Letters to the editor; Response to: a possible spurious correlation between human papillomavirus vaccination introduction and birth rate change in the United States

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In their letter to the editor, Shibata and Kataoka,1 offer a critique of my paper, “A lowered probably of pregnancy in females in the USA aged 25–29 who received a human papillomavirus vaccine injection”.2 They suggest three reasons why my conclusion that HPV vaccine uptake is related to lowered probability of ever having been pregnant could be spurious. While the lowered fertility I found among women who received the HPV shot could be related to variables other than the HPV vaccine, the finding cannot be the result of the reasons they offer. The authors do not explain my findings, and their analysis does not negate the need for more research into the possible effect of the HPV vaccine on fertility.

The first reason the authors offer is that the vaccine is recommended mainly for women who are not yet sexually active. The birth rate among such women would, by definition, be nil. This argument is weak, because even if a woman is not yet sexually active when she receives the shot, she could begin to be sexually active shortly thereafter. Precisely her concerns about a sexually-transmitted disease could spur her to obtain the shot.

The authors continue their first argument by observing that the average age of a mother at her first birth rose in the United States from 24.9 years in 2000 to 26.3 years in 2014. They appear to suggest that the lowered birth rate among younger women was offset by a higher birth rate among older women. Data from the U.S. Department of Health and Human Services do not support this argument.3 In 2007, the birth rate per 1,000 females aged 25 to 29 was 118.1 and among 30 to 44 year olds was 50.5. By 2017, the birth rate among younger women had fallen by 20.1 to 98.0 and increased by 5.7 to 56.1 for older women. The increase in the birth rate for older women does not offset the fall in the birth rate among younger women.

The second reason the authors offer for my results is that the fertility rates of countries with high HPV vaccine uptake have not fallen. They show steady overall fertility rates in Spain, Italy and the United Kingdom as well as steady fertility rates by age group in Australia.

The overall fertility rate is a very blunt measure of births among specific age groups. The girls who received the shot in the UK were 11 and 12 years old, and yet fertility measures births per 1,000 females aged 15 to 49. Girls who receive the shot are not included in the fertility measure until three years after they receive the shot. Since the UK began its nationwide program in 2009, we would not expect fertility rates to begin to fall until 2012. Even then, the fall would be relatively small, as most women who conceive are older than 15.

A more precise measure of the change in fertility in a country is to examine the birth rates by age group. The authors provide such information for Australia in their Figure 1. However, the figure is misleading in that the birth rates range from zero to 140. Such a wide span reduces the ability to detect changes in an individual age group. Additionally, the chart stops in the year 2012, too soon for much of an effect to be noticeable.

Examining the raw data on the birth rates by age group for the four countries with high HPV vaccine uptake as well as one country with low uptake is much more revealing. Table 1 shows the birth rate per 1,000 females by age group in the four countries included in Shibata and Kataoka analysis for the year in which the HPV vaccine was introduced as well as the year of the most recent data, 2015. Also included in the table is Romania, which suspended its HPV vaccine program after very low uptake.4 In the four countries with an active HPV vaccine program, the birth rates of the younger women have fallen dramatically since the introduction of the vaccine. The increases in the birth rates of older women in these countries do not offset the lowered rates of the younger women. During the same time period, Romania showed a substantial increase in birth rates for all but the youngest age groups.

Importantly, my published study is even more precise than observing fertility in age groups. The database I use – the National Health and Nutrition Examination Survey – reports vaccine uptake and pregnancy status by individual. Such information allows me to separate women who received the HPV vaccine from those who did not, allowing a more refined analysis of differences in characteristics of the women in each group. Such refined analysis renders discussion of overall fertility rates moot.

The third reason the authors offer to explain why women who received the HPV vaccine were less likely to conceive than women who did not receive the shot is the increased use of long-acting reversible contraceptives (LARCs). Such birth control is considered more effective in preventing unwanted pregnancy than other short-acting contraceptives such as the pill and the condom. The authors cite an eight-fold increase in the use of LARCs among 15 to 24 year old women between 2006 and 2013 (from 0.6% to 5.0%).

While the use of LARCs has increased, the increase appears to be among women who have had at least one birth. Kavanaugh,
Table 1. Birth rate per 1,000 females by age group for year of HPV vaccine introduction and 2015.

| Year | Age Group | 15–19 | 20–24 | 25–29 | 30–34 | 35–39 | 40–44 | 45–49 | 50–49 |
|------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|
| Australia | 2007 | 17.1 | 58.8 | 110.0 | 129.7 | 69.6 | 13.0 | 0.7 |       |
| | 2015 | 11.9 | 48.0 | 95.0 | 122.1 | 69.5 | 14.6 | 1.2 |       |
| Difference between 2015 and year of HPV shot introduction |       | −5.2 | −10.8 | −15.0 | −7.6 | −0.1 | 1.6 | 0.5 | −36.6 |
| Spain | 2008 | 13.3 | 38.0 | 67.1 | 99.8 | 60.6 | 11.3 | 0.7 |       |
| | 2015 | 7.7  | 26.1 | 57.5 | 93.3 | 63.5 | 15.9 | 1.1 |       |
| Difference between 2015 and year of HPV shot introduction |       | −5.6 | −11.8 | −9.6 | −6.4 | 4.6  | 4.6  | 0.4  | −23.8 |
| Italy | 2008 | 7.2  | 36.5 | 76.7 | 96.6 | 59.6 | 12.8 | 0.7 |       |
| | 2015 | 5.1  | 28.8 | 67.3 | 91.7 | 59.4 | 15.4 | 1.1 |       |
| Difference between 2015 and year of HPV shot introduction |       | −2.0 | −7.7  | −9.3 | −4.9 | −0.2 | 2.6  | 0.5  | −21.1 |
| United Kingdom | 2009 | 24.6 | 72.7 | 102.1 | 108.1 | 57.8 | 11.9 | 0.7 |       |
| | 2015 | 14.4 | 56.9 | 99.2 | 110.3 | 65.6 | 13.8 | 0.9 |       |
| Difference between 2015 and year of HPV shot introduction |       | −10.2 | −15.8 | −2.9 | 2.2  | 7.8  | 1.9  | 0.2  | −16.8 |
| Romania (HPV vaccine program suspended after low participation) | 2007 | 39.4 | 71.5 | 93.0 | 54.2 | 24.9 | 3.1  | 0.2  |       |
| | 2015 | 35.3 | 71.0 | 96.8 | 73.9 | 31.4 | 6.0  | 0.3  |       |
| Difference between 2015 and 2007 |       | −4.1 | −0.5  | 3.8  | 19.7 | 6.5  | 2.9  | 0.2  | 28.5  |

Source: [United Nations. World Fertility Data].

Jerman and Finer, find that nulliparous women are significantly less likely to use LARCs than women who have already given birth.

We do not know how many of the nulliparous women in my study were using birth control. The NHANES database has limited information concerning birth control; for example, it does not include widely-used methods such as intrauterine devices, sterilization, or abstinence. A follow-up study is therefore essential to determine how many women who received the HPV vaccine were actively trying to prevent pregnancy.

My data show that women who received the HPV shot were less likely to have ever been pregnant. The correlation between the HPV vaccine and lowered fertility could be spurious, but not for the reasons that Shibata and Kataoka offer. Observations of young HPV vaccine recipients experiencing premature ovarian failure have also been noted, which could provide more plausible hypotheses to explore. More research into the statistical result is essential.

Disclosure of potential conflicts of interest

In 2006, the author filed a claim under the U.S. National Vaccine Injury Compensation Program for her daughter. The claim of vaccine injury did not include the HPV vaccine.

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