Are imperfect, ‘leaky’ vaccines resulting in emergence of nastier viruses?

If a highlight reel were made of the history of modern drug development, vaccines would be the brightest star. They have been incredibly effective in fighting and eradicating infectious diseases

However, vaccines are like any other drugs: some work really, really well; others are okay, and some work just well enough that the benefits of preventing the disease outweigh the risks. But sometimes the risks can exceed the benefits.

An emerging controversial hypothesis in medicine is that vaccines that work but not extremely efficient could actually lead to the evolution of more infectious strains of a virus. These vaccines have been referred to as ‘imperfect’ or ‘leaky’ vaccines. This hypothesis pertains in particular to viruses that result in a non-lethal infection where the ‘imperfect’ vaccines would result in a reduction of infection in the host but not completely eliminate the virus from replicating. In these animals that are partially protected, particularly virulent strains of the virus would be more likely to survive and infect other animals that it came in contact with, in effect, ‘selecting’ for a more pathogenic virus, not unlike how improper use of antibiotics eventually result in resistant strains of superbugs evolving.

The implications are immediately apparent and not too encouraging. But is there any merit to this idea? If so, how worried should we? The theory was originally proposed more than a decade ago by researcher Andrew Read who is currently at Penn State University. Subsequent studies have used mathematical models to test it. However, until recently, the imperfect vaccine hypothesis had not been tested on animals. In a recent study published in the journal PLoS Biology, Read and colleagues did just that using Marek’s disease virus (MDV) a highly infectious and lethal disease in poultry to try and see if the models would bear out in live animals.

The vaccine for MDV has long been known to be ‘imperfect’ in that it does not offer complete protection. However, given the extreme nature of the disease, vaccination is the most preferred method of protection, proving to be more effective than using antivirals in infected animals. Over the years, more virulent strains of the virus have emerged in poultry, leading to speculation that imperfect vaccines have in some way contributed to the phenomenon.

The experiments conducted by Read and colleagues seemed to suggest that this was indeed the case for MDV. They infected two groups of chickens, one vaccinated and the other unprotected with three highly pathogenic strains of the virus. They found that while all the animals in the unvaccinated group died within 10 days, the vaccinated chickens survived for 30 days or more allowing the virus to be transmitted to other birds housed within the same confines.

This results confirmed the hypothesis, according to the authors of the study, leading one of the other senior authors, Professor Venugopal Nair to suggest that “these vaccines also allow the virulent virus to continue evolving precisely because they allow the vaccinated individuals, and therefore themselves, to survive”.

Read extended the idea to vaccines for human diseases, drawing a direct line between these results and deadly diseases like Ebola, quoting in the press release sent by Penn State,

> "Vaccines for human diseases are the least-expensive, most-effective public-health interventions we ever have had," Read said. "But the concern now is about the next-generation vaccines. If the next-generation vaccines are leaky, they could drive the evolution of more-virulent strains of the virus." He said it is critical now to determine as quickly as possible that the Ebola vaccines that now are in clinical trials are not leaky — that they completely prevent the transmission of the Ebola virus among people. "We do not want the evolution of viral diseases as deadly as Ebola evolving in the direction that our research has demonstrated is possible with less-than-perfect, leaky vaccines."

Though the results sound ominous, especially when invoking diseases like Ebola, several issues remain to be understood before the theory can be accepted, according to independent experts who commented on the study to the Science Media Centre in London. (The comments were also forwarded to reporters in North America by GENeS, the Genetic Expert News Service).

Firstly, while they demonstrated the ability of lethal strains of the virus to survive and be transmitted in vaccinated animals, "the [authors] have *not* demonstrated evolution of MDV from nonlethal to lethal forms in vaccinated chickens," according to Dr. Michael Skinner, an expert virologist at the Imperial College, London. Moreover, the evolution of more lethal strains of MDV since the introduction of the vaccine in the 1950s could have occurred due to many other reasons not the least of which is the exponential increase in the number of animals being housed together in the same space, he said. The absence of any direct evidence of MDV evolution in the field was also noted by Dr. Philip Minor, a researcher at the National Institute of Biological Standards and Control (NIBSC) in the UK.

But what about the possibility in humans? According to Dr. Adrian Hill who is the director of the Jenner Institute at the University of Oxford:

> [The study] does not explain why, importantly, there is no evidence of this happening with other vaccines especially in humans, where many vaccines are used safely in millions of individuals every month. The suggestion that altered pathogen virulence should be looked for after vaccinating people is not new, and there is no evidence that human vaccines have produced more virulent pathogens.

The results do not apply to mostly non-lethal diseases like mumps, measles, polio, etc. for which the vaccines prevent both infection and transmission, said Skinner.

Does that mean we don't need to worry about it? Not necessarily, according to Minor. It is "a plausible risk that needs to be taken into account in designing vaccines, as well as in the implementation of new vaccine programmes and in monitoring their impact," according to Minor.

> … these risks are already carefully considered, for example, in implementing new human vaccine programmes such as those against HPV, pneumococcal and meningitis vaccines. Extensive surveillance programmes have been set up to look for any unexpected disease patterns and changes in the distribution of infectious agents in the environment following the introduction of vaccination.

Where does that leave us? While the results of the study do support the idea of vaccine driven evolution, more evidence is needed of its existence in humans before large scale changes are made to vaccine research and vaccination programs. And while researchers and public health experts keep a close watch for the presence of any such evidence, we should trust the most successful class drugs ever created by man. And as the Read is quoted as saying in the press release, if anything, the study actually emphasizes the importance of getting vaccinated

> When evolution toward more-virulent virus strains takes place as a result of vaccination practices, it is the unvaccinated individuals who are at the greatest risk. Those who are not vaccinated will be exposed, without any protection, to the hottest strains of a virus. Our research provides strong evidence for the importance of getting vaccinated.

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