Enhanced Surveillance for Adverse Events Following Immunization

Two Years of dTap Catch-Up Among High School Students in Yukon, Canada (2004, 2005)

Samara T. David, MHScl,2
Colleen Hemsley, RN3
Paula E. Pasquali, PhD3
Bryce Larke, MD, DCISc3
Jane A. Buxton, MBBS, MHSc2
Lee Y. Lior, MD, MSc3

ABSTRACT

Background: To address the increasing age of pertussis cases, Yukon replaced the Grade 9 tetanus/diphtheria/inactivated polio booster with diphtheria/tetanus/acellular pertussis (dTap) and implemented a dTap catch-up program for Grade 12 students. The program began in June 2004, making Yukon one of the first Canadian jurisdictions to introduce dTap within five years of a tetanus booster. We implemented enhanced surveillance to monitor adverse events following immunization (AEFI) to determine whether students receiving dTap ≥3 to <5 years after their last tetanus booster were at increased risk of severe AEFI.

Methods: Students completed a self-administered AEFI questionnaire one week post-dTap vaccination. Public health professionals contacted students reporting severe AEFI. Health care providers were requested to report AEFI. Symptom rate, severity and duration were compared between students receiving dTap ≥3 to <5 years after their last tetanus booster and those receiving it ≥5 years later.

Results: The ≥3 to <5 years group was more likely than the ≥5 years group to report pain at the injection site (70.6% vs. 61.5%, p=0.038) and less likely to report injection site redness (10.0% vs. 17.3%, p=0.022), injection site swelling (8.9% vs. 16.4%, p=0.013), decreased energy (10.0% vs. 17.1%, p=0.023), body aches (2.2% vs. 7.2%, p=0.014) and sore joints (3.3% vs. 10.1%, p=0.004). Severe AEFI did not differ between the groups (3.3% vs. 5.6%, p=0.232). Health care professionals reported no AEFI.

Conclusions: Results suggest no increased risk of severe AEFI among students receiving dTap ≥3 to <5 years after their last tetanus booster.

MeSH terms: Diphtheria-Tetanus-acellular Pertussis vaccines; pertussis; vaccines; Arthus reaction; immunization programs; immunization schedule

La traduction du résumé se trouve à la fin de l'article.

1. Canadian Field Epidemiology Program, Public Health Agency of Canada, Ottawa, ON
2. Epidemiology Services, British Columbia Centre for Disease Control, Vancouver, BC
3. Yukon Health and Social Services, Whitehorse, YT

Correspondence: Samara David, British Columbia Centre for Disease Control, 655 West 12th Avenue, Vancouver, BC V5Z 4R4, Tel: 604-660-0501, Fax: 604-660-0197, E-mail: samara.david@bccdc.ca

Reprint Requests: Dr. Bryce Larke, Yukon Medical Health Officer, 4 Hospital Road, Whitehorse, YT Y1A 3H8, Tel: 867-667-5716, Fax: 867-667-8349, E-mail: bryce.larke@gov.yk.ca

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TABLE I
Demographic Features of Participants by Time Since Last Tetanus Toxoid

<table>
<thead>
<tr>
<th>Grade</th>
<th>≥3 to &lt;5 Years Since Last Tetanus Toxoid (n=180)</th>
<th>≥5 Years Since Last Tetanus Toxoid (n=444)</th>
<th>Statistical Comparison of Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
<td>#</td>
</tr>
<tr>
<td>School A</td>
<td>46</td>
<td>25.6</td>
<td>132</td>
</tr>
<tr>
<td>School B</td>
<td>69</td>
<td>38.3</td>
<td>134</td>
</tr>
<tr>
<td>School C</td>
<td>34</td>
<td>18.9</td>
<td>123</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
<td>17.2</td>
<td>55</td>
</tr>
<tr>
<td>Age Mean</td>
<td>17.5</td>
<td>14.7</td>
<td>H=366.3, p&lt;0.001 *</td>
</tr>
</tbody>
</table>

* Statistically significant difference (p<0.05)

METHODS

Information about the dTap catch-up program (including the rationale for the program, benefits of the vaccine, reasons to defer or not receive the vaccine, expected reactions and instructions on how to treat minor reactions) and consent forms were provided to all Grade 9 and 12 students in Yukon. Forms requested consent for vaccination and, for those vaccinated, consent to participate in a follow-up questionnaire. Informed consent was accepted from guardians or students aged 16 years and older.

Vaccination clinics were held at high schools for students returning completed consent forms and who did not have relative or absolute contraindications for dTap. Vaccination was either not provided or deferred for students who: received tetanus booster <3 years previously, had confirmed pertussis since 1996, had a fever on the day of the vaccination clinic, or had a history of either severe oropharyngeal swelling that limited breathing or hives in response to any previous vaccine. In 2004, all vaccines had the same lot number; two different lot numbers were used in 2005 with no significant difference in the distribution of lot numbers between the comparison groups. The public health nurses assigned to each school administered vaccine to students in both grades.

Seven days post vaccination, students were asked to complete a self-administered adverse events questionnaire (AEQ) during class time. The AEQ was a 14-item questionnaire, asking about demographics, symptoms following vaccination, severity of symptoms, missed school, and whether medical attention was obtained. To gauge the size of reactions, students completing the AEQ received packages containing two Oreo™ cookies, each 46mm in diameter.

In 2004, the vaccination program was implemented in the last few weeks of school and most Grade 12 students were asked to complete the AEQ on their own time, one week after immunization.

To ensure any severe AEFI was reported, primary healthcare providers were notified and requested to report AEFI to Yukon Communicable Disease Control.

Community health centres adapted student lists to include demographic and vaccination history from vaccination records. The AEQ and class list data were entered into EpiData™, linked non-nominally and analyzed using EpiInfo software.12

Comparing AEFI

The proportion of respondents developing each adverse reaction was compared between those who received tetanus toxoid ≥3 to <5 years previously (Shortened Interval Group, SIG) and those who received it ≥5 years previously (Recommended Interval Group, RIG), using odds ratios and Fisher’s exact tests. Symptom severity was compared between the two groups using Chi-square analysis, odds ratios and Fisher’s exact tests. The level of significance was 0.05; 95% confidence intervals (CI) were calculated.

Comparing severe AEFI

Severe AEFI were defined as self-reported:
• absence from school due to symptoms related to vaccination;
• one or more of: erythema or swelling ≥Oreo™ cookie size, fever, or marked limitation of arm movement; and/or,
• medical attention for symptoms following vaccination.

Public health professionals conducted follow-up telephone interviews with students who reported severe AEFI to validate AEQ responses by asking detailed questions about reasons for missed school, type of medical attention received and severity of symptoms.

RESULTS

Over two years, 323 (58%) students in the SIG and 580 (76%) students in the RIG were vaccinated. Of these, 110 (34%) and 444 (77%) in the SIG and RIG, respectively, completed the AEQ.

Table I outlines respondent demographics by time since last tetanus booster. The SIG was significantly older than the RIG. The RIG was mostly comprised of Grade 9 students and the SIG, Grade 12 students, although occasional overlap occurred. The immunization records contained data on gender for only 216 (35%) of respondents.

AEFI

The SIG was more likely than the RIG to report pain at the injection site (Table II). However, the SIG was less likely to report injection site redness, injection site swelling, decreased energy, body aches, and sore joints. There were no significant differences in reported symptom severity between groups.
Severe AEFI

Eighteen (10%) members of the SIG and 69 (16%) members of the RIG self-reported severe AEFI (Table III). Public health follow-up found that some respondents misinterpreted measures of symptom severity on the AEQ. Of the 87 reports of severe AEFI, 24 were found to be unrelated to dTap and 32 were re-coded to mild or moderate. Six (3.3%) students in the SIG and 25 (5.6%) in the RIG were found to truly experience severe AEFI. The proportion experiencing severe AEFI did not differ significantly between the two groups. In all instances, symptoms resolved without further complication within 2 hours to 12 days.

None of the students reported being seen by a medical professional for symptoms. One student reported visiting the emergency room for pain at the injection site, but left without receiving medical care; symptoms resolved within 24 hours. Two called medical providers and were satisfied with the advice received by phone. Health care professionals did not report any AEFI among vaccinated students.

Other factors

Participants completed the AEQ 1 to 37 days post immunization (mean=8.8, median=7.0). The SIG (44%) was more likely than the RIG (25%) to complete the AEQ more than 7 days after vaccination (p<0.001). Those completing their AEQs late were less likely than those completing it on time to report redness at the injection site, limitations of arm movement and headache (Table IV). The time between vaccination and AEQ completion did not confound or interact with the relationship.
ADVERSE EVENTS FOLLOWING DTAP CATCH-UP

TABLE IV

Reports of Adverse Events by Time Between Vaccination and Adverse Events Questionnaire (AEQ) Completion

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Completed AEQ ≥7 Days After Vaccination (n=435)</th>
<th>Completed AEQ &gt;7 Days After Vaccination (n=189)</th>
<th>Statistical Comparison of Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
<td>#</td>
</tr>
<tr>
<td>Redness at Injection Site</td>
<td>80</td>
<td>18.4</td>
<td>15</td>
</tr>
<tr>
<td>Swelling at Injection Site</td>
<td>69</td>
<td>15.9</td>
<td>20</td>
</tr>
<tr>
<td>Pain at Injection Site</td>
<td>281</td>
<td>64.4</td>
<td>119</td>
</tr>
<tr>
<td>Limitation of Arm Movement</td>
<td>200</td>
<td>46.0</td>
<td>67</td>
</tr>
<tr>
<td>Decreased Energy</td>
<td>66</td>
<td>15.2</td>
<td>28</td>
</tr>
<tr>
<td>Fever</td>
<td>28</td>
<td>6.4</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>60</td>
<td>13.8</td>
<td>14</td>
</tr>
<tr>
<td>Body Aches</td>
<td>28</td>
<td>6.4</td>
<td>8</td>
</tr>
<tr>
<td>Sore Joints</td>
<td>36</td>
<td>8.3</td>
<td>15</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>7.6</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>1.1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>2.3</td>
<td>3</td>
</tr>
</tbody>
</table>

* Statistically significant difference (p<0.05).

between time since last tetanus toxoid and reports of these symptoms. There were no significant differences in reported symptom severity between those completing their AEQs late and those completing them on time.

Public health professionals noted an increase in nausea, vomiting and diarrhea in the community during the 2005 vaccination program (Personal communication, C. Hemsley, Communicable Disease Control Officer, Yukon, 15/04/2005). Upon telephone follow-up, six students indicated onset of gastro-intestinal symptoms temporally inconsistent with vaccination or unvaccinated friends or family experiencing similar gastro-intestinal symptoms.

**DISCUSSION**

AEFI

Enhanced surveillance of AEFI during dTap catch-up in Yukon found that students receiving dTap ≥3 to <5 years since their last tetanus toxoid booster were more likely than those receiving it ≥5 years after their last tetanus booster to report pain at the injection site, but less likely to report redness, swelling, decreased energy, body aches and sore joints. The rates of adverse events reported for both groups were within the ranges observed elsewhere.13,14

Severe AEFI

Follow-up with students reporting severe AEFI revealed that, in many cases, the adverse event was less severe than initially reported. Other reported indicators (i.e., missed school) were unrelated to dTap. Overall, 31 respondents experienced severe AEFI. There was no association between experiencing severe AEFI and time since last tetanus toxoid.

Other factors

We expected the group with the shortened interval between tetanus boosters to be more likely to report symptoms or severe AEFI; however, this was not our finding. This may be explained by possible differences in reporting behaviours between younger and older students (younger students may have been more likely to report adverse events). We could not control for the differences in age in our two groups because, in general, Grade 9 students received their previous tetanus toxoid booster in Kindergarten and Grade 12 students received tetanus toxoid in Grade 9.

The observed differences in participation rates between the two groups within each school were not expected and may be attributable to other unassessed factors, such as socio-economic status or social desirability/peer pressure. These factors may also be related to the probability of reporting AEFIs.

The differing treatment of the Grade 12 students in 2004 may have resulted in recall bias, either by providing these students with a list of symptoms to consider for a week before completing the AEQ or by allowing these students to complete their AEQs at any time following vaccination. However, Grade 12 students did not consistently report more or fewer symptoms than Grade 9 students.

The community experienced increased gastro-intestinal symptoms during the 2005 vaccination program and it appeared that enteric viruses were responsible for some of the symptoms reported.

Despite collecting surveillance data over two years, the relatively small sample size may have led to less precise comparisons. However, the sample size was large enough to detect differences in individual symptoms. No difference was detected in incidence of severe adverse events between the two groups; the group of primary interest (students with a shortened interval between tetanus boosters) tended to report fewer severe reactions. As these results were based on enhanced surveillance following a public health campaign, we were not able to control all factors that may have confounded the associations of primary interest. Further research is required to support the findings of this surveillance project.

**CONCLUSIONS**

Adverse events were generally mild in the two groups. Students who received dTap ≥3 to <5 years after their last tetanus toxoid booster did not experience increased risk of severe AEFI. There was no significant difference in the severity of symptoms reported by the two groups and there was no significant difference in the proportion of respondents in either group experiencing severe AEFI. Enhanced surveillance confirmed that the benefits of this rescue program outweighed the possible risk of severe AEFI.

**REFERENCES**

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RéSUMÉ

Contexte : Afin de remédier à l’augmentation de l’âge des cas de coqueluche, le gouvernement du Yukon a décidé de remplacer le vaccin de rappel antitétanique/antidiphthérique/antipoliomyélitique inactivé, administré aux élèves de 9e année, par un vaccin contre la diphthérie, le tétanos et la coqueluche acellulaire (dTCa) et de mettre en place un programme de rappel pour les élèves de 12e année. Le programme a débuté en juin 2004, faisant du gouvernement du Yukon l’un des premiers au Canada à introduire l’administration du vaccin dTCa au cours des cinq années suivant l’administration d’un vaccin de rappel contre le tétanos. Des moyens de contrôle des MAPI indésirables (MAPI) et de déterminer si les élèves recevant le vaccin dTCa ≥ 5 ans après leur dernière injection de rappel contre le tétanos étaient plus à risque de présenter des MAPI graves.

Méthode : Les élèves ont rempli un questionnaire sur les MAPI une semaine après avoir reçu le vaccin dTCa, et des professionnels de la santé publique ont communiqué avec ceux rapporçant des MAPI graves. Les professionnels de la santé ont été tenus de signaler les MAPI. Les symptômes (fréquence, gravité et durée) des élèves ayant reçu le vaccin dTCa ≥ 5 ans après leur dernière injection de rappel contre le tétanos ont été comparés à ceux des élèves ayant reçu le vaccin dTCa ≥ 5 ans plus tard.

Résultats : Le groupe dont le délai était ≥ 5 ans était plus susceptible de signaler une douleur au point d’injection que le groupe dont le délai était ≥ 5 ans (70,6 % contre 61,5 %, p=0,038) et moins susceptible de signaler une rougeur (10 % contre 17,3 %, p=0,022) et une enflure au point d’injection (8,9 % contre 16,4 %, p=0,013), une baisse d’énergie (10 % contre 17,1 %, p=0,023), des courbatures (2,2 % contre 7,2 %, p=0,014) et des douleurs articulaires (3,3 % contre 10,1 %, p=0,004). Il n’y avait pas de différence entre les deux groupes en ce qui a trait aux MAPI graves (3,3 % contre 5,6 %, p=0,232). Les professionnels de la santé n’ont signalé aucune MAPI.

Conclusion : Les résultats indiquent qu’il n’y a pas de risque accru de MAPI graves chez les élèves qui reçoivent le vaccin dTCa ≥ 5 ans après leur dernière injection de rappel contre le tétanos.

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