Canadian Bacterial Surveillance Network

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## BREAKING NEWS – Severe Acute Respiratory Syndrome (SARS)

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On March 13th a patient at a Toronto area hospital died of an unexplained respiratory illness. Initial investigation revealed that his mother had died of a similar illness the previous week after returning from Hong Kong. Epidemiological investigations rapidly identified six other cases of this illness, termed severe acute respiratory syndrome (SARS), all of whom had direct contact with the index case or other related cases. Of the eight cases, six were family members, two of whom had traveled together to Hong Kong. The other two cases involved a family doctor who had direct, unprotected exposure to three of the cases, and a patient on an adjacent stretcher in the ER to one of the cases before the outbreak was recognized and isolation precautions instituted. These cases were the beginning of the "Toronto SARS outbreak" and part of a country outbreak of pneumonia now known to be due to a new human coronavirus.

Initial cases of this illness were reported from the Guangdong province of China, and related outbreaks have been recognized in Beijing, Hong Kong, Singapore, Taiwan and Hanoi. Experience with these outbreaks suggests that the incubation time of this illness is 2-10 days. The illness usually begins with fever and malaise, with or without myalgias, headache, and chills. Although sore throat may be present, other upper respiratory symptoms are notably absent. The fever may improve transiently on day 2, but then becomes persistent and usually >38.5C. On day 4 to 5, some chest tightness and/or a mild cough may develop; by day 7, chest x-ray infiltrates are usually present, and shortness of breath appears. On admission, the white cell count is usually normal but may be low, lymphopenia is common (but a non-specific finding), LDH is often elevated, about 40% of cases have a mildly elevated CPK, and nearly 60% are somewhat hypocalcemic. Although the first two Canadian cases died, the overall mortality has been reported to range between 3 and 10%. Age and underlying illness are strong predictors of mortality; however, deaths have been reported in healthy adults under the age of 50 (including one to date in Toronto). Treatment is generally supportive; ribavirin and steroids have been used, but whether they are efficacious is unknown.

The most common means of transmission are droplet and/or contact spread. Although there has been no widespread community dissemination of this illness, transmission within household and health care settings has been substantial and very difficult to control. In particular, there has been explosive transmission from very ill patients in hospital to health care workers; contact with a single patient in Toronto with unrecognized disease over a three day period was associated with more than 20 cases of illness in health care providers and visitors. Strict isolation precautions has dramatically reduced the likelihood of spread in hospitals, but some transmission to health care workers in Toronto has occurred despite compliance with very strict precautions.

Evidence is accumulating that this disease is caused by a novel coronavirus, although some variability in transmissibility and pathogenicity remains unexplained, and some experts believe that a co-pathogen may be involved. In the meantime, public health efforts are being directed towards raising public awareness, identifying contacts and assessing and managing probable or suspected cases. All health care workers should be aware of SARS and should consider SARS in the diagnosis of any patient presenting with a compatible clinical illness if they have recently returned from an area where disease has been reported to occur (e.g Hong Kong) or have had direct contact with a known probable case. Suspected cases should be put into contact and airborne isolation and local public health authorities contacted immediately. Additional information about this outbreak is being reported daily, and this report will likely be out of date prior to its publication. Updated information will be available on the Health Canada website as well as through the WHO and CDC. These sources, as well as public health, should be consulted for up to date information on case definitions and approaches to management.

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## *Salmonella* Infections in the Return Traveler: Fewer and Fewer Treatment Options

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In Canada , salmonellosis remains an important cause of diarrheal illness usually resulting from ingestion of foods of animal origin contaminated with the *Salmonella* species[4,5]. About 40 cases of Typhoid fever, a life-threatening illness caused by *Salmonella enterica* serotype Typhi, are seen each year in Canada, primarily in travelers returning from the developing world where the disease is still quite common[6].

Prior to the 1980's antimicrobial resistance in *Salmonella* was quite rare. However, by the 1990s dissemination of strains of multi-drug resistant *S. typhi* in South America, the Indian subcontinent, southeast Asia and the United Kingdom resulted in ciprofloxacin becoming the treatment of choice for typhoid fever in adults and ceftriaxone the first line choice in children[7, 8,9, 10]. Similarly, in response to increasing numbers of drug resistant non-typhoidal *Salmonella* infections worldwide,

flouroquinolones in adults and ceftriaxone in children, became the drugs of choice for severe *Salmonella* enteritis and invasive *Salmonella* infections where the risk of infection with resistant strains was high[12-15]. More recently, flouroquinolones have also been approved for veterinary use in many countries, especially in the swine and poultry industries. Subsequently, numerous cases of quinolone and ceftriaxone resistant *Salmonella* have now been reported from various parts of the world[16-22, 29, 30-33].

*Salmonella* isolates with reduced susceptibility to the fluoroquinolones has increased in both humans and animals, especially in Europe, southeast Asia and the Indian subcontinent. Non-typhoidal *Salmonella* strains with reduced fluoroquinolone susceptibility isolated from humans in England and Wales increased from 0.3% to 2.1% between 1991 and 1994[18,19]. In a recent Belgian study, although all of 378 human strains of non-typhoidal *Salmonella* randomly collected during 1998 were susceptible to ciprofloxacin, 19% were resistant to nalidixic acid[23]. Of the 72 strains resistant to nalidixic acid, 31 were *Salmonella* enterica serotype Hadar of which most were also resistant to ampicillin, tetracycline and sulphamethoxazole, and had elevated ciprofloxacin $MIC_{50}$s (0.25 µg/ml) and $MIC_{90}$s (1 µg/ml). In Spain, nalidixic acid resistance in non-typhoidal *Salmonella* strains increased from <1% to 11% between 1985-1987 and 1995-1998[24]. In the United States however, only 21 of 4,008 (0.5%) *Salmonella* isolates collected during 1994 to 1995 were resistant to nalidixic acid[25] and quinolone resistance is rare even in multidrug resistant *S. typhimurium* DT104 strains [12,14]. From 1996-2000, 57 (0.8%) of 6970 non-typhoidal *Salmonella* isolates tested by the National Antimicrobial Resistance Monitoring System (NARMS) demonstrated decreased susceptibility to ciprofloxacin and 7 (0.1%) of these isolates had ciprofloxacin MICs of ≥4 µg/ml[16]. Although the latter were isolated from travelers returning from developing countries, 28 of the 50 isolates with ciprofloxacin MICs >0.25 µg/ml and <4 µg/ml were from individuals who had not traveled internationally in the week before the onset of illness.

Strains of *S. typhi* with decreased susceptibility to ciprofloxacin (MIC ≥125 µg/ml) increased to 23% in the U.K. in 1999 and were isolated from patients returning from travel in Asia; strains with decreased sensitivity to ciprofloxacin were also resistant to nalidixic acid[11]. At least 10 patients infected with strains with decreased susceptibility to ciprofloxacin did not respond to treatment with fluoroquinolone antimicrobials. In Mumbai, India nalidixic acid resistance in *S. typhi* increased from zero in 1990 to 82% in 2000[26]. In 1997, an outbreak of nalidixic acid-resistant *S. typhi* with decreased susceptibility to ciprofloxacin involved more then 6000 people in Tajikistan[27]. The epidemic strain had a pulsed-field gel electrophoresis profile indistinguishable from that of isolates of multidrug resistant Vi-phage type E1 from patients infected in India[28].

Although quinolones are frequently used as first-line therapy for *Salmonella* infections in adults, because of safety concerns, ceftriaxone is first choice in children. To date there has been one report of ceftriaxone resistance in *S. typhi* from an infected patient in Bangladesh[29]. In a review of 350 *S. typhi* isolates from 1996/1997 from patients in the United States (the vast majority of whom contracted their infection overseas), there were no ceftriaxone resistant isolates.

Isolates of non-typhoidal *Salmonella* exhibiting resistance to ceftriaxone and other third generation cephalosporin antibiotics were first noted in 1984 in Tunisia[30]. Up until the mid-1990s, ceftriaxone resistant isolates were also found in other countries in Northern Africa, the Caribbean island of Martinique, Europe (France, Spain, Italy, Latvia, Turkey) and Argentina. However in Argentina a large outbreak of ceftriaxone resistant strains occurred dating from May 1989. Although Buenos Aires was predominantly affected, 12/14 Argentinean provinces recorded ceftriaxone resistant isolates by the end of 1989. By 1991, 50-60% of *Salmonella* strains occurring in hospitalized children in Buenos Aires were ceftriaxone resistant[31]. A similar large outbreak of ceftriaxone resistant strains occurred in Latvia and other nearby countries from 1994 through 1998 [32]. More than 4000 documented cases of *Salmonella* gastroenteritis occurred among children in Latvia in this period, predominantly with ceftriaxone resistant strains.

Despite these events elsewhere in the world, ceftriaxone resistance in *Salmonella* isolates occurring in the United States and the United Kingdom was very rare through the mid 1990s. However, in the last 5 years, ceftriaxone resistance has been increasing. In the United Kingdom, just 0.03% of isolates were ceftriaxone resistant in 1998 and 0.08% in 1999. In the United States, rates of ceftriaxone resistance have risen significantly – 0.1% (1996), 0.4% (1997), 0.5% (1998), 1.9% (1999)[33]. Although in the United Kingdom most ceftriaxone resistant strains were acquired overseas, in the United States the majority of strains were domestically acquired. In a case report, Fey and colleagues[34] described ceftriaxone resistant *Salmonella* infection in a 12 year old boy who had not traveled overseas. Cattle, from the farm on which he lived, were infected with *Salmonella* isolates indistinguishable from his own. In a survey of turkey and beef sold in supermarkets in Washington DC, White and colleagues[35] found that 16% of 45 *Salmonella* isolates found in the products were ceftriaxone resistant. More recently, ceftriaxone resistant *S. newport* infections have risen dramatically in the United States [36]. In 1998 just 1% of *S. newport* isolates were ceftriaxone resistant compared to 26% in 2001. A case-control study found that ceftriaxone resistant *S. newport* infections were associated with eating ground beef[36]. It is noteworthy that there is cross-resistance between ceftriaxone and ceftiofur, an advanced generation cephalosporin used in animals that form part of the human food supply.

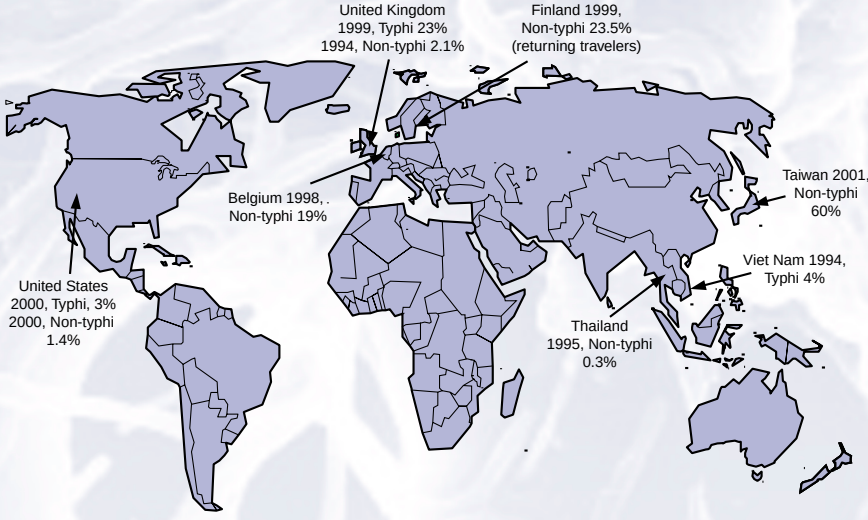



Figure. Prevalence of *Salmonella* with decreased susceptibility to ciprofloxacin (MIC >0.06 µg/ml).
Adapted from references: (19, 46, 47, 11, 21, 48)

Although case reports of infections caused by *Salmonella* with reduced susceptibility to the fluoroquinolones are rare, there is increasing evidence that such infections may be associated with a less than satisfactory outcome when treated with a fluoroquinolone[25,37-40]. This includes situations either where the original strain had reduced susceptibility to the fluoroquinolones[7,11,41] or resistance developed during therapy[19,38,39,42-44]. In most cases, isolates had ciprofloxacin MICs ≥0.125 µg/ml but ≤1 µg/ml and were associated with both systemic and enteric infections[7,11,19,38,40,41,44,45].

In Denmark in 1999, an outbreak of *S. typhimurium* DT104 causing enteric disease in 25 culture confirmed cases was reported in which 4/5 patients failed therapy and continued to have persistent diarrhea despite treatment with ciprofloxacin or fleroxacin; the strain was resistant to nalidixic acid and had reduced susceptibility to the fluoroquinolones[41]. Piddock et al[44] reported two cases where reduced susceptibility was evident during treatment and illness recurred. In one patient treated with ciprofloxacin (500 mg orally twice daily for 14 days) for a urinary tract infection due to *S. typhimurium* which recurred a month later, the ciprofloxacin MIC of the original isolate was 0.03 µg/ml and of the post therapy isolate was 2 µg/ml. In the second patient treated with 200 gm of ciprofloxacin twice daily intravenously for at least 10 days for a *S. typhimurium* infection of a hematoma arising from a ruptured aortic aneurysm, the ciprofloxacin MIC of the original isolate was 0.03 µg/ml, whereas the post-therapy isolates had MICs that ranged from 0.12 to 0.5 µg/ml[17].

In studies conducted in Viet Nam evaluating the effectiveness of short versus long course ofloxacin therapy for treatment of typhoid fever, the median time for clearance of fever was 156 hours for nalidixic-acid resistant strains compared with 84 hours for susceptible strains ($P < 0.001$)[7]. Furthermore, 6/18 (33%) of patients with nalidixic acid resistant strains required re-treatment compared with 1/132 (0.8%) infected with susceptible strains. In India, the recommended therapy for enteric fever is ciprofloxacin 750 mg twice daily for 7 days. However, since 1997 an increase in the number of patients failing ciprofloxacin monotherapy (defined as failure of patients to respond after 72 hours of monotherapy) has been reported[45].

These findings suggest that, although the clinical importance of the reduced fluoroquinolone susceptibility of *Salmonella* is anecdotal, it might be valuable for laboratories to be able to identify such isolates in patients that are failing clinically. In addition, there is the increasing possibility of fluoroquinolone-resistant strains being present in travelers returning from developing countries.

It is clear that extended-spectrum ß-lactamases (ESBL) or AmpC producing *Salmonella* isolates may have ceftriaxone MICs in the susceptible range, using current susceptibility breakpoints. Although no treatment failures associated with these enzymes in *Salmonella* have yet been clearly documented, there should be concern that treatment failures may occur (as has been observed with *Klebsiella* spp. and *E. coli*).

It is important for clinicians and microbiologists to be aware of the emergence of *Salmonella* strains that are resistant to commonly used antimicrobials. Physicians treating returning travelers, especially from developing countries must be aware of the possible risks of infections due to multidrug resistant strains of *Salmonella*.

The increased occurrence of drug resistant pathogens in foods of animal origin emphasizes the need for cooking foods thoroughly prior to consumption. Education of food handlers in the principles of safe food handling is an essential step towards reducing the incidence of food-borne disease resulting from cross-contamination during processing and preparation of foods.

*References available at microbiology.mtsinai.on.ca*

## West Nile Virus – not a foreign disease anymore

*Dr. Caitlin Pepperell, ID Resident*

The first human cases of West Nile virus (WNV) infection were reported in Canada in August 2002. These occurred in the context of a large outbreak in Southern Ontario, Quebec and most of the United States. Between August 1, 2002 and November 1, 2002 there were 247 cases of encephalitis reported to Toronto Public Health. In previous years, approximately 30 cases have been reported to Toronto Public Health during this time period. The 2002 epidemic of WNV is the largest Canadian outbreak of viral meningoencephalitis since the St. Louis Encephalitis epidemic of 1976. Elsewhere in North America, Europe and the Middle East, WNV has emerged as an important cause of seasonal urban meningoencephalitis outbreaks since the latter half of the 1990s. The clinical features of WNV encephalitis are not specific; initially, the infection may be diagnosed as bacterial sepsis, drug intoxication or another cause of febrile delirium. Later in the course of infection with WNV, the neurological features of the illness become more distinctive. Flaccid paralysis in combination with encephalitis is typical in severe cases. Anterior horn cell destruction, similar to that seen in poliomyelitis, was recently found to be the cause of the flaccid paralysis. Data on long term recovery of function and resolution of neurological deficits is limited. Clinicians involved in the Ontario outbreak of 2002 have noted prolonged deficits and significant disability among survivors of WNV infection. Diagnostic methods rely on the demonstration of specific antibody against the virus. The best screening tests for WNV infection are paired acute and convalescent serology samples for either total antibody (hemagglutination inhibition) or IgM/IgG enzyme-linked immunosorbent assay (ELISA). If a lumbar puncture is performed, cerebrospinal fluid (CSF) may be examined for the presence of WNV IgM. Currently available antigen or nucleic acid based techniques are not sensitive enough to be recommended for routine clinical use. Unfortunately, due to the close antigenic relationship between members of the flavivirus family (e.g. Dengue, St. Louis encephalitis), antibodies against these viruses may cause a false positive reaction on screening tests for West Nile virus infection. Plaque reduction neutralization is the gold standard assay for detecting specific antibody responses to West Nile virus infection and other flaviviruses. There is no specific treatment available for WNV infection. A clinical trial of interferon alpha 2b for the treatment of WNV encephalitis is currently underway in the United States. WNV enriched intravenous pooled immune globulin has also been used, but data on its efficacy is limited. Mosquito control is the cornerstone of WNV prevention. Most prevention programs prioritize larvicidal over adulticidal activities. Larvicidal activities involve the removal of standing water sources and instillation of larvicidal agents into mosquito breeding grounds. Mosquito adulticide programs involve spraying insecticide and are usually less acceptable to the public. West Nile virus is an important, emerging zoonosis in Canada. Preparations for this year's mosquito season are currently underway and clinicians should maintain a high index of suspicion for this disabling disease as the virus establishes itself in North America.

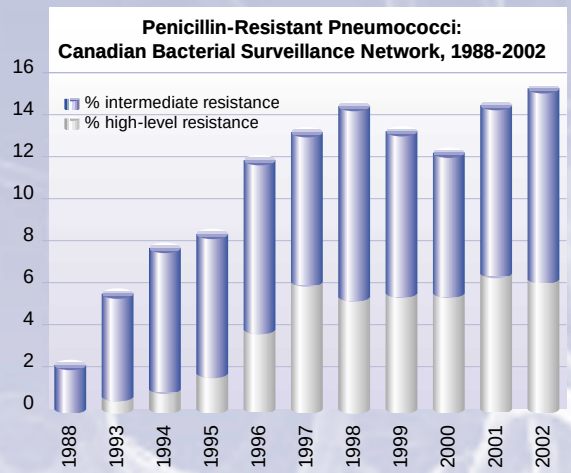
## Strep Throat Or Toxic Shock? Genes Matter In Response To Group A Strep

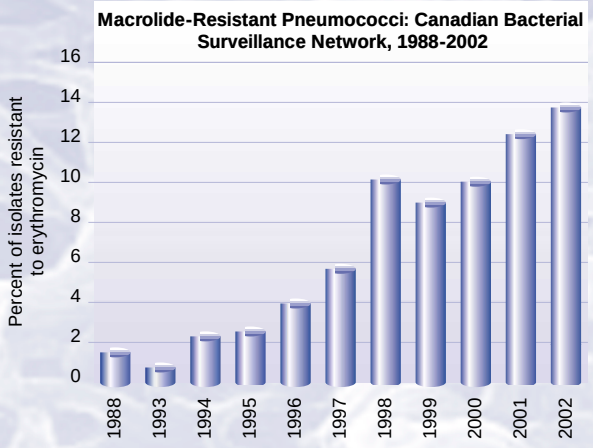
Group A streptococci causes a wide range of disease from mild infections, such as "strep throat", to life threatening illnesses like necrotizing fasciitis and streptococcal toxic shock syndrome. Why do some people walk away unscathed from Strep A infection while others succumb?

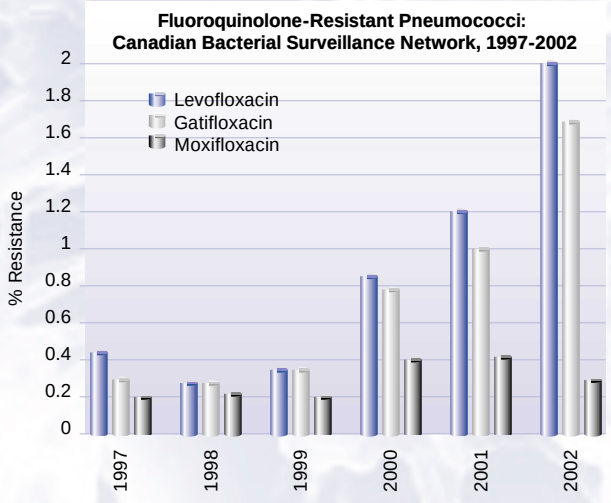
In the December issue of Nature Medicine, Malak Kotb and colleagues from the Ontario Group A Strep Study begin to answer this question. Early work suggested that a particular set of genes might have something to do with susceptibility to infection. These genes, called HLA-II genes, encode HLA-II proteins on the cell surface of cells of the immune system, such as antigen presenting cells (APCs). Group A streptococci secrete a number of toxins acting as superantigens. Superantigens bind to HLA class II proteins on APCs, and then to the variable ß-chain of receptors on T-cells. This interaction prompts bursts of cytokine production that can lead to septic shock, tissue damage and multi-organ failure. The authors hypothesized that different HLA-II proteins might interact differently with group A streptococcal superantigens, and that people with certain types of HLA-II genes might be predisposed to severe infections. The authors examined the HLA-II genes from 279 individuals with infections of varying severity and compared them to the HLA-II genes of 256 healthy individuals. Certain HLA-II gene variants were present more often in individuals with severe infection (necrotizing fasciitis and streptococcal toxic shock syndrome), while other variants were present more frequently in healthy individuals. The authors also found that people with either predisposing or protective HLA-II gene variants differed in their response to bacterial toxins. Particular HLA class II genes either protect from or predispose to streptococcal toxic shock and/or necrotizing fasciitis – the two most severe clinical manifestations of streptococcal disease. There are numerous previous reports of association between HLA variants and diseases such as multiple sclerosis, arthritis, and type 1 diabetes.

This study, however, adds to our understanding of how HLA haplotypes influence serious infections and present an opportunity for further study in animal models – mice can be engineered to express human HLA genes, and are also susceptible to infection by group A streptococci.

*Full article available at*
*http://microbiology.mtsinai.on.ca/ publications/articles/NatMed.pdf*

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