ISSN 0382-232X

Canada Diseases Weekly Report

Date of publication: July 1991 Vol. 17S4

Supplement

PROCEEDINGS OF A WORKSHOP ON

POST-MARKETING SURVEILLANCE OF VACCINE-ASSOCIATED ADVERSE EVENTS (VAAEs)

Ottawa, Ontario
26 March 1990

Santé et Bien-être social Canada
Health and Welfare Canada

Canada

Proceedings of a Workshop on Post-Marketing Surveillance of Vaccine-Associated Adverse Events (VAAEs)

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Co-sponsored by the

Bureau of Communicable Disease Epidemiology
Laboratory Centre for Disease Control

and the

Bureau of Biologics
Drugs Directorate

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INTRODUCTION

Although rare, adverse events (sometimes severe ones) can occur following the administration of vaccines. Consequently, there is a need to monitor vaccine-associated adverse events to ensure that the safest products are used. The public needs to be assured that vaccines are as safe as possible and that the government is closely and actively monitoring the use of vaccines.

This workshop brought together members of the Canadian public health, medical and nursing communities, government and non-government agencies, and the pharmaceutical industry to discuss the issues surrounding vaccine post-marketing surveillance in Canada with the goal to develop a framework for a coordinated proactive approach to optimize post-marketing surveillance (PMS) in Canada.

RESULTS OF DISCUSSION

What should be the scope of vaccine PMS in Canada?
PMS of vaccines should be defined as the coordinated, structured, systematic, ongoing collection of data and their subsequent epidemiologic analysis and dissemination on the impact of licensed vaccines in order to advise manufacturers, regulators, health-care providers, and the public.

PMS should include both (1) active surveillance activities that are planned, time-limited, and involve prospective or retrospective studies, and (2) passive surveillance reports that are centrally aggregated in a timely manner and include input from physicians, public health providers, patients and their families.

Both old and new vaccines should be included in PMS as well as their broad impact on the disease epidemiology and on the patient and his/her family. Vaccine efficacy and effectiveness should be considered as well as adverse reactions. New vaccines will require very precise surveillance over a specified period of time on certain strata of the population (children, adolescents, adults, etc).

PMS should consider common adverse events if they have not been extensively studied under field conditions similar to those likely to be experienced in Canada in Phase 3 studies. It is felt that active surveillance has been neglected in the past and needs to be encouraged while passive surveillance has to be continued.

Access to prelicensure data would allow for the design of efficient PMS.

What questions are likely to have to be addressed?
The broad questions that are likely to have to be addressed are as follows:

- Is the vaccine safe?
- What is the vaccine efficacy and effectiveness?
- What is the effect on the disease, the patient and his/her family?
- Are the contraindications appropriate?
- What is the effect of the vaccine on specific subgroups of our population?
- What is the rate of a specific adverse outcome in our population?
- What are the epidemiologic characteristics of the groups affected by a particular adverse reaction?
- What is the cost-benefit ratio of the immunization program?

How and when should the questions be determined and listed, and who should define them?

During the assessment of a vaccine by the Bureau of Biologics, prior to licensure of the vaccine, an advisory committee of experts (a specific committee or a subcommittee of the National Advisory Committee on Immunization (NACI) with additional experts who are knowledgable about that specific vaccine) should look at the data available for that specific vaccine and specify the questions that still need to be answered. The committee work would have to be performed with the consent of the manufacturer and confidentiality of the prelicensure data would have to be assured. For each new vaccine it would be the Bureau of Biologics's responsibility to determine the appropriate time for the committee to convene.

As the Bureau of Biologics reports to NACI on products about to be licensed, NACI could decide which ones are important for PMS and request the advisory committee to study the issue. After studying the prelicensure data, the committee would propose types of PMS required to respond to questions still not answered by the premarketing studies. The manufacturer would devise a system by which the committee's questions could be answered. The Bureau of Biologics and the Bureau of Communicable Disease Epidemiology would then determine what course of action should be followed to establish the PMS.

For practical and logistic reasons, it would not be appropriate for the committee to be assimilated into NACI and for issues about PMS for specific vaccines to be debated during regular NACI meetings. Funds to convene the advisory committee will have to be provided by the Laboratory Centre for Disease Control (LCDC). This committee will require one working day to deliberate and make recommendations.

Vaccines should be considered individually. In some instances it will not be necessary to request a structured PMS plan if all the required information is available before licensure. Routine PMS would be used to detect any unexpected events. At other times, a specific PMS plan will be presented to the manufacturer.

Potential requirements for licensure will be handled directly with each manufacturer by the Bureau of Biologics. No interaction with the Pharmaceutical Manufacturers Association of Canada (PMAC) is deemed necessary.

Other organizations, either directly in collaboration with Health and Welfare, or through the committee, will be given the opportunity to raise questions.

What epidemiologic tools can be applied to address the questions, and which organization can best provide these tools?

From the broad range of tools available, it is necessary to identify those that best apply to each specific vaccine and question. We should not attempt to use all of the available tools at all times.

The various tools available are as follows:

- Passive reporting system mainly used for hypothesis-generating questions and lot-to-lot monitoring
- Study of denominator data to allow for rate computation
- Prospective cohort studies
- Serologic studies for duration of immunity
- Specialized pediatricians to look at special groups of children such as those with cystic fibrosis
- Retrospective case-control studies
- Case-series studies
- Record-linkage studies such as the proposed one that would involve the Manitoba Immunization Monitoring System; other provinces should be encouraged to do the same
- Review of physician-computerized office databases
- Disease surveillance data for monitoring the epidemiologic impact of vaccines on diseases.

The following networks were identified to provide these tools:

- Paediatric Sentinel Hospital network (well-suited for studying severe events)
- Family Physician, Paediatric and Public Health clinic network (good for acute common reactions, efficacy studies, and for data collection by nurses/parents)
- Vaccine Evaluation Centre
- Network of provinces such as Manitoba that have immunization databases or a specific interest in conducting post-marketing studies
- University-based paediatric and other medical centres
- Paediatric hospital emergency room network which is computerized for collecting data on accidents.

The active surveillance of long-term rare events was considered to be unrealistic.

The basic PMS program for all vaccines would be part of the present routine ongoing government-funded passive surveillance system based on

the communicable disease surveillance model. A specific package, if needed, could be designed for a specific vaccine. The various networks could be used to address specific questions. The basic package would include specific experiences in the Canadian population.

Who should pay for PMS?

PMS must be efficient and cost-effective. No actual decision was made regarding who should be financially responsible for PMS, but it was suggested that a joint or shared approach between the Health Protection Branch (HPB), the manufacturers and the PMAC (through Research and Development funds) would be the best approach. This would have to be compatible with the Drugs Directorate's overall approach to pharmaceutical PMS. It was also noted that currently two of the vaccine manufacturing companies (Connaught and Institut Armand Frappier) do not belong to PMAC.

The government should support the existence of the networks. In addition, these networks would need multiple sources of funding to keep them financially viable between studies. Networks must be competitive in the marketplace. However, no major competition is predicted in the near future.

It was noted that, if the manufacturers are solely responsible for the cost of PMS, the cost of vaccines would be increased and the public would ultimately pay for PMS. The public expects the government to monitor vaccine safety, not private companies that have an interest in selling the vaccine. Therefore, if funding for PMS were to come from the government, the public would be more reassured.

The possibility of sharing the cost among provinces in a prorated manner according to population was rejected as not being practical because the provinces believe that PMS is a federal issue.

RECOMMENDATIONS

1. Ongoing PMS and specifically designed studies are essential to provide safe and effective immunization programs and must be funded.
2. PMS of vaccines should be defined as the coordinated, structured, systematic, ongoing collection of data and their subsequent epidemiologic analysis and dissemination on the impact of licensed vaccines in order to advise manufacturers, regulators, health-care providers, and the public.
3. PMS should include both 1) active surveillance activities that are planned, time limited, and involve prospective or retrospective studies, and 2) passive surveillance that is centrally aggregated, timely, and includes input from physicians, public health providers, patients and their families.
4. Sufficient federal government funding has to be made available on a routine and permanent basis to support PMS in order to improve life and health of Canadians.
5. If needed for specific vaccines, for special studies, active surveillance funding should be shared between HPB, the manufacturers and the PMAC.
6. PMS should apply to new and old vaccines and look at the broad impact on the disease epidemiology as well as on the patient and his/her family and should look at vaccine efficacy and effectiveness as well as adverse reactions.
7. The Bureau of Biologics advises NACI on vaccines to be licensed. NACI should decide the need to call the committee that would make recommendations on PMS of the particular vaccine. After the collection of all relevant data, the Bureau of Biologics and the Bureau of Communicable Disease Epidemiology will decide what measures should be taken to establish PMS.
8. Various networks have been identified that could be used for PMS according to specific needs.

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