ADVERSE EVENTS TEMPORALLY ASSOCIATED WITH MENINGOCOCCAL VACCINES

Andrée Yergeau,* MD, CMFC; Louise Alain,*‡ BScN, MSc; Robert Pless,*† MD, MSc; Yves Robert,§ MD

Abstract • Résumé

Objective: To determine the incidence of severe adverse events temporally associated with meningococcal vaccines administered as part of a mass vaccination program.

Design: Retrospective descriptive study of events reported to a passive provincial surveillance system.

Setting: The province of Quebec.

Participants: The 1 198 751 individuals aged 6 months to 20 years who were vaccinated against meningococcal disease between Dec. 27, 1992, and Mar. 31, 1993.

Outcome measures: Total numbers and rates of severe adverse events, including allergic reactions, anaphylactic reactions, neurological events (other than abnormal crying and screaming) and other serious or unusual events.

Results: A total of 118 reports of severe adverse events were selected from the surveillance system. The most frequent were allergic reactions (9.2 per 100 000 doses). Few anaphylactic or neurologic reactions were reported (0.1 and 0.5 per 100 000 doses respectively). There were no reports of sequelae or of encephalopathy, meningitis or encephalitis.

Conclusion: Meningococcal vaccines seem to be associated with fewer adverse events than have previously been reported. Existing surveillance programs are useful for determining the incidence of adverse events temporally associated with vaccines.

Objectif : Déterminer l'incidence dans le temps d'événements indésirables graves associés aux vaccins antiméningococciques administrés dans le cadre d'un programme de vaccination générale.

Conception : Étude descriptive rétrospective d'événements signalés à un système provincial passif de surveillance.

Contexte : La province de Québec.

Participants : Les 1 198 751 personnes âgées de 6 mois à 20 ans qui ont été vaccinées contre la méningococcie entre le 27 déc. 1992 et le 31 mars 1993.

Mesures des résultats : Nombres totaux et taux d'événements indésirables graves, y compris réactions allergiques, réactions anaphylactiques, événements neurologiques (autres que pleurs et cris anormaux) et autres événements graves ou inusités.

Résultats : On a signalé au total 118 événements indésirables graves, la réaction allergique étant la plus fréquente (9,2 par 100 000 doses). On a signalé peu de réactions anaphylactiques ou neurologiques (0,1 et 0,5 par 100 000 doses respectivement). On n'a pas signalé de séquelles ou d'encéphalopathie, de méningite ou d'encéphalite.

Conclusion : Les vaccins antiméningococciques semblent à l'origine d'un moins grand nombre d'événements indésirables que par le passé. Les programmes de surveillance existants aident à déterminer l'incidence dans le temps des événements indésirables liés aux vaccins.

*From *the Field Epidemiology Division and †the Childhood Immunization Division, Laboratory Centre for Disease Control, Ottawa, Ont., ‡Direction de la protection de la santé publique, Ministère de la Santé et des Services sociaux du Québec, Quebec City, Que., and §Direction de Santé publique des Laurentides and the Department of Social and Preventive Medicine, Université de Montréal, Montreal, Que.*

Correspondence to: *Dr. Andrée Yergeau, 40, Beausoleil, Gatineau QC J8T 7H5*

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In Quebec from 1991 to 1993 group C *Neisseria meningitidis* became increasingly prevalent, causing clusters of meningitis and septicemia that resulted in serious sequelae and deaths, particularly among children and adolescents.[1] The public health authorities initiated a mass vaccination program, and close to 1.2 million people were vaccinated. We took this opportunity to monitor adverse events temporally associated with the meningococcal vaccines.

There are not many studies of adverse reactions to meningococcal vaccines, and the results of those available are difficult to compare because of the different study designs, especially with respect to validation and active or passive case-finding, and because of the variety of meningococcal vaccines used. Overall, meningococcal vaccines have proven to be safe, with few severe reactions.

Five studies conducted during mass vaccination programs have provided some data on the adverse events temporally associated with meningococcal vaccines. In the first study, which involved 80 000 vaccine recipients, five cases of febrile convulsions were reported.[2] However, one of these cases, in which the recipient had a history of convulsions, was probably caused by a viral infection that began shortly before vaccination. The second study involved 21 007 children; reported reactions were mild (fever, erythema and pain in the vaccinated arm), with three cases of allergic reaction and no case of anaphylactic reaction.[3] In the third study, involving 46 000 recipients, there was one case of anaphylactic reaction; the individual recovered without sequelae.[4] The fourth study revealed systemic reactions (fever, axillary adenopathy, irritability and other unspecified reactions), all of which were of short duration.[5] In the fifth study 130 142 New Zealand children were vaccinated between 3 months and 13 years of age; 57 cases of paresthesia were reported.[6] Most of the cases lasted less than 48 hours, but some lasted up to 3 weeks. The reports were gathered retrospectively (most of them unvalidated) from parents after a media announcement was made seeking reports of reactions to meningococcal vaccines.

Four clinical studies, involving 26 to 396 subjects, analysed adverse events associated with meningococcal vaccines.[7–10] Local reactions were frequent, as was irritability, reported among 5.6% of 396 babies in one study.[7]

According to the US Immunization Practices Advisory Committee[11] adverse events temporally associated with meningococcal vaccines are mild and infrequent and are limited mainly to localized erythema. The product monographs of vaccine manufacturers indicate the possibility of anaphylactic shock and a potential theoretic risk for adults of severe Arthus reactions to booster doses.

Because few large studies of adverse events have been conducted, and because of the need to gather further knowledge to assist in decision making regarding vaccination during outbreaks of meningococcal disease, we reviewed reports of severe adverse events from Quebec's surveillance database to support the view that meningococcal vaccines are safe for use in mass vaccination programs.

Methods

We conducted a retrospective descriptive study of severe adverse events among the 1 198 751 individuals vaccinated between Dec. 27, 1992, and Mar. 31, 1993, through the mass vaccination program against meningococcal disease in Quebec. The ages of the recipients ranged from 6 months to 20 years.

Reports of adverse events were selected on the basis of observations from the literature. We included allergic, anaphylactic and neurologic (other than abnormal crying and screaming) reactions reported by health care providers. Also, all serious systemic or unusual events that did not fit into any of the categories suggested by the Laboratory Centre for Disease Control (LCDC)[12] but that were of medical interest were included in the category of serious or unusual events.

To be considered an adverse event a reaction had to meet specific criteria and could not be attributable to other coexisting conditions.[12] We used LCDC's definitions at first, but after an exploratory validation of reports, particularly those involving anaphylactic reactions, we found that the definitions were being interpreted in various ways and that too many cases did not meet all of the criteria for the definitions. After consultation, and in keeping with the proceedings of a workshop on the standardization of definitions for postmarketing surveillance of adverse vaccine reactions,[13] we made certain clarifications to the definitions of allergic and anaphylactic reactions in order to standardize interpretation (Table 1). These more specific definitions were circulated on Feb. 17, 1993, throughout the entire public health network. Health care providers were instructed to base their re-

Table 1: Definitions of allergic and anaphylactic reactions to meningococcal vaccines

Allergic reaction

Occurrence of at least one of the following events within 24 hours after vaccination

- Urticaria: pruritic skin eruption composed of erythematous papules with a white centre and a clearly delineated contour
- Pruritic rash
- Bronchospasm requiring treatment
- Generalized or facial edema

Anaphylactic reaction

Occurrence of both of the following events within 30 minutes after vaccination

- Cardiovascular collapse: abrupt onset, characterized by cold extremities, marked prostration, diaphoresis, cyanosis, rapid and weak pulse, drop in systolic pressure to 80 mm Hg or lower, oliguria or anuria
- Allergic reaction as defined above

ports on these two definitions for the rest of the vaccination program. The other relevant definitions proposed by LCDC[12] were used without modification.

Adverse events selected for our study were taken from a central database known as ESPRI (Effets secondaires des produits immunisants), into which all reports from the surveillance program of adverse events associated with immunizing agents in Quebec have been entered since 1990. This passive surveillance system operates as follows: a health care provider reports (usually by mail) any symptom temporally associated with vaccine administration to the public health authority in his or her region. The public health authority then validates the case in accordance with LCDC's definitions.[12] The health care provider is contacted if information is incomplete. When a case meets the surveillance definition it is entered into ESPRI by the public health authority. This database contains information on the vaccine recipient, the vaccine, the type of symptoms observed, the time elapsed from vaccination, the clinical course and follow-up, admission to hospital as a result of the adverse event, details of the person submitting the report and other useful additional information.

We selected as the numerator all reports from ESPRI that suggested the occurrence of one of the reactions under study. Although data are validated by the reporting party before they are entered into ESPRI, we contacted the reporting physician or nurse to revalidate all reports that we felt may not have matched the definitions distributed Feb. 17 (Table 1). Three of us (A.Y., L.A. and R.P.) conducted the validation. Contentious cases were discussed by the group and categorized by consensus.

Data on the vaccinated population, who formed the denominator, were collected as part of a study on vaccine coverage conducted during the same vaccination program.[14] These data were taken from forms completed for each vaccinated individual.

We processed the data using EpiInfo software (version 5.01b, US Centers for Disease Control and Prevention, Atlanta). The incidents were categorized according to the variables available in ESPRI, and the incidence rates were calculated on the basis of these cases.

Results

During the study period 1 198 751 individuals were vaccinated.[14] Three different vaccines were used: most (96%) were Polysaccharide Meningococcal A and C Vaccine (Pasteur Mérieux, Lyons, France), and the remaining 4% were either Mencevax AC (SmithKline Beecham Pharma Inc., Oakville, Ont.) or Meningococcal Polysaccharide Vaccine (Groups A, C, Y and W-135 Combined), Menomune (Connaught Laboratories Limited, Willowdale, Ont.).

Adverse events

An analysis of all the adverse events temporally associated with the vaccines is available.[14] A total of 118 severe adverse events met our criteria for inclusion after validation of the reports (Table 2). Allergic reactions were the most frequent, at a rate of 9.2 per 100 000 doses administered. Few anaphylactic and neurologic reactions were observed (0.1 and 0.5 per 100 000 doses respectively). One severe reaction did not fit into any of the predefined categories. No cases of encephalopathy, meningitis or encephalitis were reported.

Most (90.7% [107/118]) of the vaccine recipients with an adverse reaction recovered completely. Information on outcome was not available for the remaining 11 and could not be obtained at the time of validation.

Reports for 10 of the 118 recipients did not include hospital admission data. Of the remaining 108 recipients 6 had been taken to hospital. All but one, who stayed 24 hours, left hospital the same day. All recovered completely.

Allergic reaction

Of the 110 allergic reactions 3 occurred in recipients who had received at least one other vaccine at the same time as the meningococcal vaccine.

The time lapse between vaccination and allergic reaction was within 20 minutes for 24%, within 30 minutes for 35% and within an hour for 51%.

Anaphylactic reaction

The one case of anaphylaxis occurred in a 12-year-old girl 30 minutes after vaccination. She presented with bronchospasm, dyspnea and decreased blood pressure despite two doses of adrenalin. She recovered completely.

Table 2: Frequency of severe adverse events per 100 000 doses* of meningococcal vaccine administered, by reaction type

Reaction	No. of adverse events	Rate per 100 000 doses of vaccine
Allergic	110	9.2
Anaphylactic	1	0.1
Neurologic		
Anesthesia/paresthesia	3	0.3
Convulsions	3	0.3
Total	6	0.5
Serious or unusual event†	1	0.1
Total	118	9.8

*The total number of doses was 1 198 751.
†This event did not fit into any of the predefined categories suggested by the Laboratory Centre for Disease Control[12] but was of medical interest.

Neurologic reaction

Of the six neurologic events three cases of anesthesia/paresthesia, without associated motor problems, occurred in recipients 10 to 16 years old. The reaction occurred within 3 to 8 hours after vaccination. All three patients recovered completely.

Three cases of convulsions were reported. Two corresponded to febrile convulsions and occurred in children 4 years of age or less. The third, in a 19-year-old man, was apparently related to a vasovagal reaction that occurred 10 minutes after vaccination and lasted 20 to 30 seconds. Although we were not able to make a final diagnosis from the available information, this third recipient apparently experienced a similar episode a year earlier when given another vaccine.

Serious or unusual event

The one case that did not fit into any of the predefined categories involved a 16-year-old girl who presented with leg pain 3 days after vaccination and limped for 3 1/2 months. She also had transient urticaria 1 hour after vaccination that recurred 9 days later. The urticaria disappeared promptly with antihistamine treatment. No laboratory tests were done, and the girl recovered completely.

Discussion

We found very few cases of severe adverse reactions to meningococcal vaccines. Over one million people were included in our study, a sample nine times larger than any other study of this kind.

Our study had certain limitations. It was conducted in the context of intervention rather than research. No parallel surveillance system was set up during the study period. The definitions of allergic and anaphylactic reactions were modified in the middle of the program; however, we do not believe we missed any incidents before the modified definitions were distributed because we were using the initial, more general definitions. As well, validation of all reports with the use of the modified, more specific definitions ensured uniformity of all reported cases.

The incidence rates observed during our study were relatively lower than those reported during other mass vaccination programs.[2–6] Some caution is required in comparing our rates with those previously reported because the recipients, the vaccines and the study designs differed. Hood and Edwards[6] found an incidence rate for paresthesia of 44 per 100 000 doses of vaccine. Media announcements were used in the collection of their surveillance data, and most of their reports were not validated. In our study only three cases of anesthesia/paresthesia were reported, and, as Hood and Edwards found, no sequelae were linked to these incidents. The incidence rate for convulsions reported in a study by Novelli and associates[2] was higher than our rate. However, they used an active case-finding system and their sample was younger than ours (aged 3 months to 12 years). Interestingly, they found no reports of convulsions when the vaccine dose was cut in half (to 0.25 mL). Peltola and associates[3] reported an allergic reaction rate a little higher than ours. Anaphylaxis was reported in only one previous study,[4] at a rate 22 times higher than ours (2.2 v. 0.1 per 100 000 doses). It is possible that our rates were lower because we used definitions of allergic and anaphylactic reactions that were more specific than those of LCDC. However, the surveillance definitions used in the other studies were not provided.

Reporting delay was taken into consideration: 7 months after the end of the mass vaccination program, only one new case (anesthesia/paresthesia) was reported, with complete recovery.

The reliability of incidence rates of adverse events depends in part on the accuracy of the numerator and denominator. With respect to the numerator, we believe that the knowledge and wide use of the passive surveillance program and its ESPRI register since 1990, the circumstances in which the mass vaccination program took place and the information sent to the public health units on the importance of monitoring adverse events all contributed to stimulate the reporting of adverse events. As a result, those involved in the vaccination program were sufficiently aware of the surveillance system, and any serious adverse event or outcome would have likely been reported. As for the denominator, we used the number of individuals vaccinated instead of the amount of vaccine distributed in order to give a more realistic picture.

Conclusion

We found relatively low rates of severe adverse events, most reactions being allergic in nature. None of the events resulted in serious outcome or death. Our findings confirm the safety of meningococcal vaccines when used in a mass vaccination program. Also, our study demonstrates the importance and utility of an existing surveillance system in determining the incidence of adverse events temporally associated with a vaccine used in a mass vaccination program.

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THERAPEUTIC CLASSIFICATION
Angiotensin Converting Enzyme Inhibitor

INDICATIONS AND CLINICAL USE
The treatment of mild to moderate essential hypertension. May be used with thiazide diuretics.
Use when treatment with a diuretic or a beta-blocker are contraindicated, were found ineffective or have been associated with unacceptable adverse effects.
Not recommended for CHF and renovascular hypertension.
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected MONOPRIL should be discontinued as soon as possible.

CONTRAINDICATIONS
Hypersensitivity and history of angioedema related to previous ACE inhibitor therapy.

WARNINGS
Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the tongue, or glottis occurs, discontinue immediately, administer epinephrine (0.3 - 0.5 mL 1:1000) and carefully observe patient until swelling disappears. Swelling confined to the face and lips generally resolves without treatment; antihistamines may be used.
Patients with a history of angioedema may be at increased risk.

Hypotension: Usually occurs after first or second dose or when the dose was increased. More likely in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Patients with severe CHF, ischemic heart or cerebrovascular disease should start therapy under close medical supervision, then followed closely for the first weeks of treatment and whenever diuretic or MONOPRIL dose is increased.

Neutropenia/Agranulocytosis: Incidence is rare. Consider periodic monitoring of white blood cell counts.

PRECAUTIONS
Impaired Renal Function: Assess renal function before initiating therapy. Use with caution in patients with renal insufficiency, and closely monitor.

Surgery/Anesthesia: Hypotensive effects of anesthetics and analgesics may be augmented. Correct by volume expansion.

Hyperkalemia and Potassium-Sparing Diuretics: Use with caution. Risk factors include renal insufficiency, diabetes mellitus, and concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (e.g. heparin).

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes.

Anaphylactoid reactions during desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasps) venom.

Valvular Stenosis: Patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators.

Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred. Investigate fully any unexplained symptoms particularly during first weeks or months of treatment. Use with particular caution in patients with pre-existing liver abnormalities, and closely monitor response and metabolic effects.

Cough: Consider as part of the differential diagnosis of the cough.

Nursing Mothers: Do not administer to nursing mothers.

Pediatric Use: Do not use in this age group.

DRUG INTERACTIONS
Agents Increasing Serum Potassium: Should be given cautiously only for documented hypokalemia and with frequent monitoring of serum potassium.

Agents Causing Renin Release: Antihypertensive effect of MONOPRIL is augmented.

Lithium: May result in increased serum lithium levels. Coadminister with caution and frequently monitor serum lithium levels.

Antacids: Antacids may impair absorption of fosinopril. If concomitant administration is indicated, dosing should be separated by two hours.

Digoxin: Concomitant administration did not alter the bioavailability of fosinoprilat.

Furosemide: Coadministration increased AUC of fosinoprilat by 26% and Cmax by 25%. Furosemide levels were decreased.

Warfarin: Bioavailability of fosinoprilat or warfarin was not altered by coadministration.

Other: Bioavailability of fosinoprilat was not altered by coadministration with chlorthalidone, nifedipine, propranolol, hydrochlorothiazide, cimetidine, metoclopramide and propantheline.

ADVERSE REACTIONS
The most severe adverse reactions occurring in all patients treated with MONOPRIL in clinical trials (1548 patients) were: angioedema (1 case), orthostatic hypotension (2.7%). Myocardial infarction (2 cases) and cerebrovascular accident (4 cases) occurred, possibly secondary to excessive hypotension in high risk patients.
Most frequent adverse experiences which occurred in 688 MONOPRIL-treated patients in placebo-controlled hypertension trials were nausea/vomiting, diarrhea, fatigue, musculoskeletal pain, headache, dizziness and cough. Discontinuation of therapy because of adverse events was required in 4.1% of the 688 patients.
Adverse reactions occurring in ≥ 1% of 1048 hypertensive patients in controlled clinical trials treated with MONOPRIL monotherapy were: orthostatic hypotension (1.4%), rash (1.0%), sexual dysfunction (1.7%), nausea/vomiting (1.4%), diarrhea (1.4%), pyrosis (1.0%), dry mouth (1.0%), fatigue (2.8%), headache (4.6%), dizziness (3.8%) and cough (4.0%).

DOSAGE AND ADMINISTRATION
Individualize dosage. Consider recent antihypertensive drug treatment, extent of blood pressure elevation and salt restriction.
The recommended initial dose of MONOPRIL is 10 mg once daily. Adjust according to blood pressure response, at intervals of at least two weeks. Usual maintenance dose is 20 mg once daily. Do not exceed a dose of 40 mg daily.
If antihypertensive effect is not satisfactorily maintained for 24 hours, consider either twice daily administration with the same total daily dose, or an increase in dose. If blood pressure is not controlled with MONOPRIL alone, a diuretic may be added.

Concomitant Diuretic Therapy: If possible, discontinue diuretic for two to three days before beginning therapy with MONOPRIL to reduce likelihood of hypotension. If not, use an initial dose of 10 mg MONOPRIL with careful medical supervision for several hours and until blood pressure has stabilized. Titrate dosage of MONOPRIL to obtain optimal response.

Dosing Adjustment in Renal Impairment: With normal liver function no dosage adjustment is necessary. Initial dose is 10 mg once daily.

Dosing Adjustment in Hepatic Impairment: With normal renal function no dosage adjustment is necessary. Initial dose of MONOPRIL is 10 mg once daily.
No dosage adjustment is necessary in elderly hypertensives with normal renal and hepatic function.

AVAILABILITY
MONOPRIL 10 mg tablets are white to off-white, flat end diamond shaped, compressed tablets with a partial bisect bar engraved with BMS on one side and MONOPRIL 10 on the other.
MONOPRIL 20 mg tablets are white to off-white, oval shaped, compressed tablets engraved with BMS on one side and MONOPRIL 20 on the other.
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