Public Health Agency of Canada
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6th Canadian Immunization Conference

Immunization in Canada

Science – Programmes – Collaboration

December 5-8, 2004

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Introductory Note

The 6th National Immunization Conference was organized by the Immunization and Respiratory Infections Division of the Public Health Agency of Canada and the Canadian Paediatric Society, with financial support from the private sector and the provinces of Alberta, Ontario and Quebec. The theme of the conference – Immunization in Canada: Science, Programs, Collaboration – was chosen to ensure that delegates were provided with cutting-edge information on immmunization science, policy, programs and practice. The conference was also a forum for networking and knowledge-sharing among the many disciplines working in immunization.

The conference opened with presentations describing the significant contributions of Canada and Canadians to international health and immunization initiatives. On the second day, an overview of immunology was followed by presentations on vaccine development from concept to delivery. Discussions of new vaccines and their applications completed the plenary presentations that day. Breakout sessions on a wide variety of topics were held that day and the next two. In the evening, the first Dr. John Waters Lecture, on the topic of poliomyelitis, was presented. Topics on the third day of the conference included vaccines and emergency response, the costs and benefits of some of the more expensive vaccines, and an update on the status of the National Immunization Strategy, current immunization programs and immunization registries. Current challenges in immunization – public education, vaccine supply and competing priorities in health care – were addressed on the final day of the conference, and an "ask the experts" panel responded to questions raised by delegates.

Display booths from numerous organizations and companies as well as scientific posters were available for viewing throughout the conference. In addition, the Canadian Coalition for Immunization Awareness and Promotion displayed winning immunization posters designed by Grade 6 students from across Canada.

This report provides a brief account of the presentations made at the conference.

Sunday, December 5, 2004

Opening Event: Making a World of Difference: Canadians on the Front Line

Dr. Arlene King

Director, Immunization and Respiratory Infections Division, Public Health Agency of Canada (PHAC), and Chair, Canadian Immunization Conference Organizing Committee

Dr. Arlene King welcomed participants to this Canadian Immunization Conference (CIC). The theme of this first evening – Making a World of Difference: Canadians on the Front Line – was chosen to recognize the significant contributions of Canada and Canadians to international health and immunization initiatives. Every year, about 130 million infants are born; of these, 90 million are born in a developing country. About 30 million poor children do not receive the vaccinations that could save their lives, leading to 1.5 million avoidable deaths yearly. Unfortunately, by the end of the last millennium, the average vaccination coverage rate for children globally was reduced from a high in the mid-1970s of 80% to just 74%. This reduction means that one child in four in the world is not immunized against illnesses such as measles, poliomyelitis (polio), pertussis, tuberculosis and tetanus. Access to immunization varies greatly across the world. In some countries, up to 70% of children do not receive a full set of vaccines, even though immunization represents the most efficient solution to infectious diseases. PHAC and its partners are making great strides in domestic and global immunization. Canada is a member of the Global Alliance for Vaccines and Immunization (GAVI) along with other governments, the World Health Organization (WHO), UNICEF, the World Bank, foundations, private benefactors, non-government organizations and the vaccine industry. By broadening vaccination coverage in the 75 poorest countries of the world, GAVI is hoping to reach the UNICEF objective of reducing by two-thirds the mortality rate of children < 5 years of age by 2015.

The Honourable Dr. Carolyn Bennett

Minister of State for Public Health

The Honourable Dr. Carolyn Bennett, Minister of State for Public Health, Government of Canada, thanked the members of PHAC and the Canadian Paediatric Society (CPS) for organizing this significant conference. The huge number of participants at this conference indicates the importance placed on the shared goal of keeping Canadians healthy for as long as possible, a goal that has been extended to the world. In her role as the first-ever Minister of State for Public Health, Dr. Bennett has found that three things have shaped her view of her role at PHAC: science, engagement and collaboration. This conference brings together all three.

The Prime Minister has also been clear on the importance he places on immunization. In part, this emphasis stems from his own experiences with polio as a child. One result has been the inclusion in the budget of $300 million for the National Immunization Strategy, recognizing the need to put real dollars toward vaccine science and programming.

Dr. Bennett closed by thanking all the participants for all they do here in Canada and around the world.

Mr. Mario Renaud

Acting Vice President, Multilateral Programs, Canadian International Development Agency

Speaking on behalf of International Cooperation Minister Aileen Carroll, Mr. Mario Renaud welcomed participants to Montreal and the Canadian Immunization Conference. He noted that Minister Carroll is sometimes asked if the money Canada spends really changes things in the world. Indeed, it has, but equally valuable have been the contributions of Canadian nurses, physicians, epidemiologists and others who have travelled to share their expertise. Included in this group are the front-line volunteers from organizations such as the Rotary Club who participate tirelessly in immunization campaigns in developing countries.

In the past few years, the Canadian International Development Agency (CIDA) has been working hard to strengthen its support in countries and sectors where it has the expertise and resources to foster sustainable development, especially in Africa. One major goal is to cut the mortality rate of children < 5 by two-thirds by 2015. Vaccinating the world's children will help to achieve this goal. Global immunization efforts get results. They are cost effective. They save lives. They spare families and the health care system from the burden of preventable disease. But they are also a huge challenge, requiring people and organizations to work together and to combine human and financial resources. That's why Canada is working on several immunization initiatives, partnering with such organizations as UNICEF, GAVI, WHO, the Pan-American Health Organization (PAHO) and others. The initiatives include not just immunization delivery, but also the building of capacity of health care staff in epidemiology, data management, laboratory diagnostics and vaccine safety. In the past six years, more than 100,000 Canadian health care professionals have signed up for 30-month assignments in developing countries. The efforts toward the global eradication of polio mean that 99% of the world is now polio-free. There have

been setbacks, such as the suspension of polio vaccination in Northern Nigeria in 2003, resulting in numerous new polio cases (accounting, in fact for nearly 90% of new polio cases worldwide), but this setback did not dampen Africa's determination to be free of this disease. In the early fall of 2004, 25 African countries harnessed one million workers to deliver vaccine, and they did it again in November. Other initiatives have piggybacked on polio vaccine, such as the delivery of vitamin A supplements. Canada is the leading donor of vitamin A capsules.

Since the inception of GAVI 4 years ago, immunization coverage globally has expanded. For example, nearly 40 million more children have received the hepatitis B vaccine. GAVI is also introducing new combination drugs to fight hepatitis B, yellow fever, rotavirus and meningitis types A and C. Finding a vaccine is also the world's best hope for stopping the spread of AIDS. Most cases of AIDS are in Africa, but Africa receives only a small proportion of the global funds for AIDS. Canada has supported both research in Africa and the building of clinics and laboratories.

Global immunization efforts require not just the cold chain of vaccine delivery, but also the warm chain of people helping other people. It is hoped that this chain will continue to grow.

The Global Polio Eradication Initiative

Mr. Bruce Aylward

Coordinator, WHO Global Polio Eradication Initiative

The global eradication of polio has been the largest public health initiative ever undertaken, with over two billion children having been immunized. The initiative has three main strategies: routine immunization, surveillance and mop-up activities. Routine immunization in most developing countries requires national immunization days (NIDs), where every child < 5 years of age in the country is immunized over the course of 2 to 3 days. For example, over 300 million children were immunized in the fall of 2004 through NIDs. In mop-up, health workers go house-to-house to identify missed children. Strategy implementation requires policies, partnerships, people and finances. Canadians participate in all these areas, working on the front lines and in advisory committees, contributing resources (over $125 million to date, as well as technical expertise and skills) and advocating for the program. Advocacy is key, and Canada has been a leader in ensuring that polio eradication gets on and stays on the international agenda.

Canadian volunteers, such as those from the Rotary Club, have also been tremendous partners. Rotary International has been part of the polio initiative from 20 years and has given millions of dollars to the initiative, in addition to human hours. Other examples include the Canadian Public Health Association (CPHA), the March of Dimes and more.

The vaccine industry has also played a vital role. In 1999, for example, the global initiative came up with the idea of tripling its immunization campaigns. WHO contacted Aventis, which in turn started a process whereby it and other manufacturers doubled production to meet vaccine supply needs.

But the polio eradication initiative does not just take from Canada, it also gives back. Since 1988, polio has gone from being endemic in 125 countries to being endemic in just six. Canadians are thus protected significantly against importations of the disease. Also because of the near-eradication of polio, Canadians and Americans have been able to switch from live oral polio vaccine (OPV) to inactivated vaccine (IPV), significantly reducing the risk of vaccine-associated polio. The global surveillance network for acute flaccid paralysis assists Canada and other countries in identifying risks. Canada has gained highly positive international exposure for its work in developing countries. In addition, the initiative provides fantastic opportunities for Canadian individuals, who can learn about international health programming, strategic planning and the realities of living and working in developing countries.

Canada has been at the centre of the global polio eradication initiative, and its continuing support is crucial. Financing, for example, is still a significant need, with $200 million required to finish the job. Canada's expertise in reaching special and marginalized populations, in introducing new vaccines rapidly, and in dealing with vaccine safety and risk communications will help to make the global eradication of polio a reality.

Eliminating Polio from Haiti, Again

Dr. Eleni Galanis

Physician Epidemiologist, British Columbia Centre for Disease Control

In October 2000, a cluster of children in the Dominican Republic developed acute flaccid paralysis (AFP). These cases were later confirmed to have been the result of vaccine-associated polio (VAP), the first cases of polio in North America in 10 years. By August 2001, 21 cases had been identified – 13 in the Dominican Republic and eight in Haiti. In late 2001, Dr. Eleni Galanis volunteered to participate in the eighth session of the STOP (Stop Transmission of Polio) mission established to combat this VAP outbreak.

Haiti has one of the highest population densities in the world and is one of the poorest countries in the world. It has the worst health indicators in the Americas with an average life expectancy of just 49 years. A coup d'état shortly after the country's first free democratic election in 1990 was followed by a decade of social unrest and unstable government, resulting in a weakened health structure.. During the 1990s, polio vaccine coverage with three doses of OPV in children < 1 year was very low, not surpassing 40%. This low coverage led to an increased number of susceptible people on the island, which allowed OPV poliovirus to circulate and gradually accumulate genetic changes, leading to a more virulent form of the virus.

To control the spread of the outbreak, the Haitian Ministry of Public Health and the Pan American Health Organization reinforced surveillance for further cases of acute flaccid paralysis and set up a nationwide immunization campaign involving a number of international consultants. The objective of the campaign was to immunize all children < 10 years with two doses of OPV. Initially, the target population was 2.3 million, but this proved to be a serious underestimation. As a result, there was a vaccine shortage, which led to a delay in the campaign until international lobbying led to more funding and vaccines. The lack of both a recent census and up-to-date maps were serious challenges. Often, the health teams would arrive at a location where they expected a sparse rural population but instead found a burgeoning metropolis with thousands of children. Roads were in very poor conditions and many areas had to be accessed with horses or four-wheel-drive vehicles. To ensure full vaccine coverage, the health workers giving the first dose of vaccine updated their maps as they worked. The workers also did random monitoring of hard-to-access areas to identify areas of poor coverage.

Maintaining the cold chain was another challenge. Electricity was unreliable or non-existent, and few thermometers in refrigerators were working. The coloured temperature monitors on the vaccine were important guides and good tools for educating local health workers. For example, entire refrigerators full of vaccines that had been exposed to heat were thrown out, shocking local health officials but sending a clear message about the importance of vaccine management. Understandably, an outbreak of eight cases of polio was not a priority to local health care workers as they had to deal with many health issues causing substantially more morbidity and mortality. Also, many were quite demoralized after years of working in an under-resourced system. Team work, mutual problem solving, and the enthusiasm and leadership of the international workers helped re-energize local workers.

Ultimately, the campaign resulted in the vaccination of 2.9 million children. No further cases of polio were detected after the first few weeks of the campaign. International workers who had never experienced polio first-hand learned of the devastating effects of polio on children and their families. They, and the world, also learned that public health must remain vigilant to avoid another VAP outbreak, high vaccine coverage must be maintained, OPV must stop being used as soon as possible after eradication and the international community must support Haiti and countries in similarly fragile conditions. International health is not just about providing aid and expertise; it is first and foremost about collaboration.

Reaching Out – Touching Lives

Ms. Norma Chambers

Public Health Nurse, Comox, B.C.

In early 2004, Ms. Norma Chambers accepted an offer from the Canadian International Immunization Initiative (CIII) to work as a UN consultant for 3 months on the 15th STOP mission to Pakistan. CIII recruits and deploys Canadian professionals to provide assistance to PAHO, WHO, UNICEF and national ministries of health in developing countries. It also works with Rotary International and the STOP missions of the United States Centers for Disease Control (CDC).

Pakistan is about half the size of Quebec with 20 times more people – more than 160 million. The Punjab province, where the STOP mission was to occur, has a population of 80 million. The population is poor, with high illiteracy, multiple families in one dwelling, poor to non-existent sanitation and considerable migration between districts and provinces. Pakistan is one of the few countries where polio is still endemic. Because more than 40 NIDs have been held there, the local health enthusiasm for the program has dropped; "polio fatigue" is common among the health workers. Coverage is at 95% to 97% coverage, but the small missing proportion translates into thousands of children missed and a potential reservoir for polio. New cases continue to occur, although the incidence has dropped significantly each year. International teams are therefore going in to support and motivate local professionals and remind them of the goal. WHO strategies for Pakistan include high-quality campaigns, improved community mobilization, an increased number of women on the teams, increased access to children, and improved communications among remote districts, the provinces and the country. As a team leader for the Kasur District of the Punjab, Ms. Chambers had to strive to implement these strategies.

The first step was refreshing the microplans for each community, most of which were outdated. Microplans are a vital element of STOP missions. They are put together by the community to ensure detailed mapping, accurate definition of the target population and appropriate plans for social mobilization, training, supervision and finding missed children. Social mobilization is key, as the active involvement of the community shows that the campaign is not imposed from above or outside. It includes how to inform people about the campaign (posters, flyers, meetings with community and business groups, etc.) and encouraging their acceptance, participation and support (e.g., donations of cars). Despite the Muslim concept that women should remain in the home and not earn wages, the goal of increasing women's participation in the campaign met with great success. The women ranged from teens to grandmothers and brought a new motivation and energy to the program. Also, because most mothers in Pakistan do not allow unrelated men into the home, having women on the vaccine teams was critical.

The health workers on the teams had to be trained in more than just vaccine administration, which most of them had the basic knowledge and skills to do. Most also knew to use tally sheets and do chalk marking on doors and gates (the number of children in the house and the number vaccinated). Additional training stressed their role in helping families to report cases. Effective communication and interviewing skills were demonstrated using role play.

Two campaigns were planned, one each for March and April and each with a goal of immunizing half a million children in 3 days. The kick-off to the April campaign included a well-organized polio walk – a 30-minute walk through town, in which the mission team was joined by about 1,000 people, including children, health care workers, police officers, shop owners and the general public. Colourful vehicles used loudhailers to announce polio messaging. In the first 3 days of the immunization schedule, 1,000 teams went by foot, bicycle or horse from house to house in their communities, immunizing 100,000 children < 5 per day, conducting interviews, etc. On days 4 and 5, teams revisited areas to capture children on the earlier days while supervisors conducted random house-to-house visits. On days 6 through 10, Ms. Chambers led health officials house to house to assess overall coverage and try to find any missed children. By day 8, 98% of the target population had been immunized and teams were being organized to look for any remaining children.

Punjab province had 2 new cases of polio in 2004, compared to 25 in 2003. The Kasur District, where Ms. Chambers worked, has had no cases.

Monday, December 6, 2004

Welcome and Introduction

Dr. Arlene King

Director, Immunization and Respiratory Infections Division, PHAC, and Chair, Canadian Immunization Conference Organizing Committee

Dr. Arlene King welcomed participants to this 6th Canadian Immunization Conference, organized by PHAC in collaboration with CPS, and thanked the many participants, sponsors and collaborators, as well as the host city of Montreal. The conference is dedicated to the honour and memory of Dr. Victor Marchessault, who died in 2003. Dr. Marchessault was an advocate, a leader and a caregiver in the field of paediatrics and an infectious disease scholar. He devoted his career to helping children and youth.

The Honourable Dr. Carolyn Bennett

Minister of State for Public Health

The Honourable Dr. Carolyn Bennett thanked the organizers from CPS and PHAC, particularly Dr. King and her Division. It is fitting that hundreds of immunization, public health and vaccine experts from Canada and internationally have come together in the year of the 50th anniversary of the polio vaccine trial. The polio vaccine story reflects the true value of science, immunization programming and collaborative efforts and is a great tool for explaining the importance of vaccines to the public. In 1955, Paul Martin Sr., Minister of National Health and Welfare, made an extraordinarily difficult decision based on the best science about what was the best choice for the most people. He believed then that "the benefits of medical science should be made universally accessible." Today, this conference is an opportunity to reaffirm our commitment to science-based decision-making and promote citizen engagement in immunization.

In addition to being the 50th anniversary of a momentously beneficial event, this conference is being held on the anniversary of a much different sort of event that happened in this city of Montreal. Fifteen years ago, on December 6, 1989, Marc Lépine killed 14 women in an engineering class at the École Polytechnique. Hatred and bigotry are also infectious diseases, and whether the disease is bigotry or child abuse or polio, it is up to all of us as global citizens and health care providers to do what we can to eradicate it. Dr. Bennett closed by reading the names of the 14 women killed, reminding participants that in addition to the time we spend concerned about population health, we must remember that it is individuals that get taken from us, and it is individual lives that we are trying to keep well.

Dr. David Butler-Jones

Chief Public Health Officer for Canada, PHAC

Meetings such as this one present prime chances for health professionals to reconnect with colleagues from across the country and internationally to talk about some of the key issues in health care today. Today, those issues relate to things like long wait lists for knee and hip replacements and the best use of sophisticated medicines. Fifty years ago, such topics could not have been imagined by health professionals facing the challenges of polio, measles and other major diseases. If not for the work of those professionals and scientists who came before us, we would not be in a position to be even thinking about the issues we see as key today.

Public health workers are part of a conspiracy that works to deny the future that nature might call us to and aspires to one better. In the 18th century, a 50% infant mortality rate was accepted as "nature's law". Through public health measures such as good hygiene, sanitation, clean water, adequate food and housing, and immunization, infant mortality in Canada today is less than 0.5%. Yet public health professionals often take this success for granted. Public health must celebrate itself and its successes if other Canadians are to recognize its importance as well.

Dr. Philippe Couillard

Minister of Health, Quebec

Dr. Philippe Couillard welcomed participants on behalf of the Quebec government. This conference represents an opportunity both to reinforce links within public health and to forge new ones. Such collaboration is essential in facing the numerous challenges in immunization. To a certain extent, immunization is a victim of its own success. With the eradication of some diseases and with the morbidity and mortality from others significantly reduced, some people today wonder about the value of immunization.

As governments and health professionals continue to engage in extensive work to protect the public, the efforts of Quebec and the other provinces are reinforced by the National Immunization Strategy (NIS). In turn, the provinces work to reinforce the NIS. Quebec, for example, administers 2.5 million doses of vaccine annually. Its vaccine program evolves constantly as the province integrates new vaccines as recommended by the expert advisory committees.

Through such reciprocal collaboration and cooperation, this conference represents an opportunity for individuals, governments and organizations to benefit from each other's experience.

Dedication of the Conference to Dr. Victor Marchessault

Dr. Rod Bergh

Children's Hospital of Eastern Ontario

Dr. Rod Bergh met Dr. Victor Marchessault in the mid-1960s while both were involved in work with CPS, and they remained close friends until Dr. Marchessault's death in March 2003.

Dr. Marchessault became involved with CPS when he first went into practice and was a consistent and dynamic force with the Society from then on. In addition, even while involved in his busy paediatric practice in St-Lambert, Quebec, he spent some of his time doing research at the Institut Armand-Frappier. He also loved to teach, and as late as the fall of 2002 he was still involved in continuing medical education programs at the Children's Hospital of Eastern Ontario.

Dr. Marchessault's private life was equally rich and fulfilling. His wife Louise shared his interests and dedication. His children and grandchildren gave him immense pleasure. His intensity about his work was matched by his intensity about his other interests: photography, dining with friends and associates, music (especially jazz), golf, hockey and more.

Dr. Marchessault touched the lives of many people directly and he contributed enormously to the well-being of millions of others. He felt fortunate to be involved in the field of infectious diseases and immunization. The time he spent as chair of the National Advisory Committee on Immunization (NACI) was a cap to all his other activities over the years. After his death, a friend noted that he had left a lot of things undone. That untidiness would have bothered him, except that he would know that the people at this conference were among the many who were going on with his work.

Dr. Robin Walker

President, Canadian Paediatric Society

CPS was founded in 1922 by 16 paediatricians (14 men, two women). Its members are paediatricians, other physicians, other health professionals and some non-health professionals. It is a national advocacy association committed to the health needs of children and youth. NACI and CPS have recommended publicly funded access to all currently recommended vaccines for all children in Canada. Unfortunately, access to newer vaccines is not equitable across Canada. Some provinces and territories have initiated programs to provide some or all of these vaccines to children at no cost to the family. In other provinces, parents have to pay for these vaccines – up

to $1,000/child. But there has been some progress. The federal government has made three recent commitments toward the NIS: In 2003, it announced $45 million over 5 years ($10 million annually); then an additional $32 million over 5 years was announced for a national on-reserve immunization strategy; in 2004, a further $300 million over 3 years was announced to assist provinces and territories in adding new recommended vaccines to their programs. The creation of PHAC is another huge step forward.

Nonetheless, a great deal more is necessary before the NACI and CPS goal is likely to be reached. Governments at all levels need to support the full implementation of strategies for complete immunization. Health professionals and organizations must advocate for public funding of all vaccines. Continuing professional education, such as this conference, is essential. Parents, who have to wade through a mass of information and misinformation, need more support.

As part of its role in providing information and education to Canadians, CPS has established two parent sites (www.caringforkids.cps.ca and www.soinsdenosenfants.cps.ca), which together get 1,000 hits/month. It has also developed a PowerPoint presentation based on the book *Your Child's Best Shot.* The presentation can be used by health professionals to educate colleagues and the public about all aspects of immunization and to advocate for full and complete immunization.

Canadian Immunization Poster Competition: Presentation to Winner

Drs. Ian Gemmill and David Allison, co-chairs of the Canadian Coalition for Immunization Awareness and Promotion (CCIAP), presented a plaque to the winner of the Canadian Immunization Poster Competition, organized every 2 years by PHAC in partnership with CCIAP for Grade 6 students across the country. This year, 2,725 students participated. The national award winner was Christian Morin, age 12, of École Dagenais, Colombourg, Quebec. Other awards were given to the national runner-up as well as a winner in each province and territory.

Keynote Address: Practical Immunology for the Immunizer

Dr. Brian Ward
McGill University

Antibodies and cell-mediated immunity are both part of the adaptive immune system, responding to attacks by micro-organisms. These mechanisms have long been used in the creation of vaccines. Recently, however, the importance of innate immunity has been recognized. Innate immunity is what fights infection until the adaptive immune system "kicks in".

Th1 and Th2 cells produce different types of cytokines that are associated with specific immune responses to different types of pathogens. The Th1/Th2 paradigm suggests that there is a balance between antibody/humoral responses and cellular responses. The balance between Th1 and Th2 cytokines can be manipulated by stimulating cytokine production on one side or the other; ultimately, however, a balance is maintained – when one side goes up, the other goes down. This finding of a Th1/Th2 cytokine balance finding has been very useful in developing vaccine response strategies, in explaining some adverse events and in enabling a better understanding of existing vaccines. For example, in the first 1 to 2 weeks of infection, certain types of cytokines develop, but by 5 to 6 weeks almost all are of the Th2 type. Thus, in natural disease, Th1 production lasts much longer, which probably explains why cellular memory is better than acquired immunity. In vaccine development, adjuvants can be used to manipulate the cytokine balance to achieve desired immune responses. Alum, for example, stimulates Th2. The B subunit of cholera toxin B is powerful at mucosal surfaces at stimulating Th2. Cytokines themselves can be used as adjuvants, or cytokines can be blocked to achieve a desired response.

Ninety-five to 98% of the ability to present antigen to the immune system comes through dendritic cells. They are at the centre of antigen presentation for both humoral and cell-mediated responses. They are probably responsible for the maintenance of long-term immune memory, as they can store antigen-antibody complexes for a long time. However, the distribution and density of dendritic cells varies widely depending on the type of tissue. These cells are also responsible for cross-priming, whereby they can take a dead antigen and produce cytotoxic T-cells through a different mechanism. The increasing knowledge about dendritic cells has led to a better understanding of the great efficacy of the intradermal route of delivery – the rich supply of Langerhans cells results in the rapid movement of antigen-loaded dendritic cells to regional lymph nodes. Thus, antigens targeted to dendritic cells could lead to more rapid response. Also, because different populations of dendritic cells elicit different types of Th responses, antigens can be targeted to specific dendritic cell populations. Other potential applications include generating CTL against dead antigens, selecting dendritic cells and loading them with antigen *ex vivo,* and increasing the number of dendritic cells just before vaccination.

The concept of immune priming is that how, when and where the immune system first sees an antigen influences how the system will respond to that antigen forever. Thus, if science can manipulate the circumstances of that first exposure, it can bias the immune response forever.

Combining this concept with the Th1/Th2 paradigm suggests that giving a Th2-biased vaccine might bring very good anamnestic responses, but not good cell-mediated immunity. Conversely, a vaccine that primes for Th1, even if it has no or little initial effect, can prompt a longer-lived and more balanced response after the second dose. This understanding helps explain why individuals who appear not to respond to repeated doses of vaccine may actually be immune. Potential applications include low-dose priming for a Th1 response, DNA vaccine priming with a later booster, priming in the presence of maternal antibodies and priming young infants for later response.

Innate immunity is really pattern recognition, where the immune system responds to pathogen-associated molecular patterns. Pathogen recognition receptors recognize sugars and sugar moieties that are produced only by micro-organisms. The most powerful of the recognition receptors are the toll-like receptors, of which 11 are known to date. These recognize the cell wall proteins, double-stranded RNA, weirdly folded DNA strands, etc. that are in bacteria. These toll-like receptors are powerful guides for immune responses; thus, knowledge of their specific roles can be enormously valuable in informing vaccine adjuvant science.

Vaccines: From Concept to Community

The Global Vaccine Business

Dr. Alan Shaw

Merck Frosst Vaccine Division, U.S.A.

Vaccines are an unusual business product in that they are used in government-driven programs in which the end user often does not pay directly for the product and does not have a choice among products. Pricing varies by geography. As a medical product, they are preventive rather than curative.

Over the past two decades, the number of vaccine suppliers around the world has dropped dramatically, especially in the developing world. The 18 to 20 companies that once supplied vaccines in North America have been reduced to five: Merck Frosst, Aventis, GSK, Wyeth and Chiron. A recent WHO survey identified just 88 suppliers making the 36 vaccines needed for UNICEF programs. Here in Canada, ID Biomedical is emerging as a manufacturer of vaccines, and other biotech companies, such as BernaBiotech of Switzerland, are accelerating their vaccine business. The major companies in North America rely on an extensive network of relationships with other companies responsible for different aspects of different vaccines. Another major relationship is with the government, which in the United States is responsible for about half the vaccine product distribution and in Canada is responsible for much more.

The major North American vaccine manufacturers are essentially arms of larger pharmaceutical companies. An advantage is that the companies can provide the stability and long-term development funding that vaccines require (it takes 12 to 15 years for a well-run vaccine development program to go from inception to licensure and use in the field). A disadvantage is that the vaccine divisions must compete for funds and other resources with all the drugs being made by their companies. Strategic decisions are made by humans, and companies have to take shareholder interests into account. Often, a champion for the vaccine product is the key to initiating and maintaining company support.

Interest in vaccines is increasing. A number of novel vaccines are due out within the next 2 to 3 years, and there is a robust market for these new vaccines. However, the government-industry relationship needs to be refined to make this business work best.

The Compliance Revolution

Dr. Martin Wasserman

Medical Director, Immunization Practices and Scientific Affairs, GSK, U.S.A.

Vaccine research and development is a high-risk program. It can cost up to a billion dollars to produce a single vaccine and can take more than a decade of research, development and production. Biologics research costs are increasing because of more stringent licensing and the increased size and complexity of clinical trials (e.g., there are over 60,000 people in clinical trials for rotavirus vaccine right now). Product licensure requires the company to create a full-capacity vaccine production facility pre-approval at a cost of about $30 to $50 million and a construction time of 3 to 5 years.

Vaccines are more complicated and have higher standards than pharmaceutical products because they involve the transformation of live biologics and growth materials from living sources. Every batch must be tested and approved for composition and potency. The manufacturing cycle typically takes 12 to 19 month and includes growing, purifying and inactivating antigen, testing it, packaging and labelling, quality control checks and eventual lot release. Even minor changes to the cycle may require complete product review and relicensing of the production facility. Supply maintenance can therefore be difficult, as evidenced by a number of recent shortages.

In the last decade, there has been a paradigm shift – a compliance revolution – in how industry and the regulators work together. Global standards have required harmonization, the US Food and Drug Administration (FDA) has reorganized its biologics team to work better with industry, there has been an emphasis on process and validation, including electronic record validation and higher regulatory standards, as well as retrospective validation of legacy systems. The relationship between industry and government is better than ever before.

The next steps are increased compliance and collaboration amongst industry, public health and government. Governments need to understand the value of vaccines and the challenges of a global industry. Industry and public health must work together to achieve the important goals of immunization – agreeing on disease targets and vaccine needs and recognizing the lengthy lead time needed to produce vaccines.

How Vaccines Are Made

Mr. Richard Holslag

ID Biomedical, Canada

The production of influenza vaccine was described as an example of vaccine production that still uses the animal model first developed by Jenner in 1796. Influenza vaccine production has four major steps. First, embryonated eggs are inoculated and incubated, and the virus is harvested and put through centrifugation and inactivation. Second, the inactivated virus is purified through isopycnic centrifugation and filtration. Third, the virus is split, homogenized and sterilized. Formulation and filling is the final step. The whole process must satisfy strict GMP (good manufacturing processes) conditions and comply to regulatory requirements.

An influenza vaccine production cycle is 26 weeks, from the start of February to July/August. Complicating production is the fact that the vaccine is trivalent. The first viral strain is known at the start of the production cycle, the second is determined by WHO (or the Center for Biologics Evaluation and Research for the United States) at about the end of February, but the third strain each year might not be identified by WHO and CBER until as late as the end of March or early April.

A second complication for influenza vaccine production lies in planning for production capacity, including the pre-ordering of materials. Contracts with egg producers must be made in May of the year preceding production. The manufacturer must therefore try to predict the vaccine demand at least 9 months before production begins and 18 months in advance of vaccination programs.

Influenza vaccine manufacturers are also working with governments on pandemic preparedness. In the event of a pandemic, a large amount of vaccine will be needed quickly. In Canada, numerous steps involving public–private collaboration have been taken to ensure production capacity, but the problem of rapid strain identification remains.

The vaccination business is an ethical business. Vaccines are a cost-effective way of preventing disease. It has been estimated that for every 1,500 doses of influenza vaccine, one “statistical Canadian” is saved from death. ID Biomedical manufactures 8 to 9 million doses of influenza vaccine for Canada, meaning that 6,000 “statistical Canadian” deaths have been prevented.

The Promise of New Technologies in Vaccine Research

Dr. Peter Paradiso

Wyeth Pharmaceuticals, U.S.A.

Two areas of vaccine research have been particularly exciting for immunologists and vaccine researchers in the past several years: glycoconjugates and viral vaccine research.

Glycoconjugate vaccines have been developed for diseases caused by Haemophilus type b, meningococcus and pneumococcus. Since the introduction of these vaccines, cases of these diseases have dropped dramatically in the countries and populations where they are used. Over and over again, it has been shown that the linkage of a protein carrier to a saccharide produces an impressive immune response in infants. Researchers are also looking at response to these vaccines in the elderly where diseases caused by the pneumococcus have high morbidity and mortality. Glycoconjugate research is now looking to expand the serotype coverage of the existing vaccines and to target other encapsulated bacteria. The current pneumococcal conjugate, for example, has seven conjugates and is effective in North America, but in other regions of the world, other types are more prevalent. In addition research on *Staphylococcus aureus* has indicated that two of its major types – 5 and 8 – are susceptible to conjugation; a staphylococcal conjugate vaccine would be a boon to high-risk groups such as hemodialysis and surgical patients. Group B streptococcus has 5 major serogroups that cause serious disease in neonates. Polysaccharides from these bacteria have been conjugated and shown to be immunogenic in women who could pass the antibody to their neonates.

Much research in the past two decades has focused on bacterial diseases, but many viral diseases in children and adults continue to elude vaccines. Current research is looking at stimulating all arms of the immune system. Sometimes, it appears to be very difficult to attenuate a live virus sufficiently to be safe (e.g., RSV, HIV). One exciting new approach to this problem is by using a replicons. The genes for antigens of interest can be inserted into replicons and delivered to cells where they are expressed and induce both as humoral and a cellular response. Viral targets of current research interest include respiratory pathogens (RSV, parainfluenza, SARS) and sexually transmitted pathogens (HIV, HPV, HSV).

In developed countries, society has reached a near-zero tolerance for risk in medical interventions. In vaccine development, the result has been longer development timelines, greater cost and increased liability risk. However, it is crucial to remember that infectious diseases never give up, and neither must our public health diligence. The value of vaccination is unparalleled in public health, and success in vaccine research, production and delivery requires society to recognize that value.

From Product to Policy

Dr. Maryse Guay

Université de Sherbrooke and Medical Consultant to the National Institute for Public Health, Québec

Provincial/territorial health authorities are seldom involved in vaccine research and production until a vaccine is licensed. At that point, provinces and territories must determine whether and how to introduce the vaccine. Quebec uses an analytical framework to help in its decision-making process for the introduction of a new publicly funded immunization program.

In Quebec, the Ministry of Health and Social Services is responsible for deciding whether to introduce a new immunization program. The department relies on the advice of the Quebec Advisory Committee on Immunization, which reports to the National Institute for Public Health. The Advisory Committee's framework for decision-making includes eight major criteria: disease characteristics and burden, vaccine characteristics, immunization strategies (various scenarios are developed), social and economic costs and benefits (for each of the scenarios), feasibility and acceptability (resources, competition with other vaccines, addition to schedule), ability to evaluate programs, research questions and other considerations (legal, ethical, political, etc.).

The province recently used this framework to evaluate whether to implement a pneumococcal conjugate vaccine (PCV) program and whether to expand the influenza program. There was no existing PCV program. By using the framework, the committee was able to develop recommendations, with a sound rationale, for the vaccination of children with chronic diseases, children in Nunavik and all newborns and the catch-up vaccination of all children < 5 years. The first two categories were implemented in 2003, and the latter two began in December 2004. For influenza, the committee had intended to look at four scenarios: no change, children < 5 years, adults 50 to 59 and universal vaccination. However, the NACI recommendation in early 2004 to vaccinate children 6 to 23-months prompted the committee to focus on the 6 to 23-month age group to enable implementation by the fall if they decided to recommend it, which they did. Although the whole framework was reviewed, parts were done more quickly than planned. Further review is needed to try to reach the provincial goal and improve influenza vaccine coverage. Overall, the province has found that the framework enables a systematic, rigorous review that assists not only in making vaccine recommendations but also in defending the recommendations and programs to politicians and other decisions.

Panel Discussion and Question Period

Questions for the panel focused on combination vaccines, the increasingly crowded childhood immunization schedule and vaccine cost-benefit considerations. Combination vaccines may help to simplify the schedule and thus increase compliance, but developers face the common problem of interference amongst the antigens, whereby the introduction of one can reduce the efficacy of the other. Nonetheless, research and development continues, because there is enormous worldwide interest in simplifying schedules. It was suggested that re-engineering some of the old,

traditional vaccines might reduce the problems of antigen interference; however, the relatively low cost of these older vaccines and their proven efficacy offers little incentive for industry to invest years, research effort and research dollars in redesigning something to be incrementally better. Generally, re-engineering is driven by problems with current vaccines. Another method of relieving the childhood immunization schedule might be to adjust it to more age-appropriate vaccinations, as infants are given some vaccines that they do not need until they are older. Also, in the future, we may be able to introduce vaccines through means other than injection, such as through the mucosa or in food. There is a need to balance vaccines with other interventions in terms of health care spending, but the vaccines offer tremendous value in terms of preventing not only diseases and their complications but also significant costs. Price controls for vaccines were suggested, but it was noted that the dramatic decrease in vaccine manufacturers is evidence that there is little allowance for flexibility in that area. Perhaps increased promotion of vaccines would be more useful.

New Vaccines and their Applications

Therapeutic Vaccination for Cancer: A New Challenge for the Vaccine Industry

Dr. Laszlo Radvanyi

Aventis Pasteur, Canada

Cancer represents one of the greatest unmet medical needs in the world. Yet because all tumours are immunogenic, the advances in tumour immunology that have occurred in the last 10 or so years may help researchers to design immunotherapeutic approaches to cancer, including vaccines.

Aventis Pasteur decided to work in the area of therapeutic cancer vaccines 5 to 8 years ago and launched a major global initiative concentrating on two areas – melanoma and colorectal cancer – but also looking at antigen discovery and breast cancer. Therapeutic cancer vaccine approaches focus on bringing in the vaccine at an early stage to help the immune system eradicate the tumour or on bringing in a vaccine at the metastatic phase.

The three major areas to consider in designing a cancer vaccine are vaccine technology, optimizing the vaccine and immune modulators.

In terms of vaccine technology, the two key components are the choice of antigen and the platform. Aventis chose a viral-based platform because these stimulate a very strong immune response, they are strong stimulators of the innate immune system and they have been shown to break the problem of self-tolerance. The platform used is ALVAC, or the Albany vaccine, a plaque-cloned isolate of canarypoxvirus. It is stable, easily produced, very safe and can accommodate large gene inserts. It cannot replicate in human cells and does not integrate into

host DNA. For an antigen, Aventis looked for one with comprehensive coverage in tumours, homogeneous expression, no expression in normal tissues and immunogenicity. Antigens have been identified by reviewing existing cancer antigens and by developing new ones through an in-house antigen discovery program. Once antigens have been identified, they are put into the ALVAC vectors, either singly (possibly with co-stimulator molecules) or in multiples (to increase the chance of eradicating tumours, which can express different antigens at different stages).

To date, clinical trials with ALVAC-based vaccines in Canada, the United States and Europe against melanoma and colorectal cancer have shown that the vaccines are safe, that they stimulate both CD8+ and CD4+ T cells and that they show evidence of some clinical response. Further research is needed to enhance potency and to develop more non-toxic immune modulators to enhance and sustain immune response, especially in advanced disease.

New Respiratory Vaccines

Dr. Susan Tamblyn

Medical Officer of Health, Perth District Health Unit, Ontario

Current research is striving to improve influenza vaccines by increasing immunogenicity, offering needle-free delivery, improving stability and reducing the reliance on eggs.

Adjuvants are being used to improve immunogenicity, although they also present the trade-off of increased adverse reactions. The adjuvanted vaccine Fluad (Chiron), licensed in Europe for use in seniors, gets about 1.5 times higher antibody response at the expense of a small increase in local reactions.

Virosome-based influenza vaccines have a lipid-based antigen delivery system using phospholipids to build a reconstituted virus envelope. The inner genetic material is missing. Virosomes are completely biodegradable, non-toxic and non-immunogenic. These vaccines stimulate both humoral and cellular immune response. Two virosome-based products are available in Europe, Inflexal (Berna) and INVIVAC (Solvay), and have been shown to be safe, well-tolerated and effective in the elderly.

Alternative delivery systems include intradermal injection and nasal spray. Reduced intradermal doses (20% to 40%) of the standard vaccine are comparable to intramuscular injection at least up to age 60. A system that injects dry powder vaccine, which is stable at room temperature, into the skin has shown an antibody response equivalent to or higher than intramuscular injection in preclinical and Phase 1 trials, but a higher incidence of local site reactions. Nasal vaccines more closely mimic natural infection, produce mucosal immunity and may improve compliance because they are needle-free. A nasal vaccine has been used successfully in tens of millions of children in Russia for years. The first inactivated virosomal nasal vaccine, licensed in Switzerland, was withdrawn because of association with Bell's palsy (thought to be related to the adjuvant). FluMist (MedImmune) is a cold-adapted live attenuated intranasal vaccine licensed in the United States in 2003 for use in healthy 5 to 49-year-olds. Studies to date have indicated good

efficacy and safety in children and adults and cross protection against drifted strains. Further studies are under way. Here in Canada, ID Biomedical is working on an inactivated subunit proteosome intranasal vaccine, FluINsure, that is showing promising efficacy and safety results.

Cell-culture manufacture would have the advantage of faster start-up, faster scale-up, purity and no modification of the vaccine virus by growth as in eggs. Although facility conversion costs and yield issues present problems, most influenza vaccine manufacturers have cell-culture vaccines under development, and two have already been approved in Europe.

RSV and parainfluenza virus both cause severe morbidity in infants, young children and the elderly, but despite decades of research, no vaccines yet exist. Both live attenuated and subunit candidates are under development.

Enteric Vaccines: The Case of Rotavirus Vaccines

Dr. Joseph Bresee

U.S. Centers for Disease Control and Prevention

Diarrheal disease remains a significant health burden, despite great strides in the past 20 years. Mortality has gone from 4.6 million child deaths in 1982 to 2.5 in 2003, but diarrheal disease still accounts for 21% of childhood deaths in developing countries and 5% of deaths in the world in children < 5 years. And both developed and developing countries have about the same proportion of morbidity outcomes, which have decreased little over the past 20 years. The cost to society in the United States alone is almost $1 billion/year.

Virtually every child in the world is infected with a rotavirus before the age of 5 years, with the highest rates of disease in children 6 to 24 months. The most common cause of hospitalization for diarrhea is rotavirus. Rotavirus disease has a single clinical syndrome: gastroenteritis. Natural infection confers protection against subsequent infection, especially against severe disease.

In 1999, United States licensed its first rotavirus vaccine, Rotashield (Wyeth). Rotashield was a live, oral, tetravalent (representing four strains, G1–4), human-rhesus vaccine which had a three-dose schedule (2, 4, 6 months). It was considered safe and was very effective and, although expensive, had a rapid uptake. Its success was short-lived, however; 7 months after release, it was suspended and then withdrawn because of an eventually proven association with intussusception.

The initial success and later withdrawal of the vaccine offered proof that live, oral rotavirus vaccines *can* work. There is greater international recognition of the need for rotavirus vaccines. Many manufacturers reinvigorated their rotavirus vaccine research and development programs, and potential manufacturers are now looking at them. Also, the need for larger trials means that companies are having to use population samples in developing countries.

Currently, there are three licensed rotavirus vaccines. Rotavirus is still licensed and is looking for a manufacturer. LLR, a Chinese-produced vaccine, uses a monovalent lamb strain. Rotarix (GSK) is a live attenuated monovalent human vaccine licensed in Mexico in July 2004. It is protective only against serotype G1, relying on cross-protection for the other serotypes. Trials in Finland, Singapore and Latin America have shown good efficacy against any rotavirus and great efficacy against several rotaviruses, with cross-protection in the second year. Further efficacy and safety trials are ongoing in Latin America and Asia. Under development are a live, polyvalent (serotypes G1–4 and P8), bovine-human reassortant vaccine (Merck) as well as others for developing countries.

Topical Vaccines

Dr. Jan Dutz

University of British Columbia

Skin is the human body's primary barrier against microbacterial assault. In the living epidermis are skin cells known as keratinocytes, which become corneocytes as they differentiate and transform into the outer layer. Keratinocytes can develop antimicrobials. They secrete growth factors and produce the cytokines that control the immune response. Dendritic cells (DCs) also exist in the epidermis. These have many different lives, beginning as DC precursors, becoming Langerhans cells (immature DCs) and then, when stimulated, becoming mature, activated DCs. There are numerous DCs in the skin and other tissues. They capture dirt or antigens and take them to a draining lymph node, where they interact with T cells. CLA is then expressed, which allows the T cell to recirculate and go back into the skin to fight disease. In normal people, more than 30% of all immune responses come from the skin.

It was once believed that the skin provided such a good barrier that large molecules such as those in a vaccine could not pass through it. However, 10 years ago, a researcher painted large doses of ovalbumin (OVA) on mice daily over 14 days and did get an immune response. Another biologist later showed that using a smaller dose of OVA in a patch also works. In other words, large proteins can permeate the skin through protein contact sensitization. Since then, a number of researchers have identified means by which the skin's immune response to vaccines can be enhanced.

For example, tape stripping, in which cellophane tape is used to remove the top layer of skin, also enables better antibody responses (both Th1 and Th2). Adjuvants applied to the skin can enhance the immune response, are less likely than injected adjuvants to cause side effects and can prompt mucosal immune responses. One way that laboratories quantitate efficacy is to look for the amount of killing. If CpG adjuvant is put onto the skin with OVA, more killer T cells are produced and there is a greater amount of killing. Protein transduction domains can also be used to improve intradermal delivery. These domains are seen naturally in a number of proteins and viruses uses them to transfer their baggage into cells. When antigen is applied by itself to the skin, it stays on the surface layer. When a transduction domain is added, the antigen penetrates all the way down to the dermis and is more broadly distributed.

A recent small open-label trial of 100 people compared intramuscular injection of a trivalent influenza vaccine to intradermal delivery, using the outcome measure of hemagglutination inhibition. The result was that one-fifth the dose delivered intradermally performed as well as or better than the intramuscular dose. Another researcher recently showed that 40% of the dose was as effective.

Question Period

Questions focused on the cancer and rotavirus vaccine presentations. First, it was asked how a person gets into a clinical trial. Given the prevalence of cancer, those trials have not had any difficulty in finding participants. People interested can go to the website of the National Cancer Institute. For rotavirus vaccines it was noted that they clearly have a major role in developing countries, but how prominently should these vaccines be in developed countries as in North America? What about the development of vaccines for other vaccines for common gastro-intestinal illnesses, such as those caused by noroviruses? In response, Dr. Bresee noted that rotavirus disease is universal; although mortality in developed countries may not be a major issue, morbidity is – children with this disease fill ERs and hospital boards in the wintertime. In the United States, the vaccine has been proven to be highly cost-effective in the United States. Norovirus vaccines, however, have proven to have more problems. To date, the virus has not been cultured and so is hard to study. Hand washing is still the best defence.

Concurrent Breakout Sessions: Summaries

1. New Vaccines for Adolescents

Ms. Cheryl McIntyre of the British Columbia Center for Disease Control described the hepatitis B program introduced in 1992 for children at the Grade 6 level in British Columbia. Grade 6 was chosen because the children were young enough to comply with a parental decision and young enough that risk behaviours were probably still limited but old enough to understand disease information. The province initiated the program because rates of acute and chronic hepatitis B in the early 1990s were the highest in Canada, caused in part by immigration from endemic countries and the large number of illegal drug users. Since the program started, coverage has averaged 96.1%. By 1997, a drop in acute cases in the 11 to 22-year age group was being seen, and in 2002 there were no new acute cases in this age group. Concurrently, there was an overall decline in all age groups, but other factors need to be considered in this general decline.

Dr. Marc Steben, a general practitioner in Montreal affiliated with the Institut national de santé publique du Québec, outlined the characteristics, disease burden and disease symptoms of human papillomavirus (HPV). Of particular concern are the HPV-related cancers, including all cervical cancers, 85% of anal cancer and 50% of the cancers of the penis, vulva and vagina. Reflecting on the impossibility of reducing sexual activity among young people, the inefficacy of

traditional STI prevention methods, the high rate of infection at the age most critical for developing cancer and the high morbidity rates related to HPV infection, he concluded that only a prophylactic vaccine will halt the spread of HPV transmission. Two vaccines are under active scrutiny, one by Merck Frostt and one by GSK, both of which may be about 2 years from commercial availability.

Dr. Simon Dobson of the British Columbia Children's Hospital reviewed the case for using herpes simplex vaccines (HSV) in adolescents. The acquisition of HSV 2 occurs primarily in the late teen years. Efficacy trials of an HSV 2 vaccine have shown variable efficacy, with better results in women than in men. An epidemiologic model of the impact of a partially protective HSV 2 vaccine indicates that although it takes decades, a drop in both disease prevalence and symptomatic infections occurs in both sexes when women are immunized. The model indicates that the vaccine should be used universally in women. Studies by Dr. Dobson and others on HSV 2 vaccine in teenagers showed excellent immunogenicity results, common minor adverse events and rare Grade 3 events. No serious adverse events were vaccine-related. In conclusion, there is evidence that the full adult dose of HSV 2 vaccine should be given universally to 10 to 15-year-old girls.

Dr. Dobson then summarized his understanding of the presentation that Dr. Diane Sacks, delayed by weather, was to have given. Adolescents are not yet well developed in abstract thinking when their teenage years begin and as a result tend to feel invulnerable, taking high-risk behaviours even after education about potential consequences. It is key that the parents, teenagers and the general public be made more aware of diseases such as hepatitis B, HPV and HSV to encourage the universal use of vaccines. Vaccines for sexually transmitted infections should be given in schools before the years when high-risk behaviours are likely to occur and before the often emotionally charged discussions of sexual activity begin.

2. From Concept to Community: Who Decides and Gets It Done?

Dr. Elwyn Griffiths, Associate Director General of the Biologics and Genetic Therapies Directorate of Health Canada, reviewed the special regulatory considerations for vaccines and outlined the activities the directorate takes to ensure vaccine safety. The directorate's authority comes from the federal Food and Drugs Act. Unlike drug products, vaccines are biologics, some even containing or consisting of living material. Major problems are usually batch-related, making consistency of production paramount. Emerging infections present regulatory challenges such as the need for a more rapid regulatory process in the face of a rapidly emerging new infection (e.g., influenza pandemic). SARS highlighted these and other issues; Health Canada organized an international regulatory workshop on SARS in the summer of 2003. At the meeting, important new data were reported and critical regulatory issues and gaps were identified. These are being addressed.

Dr. Monika Naus, the chair of NACI, outlined NACI's role in vaccine use. Established in 1964, the committee's mandate is to provide PHAC with ongoing, timely, medical scientific and public health advice relating to the use of vaccines and certain prophylactic agents in humans, vaccine evaluation, monitoring of vaccine-associated adverse events and vaccine programs. It consists of 12 voting members with expertise in public health, clinical infectious diseases, immunology, nursing science and consumer issues as well as a number of non-voting liaison members from professional and other associations. NACI produces the quadrennial *Canadian Immunization Guide* as well as statements and updates on vaccines. The work of NACI and the new Canadian Immunization Committee complement each other, in that NACI interprets science and makes recommendations on the optimal use of new and existing vaccines, research, surveillance and best practice, while the Canadian Immunization Committee addresses immunization program operations vis-à-vis NIS goals and priorities. Dr. Greg Hammond continued the description of the Canadian Immunization Committee, which was developed to guide NIS implementation, develop common goals, provide program perspectives on immunization issues, foster collaboration, harmonize programs and communications and provide leadership. The committee comprises 15 F/P/T members plus 4 ex-officio members (representing NACI, the Immunization and Respiratory Infections Division, the Biologics and Genetic Therapies Directorate and the U.S. CDC. Further input is garnered from non-government organizations and industry. The committee has been in place since the fall of 2003 and is starting to fill the void between science and field implementation at an F/P/T level.

Dr. Philippe De Wals of the Quebec National Public Health Institute described the mandate and methods of Quebec's Immunization Committee, which provides scientific advice on immunization to the Quebec Ministry of Health, updates the *Protocole d'immunisation du Québec* (Quebec's immunization guide) and provides scientific advice to health professionals. The committee has been responsible for the introduction of many innovative programs, mass immunization campaigns and several editions of the *Protocole*. Its members include public health specialists, clinicians and scientists and further input is garnered from representatives from the Ministry of Health, the Board of regional health authorities and professional organizations. A Health Canada representative is also invited to meetings, and often there are joint CIQ/NACI members. Specific questions are sometimes referred to NACI.

Dr. Monique Landry, a consulting physician to the Quebec Ministry of Health, outlined the organization of Quebec's immunization services. About half of the immunizing in the province is done by the 148 CLSCs, with medical clinics (about 800 in the province) and physicians (about 8,000) doing the other 50%. The province's 124 hospitals assist with emergency vaccinations. The province's comprehensive, publicly funded immunization schedule is aligned with the recommended Canadian schedules and includes DaPT/IPV/Hib (2, 4, 6, 18 months), MMR (12, 18 months), DaPT/IPV (4–6 years), dTap (14 to 16 years), meningococcal conjugate (12 months), pneumococcal conjugate (2, 4, 12 months), pneumococcus (65 years) and annual influenza (6 to 23-months and > 60 years). A varicella pilot project in Grade 4 children began in 2003, and it is likely that routine immunization will begin in 2005. Reasons for the few differences from the Canadian recommendations are the result of scientific and political priorities, opportunities, program acceptability and public or provider requests.

In a concluding panel discussion, it was noted that the increasing number of routine childhood vaccines and the variation in programming across the country makes it difficult for parents who move across jurisdictional borders. Unfortunately, financial, logistical and policy differences amongst the jurisdictions makes schedule harmonization difficult. However, the new F/P/T Canadian Immunization Committee and the associated higher profile of immunization should assist in harmonization.

3. Administering Vaccines: Private Practice Versus Public Health

Ms. Marilyn McIvor, an immunization program specialist with Manitoba Health, reported that vaccine delivery in Manitoba uses a mixed model, in which infant vaccines are primarily delivered by physicians and school-based vaccines are delivered by public health nurses (PHNs). Although a mixed model should provide more opportunities to immunize and therefore result in good coverage rates, a recent review indicated < 70% coverage of age-appropriate vaccines at all child and adolescent age levels. Analysis identified a number of issues: communication with 3,700 providers yearly is difficult; it is easier to communicate with PHNs than physicians (who may be less likely to heed all of the messaging from public health); data entry into the registry may not be consistent or timely; inventory management is complex; physicians and PHNs may report coverage in different ways; there is some evidence of potential cold chain breaks in physicians' offices; and PHNs may report vaccine-associated adverse events (VAAEs) more frequently.

The immunization system in Quebec also uses a mixed model, as reported by Montreal paediatrican Dr. John Yaremko, with about half of infants being immunized by CLSCs and half by physicians and medical clinics. The vaccination coverage rate varies from 64% to 97% depending on the region. A recent study of 2-year-olds in Montreal identified a number of predictors of coverage: family predictors included the child's birthplace and rank amongst siblings and the family income; system predictors included whether the family had a regular source of care, whether the vaccine was provided by the regular caregiver and whether the vaccine was inexpensive (< $20) or free. Advantages of the physician providing the vaccine include opportunity, an established relationship, the fact that new non-funded vaccines are offered earlier in physicians' offices and the maintenance of the schedule even at periods of increased activity. Disadvantages include cold chain issues (which in some cases are discouraging physicians from offering vaccines), poorer adverse event reporting and communication issues with hard-to-reach families.

Ms. Anita Hanrahan, Director of Communicable Disease Control in Alberta's Capital Health Region, reported that virtually all childhood and adolescent immunization in the province is provided by community health nurses working under the direction of a Medical Officer of Health. The nurses are experts in vaccine administration and handling. Coverage rates for 2003 in the Capital Health Region were very good, with DTaP/IPV/Hib, for example, at 94% to 95% for children at 2 months and 1 year, 87% at 2 years and 91% at 7 years. Advantages of the public delivery system are many and include electronic records, which enable monthly monitoring of

coverage rates and ease of data retrieval; excellent cold chain maintenance; a greater likelihood of reaching traditionally hard-to-reach children; a streamlined vaccine supply system; good adverse reaction reporting; and continuing provider education. A disadvantage is that the annual influenza campaign is a competing priority that increases clinic wait times.

In the concluding panel discussion, it was noted that immunization systems can be evaluated by looking at coverage rates, adverse event rates, the maintenance of immunization standards, surge capacity, flexibility, client satisfaction, the ability of the system to deal with the initial non-public funding of new vaccines, the ability of the system to deal with shortages, the ability to monitor data, cost-effectiveness (by jurisdiction, because of different funding mechanisms), and how well it works with other programming (e.g., well child). Other issues raised included the difficulties raised by differing schedules with a mobile population (public health can probably handle this better), the importance of systematically seeking out hard-to-reach children (public health), the need for sophisticated decision-making about vaccines for people with complex health problems (physicians, or PHNs in close collaboration with physicians), and the need for detailed answers for clients who want to review the literature. Greater flexibility in vaccine providers was also suggested (e.g., LPNs, pharmacists, others).

4. Peer-Reviewed Oral Presentations

This session opened with a keynote address by Dr. Andrew Murdin, Director, External Research and Development, Aventis Pasteur, on developing vaccines for diverse pathogens. To date, vaccines have been developed for over 20 target pathogens, but there are numerous infectious diseases for which vaccines do not exist. New diseases such as SARS and West Nile virus are emerging, and old diseases such as pertussis and tuberculosis are reappearing. There remain about 50 vaccine-preventable diseases for which vaccines have yet to be developed (or for which existing vaccines could be improved). These targets tend to be difficult because of antigenic diversity (e.g., hepatitis C), pathogen biology (e.g., chlamydia), limited natural immunity (e.g., HIV) or immunopathology (e.g., SARS). However, there are means of addressing these issues – by eliciting broadly protective immune responses to account for significant antigenic diversity, by understanding and addressing specific features of the host–pathogen interaction and by distinguishing between protective immune responses and unwanted or dangerous immune responses.

Dr. Julie Bettinger described a study conducted on the epidemiology of hospitalized pertussis after the universal change in Canada from whole-cell to acellular pertussis vaccine. Using the IMPact database, the rates and characteristics of hospitalized paediatric cases of pertussis before (1991-1996) and after (1998-2004) the change were compared. Over the 13.5-year period, 2,000 cases were identified, with 1,172 during the whole-cell vaccine era and 748 during the acellular era. There was a significant difference in vaccine failures for the two eras, with a 13.1% failure rate with whole-cell vaccine and a 2.7% rate with acellular. In addition, there was a significantly greater percentage of encephalitis with whole-cell vaccine. With the acellular vaccine, there was a shift in the age distribution of cases to younger, unimmunized or incompletely immunized infants, suggesting that it may provide better protection in older infants than the whole cell

vaccine. To better protect young infants, other immunization strategies may be necessary, such as the immunization of household contacts or maternal immunization.

Dr. David Scheifele reported the results of a study to determine whether a dap booster with reduced pertussis and diphtheria content would reduce the rate of local reactions. Healthy 4- and 5-year-old children previously given 4 age-appropriate doses of Pentacel were randomly assigned to receive either DTaP-IPV or Tdap for the booster dose. The children were assessed for local reactions (local swelling or redness ≥ 50 mm diameter) daily by their parents and 2 days post-immunization by a study nurse. Of the 288 children immunized, 145 received the DTaP-IPV and 143 the Tdap. At Day 2, injection site redness ≥ 50 mm was present in 25 (17.2%) of the former group and 9 (6.3%) of the latter. Local swelling ≥ 50 mm was present in 20 (13.8%) of the DTaP-IPV group and 11 (7.7%) of the Tdap group. There was also a greater likelihood in the DTaP-IPV group of pain to touch, limited arm motion and sleep disturbance. Even though the reduced-potency vaccine did not eliminate local reactions, it did reduce them; given that booster responses to all antigens appear adequate with Tdap, it might be preferable to use it from mid-childhood onward.

Dr. Shelley Deeks reported on a study done to determine rates for bacterial meningitis in Canada, including pathogen-specific rates. A 7-year retrospective census of all hospitalized cases in Canada from 1 April 1994 to 31 March 2001 was conducted using the hospital morbidity database of the Canadian Institute for Health Information. A total of 7,227 bacterial meningitis hospitalizations were identified, ranging from 940 to 1,072 annually. The annual incidence ranged from 3.37/100,000 to 3.66/100,000. Rates for other countries for the same period vary from 1.7 to 7.2/100,000, but comparisons are difficult because some studies limit the analysis to a specified group of pathogens, a specific age group or community-acquired cases. However, it was identified that the annual incidence in Canada is similar to that in the United States. Unspecified bacteria accounted for the largest proportion of cases (37%); the most commonly identified bacterial forms were pneumococcal, streptococcal, staphylococcal and meningococcal. Rates varied by age, but the median age has increased throughout the study period, suggesting a benefit from childhood vaccination programs.

Dr. Michael Bruce described international circumpolar surveillance (ICS) for invasive pneumococcal disease (IPD) 1999-2003. The objectives were to determine rates of disease by country, serotype distribution and antimicrobial susceptibility patterns. The countries involved in ICS are United States (Alaska), Canada (North), Denmark (Greenland), Iceland, Norway and Finland. The annual incidence rate of IPD ranged from a low of 12/100,000 (n = 2,569) in Finland to a high of 30/100,000 in Northern Canada (n = 195). The other countries ranged from 16 to 20/100,000. Total number of cases was 7,196. Rates of IPD were high in indigenous peoples, children < 2 years of age and adults ≥ 65 years. In Alaska and Northern Canada, incidence rates were highest among aboriginal peoples. In Alaska, the use of PCV7 has resulted in an 80% decline in IPD rates in children < 2 with vaccine serotypes. The use of PCV7 in other Arctic countries could have a substantial impact on morbidity and mortality from IPD.

Dr. John Waters Lecture

Dr. Bryce Larke

Chief Medical Officer of Health, Yukon

It is fitting that the focus of the first-ever Dr. John Waters lecture is polio. Just 2 weeks after his death from cancer in 2001, his wife was quoted in the *Globe and Mail* as saying that Dr. Waters chose public health over private practice because of the polio outbreak he witnessed in the 1950s. During his 32 years of public health practice, child health, especially the prevention of infectious diseases, was a major focus of his career. He served on numerous committees, including over 20 years on NACI and the CPS Committee on Immunization, and he was also a member of the Canadian Working Group on Polio Eradication for 6 years, serving as its chair for the last 2. His work was recognized provincially, nationally and internationally. Among the many tributes on his death was a glowing citation from Governor General Adrienne Clarkson.

The Development of Polio Vaccines: Canada's Role in the Eradication of "The Crippler"

Dr. Luis Baretto

Vice-President, Public Affairs, Aventis Pasteur

Canada was among the nations hardest hit by major polio epidemics in the first half of the 20th century, with 50,000 Canadians affected by paralytic polio and 4,000 deaths. Feelings toward polio by the mid-1940s were probably similar to those we have today about SARS, but thousands of times worse, with many epidemics and few resources. In 1948, Minister of Health and Welfare Paul Martin Sr. introduced federal health grants of $30 million annually to boost provincial health services, which helped catalyze public health research into polio. Not coincidentally, the Martin family had personal experience with polio – Paul Martin Sr. had suffered polio in 1907, and his son, Paul Martin Jr., in the summer of 1946.

Polio research at Connaught Laboratories, Toronto, began under Dr. Andrew Rhodes in 1947. By 1951, Rhodes and his team of dedicated scientists were growing poliovirus in test tubes with the use of Medium 199, a chemically pure mixture of over 60 ingredients in which to grow the virus. Meanwhile, at the University of Pittsburgh, Dr. Jonas Salk had developed an inactivated polio vaccine that could prevent polio in monkeys, but he had no way to grow it. The two organizations collaborated, and the result was the "Toronto Method", developed in 1953 by Dr. Leone Farrell of Connaught to mass produce poliovirus using Medium 199 in large bottles incubated on a rocking machine. Also in 1953, Canada was facing one of the worst polio epidemics ever, with 9,000 cases and 500 deaths. The National Foundation for Infantile Paralysis (the March of Dimes), a Connaught polio research funder, asked Connaught's director, Dr. Robert Defries, to provide all the poliovirus fluids required for the large field trials of Salk's vaccine. Connaught met the need, rapidly scaling up production to provide the 3,000 litres

needed. The U.S. field trial began in late April 1954 with 1.8 million children enrolled to receive either the vaccine or the placebo of Medium 199. A month later, 25,000 children in Manitoba, Alberta and the city of Halifax were also enrolled. Canada began planning its own field trial, designed by Dr. E.H. Lossing of the Department of National Health and Welfare, for April 1955. Just as the Canadian trial was beginning, the United States announced that its trial had been successful, and the public was euphoric. The euphoria was shattered just a few weeks later, when 80 cases of polio were directly linked to vaccine produced by Cutter Laboratories, California. Paul Martin Sr. faced a dilemma. Should the Canadian program stop? The vaccines used in Canada were all made by Connaught and double-tested by both Connaught and the federal Laboratory of Hygiene. The Prime Minister himself asked Martin to halt the trial. But Martin trusted Connaught and decided the program would go on.

After months of research, Connaught found that its vaccine was safe and effective, and the immunization program continued. Canada was commended by the United States and the international community for its approach to the vaccine. Soon, Canada was exporting the vaccine to Great Britain, Czechoslovakia and 42 other countries. Further research resulted in the licensing of DPT-polio vaccine, DT-polio vaccine and T-polio vaccines in Canada, the development of OPV in 1959 and improved production technology. In 1961, Connaught began exporting OPV to Japan and other countries, becoming a leader in the global battle against polio. Since then, further research and others has led to improved vaccines and production methods. Most importantly, Canada has continued to participate and lead in the campaign for the global eradication of polio. Canada's successes in and contribution to the history of polio vaccine were the result of something very Canadian: partnerships. The partnerships included public health, Connaught and the University of Toronto, the March of Dimes, Rotary International, CIDA and many others. It is hoped that Canada, with the rest of the world, will be celebrating the global eradication of polio by mid-2005.

The Impact of Polio Vaccine in Canada and the World, and Remaining Challenges

Dr. Noni MacDonald

Professor of Paediatrics and Microbiology, Dalhousie University

Canadians old enough to have lived in the early 1950s remember the terror that was polio. It was a disease that there was no way to fight. It left children crippled; it put them in iron lungs – terrifying images for children, for parents, for families. And the victims were stigmatized, shunned, because of fear of contagion.

Polio has existed for a very long time. Engravings from ancient Egypt over 3,000 years old include a clearly identifiable reference to paralytic polio. Polio's history in Canada is less extensive, as epidemics began in 1927 and climaxed in 1953, but for those 26 years, it was a major public health challenge. No one was free. Everyone worried. Each summertime, parents would try new ways of keeping their children safe.

When research in Canada and the United States led to the licensing of polio vaccine, people lined up to get it, despite the Cutter incident. It was incredibly brave of Paul Martin Sr. and Health Canada to continue the program. Then when OPV was developed, new possibilities began to be seen worldwide. In 1962, Fidel Castro set out to eradicate polio from Cuba, something no one had ever considered before.

The impact of the polio vaccine was impressive. Polio epidemics disappeared in Canada. The last significant outbreak was in 1978-1979 when 11 imported cases occurred in a religious sect in three provinces. Since 1980, there have been only 12 cases of paralytic polio in Canada, one in 1988 that was imported from India and 11 others from OPV. In 1993, 22 asymptomatic cases of imported wild polio infection were documented in Alberta in the same religious sect that had seen the 1978/79 outbreak.

By the early 1980s, other countries started to wonder if polio eradication might be possible by applying the Cuban model. In 1988 the World Health Assembly voted to launch the international initiative for the global eradication of polio. WHO, CDC, Unicef and Rotary International formed the initial “Polio Partnership". At that time, there were 350,000 cases of polio every year and polio was endemic in more than 125 countries. By 2003 there were fewer than 1,000 cases in the world and only six polio-endemic countries. The Cuban model of routine immunization, NIDs, surveillance and subsequent mop up campaigns has stood the test of time.

There have been bumps on the road, one of the biggest in Nigeria. A popular myth arose that polio vaccine could give people AIDS or make them infertile. The subsequent lack of vaccination led to major outbreaks of polio. It has taken a huge international push to overcome this misinformation. Meanwhile, polio had spread to other countries previously polio-free.

The world needs to make one last big push to finish off polio for good. It is hoped that by the end of 2005, wild polio transmission will have been stopped in its tracks. Even then, public health must continue its work. By the end of 2006, supplementary immunization programs will be done, and by 2007 the international community will be working on laboratory containment of polio virus. By 2008, it is hoped that global eradication of polio will be certified. Then, because of concerns about the potential for outbreaks due to genetic changes in circulating OPV strains such as occurred in Haiti, efforts will need to be made to shift to IPV.

The eradication of polio was a dream not even imagined 50 years ago. The polio story teaches us the power of research, partnerships and community engagement. There is much to celebrate on this 50th anniversary, but there is much yet to do, both in the battle against polio and in applying the lessons learned to other problems that are plaguing our world. Dr. John Waters would be incredibly proud of how far we have come, but he, too, would not be satisfied that we’re there yet.

Tuesday, December 7, 2004

Vaccines and Emergency Response: Development and Implementation Challenges

A SAVI Response to SARS: Can We Rapidly Develop a SARS Human Vaccine?

Dr. Brett Finlay
University of British Columbia

When SARS appeared in late 2003 and began to spread around the world, Canada was the hardest hit country outside Asia, with 438 probable and suspect cases and 44 deaths. Public fear, the impact on health care workers and the economic implications made it urgent for the causative agent to be identified so work could begin on prevention and treatment.

The first major break in the epidemic was the identification of the coronavirus and genome sequence. On 13 April 2003, just 8 days after getting the strain from the National Microbiology Laboratory (NML), the British Columbia Centre for Disease Control (BCCDC) sequenced the gene. That would mean that BCCDC could patent the virus for future development. One of the major concerns about SARS was what to do if the virus broke through the quarantine measures. After much thought, it was decided that a vaccine was the best approach, because there were already several successful animal coronavirus models and because the lack of knowledge about the virus meant that a drug target would require more time. The provincial government funded the research with $2.6 million, and SAVI (SARS Accelerated Vaccine Initiative) was born.

To gain results more rapidly, BCCDC set up a program that would work on many issues in parallel: epidemiology, control measures, potential therapeutics, funding, animal infection models, GMP production, communication, industry liaison, etc. Four candidate vaccines were

chosen based on animal models: a whole inactivated vaccine; two viral-based vaccines, in which pieces of the SARS virus would be put into adenovirus and pox virus; and recombinant spike protein vaccine. All four were worked on in parallel so that a failure in one would not require restarting the whole research program. Ultimately, after testing in two animal models (ferrets and mice), the whole inactivated vaccine was identified as the best candidate for further research. Currently, BCCDC is waiting to see if SARS reappears before moving forward.

The SARS experience has demonstrated that people, organizations and facilities are very willing to participate and support necessary research in the face of a significant health threat. The biggest challenges proved not to be in lining up the scientists, but in sorting out the intellectual property and other legal agreements. Other learnings include the need for better production facilities in Canada, the importance of national and international coordination, and the need to consider how non-science issues affect research (media, funding, management, etc.).

Pandemic Influenza Vaccine Development

Dr. Theresa Tam

Associate Director, Immunization and Respiratory Infections Division, Public Health Agency of Canada

Vaccination will be a key strategy for reducing morbidity and mortality in the next pandemic. However, it takes time to isolate a virus and produce vaccine, and the pandemic virus may travel rapidly around the world. As a result, vaccines are unlikely to be available at the start of the pandemic, and even once they are available, most countries will not have enough. Therefore, strategies are needed to make sure that once developed, the pandemic vaccine can be produced rapidly and in large quantities.

One strategy for increasing the readiness for rapid, mass production of the pandemic vaccine is to increase interpandemic vaccine production and use. However, only nine countries have influenza vaccine manufacturers, which collectively produce 300 million doses annually – not enough in a pandemic. An additional option is therefore to stretch the supply through antigen-sparing strategies, such as the use of adjuvants, a more immunogenic whole virus vaccine, or an alternative and perhaps more effective route of administration.

Rapid surveillance and strain characterization will help. To reduce the lag time between virus detection and the beginning of vaccine production, it would be helpful to increase knowledge interpandemic about the optimal formulation of pandemic vaccines through mock vaccine clinical trials. In addition, a new technique called reverse genetics can reduce the time to produce the vaccine seed strain to 1 to 2 months. Also interpandemic, countries can address regulatory issues to try to reduce the time required for approval.

The recent H5N1 outbreaks in Asia have provided good testing ground for some of these strategies. A vaccine prototype strain has been available since April 2004, but a number of issues – relating to intellectual property, genetically modified organisms, biosafety, investment,

liability and timing – have prevented clinical trials to date. None of these issues is insurmountable, however, and clinical trials are planned in the United States, Europe and Japan.

In Canada, vaccination is the primary strategy for disease prevention and control in a pandemic. The goal is to provide enough vaccine for one dose for every Canadian, which requires ensuring security of supply by having sufficient infrastructure and capacity to produce 100% of domestic supply needs. This goal has required extensive public–private sector collaboration. The federal government has a 10-year contract with ID Biomedical, the domestic supplier, which includes a pandemic readiness component; the manufacturer has to have the production capacity and raw materials to produce a minimum of 8 million monovalent doses/month for 4 months. International discussions are also under way; in collaboration with WHO, the other G7 countries and Mexico, Canada is looking at conducting mock pandemic vaccine clinical trials.

Implementing a Pandemic Influenza Emergency Preparedness Plan

Dr. Karen Grimsrud

Deputy Provincial Health Officer, Alberta Health and Wellness

Work on the Pandemic Influenza Contingency Plan for Alberta began in spring 2000, when a large meeting of stakeholders was held. Alberta Health and Wellness took the lead but formed a close tie with government colleagues in disaster planning. Working groups were set up for planning various areas, culminating in the release of the first draft of a plan in 2002. Since then, a number of annexes have been developed, including infection control, antiviral use and clinical practice guidelines. The annexes are quite detailed to enable use by regional health authorities. Working groups continue to look at the complex issues of finding and storing medical supplies and the deployment of health care workers. In 2003, a series of exercises were held to test the plan and identify gaps.

Amendments have been made to the province's Public Health Act to enhance the province's ability to determine the existence of a pandemic or other health emergency and respond to it. The ministry's pandemic website is being expanded; originally, it was just for the use of the working groups, but it is being revitalized for use by health professionals and the general public. A secure site for emergency communications is being maintained.

Currently, the province is working on the command and control system, a self-care strategy and communication and coordination with the regional health authorities. For the first, the province chose the Incident Command System, which has five components: command, planning (surveillance, etc.), operations, logistics and finance. This system has clear reporting and documentation procedures and is modular, making it easy to expand or reduce as needed. The self-care strategy is part of the foundation of the health services response to ensure in a pandemic people can care for themselves and their families as long as they can. The planning committee is developing an information package so that, beginning with the 2005-2006 influenza season, health care workers can talk with their patients about pandemic influenza and self-care. A public

awareness campaign is also planned. To ensure good communication and coordination with the regional health authorities, an exercise in the fall of 2005 will test the regional pandemic plans.

Outstanding issues include ethics, funding, new sections for the plan on public health measures and antivirals, and further national discussions about such things as funding, stockpiling of antivirals, delivery of care to First Nations, the intra-provincial transfer of patients, etc. In addition, after SARS, the Ministry recognized the need for an all-hazards plan for infectious diseases (e.g., anthrax, SARS). A basic plan has been developed, and subplans (e.g., smallpox) are now being drafted.

Question Period

In the question period, new approaches to antigen sparing were outlined. Other questions asked for specifics about the Alberta all-hazards approach (which hazards are being considered), the workability of self-care in a pandemic (it will be necessary given the resource stringencies and will be promoted in advance), the possibility of mock pandemic vaccine trials in Canada (planners are optimistic), the relative value of influenza vaccine vs. antivirals in a pandemic (antivirals are a key component of the Canada plan and options are being considered, but vaccines are easier to implement), and the difference between a pandemic and the current H5N1 cases in Asia (the Asian cases are sporadic and not easily transmissible human to human, but the world is on alert).

Big Ticket Items: Do Children Benefit From What We Pay For?

Meningococcal Conjugate Vaccines

Dr. Philippe de Wals

Laval University and Quebec National Public Health Institute

Meningococcus virus has 13 serogroups, of which four are key: Group A is the leading cause of epidemics in Africa and Asia; Groups B and C are the major causes of sporadic outbreaks in Europe and the Americas; Group Y has been increasing over recent years as a cause of sporadic cases in Europe and the Americas, particularly in British Columbia and Ontario.

Essentially, Group B viruses cause disease of early childhood: < 5 years of age. Group C causes disease of children and youth – about three-quarters of the cases occurred before 25 years of age, with cases concentrated in the first 5 years and adolescence. Serogroup Y cases are less common but have a more even distribution. More than half the cases occur in adulthood and there are many clinical presentations, although pneumonia is common.

Three meningococcal conjugate vaccines have been certified in Canada, all of which have slightly different formulations, which may or may not be significant to immunogenicity. Studies have indicated that one dose of conjugate vaccine in children < 6 years primes the immunologic memory for at least 5 years. To attain protective levels of serum antibody concentrations, two doses are needed in children < 1 year and one dose for children > 1 year. The vaccines produce antibodies in mucous membranes. Over time, serum antibody concentrations decrease at a rate that can be determined by the number of doses and age of administration.

In children aged 2 months to 20 years, there has been one case of vaccine failure in 1.5 million vaccinated, indicating a success rate of about 97%, which is vastly greater than that for polysaccharide vaccine (78%). Data from the United Kingdom indicate that over the short term, the vaccine is effective in all age groups, but over the long term efficacy varies. There may be a loss of effectiveness over time for the 2 to 4-year age group. Also, after a mass campaign, this vaccine reduces the carriage rate of Group C virus.

It is postulated that the most efficacious schedule would be 2-months, 4-months, 2-years, with a booster between 10 and 12 years. The most cost-effective schedule would probably be a single dose at 12 months with a booster at 10 to 12 years. Other schedules are possible, and current programming in Canada shows many variances.

In conclusion, the long-term efficacy of meningococcal conjugate vaccines is unknown. The epidemiology of the disease is unpredictable, so control strategies and immunization schedules should be flexible. It would be interesting to explore the potential for using conjugate vaccines for priming immune memory and polysaccharide vaccine for better boosting of antibody production.

Pneumococcal Conjugate Vaccine: Do Children Benefit from What We Pay for?

James Kellner

Alberta Children's Hospital, Calgary

Is pneumococcal conjugate vaccine (PCV7) expensive? Some would say, "Yes." But for most if not all provinces and territories, vaccination represents an extremely small proportion of the health care budget; in Alberta, for example, vaccination is just ½ of 1 per cent. The key question, instead, is whether PCV7 is as good as it is marketed to be, whether is less effective, or whether it may be even better.

When PCV7 first came out, a major trial in Northern California showed 97% efficacy. At the same time, data showed a modest effect on otitis media and a bigger effect on tympanostomy tube placement. Further efficacy studies in the past few years in special populations have shown a 77% efficacy to reduce invasive infections in North American aboriginal populations, an 85% efficacy in South African children who were HIV-, and a 65% efficacy in South African adults who were HIV+. Studies in Northern California and South Africa have also shown some small

efficacy on pneumonia. The South African studies also showed a significant reduction in antibiotic-resistant invasive infections.

Studies on the effectiveness of PCV7 after the start of universal programs for infants and high-risk children show a dramatic decline in invasive pneumococcal disease from the prevaccine period. There has also been a significant decline in disease in adults > 65 years and in adults 20 to 40 years, which indicates that grandparents and parents are gaining some protection. A study in children's hospitals also showed an impressive drop in antibiotic-resistant disease.

Here in Canada, PCV implementation is proceeding in most parts of the country. In late 2002, Alberta began its program for all infants born after July 1, 2002, with catch-up for high-risk and aboriginal children < 5 years. Data from Calgary show a two-thirds drop in invasive *S. pneumoniae* disease in children 6 to 23 months in the first 2 years of the program, and further decline is expected. At the same time, there has been a decline in cases in adults > 65 years. Also, there were no cases of antibiotic-resistant cases in children < 16 years in 2003.

In summary, studies show great efficacy against invasive pneumococcal disease in both healthy and disadvantaged populations, reduced cases of antibiotic-resistant disease a probable herd effect in both children and adults. In other words, it appears to be having an even better result than expected.

Palivizumab: A Big-Ticket Item

Dr. Sheldon Spier
University of Calgary

The palivizumab (PVZ) molecule is a monoclonal humanized anti-F glycoprotein IgG. It is about 5% mouse and 95% human, so there have been some concerns about side effects, but over the first 2 years of one study there was essentially no antibody produced. About 15 mg/kg is needed to maintain the level > 40 mcg/mL. The cost is significant – $5,000/year.

PVZ has a remarkable safety profile. In over 25,000 high-risk infants who have received it in 4 years there have been minimal side effects, no interference with other vaccines and no evidence of resistance. In terms of effectiveness, an IMPact study in children born < 35 weeks gestational age indicates an overall PVZ efficacy of 55%; for bronchopulmonary dysplasia (BPD), there was a 79% drop (although the study's definition of BPD was quite broad). About one-third of the infants were admitted to ICU, so the PVZ did not appear to affect severity in this study, although a smaller study did show that severity of illness was reduced. In a study of hemodynamically compromised infants < 2 years, hospitalization was decreased by 45%; again, one-third were submitted to ICU. Given the limited efficacy, the cost of PVZ may seem extreme; however, a lot of money is already being invested in these high-risk infants – easily $100,000/infant. If PVZ reduces hospitalization costs in just a proportion of these infants, it may still represent an overall saving, particularly if one looks at the savings in work-loss and emotional costs of the parents.

Cost-benefit analyses of PVZ have widely disparate findings, with one in the United States showing savings and others showing various levels of expense.

Ultimately, to identify effectiveness and costs of PVZ, there is a need to accurately define the population, to better identify the value of hospitalization and to better define the optimal dosing.

Question Period

Questions for the presenters centred on the efficacy of the conjugate vaccines, particularly in special populations. British Columbia has been considering a 2- and 12-month schedule for meningococcal conjugate, whereas Quebec has found a 2, 4, 12 schedule most effective. Dr. De Wals noted that the decision in Quebec was based on immunogenicity data, clinical data and cost-effectiveness analysis. For pneumococcal conjugate, the reduced efficacy in the aboriginal population in the southern United States is probably more of a factor of poorer general health and other disadvantages than a biologic difference, although that has not been evaluated. In response to a question about the revaccination with pneumococcal vaccine of children > 2 years before bone marrow transplant, Dr. Kellner suggested immunization with PCV7 to enable a greater booster response with polysaccharide later.

Concurrent Breakout Sessions: Summaries

5. Emerging and Re-emerging Infections and Vaccine Challenges Infections

Dr. Chris Archibald, Director of the Surveillance and Risk Assessment Division of PHAC, explained why a Canadian HIV vaccines plan is needed and how Canada has been working toward it since then–Prime Minister Chrétien announced $50 million for the International AIDS Vaccine Initiative (IAVI) in 2002 at a G8 summit. The Canadian plan has four components: commitment to the development of HIV vaccines, public engagement, strategic integrated plans for HIV vaccines development, and equitable vaccines access and delivery. Since 1987, about 30 candidate vaccines have been tested in about 60 phase 1 and 2 trials. One phase 3 trial has been completed, another is almost done, and a third is about to start; Canada is participating in one of these phase 3 trials. Next steps for the Canadian plan are to finalize the documentation on components and vision, to develop a comprehensive plan with commitments from all partners (with a target plan completion date of 1 December 2005) and hold an international consultation/launch in Toronto in 2006.

Dr. Peter Buck of PHAC's Foodborne, Waterborne and Zoonotic Infections Division noted the conflicting opinions on the value of developing a West Nile virus vaccine. Although the frequency of the disease has increased dramatically since the pathogen was introduced to North America, with many cases of severe disease, a number of related deaths and evidence of both

short- and long-term sequelae, the majority of cases are of mild disease or asymptomatic infection. Nonetheless, the absence of effective antiviral or immunoglobulin therapy and the potential value of a vaccine for high-risk individuals have prompted research. Several candidate vaccines have been developed, including a chimeric vaccine, a recombinant DNA vaccine, a subunit vaccine and a heterologous flavivirus vaccine.

Dr. James Anderson of the Centre for Emergency Preparedness and Response identified several reasons why biologics make good candidates for weapons of terror. Agents of the highest concern include smallpox, plague, viral hemorrhagic fevers (VHF), anthrax, tularemia and botulinum toxin. No vaccines are available for VHF, tularemia or botulinum toxin. Plague vaccine was licensed until 1999, but is no longer made. Anthrax vaccine is available but is currently recommended only for high-risk populations; there may be some rationale for its use post-exposure. Production of smallpox vaccine has been reinitiated and Canada is stockpiling over 10 million doses. Indications for use include pre-exposure prophylaxis in laboratory works and public health first responders and outbreak control. Contraindications are numerous, but in an emergency situation, there would be no absolute contraindications. An eight-phase smallpox contingency plan has been developed for Canada.

6. Selected Safety Topics

Dr. Elwyn Griffiths of the Biologics and Genetic Therapies Directorate of Health Canada reiterated that as the incidence of vaccine-preventable disease falls, public awareness about the severe consequences of those diseases rapidly disappears. It becomes an important public health issue when vaccine uptake then drops off, often in response to mythical associations between a vaccine and an adverse effect, and there is a re-emergence of the disease. It is vital to distinguish between vaccine side effects and unrelated chance occurrences. Vaccines have extremely high safety standards, with extensive pre-licensure research and testing, post-licensure safety monitoring, lot evaluation and VAAE reporting. Nonetheless, there is no such thing as zero risk with any medical intervention: the aim must be to minimize and manage risks while maximizing benefits.

Referring to the simian virus 40 contamination of the polio vaccine between 1955 and 1963, Dr. Martin Lavoie of the David Thompson Health Region in Alberta noted that vaccine safety exists not just in scientifically measurable ways, but also in public perception. Even though it is > 40 years since SV40 was eliminated from the vaccine, the seeds of doubt and fear remain, with numerous media articles and Internet sites linking SV40 contamination to human cancers. People want to know about vaccine safety and risks related to immunization, and different groups offer answers in attractive packages. More often than not, the experts are kept busy reacting to allegations. Too often, the expert message is just a repetition of “Vaccines are safe.” The experts must do more to explain *why* vaccines are safe, to provide balance in the information about vaccines and to actively help parents make informed decisions.

Dr. Philippe Duclos of WHO reviewed the thimerosal controversy. In July 1999, the American Academy of Paediatrics and the U.S. Public Health Service issued a joint statement that thimerosal (a preservative, a bactericide and a stabilizer which contains ethyl mercury) in

vaccines exceeded the cut-off levels for ingested methyl mercury and recommended removing thimerosal as soon as possible from routine infant vaccines. The statement focused the attention of the anti-immunization lobby, and there has been a flurry of pseudo-scientific articles purporting misinformation and alleging links with autism and neurodevelopmental disorders. At a global level, there would be an immediate and major impact on developing countries if thimerosal was not used in vaccines – the requirement for monodose preparations would increase vaccine costs 6- to 10-fold, and the cold chain could not cope with the 4- to 10-fold increase in volume. WHO's Global Advisory Committee on Vaccine Safety (GACVS) investigated the issue and concluded that there is no evidence of thimerosal toxicity and no reason to change current immunization practices. GACVS is working with international partners, including Canada, to find ways to enhance communication between experts and the public about vaccines.

Mr. Ken Moore of Health Canada's Biologics and Therapeutics Directorate offered a regulator's perspective on vaccine safety. Their approach to risk management and risk communication includes the precaution principle: when there is the possibility of severe and irreversible harm, one should not wait for scientific certainty to take action. Recognizing its influence on the public's perception of vaccine safety, the Directorate's risk communication strategy strives for audience-appropriateness, scientific accuracy, consistency and timeliness. Vaccines are distinct from other products in that an individual's choice could affect the health of others, so widespread resistance to a vaccine would have public health implications. Also, specific risk information that relates only to one vaccine will nonetheless influence general perceptions about vaccine safety. Therefore, when communicating risk information, the Directorate consistently reinforces the safety of vaccines and the benefits of immunization.

7. Keeping It Cool: Monitoring Cold Chain Issues on the Front Line

Ms. Lucie St-Onge of Quebec's Ministry of Health reported on a 3-year program (1998-2001) to support pharmacies and local health units in applying provincial standards and procedures for the management of vaccines. Min/max thermometers, graphic recording thermometers, freeze and heat indicators, and electronic monitors were provided to the vaccinators. A printed guide on standards and practices, materials for trainers and printed procedure sheets were given to trainers and vaccinators. Later evaluation of the program indicated good compliance with standards. There were some technical problems and some transportation issues, but the ministry support, a cooperative approach, the distribution of the tools and ongoing access to technical expertise made the project a success. Awareness and expertise were enhanced, the management system was improved and other partners have become interested.

Ms. Agnes Honish of Alberta Health and Wellness described an initiative that applied cost considerations to a review of breaches in the cold chain for 2003-2004. About $20.8-million worth of vaccine was distributed in Alberta in the 2003-2004 fiscal year. Of that, $638,123.24 worth (3.4% of the vaccine distributed) was exposed to incorrect temperatures, and of that, $141,404 worth was discarded. Causes of the 168 cold chain breaks were identified as

refrigerator malfunctions, power disconnections, power outages, human errors and "other" causes. Cold chain monitoring is essential to client safety. Staff must be educated; thermometers must be in place and working; written procedures must be on hand. All personnel who are links in the cold chain are important. Reporting of vaccine losses and the reasons for them will lead to preventive measures. Copies of the report can be requested from elaine.sartison@gov.ab.ca.

On Thursday, August 14, 2003, a transmission system problem in the hydroelectric system in Ohio led to cascading electric grid failures that, within 6 minutes, plunged most of Southern Ontario and large sections of north-eastern United States into darkness. The blackout lasted 2 days, and rolling blackouts continued for a week. In the Niagara Health Unit, Dr. Robin Williams, the Medical Officer of Health focused on two concerns: food safety and vaccine stability. For the latter, the 65 physicians' offices in the region were contacted and instructions given for moving vaccines to refrigeration facilities known to be working in their areas. Later, a vaccine stability form was faxed to all these offices to help them determine what vaccines had been exposed to the power outage and what actions were needed. Dr. Williams identified five issues raised by the blackout: regular cold chain vaccine monitoring is less than ideal (about $3-million worth of vaccine is discarded annually); cold chain principles are not well understood by all health care workers; the refrigeration systems at public health departments and hospitals (backed up by generators) are critical to maintaining the cold chain, and physicians need to have emergency plans in place that incorporate these facilities; the system of communications needs to be improved between physicians and public health (e.g. in this emergency most physician's offices could not be contacted, especially after hours) and a tremendous amount of vaccine was lost because of the blackout (about $2.1 million-worth in the province, or $0.19/resident, and about $80,000 in the region, or $0.06/resident).

8. Peer-Reviewed Oral Presentations

Dr. Murray Krahn reported on a Health Canada-commissioned cost-effectiveness analysis of universal hepatitis A vaccination (HAV) for children and adolescents. Seroprevalence data were fitted to an incidence model to predict the incidence of new hepatitis A infections in different age groups, and a Markov decision analysis model was used to describe the outcomes in vaccinated and non-vaccinated cohorts. The models indicated that the universal vaccination of adolescents would cost an incremental amount of about $50,000 per quality of adjusted life year gained. For each 100,000 children vaccinated, 1,400 acute cases of hepatitis A would be prevented. About 11 deaths would occur in the absence of vaccination and four deaths with universal vaccination. The net cost per death averted would be about $250,000 in direct costs or $150,000 when indirect costs are included. The researchers concluded that universal vaccination against hepatitis A would be cost-effective, although the savings in life years gained would not be substantial. It may not be economically attractive in regions of lower incidence.

Children with laboratory-confirmed influenza who were hospitalized at nine IMPact hospitals in 8 cities in six provinces during the 2003-2004 influenza season were the basis for a study described by Dr. Dorothy Moore. To establish a baseline before the anticipated changes in influenza vaccine recommendations, the study identified the characteristics of the children and

documented the disease manifestations and resources used. During that season, 500 children were hospitalized – 495 with influenza A and five with influenza B. Just over half (57%) were < 2 years of age, 29% were 2 to 5 years, 8% were 6 to 12 years and 6% were > 12 years. Just over half (53%) were previously healthy. Only nine children were identified as having been fully immunized. The researchers concluded that influenza does cause significant illness in both healthy children and those with underlying diseases and causes considerable use of health care resources. It is anticipated that vaccinating young children and their close contacts will decrease the influenza disease burden.

Dr. Bernard Duval described research that measured antibodies in pre-teens 1 month and 5 years after hepatitis B vaccination to learn more about long-term immunity. Anti-HBc and anti-HBs were measured in 560 children who were vaccinated at age 9 with either Engerix-B or Recombivax HB. Anti-HBs were also measured 1 month and 1 year after a booster was given at age 14. All children were seroprotected 1 month after the primary vaccination, but titres decreased after 5 years to < 10 mIU/mL in 12.6% of the children who received Engerix-B and 18.4% of children who received Recombivax HB. One month after the booster, 99% of the children were once again seroprotected. One year later, 98.5% were seroprotected. In conclusion, almost all teenagers were still protected against hepatitis B 5 years after vaccination. The proportion of teenagers with high titres was substantially increased by the booster dose, and in most of the children, the titres remained very high 1 year after the booster.

Dr. Nicole Le Saux reported on a study that used IMPact data for 1993-2003 to determine the number of children hospitalized for encephalopathy, encephalitis or other serious neurological event 5 to 30 days after receiving a measles-containing vaccine (an estimated 6.87 million doses of measles vaccine were given during that period). Ten children were identified, all of whom received MMR alone, 8 to 28 days (median 15.5) before onset of the neurological symptoms. The neurological symptoms included seizures or a decreased level of consciousness (n = 6), ataxia or decreased level of consciousness (n = 3) and cranial nerve palsy plus myalgia, lethargy and diffuse encephalomyelitis on MRI (n = 1). There were other potential causative factors in at least six of the 10 cases. Of the seven children with encephalitis/encephalopathy, six had returned to baseline within 3 months and one (parainfluenza, normal MRI/CT) had global developmental delay. Of the three children with ataxia, one recovered and two still had mild ataxia at 3 months follow-up.

Immunization: The State Of The Nation

The National Immunization Strategy: Progress and Challenges

Dr. Arlene King

Director, Immunization and Respiratory Infections Division, PHAC, and Chair, Canadian Immunization Conference Organizing Committee

The NIS has progressed significantly in the component of equitable access through collaborative program planning since the 2002 Canadian Immunization Conference, partly because of the federal funding announcement in the 2004 budget. Numerous provincial and territorial immunization programs have been launched, expanded or announced in meningococcal conjugate vaccine, pneumococcal conjugate vaccine and varicella vaccine. Most impressive are the changes in adolescent acellular pertussis vaccine, which is now available everywhere in Canada to all children 13 to 16 years of age.

Canadian Immunization Conference is a means to effecting federal, provincial and territorial collaboration in immunization leadership through the analysis, development and recommendation of national goals and through cost-effective immunization programs. Its members are public health officials who are responsible for making immunization recommendations to their governments. It is supported by four working groups that develop recommendations to submit either to Canadian Immunization Conference or to NACI. The Canadian Immunization Conference is part of the proposed Canadian Public Health Network.

The activities of the program monitoring and evaluation team of the Immunization and Respiratory Infections Division (IRID) include national goals and objectives, immunization registries, national immunization coverage surveys, program monitoring, implementation of the *i*-Field Surveillance Officer program and evaluation of the NIS. The team has scheduled a NIS goals and objectives consensus conference for June 2005. They are developing and maintaining national data standards for electronic immunization surveillance and are also working on a vaccine identification database system and a vaccine bar coding initiative. The 2004 Immunization Coverage Survey has been completed, and a 2005 adult survey is planned. The team is also working with the Canadian Nurses Coalition for Immunization to ensure that up-to-date information on the status of publicly funded immunization programs is readily available.

The vaccine supply team is working with the F/P/T Vaccine Supply Working Group and Public Works and Government Services Canada. A nationally coordinated process for resolving vaccine supply issues is being increasingly adopted. The NACI support team gives scientific and administrative support to NACI. The immunization research team has just launched an RFP for comparative influenza immunization program evaluation (targeted vs. universal). They are also working on a vaccine research and development strategy and developing an

influenza research agenda for 2005. The professional and public education team organized this Canadian Immunization Conference and its associated workshops. A professional education working group will be established in 2005 to develop an overall communication strategy for the NIS. The main emphasis of the vaccine- preventable disease surveillance team is to strengthen data quality, analysis and feedback. It is hoped to establish an immunization and respiratory infections surveillance working group that will advise the NIS. The vaccine safety team is improving the reporting from the VAAE system and developing a VAAE telephone working group. They are participating in the Brighton Collaboration (working on data definitions). An expert working group on vaccine safety is being developed.

Current challenges for the NIS include finding ways to meet the immunization needs of special populations (e.g., aboriginal people, immigrants, refugees, travellers), information technology as it relates to immunization, vaccine research and manufacturing, collaborative program planning and harmonization, and the competing priorities for health care funding.

Impacts of Current Programs

Dr. Greg Hammond

Director, Public Health Branch and Communicable Disease Control, Manitoba Health

Immunization is clearly the best defence against vaccine-preventable diseases. Before vaccine, Canada experienced up to 20,000 annual cases of polio; in 2001, there were none. Before vaccine, there were up to 9,000 annual cases of diphtheria, in 2001, there were none. Rubella, mumps, Hib, measles and pertussis have all been dramatically reduced. And compared to other protective measures, childhood immunization is the exception in that cost is so significantly offset by savings that the cost per life-year saved is < $0. Comparatively, seatbelts cost about US$69/life-year saved, breast cancer screening costs about US$810/life-year saved, drinking water chlorination costs about US$3,100/life-year saved and neonatal intensive care for low birth weight infants costs about US$270,000/life-year saved. Figures like these need to be used when looking at competing priorities for health care funding.

In Canada, the cornerstone of immunization surveillance is IMPact (Immunization Monitoring Program, ACTive), which conducts active surveillance of selected targets at major Canadian tertiary care paediatric centres (IMPact covers 90% of tertiary care paediatric beds in Canada). Its objectives are to determine the occurrence of serious or unexpected adverse events associated with the child immunization and to accumulate epidemiological information pertinent to communicable disease epidemiology and decision-making on routine immunization programs. IMPact confirms the decline in invasive Hib from over 600 cases/year pre-vaccine to < 40/year. Pertussis has also fallen since vaccine was introduced – more and more, the cases that do occur are in children < 2 years, which is before immunization. Similarly, measles cases have been dramatically reduced, from thousands of cases annually to only seven cases in 2002.

British Columbia initiated a hepatitis B vaccine program for preadolescents in 1992. A 1999 study of hepatitis B surface antibody among pregnant women in the province showed a decreased rate of infection and a higher rate of protection than in previous cohorts. In Spain, the meningococcal vaccine has significantly decreased the rate of meningococcal C disease, and the death rate fell 90% over just 6 years. Quebec's one-year experience with meningococcal conjugate vaccine shows 98% effectiveness to date. Pneumococcal conjugate vaccine has been hugely successful. U.S. experience shows a reduction in rates of pneumococcal disease in all children < 5, but the drop in cases in black children is remarkable; this vaccine has eliminated inequalities of poor health. The U.S. reductions have come about even with only three-quarters of children immunized, indicating a significant herd immunity effect. As a result, GAVI is accelerating its plans for using the vaccine in developing countries. Also in the United States, 85% of 19 to 35-month-old children have been vaccinated for varicella, resulting in a 74% drop in hospitalizations for varicella from 1995 to 2001 and savings of about US$95 million.

The impact of influenza vaccination is harder to evaluate, because programs strive not to control or eliminate the disease, but rather its complications. Nonetheless, there is evidence of effectiveness in both children and adults, even without a full match between vaccine strains and virus strains. In particular, influenza vaccine recipients > 65 years show decreased hospitalization risk for heart disease, stroke and pneumonia and decreased all-cause mortality. Canada has the highest influenza vaccination coverage rate in the world.

When America's second-largest supplier of influenza vaccine suspended shipments, there was additional pressure on Canadian supply and programs, showing how shortages and the resulting media reports can stimulate overuse and affect public confidence. Similarly, the anti-vaccine movement can have a major impact on public confidence. When anti-vaccine propaganda in the 1970s significantly reduced the uptake of vaccine, there was a major increase in pertussis cases; the uptake subsequently increased to beyond the original point.

Despite the ongoing evidence of the positive impacts of immunization programs, Canada cannot be complacent. Coverage rates are not optimal. Immunization programming must continually strive for clear goals and evaluate outcomes.

Introduction of a New Vaccine: Challenges and Successes

Ms. Mahnaz FarhangMehr

Nova Scotia Department of Health

An informal survey of members of the Canadian Nurses Coalition for Immunization (CNCI) revealed that all provinces and territories base the introduction of a new vaccine on a sound planning process.

The first step is to define the desired outcome. All the provinces and territories have a clear vision of the goal of the vaccine program, developed by considering the epidemiology of the disease, the impact on the target group and the impact on the health system. The second step is

to involve the right people in the process. Again, all jurisdictions strongly believe in the importance of involving the stakeholders – providers, policy makers, decision makers, experts, etc. – in planning to ensure the best decisions and buy in. Third, a full analysis is done, including the cost of introducing and sustaining the program, scheduling, lead time (to ensure supply, training, resources, communication), costs and benefits, communications, training and promotion of providers, and the identification and development of resources. The fourth step is to develop an option paper or Treasury Board submission. Most provinces and territories provide 2 to 3 options with descriptions of pros and cons. Others may choose an incremental approach to increase chances for approval and to inform decision makers about each option. The option paper includes costing for all aspects of the program.

The next stage in introducing a new program is approval. In the smaller jurisdictions, planning is done by those who will ultimately be accountable for the programming; they usually just go directly to Treasury Board to seek budget approval. Planners in larger jurisdictions face a much more complicated process, where the option paper may have to go to an immunization committee for approval, then to the regions or districts for their buy in, then through program approval at a ministry level, then to the finance section of the department or ministry and finally to the Treasury Board or Cabinet for budget approval. In all jurisdictions but two, this must all occur during the annual budget process.

During implementation, the jurisdictions continually monitor the process to ensure that the plan is followed. Once a program is under way, evaluation is put in place; most jurisdictions use coverage rate as a means for evaluation. The final stage in planning should be acknowledgement and celebration of the results, but none of the provinces and territories in the survey indicated any activity in this area.

There are many challenges for the introduction of a new vaccine. The biggest challenge is securing funding. Thanks to the NIS, provincial funding for the last four new vaccines did not have to include the vaccine purchase costs, but administration and program delivery costs are not insignificant. Also, as more and more vaccines are added to the immunization schedule, more human resources are needed, but public health faces a shortage of health professionals, particularly nurses. Another challenge is the governance structure and approval process, and regionalization adds yet another government layer. The perpetual competition of priorities within public health is another issue. Acceptance by vaccine providers is another challenge, involving the provider's perception of the importance of the disease, the complexity of the immunization schedule and the reluctance of many providers to do multiple injections at one visit. The survey respondents also identified inadequate support within their own department or ministry as a problem, not just because of competing priorities but also because of the complexity of the decision-making process. Similarly, there is often inadequate support within regional public health in terms of finding the financial and human resources needed (the province used to just tell regions to implement a program, and they did; now, they ask for resources) and in terms of competing local priorities. Hard-to-reach populations are a challenge everywhere.

Survey respondents identified the keys to success as securing funding, acceptance by the providers, the education and training of the providers, consistent support from leaders and program managers, effective communication strategies for both the public and the target groups, and evaluation of programs. In addition, it is important to apply immunization successes – and there are many – to the ever-evolving challenges. There has been a breathtaking decline in morbidity and mortality from vaccine-preventable diseases in the past 50 years. Public health needs to acknowledge, celebrate and communicate those successes among ourselves and to politicians, decision makers and the public. We need to congratulate the vaccine providers. We need to remain visible at all levels. We need to change our paradigm from "victims of our own success" to "celebrating our success".

Keeping Count: Progress Report on Registries and Other Technologies

Ms. Heather Schouten-Deehan

Public Health Agency of Canada

An immunization registry is a confidential, population-based computer information system that collects immunization data on children within a geographic area. The goal is a database by which health care providers can monitor the immunization status of clients at each encounter, regardless of where the original immunization record was created. The database will be a tool to consolidate vaccination records at all levels and could be used to generate reminders and recall notices for individual clients. It will be able to produce official immunization records. It will be able to provide official vaccination coverage assessments.

A recent survey identified that four jurisdictions – Alberta, Saskatchewan, Manitoba and Prince Edward Island – have over 90% of their population of children aged 0 to 7 years in an immunization registry. Newfoundland has been able to double its registry from 5% to 10% of children.

A goal of the National Immunization Registry is to develop national standards and definitions for a minimum data set, as well as functional and technical standards and business rules for registries. The functional standards have been published and are available through the *Canada Communicable Disease Report* (CCDR). Some of the standards have been modified.

Over the past 2 years, logic rules have been used to review the NACI schedule and place it in the national system. Now, within *i*-PHIS, administrators can send letters of consent to individuals or parents identifying vaccines that are due. Parents can sign the letters and send them in to their provider. Parents could be reminded that their children are overdue for specific vaccinations. Postcards could be sent to new parents to remind them of the schedule and the importance of immunization. (In response to a later question, Ms. Schouten noted that the US CDC has an interactive web-based system whereby an individual can enter a birthdate and get a listing of the recommended vaccine schedule; a similar system could be devised in Canada, although it is not in the current plans.)

Almost every jurisdiction has achieved or is en route to achieving the collection of elements in the core data standards.

Currently, two key projects are automated identification and the evaluation of registries. The former looks at bar coding and data matrixes. These data carriers carry information from one system to another. A bar code can fit on an ampoule of vaccine. A data matrix is even smaller and can fit on an ampoule or vial for scanning at time of delivery. Radio frequency identification is another new system and a fantastic tool for monitoring cold chains. A small chip can record the cold chain from manufacturer release to time of use. This could be invaluable for lot tracking, shipping accuracy, etc. Also, peer reviewed evaluations of immunization registries will begin in 2005 to ensure that registries are meeting national standards and can accomplish key functions in a timely manner.

■ Question Period

With reference to the implementation of a new vaccine, it was noted that political influence at all levels must be acknowledged. The lobbying of influential individuals or groups can make a tremendous difference. Most other questions related to the immunization registries. The importance of entering a trade name was noted. When the issue of confidentiality was raised, Ms. Schouten described how the registries could ensure privacy (e.g., by ensuring that only generic reminders and messages were sent via postcard; specific reminders would be sent in sealed envelopes). In addition, she identified a process whereby authorization for individual health care providers could be provided based and depending on provincial policies, laws and procedures. The lack of a registry for any of the territories was noted, highlighting the need for lobbying. For clarification, it was noted that there will be no one national registry; rather, there will be a network of provincial and territorial registries that will be linked at the national level and will include First Nations.

Concurrent Breakout Sessions: Summaries

9. Immunization Programs for Special Populations

Ms. Andrea Derban of BCCDC described the process she used to promote immunization of the people who need it most – those with chronic and pre-existing medical conditions – by engaging their care providers. After identifying clinics that dealt with high-risk clients, she met with the coordinator at each to ask what they were currently doing about immunization for these clients, to show them the current recommendations and then to ask whether they would be willing to immunize or at least endorse immunization (i.e., give clients a letter recommending the vaccines they should get and having them report back). She then provided them with education materials and a process model to support whichever they agreed to do. The method met with some success, and she learned that face-to-face meetings are essential. An internal champion is vital, and the

medical directors must be involved from the start. It is important to communicate a clear vision as well as clear roles and responsibilities and to provide lots of support and a process model.

Dr. Erika Eason, an associate professor in obstetrics and gynecology at the University of Ottawa, noted that half of the babies with congenital rubella syndrome (CRS) are born to mothers who have had previous births. In other words, previous opportunities to vaccinate with MMR, which would have prevented the CRS, were missed. Having done a study that indicated much improved practices with printed postpartum standing orders regarding MMR, Dr. Eason suggests that such orders should be a CCHFA (Canadian Council on Health Facilities Accreditation) standard. She further recommends the MMR vaccination of all immigrants and refugees, as more than half the cases of CSR in Canada are in the children of immigrant women.

Many people may assume that any vaccination in pregnancy is dangerous, but Dr. Carol Baker of the Texas Children's Hospital Foundation and Baylor College of Medicine observed that many vaccines can be safely administered during pregnancy, and indeed the obstetrical care provides an immunization opportunity. The optimal timing would be beyond 20 weeks to avoid unrelated adverse outcomes and to maximize specific IgG levels. A number of vaccines are contraindicated: MMR, varicella, OPV, live attenuated influenza and smallpox. Others are specifically recommended: tetanus toxoid and trivalent inactivated influenza for all pregnant women; hepatitis A or B, pneumococcal polysaccharide and meningococcal polysaccharide for at-risk women; and IPV, hepatitis A or B, and yellow fever for travellers. Maternal immunization has long been a safe and practical method of providing protection against potentially fatal infections in young infants. Millions of lives have been saved through tetanus immunization, and this model could be used to prevent Guillain-Barré syndrome, RSV, pneumococcal and Hib disease in young infants.

10. Who's Listening? Messages for the Masses and One-on-One Strategies

Communicating vaccinology is both a science and an art, according to Dr. Danielle Grenier, Medical Affairs Officer of CPS. It requires both up-to-date vaccine knowledge and skills in effective risk-benefit communication. Fortunately, only 5% of parents of children < 7 years of age are adamantly against vaccines. Most parents (90%) believe in vaccines, and 75% of them turn to their health care providers for information. Therefore, it is important for providers to meet their professional responsibilities in terms of science, ethics and the law. Also, because an initial vaccine refusal does not mean an eternal refusal, providers have a responsibility to be good communicators – listening carefully, talking about vaccines in a clear and understandable way, acknowledging vaccine imperfections and recommending strongly. Parents want the facts about vaccine efficacy, safety and side effects. They need to know not just the risks presented by vaccines, but also the risks of diseases, such as fatality rates and rates of both serious and transient sequelae.

Ms. Lynn Cochrane, Immunization Project Manager for New Brunswick Health and Wellness, elaborated on the elements of communication between provider and parent. First, providers must themselves believe in the value of immunization. Second, they must recognize that it is a client decision and apply the principles of informed consent: providing relevant information, describing risks and benefits and allowing time for discussion. If parents remain apprehensive, providers should identify the source of concern so that they can deal with it. It is helpful to involve pre-school children themselves in the discussion. Trust is paramount, both the parents' trust of the provider and the provider's trust that the parents will make the decision that is right for them. Additional challenges for providers are presented by cultural sensitivities, working through a translator and discrepancies in health care provider information.

An objective of the Canadian Coalition for Immunization Awareness and Promotion (CCIAP) is high (> 90%) vaccination uptake to control and eradicate disease. Ms. Mary Appleton, Senior Manager of the CCIAP Secretariat, outlined the challenges in meeting that objective, including the overload of health news (both accurate news and misinformation), science illiteracy and the many factors affecting risk perception (both risks of diseases and risks of vaccines). The credibility of the messenger is vital to getting the correct message across, and although most parents trust their health provider first, many also look to the Internet, family, friends and other sources that may or may not be accurate. Recognizing that, organizations such as CCIAP see support to front-line health care providers as one of their most vital functions. Establishing and promoting accurate Internet-based information is also increasingly important. Among the rules for risk communication, perhaps the most critical is working with other credible sources to ensure consistent messaging.

11. Information Technology and Immunization

Ms. Rosalie Tuchscherer, a public health nursing consultant with Saskatchewan Health, described the Saskatchewan Immunization Management System (SIMS), a confidential, web-enabled, computerized immunization database that collects immunization data on all children receiving services in regional health authorities in the province. As of November 2004, there were 234,387 clients entered in SIMS, having 1,267,579 immunization events. It employs techniques to eliminate duplicate entries and minimize data entry errors. It can generate reports on individual client history, clients immunized with a given antigen, antigens administered to specific age groups, errors, coverage rates by antigen and overdue clients. For the last, recall or reminder letters can be generated. Challenges include the mobility of children, missing postal code information and a lack of integration with First Nations immunization programs.

Ms. Tara Mawhinney, a program consultant with Manitoba Health, reviewed the 2003 coverage reports generated by the Manitoba Immunization Monitoring System (MIMS), including preliminary mapping of the coverage data using a geographic information system (GIS). MIMS has been in place since 1989 for children's immunization data, and adults were added in 2000. It is populated through the provincial health registry using electronic capture of physician billings plus data entry by public health and thus includes about 98% of the population. Once a month, MIMS generates reminder letters for children's immunizations at 5½ years of age by running the

child's record to check for valid doses by antigen. For children with incomplete coverage, a letter is produced that includes the child's complete history, with missing doses highlighted. Provider follow-up letters are also sent out at ages 1, 2 and 6 years for children with incomplete histories. The provider is asked to vaccinate or to provide the missing dose information.

Dr. Wikke Walop, Assistant Head of PHAC's Vaccine Safety Unit, presented an historical perspective on the legal authority behind the Vaccine Adverse Event Surveillance (VAAE) system and on the system itself, followed by an overview of the current VAAE database. As of 1 June 2004, the database has been web-enabled. All data collected since 1987 are in the database, which enables staff members to generate rapid, although limited, reports. The unit will soon be importing VAAE data electronically from Alberta and is working with *i*-PHIS to enable the two systems to "talk" with each other. Data can also be sent electronically to WHO. Provinces and territories can be sent subsets of their own data. The unit is working with industry on a protocol for their data to assist them in their periodic safety updates and reviews. A consumer access website is being contemplated.

12. Science to Policy

Mrs. Barb Shea, Vice President of Common Drug Review (CDR) for the Canadian Coordinating Office for Health Technology Assessment, outlined the process CDR uses to review drugs for potential coverage by public drug benefit plans in all provinces and territories except Quebec. The process includes systematic review of the clinical evidence and pharmacoeconomic data and then a listing recommendation with rationale by the Canadian Expert Drug Advisory Committee (CEDAC). CEDAC may recommend listing, listing with conditions or not listing, or may defer its recommendation pending clarification. An initial, confidential CEDAC recommendation is sent to drug plans and the manufacturer. There is a 10-day embargo period during which the manufacturer may request reconsideration and drug plans may request clarification. The final recommendation and rationale are posted on the CDR website. Since established in September 2003, CDR has had 23 submissions, with eight requests for priority review. Thirteen final recommendations have been issued, and the remaining reviews are on target, including four requests for reconsideration. An evaluation of the program will be conducted in early 2005.

Dr. Arlene King, Director of the Immunization and Respiratory Infections Division, PHAC, described the factors leading to the successful initiation of the NIS. Throughout the 1990s and early part of this decade, there was increasing support for a national approach to immunization, from the Advisory Committee on Population Health and Health Security, the 2002 Romanow Report, the 2003 First Ministers Accord on health renewal, the October 2003 Naylor Committee recommendation, the Standing Senate Committee on Social Affairs, Science and Technology, and the Conference of Deputy Ministers of Health. As a result, the 2003 federal budget included $45 million over five years for a NIS, and the 2004 budget made $300 million over 3 years available to provinces and territories for the introduction of new immunization programs. Assisting in the support was the precedence of the federal government's well-recognized role in immunization and pandemic influenza preparedness; the value of the NIS as a comprehensive, cost-effective,

evidence-based product; promotion and advocacy by provincial and territorial governments, public health, clinicians, the media and others; and perseverance by key public health leaders.

Dr. Richard Massé, CEO of Quebec's National Institute of Public Health, said that although science must guide policy-making, social and political realities introduce complexities that defy linear thinking. Drug evaluation criteria – including vaccine characteristics, cost-effectiveness and feasibility – may be constant, but will not always bridge the gap between political and social calculations of a vaccine's worth. What many may see as a profitable intervention may strike others as a net outlay of spending. The Quebec Immunization Committee provides scientific advice on immunization to the Quebec Ministry of Health on which programs to implement and how. Nonetheless, since each criterion can be weighted differently, it is the job of public health professionals to act as information brokers for governments and the public at large.

Wednesday, December 8, 2004

Current Challenges in Immunization

Public Education About Immunization: What Should We Say and How Should We Say It?

Dr. Ronald Gold

The major barrier to public education about immunization is the high prevalence of scientific illiteracy among the public – parents, the media and politicians. As a result, many believe anecdotes to be proof of causation, and they have faith in and use alternative medicine, astrology and other forms of magical thinking. Anti-vaccination groups thus have fertile ground for their myths, which are given widespread airing in media and have major negative consequences.

For example, the myth that pertussis vaccine causes brain damage has brought an epidemic of lawsuits in the United States, a decrease in the number of vaccine manufacturers and a decline in DPT coverage followed by epidemics in the United Kingdom, Japan, Sweden and the former Soviet Union. The myth that MMR causes autism has resulted in pending lawsuits in the United Kingdom and the United States, a decline in MMR coverage in the United Kingdom, Ireland and Australia and an increased incidence of measles, mumps and rubella in those nations. The myth that thimerosal causes autism has led to the removal of thimerosal – the most effective preservative for multi-dose vials – from all childhood vaccines except influenza in the United States. The list goes on. Anti-vaccine messages cause real, identifiable harm. They increase parental fears about vaccine safety and cause a resulting decrease in vaccine coverage and hence an increase in the incidence of vaccine-preventable diseases. They cause lawsuits. They decrease the number of vaccine manufacturers and increase the cost of vaccines. They result in expensive, time-consuming research undertaken to disprove anti-vaccination myths.

Can public health take a proactive approach to combatting anti-vaccination myths? Can we address issues relating to vaccine safety before the anti-vaccination lobby creates hysteria by alleging yet another association between vaccines and serious reactions? One of the barriers to this approach is that it is difficult for public health to predict what the anti-vaccinators will say next. Any disease of unknown etiology – and there are many – is likely to be linked by anti-vaccinators to a vaccine. And the media are more interested in controversy than public education. Unfortunately, other than trained medical reporters, most reporters suffer the same scientific illiteracy as the rest of the public. Also like many of the public, reporters tend to distrust authorities, especially government institutions.

The enormous success of immunization in the past 100 years means that we will soon have two or three generations of parents, reporters and physicians who have no direct experience with most or all vaccine-preventable diseases. Without the fear of the disease and its consequences, the major concern of parents turns to vaccine safety. Therefore, public health's biggest education effort must be on vaccine safety – not just *saying* that vaccines are safe, but educating people about why they are safe based on science. Public health must also demonstrate to the public what is being done to monitor and investigate vaccine safety on an ongoing basis, for both new and long-existing vaccines.

Current Challenges in Immunization: The Delicate Balance of Vaccine Supply and Demand

Dr. Rob Van Exan

Chair, Vaccine Industry Committee of BIOTECanada

Since Jenner developed the smallpox vaccine in 1796, about 40 vaccines have been developed. Most of the new vaccines and new developments in vaccine technology have occurred in the last decade. Overall, the process has not changed significantly, but a greater change has occurred in the way quality control is viewed. A 100 years ago, it was considered sufficient simply to do end-product tests for sterility and potency. Over time, testing grew to include the seed banks and raw materials. Today, global standards dictate extremely tight control of the entire production process and environment, which greatly increases the assurance of vaccine safety, but also greatly increases production cost. Given the costs of the new technologies, the new vaccines and the new compliance requirements, it is not surprising that the number of vaccine manufacturers has dropped to the point where 80% of the world's vaccines are made by just five companies. These trends of increasing costs and fewer suppliers are a recipe for increased chance of supply disruption. In other words, the imbalance between increasing manufacturing costs and vaccine prices has increased the fragility of the vaccine supply.

A number of things can cause rapid changes in vaccine demand – outbreaks, emerging diseases, bioterrorism, public awareness, cold chain problems, public health policy, purchasing policy. Since it takes 12 to 18 months to produce a vaccine lot, these rapid changes in demand can cause

shortages of supply. Also, if any company wanted to increase capacity, it would take 5 years to build and validate a manufacturing facility.

Vaccination already exists as a partnership between industry and public health, but this partnership needs to be enhanced. With greater collaboration, communication and planning between industry and government, almost every one of the supply issues can be overcome. For example, the rising costs in the vaccine industry could be dealt with through negotiated procurement reform. Product supply, inventory management and cold chain issues could be solved through shared responsibility and communication between public health and industry. Emergency preparedness can be developed through joint planning. Canada is a leader in streamlining regulations and harmonizing with European companies; regulation streamlining at home could help the industry. Vaccine safety and research could be enhanced through aligned objectives and joint investment.

Competing Priorities in Public Health

Dr. Horacio Arruda

Director of Public Health Protection, Ministry of Health and Social Services, Quebec

Despite the proven efficiency and effectiveness of immunization and its favourable cost-benefit ratio compared to other health interventions, it can still be difficult for public health to gain approval for new or expanded programs. The reasons lie in the competing priorities for health dollars. The objectives of health and social service systems are to improve the health and well-being of populations, to reduce social and health inequalities and to respond to the needs of the population by providing accessible, ongoing and high-quality care. In addition, the needs of special populations must be considered.

One of the big challenges in health budgeting is adapting to the new demographic, epidemiological and technical realities. The population is aging rapidly, with the proportion of people > 65 years going from about 13% today to 27% by 2031; the number of people 80+ will increase threefold. Another challenge is dealing with inequities in the social determinants of health. A poor person has a life expectancy that is 6 years less than the general population, and that person is more likely to have serious disease. Poor children are more likely to have physical and psychosocial problems. Cardiovascular diseases, respiratory diseases and cancers cause the greatest number of early deaths. Other problems that health must deal with include social issues in youth such as depression and suicide, emerging and re-emerging infectious diseases and so on.

To accommodate these many issues, the Quebec health budget needs to increase 4.8%/year until 2020, but that growth will be harder and harder to reconcile with the general government budget, which will increase by only 3%/year. Thus, health science and finding the means to explain that science to decision makers are more important than ever before. Program evaluation is critical, and proposals must include data on the systems that will be used to audit a program and assess whether goals are being met. Economic studies often help orient decision making; it can be very difficult for decision makers to compare the wide variety of health programs and

interventions competing for dollars. With immunization, the public and provider acceptability of the proposed program is important. The actions of other jurisdictions can influence decisions. Risk perception and population expectations are also considered.

Public health must continually remind both the public and decision makers about the importance of immunization – give "booster doses" to prompt the population memory of diseases such as polio and their consequences.

Immunization programmers need to take advantage of any opportunities that arises, even crises such as SARS and bioterrorism, to rekindle public and political interest.

Question Period

A number of suggestions were offered for increasing public knowledge about immunization and "immunizing" them against the tactics used by anti-vaccinators: hiring investigative reporters to question the pseudo-science (but it must be remembered that reporters will set their own agenda), begin immunization education at an early age in schools (unfortunately, science education is increasingly minimal) and strengthening the link between physicians and public health (given that family physicians are a primary and trusted source of information about immunization). It was further suggested that a vaccine compensation fund would increase public confidence in vaccine safety.

Ask The Experts: Panel Discussion

Drs. Bryce Larke, Monika Naus, Shelley Rechner, David Scheifele and Theresa Tam and Ms. Agnes Honish formed an expert panel to respond to questions submitted by conference participants.

1. *Some clinicians recommend a wider use of pneumococcal vaccinations. Is there any reason to support pneumococcal vaccination in well adults in health care roles, even if they would pay for it themselves? Is the burden of disease higher for health care workers? Is there any concern about using PPV-23 in healthy adults?*

   There is room for wider use of pneumococcal vaccine in adults, especially those with chronic conditions. At least 20% of adults 50 to 65 years of age have a condition for which influenza and pneumococcal vaccines are indicated, but the ability to deliver is quite limited and there is poor uptake. There is no specific reason to give it to health care workers; pneumococcal disease is not highly contagious. There is no safety issue in giving the vaccine to a healthy adult; however, polysaccharides do not induce immune memory, so there may be a danger that the recipient believes himself or herself to be protected and thus not seek pneumococcal vaccination if they do develop a chronic disease. None of the panel members was aware of any practice whereby laboratorians who handle specimens that might contain this organism were vaccinated, as biosafety procedures should be sufficient to prevent the risk of primary infections.

2. *Regarding immunization registries:*

   a) *Who will be responsible for data entry? School boards? Nurses? Other health care providers?*

   The jurisdictions would decide who should do the data entry. The best might be whoever gives the immunization. The goal would be that wherever a vaccination is given, it can be captured by a central registry. Most data entry is by clerical staff and sometimes public health nurses. It would be ideal if manual data entry could be eliminated altogether through the use of bar coding of vaccines, which would speed both data entry and accuracy.

   b) *Would it be better if all immunizations were administered by public health nurses?*

   Public health nurses are probably the best qualified to administer immunizations. They are also perhaps best positioned and educated for reporting coverage rates and adverse events. However, given the importance of using every opportunity to check immunization history and offer vaccination if necessary (e.g., during a visit to a family physician), it is important that immunization not be restricted to any one type of provider. In general, immunizations should be administered by providers prepared to do the job right. It might be valuable to have an education package leading to certification as a vaccine provider. The Canadian Nurses Coalition for Immunization has been advocating for certification for immunizers for some time, and many provinces and territories have an immunization certification program for public health nurses. This subject will be taken forward to the Professional Education Subcommittee of the NIS, which will hold its first meeting early in 2005.

   c) *Would vaccinees be able to have a password so they can guard access to their record? Could they decide who gets access?*

   The question presupposes that people will be able to access their own records, which is probably not operational in the near future, although it might be an area to address in talking about electronic health records in general. It should also be remembered that when information is collected for any health registry, there must be an informed consent process, part of which is identifying who has access and what use will be made of the data.

3. *The tuberculosis skin test is used regularly (q 2 to 4 years) for screening in special populations. Considering the characteristics of dendritic skin cells, should this test be reconsidered?*

   The tuberculosis skin test is meant to reveal prior sensitization to the tuberculosis bacterium. When it is injected into the skin, the dendritic cells then go out to look for tuberculosis proteins. Used in the small doses and at the recommended spacing in time, the purified protein derivative does not in itself serve to sensitize.

4. *When there is routine hepatitis B immunization in special populations, should we verify immune status/response? When is the ideal time? When is the result misleading? What are the current recommendations?*

   Recommendations for post-vaccination testing for specific groups are in the *Canadian Immunization Guide.* Infants born to carrier mothers should be tested for response 4 to 6 weeks after completion of the series. Immunocompromised individuals receive a special formulation of hepatitis B vaccine because of their weak immune response; they should be tested at the end of the series. It is the practice to test health care workers after the

completion of the series and is a policy in many settings to inform the management of status. The alternative is to check their immune status post-exposure. People whose antibody titres become low years after vaccination often have residual immunity and may have very good response.

5. *What should the adult immunization schedule look like? Canadian perspective? Workplace? Short vacation traveller?*

   There is a good chapter in the *Canadian Immunization Guide* on adult immunization. Recommended vaccines are Td or TdP, hepatitis B and influenza. Health care workers need to know their MMR status, as well as tuberculosis and hepatitis B. MMR is particularly important for immigrants and susceptible women of childbearing age. The latter group should also be tested for antibody if they have no history of chickenpox, because most will have had subclinical infection; varicella vaccine should be offered if not.

6. *Is NACI considering including susceptible women of childbearing age in the high-risk group for varicella vaccine given the increased risk of complications for the pregnant woman? Also, immigrants from tropical countries are more likely to be susceptible but often cannot afford the vaccine.*

   There is a NACI recommendation that susceptible women of childbearing age should be immunized. If a woman is inadvertently immunized during pregnancy, there is no recommendation for abortion, as the risk is theoretical but not proven. One of the manufacturers does maintain a pregnancy registry and has accumulated several hundreds of instances of inadvertent administration during pregnancy with no observed bad effects.

7. *Should pneumococcal conjugate vaccine be used in high-risk adults?*

   The current NACI recommendation is to use polysaccharide vaccine in that group. The conjugate vaccine has been designed specifically for the risks that exist in childhood, and there is a shift in serotypes in adults.

8. *Pneumococcal 23 valent vaccine does not confer lifelong immunity. Should boosters be given?*

   There is a gap in the recommendations on that question, given that NACI recommends that 65-year-olds warrant immunization with that vaccine but does not make reference to later re-immunization if the person lives into old age and has therefore outlived protection. More research is needed.

9. *In intramuscular (IM) vaccine administration, should aspiration be done or not?*

   The *Canadian Immunization Guide* recommends aspirating before IM injection. A recent literature search revealed that harm related to IM injection was usually the result of medications being injected IV when they were meant to be IM. An informal poll of nurses who immunize a lot identified that blood does come back into the plunger sometimes. The research will be published, and NACI will continue to recommend aspiration.

Concurrent Breakout Sessions: Summaries

13. First Nations Immunizations

Ms. Wanda White, Communicable Disease Consultant for the Northwest Territories (NWT) Department of Health and Social Services, reviewed the advantages and challenges for First Nations immunization in her territory. In over a million square kilometres, NWT has a population of under 42,000 (over half of which is aboriginal). Advantages for First Nations immunization in NWT are many and include access to service data for the total population, the identifiability of ethnicity, the fact that there is only one service provider for immunization, improvements in the availability of data, the restriction of immunization delivery to public health nurses (all certified), ease of communication, the involvement of community health representatives, and the generally high acceptance of vaccines (coverage rates are about 80%). Challenges include the variety of languages, the difficulty of reaching some families and communities, the lack of facilities for health care staff, the competition between acute care and public health, cold chain integrity and more. Three new public health clinics in 2005 will assist with surge capacity, and participation in CNCI and F/P/T committees is hoped to enhance programs and delivery in the North. Further improvements should be seen through the NIS.

Dr. Wadieh Yacoub, Medical Officer of Health and Director of Health Protection for the First Nations and Inuit Health Branch (FNIHB), described what happened when it was decided to discontinue vaccination with Bacille Calmette-Guérin (BCG) vaccine in First Nations populations, with particular reference to Alberta communities. In Alberta, BCG vaccination had already been in decline. FNIHB Alberta region and Alberta Health and Wellness decided to replace the BCG vaccination program with an expanded program of preschool tuberculosis surveillance and education. First, Health Directors and Nurses were engaged in discussions on the value of BCG, the benefits and risks of BCG, and the need for community education on TB risk and risk management. Then the tuberculosis risk (annual rate of infections) for each community was analysed. Educational activities were expanded to ensure that source cases were diagnosed early. Beginning April 1, 2004, BCG was discontinued in all communities except (4/44) those with 15/100,000 or more pulmonary smear positives per year plus a high BCG uptake. Enhanced preschool screening for tuberculosis is also ongoing.

Dr. Robert Carlin, a family physician in the Public Health Department of the Cree Territory of James Bay, reviewed the experience of implementing and maintaining vaccination programs in Eeyou Istchee (the Cree territories and communities of James Bay). Vaccinations in the region follow the *Protocole d'immunisation du Québec* and are delivered by nurses in the villages. All routine childhood vaccines recommended by NACI (including hepatitis B, conjugated pneumococcal and meningococcal vaccines) are given except for varicella. The BCG was given until 2004. Influenza vaccination is done following the provincial guidelines. Regional hospital admissions for pneumonia or flu are at a rate 4 times higher than in the province as a whole and clinical surveillance for influenza-like illness was implemented in 2003-2004. Influenza vaccine coverage is generally high amongst at-risk individuals but varies for other target populations. The

challenges in reaching this population are many, but a key challenge is not labelling every First Nation as vulnerable, as that may not reflect local reality.

14. Professional Education

Dr. Barbara Law of the Winnipeg Health Sciences Centre and University of Manitoba outlined the Canadian Residents Vaccine Training Program developed by CAIRE and administered by CPS with the assistance of a grant from GlaxoSmithKline. The first course was given in November 2002 and it has been given twice since then. The course is designed to facilitate trainees to become exemplary vaccine providers, to provide them with the skill sets needed to be vaccine advocates, to provide resources for continued self-learning and to foster interdisciplinary approaches and networking with health colleagues. Each year, 60 residents from paediatrics, family practice, community health and infectious diseases are invited to participate. It is intended that new course modules will be developed each year to define a core curriculum in vaccinology. The three courses given to date have been extremely successful.

Ms. Theresa Saunders of the David Thompson Health Region described a multiple injection video being used as an educational tool for inexperienced immunizers and a review and consistency check for experienced immunizers. The video is aimed at public health nurses, who now routinely administer Pentacel, meningococcal conjugate and pneumococcal conjugate to infants 2 to 6 months of age by separate injections during a single clinic visit. The purpose is to address the multiple injection issue and not to demonstrate how injections are administered. It includes best practice guidelines and demonstrations of three clinic visits (a 2-month-old, a 12-month-old and 4 to 6-year-olds). A workbook is included that contains pre-reading material, illustrations of multiple injections in various sites, a discussion guide, frequently asked questions, literature reviews and additional resources. The video and workbook have been shared with every member of CNCI, and in January 2005 a discussion will take place with PHAC to determine how this resource can be further shared. In the meantime, interested individuals can contact Elaine Sartison at Alberta Health and Wellness (elaine.sartison@gov.ab.ca.).

Ms. Carla Troy is the National Manager of PHAC's on-line continuing education program “Skills Enhancement for Health Surveillance”. This web-based program was developed in response to a survey that found that the skills to understand and use health information varied widely across the country. Four modules in French and English have been launched to date: Orientation to On-line Learning, Basic Epidemiological Concepts, Measurement of Health Status and Descriptive Epidemiologic Methods. Learners need only a standard Internet browser with any form of connection and a word processing tool. Each module offers written text and graphics, audio information, a bulletin board discussion and more. Each learner must do a pre-test and post-test, provide satisfactory responses and participate in all bulletin board activities. Over 600 people from across Canada have taken one or more modules to date. About half are public health nurses, with the rest being environmental health officers, dental hygienists, nutritionists, medical officers of health, researchers, evaluators, health educators, program managers and others. Further modules are planned, and evaluation is continuous. The program is offered free of charge.

15. The Impact of Inequity: When the Bottom Line Hits the Front-Line

Montreal paediatrician Dr. John Yaremko used the cases of three children to illustrate the medical, ethical and medico-legal implications of physicians not offering new, non-funded vaccines to parents. The cases involved infants who became severely ill from varicella, pneumococcus and meningococcus with the outcomes of death or long-term serious sequelae, and in one case with the physician being sued. In each case, physicians had opportunities to offer vaccine that would have prevented the illnesses and their consequences but did not, in large part because these vaccines were not yet publicly funded. Health professionals must stay well informed about new NACI-recommended vaccines, and these should be recommended and administered even if not government funded. Ethically, physicians cannot decide their patients' priorities for spending their money. The physician's role is to give medical information (about vaccines, diseases and the possible consequences of not vaccinating) and clear, firm recommendations and assure that vaccine is available.

Dr. Yann Cosma, a physician, a lawyer and a legal consultant to the Montreal Department of Public Health, further explored the legal responsibilities of physicians and nurses. The Code of Ethics for physicians in Quebec states that physicians have a duty to stay up to date in knowledge and skills, to promote health and well-being at the individual and collective level, and to respect life and the dignity and freedom of the person. Among the practical consequences of these dictates, physicians must offer the best advice for care, whether or not that care is publicly funded. Similarly, the nursing Code of Ethics in the province requires nurses to stay up to date, to act with respect toward clients and their families, and to give complete and accurate counselling. In addition, guidelines for vaccinators require that they give relevant information on the vaccines recommended, whether publicly funded or not. Thus, both nurses and physicians are ethically and professionally obligated to advise their clients about all recommended vaccines. For patients, although Canadian law does not guarantee the right to necessary medical care, some people with chronic diseases or disabilities may be legally entitled to certain vaccines, depending on their disease and the specific circumstances.

Dr. John Carsley, the Head of the Infectious Diseases Unit at the Montreal Public Health Department and Chief of the Infectious Diseases Division of the Public Health Department, McGill University Health Centre, put vaccination in the larger context of how prevention is or is not funded. The incongruencies between NACI recommendations and provincial/territorial programming are not unique. Ethical prevention measures work as they are publicized to work, are safe and are available to all who would benefit. Vaccines fit those criteria well. Secondary prevention measures tend to meet the three criteria of efficacy and safety less completely (e.g., false positives could lead to more dangerous procedures), yet they tend to be more available, at least on an individual level (e.g., in Quebec, until recently, breast cancer screening was not covered by provincial health insurance, but physicians routinely used “query fibrocystic disease” to enable women to have provincially covered mammograms). Immunizers need to ensure that in addition to sound science, vaccination programs are evaluated on the basis not just of their

direct costs, but also on the basis of the cost of not doing them. They need to be compared to other primary prevention measures. Because the most ethical efforts strive for the best health for the most people for the least price, public health must keep lobbying to reduce the time lag between the introduction of new vaccines and their public funding.

16. Peer-Reviewed Oral Presentations

Dr. Bernard Duval opened this session with an overview of the challenges in public health immunization research, including research in the areas of fundamental mechanisms for disease control, surveillance, interventions and program delivery. Vaccine research is conducted to develop new and effective vaccines, to gather evidence on the optimal uses of new vaccines and to evaluate current programs. Research is conducted by industry, academics and public health. In public health based research, even existing is a challenge. There is a need for a clear mandate from public health leadership, more specifically research-skilled researchers and a more supportive infrastructure, including funding and time. A second challenge is in producing results. More must be done to select appropriate research priorities and assure both quality of research and communication of results to decision makers. The third challenge is the solving of actual problems, such as relieving the crowded primary immunization schedule, optimizing current programs, gathering evidence for the optimal use of new vaccines and resolving delivery questions (e.g., actual coverage, acceptability of minor adverse events, etc.).

Ms. Karen Pielak described a British Columbia study that looked at the concurrent administration of meningococcal C conjugate and hepatitis B vaccines in pre-teens to compare the differences in local and systemic reactions between children having both injections in one arm and children having one injection in each arm. Schools were randomized for the “one-arm” group and the “both arms” group. When both arms were used, Neis Vac-C was given in the left arm and Recombivax HB in the right arm. Structured telephone interviews 48 to 96 hours after administration were conducted to ask about reactions, interference with school or other activities, the need for medical attention and parental time loss from work. Results from the 202 students in the “one-arm” group and the 188 in the “both arms” group indicated no significant differences between reactions or other outcomes in the two groups. The “both arms” group did have more moderate to severe tenderness, local redness and drowsiness. The Neis Vac-C tended to cause more reactions than the Recombivax; therefore, it is recommended that if two arms are used, the Neis Vac-C be given in the non-dominant arm. However, both vaccines can be administered in one arm without concern about an increase in local reactions.

Mr. Samara David reported on the results of enhanced surveillance for VAAEs in the Yukon after a Grade 9 TdIPV program was replaced with dTaP, with a dTaP catch-up for Grade 12 students. The surveillance was intended to determine whether students receiving dTaP 3 to 5 years after their last tetanus booster were at increased risk of severe VAAEs. Methods of surveillance included reporting by health care providers, a self-administered student questionnaire and telephone follow-up by public health for any students who reported any of the symptoms used to define severe VAAEs. In the students who completed the questionnaire, 58% had received their last tetanus booster 5 or more years previously, and 30% had received it 3 to 5 years previously.

Those in the latter group were significantly more likely to report pain at the injection site but less likely to report swelling, limitation of arm movement, headache, body ache or sore joints. There was no significant difference in reports of redness, decreased energy, fever, nausea, vomiting, diarrhea, severe VAAEs, symptom severity or symptom duration. The researchers concluded that there was no increased risk of severe VAAEs among students receiving dTaP 3 to 5 years after their last tetanus booster.

Dr. Patricia Hudson described a population-based survey of 2-year-old children in Montreal to identify vaccine coverage. In a random sample of 600 children, 505 parents completed either a telephone interview (n = 461) or a mailed questionnaire (n = 44) to identify socio-demographic characteristics, sources of health care and vaccine doses. For 84 children, records were validated with health care providers. Six per cent of the children were born outside Canada (17 different countries), and half of these arrived during the first year of life. Nearly half (45%) of the parent-respondents were born outside Canada (67 different countries). Overall, the study found very high rates of vaccination series initiation for all recommended vaccines; however, only half of the children had complete vaccinations for their age. The researchers also noted the importance of complete information and of the type of coverage measure used.

Dr. Geneviève Petit reviewed research on the scope, outcomes and barriers in the vaccination practices of nurses in Quebec. Eighteen experts reviewed consultation responses, identifying 35 vaccination practices in 12 categories. Eleven predicted outcomes were also identified and prioritized. In addition, 47 barriers to effective vaccination were identified. Overall the experts concluded that vaccination practices vary significantly and involve technical as well as interpersonal and community actions. The findings of this study will lead to the development of new intervention strategies.

Late Breakers

2004 National Immunization Coverage Survey of Routine Childhood Vaccines: Preliminary Results

Ms. Lisa Belzak

Program Monitoring and Evaluation Unit, IRID, PHAC

The National Immunization Coverage Survey (NICS) is conducted biennially to identify areas or populations with low coverage and to evaluate progress toward national immunization goals. From 1994-1998 the survey was mailed; in 2002 and 2004 a telephone survey was done. NICS will continue to be implemented biennially until immunization registries across the country are fully functional.

The telephone survey used a convenience sample of the parents or guardians of 2-, 7- and 17-year-olds. The respondents reported immunization history based either on an immunization

record or on recall. The following preliminary results are based only on the respondents who reported from a written record. Those reporting from recall will be part of the sample for knowledge, attitudes and beliefs but not coverage. The survey itself was based on that used in 2002, with the enhancements of a more comprehensive knowledge, attitudes and beliefs component, the addition of the four newly funded vaccines and the addition of the adolescent cohort. Validation will be done in early 2005 by comparing 10% of responses to the actual immunization records for those individuals (ethics approval and data agreements have been obtained).

Among 2-year-olds (*n* = 399), MMR coverage is 95% to 96%, close to the national goal of 97% and representing a slight increase in coverage since the 2002 survey. DPT, IPV and Hib coverage ranges from a low of 75% coverage for Hib to a high of 90% coverage for polio. Overall, there is a mean increase of 6.1% for these five antigens. The national goal is 95% coverage. For the new vaccines, varicella coverage is at 36%, pneumococcal conjugate at 11% and meningococcal conjugate at 32%.

Among 7-year-olds (*n* = 448), MMR coverage is 79% to 82%, showing an average increase of 5%. DTap, IPV, and Hib coverage ranged from a low of 68% for pertussis to a high of 81% for polio, for a mean increase of 6.1%.

Among 17-year-olds (*n* = 386), diphtheria coverage is 51%, tetanus is 66%, measles is 66%, hepatitis B is 61%, pertussis is 25% and meningococcal C conjugate is 33%.

Overall, although coverage has increased, some estimates fall short of national targets. A trend toward decreasing coverage with increasing age is observable, which could relate to the fact that 70% of the parents of 17-year-olds were able to locate their children's written record, compared to 88% and 82%, respectively, of the parents of 2- and 7-year-olds. The validation study will explore this issue further. An adult coverage survey is planned for March 2005.

Hepatitis B Virus Surface Antigen Co-administered with an Immunostimulatory Phosphorothioate Oligonucleotide Achieves Protective Antibody Levels More Quickly and with Fewer Doses than a Licensed Hepatitis B Vaccine

Dr. Scott Halperin

Dalhousie University and IWK Health Centre, Halifax

Universal immunization for hepatitis B is recommended in Canada and around the world, but current vaccines require three doses for adequate antibody response, which affects uptake.

Immunostimulatory-sequence (ISS) containing phosphorothioate-stabilized oligonucleotides are DNA sequences containing CpG motifs that stimulate immune response. They have multiple effects on the immune system, including induction of B-cell proliferation and immunoglobulin production, secretion of IFNα-β, IL-6, IL-12 and IL18, and IFNγ secretion from natural killer cells. The particular ISS studied here has increased the magnitude of antibody response against

surface antigen in animal models and was well tolerated immunogenically in healthy adults in a phase 1 trial.

A phase 2 clinical trial was conducted to compare the immune response and safety of hepatitis B vaccine (HBV) co-administered with ISS (HBV-ISS) with the response and safety of a licensed hepatitis B vaccine (Engerix B, or HBV-Eng) when administered to healthy adults. The study design was a randomized, double-blind, placebo-controlled trial at two Canadian sites. The sample was 99 healthy adult volunteers (65% female) aged 18 to 28 (mean 22.6) with no history of hepatitis B infection or immunization and who were seronegative for antibody to HBsAg, anti-HBs and anti-HBc at study entry. They were randomly allocated to receive either HBV-ISS (0 and 8 weeks with "placebo" meningococcal vaccine at 24 weeks, with the latter chosen to give benefit for every injection) or HBV-Eng (0, 8 and 24 weeks).

Results included five serious adverse events reported during the study, but none were related to immunization. There were no clinically significant changes noted in any of the laboratory safety measures, including antinuclear antibodies or anti-DNA antibodies. Mild injection tenderness was more common after HBV-ISS than after HBV-Eng, and there were no differences between the two vaccines in systemic adverse events. In general, HBV-ISS was found to be safe and well tolerated, and there were no increases in adverse events after the second dose compared to the first dose. In terms of immunogenicity, the HBV-ISS was associated with significantly increased and more rapid antibody responses to HBsAg. It achieved protective levels more quickly and after fewer doses than the HBV-Eng, and protective levels were sustained at least 1 year post-immunization.

Pneumococcal Conjugate Vaccine: 4, 3 or 2 Doses?

Ms. Adrienne Morrow

Université Laval

PCV7 was licensed in the United States in February 2000, and the U.S. Advisory Committee on Immunization Practices (ACIP) recommended a four-dose schedule. When a shortage began in August 2001, ACIP recommended deferring the vaccination of healthy children > 24 months. In December of that year a three- or two-dose schedule was recommended. After the shortage was resolved in 2004, the four-dose schedule was reinstated. CDC took the opportunity to study the effects of the different schedules. What they found was that a one-dose schedule was not very effective, schedules of two or more doses provided over 90% protection, and there was no significant difference for three- or four-dose schedules.

Given those findings, the Quebec National Public Health Institute decided to compare the costs and benefits of PCV7 immunization schedules that differed in number and dose. A simulation model was developed from the perspective of an immunocompetent child. The schedules compared were two doses at 2 and 4 months; three doses at 2, 4 and 6 months; three doses at 2, 4 and 12 months; and four doses at 2, 4, 6 and 12 months. Age-specific effectiveness rates from 2 months to 9 years were determined by experts based on the Kaiser-Permanente trial and the

CDC case-control study, with waning immunity calculated at 3%/year. The cost of the vaccine was estimated at $70/dose.

The results indicated little difference in the number of cases of invasive disease prevented, but the difference in cost was significant. The most effective option is the four-dose schedule, but it is also the most expensive, with a cost of $141,000/case of disease prevented. The least effective option is the two-dose schedule, for which the cost is $71,000/case prevented. The three-dose schedule at 2, 4 and 12 months represented a cost of $103,000/case prevented. Given that the four-dose schedule would prevent just one more case/100,000 people, at a total cost of $12 million, the four-dose schedule would be difficult to justify.

In the United Kingdom, a high rate of vaccine failure was recently observed in children who did not get a booster. This failure was not noted in Canada, where a 2-year booster is given. Thus, the study probably underestimated the benefits of a booster. The study did not consider variations in vaccination coverage or the effect of her immunity. Serotype replacement was not considered, and non-invasive outcomes were not considered. Nonetheless, it was concluded that a three-dose schedule at 2, 4 and 12 months is the most attractive option – significantly increasing protection over a two-dose schedule while costing much less than a four-dose schedule. A two, four, 12 dose schedule was implemented in Quebec in November 2004.

Safety and Immunogenicity of Quadrivalent Meningococcal Diphtheria Conjugate Vaccine Given to Adolescents Concurrently or Separately with Tetanus-Diphtheria Vaccine

Dr. Mark Blatter

Primary Physicians Research, Pittsburgh

Meningococcal disease is the most common cause of bacterial meningitis, which can cause outbreaks and epidemics and strikes previously healthy individuals. It is difficult to diagnose, so the mortality and morbidity rates are high. Although Canadian adolescents are routinely immunized with monovalent meningococcal C vaccine, the continually shifting serotypes mean that about 40% of the disease is occurring in serogroups not protected against.

A multi-centre, double-blind, active, comparator controlled, randomized study was done to compare the tetanus and diphtheria toxoid booster responses in healthy adolescents receiving a quadrivalent meningococcal diphtheria conjugate vaccine (MCV-4) concomitantly with Td or placebo plus Td and to compare the antibody responses against serogroups A, C, Y and W-135 in healthy adolescents receiving MCV-4 concomitantly with Td or 28 days after Td. A total of 1,021 adolescents aged 10 to 17 years were enrolled and randomly assigned to receive either MCV-4 plus Td on Day 0 and placebo on Day 28, or placebo plus Td on Day 0 and MCV-4 on Day 28.

Immediate reactions were assessed during the 30 minutes after each vaccination, and solicited systemic and local reactions were recorded at 7 days. Unsolicited adverse events and serious events were recorded throughout the study. The majority of local and systemic reactions were

mild and resolved within 2 to 3 days. The majority of adverse events were not serious and were not related to vaccination. Three participants reported one or more serious adverse events, but none of these was related to the vaccine. Both local reactions and systemic reactions were reported in a similar number of participants in both groups.

Antibody responses to diphtheria, as measured by geometric mean titres, were augmented when Td was administered concomitantly with MCV-4. Similarly, antibody responses to meningococcal serogroups C, Y and W-135 were significantly augmented when the two vaccines were administered concomitantly.

In conclusion, concomitant administration is well tolerated and can increase response.

Question Period

It was noted that although the preliminary results of the National Immunization Coverage Survey showed a slight increase in coverage, the increases were usually within the estimated margin of error; therefore, the data may be showing no gains at all. The results indicate the importance of having immunization registries. In response to a question about the two-dose schedule for HBV-ISS, Dr. Halperin explained that it is the interval between the doses that is critical in terms of optimal immune response. For PCV7, it was noted that despite the shortage in the United States, there was no dramatic increase in pneumococcal disease, which indicates good herd immunity, possibly making the three-dose schedule even more safe.

Winners of the Poster and Oral Presentations
(Scientific Highlights)

Dr. David Scheifele, Chair of the Scientific Planning Committee for this conference and a member of CAIRE, announced the winners of the poster and oral presentations and thanked the 10 CAIRE judges who did the scoring. The best poster in bacterial diseases and vaccines was "Characterization of *Haemophilus influenzae* species isolated in Canada between 1993 and 2003", by M. Sill, D. Law, J. Martin, K. Bernard and R. Tsang. The best poster in viral diseases and vaccines was "Pro-MV is a novel intranasal proteosome-based measles vaccine that induces both systemic and mucosal humoral immunity", by S. Chabot, D. Bhavnani, A. Brewer, C. Rodeheffer, D. Burt and B. Ward. The best poster in public health practice was "Validation of vaccination and population files in three Quebec regions", by M. Guay, N. Boulianne, S. Menard, A. Clouatre, P. Clemont, et al. The winner of the oral presentations was "Canadian children hospitalized for influenza at IMPact centres 2003–2004", by D. Moore, W. Vaudry, D. Scheifele, S. Halperin, et al.

Closing Remarks

Dr. Monika Naus
Chair, NACI

The 4 days of this conference gave the over 900 participants the opportunity to meet with colleagues from around the country to share information that will bring immunizers and public health closer to that ever elusive goal of best practice. It was the first Canadian Immunization Conference to have been graced by opening remarks from a federal minister of health, reflecting the increasing importance and recognition of immunization in the political sphere. It was also the first Canadian Immunization Conference held under the auspices of the newly created PHAC.

The many participants who also attended the 2002 Canadian Immunization Conference will recall that NIS was still just a gleam in the eyes of Drs. King and Hammond. The prospects for funding did not appear promising, especially when the Senior Director General of Health Canada's Population and Public Health Branch reminded everyone that health is a provincial/territorial responsibility. It sounded like a funeral knell, but what happened instead was a healthy birth, graphically illustrated in the maps of Canada Dr. King presented this week showing the accomplishments in new immunization programming. Thanks to efforts at the federal, provincial and territorial level and to the significant federal funding commitment, the NIS has shown great progress.

Based on participant feedback after the last Canadian Immunization Conference, this conference increased the science content. There have been presentations on immunology, new vaccines, immunization schedules, epidemiology, vaccine safety and much more. Speakers and participants have come from a breadth of backgrounds, informing the discussions and presentations with a range of perspectives – physicians, nurses, industry and many others. In particular, the higher profile of industry in this conference represents the ongoing collaboration that is working to solve thorny issues of vaccine supply. Several presentations have offered practical advice for delivery.

The Seventh Canadian Immunization Conference will be held in Winnipeg, December 3-6, 2006. Plan to participate. The future of immunization programming sits squarely on our shoulders, but science is not enough. We must develop the skills of our health promotion partners. We must build on successes and borrow from lessons learned in other health arenas. We must make visible the diseases that immunization prevents. We must carry forward the enthusiasm and commitment from this conference and use that spark to kindle similar enthusiasm in others.