Interview

Dr Kevin Ault speaks to Charlotte Barker, Commissioning Editor

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Dr Kevin Ault is currently an Associate Professor of Gynecology and Obstetrics at Emory University (GA, USA). Dr Ault gained his medical degree at the Indiana University School of Medicine (IN, USA) and is a board-certified gynecologist, with clinical interests in cervical dysplasia and sexually transmitted infections. Dr Ault's research focuses on infections of the female genital tract, and he is an investigator in clinical trials for both Cervarix® (GlaxoSmithKline, London, UK) and Gardasil® (Merck & Co., Inc., NJ, USA). He was an investigator on one of the earliest trials to show efficacy of human papillomavirus (HPV) vaccination in preventing precancerous lesions, and has been featured widely in the US media as an expert on the vaccine. His research has been published in the Lancet, *the* New England Journal of Medicine *and the* American Journal of Obstetrics and Gynecology, *and he has lectured extensively on HPV vaccination and related topics.*

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How did you first get involved in human papillomavirus vaccine development and what is the focus of your current research?

I am a gynecologist, so my interest in this area has mainly come through cancer prevention, but I am also interested in infectious diseases. I was at a microbiology meeting 10–12 years ago with Alan Shaw from Merck & Co., Inc. (NJ, USA), and at the cocktail reception afterwards, Dr Shaw was telling me about the animal experiments they had performed with papillomavirus vaccines and how it appeared to be very promising. So I gave him my business card and I have been doing this research ever since.

I have worked with both companies that have commercially available versions of the human papillomavirus (HPV) vaccine on the market (Cervarix™, GlaxoSmithKline, London, UK, and Gardasil®, Merck & Co., Inc., NJ, USA), but currently I am trying to work with some of the immunologists we have here at Emory University (GA, USA) to investigate long-term immune responses.

There has been some concern regarding the lack of long-term data on the new vaccines and reports of potential side effects. Is it too soon for large-scale vaccination programs?

When I first started hearing those comments, I looked at some of the vaccines that have been approved most recently in the USA and found that the meningococcal conjugate vaccine (Menactra®, sanofi pasteur, Lyon, France) only had 5-year follow-up data when it was approved. So, 5 years appears to be a fairly standard follow-up period, at least for the last few vaccines that have been widely available in the USA.

With regard to adverse effects, when there are 10 or 20 million young women who have been vaccinated, of course events are going to occur, which may or may not be related to vaccination. One of the examples given at the CDC meeting was that 50 of 100,000 women of this age group will develop Guillain–Barré syndrome (which has been reported as a potential side effect of the HPV vaccine) spontaneously, and so you would expect dozens of cases in the cohort that received this vaccine. We are actually not seeing that: if anything, the rate is a little decreased.

I am sure part of the reason that the HPV vaccine has attracted controversy is because it is a relatively unique vaccine in that it is aimed at a sexually transmitted infection (STI), a STI that people did not know a lot about before the vaccine came along.

What are the major barriers to effective implementation of HPV vaccination and how might these be addressed?

We have already touched on one of the barriers: the lack of long-term data. Another factor is that this is a very expensive vaccine. Increasing costs have been a trend among all new vaccines over the past few years, and that makes it difficult to provide on a large scale, especially when we are talking about areas of the USA, and indeed the world, that are resource poor. Both GlaxoSmithKline and Merck have stepped up and made an effort to make sure the vaccine is available in regions such as south Asia and Africa: places where it can do the most good.

In terms of cost, an important question is whether we need three injections of the vaccine. Many of the same complaints were made about the cost of the hepatitis B vaccine 20 years ago. It took a long time for us to work out alternate, less frequent, dosing strategies for the hepatitis B vaccine, and we could probably learn some lessons from that. We certainly have better immunological tools available now than we did then, which can help answer those questions.

Currently, vaccination is only recommended for young females. Should young males also be vaccinated?

There are at least three reasons why we should think about vaccinating young men and boys. First, is that the Merck version of the vaccine has HPV 6 and 11 in it, which cause genital warts. Of course, genital warts are not cancer, but they still do considerable harm to patients due to the psychosocial consequences of having a STI, plus they are very hard to treat so anything we can do to prevent them would be a good idea. Second, there are some HPV-related cancers that affect men. A good friend of mine who is involved in research in this area, Anna Giuliano (Moffitt Cancer Center, Tampa, FL, USA), estimates that the number of cases of HPV-related cancers in men is equivalent to the number of cases of cervical cancer in the USA. There is a burden of HPV-related cancer in men as well. Third, there are lessons to be learnt from the experience with the Rubella vaccination. The main public-health benefit of the Rubella vaccination is to prevent congenital Rubella syndrome. In Britain and Sweden, the vaccine was given to women only for a long time, but vaccination did not work as a strategy to prevent pregnancy complications until both genders were vaccinated. So, the idea of herd immunity is another strong reason for vaccinating boys.

How strong is the evidence that HPV vaccination might protect against non-cervical HPV-related cancers?

With vulval and vaginal cancers, the current trials have enough participants and have been running long enough to gather evidence that the vaccine can prevent those cancers, which are mainly HPV 16-related cancers. It becomes more difficult for less common HPV-related cancers. There are some researchers looking at the effect of HPV vaccination on anal cancer, particularly in men who have sex with men: that is an ongoing clinical trial. Once you start looking at head and neck cancers, the lag time is quite a lot longer between exposure and cancer and there is no precancer stage, so that may be the toughest area to look into. As you get to these rarer and rarer cancers, it becomes increasingly challenging to carry out clinical trials

Will vaccination eventually eliminate the need for Pap screening?

I suspect that is on the horizon, I just do not know if it is going to happen during my generation or a couple of generations behind me. Some of the recent research suggests that HPV 16 and 18 are the most oncogenic HPV types, and the other HPV types that are not in the vaccine may not be so oncogenic, so we hope the vaccine will really make a dent in cervical cancer rates. Certainly, we can envisage a situation where there are fewer Pap smears and fewer abnormal Pap smears. The Pap smear itself is undergoing a revolution of its own in terms of techniques and technology in

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HPV testing. There was a particularly interesting Canadian article published in the *New England Journal of Medicine* [1], regarding the sensitivity of HPV DNA testing. In the USA, we only have one technique right now, but there are others that are going to be on the marketplace in the next few years.

What are the main unanswered questions regarding HPV vaccination?

The main unanswered question is probably the duration of the immune response. Since the vaccine is so expensive, needing boosters at 10 years really makes a dent as far as the cost–effectiveness of the vaccine is concerned. I was a medical student 20 years ago, when health workers were starting to get the hepatitis B vaccine and I was told I would need a booster in 2 years, then in 5 years and then eventually I was told I would never need a booster, so hopefully that will also be the case with this vaccine, but that is what we are hoping to find out.

What do you expect to be the focus of your research over the next 5 years?

I think there are a lot of unanswered questions regarding the immunology of this vaccine, and that also relates to other vaccines, such as HIV, herpes and other pathogens of the female genital tract. We are giving women an injection in their arm and it is protecting them against an infection that is localized to their vagina and cervix. The mechanism behind that immunologic protection is an interesting project to work on, and it is going to take a fair amount of good-quality clinical work, as well as basic science work, to figure that out.

Financial & competing interests disclosure

Kevin Ault has worked with both GlaxoSmithKline and Merck as a clinical investigator in the development of their vaccines. He is currently working on a clinical trial with GenProbe, and has also served as an advisor to the Centers for Disease Control and Prevention, The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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