Meet a Trailblazing Expert in Evaluating the Effects of Vaccine Studies

Fred Hutch pioneer Dr. Elizabeth Halloran, who helped write the bible of biostatistics on vaccine analysis, transitions to emerita.

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The leaders in the smallpox field were stuck. It was shortly after the 9/11 terrorist attack on New York City and U.S. government officials feared that smallpox might be the next weapon of choice.

The group of scientists, including D. A. Henderson, the world's foremost authority on smallpox and the father of the World Health Organization's smallpox eradication efforts, were working on a systematic natural history of smallpox — its symptoms, transmission and disease progression — that could be used to model a smallpox pandemic.

In front of an easel and flip chart, Henderson hemmed and hawed. The other experts dithered. Then Elizabeth "Betz" Halloran, MD, MPH, DSc, stepped up.

The only woman in the room, Halloran took the marker from Henderson and started writing.

"She outlined all these different paths that the model should take on each level. And Henderson was astounded. His mouth fell open and he just kind of backed away," said University of Florida biostatistician Ira Longini, PhD, Halloran's long-time collaborator who had also been invited to the Secretary of Health and Human Service smallpox working group at the National Institutes of Health's Stone House.

Halloran mapped out three different timelines of interest; she took the paper and its three diagrams back to Emory and shared it with other smallpox modeling groups. The resulting paper (Halloran's first in Science) was a watershed moment in smallpox modeling, Longini said.

"The way she took over, because everybody else was lost and confused, straightened everything out and did it systematically in front of the world's expert on the topic, in fact — literally taking the marker out of his hand — it was amazing," Longini said. "She's a very accomplished systematic thinker. She's able to simultaneously think about many, many complex systems and processes and bring it all together and synthesize it, probably better than anybody else I've ever worked

with.”

This ability enabled Halloran to bridge the fields of statistics, infectious disease modeling and vaccine trial design and analysis — seamlessly, said Longini, who has collaborated with Halloran on 145 papers and one textbook. She also co-developed the concept of causal inference with interference, which enables biostatisticians to estimate how much the vaccination status of others influences an individual’s outcome.

After more than 40 years of innovation, 19 of them at Fred Hutch Cancer Center, Halloran transitioned to emerita last year. Many of the watershed moments in her career lingered in paper form in her drawers and bookshelves, surviving moves from the Harvard School of Public Health to Emory University and finally to Fred Hutch and the University of Washington in Seattle.

A copy of the cooperative grant that sprang from the pivotal smallpox working group nestled in a drawer in her office at Fred Hutch. A filing cabinet housed the NIH vaccine efficacy proposal from 1992 that eventually morphed into her NIH MERIT Award on Methods for Evaluating Vaccine Efficiency. She even unearthed the original draft of “Design and Analysis of Vaccine Studies,” the definitive textbook she co-authored with Longini and fellow biostatistician Claudio Struchiner, MD, MS, DSc, now at Fundação Getulio Vargas in Brazil.

“I was quite active in how to evaluate vaccines in the field and different effects of vaccines,” said Halloran, who has studied infectious diseases ranging from HIV to dengue, malaria to SARS-CoV-2.

Her work on modeling interventions against a potential bird flu pandemic garnered her attention outside academia, when Vogue featured Halloran as a “power player” in their March 2006 issue. Her knack for making connections (between sciences and scientists) has shaped a generation or more of researchers, as well as the fields they pursue.

Halloran created, facilitated and secured the funding for the long-running Summer Institute in Statistics and Modeling Infectious Diseases (SISMID). Housed at UW from 2009–2023, SISMID introduced generations of young infectious disease scientists to modern methods of statistical analysis and mathematical modeling.

She headed the Center for Inference & Dynamics of Infectious Diseases, a National Institute of General Medical Sciences MIDAS Center of Excellence, from 2014–2023, and Fred Hutch’s Program in Biostatistics, Bioinformatics and Epidemiology in Fred Hutch’s Vaccine and Infectious Disease Division from 2020-2024. Halloran is an elected Fellow of the American Association for the Advancement of Science (AAAS), the American Statistical Association and the Royal Statistical Society. Her honors include election to the National Academy of Medicine and receipt of the Nathan Mantel Lifetime Achievement Award of the American Statistical Association.

Science: innovation and seamless integration

Halloran’s career has taken her around the world, although not quite how she originally

anticipated.

She initially dreamed of becoming a “flying doctor” (having obtained her pilot’s license before entering medical school) and treating tropical diseases in far-flung regions. Instead, Halloran pioneered modern methods to model infectious diseases and design and analyze vaccine trials and also helped shape public health policy and pandemic preparedness.

After studying physics and math at the University of Oregon, Halloran obtained her MD from Freie Universität Berlin in what was then West Berlin, the walled, Allies-controlled city surrounded by East Germany. She completed a diploma in tropical medicine and parasitic diseases at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, West Germany, and then attended Harvard School of Public Health for a master’s degree in tropical public health.

“At the time, there was a lot of hope for the malaria vaccines — it was so exciting,” Halloran recalled. In her application to the Harvard School of Public Health, she described how malaria vaccines could transform the world.

Fascinated by the early malaria modeling papers written by Ronald Ross, FRCS, who won the Nobel Prize in Physiology or Medicine for showing that mosquitos transmit malaria, Halloran decided she wanted to model malaria vaccines. Her instructor connected her with Struchiner, a Brazilian graduate student who had the necessary programming background.

‘She’s a very good listener. I always say, when she speaks, just stop. Listen, because it’s not brainstorming, it means that she has some insight.’
— Dr. Alessandro Vespignani, Sternberg Family Distinguished University Professor of Physics, Computer Science and Health Sciences at Northeastern University, Boston

With Struchiner, Halloran outlined the modern concept of causal inference with interference, the idea that an individual’s outcome (such as whether they contract an infection) is influenced by the treatment (i.e., vaccination) status of others.

“The thing about causal inference is that there’s usually an assumption that the treatment of one

individual doesn't affect the outcome of others," Halloran said. "There's this independence assumption. And you don't have to have a lot of neurons firing to realize that doesn't work in infectious diseases."

The assumption that one individual's treatment doesn't affect others works pretty well in certain cases, such as testing cancer treatments, said University of Washington statistician Thomas Richardson, PhD, who taught a course on causal inference in Halloran's summer institute from 2009-2023.

But this assumption of independence was hampering research into infectious diseases and vaccine effectiveness.

"In the '80s, [interference] was assumed absent; Halloran and Struchiner gave us the language to say what was going on," Richardson said. They developed an intellectual framework that incorporated both direct and indirect effects of vaccination and allowed scientists to estimate how much an individual is protected from disease based on how many others around them are (or are not) vaccinated.

As vaccine trial designs evolved over the early and mid-2000s, "Accounting for interference was key to evaluating the effects of policy interventions on communities, by finding the herd effect," Richardson said. "They were able to show that even though the cholera vaccine is not 100% effective, there is an additional advantage to vaccination because of the herd immunity effect."

Vaccinated individuals get protection from the vaccine, and the herd immunity effect helps protect unvaccinated members of the community.

Prior to joining Fred Hutch and the University of Washington in 2006, Halloran was a faculty member in Emory University's Department of Biostatistics (there was no stats department at the time). Throughout the early and mid-90s, Halloran connected with statisticians who were breaking new ground. Back at Emory, she developed and taught courses on Bayesian statistical methods and mentored students focused in this area.

Halloran built on these breaking methods to push the boundaries of her own field, innovating the mathematical modeling of infectious diseases and the design and analysis of vaccine trials.

"I did really make a lot of contributions to the different kind of vaccines effects and the different parameters you can use to estimate it," she said. "And that's what turned into the 400-page book that we published in 2010."

Halloran, with her colleagues Longini and Struchiner, wrote the textbook "Design and Analysis of Vaccine Studies," which Northeastern University network scientist and longtime Halloran collaborator Alessandro Vespignani, PhD, called a 'Bible' of the field.

"For vaccine trials, for efficacy estimation or vaccine efficacy estimates, she is probably one of the absolute leaders. Some of the algorithms and approaches that she developed are the state of the

art and what are used every time that we try to understand how to work with vaccines," said Vespignani, who teamed up with Halloran and others to form Epistorm, a consortium focused on analyzing and predicting epidemics.

With Longini and Struchiner, Halloran "laid down, more or less, the modern precepts for the design and analysis of vaccine studies, taking a very analytic statistical approach," Longini said. "We came up with a completely new systematic for evaluating direct, indirect, total and overall vaccine effectiveness … and more importantly, how you measure all these effects statistically and mathematically."

Though Halloran was not directly involved in the trial itself, the 2015 Ebola ring vaccine trial put the precepts they'd developed into practice, he said. Working with the World Health Organization, the team found the contacts of infected individuals, and those contacts' contacts. People were randomized to either receive the Ebola vaccine immediately or 21 days later.

"Not only could we estimate that the vaccine was highly effective in this case — close to 100% — but we could also estimate how much the vaccine protected those who were not vaccinated," Longini said. "We went from nothing to finding an Ebola vaccine that was effective in about two months."

Mentorship: support and high standards

Despite her astounding achievements, Halloran doesn't brag — unless it's about her mentees. Throughout her career, Halloran has prioritized guiding young scientists and helped foster connections among many others.

"So many times, she was the only woman in the room," Longini said. "So she was especially good with women trainees and students, helping them get the confidence to do what needed to be done."

Her mentees included epidemiologist Nicole Basta, PhD, MPhil, now an associate professor at McGill University in Montreal. Basta applied to the epidemiology graduate program at the University of Washington to work with Halloran.

"What interested me most was the work Betz was doing on estimating vaccine efficacy and planning for an influenza pandemic," Basta said.

Basta found that Halloran was committed to supporting her students' interests. Halloran connected Basta with the leader of the Arfican Meningococcal Carriage Consortium, MenAfriCar, working to prepare for the introduction of a meningococcal A vaccine, MenAfriVac, into countries in the African meningitis belt. Basta spent most of her PhD working with the consortium and Mali's Center for Vaccine Development.

This meant Basta spent many months a continent and an ocean away from her mentor, but

Halloran (herself no stranger to conducting research outside the United States) ensured that she remained a resource: During Basta's time in Mali, Halloran visited to check Basta's progress and meet with her collaborators.

"Being able to tap into Betz's expertise as I was collaborating with researchers abroad was really, really valuable," Basta said. "What really impresses me about Betz's mentorship style is that she models a high standard of excellence in all that she does, and her advice is targeted towards helping her trainees also attain that level of achievement and dedication."

Epidemiologist and former mentee Madhura Rane, PhD, ScM, MS, now a research scientist at the Institute for Implementation Science in Population Health at the City University of New York, echoed Basta's sentiments.

"She would be very straight with me … about what the feasibility of the research question is, and what are the questions that we can and cannot answer with the data," said Rane, who added that working with Halloran was her chance to train with 'the best' at developing vaccine studies. "As an independent researcher now, this way of thinking helps me evaluate whether a question is feasible and encourages me to begin with the question, then identify the data required to answer it."

During her graduate training, Rane hoped to study outstanding questions surrounding the pertussis vaccine. Halloran offered connections — Rane met an expert in pertussis through Halloran's summer institute — and scientific expertise.

"That's really her forte," Rane said. "Who better than Betz to guide me?"

Halloran also helped Rane, an international student, secure summer internships and stay on top of her visa paperwork. At the time, Rane's marriage was also long-distance (her husband was in New York while she completed her studies in Seattle), and Halloran supported Rane's trips back to the East Coast, trusting Rane to work remotely long before that became commonplace.

"I count myself so lucky [to have Halloran as a mentor] because a PhD can be a very, very difficult experience if you don't have a mentor who's supportive," Rane said. "Once you're her student, she will ensure it's a positive experience for you, make sure you graduate on time, make sure that you get to work on the projects you want to work on."

When Rane wanted more exposure to international public health, Halloran made it happen. She put Rane in touch with the World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE) working on the Ebola vaccine. Rane put together a systematic review of Ebola vaccines in the pipeline and presented it at the 2018 WHO SAGE meeting.

"I don't know anyone else in my program who had that kind of exposure," Rane said. "It was incredible, and she made it happen."

Both Basta and Rane said Halloran's mentorship continues to inspire them.

"Every day I think of something that has shaped me as a researcher," Rane said. "I learned the

importance of writing clearly, interpreting results with precision, and communicating findings to the lay public. … I try to give my intern encouragement and independence to do [her research] in her style, but whenever she has questions, I'm there."

Basta also models much of her mentorship on Halloran's.

"When I was a student, Betz made being a researcher and a professor and an academic seem very effortless," Basta said. "It wasn't until I became a professor myself that I realized the level of commitment that is required by the mentor and by the faculty member behind the scenes to ensure that students progress smoothly through their training and are able to accomplish their goals."

Vespignani also credited Halloran with nurturing his career. The two first met at a conference at the research and policy-focused Brookings Institution when Vespignani, who trained as a physicist, was first moving into epidemic modeling. Halloran approached him and began querying the junior scientist and newcomer about his work.

"I was impressed by her curiosity and how much she was humble, although for me she was a goddess of the field," Vespignani said. "Betz was so supportive, was such a good friend, such a wonderful colleague. … My gratitude, it's really infinite to her. Also, she does it in a very gracious, elegant and wonderful way. … She's a special person on the human side."

Summer Institute: Shaping a generation

In 2009, Halloran established the Summer Institute in Statistics and Modeling in Infectious Disease, or SISMID, an annual two-and-a-half-week-long program that attracts experts in statistics and infectious diseases from around the world as faculty. It wasn't her only labor of love at the time: the inaugural SISMID program opened the same day Halloran submitted the manuscript for "Design and Analysis of Vaccine Studies" to her publisher.

Until 2023, Halloran staffed and funded the program single-handedly, drawing instructors from her wide-ranging scientific network and ensuring it stayed funded even in lean times. After 15 years at UW, SISMID relocated to Emory University in Atlanta after Halloran passed on the reins.

Aside from Halloran's great scientific contributions, "She really took charge of the community, she took charge of people. She was promoting people. She was connecting people," said Vespignani, who has led SISMID courses since 2010. "She has been a focal point of the [infectious disease and biostatistics] community with SISMID. So many generations have gone through that school and in a sense the entire field now has been — I would say — formed through that school."

At SISMID, students like Rane meet experts who can help shape their research and careers, and instructors also make fruitful connections. Basta returned from Mali just to attend SISMID.

"It was really a great interplay between having that field epidemiology experience and the

research I was doing, and then returning to the Summer Institute, really soaking up a lot of new knowledge about the theory and context that I would need to understand infectious disease dynamics," she recalled. "It was a remarkable addition to my training as an epidemiology PhD student."

She and Vespignani both ensure that their students get the same experience. And it's not just the students who find that it can shape their work.

Richardson, who co-taught a SISMID module on causal inference, found his own work unexpectedly influenced after Halloran paired him with University of North Carolina biostatistician Michael Hudgens, PhD, who has made substantial contributions to causal inference with interference.

"Co-teaching had a very large impact on my thinking," Richardson said. The two researchers approached the concept of causation from different directions, and working with Hudgens was the catalyst to Richardson co-developing a unifying framework.

Halloran also found the opportunity to foster connections that went beyond the scientific, her colleagues said, by hosting outdoor dinners for instructors and local colleagues at her home.

"Everybody looked forward to that because it was so relaxing," Longini said. "The food was good, and every evening after dinner, we would all walk down to the park and look at Rainier as the sun set."

Mount Rainier isn't merely a nice backdrop to Halloran: an avid hiker, she still hikes strenuous trails around the mountain. And though she maintains a high degree of excellence in every aspect of her life, it may take years for her colleagues to discover just how excellent. Halloran plays the piano almost daily, but Longini didn't discover she was nearly concert-pianist level until years into their collaboration.

Luckily, Halloran isn't reticent about science.

"She is a marvelous scientist for one atypical aspect that you don't find very often in colleagues: She's a very good listener," Vespignani said. "I always say, when she speaks, just stop. Listen, because it's not brainstorming, it means that she has some insight."

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