

Français	Contact Us	Help	Search	Canada Site
Home	Centres & Labs	Publications	Guidelines	A-Z Index
Child Health	Adult Health	Seniors Health	Surveillance	Health Canada

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EXPOSURE TO THIMEROSAL IN VACCINES USED IN CANADIAN INFANT IMMUNIZATION PROGRAMS, WITH RESPECT TO RISK OF NEURODEVELOPMENTAL DISORDERS

Background

Thimerosal is a mercury-containing preservative that has been used as a vaccine additive for > 60 years. High-dose, acute or chronic mercury exposure of children and adults can cause neuro- and nephrotoxicity⁽¹⁻⁴⁾. However, there are limited data examining the effects of low-dose, intermittent mercury exposure, for example, when infants are immunized with thimerosal-containing vaccines. Currently, the only thimerosal-containing vaccine in *routine* use in the infant immunization schedules of some Canadian jurisdictions is hepatitis B vaccine.

In a statement released in December 1999⁽⁵⁾, Canada's National Advisory Committee on Immunization recommended no change to existing infant immunization programs for three reasons:

- absence of exposure (in eight provinces), or very low cumulative exposure of Canadian infants to vaccine-derived thimerosal (in two provinces and both territories where thimerosal-containing hepatitis B vaccine was, at that time, used in *routine* infant immunization programs*);
- lack of evidence of harm from exposure to the dose of mercury in thimerosal-containing hepatitis B vaccine given to infants < 6 months age; and,
- no thimerosal-free hepatitis B vaccine was licensed for use in Canada at that time.

Thimerosal-derived mercury in vaccines remains a vaccine safety issue, with public attention and scientific scrutiny focused on whether thimerosal exposure from immunization in the first 6 months of age causes neurodevelopmental disorders, such as autism, attention deficit/hyperactivity disorder, or speech or language problems⁽⁶⁻⁸⁾. The purpose of this review is to examine the risk of neurodevelopmental disorders, including autism, in Canadian children as a result of mercury exposure from thimerosal-containing vaccines routinely used in some provincial/territorial universal infant and early childhood immunization programs.

Methods

An Internet-based search and review of MEDLINE English language literature was conducted in November and December 2001^{**}. The following Boolean key word combinations were used: "(thimerosal or mercury) and (hepatitis B vaccine or vaccine)", and "(thimerosal or mercury) and (autism or neurotoxicity or neurodevelopmental delay)".

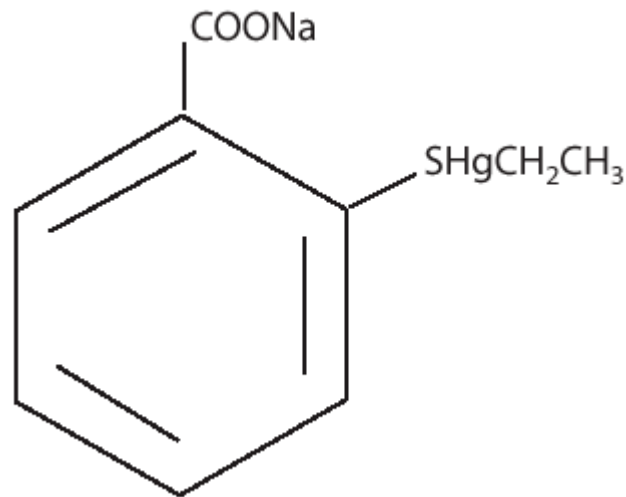
To minimize publication bias, an identical electronic search using a commercial search engine[†] was also conducted. Additional relevant unpublished information was sought from Health Canada and from sources identified or cited in published literature. An electronic survey of Canadian provincial/territorial epidemiologists in jurisdictions with universal infant hepatitis B immunization programs, was undertaken in December 2001 and January 2002, to determine whether thimerosal-free hepatitis B vaccine was used in their infant program.

Results

Thimerosal -chemical properties and uses

Thimerosal (C₉H₉HgNaO₂S or ethylmercurithiosalicylic acid) is an organo-mercurial compound (Figure 1) that dissociates as 49.6% ethyl mercury by weight, and thiosalicylic acid^(9,10). Thimerosal has been added to drugs and vaccines primarily as a preservative to prevent bacterial or fungal contamination of these products. It is also used as an inactivating or bacterio- static agent in the manufacturing process of some vaccines^(9,10). Over 20 vaccines licensed in Canada contain thimerosal, in concentrations ranging from 0.005% to 0.01%⁽¹¹⁾.

Figure 1. Thimerosal chemical structure



Regulatory agency reviews

Public concern about thimerosal-containing vaccines first arose in Europe and the United States (U.S.) in 1999. The European Agency for the Evaluation of Medicinal Products (EMA) issued a public statement in July 1999, recommending elimination of organo-mercurial preservatives in vaccines used for infants and toddlers, with a view to limiting cumulative exposure to ethylmercury from a range of sources, including food and medicinal products⁽¹²⁾. At the same time, a U.S. congressional-mandated review by the U.S. Food and Drug Administration (USFDA) revealed that the cumulative vaccine-derived exposure by American infants in the first 6 months of life to the ethylmercury metabolite of thimerosal exceeded the recommended U.S. Environmental Protection Agency (USEPA) exposure limit for a closely related organic mercury compound, methylmercury⁽¹³⁻¹⁵⁾. Exposure to the fetus or infant in the first 6 months after birth is of particular concern because of susceptibility of the developing nervous system to mercury toxicity⁽¹⁻⁴⁾.

Autism

Similarities between autism and neurologic effects of mercury (discussed below) have led some to argue that vaccine-derived thimerosal might cause autism⁽¹⁵⁾. Autism is a life-long developmental disability, characterized by impaired social interaction and communication and a pattern of restrictive, repetitive and stereotypic behaviours, interests and activities⁽¹⁶⁾. These characteristics present across a wide spectrum of clinical severity and most commonly are recognized in children 18 to 30 months of age. Boys are more commonly affected.

The cause(s) of autism is/are unknown although a variety of different factors have been implicated⁽¹⁷⁾. A genetic component is suggested by studies that show an identical twin of a child with autism having a 75% to 90% chance of having autism, compared with a fraternal twin of a child with autism having only a 5% to 10% chance. Families with autism have a 10% to 40% increase in diagnosis of other developmental or learning disabilities. Cited environmental causes include: exposure to heavy metals such as lead or mercury; nutritional deficiency (e.g., iodine); metabolic disease (e.g., iron overload); or infectious diseases (e.g., congenital rubella syndrome or meningitis caused by *Haemophilus influenzae* or *Neisseria meningitidis*). Another theory posits a genetic predisposition to unspecified heavy metal intoxication in some children, related to metallothionein protein dysfunction, which has been suggested to have a role in metabolism of these compounds⁽¹⁸⁾.

Health effects of methylmercury and ethylmercury -acute or chronic high-dose exposures

Both methylmercury and ethylmercury can cause peripheral and central nervous system injury in adults and children following acute or chronic, high-dose dietary exposure^(1,10,19). Symptoms may include tremors, spasms, numbness and tingling of extremities, and a range of psychomotor and psychologic effects including irritability, restlessness, difficulty concentrating, decreased memory, and depression. Many of these symptoms and signs resemble those found in autistic children. Studies of the effects of ethylmercury and methylmercury in rats suggest comparable observable neurologic effects of intoxication between these two compounds^(14,20,21).

Cases of acute, high-dose thimerosal poisoning are also reported in the literature, involving oral or injection exposures to thimerosal in the range of 100 mg/kg or higher, among children and adults⁽²²⁻²⁴⁾. Several deaths attributable to acute mercury toxicity, and a similar range of neurologic symptoms as cited above, were reported. Animal experiments of acute thimerosal toxicity reveal an oral lethal dose for half of exposed mice (LD₅₀) (oral) to be 91 mg/kg body weight and an LD₅₀ (subcutaneous) in exposed rats of 98 mg/kg body weight⁽²⁵⁾.

Other documented reports of high-dose oral ethylmercury poisoning relate to consumption, over periods of weeks to several months, of grains or foods contaminated by mercury-containing fungicide (e.g., rice, bread, or meat from grain-fed animals). Neurologic symptoms included ataxia, unsteady gait and balance, speech disturbances, and tremors⁽²⁶⁻²⁸⁾.

Health effects of methylmercury and ethylmercury -chronic (e.g., dietary) or intermittent low-dose (e.g., vaccination) exposures

To date, the most common vaccine-associated adverse event to which thimerosal has been possibly implicated is minor, contact allergy (delayed-type hypersensitivity) skin reactions^(9,29). Between 1% and 16% of tested individuals have exhibited such a reaction on skin patch testing⁽³⁰⁾.

Immediate hypersensitivity (e.g., anaphylaxis) and immune complex-mediated disorders (e.g., glomerulonephritis) have been reported in association with exposure to thimerosal-containing products although it is uncertain if thimerosal was the responsible allergen^(14,29).

There is currently no direct evidence that thimerosal-containing vaccines causes autism or any other neurodevelopmental disorder in humans^(10,14,29,31). No long-term, prospective, controlled epidemiologic studies of the neurologic or neurodevelopmental effects of intermittent, low-dose exposure to thimerosal or ethylmercury are reported in the scientific literature. Dose-response relationships to low-dose methylmercury or ethylmercury exposures are unknown, although two population-based studies conducted in the Seychelles Islands⁽³²⁾ and Faroe Islands⁽³³⁾, are evaluating the neurotoxic effects of exposure to methylmercury *in utero* as a result of mothers' dietary intake of mercury-contaminated seafood. The mercury exposure profiles *in utero* and infancy differed in these two settings. In the Seychelles, mothers' daily diet consisted of fish with lower levels of mercury contamination, resulting in chronic, low level mercury exposure to their infants, whereas Faroese mothers exposed their unborn children to intermittent, higher dose exposures as a result of periodic consumption of more highly contaminated pilot whale meat.

The Seychelles study, which used maternal and child hair to evaluate prenatal and childhood mercury exposure respectively, and primarily global neuropsychiatric scales to assess outcome, has found no neurologic impairment among children <= 9 years of age^(29,34). The Faroe Islands study, which used umbilical cord blood and child hair to evaluate prenatal and postnatal mercury exposure respectively, and domain-specific neuropsychiatric testing to assess outcome, reported subtle neurologic deficits in memory, attention and language scores among 7-year-old children tested. Postnatal mercury exposure was less predictive of these effects than prenatal exposure⁽³⁵⁾. Further study is required to properly evaluate these discordant findings, particularly in view of the fact that infant neurodevelopment test results have not consistently been shown to predict later dysfunction⁽³¹⁾.

One unpublished retrospective cohort study was reported in 2001 in a review of thimerosal-containing vaccines by the U.S. Institute of Medicine's Immunization Safety Review Committee⁽²⁹⁾. This study examined 10 years of data from the Vaccine Safety Datalink (VSD), a large U.S. database, covering approximately 2.5% of the U.S. population. The VSD links vaccination, clinic, hospital discharge and demographic data from seven health maintenance organizations (HMO's). A statistically significant, but weak, association (relative risk ratio < 2) was found between various cumulative exposures to thimerosal and some neurodevelopmental diagnoses, such as speech delay and attention deficit disorder, but not autism. No significant difference in risk of any neurologic or

neurodevelopmental disorder was identified, although small sample size limited the power of the study to detect a small effect. Potential limitations of this analysis include biases related to healthcare-seeking behaviour, diagnostic ascertainment, and misclassification biases and lack of data on familial or genetic predispositions to neurodevelopmental outcomes⁽²⁹⁾.

One study examined blood mercury levels in infants vaccinated with thimerosal-containing hepatitis B vaccine⁽³⁶⁾. Blood mercury increased from a baseline (prevaccination) level < 1 µg/L to 2.24 µg/L (standard deviation [SD] ± 0.58) and 7.36 µg/L (SD ± 4.99) for preterm and term infants respectively, within 48 to 72 hours after a single dose of vaccine. However, maternal hair mercury level (an indicator of *in utero* exposure) was not examined, and neurodevelopmental testing was not done, to evaluate the clinical significance of this increase in blood mercury. The toxicologic relevance of this is further complicated by uncertainty of the pharmacokinetics (e.g., rates of metabolism and excretion) of mercury in blood⁽²³⁾, and reports from other studies that maternal blood levels of 100 µg/L to 200 µg/L were not associated with detectable abnormalities in infants exposed *in utero*^(37,38).

Sources of environmental mercury exposure

Mercury is a ubiquitous element in the natural environment⁽¹⁾. Mercury is present in soil at average concentrations between 0.05 µg/g and 0.08 µg/g of soil and 0.2 µg/L in fresh water lakes⁽²⁾. Mercury vapour is present in ambient air, with concentrations in uncontaminated areas averaging < 10 ng/m³⁽³⁹⁾. Natural sources contribute an estimated 2,700 to 6,000 tonnes per year to global emissions, compared with <= 3,000 tonnes per year from human activities⁽⁴⁰⁾.

Table 1 shows that the main population sources of exposure to elemental and methylmercury are dental amalgam and dietary fish, respectively⁽⁴¹⁾. Organic mercury compounds occur in high concentrations in certain species of dietary fish. For example, in a survey of U.S. food market baskets conducted between 1991 and 1999 by the USFDA, canned tuna, packed in oil was reported to contain an average 0.165 µg/g of mercury⁽⁴²⁾. In the same survey, USFDA reported mean mercury concentrations of 0.070 µg/g for pan-fried haddock, 0.029 µg/g for salmon, and 0.027 µg/g for boiled shrimp.

Table 1. Estimated daily intake and retention (µg /day) of elemental and mercuric compounds in the general population not occupationally exposed to mercury*

Exposure	Elemental mercury vapour, µg /day	Inorganic mercury compounds µg /day	Methylmercury µg /day
	intake/retention	intake/retention	intake/retention
Air	0.030 (0.024)	0.002 (0.001)	0.008 (0.0064)
Food -fish	0	0.600 (0.042)	2.4 (2.3)
Food -non-fish	0	3.6 (0.25)	0
Drinking water	0	0.050 (0.0035)	0
Dental amalgam	3.8-21 (3-17)	0	0
Total	3.9-21 (3.1-17)	4.3 (0.3)	2.41 (2.31)

* *Environmental Health Criteria 101: Methylmercury*. Geneva: World Health Organization, 1990.

Sources of mercury exposure in infants

Typical dietary consumption of fish, including species mentioned above, by pregnant or lactating women, can result in fetal or infant mercury exposure far exceeding those from thimerosal-containing vaccines, since these compounds can cross the placenta and are also excreted in breast milk^(10,19,31,43). The U.S. EPA estimates that 7% of U.S. women of childbearing age consume >= 0.1 µg/kg per day of mercury from fish harvested in high risk areas⁽⁴⁴⁾.

Potential thimerosal exposure through Canadian routine infant immunization

As of January 2002, three provinces (New Brunswick, Prince Edward Island and British Columbia), along with Yukon, Northwest Territories and Nunavut, had incorporated hepatitis B vaccine into their routine infant immunization schedules (Dr. T. Tam, Health Canada, Ottawa: personal communication, 2002). Across these six jurisdictions, five different schedules of infant hepatitis B vaccination have been implemented, offering three doses of hepatitis B vaccine at various times between birth and 15 months of age.

Two licensed recombinant hepatitis B vaccines (Engerix B™ [Glaxo Smithkline] and Recombivax B™ [Merck Frosst Canada]) have been available in Canada since these programs were initiated, containing thimerosal at a concentration of 0.005% or 50 µg/mL. A regular infant dose of 0.5 mL Engerix B™ contains 12.5 µg of ethylmercury, while a regular infant dose of 0.25 mL of Recombivax B™ contains 6.25 µg. Depending on the product and hepatitis B immunization schedule, Canadian infants from the above six Canadian jurisdictions could have been exposed to between 12.5 µg and 37.5 µg of ethylmercury in the first 6 months of life (or an average of 0.069 µg/day to 0.206 µg/day), from thimerosal-containing hepatitis B vaccine.

All Canadian provinces and territories also offer hepatitis B immunoprophylaxis to high-risk infants whose mother is identified through antenatal testing as a hepatitis B carrier. Such infants (approximately 2,000 per year in Canada) are routinely immunized with three doses of hepatitis B vaccine in the first 6 months of life, and in this circumstance, the recommended dose of either recombinant hepatitis B vaccine is 0.5 mL. Consequently, immunized, high-risk infants will have been exposed to 37.5 µg of ethylmercury in the first 6 months of life, from thimerosal-containing vaccine.

Organic mercury metabolism in humans

Limited human toxicologic and pharmacokinetic data are available for ethylmercury, particularly from episodic, low-dose, intramuscular exposure. Comparison is made to methylmercury, for which gastrointestinal exposure in particular has been studied more extensively^(1,19,25,29). Although methylmercury binds with cysteine to form a complex that readily crosses the blood-brain barrier and enters neurons, it is unknown if a similar transport mechanism exists for ethylmercury⁽⁴⁵⁾. The biologic half-life of methylmercury in humans is about 70 days^(25,29), but it is likely less for ethylmercury due to more rapid conversion in the lungs, liver and red blood cells to inorganic mercury -which does not cross the blood-brain barrier as readily^(20,46-48). On the other hand, once in the brain, ethylmercury is converted to its inorganic form, resulting in higher cumulative neural exposure to mercury, again due to less efficient inorganic mercury transport across the blood-brain barrier⁽²⁰⁾. Organic mercury also binds to glutathione, which may play a protective role in transporting mercury out of cells, as well as to metallothionein and other plasma proteins⁽¹⁹⁾. The metabolic and toxicologic effects of these mercury-containing complexes are poorly understood⁽¹⁹⁾.

Methylmercury is absorbed from blood and incorporated into scalp hair in a fixed concentration that is highly correlated to blood levels, at an approximate ratio of hair to blood mercury of 250:1⁽⁴¹⁾. Thus, hair represents a reliable biologic monitor of past mercury exposure⁽³⁾. Ninety per cent of methylmercury is excreted through bile in feces, mostly as inorganic mercury⁽¹⁰⁾.

Exposure limits to methylmercury

There are no relevant studies for evaluating a "no observed effect level" (NOEL) for thimerosal and, no "allowable daily intake" (ADI) has been proposed⁽²⁵⁾. Various agencies' "worst-case" scenarios of calculated cumulative exposure limit to methylmercury exposure for infants in the first 6 months of life are depicted in Table 2⁽¹⁴⁾. Such scenarios assume administration of three doses of hepatitis B vaccine containing 12.5 µg of ethylmercury per dose to a female infant in the lowest 5th percentile of mean body weight during the first 6 months of life.

It should be pointed out that the suggested exposure limits in [Table 2](#) do not represent absolute levels above which toxicity occurs but, reflect an *average daily* intake of methylmercury from all sources *over a lifetime*, below which there is no known, appreciable health risk^(29,49). The differences in suggested methylmercury exposure limit between the various agencies reflects the limited epidemiologic data available, differing data sources used and differing risk assessment methodologies that incorporate a range of exposure and health effect variables^(14,29). For example, the Health Canada figure is based on an approximated bench-mark dose of 10 parts per million (ppm) maternal hair concentration for women of child bearing age and children. The hair mercury concentration is converted to an equivalent blood mercury concentration and daily mercury intake. An uncertainty factor of five is applied to give the interim tolerable daily intake (TDI). The USEPA follows a similar review of the scientific information on dose-response, but applies an uncertainty factor of 10 to derive their reference dose (RfD). It is worth noting that the

variability between the suggested limits is less than one order of magnitude. In general, these limits are intended to be protective of the fetus, whose developing brain is presumed to be most susceptible to mercury toxicity^(4,10,14,50).

Exposures early in life are reasonably of greater health concern, not only because of greater brain organ susceptibility, but also due to methylmercury's extended biological half-life in the central nervous system⁽⁵¹⁾. It is unknown whether organic mercury exposure in the first 6 months after birth poses as great a risk as *in utero* exposure^(10,29). The validity of the suggested limits is also constrained by the few studies undertaken and the sensitivity of methods utilized to detect and measure cumulative low-dose exposures to methylmercury or ethylmercury or subtle neurodevelopmental effects in young children.

Table 2 "Worst-case scenario" cumulative exposure limit to methylmercury for infants <= 6 months age, based on 5th percentile of female infant body weight*

Agency	Suggested daily dietary exposure limit to methylmercury - $\mu\text{g}/\text{kg}$ body weight per Day/week	Calculated cumulative exposure limit to methylmercury for infant <= 6 months of age (μg) [†]	Maximum cumulative ethylmercury content of three doses hepatitis b vaccine (12.5 μg per dose)	% ratio of cumulative hepatitis B vaccine-derived ethylmercury to agencies' calculated cumulative exposure limits for methylmercury
Health Canada**	0.2 (1.4)	138.7	37.5 μg	27%
World Health Organization	0.47 (3.3)	327.7	37.5 μg	11%
U.S. Environmental Protection Agency (U.S. EPA)	0.1 (0.7)	69.3	37.5 μg	54%
U.S. Food and Drug Administration (USFDA)	0.4 (2.8)	277.4	37.5 μg	14%

* Based on: Ball LK, Ball R, Pratt RD. *An assessment of thimerosal use in childhood vaccines*. Pediatrics 2001;107:1147-54.

[†] Calculated as dose/kg body weight/week x mean weight x 26 weeks and based on the mean of lowest 5th percentile of weight for a female infant between birth (2.36 kg) and 6 months age (5.25 kg) -i.e., 3.81 kg.

** Clarkson TW. *Mercury: major issues in environmental health*. Environ Hlth Perspect 1993;100:31-8.

Discussion

Adverse neurodevelopmental effects following vaccine-related ethylmercury exposures -if these adverse effects do exist -are either extremely subtle and difficult to measure or occur at a frequency that is so low that they have escaped reliable detection^(14,29,31). Nevertheless, additional studies are being undertaken to further evaluate whether there is any association between neurodevelopmental disorders and exposure to thimerosal-containing vaccines⁽²⁹⁾.

It is worth emphasizing that agencies' recommended limits to methylmercury shown in [Table 2](#) are based on critical mercury concentrations in hair or blood that are measures of ongoing mercury exposure. With a half-life in blood of about 70 days, two or three discrete exposures of ethylmercury from thimerosal-containing hepatitis B vaccine will not produce the same steady-state blood mercury concentration as an ongoing exposure to this as a daily dose. Therefore for example, it is not correct to infer from agencies' guidelines that a single dose of 12.5 μg ethylmercury from thimerosal-containing hepatitis B vaccine administered to a 2-month-old, 3 kg infant, (i.e., 4.2 $\mu\text{g}/\text{kg}$) represents a 1-day exposure to ethylmercury that is 21 times the suggested daily limit for methylmercury set by Health Canada.

A thimerosal-free hepatitis B vaccine, Recombivax BTM (Merck Frosst Canada) was licensed in Canada on 16 March 2001, and licensure of a second such product is anticipated in early 2002. By December 2001, four of six

Canadian jurisdictions (British Columbia, New Brunswick, Prince Edward Island and Yukon) which routinely immunize all infants with hepatitis B vaccine, had switched to thimerosal-free vaccine. Other routine childhood vaccines used in Canada, such as those for measles, mumps, and rubella (MMR) and PENTACEL™ (for diphtheria, tetanus, acellular pertussis, *H. influenzae* type b, and inactivated polio) do not contain thimerosal preservative⁽¹¹⁾.

Therefore, at this time, exposure of Canadian infants in the first 6 months of life to ethylmercury from thimerosal-containing vaccines used in the routine immunization schedule, has been eliminated. This does not mean that all thimerosal-containing vaccines have been eliminated in Canada. A number of other thimerosal-containing vaccines are licensed that are used in special circumstances, that could continue to expose infants < 6 months of age to ethylmercury.

These include some single antigen acellular pertussis and conjugate *H. influenzae* vaccines, diphtheria-tetanus, and diphtheria-tetanus-acellular pertussis combination vaccines, all of which contain thimerosal in a concentration of 0.01%, and represent an exposure of 25 µg ethylmercury per 0.5 mL dose⁽¹¹⁾. Thimerosal-containing hepatitis B vaccine continues to be used in some Canadian jurisdictions to protect high risk infants born to chronic hepatitis B infected mothers. Influenza vaccines that are licensed in Canada also contain 0.01% thimerosal but are not recommended or used in infants < 6 months of age because of lack of effectiveness early in life.

In part, media and public concern about thimerosal likely reflects increasing public intolerance of avoidable exposure of children to real or even theoretical risks from all sources. The balance of benefit versus risk strongly favours continued use of thimerosal-containing vaccines, where no alternatives exist. As thimerosal-free vaccines come to market, it is prudent for Canada to incorporate these products into immunization programs, to minimize to the extent possible, the total burden of organic mercury exposure to children. Suitable thimerosal-free alternatives include preservative-free single dose vaccines, or products that use nonmercurial preservatives, such as phenoxyethanol.

Important lessons can be learnt from the confusing process of implementing transition to thimerosal-free childhood vaccines in the U.S. during 1999-2000, which in some instances resulted in inappropriate deferral of hepatitis B immunization for high-risk infants⁽⁵²⁻⁵⁴⁾. A carefully defined and co-ordinated policy, and effective communication to practitioners and the public, are essential components of a successful transition. In the meantime, thimerosal-containing vaccines should continue to be offered to children in all instances where no thimerosal-free alternative is available.

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* New Brunswick, Prince Edward Island, Yukon and Northwest Territories were the only jurisdictions in Canada with a universal infant hepatitis B immunization program in 1999.

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