An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)†

Updated recommendations for the use of varicella zoster immune globulin (VarIg) for the prevention of varicella in at-risk patients [1]

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

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TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

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Mise à jour des recommandations relatives à l'utilisation d'immunoglobulines antivaricelleuses-antizosteriennes (VarIg) pour la prévention de la varicelle chez les patients à risques

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

TABLE OF CONTENT

SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

1. What

Varicella (chickenpox) is a viral disease that typically occurs in childhood. Immunization is recommended as a part of the childhood schedule.

For some susceptible individuals, prophylactic immunoglobulin (VarIg) can be offered after exposure to prevent or to mitigate disease.

2. Who

VarIg is recommended for individuals who are at increased risk of severe varicella if significant exposure has occurred. These individuals include:

- Susceptible pregnant women;
- Newborn infants of mothers who develop varicella from 5 days before until 48 hours after delivery;
- Selected neonates in neonatal or pediatric intensive care settings;
- Susceptible immunocompromised individuals, including susceptible HIV infected persons and hematopoietic stem cell transplantation recipients.

3. How

For maximal benefit, VarIg should be administered as soon as possible after exposure, ideally within 96 hours after the first exposure, but it can be administered up to 10 days after last exposure.

4. Why

VarIg can prevent and attenuate varicella infection in those at high risk of severe disease.

I. INTRODUCTION

With new data now available, the benefit of administering Varicella zoster immune globulin (VarIg) beyond 96 hours and up to 10 days following varicella exposure was assessed by the National Advisory Committee on Immunization (NACI). In 2013, the US Advisory Committee on Immunization Practices (ACIP) had revised its recommendations, based on the FDA Approval of an extended period for administering VariZIG® for post-exposure prophylaxis of varicella during the expanded access program for VariZIG.[2] The use of VarIg within 10 days of varicella exposure had previously been approved in several other jurisdictions.[3][4]

II. METHODS

NACI reviewed the key questions for the literature review as proposed by the Varicella Working Group, including data from four studies reviewed by FDA and CDC (VZ-006 and VZ-009[5] Enders et al[6], Miller et al[7]), the information from the Updated Recommendations for Use of VariZIG® — United States (2013),[8] and the summaries of VarIg product characteristics.[9] An additional five studies were identified through a literature search[10]-[14] (Table1). Consideration was also given to the potential impact of VarIg administration on the clinical course and outcomes of varicella. The knowledge synthesis was performed by medical specialists at the Agency and supervised by the Working Group. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 1) were prepared, and proposed recommendations for vaccine use developed. The Working Group chair presented the evidence and proposed recommendations to NACI on February 6, 2014. Following thorough review of the evidence and consultation at the NACI meetings of October 1-2, 2014, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

III. EFFICACY AND EFFECTIVENESS DATA

In the VZ-006 study, VarIg was provided to pregnant women not immune to varicella zoster virus (VZV); these women were randomized to receive 625 IU of VariZIG® IM, VariZIG IV or commercial VZIG IM, following exposure to VZV. Although the difference in varicella's incidence between the group that received Immunoglobulins (Ig) on days 1-4 or 5-14 (most of whom received the VarIg at 10 days or less post-exposure) was not found to be statistically significant (12/34 and 7/23, respectively), women who received treatment within 1-4 days of VZV exposure had milder symptoms as compared to those who were exposed 5-14 days prior to Ig administration.[5] Study VZ-009 was a Phase 3, open-label, expanded access protocol (EAP) designed to provide VarIg to high-risk individuals in the U.S.A. on an individual case basis. The objective of VZ-009 study was to assess the safety and efficacy of VarIg in the mitigation of infection and complications resulting from varicella infections in high-risk populations. VarIg was administered to eligible high-risk individuals at a dose of 125 IU/10 kg, up to a maximum dose of 625 IU. The population of high-risk individuals included in the efficacy analysis consisted of: immunocompromised adult and pediatric patients, infants, healthy susceptible adults and pregnant women. The primary endpoint for the VZ-009 study was the incidence of clinical varicella in each high-risk population. In the interim efficacy data and analysis of the study provided to FDA, only 9 out of 297 study participants received VarIg treatment up to 10 days from VZV exposure. Of these 9 individuals, only 1 developed clinical varicella. From the additional six individuals who were initially not included in the primary analysis and who received VarIg more than 96 hours after VZV exposure, none developed clinical varicella.[5] Supplementary information from the final report provided to NACI included data from additional subjects.[15] In this study, 6/111 pregnant women (5.4%; 95%CI 2.0-11.4) who received VarIg in the first 96 hours developed varicella compared to 15.4% of women who received VarIg more than 96 hours after exposure. There was no difference in the proportion of immunocompromised patients (4.5% vs. 4%) and high-risk infants (12.1% vs. 7.7%) who developed varicella, whether VarIg was administered in the first 96 hours or after 96 hours following exposure.

In the study of 212 seronegative pregnant women conducted by Enders et al, VarIg was administered up to 3 days (n=153), 4-5 days (n=46) and 6-10 days (n=13) post VZV exposure. The proportion of modified or normal varicella (41%, 39% and 46%, respectively) was similar and not statistically significantly different between the three groups.[6] Similar data from 44 seronegative pregnant women who were stratified based on the time of VarIg administration were reported by Miller et al. These authors did not find any statistically significant differences between groups that received VarIg up to 3 days compared to 4-10 days post exposure. Immunocompromised patients exposed to VZV following VarIg administration in the 4-10-day group had an observed reduction in the clinical attack rate of varicella (54%) compared to the historically expected rate of 90%.[7]

A study by Evans et al. of 21 susceptible children who received zoster immunoglobulin (ZIG) up to 7 days following exposure to varicella did not show any differences when ZIG was given within 3 days of contact or later. Severe disease was reported in one patient that was given ZIG on day 10 following exposure and in another who had received ZIG 15 days before contact (varicella symptoms developed 32 days after ZIG administration).[10] Judelsohn et al. reported similar results from a study of children receiving chemotherapy, in which no difference was observed between the group that received ZIG 1-3 (6/49) and 4-7 (1/6) days following exposure to varicella.[13] A study conducted by Koren et al. that looked at VarIg administration following

varicella exposure of pregnant women also did not show differences between the 1-4 day (5/11) and 5-14 day (3/8) group.[14]

Feldman et al. reported the outcomes of VarIg administration in children with cancer who received VarIg more than 4 days following exposure to varicella. Three of four children developed clinical disease in the 4-5-day group compared to only three of 12 children who received VarIg up to 3 days post exposure.[11] In a study by Winsnes et al. of 121 children receiving immunosuppressive therapy, a statistically significant difference was observed between children receiving ZIG up to 72 hours (3/105) compared to those receiving ZIG more than 72 hours after exposure (7/16).[12] The small sample size in all the reviewed studies should be noted.

A further analysis of pooled data from studies in which VarIg was administered up to 96 hours and between 96 hours and 10 days post exposure to varicella did not show a significant difference in the incidence of varicella between two groups (p=0.125078).

IV. RECOMMENDATION

After reviewing the available data, NACI is recommending that for maximal benefit, VarIg should be administered as soon as possible following exposure, and ideally within 96 hours after first exposure. In the case of prolonged exposure, the exact timing of transmission may be unknown and therefore it may be used within 96 hours of the most recent exposure. If more than 96 hours but less than 10 days have elapsed since the last exposure, VarIg may be administered to individuals for whom it is indicated; when given more than 96 hours after exposure, its primary purpose may be attenuation rather than prevention of disease. The benefit of administering VarIg after 96 hours is uncertain. (*NACI Grade B Recommendation*)

VarIg is not indicated for healthy adults and healthy children. Eligibility criteria for VarIg administration are provided in the Varicella vaccine chapter of the Canadian Immunization Guide: http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-vari-eng.php#post_exposure.

V. TABLES

Table 1: Summary of data from reviewed studies

Study	Population (Ig)	Outcome	Interval between contract and Ig administration			
			Up to 72 hours		More than 72 hours	
			No.	(%)	No.	(%)
Evans EB, Pollock TM, Cradock-Watson JE, Ridehalgh MK. Human anti-chickenpox immunoglobulin in the prevention of chickenpox. Lancet 1980; 315:354–6.	Older infants or children receiving immunosuppressant drugs (ZIG)	Not infected or asymptomatic infection	2	28	3	30
		With symptomatic infection	8	72	7	70
Feldman S, Lott L. Passive immunization against varicella in Children Receiving Cancer Chemotherapy. Pediatrics. 1988 Dec;82(6):953-4.	Children receiving cancer chemotherapy (VarIg)	Not infected or asymptomatic infection	9	75	1	25
		With symptomatic infection	3	25	3	75
Winsnes R. Efficacy of zoster immunoglobulin in prophylaxis of varicella in high-risk patients. Acta Paediatr Scand 1978;67:77–82	Immunocompromised children receiving immunosuppressant drugs (ZIG)	Not infected or asymptomatic infection	102	97	9	56
		With symptomatic infection	3	3	7	44

Study	Population (Ig)	Outcome	Interval between contract and Ig administration			
			Up to 72 hours		More than 72 hours	
			No.	(%)	No.	(%)
Judelsohn RG, Meyers JD, Ellis RJ, Thomas EK. Efficacy of zoster immune globulin. Pediatrics. 1974; 53(4):476-80	Children receiving chemotherapy (ZIG)	Not infected or asymptomatic infection	43	86	6	83
		With symptomatic infection	6	14	1	17
Koren G, Money D, Boucher M, et al. Serum concentrations, efficacy, and safety of a new, intravenously administered varicella zoster immune globulin in pregnant women. J Clin Pharmacol 2002;42:267–74	Pregnant women (VarIg)	Not infected or asymptomatic infection	6*	55	5**	62
		With symptomatic infection	5*	45	3**	38
Enders G, Miller E. Varicella and herpes zoster in pregnancy and the newborn. In: Arvin AM, Gershon AA, editors. Varicella-zoster Virus. Cambridge: Cambridge University Press; 2000; 317-347	Pregnant women (VarIg)	Not infected or asymptomatic infection	90	59	35	59
		With symptomatic infection	63	41	24	41

Study	Population (Ig)	Outcome	Interval between contract and Ig administration			
			Up to 72 hours		More than 72 hours	
			No.	(%)	No.	(%)
Miller E, Marshall R, Vurdien J. Epidemiology, outcome and control of varicella-zoster infection. Rev Med Micro. 1993; 4:222-230	Pregnant women (VarIg)	Not infected or asymptomatic infection	11	52	12	52
		With symptomatic infection	10	48	11	48
VZ006	Pregnant women (ZIG)	Not infected or asymptomatic infection	6*	55	5**	83
		With symptomatic infection	5*	45	3**	38
	Pregnant women (VarIg)	Not infected or asymptomatic infection	6*	55	5**	62
		With symptomatic infection	5*	45	1**	17
VZ009	Pregnant women, Immunocompromised individuals and Infants <1 year of age (VarIg)	Not infected or asymptomatic infection	417*	94	58**	91
		With symptomatic infection	28*	6	6**	9

*Ig provided less than 96 hours post exposure to varicella

**Ig provided more than 96 hours post exposure to varicella

Table 2. NACI Recommendation for Immunization -- Grades

Grade	Recommendation
A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

VI. LIST OF ABBREVIATIONS

Abbreviation	***Term***
ACIP	Advisory Committee on Immunization Practices
CDC	Centres for Disease Control and Prevention
EAP	Expanded Access Protocol
FDA	Food and Drug Administration
HSCT	Hematopoietic stem cell transplantation
Ig	Immunoglobulins
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
VZV	Varicella Zoster Virus
VarIg	Varicella Zoster Immune Globulin
ZIG	Zoster immunoglobulin

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†**NACI Members:** Dr. I. Gemmill (Chair), Dr. C. Quach (Vice-Chair), Dr. S. Deeks, Dr. B. Henry, Dr. D. Kumar, Dr. M. Salvadori, Dr. B. Seifert, Dr. N. Sicard, Dr. W. Vaudry, Dr. R. Warrington.

Liaison Representatives: Dr. J. Blake (Society of Obstetricians and Gynaecologists of Canada), Dr. J. Brophy (Canadian Association for Immunization Research and Evaluation), Dr. J. Emili (College of Family Physicians of Canada), Dr. M. Lavoie (Council of Chief Medical Officers of Health), Dr. C. Mah (Canadian Public Health Association), Dr. D. Moore (Canadian Paediatric Society), Dr. A. Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada), Ms. E. Sartison (Canadian Immunization Committee).

Former Liaison Representative: Dr. A. Mawle (Centers for Disease Control and Prevention, United States)

Ex-Officio Representatives: Ms. G. Charos (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC], Dr. G. Coleman (Biologics and Genetic Therapies Directorate, Health Canada [HC]), Dr. (LCol) P. Eagan (National Defence and the Canadian Armed Forces), Dr. J. Gallivan (Marketed Health Products Directorate [MHPD], HC), Dr. B. Law (CIRID, PHAC), Ms. M. St-Laurent (CIRID, PHAC), Dr. T. Wong (First Nations and Inuit Health Branch [FNIHB], HC).

Former Ex-Officio Representatives: Dr. D. Garcia (FNIHB, HC),

†**This statement was prepared by** Drs. O. Baclic and C. Quach and approved by NACI.

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