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Vaccines, Bird Flu and the Media

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This topical symposium was held November 17th, 2006 in Ballroom B, New Residence Hall, McGill University, 3625 Avenue du Parc. The half-day event was organized to launch Immunology Montreal, a new collaborative venture between three Universities, namely McGill University, University of Montreal and INRS-Institut Armand Frappier (University of Quebec) based in the greater Montreal area.

The objective of the symposium was to provide important timely information about vaccines, and the strategies used to make effective vaccines with limited side effects (adverse events). Information was provided about just how important vaccinations are to our health and well being. The focus then turned to influenza and information was presented about the 1918 Pandemic in Montreal from the perspective of what impact it had on the city at the time and the measures taken then with the objective of seeing if we could take any lessons from the experience. Information was presented about where we stand at present with the current vaccine / anti-viral therapies and the challenges ahead to prevent a future pandemic. Finally issues about informed media coverage and the role of the media in disseminating such information were discussed. This successful symposium generated much fruitful discussions, and we hope that the seeds for future research on these topics were sown which will benefit in the future the health of all Canadians. There was coverage of the Symposium reported by the local press (The Montreal Gazette, Journal de Montréal) and indeed the Gazette piece was picked up by the Vancouver Sun as being of interest to their readership.

The participants (~120) included trainees (CEGEP, University undergraduate, graduate students and post-doctoral fellows), university staff, including clinicians, as well as interested citizens primarily from the greater Montreal area.

Overview of Symposium

Dr. Emil Skamene (*McGill University, Montreal*), the former President of the International Congress of Immunology held in 2004 in Montreal, from which the seed funds for the establishment of *Immunology Montreal* were derived, provided background information about this new organization and the plans to inform the community about topical issues in Immunology by having sessions on topics of interest to the community such as this in the future.

Dr Alain Beaudet (*Montreal*) the Chairman, Board of Directors President and CEO of the Fonds de la recherche en santé du Québec (FRSQ), the primary provincial funding agency for medical research, **outlined how important Immunology research is and how widely it impacts on many disciplines**. Approximately 29% of all of their funds provide infrastructure and human resources support for topics in Immunology and Infectious Diseases. He illustrated how important such research is by discussing the impact that *Clostridium difficile* infections continue to have on our community. Dr Beaudet is strongly in favor of organizations such as *Immunology Montreal* that bring together people from the major greater Montreal area Universities that have shared interests in Immunology.

Strategies to improve vaccines

Dr. Brian Ward (*McGill University, Montreal*) **presented an overview of the human immune system** and explained how knowledge of this has led to the current **strategies being taken to elicit appropriate immune responses to respiratory viruses**. Dr. Ward discussed the Immune "tool box" used to defend ourselves against infectious diseases, specifically the major components of the innate and adaptive immune responses. Whereas there is much known about the role of antibodies in blocking various aspects of influenza infections, much less is known about the role of T-lymphocytes in helping the B-cells or acting as cytotoxic cells to kill the virally infected

cells. He suggested that a balanced T-cell response is required for an effective anti-viral response. At present even less is known about the role of the innate response to viruses such as influenza and it is an area of much current research. By better understanding the correlates of immunity to an infection such as influenza, more effective vaccines can be developed. At present the vaccines available are not as optimized to take advantage of all of the aspects of the immune system as they could be and thus additional approaches are required. He closed on an optimistic note that there is an army of researchers working on this and this bodes well for an effective vaccine against influenza in the future.

Dr. Risini Weeratna (*Coley Pharmaceuticals, Ottawa*) **discussed Toll-Like Receptor 9 Agonists, specifically CpG DNA as Vaccine Adjuvants.** She presented information about how adjuvants are an important component of any vaccine as they help boost the immune response to make it more effective. As well a real advantage of using adjuvants she pointed out is that smaller amounts of the antigen(s) are required which will not only make it possible to vaccinate more people, but also help to keep the costs down. Toll-like receptors (TLR) play an important role in the innate immune response and are capable of activating the innate immune system through binding to a wide array of unique microbial products. The TLR receptors recognize structures that are conserved among pathogens yet not present on cells of our bodies. Ten different TLR have been identified in humans. One such TLR receptor, TLR9 binds bacterial DNA through recognition of specific nucleotide sequences called CpG motifs which consists of cytosine and guanine dinucleotides in a specific base context. CpG motifs are present at the expected frequency in bacterial cells but are present in very few numbers in our cells. Even when they are present in our cell, often the cytosine is methylated so that it cannot activate the innate immune system through binding to TLR9. By including synthetic DNA containing CpG motifs in vaccines, it is possible to improve antigen presentation, and antigen specific antibody and cell mediated immune responses to both injectable as well as mucosal vaccines. This is particularly important in disease such as influenza where mucosal immune responses in the lung would be key to preventing infection and this could be achieved by adding adjuvants such as CpG DNA into vaccines that would be delivered directly into the respiratory tract such as in the form of nasal sprays. CpG DNA as an adjuvant even works well in the very young, and can help overcome vaccine unresponsiveness even in immune compromised individuals. Dr. Weeratna showed clinical data where individuals infected with HIV who would be immune compromised due to their disease were capable of mounting a significantly stronger immune response against hepatitis B virus when CpG DNA was added to the standard vaccine. Furthermore, individuals receiving CpG DNA with their vaccines had longer lasting immunity against hepatitis B than individuals receiving standard vaccine. Similar data were shown when healthy individuals were vaccinated against hepatitis B virus or anthrax with addition of CpG to standard vaccines. CpG was well tolerated in the clinic with limited side effects. Clinical trials using this approach are being conducted for other pathogens as well such as malaria, Anthrax etc. To date the adjuvant is not approved for general public use, but there is hope that regulatory bodies will approve it as it appears to be beneficial from a number of perspectives.

Vaccines – Real and Alleged Adverse Events

The real and alleged adverse events associated with vaccination were discussed by Dr. Barbara J Law (Ottawa). That vaccinations work has been supported by much research. However, Dr. Law said that there is an apparent perception by the general population that there may be safety concerns, but such concerns are often unfounded. This fear of vaccination can have a real impact on the spread of infectious diseases. When the population at large avoids vaccination because of preconceived notions there is often a resurgence of the disease in question. Dr. Law discussed some notable instances such as with Whooping Cough where although there may be rare side effects associated with this vaccine, the burden of the disease without vaccination to the population at large is enormous. Additionally not only do vaccines save lives but they can also save on health care dollars. The opposition to vaccines continues to be a real problem to the health care community and new solutions are required.

Unfortunately as Dr. Law pointed out, vaccines are not 100% effective and thus the small percentage that is not “protected” can perpetuate non-compliance. The population that avoids vaccination for a variety of reasons varies over time. When the percentage of the populations that is non-compliant increases to a critical level there is often an outbreak of the disease with loss of life. When this occurs there is resumption in the acceptance of vaccinations as being an important way to protect people from disease and thus there appears to be a cycle of acceptance/rejection/acceptance. Dr. Law discussed the fact that vaccinations (materials, protocols) are always being improved and are constantly being scrutinized for benefit versus associated adverse events. Of the rare adverse events associated with vaccines, the most common are associated with local reactions at the site of injection that occur even with the placebo. The more serious adverse events according to Dr. Law include hypersensitivity to a component of the vaccine, or mild symptoms of the disease being vaccinated against, the latter particularly associated with the live attenuated vaccines (i.e. measles, mumps, rubella, varicella, BCG). In individuals who are immunosuppressed vaccines can cause more serious and at times even life threatening disease. Surveillance data is now being accumulated at a number of sources to document the safety, efficacy of

vaccines. Unfortunately there are limitations to many of the studies on vaccines, in that often there is an absence of an appropriate control group. There can also be a reporting bias, incomplete information, underreporting and in some cases insufficient numbers. The types of research needed to assess vaccine safety are well designed population-based epidemiological studies, ecological studies as well as rigorous case studies. Appropriate peer reviews, as well as systematic reviews of these studies are critical. According to Dr. Law, there is also a need to better educate the population about vaccines. Several diseases that occur fairly commonly in the population for which the cause is unknown (such as inflammatory bowel disease, autism etc.), are “said” by the anti-vaccine lobby to be induced by vaccines. However there is no hard evidence to show this, but such beliefs exist in the population at large and these concepts are not only hard to disprove, but it is also hard to get out the data disproving these putative associations to the population at large who can benefit from vaccines. Dr. Law discussed how it is important to recognize the difference between facts and beliefs when thinking about real and alleged adverse events associated with vaccination. Overall the message that needs to get out is that scientists take these ideas seriously and are both interested in improving vaccines and in limiting any side effects.

Influenza pandemic

Heather MacDougall (Waterloo) a medical historian focused her talk on the 1918 Flu Pandemic in Montreal with the idea that we must not forget the lessons learned from the past, as they can certainly impact on the future. In 1918 Montreal was much smaller geographically with a population of ~618,000, with the ethnic distribution predominantly Francophone and Anglophone with ~5-7% Jewish, Italian or Chinese (as the major groups). The mayor at the time, Médéric Martin headed up a commission-style government that had difficulty controlling their finances. The provincial government in February 1918 placed the municipal management under an administrative commission in order to control the deficit. This had an impact on the Flu epidemic that took place in the fall of that year. Another predominant feature at that time was that many of the residents were involved in the war efforts.

The sequence of events of the pandemic in 1918 in Montreal were: first case was in the Royal Engineers' Camp Saint-Jean, which then spread to students at nearby Victoriaville College in August. From the information that Dr. MacDougall gleaned from *Le Devoir*, on Sept 26th Camp Saint-Jean had 400 cases of Influenza and was placed under quarantine the following day. Many of the patients were sent to the Montreal General Hospital or the Royal Victoria Hospital. On Oct. 1st the *Bureau d'hygiène* began an official recording of cases and deaths. The major epidemic occurred over the period of Oct 15th to the 27th with ~900-2000 new cases daily and with 70-200 deaths daily. Overall according to the available statistics there were 17,252 cases and 3,028 deaths caused by the Influenza virus in Montreal from Oct 1st to Nov 1918.

Measures taken to stem the infection were very much ad hoc and relied heavily upon volunteers. The *Bureau d'hygiène* headed by Dr. S. Boucher had a staff of 157 which was clearly insufficient to deal with the numbers of cases and deaths involved. Cars and drivers were commandeered to take medical staff to visit the sick at home. Along with community leaders the decision was made to limit the numbers of people that congregated in any one place so schools, theatres, churches etc were closed for the duration of the outbreak. Because it was deemed an important measure to limit the spread of the disease the dead were buried in an expedited manner without the traditional funeral services. This according to Dr. MacDougall left a lasting memory. The medical community took an active role in the response with representatives from both McGill and Laval Universities playing key roles. Volunteers provided funds, food, fuel and clothing for the ill and their families and as well staffed emergency hospitals created in schools. By the end of the epidemic there were 14 hospitals functioning. Communications then were more limited than now, as the primary sources were the print media and the telephone. Dr. MacDougall pointed out that with power outages communications even today can be severely limited. At that time there were no effective vaccines, but measures of sanitation and the wearing of masks were encouraged in the Montreal area.

The primary lessons that can be learned from the 1918 experience, as Dr. MacDougall pointed out, are that (1) there should be a clear chain of command and those individuals in the community/government who are the front line should have the appropriate resources; (2) with world wide surveillance of influenza there should be advance warning but the media and other modes of communication should inform but not panic the population at large; (3) to limit the spread of disease everyone should learn to cough in their sleeves, not shake hands, and be more diligent about washing hands; (4) the scientific world will have a challenge to respond rapidly if an outbreak such as the Montreal epidemic in 1918 were to occur again and it will likely be necessary for the community to work together with the scientists/medical teams in harmony to limit the spread and protect as many as possible and not let egos, racism or turf wars occur.

Dr. Danuta Skowronski (Vancouver), a leading authority on influenza titled her talk “Why all the flap about avian influenza?” She presented an immuno-epidemiologic perspective on avian influenza and its

relationship to pandemics and their past and possible impacts. To set the stage for her talk Dr. Skowronski started with giving a primer on influenza (three types: A, B and C of which only influenza A triggers pandemics) and how the virus changes and adapts over time and periodically crosses the species barrier from birds to humans. The H (for hemagglutinin) and N (for neuraminidase) are surface proteins of the influenza virus in multiple forms that predominantly interact with the humoral immune response. Influenza viruses are further categorized as serotypes based on the H and N proteins (such as H5N1 or H3N2 etc). Influenza virus serotypes are their most diversified in wild waterfowl and periodically a serotype from birds can be newly introduced into humans, and, if able to transmit easily from person-to-person can trigger a pandemic. Spontaneous mutation, reassortment or recombination of virus components also leads to periodic pandemics which have occurred irregularly every 10-40 years for centuries, including three in the last century alone: 1918 (direct mutation and adaptation of an avian influenza virus to humans), 1957 and 1968 (triggered by reassortment between avian and human influenza viruses). Once introduced into humans, further specific changes in the hemagglutinin protein over time enable the virus to continue to evade the immune response year-after-year and trigger winter outbreaks. She pointed out that there are many different causes of illnesses collectively termed "flu" which are not at all related to influenza and she would like a concerted effort by all to name "influenza" when referring to illness caused by the influenza virus specifically. While the very young and the very old are classically most at risk of serious influenza complications (hospitalization/death) during seasonal influenza, a shift toward younger age groups is recognized as a pandemic signature with young adults at higher risk of influenza complications during pandemics. This was especially noted during the pandemic of 1918, but also occurred to a lesser extent in 1957 and 1968. Clearly, as she pointed out, further research into the immuno-epidemiologic explanation for pandemic patterns in disease burden needs to be undertaken to better understand the reasons and implications of this. Similarly more than 90% of cases and 95% of deaths in humans (in ten countries) associated with recent poultry outbreaks (in more than 50 countries) of the avian influenza H5N1 virus are in persons less than 40 years of age. The highest case fatality is in children and young adults and this is a disproportionately youthful pattern, even after adjusting for the population demographics of affected countries..

Dr. Skowronski also explained how current influenza vaccines are generated using eggs with one egg giving rise to enough vaccine for about one person. The technology as she pointed out is old and inefficient though effective, and does not have the capacity to react rapidly to a radical change in the H/N structure, should a pandemic occur. Improved technologies are needed. Governments in Canada (Federal, Provincial, Local) have begun to set up contingency plans, but one of the problems in modern society is the global travel and the rapid dissemination of disease. When someone gets infected with influenza they are typically infectious starting even before they exhibit symptoms. Thus this makes containment extremely difficult if virtually impossible. Underlying immunologic cross-protection, virus shedding and intrinsic transmissibility, hygiene, social distancing and interactions, population densities and urban versus rural structure etc are factors that will influence the spread of influenza. For instance, in 1918, Montreal experienced a rapid, intense outbreak over a very short time frame) whereas the 1918 experience in Winnipeg was quite different being more protracted and the "longer time course". While governments are awaiting vaccine, efforts will be made to draw out and delay the impact of a pandemic wave to buy time. Undoubtedly the amount of vaccine available to protect the population will be limited, especially in the beginning, and decisions will have to be made about whom to vaccinate first. The extent of underlying immunological protection will also vary with the serotype or strain causing a pandemic and whether there are shared components with previously circulating viruses that may confer some cross-protection, especially to older adults. This was seen during the 1957 and 1968 pandemics and also in 1976 with re-emergence of a previously circulating serotype against which persons 20 years of age and older had some pre-existing protection that dampened its overall impact. It may be necessary to review current pandemic vaccine priority groups in that context and incorporating broader ethical and immuno-epidemiologic perspectives than simply basing this on individual seasonal risk of dying from influenza. Currently the anti-viral drug oseltamivir which helps to control the symptoms and severity of the disease, is stock piled by the government but this may represent costly "insurance" that varies in its effectiveness based on time to presentation, viral load and with the ongoing risk of expiry and resistance. Other ways to protect the population and to add to the treatment options are needed. Governments have been sensitized to the possibility of a pandemic and are starting to make more research dollars available for studies to improve response capacity. The challenges are huge to the research community but if the necessary funds are made available, much can be learned in advance about influenza and the impact of interventions, including investigation during "seasonal" rehearsals, reviewing patterns of previous pandemics and by establishing empiric and epidemiologic studies of modern technologies now.

Veronique Morin (Montreal) former president of the Canadian Science Writers Association **discussed how knowledgeable reporters/journalists are about influenza and about their role and duty in the balanced dissemination of information.** She presented a dilemma that whereas the role of the media (with the focus on mainstream media) is important in engaging, informing and educating the public there is a flip side in that there should be a balance with appropriate reporting yet minimal sensationalization in order not to contribute to panic

in situations of crisis such as would occur with a pandemic. How journalists get their information is also key and depends on the transparency of the source and whether or not any “filtering” of information is occurring. In the case of a pandemic both the medical authorities and the politicians would potentially be the main source of information and unfortunately some people in power, according to Ms. Morin, believe that journalists should not be kept informed. She made the case that there should be a trust built with the media by such individuals in the name of public health and their right to know, especially in times of crisis and emergency measures. She cited the recent case of *Clostridium difficile* in our hospitals, where 2000 people had already died in Quebec before news of the outbreak was reported. The reasons why some in authority think that the public should not be informed vary, but regardless of the reason, the public does have the right to be informed.

In terms of a possible influenza pandemic, at present Canada is in the phase termed “preparedness”. What this means is that there is minimal press coverage and the topic could be viewed to be on an artificial respirator. Some health officials feel it is unwise to warn the public about an impending pandemic at this point in time until there is actual evidence that it is happening. Journalists have been known to “hype” stories and this is to be avoided. Unfortunately when there is a period of much news coverage and then the topic dies, the public is often left dangling, neither informed enough nor prepared appropriately. This according to Ms. Morin happens frequently in the main stream media, especially for complex scientific issues. In the case of a possible influenza pandemic, financial and political issues as well as scientific come into play. Some groups stand to profit from such a pandemic, as with the stockpiling of Tamiflu and the public have the right to know this.

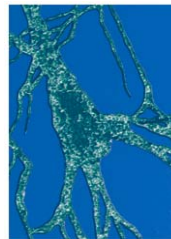
What Ms. Morin stressed was that responsible science journalism is essential. As she pointed out often these topics are assigned to general news reporters who don’t necessarily have the appropriate background in science. Only informed approaches are able to challenge the sources of information and get to the bottom of the story. She suggests that to the best way to prepare journalists are: 1) sensitize the news directors and editors to the importance of covering science and health topics; 2) develop better science education for journalists by making some science courses mandatory in journalism schools; and 3) provide a balanced ongoing but low key coverage whereby the public become acquainted with the concepts of a pandemic (probability, risk, disease/immune features etc). By so doing she hopes that increased and better Science journalism can help the media better fulfill its role to inform the public.

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