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New clues on the history of the smallpox vaccine virus

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Smallpox - simply hearing the word evokes images of countless people suffering gruesome deaths throughout recorded history. Known scientifically as variola, the virus had 30 percent mortality rate and survivors were branded with pox scars for life. For millennia, physicians often did more harm than good. Smallpox victims were bled, poked with golden needles, kept in overheated rooms while febrile, and the list goes on. At best, the treatments were uncomfortable; at worst, they killed even faster than the virus.

But in the 1790s, English physician Edward Jenner used fluid from fresh pustules on the hands of young dairymaid Sarah Nelms, who had a much more mild disease called "cowpox" , to create vaccination (a word that comes from the Latin "vacca", meaning cow). This "vaccination" replaced the "variolation", an earlier inoculation technique that was much more dangerous. However, some believe that the virus Jenner used in his vaccination was not the cowpox virus but a related one that infects both humans and cows, or even the horsepox virus, which is closely related to the vaccinia virus.

Eradication was achieved in 1980 using various vaccinia viral strains—forms of the virus that differ slightly in their DNA sequences and in how they affect humans or animals. Although all vaccinia strains used in inoculation campaigns were effective in rendering people immune to smallpox, different clones differed in terms of immunogenicity and in their side effect profile. This led the World Health Organization to recommend that vaccination was no longer

necessary after smallpox eradication in 1980.

Recent studies using sequencing technologies have indicated that the first generation of vaccines actually included a genetically heterogeneous pool of the vaccinia virus. In fact, no one really knows about the origins of the vaccinia virus (VACV) or how the different strains relate to each other. To gain new insights into the topic, researchers in Brazil from Universidade Federal do Rio de Janeiro teamed up with colleagues in the US and Germany to elaborate animal testing and genomic analyses on the VACV-IOC, the smallpox vaccine strain used to eradicate smallpox in Brazil. The group worked with two clones of the VACV-IOC, named B141 and B388, and compared their virulence and the immune response they elicited with other VACV strains, including the second-generation vaccine currently produced in the USA (ACAM2000).

The study shows that in mice, both clones induce a protective immune response against a lethal vaccinia infection and have low virulence, which indicates that these clones would not cause disease if inoculated. In particular, the B141 clone showed the lower virulence and thus is a good candidate for a second-generation vaccine.

The research group also sequenced the DNA of each clone to better understand their evolutionary relationship with other VACV strains and found interesting, new revelations about the history of the vaccinia virus. By combining DNA sequencing data with historical accounts, the study indicates that the VACV-IOC is related to Cantagalo virus (CTGV), a vaccinia strain that infects dairy cattle and milkers in Brazil, and that both strains may have originated from the same ancient vaccine virus (which was related to the horsepox virus). "Our historical research indicates that the CTGV virus is a feral VACV strain that escaped to nature from a sample imported from France to Rio de Janeiro in 1887, known as the Beaugency strain. We found historical records on vaccinated cows in Rio de Janeiro that were transported everywhere in

the country, which may have created the opportunity for the virus to escape to nature. Also, records from the beginning of the 20th century report on the transmission of the vaccinia virus in dairy cattle from vaccinees." says Clarissa Damaso, who led the study. Surprisingly, combining DNA data and history reveals that the Dryvax virus that led to the development of the second-generation smallpox vaccine in the USA might have the same origin as the Brazilian VACV-IOC, which derived from the French Beaugency strain, and not the English strain, as previously thought.

Given the fear that some form of variola virus could be reintroduced to humans in weaponized form, new generations of smallpox vaccines are highly needed. Thus, a better understanding of how all the strains relate to each other and finding new clones that may be used to develop new smallpox vaccines are of great value.

More information: The study entitled "Genomic analysis, phenotype, and virulence of the historical Brazilian smallpox vaccine strain IOC: Implications for the origins and evolutionary relationships of vaccinia virus" was recently published online by the *Journal of Virology* and is available at jvi.asm.org/content/early/2015 … 833-15.full.pdf+html

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