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Burdens of biodefence

Working with nature's nastiest microbes offers a chance to help ensure public safety. **Karen Kaplan** details the profession's risks and rewards.

Each time he walks into his lab, Ricardo Carrion faces a safety routine of up to half an hour. When he leaves, even just to grab a pen, that routine doubles in length. And every time he goes back in or out, he must follow the same procedures, step by step.

Carrion, an assistant scientist at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio, Texas, is conducting research on microbes, but not within the comparatively tame confines of a lab bench. He's one of a number of researchers around the globe who go through these procedures several times a day as part of their work investigating ways to protect against bioterrorism and combat infectious diseases. These positions, despite their inherent dangers, offer the opportunity to contribute to public safety and security. And, for those with a thrill-seeking streak, they also offer a bit of daily excitement on top of the usual research routine.

Carrion, who manages the SFBR's biosafety level (BSL) 4 lab, helps to develop vaccines for viruses that cause haemorrhagic fever. BSL-4 facilities deal with biological agents that can cause serious or fatal illness in humans and for which no treatment is available; there are about half a dozen in the United States and roughly two dozen worldwide, in 17 nations. The daily routine can be exhausting: once Carrion confirms that all gauges are working properly, he dons a set of scrubs and a headset to maintain contact with an external safety team. Next, he pumps air into his vinyl hazardous-materials (hazmat) suit, making sure that the fabric and seams are airtight. Potential leaks are doused with soapy water. If bubbles appear, Carrion discards the US$2,000 suit — they last for eight months on average — and selects another. Self-enclosed and pressurized, fitted with internal air filters and an opening for an air hose, the hazmat garment, which has three layers of gloves, resembles a space suit and weighs about 15 pounds.

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Before the terrorist attacks of 11 September 2001 in the United States, policy-makers deemed biodefence an esoteric sub-specialty, its funding half-buried as an obscure line item in federal defence budgets. But following those strikes and the anthrax attacks a month later, the country started shovelling money into bioterrorism research. In 2001, for example, the annual budget for the National Institute of Allergy and Infectious Disease (NIAID) in Bethesda, Maryland— the division of the National Institutes of Health that handles biodefence and infectious-disease research — was $42 million. By 2002, it had ballooned to $187 million, a 345% increase.

Such increases have now fallen off at all US federal agencies and the field is redefining itself, shifting away from its bioterrorism agenda of the early 2000s that concentrated on pathogen-specific vaccines. Almost a decade later, that tight focus has been widened to include treatments for emerging diseases,

says Michael Kurilla, director of the NIAID's Office of Biodefense Research Affairs. "Now, rather than trying to prepare pre-event, the focus is on prophylaxis," Kurilla says, noting research targets such as broad-spectrum antivirals, rather than specific vaccines. Gigi Kwik Gronvall, a senior associate at the Center for Biosecurity in Pittsburgh, Pennsylvania, emphasizes the continued importance of shortening the time between identifying a disease and developing a vaccine or anti-viral. "Right now there's an 8–10-year timeline," she says. "I hope it's not the best we can do."

Worldwide, several BSL-4 labs are under construction and scheduled to begin operating within the next year or so, including in Germany, Switzerland and the Netherlands. In the United States, a handful of BSL-4 labs operated by various federal agencies or universities in Kansas, Maryland and Georgia are scheduled to be opened or commissioned over the next couple of years. All are likely to hire dozens of researchers and postdocs.

Postdoc positions are available in the United States at a number of labs, including through the National Research Council fellowship programme at the US Army Medical Research Institute of Infectious Diseases (USAMRIID) in Frederick, Maryland. The SFBR, where Carrion started as a postdoc, also has a postdoc programme.

Aspirants should have a doctorate in a field such as immunology, bacteriology, virology, pathology, microbiology or physiology. Carrion, for example, has a PhD in immunology and microbiology and a master's in biology. It is also helpful, some researchers say, to attend graduate school at a university that operates a BSL-4 lab.

Playing it safe

The step-by-step protocols that Carrion must follow to enter and exit his lab reflect the risk inherent in the agents that he uses. Lab work, even without these biohazards, can be dangerous or even fatal (see *Nature* **458,** 664–665; 2009). But biodefence researchers routinely handle pathogens that kill or severely sicken people, animals and plants. Those defined by the US government as 'category A' bioterrorism threats include anthrax, botulism, bubonic plague, tularemia, smallpox and viral haemorrhagic fevers such as filoviruses (Ebola and Marburg) and arenaviruses (Lassa and Machupo).

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Labs and governments have developed an elaborate set of safety regulations and procedures, including those that govern entering and leaving the lab. In the United States, the European Union and Canada, biodefence researchers must pass government or police checks and clearances — including medical clearances — before accepting a post. Non-US researchers seeking a US position must be able to obtain Federal Bureau of Investigation clearance, which can be a lengthy process. Next, they undergo months of training that covers biocontainment protocol, safety procedures, emergency operations and use of the hazmat suit, lab systems and engineering operations. The trainee, typically a postdoc, learns how to work with biosafety cabinets, store and keep written records of pathogens, and clean up and decontaminate a spill.

The researcher then begins working with live pathogens in the lab, under the direct supervision of a mentor. This stage usually lasts for three to six months, the length of time that it takes an average trainee to become adept at all the necessary procedures and operations while wearing the hazmat suit. Then the researcher can enter the lab on his or her own. The process takes up to a year, and lab staff must be retrained annually.

"It's definitely overwhelming at first," Louis Altamura says of the protocols, procedures and paperwork. A postdoc in the virology division of the USAMRIID, Altamura works with bunyaviruses, including certain haemorrhagic fever viruses such as the Crimean-Congo. "You have to be a little bit of a lab manager even within your own project. I don't want to say it's all a distraction, but it is something you need to account for."

Verena Krähling, a postdoc working with filoviruses at the Institute for Virology at the Philipps University of Marburg, Germany, says that she is sometimes worn out by the extensive safety precautions, especially those involving the weighty hazmat suit. "We have to know all the emergency training," she says. It includes learning policies on and practices for handling spills, releases, loss or theft of pathogens inside or outside a biological safety cabinet and dealing with infections of, or injuries to, lab staff. "The time, the preparation — it's kind of exhausting," says Krähling. The suit's air supply dries out the skin and respiratory system, she says, and those who breathe it daily for more than four hours are often susceptible to colds or respiratory infections.

Ricardo Carrion (top) and Louis Altamura.

Helping humankind

So why tolerate the regulations and laborious trappings of the research? Investigators cite several reasons: it is exciting, they feel they're contributing to public health and safety, and they can see the results of their work far more quickly than is likely in, for example, pharmaceutical research, where it takes years to identify and develop a potential drug, let alone to see its beneficial effects.

"I wasn't as interested in academia: I wanted something closer to the front lines," says Daniel Sanford, a senior research scientist at Battelle, a contract research lab based in Columbus, Ohio, that operates BSL-3 facilities, dealing with dangerous or lethal pathogens for which treatments exist. Sanford studied basic cancer research as a graduate student; it was difficult, he said, to see the direct benefits. At Battelle, he's helping to develop animal models for vaccine and therapeutic products, to determine whether they are safe and efficacious. "That in itself is gratifying," he says.

Steven Jones, head of the Emerging Bacterial Diseases section at the National Microbiology Laboratory in Manitoba, Canada — the nation's only BSL-4 lab — says that he too likes the immediacy of the work and results. Because vaccines and therapeutic candidates are tested on animals, researchers get instant feedback on whether they work and how safe they are, he says.

It is comforting to some to know that they're helping to mitigate the effects of an attack. "I don't think you could stay here and do this work and deal with all the logistical issues if you weren't doing something that you believe is serving the greater good," says Lisa Hensley, a microbiologist and principal investigator at the USAMRIID who researches filoviruses, arenaviruses and the pox family of viruses.

Carrion agrees. In the suit room, in full hazmat garb, he walks through a decontamination chamber — lab staff don't need to be decontaminated on the way in — and then an airlock. Only after the airlock's double doors close completely can he open the door to the lab. Once inside, company regulations permit him to remain for five hours; some labs allow only four. Each time he leaves, Carrion enters the decontamination chamber and showers under a disinfectant cycle with the suit, rinses it and hangs it to dry. Then he enters a second chamber, puts his scrubs in an autoclave and takes a personal shower for at least five minutes. Then, finally, at long last, he puts his street clothes back on. ■

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