New York Times: Opinion: We Need a New Kind of National Guard. One that Mobilizes Scientists.

To rapidly scale up testing, we propose a biomedical version of the National Guard, a rapid response force of microbiologists and other scientists who could help reinforce the health care system during pandemics.

THE BEST OF ASM PODCASTS

TWiM (The Week in Microbiology): A coronavirus outbreak and IRF4 deficiency in Whipple's disease

The TWiM team reviews the coronavirus outbreak that began in Wuhan, China, and the finding that a TLR4 deficiency underlies Whipple's disease.

BacterioFiles: Special Sea Species Swallows Cell

A newly discovered species of bacteria consumes other bacteria as prey by engulfing them!

Meet the Microbiologist: Coronavirus Antiviral Drug Discovery with Timothy Sheahan

Dr. Sheahan speaks about his drug discovery work on a compound that can inhibit all coronaviruses tested so far.

microTalk: The Chicken Runs: Campylobacter Diarrhea with David Hendrixson

Why is *C. jejuni* preferentially found in chickens and other birds?

TWiV (This Week in Virology): Kate Rubins from the International Space Station

From Expedition 64 of International Space Station, Flight Engineer Kate Rubins joins TWiV to discuss experiments that she is working on, including cell cultures, genome sequencing and plant growth.

Visit asm.org for more resources on the most pressing issues in microbiology.