VarIg

There is a remote risk of an anaphylactic reaction to VarIg in individuals with hypersensitivity to blood products.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Herpes zoster

Herpes zoster has been reported after varicella immunization due to reactivation of either the vaccine or wild-type strain. The risk of herpes zoster developing is 4-fold to 12-fold lower in vaccinated as compared with unvaccinated children under 10 years of age. The risk of herpes zoster after vaccination with MMRV vaccine is unknown.

Transmission of vaccine virus

Transmission of vaccine strain virus from a healthy vaccinee is very rare. There have been few documented cases, all associated with a rash in the vaccinee.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Febrile seizures within 30 days after vaccination with varicella-containing vaccine
- Varicella that is moderate (50 to 500 lesions) or severe (more than 500 vesicular lesions or associated complications or hospital admission) and occurs 7 to 21 days after vaccination with varicella-containing vaccine
- Any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization or a change in the frequency of a known AEFI.

Refer to *Box 1* in *Vaccine Safety* in Part 2 and http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php for additional information about AEFI reporting.

CONTRAINDICATIONS AND PRECAUTIONS

Varicella-containing vaccines and VarIg are contraindicated in persons with a history of anaphylaxis after previous administration of the product and in persons with proven immediate or anaphylactic hypersensitivity to any component of the product (with the exception of egg allergy for MMRV vaccine [see below]) or its container. Refer to *Table 1* and *Table 2* in *General Considerations* in Part 1 for lists of all vaccines and passive immunizing agents available in Canada and their contents. For varicella-containing vaccines, potential allergens include:

- PRIORIX-TETRA™: egg protein; neomycin sulphate
- VARILRIX®: neomycin sulphate
- VARIVAX® III: neomycin, porcine gelatin

In situations of suspected hypersensitivity or non-anaphylactic allergy to vaccine components, investigation is indicated which may involve immunization in a controlled setting. Consultation with an allergist is advised.

The measles and mumps components of MMRV vaccine are produced in chick embryo cell culture and may contain traces of egg protein. The amount of egg protein in the vaccine appears to be insufficient to cause an allergic reaction in egg-allergic individuals. Skin testing is not recommended prior to vaccination. MMRV vaccine can be administered in the routine manner to people who have a history of anaphylactic hypersensitivity to hens' eggs. Prior egg ingestion is not a prerequisite for immunization. For all vaccines, immunization should be performed by personnel with the capability and facilities to manage adverse events post-vaccination. Refer to *Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens* in Part 2 for additional information.

Children with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive live vaccines unless their immune competence has been established.

MMRV vaccine is contraindicated in persons with impaired immune function, including primary or secondary immunodeficiency disorders. Vaccination with univalent varicella vaccine may be considered in select disorders. Refer to *Immunocompromised persons*.

Varicella-containing vaccines are contraindicated during pregnancy. Refer to *Pregnancy and lactation*.

VARIVAX® III is contraindicated in individuals with active, untreated tuberculosis. Initiating anti-turberculous therapy is advisable before administering varicella-containing vaccines.. Tuberculosis may be exacerbated by natural measles infection. However, there is no evidence that measles-containing vaccine such as MMRV has such an effect.

A history of febrile seizures or a family history of seizures is not a contraindication for the use of MMRV vaccine.

Administration of varicella-containing vaccine should be postponed in persons with moderate or severe acute illness and should be delayed by at least 4 weeks (ideally 6 weeks, if feasible) following measles infection. Persons with minor acute illness (with or without fever) may be vaccinated.

Following MMRV vaccine, transmission of measles, mumps and rubella vaccine viruses from vaccinees to susceptible contacts has not been documented and transmission of varicella vaccine virus may occur very rarely between healthy vaccinees who develop a varicella-like rash and susceptible contacts.

It is recommended to avoid the use of salicylates for 6 weeks after immunization with varicella-containing vaccine. Refer to *Drug Interactions*.

Persons with specific immunoglobulin A (IgA) deficiency have increased potential for developing antibodies to IgA after receipt of blood products including VarIg and could have anaphylactic reactions to subsequent administration of blood products containing IgA, such as VarIg.

Refer to *General Contraindications and Precautions* in Part 2 and *Passive Immunization* Part 5 for additional general information.

DRUG INTERACTIONS

Systemic antiviral therapy (such as acyclovir, valacyclovir, famciclovir) should be avoided in the peri-immunization period, as it may reduce the efficacy of varicella-containing vaccine. On the basis of expert opinion, it is recommended that people taking long-term antiviral therapy should discontinue these drugs, if possible, from at least 24 hours before administration of varicella-containing vaccine and should not restart antiviral therapy until 14 days after.

The measles component in MMRV vaccine can temporarily suppress tuberculin reactivity, resulting in false-negative results. The effect of other live virus vaccines, such as univalent varicella vaccine on tuberculin reactivity is unknown. Until data are available, if tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) is required, it should be done on the same day as immunization or delayed for at least 4 weeks after varicella vaccination. Vaccination with measles and/or varicella-containing vaccine may take place at any time after tuberculin skin testing has been performed and read.

Varicella-containing vaccine manufacturers recommend avoidance of salicylate therapy (medications derived from salicylic acid, e.g., acetylsalicylic acid [ASA]) for 6 weeks after varicella immunization because of an association between wild-type varicella, salicylate therapy and Reye's syndrome. Health care providers should weigh the theoretical risks associated with varicella vaccine against the known risks associated with wild-type varicella infection. Because adverse events have not been reported with the use

of salicylates after varicella immunization, people with conditions requiring chronic salicylate therapy should be considered for immunization, with close subsequent monitoring.

Passive immunization with human immune globulin or receipt of most blood products can interfere with the immune response to varicella-containing vaccine. These vaccines should be given at least 14 days prior to administration of an immune globulin preparation or blood product or delayed until the antibodies in the immune globulin preparation or blood product have degraded. If the interval between administration of vaccine and subsequent administration of an immune globulin preparation or blood product is less than 14 days, immunization should be repeated. The recommended interval between administration of an immune globulin preparation or blood product and subsequent immunization with a live vaccine such as varicella varies, depending on the immune globulin preparation or blood product. Palivizumab (RSVAb) and washed red blood cell transfusion do not interfere with the antibody response to varicella-containing vaccines. Refer to *Recent Administration of Human Immune Globulin Products* in Part 1 for additional general information.

OTHER CONSIDERATIONS

SURVEILLANCE

Virus identification from clinical specimens (e.g., vesicle scraping) by laboratory methods in order to differentiate wild type from vaccine-derived VZV should be considered when:

- A severe post-vaccination rash occurs
- A previously vaccinated child develops varicella (breakthrough varicella) that requires admission to hospital
- Herpes zoster occurs in a previously immunized (especially immunocompromised) individual
- A varicella-like illness occurs in an immunized health care worker with subsequent spread in the health care setting
- A varicella-like illness develops in a pregnant or immunocompromised contact of a recent vaccinee with a varicella-like rash

Polymerase chain reaction testing to differentiate vaccine-derived from wild type varicella virus can be performed by the National Microbiology Laboratory in Winnipeg.

INTERCHANGEABILITY OF VACCINES

For a two-dose schedule, it is recommended that the same manufacturer's univalent varicella vaccine or MMRV vaccine be used to complete the schedule unless there are unavoidable barriers (e.g., the vaccine used for the first dose is not available). Refer to *Principles of Vaccine Interchangeability* in Part 1 for additional general information.

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PART 4

YELLOW FEVER VACCINE

KEY INFORMATION (refer to text for details)

What	• Yellow Fever (YF) virus is transmitted to humans through the bite of an infected mosquito. • YF is endemic and intermittently epidemic in sub-Saharan Africa and tropical South America. • Risk for acquiring YF is low for most travellers, particularly those staying in highly developed major urban areas. • YF is unique among diseases in that there are international health regulations which outline the requirements for proof of vaccination when travelling to specific countries. In Canada, YF vaccine is only available at Yellow Fever Vaccination Centres designated by the Public Health Agency of Canada (PHAC) • YF vaccine has a seroconversion rate of 95% to 99%; immunity persists for more than 10 years following vaccination. • The most common adverse events following YF vaccination are pain, inflammation and swelling at the injection site; weakness; headache; and myalgia.
Who	• YF vaccine is recommended for healthy persons 9 months of age to less than 60 years of age. YF vaccine may be considered in infants 6 to 8 months of age and in people aged 60 years and over travelling to areas where risk of YF is highest (endemic or transitional regions). • YF vaccine is recommended for laboratory personnel who work with YF virus.
How	• One dose of YF vaccine should be administered. • The *International Certificate of Vaccination or Prophylaxis* becomes valid 10 days after primary vaccination and immediately upon revaccination. • In general, immunocompromised persons, pregnant or lactating women, and persons with a history of thymus disease should not receive YF vaccine. • Re-immunization is recommended every 10 years for immunocompetent people, if indicated.

Why	• YF immunization (documented by an *International Certificate of Vaccination or Prophylaxis*) is required to enter certain countries in Africa and South America regardless of the traveller's country of origin. Other countries require YF vaccination of travellers if the traveller has passed through endemic areas. • Since 1970, there have been nine cases of YF reported in unvaccinated travellers from the United States and Europe who visited YF endemic areas of Africa and South America. Eight of the nine travellers died.

Since the publication of *2006 Canadian Immunization Guide*:

- The Word Health Organization (WHO) and the United States Centers for Disease Control and Preventions (CDC) have harmonized the mapping of yellow fever (YF) risk areas
- Recommendations for YF vaccination of travellers have been updated
- Transmission of YF virus via blood products after vaccination of the donor has been reported
- Transmission of vaccine strain of YF virus to an infant through breastfeeding has been reported and recommendations for YF vacation of lactating mothers have been revised.

For further information, refer to the Committee to Advise on Tropical Medicine and Travel (CATMAT) *Statement for Travellers and Yellow Fever*. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-11/index-eng.php)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent

Yellow fever (YF) is caused by a ribonucleic acid (RNA) virus from the family *Flaviviridae*.

Reservoir

Humans and non-human primates

Transmission

YF virus is transmitted to humans through the bite of an infected mosquito, primarily *Aedes* or *Haemogogus* species. The incubation period is 3 to 6 days. Humans infected with YF virus experience the highest levels of viremia and are infectious to mosquitoes shortly before the onset of fever and for 3 to 5 days afterwards. Because of the high level of viremia in humans, bloodborne transmission of YF virus can occur through transfusion of blood products, intravenous drug use and needlestick injuries. Probable transmission of vaccine strain YF virus from a mother to her infant through breastfeeding has been reported. Vaccine-associated viremia occurs 4 to 10 days after primary YF vaccination and lasts for up to 5 days. Sustained transmission is not possible in Canada because the recognized mosquito vectors are not present.

Risk factors

A traveller's risk for acquiring YF is determined by multiple factors including: immunization status, use of personal protection measures against mosquito bites, location of travel, duration of exposure, activities while travelling, and local rate of virus transmission. The risk for acquiring YF is low for most travellers, particularly those staying in highly developed major urban areas. Greater risk exists for travellers who:

- visit rural or jungle areas;
- stay for longer periods of time; and

- participate in outdoor activities such as recreation or fieldwork.

For example, risk is greater for travellers who stay in a rural area of an endemic country for over two weeks, whereas risk is low for travellers staying in an urban area in a transitional country for one week.

Seasonal/temporal pattern

In West Africa and South America, YF virus transmission is usually associated with the mid-to-late rainy season when the number of mosquitoes generally increases. However, YF virus can be transmitted during the dry season.

Spectrum of clinical illness

Clinical presentation of YF varies in severity from asymptomatic to fatal. When symptomatic, YF is typically characterized by an acute onset of symptoms including fever, chills, headache, backache, muscle pain, joint pain, nausea, vomiting, photophobia, mild jaundice, and epigastric pain. In about 85% of YF cases, the disease resolves when the acute symptoms subside. For others, after a brief remission lasting anywhere between hours to a day, symptoms worsen and the disease advances, eventually leading to renal failure, haemorrhagic symptoms, and thrombocytopenia. Treatment is symptomatic and supportive.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

The World Health Organization (WHO) estimates that approximately 200,000 YF cases occur annually, with up to 30,000 deaths. YF is endemic and intermittently epidemic in sub-Saharan Africa and tropical South America. In South America, transmission of YF virus occurs mainly in forest areas rather than in urban areas. In Africa, the majority of outbreaks have been reported from West Africa. The mosquito vectors are present in Asia; however, there have been no documented cases of transmission.

Since 1970, there have been nine cases of YF reported in unvaccinated international travellers from the United States and Europe who visited YF endemic areas of Africa and South America. Eight of the nine travellers died. One case of YF has been documented in a vaccinated traveller.

The risk of YF varies widely within areas of transmission. One mathematical model suggested that for an unimmunized person taking a two week trip to an area of epidemic YF activity the risk of becoming ill from YF could be as high as 1:267 and the risk of death from YF could be as high as1:1,333. Although the actual risk for most travelers is probably less, it is very hard to quantify. It is for this reason that revised guidelines were required in order to make it easier for health care providers to give advice and care to travellers.

YF is unique among diseases in that there are international health regulations which outline the requirements for proof of vaccination when travelling to specific areas. In 2011, the WHO published revised recommendations for YF vaccination for international travellers, in consultation with international travel medicine experts. The revisions include:

- Updated criteria for the designation of areas with risk for YF virus activity. The classification of geographical areas, according to risk of transmission of YF, was outlined in four categories; endemic, transitional, low potential for exposure, and no risk. *Table 1* contains a list of endemic and transitional countries with risk of YF transmission and *Table 2* provides a list of countries with low potential for exposure to YF virus.

- Countries and geographic areas with a risk of YF transmission were reassessed with the new criteria, and vaccine recommendations were made based on the level of risk. Refer to *Travellers* section as to how these criteria are applied.

Minor changes have been made to rules regarding travellers rapidly transiting (less than 12 hour stay) through airports in regions of yellow fever transmission and then entering countries with no history of disease but potential for transmission (primate population and suitable insect vectors).

Table 1: Endemic and transitional countries*† with a risk of yellow fever transmission by continent, 2011

Africa		Central and South America
Angola	Guinea	Argentina†
Benin	**Guinea-Bissau**	Bolivia†
Burkina Faso	Kenya†	Brazil†
Burundi	**Liberia**	Colombia†
Cameroon	**Mali†**	Ecuador†
Central African Republic	Mauritania†	**French Guyana**
Chad†	**Niger†**	Guyana
Congo	Nigeria	Panama†
Côte d'Ivoire	**Rwanda**	Paraguay
Democratic Republic of the Congo†	Senegal	Peru†
Equatorial Guinea	**Sierra Leone**	Suriname
Ethiopia†	Sudan†	Trinidad and Tobago†
Gabon	**Togo**	Venezuela†
Gambia	Uganda	
Ghana		

* Designation of regions with risk of YF transmission is subject to change. **Travellers and health care providers should refer to current information** available from the World Health Organization (WHO).

† Countries in **bold-type** require proof of YF vaccination and are subject to change. Additional countries require proof of YF vaccination from travellers arriving from an endemic country. †Only a portion of the country has risk of yellow fever transmission. Refer to the WHO map of the areas in the Americas where YF vaccination is recommended (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_americas.png) or the map of the areas in Africa where YF vaccination is recommended, (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_africa.png)

Table 2: Countries*† with low potential for exposure to yellow fever virus, 2011

Africa
Eritrea†
São Tomé and Principe
Somalia†
Tanzania
Zambia†

* Travellers and healthcare providers can view areas at risk for yellow fever transmission on maps through the World Health Organization (WHO). (http://www.who.int/ith/chapters/ith2011annexs.pdf)

† Countries in **bold-type** require proof of YF vaccination and are subject to change.

† These countries are classified as having "low potential for exposure to YF virus" in only some areas; the remaining areas of these countries are classified as having no risk of exposure to YF virus.

Designation of regions with risk of YF transmission is subject to change. Some countries require yellow fever vaccination if traveling from or transiting through a country with risk of YF transmission. View a complete listing of country-specific requirements available from the CDC (http://wwwnc.cdc.gov/travel/page/2012-yellow-book-updates.htm) or the WHO. (http://www.who.int/ith/chapters/ith2012en_countrylist.pdf)

National

To date, there have been no cases of YF reported in Canada. YF is a nationally and internationally notifiable disease; therefore, cases diagnosed in Canada must be urgently reported through local public health officials.

RECENT OUTBREAKS

Yellow fever outbreaks are reported in the WHO Disease Outbreak News. (http://www.who.int/csr/don/en/index.html)

PREPARATIONS AVAILABLE FOR USE IN CANADA

In Canada, YF vaccine is only available at Yellow Fever Vaccination Centres designated by the Public Health Agency of Canada (PHAC). A list of Yellow Fever Vaccination Centres in Canada can be obtained from the Public Health Agency of Canada (http://www.phac-aspc.gc.ca/tmp-pmv/yf-fj/index-eng.php) or telephone at: (613) 957-8739 or email to: yfinfofj@phac-aspc.gc.ca

YELLOW FEVER VACCINE

- YF-VAX® (live, attenuated, yellow fever vaccine), sanofi pasteur Ltd. (YF)

For complete prescribing information, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Refer to Table 1 in Contents of Immunizing Agents Available in Canada in Part 1 for a list of all vaccines available for use in Canada and their contents.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

Efficacy studies of YF vaccine have not been performed; however, unpublished reports comparing YF incidence among vaccinated and unvaccinated populations during a 1986 epidemic in Nigeria estimated vaccine effectiveness to be approximately 85%.

IMMUNOGENICITY

More than 80% of persons immunized with YF vaccine develop neutralizing antibodies 10 days after vaccination and more than 99% by 28 days after vaccination. Immunity persists for more than 10 years.

RECOMMENDATIONS FOR USE

HEALTHY INFANTS AND CHILDREN (9 months to 17 years of age)

YF vaccine is recommended for healthy children 9 months of age and older travelling to areas where YF is considered endemic or transitional (refer to *Table 1*).

YF vaccine is contraindicated in infants less than 6 months of age because of an increased risk of post-vaccination encephalitis; travel to YF endemic or transitional countries should be discouraged for children less than 6 months of age. If travel to an YF endemic or transitional country is unavoidable, the need for protection from mosquitoes at all times should be emphasized.

In children 6 to 8 months of age YF vaccination is generally not recommended due to continued increased risk of adverse events and decreased immunogenicity. Whenever possible, infants aged 6 to 8 months should not travel to countries where YF is transmitted. If travel is unavoidable, the decision to vaccinate needs to balance the risk of YF exposure with the risks of vaccination. Although the risk of serious adverse neurologic events is less than that of infants less than six months of age, it is still higher than that of infants 9 months and older. At 9 months of age, the risk of serious adverse events becomes much lower and antibody response improves, thus improving the safety and efficacy profiles of the YF vaccine.

If an infant receives YF vaccine at 6 to 8 months of age, and subsequently travels after 9 months of age, serology should be done (if available), and a booster dose considered. Personal protective measures should be emphasized.

ADULTS (18 years of age and older)

YF vaccine is recommended for laboratory personnel who work with YF virus and for healthy adult travellers less than 60 years of age travelling to areas where YF is considered endemic or transitional (refer to *Table 1*).

Persons 60 years of age and older should be considered for primary YF vaccination only if travel to areas where YF is considered endemic or transitional cannot be avoided and a high level of protection against mosquito exposure is not feasible. Serious adverse reactions in older vaccinees have only occurred in primary vaccinations. Booster doses of YF vaccine may be given to people over 60 years of age. Refer to *Other reported adverse events and conditions* for additional information.

Refer to *Travellers* and *Schedule* for additional information.

PREGNANCY AND LACTATION

In general, YF vaccine, like other live viral vaccines, should be avoided in pregnancy. Pregnant or lactating women should be considered for YF immunization only if they are travelling to endemic or transitional areas, travel cannot be postponed, and a high level of protection against mosquito exposure is not feasible. While the effects of YF vaccine in pregnancy are not well documented, many pregnant women have received the vaccine without significant adverse events. In one study of women exposed to YF vaccine early in pregnancy there was slight increased risk noted for minor malformations (mainly skin) in the babies; no increased risk of major malformations was found. Inadvertent immunization of women in pregnancy is not an indication for termination of pregnancy.

Seroconversion rates are lower in pregnant women who are immunized, especially in the third trimester. Antibody titres should be checked post-immunization to ensure appropriate immune response in women who remain at risk for YF. If serology is not available and a woman is travelling to an endemic country after completion of her pregnancy, revaccination prior to travel should be considered.

If pregnant women must travel to a country that requires documentation for YF but is not endemic or transitional, a waiver or *Certificate of Medical Contraindication to Vaccination* should be provided. Refer to *Travellers* for additional information.

Probable transmission of vaccine strain of YF virus from a mother to her infant through breastfeeding has been reported; therefore, in general, lactating mothers should not be vaccinated. Refer to *Contraindications and Precautions* for additional information. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

In general, immunocompromised persons should not receive YF vaccine because of the risk of disease caused by the vaccine strain. When considering immunization of an immunocompromised person, approval from the individual's attending physician should be obtained before vaccination. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

For the immune suppressed traveller, the potential risks associated with administering the YF vaccine should be weighed against the potential benefits. Where there is a country-specific vaccine requirement but the risks associated with vaccine administration outweigh the medical benefits, a *Certificate of Medical Contraindication to Vaccination* should be provided. Travellers thought to have mild to moderate degrees of immune suppression who will be at significant risk for acquiring YF (e.g., travel to an area of endemic or transitional transmission risk), should be offered YF vaccine and advised of the theoretical risks. Profoundly immune suppressed travellers who, in spite of being informed of the risks, plan a trip to an area of active YF risk, should obtain advice from a travel medicine expert and should rigorously adhere to mosquito protection measures.

Acquired (secondary) immunodeficiency

Malignancies

YF vaccine is contraindicated in people with leukemia, lymphoma, thymoma, and generalized malignancies.

Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)

HSCT recipients may receive YF vaccine if clearly indicated, if the recipient is at least 24 months post-transplant, has not received immunosuppressive medications for at least three months, and has no active graft versus host disease for the past three months. Persons should be considered immunocompetent by their HSCT specialist.

Solid organ transplantation

Solid organ transplant recipients should not receive YF vaccine at any time after transplantation.

Immunosuppressive therapy

YF vaccine is contraindicated for persons whose immunologic response is either suppressed or modulated by current or recent radiation therapies or drugs (e.g., high-dose systemic corticosteroids [2 mg/kg per day for a child or 20 mg/day or more of prednisone or its equivalent for an adult] for 14 days or more; chemotherapy; radiation therapy; azathioprine; cyclosporine; cyclophosphamide; infliximab).

If indicated, YF vaccine should be administered at least 4 weeks before the initiation of immunosuppressive therapy. If this cannot be done, a period of at least 3 months should elapse after immunosuppressive drugs (except high-dose systemic corticosteroids) have been stopped before administration of live vaccines. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and the administration of live vaccines.

Corticosteroid therapy is not a contraindication to administering a live vaccine when steroid therapy is short-term (i.e., less than 14 days); or a low-to-moderate dose (less than 2 mg/kg/day for a child or less than 20 mg/day of prednisone or its equivalent for an adult); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled, or locally injected (e.g., joint injection).

HIV-infected

A specialist in HIV infection should be consulted for advice on YF immunization in HIV-infected people. YF vaccine may be considered for people who have asymptomatic HIV infection and who

are not severely immunosuppressed (i.e., CD4 count greater than 200 x 10^6/L) but vaccination should take place well in advance of travel in order to monitor potential adverse events, and antibody titres should be considered to assess efficacy of the vaccination. Persons with HIV respond suboptimally to YF vaccine with lower antibody titres, more often demonstrate non-protective titres, and may experience a more rapid decline in antibody titres following vaccination. Booster doses may be required.

- Refer to *Booster doses and re-immunization*, *Serologic testing*, and *Contraindications and Precautions* for additional information. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

PERSONS WITH CHRONIC DISEASES

Hyposplenism or asplenia

Persons with hyposplenism or asplenia (congenital absence, surgical removal or functional [e.g., sickle cell disease]) may receive YF vaccine, if indicated.

Chronic renal disease/dialysis

Persons with chronic renal disease or undergoing dialysis may receive YF vaccine, if indicated.

Autoimmune diseases

Although definitive data are lacking, individuals with autoimmune disease **not being treated with immunosuppressive drugs** are not considered significantly immunocompromised and may recieve YF immunization following consultation with a physician. Rheumatic disease modifying agents such as hydroxychloroquine, sulfasalazine, or auranofin are not considered immunosuppressive.

The safety and efficacy of live vaccines during **low dose intermittent or maintenance therapy with immunosuppressive drugs** (other than corticosteroids) for autoimmune disease is unknown. These drugs include therapeutic monoclonal antibodies, especially the anti-tumour necrosis factor agents adalimumab, infliximab, and etanercept and others (azathioprine, methotrexate, leflunomide, and abetacept). These have been reported to cause reactivation of latent tuberculosis infection and predisposition to other opportunistic infections. Therefore, until additional information becomes available, avoidance of live vaccines during intermittent or low dose chemotherapy or other immunosuppressive therapy is prudent.

Thymus disease

There is an association between YF vaccine-associated viscerotropic disease (YEL-AVD) and a history of thymus disease. Therefore, YF vaccine is not generally recommended for persons with a history of thymoma, thymectomy or myasthenia gravis. Refer to *Other reported adverse events and conditions* for additional information.

TRAVELLERS

YF vaccine is recommended for healthy travellers (9 months to less than 60 years of age) passing through, visiting or living in areas where YF is considered endemic or transitional (refer to *Table 1*) or if YF immunization is required to enter the country (refer to *Table 1* and *Table 2*).

Transit times of 12 hours or less in an international airport poses very low risk for YF virus transmission irrespective of the YF risk classification of the country in which the airport is located. Thus, such a transit typically does not warrant vaccination. Recent updates in international health agreements suggest that travellers fitting this strict criteria are not required to be vaccinated. This includes those travellers transiting to a country with an entry requirement for YF vaccination but no history of endemic disease. Defining specific entry requirements is under the control of each individual country. Some countries will not allow entry without proper documentation of vaccination or certificate of medical contraindication. Travellers without proper documentation may be denied entry or subjected to vaccination at the airport.

This should be considered during review of itineraries and pre-travel counseling. If there is concern that lack of documentation will put the traveller at risk, yet vaccination is not medically indicated, then providing a medical certificate of contraindication may be considered. Unfortunately, some countries may deny entry despite proper documentation of medical contraindication to vaccination.

YF vaccination is generally not recommended in areas where there is low potential for YF virus exposure (refer to *Table 2*). However, vaccination might be considered for a small subset of travellers to these areas who are at increased risk of exposure to mosquitoes because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Vaccination is not recommended for travellers whose itineraries are restricted to areas with no risk.

The decision to immunize a traveller against YF should take into account the traveller's itinerary and the associated risk for exposure to YF virus, the requirements of the country to be visited (including stopovers and airport transit), individual risk factors (e.g., age, immune status), and the potential for serious adverse events following vaccination. Vaccine providers should check either the CDC or WHO website for an updated list of countries considered endemic or transitional for YF and/or requiring YF vaccination for entry.

Under the WHO's International Health Regulations, YF immunization (documented by an *International Certificate of Vaccination or Prophylaxis*) is required to enter certain countries in Africa and South America regardless of the traveller's country of origin. Other countries require YF vaccination of travellers if the traveller has passed through endemic areas. In some Asian and tropical countries where YF disease does not exist but the transmitting mosquito is present, immunization is required for travellers arriving from an endemic country to prevent importation of the disease. Some countries do not require YF vaccination of infants younger than a certain age (e.g., less than 1 year).

The *International Certificate of Vaccination or Prophylaxis* is valid for 10 years, beginning 10 days after primary immunization and immediately after re-immunization, if re-immunized within the 10 year period. Travellers requiring the certificate but in whom the YF vaccine is medically contraindicated (refer to *Contraindications and Precautions*) can be provided with an *International Certificate of Medical Contraindication to Vaccination* by the Yellow Fever Vaccination Centre following an individual risk assessment. Travellers without a valid *International Certificate of Vaccination or Prophylaxis* or a *Certificate of Medical Contraindication to Vaccination* may be denied entry into a country requiring such documentation, quarantined, or offered immunization at the point of entry (e.g., at the airport), potentially putting the health of traveller at risk.

In Canada, only Yellow Fever Vaccination Centre clinics designated by PHAC can provide the *International Certificate of Vaccination or Prophylaxis* or *International Certificate of Medical Contraindication to Vaccination*. A list of Yellow Fever Vaccination Centres (http://webqa.phac-aspc.gc.ca/tmp-pmv/yf-fj/index-eng.php) can be obtained from Public Health Agency of Canada (PHAC) (http://www.phac-aspc.gc.ca/tmp-pmv/yf-fj/index-eng.php) or telephone at: (613) 957-8739 or email to: yfinfofj@phac-aspc.gc.ca

Additional and updated information regarding countries with risk of yellow fever transmission and requirements for YF vaccination is available from local public health officials, PHAC or the WHO:

- A Yellow Fever Fact Sheet is available from PHAC. (http://www.phac-aspc.gc.ca/tmp-pmv/info/yf-fj-eng.php)
- View areas in the Americas where YF vaccination is recommended available through the WHO. (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_americas.png) View the map of the areas in Africa where YF vaccination is recommended available from the WHO. (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_africa.png)
- View the list of country-specific yellow fever vaccination requirements and WHO recommendations available through the WHO. (http://www.who.int/ith/chapters/ith2012en_countrylist.pdf)

Refer to Immunization of Travellers in Part 3 for additional general information.

WORKERS

Laboratory personnel who work with YF virus should receive YF vaccine. Refer to Immunization of Workers in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Each dose is 0.5 mL.

Route of administration

YF vaccine should be administered subcutaneously. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

One dose of YF vaccine should be administered.

BOOSTER DOSES AND RE-IMMUNIZATION

Re-immunization is recommended every 10 years for immunocompetent individuals, if indicated. Re-immunization boosts antibody titre, although evidence from several studies suggests that immunity persists for at least 30 to 35 years after a single dose and probably for life. If vaccine is appropriate for an immunocompromised person, serologic testing and revaccination (if indicated based on serology results) should be considered two to five years post-immunization.

SEROLOGICAL TESTING

Serologic testing is not recommended for non-pregnant healthy persons before or after receiving YF vaccine. For immunocompromised persons, serologic testing should be considered two to five years post-immunization. For women vaccinated during pregnancy, antibody titres should be checked post-immunization to ensure appropriate immune response in those who remain at risk for YF. An antibody titre of greater than 1:10 indicates immunity.

STORAGE REQUIREMENTS

Store YF vaccine in a refrigerator at +2°C to +8°C. Do not freeze. Refrigerate the reconstituted vaccine and use within 1 hour following reconstitution. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

YF vaccine may be administered concomitantly with the following vaccines: measles, mumps, rubella, polio, diphtheria, tetanus, pertussis, hepatitis B, hepatitis A, oral cholera, and oral or parenteral typhoid. Different injection sites and separate needles and syringes must be used for concomitant parenteral injections. If not given concurrently, a minimal interval of 4 weeks is recommended between administration of YF vaccine and other live parenteral vaccines. Oral typhoid or oral cholera vaccine can be administered at any interval before or after YF vaccine. There are no data available regarding possible interference between YF vaccine and rabies, human papillomavirus, Japanese encephalitis, live attenuated influenza, or varicella vaccines. Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

In a comparative study, 71.9% of subjects vaccinated with YF vaccine reported one or more non-serious adverse events assessed as related to vaccination. Injection site reactions were reported by 5.7% to 39.4% of subjects (pain at the injection site 39.4%; inflammation 29.4%; edema 19.9% and other injection site reaction 5.7%). Systemic reactions were reported by 10.1% to 31.4% (chills 10.1%; fever 14.0%; weakness 29.5%; headache 31.4%; myalgia 25.1% and malaise 17.8%) of subjects up to 10 days post vaccination.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

Serious adverse events are rare following immunization and, in most cases, data are insufficient to determine a causal association. Hypersensitivity reactions including rash, urticaria, asthma and anaphylaxis are very rare, with observations over the past decades of an incidence of less than 1 per million. However, reporting rates to the United States Vaccine Adverse Event Reporting System based on two reviews 10 years apart were higher: 0.8 per 100,000 doses distributed in the earlier study and 1.8 in the more recent study. The primary risk factor appears to be gelatin and egg protein sensitivity.

Two additional serious adverse events, YF vaccine associated neurotropic disease (YEL-AND) and YF vaccine associated viscerotropic disease (YEL-AVD), are described below.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

YF vaccine-associated neurotropic disease (YEL-AND)

YEL-AND is a group of clinical syndromes that includes meningoencephalitis (neurotropic disease), acute disseminated encephalomyelitis, Guillain Barré syndrome, and acute bulbar palsy. Neurotropic disease occurs as a result of YF vaccine virus invasion of the central nervous system (CNS). The other syndromes are autoimmune manifestations in which antibodies and/or T-cells produced in response to the vaccine cross-react with neuronal epitopes leading to CNS or peripheral nerve damage. The clinical course is typically brief with generally complete recovery. Fatality is rare. YEL-AND can present in any age group, between 4 and 23 days post vaccination (typically 7 to 21 days) and is seen almost exclusively in primary vaccine recipients. Children less than six months of age and older persons are at greater risk for YEL-AND. The US CDC reports an incidence of YEL-AND of 0.8 per 100,000 doses administered. The rate is double for those 60 to 69 years of age (1.6 per 100,000 doses) and almost 4 times higher in those over 70 years of age (2.3 per 100,000 doses). When infants and elderly are not given the vaccine, recent surveillance data suggest population-based incidence rates drop close to zero.

YF vaccine-associated viscerotropic disease (YEL-AVD)

YEL-AVD is characterized by severe illness and multi-organ failure. It resembles wild-type YF infection with onset within 2 to 5 days of vaccination. The risk of YEL-AVD increases with age. Incidence is estimated to be 1.0-1.1 per 100,000 for those 60-69 years of age; 2.3-3.2 per 100,000 for those over 70 years of age; and 0.1 per 100,000 for those less than 60 years of age. The case fatality rate is 65% overall and is higher in women than men (90% vs. 50%). YEL-AVD is seen almost exclusively in primary vaccine recipients. Extensive investigations of cases suggest that YEL-AVD is linked to various host factors including older age, and thymus disease (thymoma, myasthenia gravis, thymectomy), and is not associated with a change in virulence of the vaccine virus.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- YF vaccine-associated neurotropic disease
- YF vaccine-associated viscerotropic disease
- Any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization, or a change in the frequency of a known AEFI.

Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada (http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php) in Vaccine Safety Part 2 for additional information about AEFI reporting.

CONTRAINDICATIONS AND PRECAUTIONS

YF vaccine is contraindicated in persons with history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Refer to Table 1 in Contents of Immunizing Agents Available in Canada in Part 1 for a list of all vaccines available for use in Canada and their contents. For YF-VAX® vaccine, potential allergens include chick protein, egg protein, gelatin, and latex in the stopper of diluent vial.

Individuals requiring YF immunization who have suspected hypersensitivity or non-anaphylactic allergy to vaccine components, should be referred to an allergist for evaluation.

Infants

In general, infants under the age of 9 months should not be vaccinated against YF. Infants less than six months of age are at greater risk for YEL-AND following YF vaccination and should not receive YF vaccine. However, the Advisory Committee on Immunization Practices (ACIP) in the United States recommends that for infants 6 to 8 months of age travelling to an endemic or transitional area, when travel is unavoidable, the decision to vaccinate needs to balance the risks of YF virus exposure with the risk for adverse events following vaccination.

Persons 60 years of age and older

Persons 60 years of age and older are at greater risk for YEL-AND and YEL-AVD following primary YF vaccination; therefore, primary YF vaccination is not generally recommended. Booster doses may be given.

Pregnancy and breastfeeding

The effects of live YF vaccine in pregnancy are not well documented and vaccination should be avoided if possible. If a pregnant woman must travel to a highly endemic or epidemic area, the risk of actually contracting the disease may outweigh the risks of vaccination to the mother and fetus.

Probable transmission of vaccine strain of YF virus from a mother to her infant through breastfeeding has been reported; therefore, in general, lactating mothers should not be vaccinated. Until recently, there was only a theoretical risk of transmission of the live virus in breast milk and no cases reported despite many breastfeeding women having been immunized during emergency vaccination campaigns. Two recent cases have documented the possibility of transmission through breast milk. A case in Brazil demonstrated laboratory confirmed evidence of yellow fever virus transmission in breast milk. In Canada, there was a case of yellow fever in an infant who had been breast fed by a recently vaccinated mother, which was highly suggestive of breast milk transfer. These two cases should raise the level of caution when considering vaccinating women who are actively breastfeeding. If there is no risk of acquiring yellow fever in the region to be visited, a waiver of vaccination should be given. If travel is to a highly endemic area, then the risks of vaccination should be weighed against the risk of disease.

Immunocompromised persons

In general, YF vaccine should not be given to immunosuppressed individuals. Refer to *Immunocompromised persons*.

Thymus disease

There is an association between YEL-AVD and a history of thymus disease; therefore, YF vaccine is not generally recommended for persons with a history of thymoma, thymectomy or myasthenia gravis.

Acute illness

Administration of YF vaccine should be postponed in persons with moderate or severe acute illness. Persons with minor acute illness (with or without fever) may be vaccinated.

Refer to General Contraindications and Precautions in Part 2 for additional general information.

DRUG INTERACTIONS

The effect of YF vaccine on tuberculin reactivity is unknown. Until data are available, if tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) is required, it should be done on the same day as immunization or delayed for at least 4 weeks after YF vaccination. Vaccination with YF vaccine may take place at any time after tuberculin skin testing has been performed and/or read.

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

Persons who receive YF vaccines in countries other than the US and Canada should be considered protected against YF. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

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Overview of the efficacy/safety clinical studies of IPV-Vero

Location of study report	Study objective	Study design	Tets product	Control product	Number of subjects
Module 5.3.5.1	comparison of efficacy and safety of standard (marketed) IPV-MK versus test product IPV-Vero	Open controlled repeated dose study on immunogenicity and safety of IPV-Vero vs control IPV-MK in infants, 6, 7-8 and 16 months	s.c. 0.5 ml 40-8-32* No 2-pe	s.c. 1 ml 40-8-32 5 mg 2-pe	IPV-Vero: 34 IPV-MK: 16
Module 5.3.5.4	comparison of efficacy and safety of standard (marketed) IPV-MK versus test product IPV-Vero	Open single dose (booster) study on immunogenicity and safety of DT-IPV-Vero and DPT-IPV-Vero vs control DT-IPV-MK and control DPT-IPV-MK in children 4 years of age	i.m. 1 ml 40-8-32* 5 mg 2-pe**	i.m. 1 ml 40-4-7.5 5 mg 2-pe	DT-IPV-Vero: 22 DPT-IPV-Vero: 23 DT-IPV-MK: 23 DPT-IPV-MK: 21

* 40-8-32 units is the D-antigen content of resp. poliovirus type 1, 2 and 3 in one vaccine dose
** one vaccine dose contains 5 mg of the preservative agent, 2-phenoxyethanol

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5.3.5.1 –Study Report of Controlled Clinical Study (Study 88A)

Clinical trial on the immunogenicity and safety of a trivalent inactivated poliomyelitis vaccine grown on Vero cell culture (IPV-Vero) given at ages 6, 7-8 and 16 months

Study 88a

Tested product:	Inactivated poliomyelitis virus vaccine produced using Vero cells (IPV-Vero; lot E94-3-3B)
Indication studied:	The safety and immunogenicity of three injections of IPV-Vero was studied in immunologically naive infants
Brief description:	The study was an open, randomised, controlled, prospective, phase II study on immunogenicity and safety of IPV-Vero compared to the control IPV vaccine manufactured using monkey kidney cells (IPV-MK). Each participant was randomised to receive three injections with either IPV-Vero or IPV-MK by subcutaneous injections in thigh or upper arm at ages 6, 7-8 or 16 months. Fifty infants completed the study according to the protocol. Thirty-four infants received IPV-Vero and 16 infants received IPV-MK. The study was performed from 24 January 1997 to 5 May 1999.
Name of the sponsor:	Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Antonie van Leeuwenhoeklaan 11 3720 AL BILTHOVEN The Netherlands
Protocol identification:	Study 88A
Development phase of study:	Phase II study
Study initiation date:	24 January 1997
Study completion date:	5 May 1999
Principal investigators:	Sandbu S, MD, PhD
Name of sponsor signatory:	Rümke HC, MD, PhD
Statement:	This study was performed in compliance with Good Clinical Practices (GCP) (CPMP/ICH/135/95).
Date of report:	27 September 2004

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2. SYNOPSIS

Name of sponsor/company: Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Antonie van Leeuwenhoeklaan 11 3720 AL Bilthoven The Netherlands	*(For Authority use only)*
Name of finished product: IPV-Vero (lot E94-3-3B)	
Name of active ingredients: Formaldehyde-inactivated poliovirus produced with Vero-cells (poliovirus strains Mahoney, MEF-1 and Saukett), type 1, 2 and 3: 40-8-32 D-antigen units respectively, and formaldehyde: 0.025 mg in phosphate buffer.	
Title of study: Clinical trial on the immunogenicity and safety of a trivalent inactivated polio vaccine grown on Vero cell culture (IPV-Vero) given at ages 6, 7-8 and 16 months	
Investigators: Sandbu S	
Study centre: Ski Municipality Health Services, Akershus County, Norway	
Publications: None	
Studied period: 24th January 1997 to 5th May 1999	Phase of development: Phase II clinical study
Objectives: The study was conducted to investigate the safety and immunogenicity of IPV-Vero in comparison with IPV-MK in immunologically naive infants.	
Methodology: The present clinical trial was a randomised, controlled, prospective study on comparison of immunogenicity and safety of IPV-Vero with the standard IPV vaccine manufactured using monkey kidney cells (IPV-MK). Each child was randomised to receive three injections with either IPV-Vero or IPV-MK by subcutaneous injections in thigh or upper arm at ages 6, 7-8 or 16 months. A total of our venous blood samples were taken for efficacy analysis (immunogenicity). The first blood sample was taken 0-7 days before the first vaccination, the second blood sample was taken 4-8 weeks after the second dose, the third blood sample was taken 0-7 days before the third vaccination and the fourth blood sample was taken 4 weeks after the third vaccination. Serum neutralising antibodies were determined with Vero cells as indicator cells and wild poliovirus strains for challenge (Albrecht, 1984). For statistical comparison of antibody levels between IPV-Vero versus IPV-MK vaccinated children the Kruskall-Wallis test was used. Safety information was collected through diaries completed by parents. The rate and intensity of adverse events were compared between the two vaccine groups.	
Number of patients: A total of 120 children were planned to be included in the study. However inclusion was more difficult than presumed, and finally 74 infants were included in the study. A total of 56 children completed the study. Six out of the 56 children did not receive all vaccinations according to the protocol, but with	