This supplementary statement provides information on the use of a new, injectable vaccine against typhoid fever recently licensed in Canada, augmenting recently published recommendations on typhoid fever prevention from Health Canada\(^1,2\).

**Introduction**

Typhoid fever is caused by *Salmonella typhi*, which differs from most other *Salmonella* species in that it infects only humans and frequently causes severe systemic illness. It is usually transmitted by food and drink that has been contaminated with fecal material from a patient with typhoid fever or an asymptomatic carrier of *S. typhi*. The fatality rate ranges from 16% in untreated cases to less than 1% in those given appropriate antibiotic therapy. Chronic carriage, which may last for years, develops in 2% to 5% of cases. The risk of severe illness is increased in persons with diminished gastric acid levels due to gastrectomy or treatment with antacid or H2-antagonists, or in immunocompromised persons, e.g., AIDS patients and chemotherapy recipients.

In endemic areas, typhoid fever is primarily a disease of persons 5 to 19 years of age\(^3\); cases in children < 5 years of age account for fewer than 5% of the total number\(^4\) and typhoid fever in children < 2 years of age is infrequently reported\(^5\). The reason for the lower risk of typhoid fever in children < 5 years of age is unclear, but the observation is important in light of our incomplete knowledge of vaccine immunogenicity and efficacy in this age group.

The incidence of typhoid fever has declined steadily in Canada. Approximately 80 cases are reported annually. Most of these infections are contracted abroad but a small number are acquired in Canada. The decline in incidence of the disease has been primarily due to improved living conditions and to water and sewage treatment. For travellers to areas where sanitation is likely to be poor, immunization is not a substitute for careful selection and handling of food and water. However, immunization with vaccine is expected to further reduce the risk of typhoid fever among healthy visitors to areas with endemic disease.

In January 1995, a new vaccine for typhoid fever prevention, Typhim Vi\(^\text{TM}\), was licensed in Canada. Like the oral, live attenuated vaccine (Vivotif Berna\(^\text{TM}\)) that is currently available, it is efficacious and mildly reactogenic. A third licensed vaccine consisting of phenol-inactivated whole bacterial cells is no longer distributed in Canada. Its characteristics were described in the 4th edition of the *Canadian Immunization Guide*\(^1\).
distributed in Canada by Connaught Laboratories Ltd. under the trade name of Typhim Vi™. Each 0.5 mL dose of vaccine contains 25 µg of polysaccharide, which stimulates a specific, humoral antibody response that confers protection against infection. Controlled trials have demonstrated that the serologic response to vaccine correlated with protective efficacy (4). The same dose is used for children and adults. The manufacturer (Connaught Laboratories, unpublished data) does not recommend this vaccine for use in children < 2 years of age.

A single intramuscular dose of vaccine has been shown to evoke a four-fold or greater rise in circulating anti-Vi antibody in most healthy individuals but subjects < 2 years of age (4) and those with pre-existing antibody generally respond less well (6). In persons with no pre-existing anti-Vi antibody (whose responses are likely to resemble those of Canadian vaccinees), response rates differed with age, from 63% in a small number of toddlers < 2 years to 86% in children 2 to 5 years and 93% to 96% in subjects 5 to 44 years of age (Connaught Laboratories, unpublished data).

Comparison of Oral, Live Ty21a and Typhim Vi™ Polysaccharide Capsular Vaccines

These two vaccines are efficacious, similar in reactogenicity and have different side-effect profiles. They differ in the number of doses required for immunization, route of administration, suitability for children 2 to 5 years of age, recommended interval before reimmunization, and contraindications. Because both vaccines are relatively new, experience with them is limited.

No comparative trials of the two available vaccines have been reported. Typhim Vi™ prevented typhoid fever in 75% to 81% of healthy residents 5 to 44 years of age in endemic areas (4). Oral live Ty21a vaccine prevented disease in 17% and 59% of schoolchildren cohorts 5 to 9 years of age in two different studies; protection was 54% and 72% in two studies among schoolchildren 10 to 19 years of age (7-8).

Side effects are modest to minimal with both vaccines but differ in some respects. Fever has been reported in 0% to 1% of recipients of Typhim Vi™ vaccine and 1% to 6% of adults taking the oral vaccine, and headache in 2% to 3% (Typhim Vi™) and 0% to 5% (oral vaccine) of vaccine recipients (9). Local erythema and induration at the injection site have been observed in 7% of Typhim Vi™ recipients, whereas gastrointestinal symptoms (abdominal pain, nausea and vomiting) have been reported in 1% to 6% of adults taking the oral vaccine. These rates of reactions following the oral vaccine were not significantly different from placebo; the same was true in placebo-controlled trials in children.

**Recomended Use**

Based on the published field trials and immunogenicity studies, all the typhoid vaccines are recommended for the following groups:

1) Travellers to areas where there is a recognized risk of contracting typhoid fever. This includes all developing countries where the safety of the water supply is not known.
2) Persons who have intimate exposure (e.g., household contact) with a known carrier of S. typhi. Laboratory technicians who work frequently with S. typhi.
3) Vaccine is not routinely recommended for other Canadians, including sewage workers.

The recommended immunization schedule for Typhim Vi™ is one dose of 0.5 mL injected intramuscularly. The schedule for oral live Ty21a vaccine is four doses ingested as one capsule on alternate days.

Typhim Vi™ vaccine is approved for administration to persons ≥ 2 years of age, and oral live Ty21a vaccine for persons > 5 years of age.

The duration of vaccine efficacy is not well established for either vaccine. The ViCPS vaccine maintained its protective efficacy at 17 months (4) and 21 months (6); however, Vi antibody has been observed to decline by about 35% at 11 months and by about 60% at 27 months after immunization (10). An additional dose of ViCPS vaccine injected as late as 34 months restored antibody levels to those seen after primary immunization. For oral live Ty21a vaccine, protection persisted for at least 5 years after immunization in the longest reported follow-up of vaccinees (11).

If prolonged exposure to S. typhi is anticipated, booster doses of vaccine are required to maintain immunity. No data are available on the immunogenicity of ViCPS vaccine in individuals who have previously received other vaccines to prevent typhoid fever, but it is anticipated that a single dose of ViCPS vaccine will be as immunogenic in them as in unvaccinated persons.

Based on these data, the following reimmunization schedules are recommended by the manufacturers: ViCPS, one dose every 2 years and oral live Ty21a, a repeat course of four doses every 7 years.

**Contraindications**

There are no absolute contraindications to the use of the ViCPS vaccine except a history of a severe reaction to a previous dose. The oral Ty21a vaccine is contraindicated in immunocompromised individuals and taken concurrently, the antimalarial drug, mefloquine (12), sulfonamides or other antimicrobial agents may affect the viability and, theoretically, the immunogenicity of this vaccine. If individuals are receiving an oral antibiotic, oral live Ty21a vaccine is recommended to be administered ≥ 24 hours after a dose.

**Limits of Knowledge**

The immunogenicity, protective efficacy and safety of the two currently available typhoid fever vaccines have not been thoroughly studied in healthy vaccinees from countries like Canada that are free from endemic typhoid fever, nor in immunocompromised patients, individuals with chronic diseases, pregnant women, children < 5 years of age or adults > 44 years of age.

**Conclusion**

A single intramuscular dose of ViCPS vaccine offers Canadian physicians an alternative to four doses of oral Ty21a typhoid fever vaccine. Side effects are similar in frequency, slightly different in character, but not more serious. Compliance with ViCPS is assured whereas the potential for self-administration errors exists with oral, live Ty21a vaccine. Unlike live Ty21a vaccine, ViCPS is approved for administration to children 2 to 5 years of age, although neither vaccine is of proven value in children < 5 years of age.
ANAPHYLAXIS: STATEMENT ON INITIAL MANAGEMENT IN NON-HOSPITAL SETTINGS

This statement is updated from the version published in the Canadian Immunization Guide (4th edition, 1993). Dosage guidelines for epinephrine have been modified to better suit preadolescents.

This statement is intended to be a guide for initial management of patients in a public health clinic or similar non-hospital setting. In a patient with severe, life-threatening anaphylaxis, establishment of intravenous access for drug and fluid administration will be necessary and endotracheal intubation and other maneuvers may be required. These interventions are ordinarily best performed in a hospital’s emergency room.

Anaphylaxis is a rare and potentially life-threatening allergic complication of immunization that should be anticipated in every vaccinee. Prevention is the best approach. Pre-vaccination screening should include questions about possible allergy to any component of the product(s) being considered to identify this contraindication. As avoidance is not always possible, every vaccine provider should be familiar with the symptoms of anaphylaxis and be ready to administer appropriate medications. Vaccine recipients should be kept under supervision for at least 15 minutes post-immunization.

Anaphylaxis is one of the rarer events reported in the post-marketing surveillance system for vaccine adverse events. Based on the last 5 years of complete national data, the annual rate of anaphylaxis ranges from 0.11 to 0.31 reports per 100,000 doses of vaccines distributed.

Anaphylaxis must be distinguished from fainting (vasovagal syncope), which is a more common and benign reaction. Fainting is simply managed by placing the patient in a recumbent position. Rapidity of onset is a key differentiator. With fainting, the subject changes from a normal to an unconscious state within seconds. Fainting is sometimes accompanied by brief clonic seizure activity but this generally requires no specific treatment or investigation. With anaphylaxis, changes develop over several minutes, may involve multiple body systems (skin, respiration, circulation) and may progress to unconsciousness only as a late event in severe cases. Rarely is unconsciousness the sole manifestation of anaphylaxis.

Anaphylaxis usually begins a few minutes after injection of the offending substance and is usually evident within 15 minutes. Symptoms can include sneezing, coughing, itching, "pins and needles" sensation of the skin, flushing, facial edema, urticaria, anxiety, respiratory difficulties and hypotension, which may progress to shock and collapse. Cardiovascular collapse can occur without respiratory symptoms. Early recognition and treatment of anaphylaxis is vital. Measures outlined here are appropriate for initial management in non-hospital settings.

1. Place the patient in a recumbent position (elevating the feet if possible).
2. Establish an oral airway if necessary.
3. Place a tourniquet (when possible) above the site of vaccination. Release for 1 minute every 3 minutes.
4. Promptly administer 0.01 mL/kg (maximum 0.5 mL) of aqueous epinephrine 1:1,000 by subcutaneous or intramuscular injection in the opposite limb to that in which the immunization was given.

The subcutaneous route of epinephrine injection is appropriate for mild or early cases. Severe cases should receive intramuscular injections because they lead more quickly to generalized distribution of the drug. A single subcutaneous injection is usually sufficient for mild or early anaphylaxis.

Dosing can be repeated twice at 20-minute intervals, if necessary. Severe reactions could require these repeat doses to...
be given at shorter intervals (10 to 15 minutes).

**Speedy intervention is of paramount importance: failure to use epinephrine promptly is more dangerous than using it improperly.**

Epinephrine dosage should be carefully determined. Calculations based on body weight are preferred when weight is known. Recording the weight of children prior to routine immunization is recommended when feasible. Excessive dosages of epinephrine can add to subjects’ distress by causing palpitations, tachycardia, flushing and headache. Although unpleasant, such side effects pose little danger. Cardiac dysrhythmias may occur in older adults but are rare in otherwise healthy children.

When body weight is not known the dosage of epinephrine 1:1,000 can be approximated from the subject’s age as follows:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage (mL)</th>
<th>(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 6 months*</td>
<td>0.07</td>
<td>(0.07)</td>
</tr>
<tr>
<td>12 months*</td>
<td>0.1</td>
<td>(0.1)</td>
</tr>
<tr>
<td>18 months* to 4 years</td>
<td>0.15</td>
<td>(0.15)</td>
</tr>
<tr>
<td>5 years</td>
<td>0.2</td>
<td>(0.2)</td>
</tr>
<tr>
<td>6 - 9 years</td>
<td>0.3</td>
<td>(0.3)</td>
</tr>
<tr>
<td>10 - 13 years</td>
<td>0.4</td>
<td>(0.4)</td>
</tr>
<tr>
<td>≥ 14 years</td>
<td>0.5</td>
<td>(0.5)</td>
</tr>
</tbody>
</table>

* Dosage for children between the ages shown should be approximated, choosing dose volumes intermediate between those shown or the next larger dose, depending on practicality.

The anaphylactic state in patients on beta adrenergic antagonist therapy (for elevated blood pressure) will be more resistant to epinephrine therapy.

Since anaphylaxis is rare, epinephrine vials and other emergency supplies should be checked on a regular basis and replaced if outdated.

**Announcement**

**GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION**

**Vaccine Research and Development**

In 1996, the WHO Global Programme for Vaccines and Immunization will provide seed funds for goal-oriented research projects in the following priority areas. Research proposals should be received by the deadline indicated for each component of the Programme.

**Disease-Specific Vaccinology**

- **Bacterial and viral diarrhea and typhoid fever**
  **[Deadline: 22 February, 1996]**

  Infant vaccines against *Shigella*, *enterotoxigenic Escherichia coli* and typhoid fever: non-living vaccines in oral delivery systems; live attenuated strains or live vectorbase vaccines; in vitro correlates of immunity.

  Vaccines against rotavirus: identification of immunologic correlates of protection; development of subunit candidate vaccines and of attenuated rotavirus strains; live viral and bacterial vector-based vaccines; appropriate animal models.

- **Meningococcal diseases and pneumococcal pneumonia**
  **[Deadline: 10 January, 1996]**

  Clinical trials of *Neisseria meningitidis* (A + C) and *Streptococcus pneumoniae* conjugate vaccines; development of *N. meningitidis* B vaccines (polysaccharide, LPS or protein vaccines); innovative approaches towards less expensive conjugate vaccines; epidemiologic studies of invasive diseases due to encapsulated bacteria.

- **Tuberculosis and leprosy**
  **[Deadline: 22 February, 1996]**

  Subunit vaccines and vaccines based on rational attenuation of mycobacteria and on live vectors; nucleic acid vaccines; immunologic correlates of protective immunity against tuberculosis; new vaccination strategies; epidemiology of tuberculosis and leprosy.

5. If the vaccine was injected subcutaneously, an additional dose of 0.005 mL/kg (maximum 0.3 mL) of aqueous epinephrine 1:1,000 can be injected in the vaccination site to slow absorption. Local injection of epinephrine into an intramuscular vaccination site is contraindicated because it dilates vessels and speeds absorption.

6. **As an adjunct to epinephrine, a dose of diphenhydramine hydrochloride (Benadryl®) can be given.** It should be reserved for patients not responding well to epinephrine or to maintain symptom control in those who have responded (epinephrine being a short-acting agent), especially if transfer to an acute care facility cannot be effected within 30 minutes. Oral treatment is preferred for conscious patients who are not seriously ill because Benadryl® is painful when given intramuscularly. This drug has a high safety margin making precise dosing less important.

The approximate dosages of diphenhydramine HCI (Benadryl® for injection 50 mg/mL solution) are shown in the following table:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage (mL)</th>
<th>(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 years</td>
<td>0.25</td>
<td>(12.5)</td>
</tr>
<tr>
<td>2 - 4 years</td>
<td>0.5</td>
<td>(25)</td>
</tr>
<tr>
<td>5 - 11 years</td>
<td>1.0</td>
<td>(50)</td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>2.0</td>
<td>(100)</td>
</tr>
</tbody>
</table>

7. **Arrange for rapid transport to an emergency room.** For all but the mildest cases of anaphylaxis, patients should be hospitalized overnight or monitored for at least 12 hours.

**Reference**

skin tests for leprosy; nature and control of nerve damage during lepra reactions.

• Measles  
[Deadline: 10 January, 1996]
Immunobiology of measles virus infection and immunization; development of infectious clones; vaccines that are protective in the presence of pre-existing antibodies and not disease potentiating; subunit vaccines; live vectors of measles virus proteins; improved live attenuated vaccines and nucleic acid vaccines.

• Dengue and Japanese encephalitis  
[Deadline: 10 January, 1996]
Infectious clones; development of candidate vaccines; evaluation of safety and protective efficacy in animal models; initial clinical trials.

New Vaccination Approaches  
[Deadline: 10 January, 1996]
The general objective is to improve vaccine immunogenicity and simplify vaccine delivery through:

a. NEW IMMUNIZATION APPROACHES

• Nucleic acid vaccines: novel constructs, combination of pathogens and cytokines genes, delivery systems.

• Mucosal immunization: adjuvants, nasal delivery.

• Neonatal vaccinology: qualitative analysis of responses to existing vaccines in neonates.

b. NEW DELIVERY SYSTEMS

• New adjuvants: to both reduce number of doses and amount of antigen in a cost-effective manner, carriers for conjugate vaccines.

• Live vectors: safety in immunocompromised hosts.

Application forms and information on priorities can be requested from Global Programme for Vaccines and Immunization, Vaccine Research and Development Unit, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland, Fax number (41-22) 791 4860. E-mail: EIDM@WHO.CH. Form and information are also on WHO-INTERNET-Gopher/MAJOR PROGRAMMES/ GP\VWRD (TELNET: HQVAX1.WHO.CH). Information will be sent to E-mail addresses, if indicated.

Notice

TO ALL OUR SUBSCRIBERS

In the September 30th issue, we announced that, beginning in January 1996, the Canadian Medical Association (CMA) would be responsible for the printing, distribution, marketing and management of subscriptions for the Canada Communicable Disease Report.

Renewal notices will be distributed soon by the CMA. Any future inquiries regarding subscriptions or copies of particular issues should be directed to the Information Technology Group, Canadian Medical Association, P.O. Box 8650, Ottawa, Ontario, K1G 0G8 [Tel: (613) 731-9331, ext. 2028; Fax: (613) 731-9102].

Any inquiries regarding particular issues during 1995 should be directed to Eleanor Paulson, Editor-in-Chief, Canada Communicable Disease Report, Laboratory Centre for Disease Control, Health Canada, Tunney’s Pasture, Ottawa, Ontario, K1A 0L2 [Tel: (613) 957-1788; Fax: (613) 998-6413].