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1 Evidence of HPV vaccination efficacy comes from more than clinical trials
2 Peter Sasieni and Alejandra Castanon
3 King's College London | Faculty of Life Sciences & Medicine| School of Cancer &
4 Pharmaceutical Sciences | Cancer Prevention Group
5 Innovation Hub, Guys Cancer Centre, Guys Hospital, Great Maze Pond, London
6 SE1 9RT

7 Corresponding author contact details

8 Alejandra Castanon

9 Cancer Prevention Group

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

12 E: alejandra.castanon@kcl.ac.uk

13 T: 0207 848 5422

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

25 **Observational research evidence of HPV vaccine efficacy**

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

33 Out of 5 randomised controlled trials the lowest observed efficacy against persistent
34 infection with the HPV types targeted by the vaccine in HPV naïve women was
35 90.3% (96.1% CI: 87.3-92.6).[5] Further these trials showed substantial protection
36 against closely related types up to 8 years post vaccination.[5-10] Efficacy against
37 CIN2+ associated with HPV16/18 in girls who were HPV negative at first dose is
38 near perfect: meta-analysis of the trials shows that vaccination prevented 99% (95%
39 CI 95% to 100%) of such disease.[11]

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

44 Cohort studies and surveillance statistics show dramatic falls in the proportions of
45 young women infected with these HPV types in countries that have implemented
46 HPV vaccination.[14-22] In England the prevalence of HPV16/18 in sexually active
47 females aged 16-18years prior to vaccination was 15% this has dropped to 2%
48 among those offered vaccination at age 12-13 years. Further in 2018, among 584
49 women tested at ages 16-18years there was no HPV detected (0%, 95%CI 0.0%-
50 0.6%).[23]

51 Many years ago, a gynaecologist in New Zealand did not think CIN3 needed to be
52 treated. A third of his patients developed cervical cancer over the next 10-15
53 years.[24, 25] The randomised controlled trials showed a reduction in the pre-
54 cancerous lesions that are most likely to progress to cancer (i.e. CIN3). This was
55 shown for all CIN3 lesions in all women vaccinated aged 15 to 25years (45.6%,
56 95%CI: 28.8-58.7). The effect was strongest among CIN3 lesions associated with
57 HPV types 16 and 18 and in women who had not been infected with HPV before
58 they were vaccinated (100%, 95%CI: 85.5-100).[26] Others have found that CIN3
59 with HPV16 is more likely to progress to cancer than CIN3 with other HPV types[27]
60 and that the prevalence of HPV types other than 16 and 18 among invasive cervical
61 cancers is low (21%).[28]

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

68 Except in very rare cases, it takes at least 8 years to develop cervical cancer after
69 getting an HPV infection and cervical cancer is very rare under the age of 24. Since
70 most vaccination programmes were introduced in 2008/09 for women aged 11-
71 15years, it is generally too soon to see an impact of HPV vaccination on cervical
72 cancer rates. However, women in Finland who were vaccinated as part of one of the
73 original HPV vaccine trials have been followed. In the HPV vaccinated group there
74 were no cervical cancers whereas in a comparison group (that was nearly twice as
75 large) there were eight cases.[31] Preliminary data from Sweden also suggest a
76 substantial reduction in cervical cancer incidence rates among vaccinated
77 women.[32]

78 Various groups have carefully modelled what levels of screening are appropriate for
79 women who have been vaccinated against HPV as adolescents. The answer
80 depends somewhat on which HPV vaccine the woman has had (there are three
81 commercially available vaccines), but most researchers estimate that between 1 and
82 3 screens over a lifetime (compared with 12 currently recommended) would provide
83 an extremely high level of protection.[33-35]

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

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

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

129 shown decreases in non-vaccine HPV types among vaccinated women.[15,
130 17]

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

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

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

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