vaccine effectiveness under most real-world assumptions [9–11]. In particular, a re-analysis of data from 4 randomized clinical trials (RCTs) found that efficacy estimates and confidence intervals for the gold standard RCT analysis and the alternative TND analysis were virtually identical [11]. Other than age, confounding variables have been notably absent in most vaccine effectiveness studies using the TND. Medication confounding may be more plausible in older age groups, but only 10% of participants in the study by Bateman et al [1] were elderly. Our vaccine effectiveness studies adjusted for age, high-risk conditions, and calendar time of illness onset, and the unadjusted and adjusted vaccine effectiveness estimates are often quite similar. This does not rule out unmeasured confounding, but it does suggest that the TND has lower potential for confounding, compared with studies using non-specific end points.

We support Fedson’s suggestion that further research is needed regarding the potential impact of statins on the severity of respiratory infections, including those caused by influenza virus, other viruses, and bacteria. However, it is important to recognize that statin use is unlikely to affect the validity of influenza vaccine effectiveness estimates using the TND. We plan to specifically examine the relationship between statin use and influenza among patients who have been enrolled in prior vaccine effectiveness studies at Marshfield Clinic.

Note
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Reduction in HPV Prevalence—No Evidence to Support HPV Vaccination reduces HPV Prevalence

To The Editor—The recent Centers for Disease Control and Prevention (CDC) study by Markowitz et al [1] provides limited and inconclusive data on 111 sexually active females between 14 and 19 years of age who received at least 1 dose of quadrivalent human papillomavirus vaccine (HPV4). The broad ranging conclusions are inconsistent with current knowledge about risk factors for HPV infection and HPV prevalence among US adolescents, herd immunity, and vaccine efficacy evaluation with fewer than 3 doses.

The single most important risk factor for HPV infection, after human immunodeficiency virus (HIV) infection, is number of lifetime sexual partners [2]. Markowitz’s study aligns with this knowledge by showing for the 2007–2010 (postvaccination) time frame, a 4-fold increase in HPV prevalence among sexually active 14–19-year olds who have 3 or more lifetime sexual partners compared to those with fewer than 3 partners.

However, the study reports an adolescent cohort composed of twice as many adolescents who are both unvaccinated and minimally sexually active (hence, likely to have a low prevalence of HPV infection) as are vaccinated and highly sexually active. Combining these 2 groups lowers the overall reported postvaccination HPV prevalence leading to the false conclusion that vaccination lowered the HPV prevalence rates.

Reducing sexual activity is a potent prevention strategy for reducing HPV prevalence. Another recent CDC report indicates that 73% of 15–17 year-old females in the postvaccination era have not initiated sexual activity [3]. Indeed, condom use is also proven to reduce HPV infection rates. Other significant successes reported by the CDC among adolescents in this same postvaccination time frame include an increased use of condoms, a decrease in the overall number of
sexual partners during adolescence, and a large decrease in the number of teenage pregnancies [4, 5].

In addition, adolescent sexual mating has been defined as an assortative mixing pattern, where males are twice as likely to be cutpoints as females [6]. This means that vaccination of males, not females, is more likely to interrupt HPV transmission (and provide herd immunity) among females in the short term. Herd immunity is an unlikely scenario as the proportion of males receiving 3 HPV4 doses in the United States is reported to be only 6% [7]. Therefore, the decrease in HPV prevalence reported in the Markowitz study is less likely due to HPV vaccination than to due to adolescent sexual behavioral changes.

Similarly there are inconsistencies in the prevaccination HPV prevalence reported by Markowitz. Prevalence of any HPV type during the prevaccination timeframe 2003–2004 among 14–19-year-old adolescents is reported by the same group of researchers [8] and does not differ from the postvaccination rates contrary to what was reported in Markowitz’s study (Table 1). The 2003–2004 prevaccination cohort includes 652 adolescents 14–19 years old. The prevalence of any HPV among those sexually active was 39.6%; this rate significantly falls to 24.5% when adolescents who report no sexual activity are included.

The Markowitz study adds 2 years to the prevaccination cohort (2003–2006), reporting on a total of 736 adolescents, 84 more subjects than in the 2003–2004 cohort. Compared with the 2003–2004 cohort, the 4-year prevaccination cohort has a significantly higher prevalence of any HPV among both sexually active adolescents (53.1% vs. 39.6%) and among all adolescents regardless of sexual activity (32.9% vs. 24.5%). These data inconsistencies indicate that the reported decrease in HPV prevalence is suspect at best.

In addition, to celebrate HPV4 efficacy with fewer than 3 doses is premature and unsupported in this study. Although there are efficacy data for only 1 dose of HPV2, there are no HPV4 efficacy studies of 5 years or longer with fewer than 3 doses. The HPV4 published studies to date use antibody titers as the surrogate endpoint for efficacy [9], an unsupported endpoint as there is no immunologic surrogate of protection yet identified. The antibody studies indicate that over 5 years, 32% of females having received 3 doses will no longer have detectable HPV 18 antibodies [10]. The supplementary table of Markowitz’s study indeed shows that there is no difference in HPV 18 prevalence rates between the pre- and postvaccination time frames, supporting the lack of long-term efficacy for HPV 18 protection.

Finally, the self-sampling methodology is a point for further exploration, as it is well documented that vulvar swabbing will result in a significantly lower prevalence of HPV than vaginal swabbing [11]. How well these adolescents were able to self-swab must be quality controlled for future studies.

The only supportable conclusion from this work is that the many sexually active adolescents are receiving at least 1 dose of HPV4.

Table 1. HPV Prevalence Reported in Two CDC Studies

<table>
<thead>
<tr>
<th>HPV Prevalence Among Sexually Active 14–19 y Olds (%), 95% Confidence Interval</th>
<th>HPV Prevalence Among All 14–19 y Olds Including Those not Reporting any Sexual Activity (%), 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>N &lt; 652</td>
<td>N = 736</td>
</tr>
<tr>
<td>Any HPV</td>
<td>39.6 (32.9, 47.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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Reply to Groner et al and Pei et al

To The Editor—The comments from Groner and colleagues relating to human papillomavirus (HPV) DNA prevalence among 14–19 year olds in the prevaccine and vaccine eras [1] reflect their profound misunderstanding of the data that we would like to correct. Prevaccine era HPV data from the National Health and Nutrition Examination Surveys (NHANES) 2003–2004 were first published based on a less sensitive HPV assay than the one we currently use [2]. We subsequently documented the impact of an assay change [3] and published updated data on HPV prevalence from NHANES 2003–2006 in order to be able to monitor HPV prevalence trends [4]. The data in our recent article, showing a decline in vaccine type HPV prevalence after vaccine introduction...