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National Advisory Committee on Immunization (NACI)*

SUPPLEMENTARY STATEMENT
MMR VACCINE AND ANAPHYLACTIC HYPERSENSITIVITY TO EGG OR EGG-RELATED ANTIGENS

*The fourth edition of the **Canadian Immunization Guide** (1993) recommends that "persons who have a history of anaphylactic hypersensitivity to hens' eggs (urticaria, swelling of the mouth and throat, difficulty in breathing or hypotension) should not be given measles vaccine except under special precautions." The precautions outlined include skin testing with diluted vaccine and graded- challenge vaccination if the skin test is positive. Results of several recent studies have questioned such a cautious approach. NACI has reviewed all available data and revised its guidelines accordingly. The following revised guidelines are a major departure from the previously published recommendations. They will appear in the next edition of the **Canadian Immunization Guide**.*

A measles-rubella combination vaccine (Mo-Ru Viraten Berna™) recently licensed in Canada contains no avian proteins and therefore can be used without regard to egg allergy.

Vaccines that contain small quantities of egg protein can cause hypersensitivity reactions in some people with egg allergy. Adverse reactions are more likely with vaccines, such as yellow fever and influenza vaccines, that are grown in embryonated eggs. In contrast, measles and mumps vaccine viruses, which are most widely used in Canada, are grown in chick-embryo cell culture. Even after extensive purification, final vaccine products may contain trace quantities of avian proteins resembling proteins present in hens' eggs[1,2]. Anaphylaxis after administering measles-containing vaccines is rare and has been reported in individuals with anaphylactic hypersensitivity to eggs as well as those with no history of egg allergy. In some of these instances, allergy to neomycin[3,4] or gelatin[5] was hypothesized but, in most cases, no allergen was identified[6-8].

Because of rare anaphylactic reactions after measles- containing vaccines, NACI had recommended that measles-mumps- rubella (MMR) skin testing be performed in individuals with anaphylactic hypersensitivity to eggs. Recent studies have raised questions about the usefulness of and a rationale for these recommendations. These studies have reported uneventful routine MMR

immunization in egg-allergic individuals[8-11] and in those with positive MMR skin tests[12]. Others have reported occasional adverse reactions despite the use of MMR skin testing and graded challenge[13-15]. In a Canadian study, 500 egg-allergic children including 33 with respiratory distress associated with egg ingestion were safely immunized; skin testing was abandoned after the first 120 children because of its lack of predictiveness[16]. Most recently, 54 children with egg allergy, including three with positive MMR skin tests, were routinely immunized without problem[17]. In reviewing the literature, these investigators calculated that over 1,200 individuals with egg allergy have been assessed for measles immunization. None of the 284 children with egg allergy confirmed by blinded food challenge had any problem with routine measles immunization (95% confidence interval [CI] - 99.0% to 100%). Routine immunization was tolerated in all of 1,209 children with positive skin tests for egg allergy (95% CI - 99.75% to 100%) and in 1,225 (99.84%) of 1,227 children with histories of egg allergy (95% CI - 99.41% to 99.98%). In addition, a total of 38 anaphylactic reactions after measles immunization have been reported in the literature in individuals without a history of egg allergy; MMR skin tests were positive in only 4 (44.4%) of the 9 individuals tested[17].

Recommendations

In view of the cumulative data indicating the safety of measles immunization in individuals with a history of anaphylactic hypersensitivity to hens' eggs and the lack of evidence of the predictive value of MMR skin testing, NACI has revised its recommendations for MMR immunization of individuals allergic to eggs as follows:

1. As previously recommended by NACI, all immunizations should be administered by persons capable of managing vaccine-associated adverse reactions such as anaphylaxis and should take place in appropriate facilities.
2. Egg allergy is not a contraindication to immunization with MMR. In individuals with histories of anaphylactic hypersensitivity to hens' eggs (urticaria, swelling of the mouth and throat, difficulty breathing or hypotension), measles immunization can be administered in the routine manner without prior skin testing. However, immunization should take place where adequate facilities are available to manage anaphylaxis. Persons at risk should be observed for 30 minutes after immunization for any signs of allergic reaction. No special precautions are necessary for children with minor egg hypersensitivity, which permits uneventful ingestion of small quantities of egg, or when measles-rubella vaccine free of avian proteins is used. No special measures are necessary in children who have never been fed eggs prior to MMR immunization. Prior egg ingestion should not be a prerequisite for MMR immunization.
3. Measles vaccine (or MMR) is contraindicated in individuals with a previous anaphylactic reaction to a measles-containing vaccine. If there is a compelling reason to re-immunize an individual who has had a prior anaphylactic reaction to measles vaccine, MMR skin testing and graded challenge in an appropriately equipped facility can be considered. However, the possibility of a hypersensitivity reaction to the MMR skin test or during the graded challenge must be considered.
4. Surveillance for post-measles vaccine anaphylaxis should be improved and prospective studies should be initiated to better define the risk in individuals with egg allergy.

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National Advisory Committee On Immunization (NACI)

INTERIM ADVISORY ON MEASLES REVACCINATION OF PERSONS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

In a recent *Supplementary Statement on Measles Elimination in Canada* (CCDR 1996;22:9-15), NACI supported routine measles vaccination for infants infected with human immunodeficiency virus (HIV) if their immune function at 12 to 15 months of age is compatible with measles-mumps-rubella (MMR) vaccination. The committee decided that second doses of measles vaccine should also be safe later in the second year of life if immune function remains stable. The committee noted, however, that safety of doses at later ages is uncertain because immune function can be expected to decline with age. The committee has recently been advised of a case that emphasizes this point.

A progressive pneumonia occurred in a 21-year-old American male with AIDS who had received a second dose of live attenuated measles vaccine about 1 year earlier when his immune function was severely impaired. Measles virus was repeatedly isolated from lung biopsy and bronchial-alveolar lavage specimens and was most closely related to the vaccine strain in genetic tests. The case is alleged to be the first instance of disease due to vaccine-strain measles virus in a patient with advanced HIV disease. Details will be reported in the coming months.

This isolated case reinforces concerns over the safety of routine re-immunization with a second dose of measles vaccine of persons with advanced HIV infection. In light of the decreasing risk of wild-strain measles virus infection in Canada associated with current, aggressive control measures, the risk-benefit ratio of measles vaccination and re-vaccination in HIV-infected persons with advanced disease may need to be reassessed. Until this reassessment is complete, NACI recommends:

1) HIV-infected persons who have not demonstrated evidence of advanced immunodeficiency should be immunized with a first dose of MMR vaccine (1994 Pediatric HIV Classification categories, E, N1, A1)[1]. This should be undertaken at 12 months of age or as soon as possible thereafter. This recommendation is unchanged from the recent supplementary statement.
2) A second dose of measles-containing vaccine should be deferred for HIV-infected persons with moderate or advanced immunodeficiency[1]. Consultation with an expert in the care of HIV-infected persons may be required to determine the presence or absence of significant immunodeficiency in individual cases. At present, significant immunodeficiency can be assumed to exist in children receiving long-term anti-retroviral therapy, prophylaxis against *Pneumocystis pneumonitis* or intravenous immunoglobulin infusions.

Measles re-vaccination may still be appropriate for HIV-infected persons with moderate immunodeficiency[1] if there is a high risk of wild-strain measles in the local community or travel to an area where measles is endemic. Consultation with local public health authorities will assist in determining the local level of wild-strain measles activity and risks to travellers abroad.

Passive immunoprophylaxis with immune globulin (IG)[2] is an option for HIV-infected persons with moderate or advanced immunodeficiency and short-term risk of exposure to wild measles, e.g., during community outbreaks or travel abroad. IG is also warranted after exposure to measles because prior vaccination does not reliably protect HIV-infected persons.

3) Protracted measles virus infection should be considered in HIV-infected persons who present with chronic pneumonitis within a year after receiving vaccine. An attempt should be made to isolate the virus from appropriate specimens. Isolates should be sent to LCDC for further characterization.

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THE SAFETY OF IMMUNE GLOBULINS

Background

Near the end of 1995, an Ottawa hospital started a patient notification program. Patients who were identified as having received blood or blood products before anti-human immunodeficiency virus (HIV) and/or anti-hepatitis C virus (HCV) testing of blood donations began, were informed that they might wish to consider being tested for HIV and/or HCV infection. Blood products listed by the hospital as presenting a risk included most of the intramuscular (IM) immune globulin (IG) products. The program subsequently received print and media attention.

Aim

The purpose of this statement is to clarify Health Canada's position regarding the safety of IGs.

Discussion

Intramuscular IG

IM IGs have a long and excellent safety record. Although transmission of hepatitis B virus (HBV) through IM IG occurred in the 1970s[1], transmission of viruses has not been documented since then despite evidence of incomplete removal of HCV during Cohn cold-ethanol fractionation[2] and HCV RNA (unknown if infectious or not) being found in IM IG[3]. Statements on the safety of IM IGs have been made by the United States Centers for Disease Control and Prevention (CDC)[4] and by the National Advisory Committee on Immunization (NACI)[5]. Since IM IG products are not considered a known risk for viral transmission, it is not necessary that persons who have received only these IM products be tested for infection with HIV and/or HCV.

Intravenous IG

Intravenous (IV) IG products, including IV IG[6] and IV Rh(D) IG[7,8], have been implicated in the transmission of HCV (but not HIV). The reasons for virus transmission through the use of these products (both generic and specifically implicated products) remain unclear. In North America, a specific IV IG product (Gammagard, Baxter Healthcare Corporation) was implicated*; this product was never licensed in Canada but was available through the Emergency Drug Release Program (EDRP). The manufacturing process for Gammagard did not include a viral inactivation stage (licensed IV IG products in Canada have such a step). Further, there is some evidence that the complexing of anti-HCV with HCV may have a substantial effect upon the partitioning of HCV during fractionation, diverting the virus into fractions other than IG; hence, exclusion of anti-HCV donor units may adversely affect this protective effect[9].

IV Rh(D) IGs were implicated in the Irish and German HCV outbreaks[7,8]. These were produced by the anion-exchange chromatography method as opposed to the Cohn cold-ethanol fractionation method employed for most IG products[10]; it is not known if this made any difference. At least one Rh(D) IG product licensed in Canada (WinRho SD or its predecessor, WinRho) uses the anion-exchange chromatography method and is licensed for IV as well as IM use. The product appears to have an excellent safety record and no reports of transmission through its use have been identified despite a million doses being given. Its current manufacturing process incorporates a step for solvent-detergent viral inactivation. This treatment effectively inactivates enveloped viruses such as HIV and HCV.

Whether to recommend consideration of HIV or HCV testing for persons who received an IG by the IV route is not a straightforward matter. If there is any risk, it is likely to be very small overall. It is reasonable that persons who received Gammagard after 1 April, 1993, but before 24 February, 1994† consider being tested for HCV infection; this is consistent with the recommendation of the CDC[6]‡. Based on current knowledge, it is not necessary to recommend such testing for persons who have received other IG products by the IV route.

Active Immunizing Agents

The plasma-derived HBV vaccine, which was mentioned in the media coverage of the notification program, is no longer available. A recombinant vaccine has replaced it. The plasma-derived vaccine was and is felt to be safe from viral transmission[11]. Similarly, there are no reports of HIV or HCV transmission by other active immunizing agents and these products are not considered to pose a risk of such transmission.

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* A second product, Polygam (Baxter Healthcare Corporation) was implicated in a single case. This product was not available in Canada under the EDRP.

† Distribution of Gammagard under the EDRP ceased on this date. Gammagard-SD,which has a viral inactivation step in its manufacture, subsequently replaced Gammagard in the EDRP.

‡ According to available records, only 11 EDRP requests for Gammagard were made during this period. The manufacturer informed requesting physicians of the situation in 1994.

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Source: *M Tepper, MD, MHSc, P Gully, MB, ChB, Blood-borne Pathogens Division, Bureau of Infectious Diseases, LCDC, Ottawa, Ontario.*

International Notes

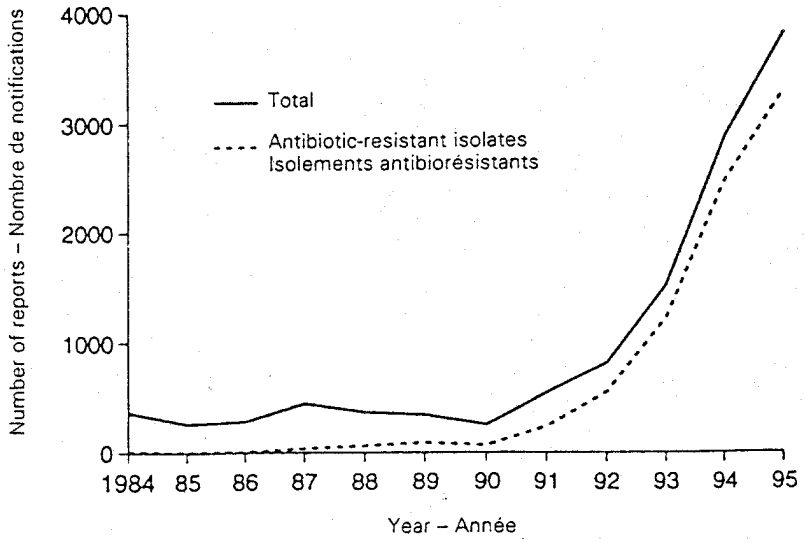
SALMONELLA TYPHIMURIUM INFECTIONS IN HUMANS — UNITED KINGDOM

Almost 6,700 reports of *Salmonella typhimurium* were received in 1995, compared with just over 5,500 in 1994. More reports were received in each month of 1995 than in the corre- sponding months of 1994, and the largest increases were seen in the second half of 1995. Almost 3,700 reports of *S. typhimurium* definitive type (DT) 104 were received in 1995. DT104 accounted for 55% of all reports of *S. typhimurium* in 1995, compared with 52% of reports in 1994 and 32% in 1993. *S. typhimurium* DT104 is now the second commonest *Salmonella* isolated from humans in England and Wales, exceeded only by *S. enteritidis* phage type (PT) 4.

A strain of *S. typhimurium* DT104 resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (R-type ACSSuT) was first isolated in 1984. The number of isolates from humans rose slowly from 1984 to 1990, and has risen more rapidly since then (Figure 1). Most isolates are R-type ACSSuT, but an increasing number are also resistant to trimethoprim and a few to ciprofloxacin.

Like other foodborne salmonelloses, disease due to *S. typhimurium* DTl04 is a zoonosis. Infections have been reported in many species, including sheep, pigs, and poultry, but *S. typhimurium* DTl04 is primarily a pathogen of cattle. The infectious agent can be transmitted via foodstuffs and other routes directly and indirectly from animals to humans.

Figure 1
Antibiotic resistance in *Salmonella typhimurium* DT104, England and Wales, 1984-1995



Source: *WHO Weekly Epidemiological Record, Vol 71, No 18, 1996.*

Reminder

Canadian National Immunization Conference

IMMUNIZING FOR HEALTH: ACHIEVING OUR NATIONAL GOALS

8-11 December, 1996
The Royal York Hotel, Toronto, Ontario

This 4-day conference, organized by the Laboratory Centre for Disease Control and the Canadian Paediatric Society, with support from the private sector, primarily will focus on childhood immunization. Issues such as vaccine supply and delivery, education, assessment of vaccine programs, regulations and legislations, and global immunization efforts will be discussed. The progress towards the achievement of recently established Canadian national goals for the reduction of vaccine-preventable diseases of infants and children will also be be examined.

The program has been approved for continuing education credits from the Royal College of Physicians and Surgeons of Canada, and the College of Family Physicians of Canada. Members of the *Fédération des médecins omnipracticiens du Québec* may claim credits through the College of Family Physicians of Canada.

To obtain additional information, a registration package and an abstract form, contact **Mr. C. Schouwouwer, Conference and Committee Coordinator, Division of Immunization, Bureau of Infectious Diseases, Laboratory Centre for Disease Control, P.L. 0603E1, Tunney's Pasture, Ottawa, Ontario, K1A 0L2, Fax: (613) 998-6413.**

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