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# Evidence of HPV vaccination efficacy comes from more than clinical trials

Peter Sasieni and Alejandra Castanon

King's College London | Faculty of Life Sciences & Medicine| School of Cancer & Pharmaceutical Sciences | Cancer Prevention Group

Innovation Hub, Guys Cancer Centre, Guys Hospital, Great Maze Pond, London SE1 9RT

Corresponding author contact details

Alejandra Castanon

Cancer Prevention Group

Innovation Hub, Guys Cancer Centre, Guys Hospital, Great Maze Pond, London SE1 9RT

E: alejandra.castanon@kcl.ac.uk

T: 0207 848 5422

A recently published article by Claire Rees and colleagues[1] argues that clinical trials investigating HPV vaccination have generated significant uncertainties, undermining claims of efficacy in these data. They conclude that there are too few data to prove that HPV vaccine prevents cervical intraepithelial neoplasia grade 3 or worse (CIN3+). In this short piece we argue that whilst Rees and colleagues provide valid criticisms of the trials of HPV vaccination and point out some of the gaps in our understanding of how HPV infection causes cervical cancer, their conclusions and the way they have been reported in newspapers is quite misleading. We discuss the huge amount of non-trial research evidence that enables most scientists to conclude that HPV vaccination will prevent most cervical cancers. We also address the key conclusion points raised in the Rees article.

## Observational research evidence of HPV vaccine efficacy

Epidemiological studies have estimated that about 70% of cervical cancer is caused by HPV types 16 and 18.[2, 3] They have also shown that persistence of the HPV infection is needed for the development of cervical cancer. Whilst there are some uncertainties of exactly how the virus causes cancer, we do understand what is going on at a molecular level.[4] High-risk HPV types drive cell division in neoplasia through the ability of their E7 and E6 proteins to bind and degrade pRb and p53 – the two most potent tumour suppressor genes

Out of 5 randomised controlled trials the lowest observed efficacy against persistent infection with the HPV types targeted by the vaccine in HPV naïve women was 90.3% (96.1% CI: 87.3-92.6).[5] Further these trials showed substantial protection against closely related types up to 8 years post vaccination.[5-10] Efficacy against CIN2+ associated with HPV16/18 in girls who were HPV negative at first dose is near perfect: meta-analysis of the trials shows that vaccination prevented 99% (95% CI 95% to 100%) of such disease.[11]

There is mounting evidence that antibody responses after two doses [12] of the vaccine are comparable to those after three (as originally licensed) and that one dose[13] is also effective at preventing high-grade disease suggesting greater vaccine effectiveness than previously anticipated.

Cohort studies and surveillance statistics show dramatic falls in the proportions of young women infected with these HPV types in countries that have implemented HPV vaccination.[14-22] In England the prevalence of HPV16/18 in sexually active females aged 16-18years prior to vaccination was 15% this has dropped to 2% among those offered vaccination at age 12-13 years. Further in 2018, among 584 women tested at ages 16-18years there was no HPV detected (0%, 95%CI 0.0%-0.6%).[23]

Many years ago, a gynaecologist in New Zealand did not think CIN3 needed to be treated. A third of his patients developed cervical cancer over the next 10-15 years.[24, 25] The randomised controlled trials showed a reduction in the pre-cancerous lesions that are most likely to progress to cancer (i.e. CIN3). This was shown for all CIN3 lesions in all women vaccinated aged 15 to 25years (45.6%, 95%CI: 28.8-58.7). The effect was strongest among CIN3 lesions associated with HPV types 16 and 18 and in women who had not been infected with HPV before they were vaccinated (100%, 95%CI: 85.5-100).[26] Others have found that CIN3 with HPV16 is more likely to progress to cancer than CIN3 with other HPV types[27] and that the prevalence of HPV types other than 16 and 18 among invasive cervical cancers is low (21%).[28]

In addition to the randomised controlled trials, real world data from studies in countries with HPV vaccination programmes have shown a substantial reduction in CIN3 in vaccinated cohorts.[15, 29] A recently published study linking data between the cervical cancer registry and immunization registries reported an incidence rate ratio of 0.26 (0.16-0.42) for CIN3+ among women vaccinated at age 9-14y compared to unvaccinated women.[30]

Except in very rare cases, it takes at least 8 years to develop cervical cancer after getting an HPV infection and cervical cancer is very rare under the age of 24. Since most vaccination programmes were introduced in 2008/09 for women aged 11-15years, it is generally too soon to see an impact of HPV vaccination on cervical cancer rates. However, women in Finland who were vaccinated as part of one of the original HPV vaccine trials have been followed. In the HPV vaccinated group there were no cervical cancers whereas in a comparison group (that was nearly twice as large) there were eight cases.[31] Preliminary data from Sweden also suggest a substantial reduction in cervical cancer incidence rates among vaccinated women.[32]

Various groups have carefully modelled what levels of screening are appropriate for women who have been vaccinated against HPV as adolescents. The answer depends somewhat on which HPV vaccine the woman has had (there are three commercially available vaccines), but most researchers estimate that between 1 and 3 screens over a lifetime (compared with 12 currently recommended) would provide an extremely high level of protection.[33-35]

A very small number of cervical cancers are not caused by HPV. Vaccination will not prevent these very rare cancers. However, without screening rates of cervical cancer would be dramatically higher.[36] In the UK it is estimated that without screening (over the past 30 years) there would be some 4,700 women diagnosed with cervical cancer each year (three times more than currently observed).[37] With HPV vaccination and minimal screening that number might be reduced to 250 in 50 years from now.[33]

**Response to key messages of the Rees paper**

1. *It is uncertain whether HPV vaccination prevents cervical cancer*. As explained above whilst it is mostly too soon to see an impact on cervical cancer incidence, we know so much about the natural history of cervical cancer, that it is inconceivable that it will not have a substantial impact. In fact, the impact of vaccination in the population is probably greater than one might predict from the trials because by vaccinating a high proportion of the population, women who have not been vaccinated also receive some protection (herd immunity). Such head immunity has been observed in Australia, Scotland and England.[17, 38, 39]
2. *We do not have enough data on the impact of the vaccine on CIN3*. There is plenty of data and it has been summarised in two meta-analyses: one of randomised controlled trials[14] and one of real-world data.[40]
3. *RCTs may overestimate efficacy because a) testing was done too often, b) trials used endpoints that are not clinically relevant; and c) subgroups were over-analysed*. Most trials used persistent infection. If the trials evaluated infection at a single point in time, frequent testing might be a valid criticism, but they did not. It is established that HPV persistence is the best predictor of future CIN3.[41] The link between CIN3 and cancer is widely recognised. Cervical screening programmes prevent cervical cancer by detecting and treating CIN3. Many of the trials also showed impact on CIN3. Other than in women already infected with HPV, the vaccines worked uniformly well in all subgroups.
4. *The trials were not relevant to the real world because many of the women were older*. There is plenty of real-world evidence on women who were vaccinated before exposure to HPV[15, 17, 30] and several trials comparing the antibody response in women vaccinated at different ages.[9, 26] The authors claim that HPV epidemiology varies globally and that none of the studies have been conducted in Africa. Most of the cervical cancer in sub-Saharan Africa is caused by HPV types 16 and 18. Cervical cancer is the most common female cancer in most of Sub-Saharan Africa with some of the highest rates anywhere in the world. Vaccination of adolescent girls would clearly prevent those infections and thereby prevent cervical cancer which has poor survival in most of Africa.
5. *Cross-protection and HPV-type substitution*. There is concern about HPV-type substitution, however this is being very closely monitored and the latest evidence from the UK does not suggest an increase in the prevalence of other HPV types.[17] In addition to the clinical trials data, real world evidence has

shown decreases in non-vaccine HPV types among vaccinated women.[15, 17]

6. *Trials report relative rather than absolute effects and none provided numbers needed to vaccinate.* All the trials present the data so that absolute effects can be calculated. But they are not relevant for establishing efficacy. The relative efficacy is reasonably generalisable and can then be applied to populations with different levels of HPV infection and cervical cancer to calculate the likely absolute benefit. Further, the absolute benefit depends critically on the duration of follow-up. There are numerous modelling studies that estimate the likely impact of HPV vaccination on the lifetime risk of cervical cancer in various countries.[42]

There remain some unanswered questions such as how often vaccinated women need to be screened and whether there is a need for a vaccine booster dose. Modelling studies and data from Scotland show that it does not really make sense to continue to screen cohorts vaccinated before exposure to HPV at the same frequency. We also know that (unlike with other vaccines) there is absolutely no sign of waning efficacy 12 years after vaccination[43] and more data on long-term protection accrues each year.

Dr Rees is quoted in the Guardian as saying: “We found insufficient data to clearly conclude that HPV vaccine prevents the higher-grade abnormal cell changes that can eventually develop into cervical cancer”. This is a little like saying that there is no evidence that a child knows anything about physics having been given a mark of zero on a test because she forgot to put her name on the paper when in fact she answered virtually all the questions correctly and would have had a score of 90%!

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