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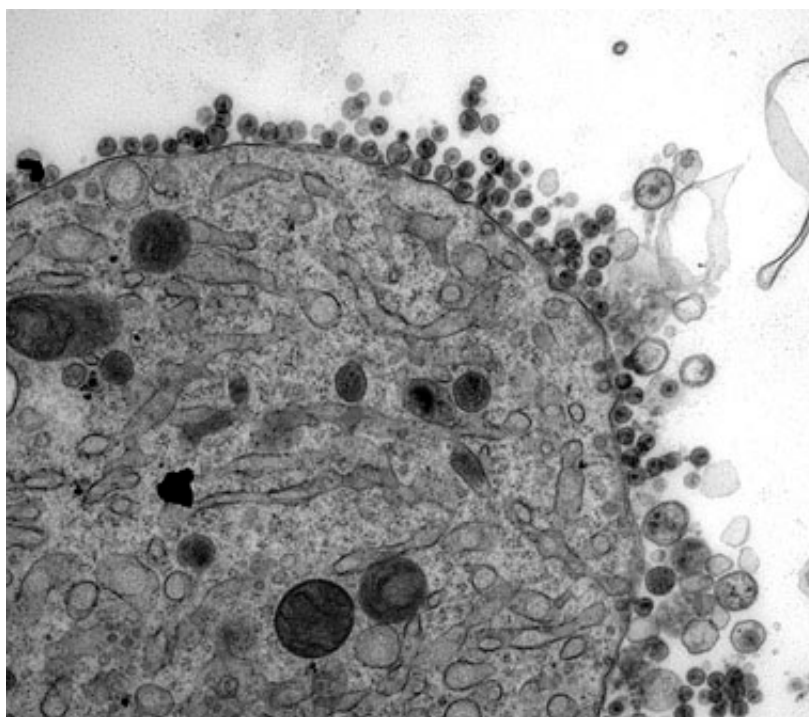
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## Smallpox's Medieval Legacy

It seems like an extremely prescient twist of genetic fate: A mutation that confers HIV resistance became common in Europe centuries before the AIDS epidemic. The reason the mutation persisted, it's long seemed, is that it protected people from bubonic plague. But mathematical modeling reported online this week in the *Proceedings of the National Academy of Sciences* suggests that the real root of resistance is another scourge of the Middle Ages, smallpox.



**A pox on thee!** The legacy of resistance to smallpox in the Middle Ages may be modern resistance to HIV (pictured).

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About 10% of Europeans carry a mutation that gives them resistance to HIV infection by deleting the virus's target on immune cells, a protein called the CCR5 chemokine receptor. Because the mutation is thought to have popped up 700 years ago, long before AIDS appeared, biologists have assumed that the mutation confers resistance to a second pathogen, *Yersinia pestis*, which killed up to 40% of Europeans in the 14th century. The mutation would survive in the population because it would protect carriers from subsequent outbreaks of plague.

But calculations by Alison Galvani and Montgomery Slatkin, population geneticists at the University of California, Berkeley, indicate that *Yersinia* didn't keep the mutation in the gene pool. Although bubonic

plague did kill more Europeans in a shorter period of time than any other disease, Galvani and Slatkin's mathematical model indicates that outbreaks were too rare to have made the CCR5 mutation as common as it is. But smallpox, which has infected Europeans for at least 2000 years, has racked up far more death than the plague. And smallpox is viciously talented at favoring the

mutation: Unlike the plague, it predominantly kills children, preventing the nonresistant gene from being passed on. Galvani and Slatkin also argue that the smallpox virus makes better biological sense because it infects immune cells in a similar way as HIV does.

The case is compelling, says Michael Stumpf, a mathematical biologist at Imperial College, London. "The original link between HIV and *Yersinia pestis* has been rather circumstantial," says Stumpf, because the origin of the CCR5 mutation "happened to fall into the time of the plague." However, he says, the mutation could actually be much older.

**--JOHN BOHANNON**

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