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Tobacco Smoking and Thyroid Function: Is Weight Gain a Confounder?

Åsvold et al[1] have recently reported on lower thyrotropin levels in smokers vs nonsmokers and increasing thyrotropin levels with time following smoking cessation. The data are interesting and may further support the recommendation for patients with Graves disease to stop smoking. However, previous studies have pointed out a direct correlation between thyrotropin level and body mass,[2,3] and in addition there is a well-recognized weight-gaining influence of smoking cessation.[4,5] Therefore, I wonder if the observed effect of smoking on thyrotropin level could have, at least partially, been attributed to differences in body mass between smokers and nonsmokers and by weight gain following smoking cessation.

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In reply

In assessing whether effects of smoking on thyroid function may be confounded by body mass, it is important to consider the possible causal directions of the association between thyroid function and body mass. A Danish population-based study showed that body mass index (BMI) was positively associated with thyrotropin level but negatively associated with free thyroxine level, suggesting that thyroid function may influence BMI.[1] With this causal direction, BMI does not fulfill the criteria for being a confounder or a mediator of the associations of smoking with thyroid function.[2,3]

However, other studies indicate that thyroid function may be influenced by weight reduction among obese individuals[4] or by weight gain in patients with anorexia nervosa.[5] We had no information about weight change in our study and cannot address whether change in weight may influence thyroid function. However, adjustment for current BMI did not substantially influence the associations between smoking status and thyroid function in our data. Thus, our results do not indicate that the associations of smoking with thyroid function are confounded or mediated by body mass.

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Preattack Vaccination Against Anthrax May Be Cost-effective in Certain Populations

Schmitt et al[1] report that preexposure anthrax vaccination of US Postal Service (USPS) employees is more costly and results in more anthrax infections and deaths than postattack intervention. We believe that these conclusions are incorrect owing to a flawed study design and several questionable parameter estimates.

The most important flaw is the assumption that unvaccinated workers would be denied antibiotics after an attack, especially when 50% adherence to preattack vaccination is presumed. If instead these workers were modeled to receive antibiotics, quality-adjusted life years (QALYs) gained preventing anthrax cases would exceed QALYs lost to vaccine adverse events. Based on the presented incidence, duration and quality-of-life effects of vaccine adverse effects, 0.0000148 QALYs are lost per vaccination series. With a 50% adherence assumption, 2.6 QALYs would be lost because of adverse events. If one assumes that preexposure vaccination is 92.5% effective and considering the data in Table 3 of the article by Schmitt et al,[1] a strategy providing antibiotics to exposed but unvaccinated workers would reduce anthrax cases and deaths by 39% (2.4 and 0.7, respectively), providing a gain in QALYs far outweighing QALYs lost to vaccine adverse events. These improved health outcomes can only be assigned to the addition of preattack vaccination to a postattack intervention using antibiotics. Adding postexposure vaccination for these workers would reduce cases and deaths and further improve QALYs gained.

The benefits of preattack vaccination beyond 10 years are also not considered. For new workers vaccinated near the end of the 10-year model, vaccination costs are fully captured, while only a few months of vaccine protection are assumed.

The authors propose that even if vaccination served to deter an attack on a USPS facility, preattack vaccination would not be cost-effective. Since the cost of preattack vaccination is placed at $105.6 million and the US government spent a greater sum in anthrax remediation efforts at Brentwood (Washington, DC) and Trenton (New Jersey)[2] alone, it seems impossible that preattack vaccination would not be cost-effective.

We note that Schmitt et al[1] assumed a vaccine efficacy of 92.5%. In fact, 100% efficacy was seen in an observational study conducted by the Centers for Disease Control and Prevention of industrial mill workers during 1962 to 1974.[3] In this study, no cases of anthrax occurred among workers who received at least 3 vaccinations. Schmitt et al[1] assume the cost of giving subcutaneous injections to healthy adults is $20.35, while the mean administration cost assumed in recent studies of workplace influenza vaccination is $8.85 per dose.[4-8]

The cost-effective use of preventive medical interventions requires targeting individuals at sufficiently high risk. Schmitt et al[1] did not consider that certain USPS employees are at greater risk owing to job duties or geographic location. Working near high-speed sorters that could aerosolize anthrax spores is identified as a risk factor by the Occupational Safety and Health Administration.[9] Finally, the study did not consider an attack more devastating than that experienced in 2001. Should a much higher rate of infection be modeled because of the very likely possibility of an attack using weapons-grade and/or antibiotic-resistant spores?

Future examinations of this subject should recognize that preattack and postattack interventions are complimentary and that individual risk may vary. Such a study will likely find that the best health outcomes will come from preexposure vaccination combined with postexposure vaccination plus antibiotics for previously unimmunized individuals.

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Financial Disclosure: Drs Hopkins, Waytes, and Zink are employed by Emergent BioSolutions (Rockville, Maryland), the manufacturer of the licensed anthrax vaccine Biothrax.

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In reply

Hopkins and colleagues from Emergent BioSolutions identify several issues with our model for responding to a small scale anthrax attack.[1] They are concerned that our model of preattack vaccination denied unvaccinated workers postattack antibiotics, that we underestimated vaccine efficacy, and that our 10-year time horizon was inadequate. They argue that these deficits produced an erroneous effectiveness assessment of preattack vaccination. Furthermore, they suggest we overestimated vaccine administration cost and excluded costs of cleanup and work force displacement inflating total cost of a preattack vaccination strategy. Lastly, they were concerned we had not stratified exposure risk among workers within the USPS.

They are correct in noting that we did not model preattack vaccination combined with postattack antibiotic prophylaxis for vaccine-noncompliant postal workers. Would this alternative strategy be equivalent or better than combined postattack antibiotics and vaccination—the optimal strategy identified in our model? Although their alternative strategy would achieve relative minor QALY gains, they must be measured against the cost.

In our analysis, we found that full compliance with preattack vaccination sufficient to prevent an attack would still cost nearly $2.6 million per QALY relative to postattack antibiotics alone, and partial compliance with the same effect of preventing an attack would cost nearly $1.5 million per additional QALY. A combined preattack vaccination and postattack antibiotic strategy would incur significantly greater prophylaxis and treatment costs, with only limited QALY gains. The key to the lack of cost-effectiveness of this or any other preattack vaccination strategy is the high relative cost of vaccination to a low event rate. In the case of a mass anthrax attack scenario with a substantially greater probability for an event, there may be a role for combined preattack and postattack strategies. We are currently evaluating these combined strategies in the setting of a large-scale anthrax attack.

We chose a 10-year time horizon because likely threats, available public health interventions, and possible policy decisions would all likely differ over a 10-year period.

It is also not clear conceptually that preattack vaccination would eliminate anthrax spore cleanup or prevent work force displacement. If exposed sites remained in operation without cleanup, mail passing through the facilities would go to those unvaccinated, and some of the casualties of 2001 were believed to have occurred by passive spore transmission. We did not model variations in risk by site within the USPS—and this may well be an issue.

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