

The story of Canada's Ebola vaccine

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The development of an effective Ebola vaccine by Canada's National Microbiology Laboratory is a great Canadian contribution to global public health. A linked study in *CMAJ* reports on a phase 1 trial of a recombinant vesicular stomatitis virus (VSV) Ebola vaccine developed in Canada.¹ This is the story of its development.

Ebola, a hemorrhagic fever filovirus, endemic in parts of Africa, was first recognized in 1976 in what is now the Democratic Republic of the Congo and first isolated at the Institute of Tropical Medicine in Antwerp.^{2,3} In 1996 Jack Rose described a reverse genetics system for VSV (an animal virus that infects humans but does not cause much in the way of human disease),⁴ showing that recombinant VSV could act as a gene expression vector and, subsequently, that exogenous proteins could be incorporated into the membrane of the virus particles. In 2001 Rose's group showed that HIV Env and Gag proteins could be expressed using the recombinant VSV vector with potential to be effective vaccine vectors.

In 1997, Yoshihiro Kawaoka created a new tool for the study of Ebola virus. He developed a replication-incompetent VSV⁵ vector that had a green fluorescent protein gene in place of the VSV glycoprotein; Ebola virus glycoprotein was supplied to the virus as it formed in cell culture from a separate expression system. Kawaoka's group successfully used this pseudotyped replication-deficient virus as a research tool to study the structure and function of the Ebola virus glycoprotein (EBOV).

Fifteen years before the 2014–2015 Ebola outbreak in West Africa, in 1999, Heinz Feldman, newly recruited to the National Microbiology Laboratory, set out to study the pathogenic effects of the EBOV, believing the glycoprotein to be key to the severity of Ebola infection. In collaboration with Ute Ströher, the team developed a replicating recombinant VSV vector in which the VSV glycoprotein was functionally replaced with the EBOV. Early experiments to test its predicted pathogenicity saw mice inoculated with the EBOV using the VSV viral vector and then challenged with the mouse-adapted Ebola virus. The mice did not develop Ebola as expected; they were completely protected, which was essentially a failure, but this turned out to be an important breakthrough in Ebola vaccine research.⁶ The vaccine was shown to be highly protective even when used postexposure in animal models, and that it was possible to

KEY POINTS

- After the Ebola outbreak in West Africa in 2014–2015, a vaccine was quickly brought to clinical trial in the field.
- However, the development of an Ebola vaccine represents a great Canadian scientific effort and international collaboration that spanned almost two decades.
- The success of the vaccine may mean the end of Ebola virus infection as a global health threat.

immunize orally and intranasally and protect against a systemic challenge.⁷

In 2001, the Public Health Agency of Canada's National Microbiology Laboratory began to work on developing a vaccine. The risk that a virulent agent like Ebola could spread quickly from small community outbreaks to a major global epidemic was well appreciated and Ebola was widely regarded as a bioterrorism threat. However, many systemic failures slowed progress from early observations of an immune response in mice to a safe, injectable Ebola vaccine for humans. It took several years to convince funding agencies of the value of spending the National Microbiology Laboratory's limited resources on Ebola vaccine research over other pressing public health issues in Canada. In 2005, a change in funding body leadership, an increasing body of efficacy data and strong advocacy by scientists resulted in the research team securing half the requested funding for development of the Ebola vaccine. There followed the dogged work of building the vaccine program, putting contracts in place and securing sign-off from Ottawa.

The goal of the vaccine development program was to develop current Good Manufacturing Practice (cGMP) virus stocks that would be suitable for phase 1 and 2 clinical trials, as well as being suitable for emergency use; e.g., in the event of a laboratory exposure. The team partnered with IDT Biologika GmbH in Dessau-Rosslau, Germany, although there were obstacles to placing a vaccine development contract with a German manufacturer. At the National Microbiology Laboratory, all the reverse genetics system plasmids were recloned and sequenced, and the viruses were rescued again using cell lines with safety provenance, necessary for regulators. Initial safety and efficacy trials

were repeated in animals using the new cGMP vaccine. IDT then began the process of increasing production of the VSV-Ebola vaccine to industrial scale.

By 2015, there was enough human-grade material on hand that Canada could offer 1000 doses of the vaccine to the World Health Organization (WHO) at the height of the 2014–2015 Ebola outbreak. The total time from project approval and partnering with IDT Biologika, awarding of the contract and delivery of the final cGMP vaccine materials was more than six years.

Because the market for an Ebola vaccine was considered to be small, stockpiling by the US, UK and Canadian militaries, and civil protection, comprised the main focus early on. There was little interest in the vaccine from the pharmaceutical industry. A licence for what was now known as VSV-EBOV was eventually granted to a small American company, with which the team from the National Microbiology Laboratory worked to seek funding and push the development of the cGMP vaccine through safety and efficacy studies. During the Ebola outbreak in West Africa, Merck purchased the rights to develop VSV-EBOV and brought it into large-scale production for clinical trials.

Given the uncertain intellectual property of the VSV-EBOV, ensuring that the government of Canada had rights to use and develop the vaccine took substantial work. The National Microbiology Laboratory's director of business development negotiated a licence for use of the vaccine in the viral hemorrhagic fever field and Canada obtained a licence to develop vaccines for Ebola, Marburg virus and Lassa fever.

The 2014–2015 Ebola outbreak in West Africa garnered unprecedented support for clinical trials. In addition to donating over 1000 clinical trial vaccine lots to the WHO, Canada provided funding through the Canadian Institutes of Health Research for phase 1 safety trials and more than \$100 million over a six-week period to the WHO through the Department of Foreign Affairs, Trade and Development (now Global Affairs Canada) and the International Development Research Centre for phase 3 trials and other Ebola countermeasures.

The first reported phase 1 studies showed that the vaccine was well tolerated and immunogenic.⁸ A group based in Halifax undertook further phase 1 studies, as reported in the linked study.¹

The next big step — design and implementation of a randomized controlled trial in Guinea — was led by Norway and the WHO but included important Canadian components and funding.

Researchers used a unique study design, called ring vaccination,⁹ which randomized contacts of Ebola index cases to receive either VSV-EBOV or initial placebo with delayed vaccine. Within the rings that received the vaccine, no secondary cases were observed after the 10-day period required to generate an immune response.⁹ Indeed, this trial may have contributed to control of the Ebola outbreak in Guinea. The vaccine is now on the pathway to licensure and will likely be used in any future Ebola outbreaks.

Vaccine development moved from cGMP material to a randomized controlled trial in West Africa in a matter of months following the unprecedented Ebola outbreak in West Africa in 2015. However, this was preceded by 15 years of fundamental research — laboratory and preclinical work — and a huge effort to get cGMP vaccine produced for human use. Canada played a major role in the development of this vaccine by conducting early research, performing phase 1 clinical trials and providing essential funding. The vaccine may mean the end of Ebola virus infection as a global health threat, and Canada has contributed a model for global responses to new infectious disease threats.

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Competing interests: Steven Jones is a listed inventor on the Ebola vaccine patent (held by the Crown as per Jones' contract while a Crown employee); he also reports receiving royalty payments for exploiting the vaccine patent, in line with Treasury Board guidelines. Both authors were formerly with the National Microbiology Laboratory, Public Health Agency of Canada, and played key roles in the development of Canada's Ebola vaccine. Francis Plummer was the Scientific Director of the National Microbiology Laboratory, 2000–2014. From 2010 he was the Scientific Champion for VSV-EBOV clinical trial lots.

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