

# The Struggle Against Pandemic Influenza A (H1N1) 2009

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## التصدي لوباء انفلونزا 2009 (H1N1) الجائحة

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In the new millennium, the world has seen the emergence of three novel human respiratory viruses: SARS virus (a novel Corona virus) in 2003, Influenza A H5N1 ('Avian flu') in 2004 and in the past six months, a pandemic caused by a new strain: the Influenza A (H1N1) 2009 virus.<sup>1</sup> In sharp contrast to the SARS and Avian Influenza A H5N1 viruses which emerged from the Asian continent, the Influenza A (H1N1) 2009 virus emerged from North America and unlike the SARS and Avian Influenza A H5N1 viruses, which were never reported in Oman, the novel Influenza A (H1N1) 2009 virus has already been detected here in more than 2,500 patients.

Influenza viruses by nature are highly unpredictable and unstable.<sup>2</sup> They have the unique distinction of having a segmented genome which permits them to re-assort their genetic structure resulting in the evolution of new subtypes. This genetic restructuring occurs regularly in nature and at times provides the virus with the unusual capability to cause widespread disease in immunologically naïve populations and swiftly move across geographical borders to cause pandemics.

The 20<sup>th</sup> century saw three such pandemics; the first (Spanish flu) caused by influenza A (H1N1) killing between 20-50 million people.<sup>3</sup> The other two pandemics, in 1957 and 1968, were relatively milder, but still killed nearly one million.

There are several key epidemiological features that determine the occurrence of a pandemic influenza. According to Miller *et al.*<sup>4</sup> who recently analysed the "signature features" of the three previous influenza pandemics (A/H1N1 in 1918, A/H2N2 in 1957 and A/H3N2 in 1968) four

important factors emerge as key determinants: 1) occurrence of a shift in the virus subtype; 2) shifts of the highest death rates to younger populations; 3) successive pandemic waves, and 4) higher transmissibility than that of seasonal influenza.

While the world was grappling with H5N1 Avian flu "which had caused 442 cases and 262 deaths in 15 countries as of September 24<sup>th</sup> 2009",<sup>5</sup> and while the world was preparing for a pandemic that could emerge, another influenza virus made a dramatic appearance in Mexico in March 2009 in the form of a novel H1N1 subtype. Many of us were surprised when, instead of H5N1 acquiring mutations necessary for efficient person-to-person transmission, reports emerged from Mexico about a novel influenza virus that was killing young people. The novel Influenza A (H1N1) virus has the genetic structure resulting from re-assortment of genes from four influenza viruses: North American swine influenza, Asia/Europe swine influenza, human influenza and avian influenza (non H5). The virus has a unique genetic composition that has never been seen earlier. As a result of this, within a short period of six months the virus had spread to 189 countries, caused more than 414,000 confirmed cases (the number of cases reported actually understates the real number of cases) and at least 5,000 deaths.<sup>6</sup> In Oman as of the latest update, 2,681 people have been reported as infected with the A (H1N1) virus of which 153 cases required hospitalisation and 24 have died.

Most cases described during the three influenza pandemics of the 20<sup>th</sup> century and during seasonal influenza involved transient illness not requiring hospitalisation. Most deaths are described in the

very young or the elderly or those with underlying disease. The available information also indicates that, unlike seasonal influenza, the current H1N1 pandemic has primarily affected younger adults. This is in contrast to the fact that complications of seasonal influenza affect primarily the elderly or young children.

The reported clinical presentation of the novel Influenza A (H1N1) infection ranges broadly from mild uncomplicated infection to severe pneumonia that can result in death. The available data show that the clinical features of fever, cough and sore throat are similar to those of seasonal influenza. To date, the case fatality ratios (CFR) attributable to the current H1N1 pandemic has been estimated at around 0.4%, based on surveillance data from Mexico and mathematical modelling.<sup>7</sup> This CFR is higher than that of average seasonal influenza, but remains of the same order of magnitude. Whether this will change is unknown. The WHO Regional Office for the Eastern Mediterranean (EMRO) reported that 96 of the 14,739 laboratory-confirmed cases as of October 23, 2009 had been fatal.<sup>8</sup> Most of these deaths were related to respiratory failure resulting from severe pneumonia with multi-focal infiltrates and acute respiratory distress syndrome.

Unlike most seasonal influenza strains, this pandemic H1N1 2009 strain seems to invade the lower airway and alveoli, not just the upper airways, resulting in more severe illness.<sup>9,10</sup> The world's experience so far tells us that serious illness associated with this virus often manifests as acute lung injury resulting in overwhelming hypoxaemia. Advanced life-support technologies for prolonged periods are often required to save lives.

There are few data on risk factors, severe cases and deaths associated with the pandemic H1N1 influenza 2009. Analysis of available data suggests that the elderly may to some extent be protected from infection. There was underlying disease in at least half of the fatal cases (574 studied). Two risk factors seem of particular importance: pregnancy and metabolic condition (including obesity which has not been considered as risk factor in previous pandemics or seasonal influenza).<sup>11</sup>

The transmission is thought to occur in the same way as seasonal influenza which is mainly person-to-person transmission through coughing or sneezing of people infected with this virus. People may be infected by touching something

with influenza viruses on it and then touching their mouth or nose.

The recommended procedure for laboratory diagnosis of Influenza A (H1N1) 2009 virus infection is real-time reverse-transcriptase polymerase chain reaction (RT-PCR).<sup>12</sup> In Oman, this facility is only, at present, available at the Public Health Laboratory (PHL) Muscat, and at Sultan Qaboos University Hospital (SQUH), Muscat.

Two classes of anti-viral medication are available for the treatment and post-exposure chemoprophylaxis of seasonal human influenza: neuraminidase inhibitors (oseltamivir and zanamivir) and adamantanes (amantadine and rimantadine). However, the novel Influenza A (H1N1) 2009 virus is resistant to amantadine and rimantadine, but is sensitive to oseltamivir (Tamiflu) and zanamivir (Relenza).<sup>13</sup> Based on experience with other influenza viruses, treatment would be most effective if given within two days of symptom onset. The data show that the virus continues to remain susceptible to oseltamivir and zanamivir. The access to these drugs and their rational use are critical in mitigating the disease as well as prolonging the utility of the drugs by obviating the emergence of resistance.

Presently, a vigorous development process is underway to develop the pandemic vaccine. It is believed that manufacturers could produce 2.5 billion doses of pandemic vaccine in 12 months following receipt of the production strain and global demand can be met within 2-3 years. However, the supply of vaccine, at least during the first year of the pandemic, will be limited and not easily accessible to the vast majority of people living in developing countries. We must therefore identify vulnerable or at-risk groups as a first step. It is also important to note that no immunisation programme is 100% effective and, if therefore a sufficient number of cases are not prevented, we can expect more young critically ill patients to fill all tertiary-level intensive care beds. It is important to highlight here that fair access to the vaccine against the pandemic novel H1N1 influenza virus is an ethical issue involving justice for all. It is also a prerequisite for the success of the global pandemic strategy to safeguard global health.

Intensive public education for adopting cost-effective non-pharmaceutical interventions can yield substantial results.<sup>14</sup> Non-pharmaceutical

prevention through repeated hand washing and following cough/sneeze etiquettes can be easily employed at all levels in communities and prevent the spread of the disease. Isolation of cases and proper case management, including infection control, are equally important to cut down on the transmission of the disease.

National leadership is needed in all countries. A visible independent health care leadership, with executive powers across all jurisdictions and ultimately accountable to the highest office in the country, must be in place. Next, local leaders must be identified. All stakeholders should have clear communication with and rapid access to experts. We need leaders at all levels who will work together quickly and collaboratively to solve problems such as moving equipment and personnel from one area of a country to another as required without barriers imposed by licensing and hospital privileges.

Since 2003 when Influenza A (H1N1) 2009 emerged as a potential influenza pandemic, the national authorities in Oman have been engaged in strengthening their response efforts with assistance from World Health Organization. The National Influenza Pandemic Preparedness Plan has provided a valuable framework of action and, with minor modifications, was activated to launch an effective response to the current pandemic. The pandemic, however, is far from over, and deaths will unfortunately continue to occur. We should therefore plan for important increases in pandemic H1N1 2009 cases that manifest at the two ends of the spectrum of disease severity.

We must not underestimate a foe like pandemic H1N1 2009, especially now. This pandemic has already created chaos in communities worldwide. The virus's place of origin, the speed of its spread and the severity of the illness in otherwise healthy people could not be anticipated before the initial outbreaks, even by experts. In addition, containment, a first step in the control of an outbreak, has failed.

It would be naïve to extrapolate the impact of the 1918 pandemic to the current event because today effective tools are available including drugs, diagnostics and a high level of preparedness in place in many countries including such measures as infection control practices, case management facilities and mass media reach for public awareness and risk communication. Advances in technology are now swiftly translatable into tools.

While we still hope for the best, we need to act now to deal with the worst that pandemic H1N1 2009 may deliver. Doing so will save lives.

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# The Trend to Seek a Second Opinion Abroad amongst Cancer Patients in Oman Challenges and opportunities

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نزعة الحصول على رأي ثانٍ من الخارج  
في علاج مرضى السرطان في عُمان  
تحديات وفرص

اكرام برني

**A** 55 year-old man was diagnosed as having metastatic colon cancer following an endoscopic biopsy at my university hospital in Oman, and was referred to a medical oncologist. The patient, together with his son, travelled to an other asian country seeking a 'second-opinion.' There he was initially treated with a colonic stent, resulting in the perforation of the colon. He underwent emergency resection of the perforated segment, leading to intestinal obstruction. A second surgery was performed to relieve the obstruction, and combination chemotherapy (including the anti-angiogenic drug, bevacizumab) was started. During the first course of treatment, the patient developed urinary retention, was catheterised, and then went on to develop haematuria. He returned to Oman with severe haematuria, a prescription to continue the combination chemotherapy, and radiographic evidence of a bilateral pulmonary artery embolism.

Stories like this are not uncommon and are frequently encountered during routine medical practice in general, and in oncology practice in particular. What is not mentioned in the above story is the fact that the duration between the diagnosis of cancer in Oman and arriving at the hospital abroad was about 4 weeks, during which time the metastatic disease in the liver had increased considerably and the patient's performance status had declined. Inserting a stent was unnecessary

in a non-obstructing bowel, a procedure which ultimately led to two needless surgeries and a further delay in starting standard systemic treatment. The expensive anti-angiogenic drug was contra-indicated in a patient with two recent surgeries, and is definitely contra-indicated following a diagnosis of a pulmonary embolism. The patient spent the equivalent of 28,000 Omani riyals (US\$ 45,000) during his 4 week stay abroad. He regretted the decision made by his family members.

What is a second opinion? And why do patients, especially those with a diagnosis of cancer, seek one? What are the challenges that face both patients and health providers when a second opinion is sought? Indeed, is the desire to get a second opinion problematic and, if so, can the situation be improved?

Asking for a second opinion is understandable. When it comes to choice (be it selecting food in a restaurant, buying a car, or purchasing a new house) we all value the opinions of others, and sometimes we may even look for a third or fourth opinion. Seeking a second opinion is a way of making choices. However, it is not quite the same when one has received the diagnosis of a cancer. In such a situation, with the likelihood of extensive surgery, chemotherapy and/or radiotherapy, opinions should be sought to see if alternative forms of treatment or cure were available. From the point of view of the

oncologist, seeking a second opinion is desirable and, in some cases, obligatory. The vast majority of cases are straightforward, and treatment begins as soon as diagnosis and staging are known. In cases of less common cancers, borderline cases or cancers of unknown primary sites, practising doctors frequently invite a second opinion from their colleagues. Seeking a second opinion is a recognised practice in the specialty of oncology. However, the situation described in the above story is something commonly encountered in oncology-related practice in Oman: the seeking of a second opinion abroad before any treatment at home in Oman. A significant number of patients, especially from small towns, bypass the tertiary care/specialist hospitals available to them in bigger centres and immediately go abroad. Once overseas, they may not be provided with a second opinion, but instead are started on the first stage of treatment even when it is uncalled for. Patients invariably return home to continue the treatment. Although the off-shore clinics are very quick to commence 'treatment', valuable time, not to mention savings or borrowed money, is often lost in the making of travel arrangements.

The tendency to seek a second opinion abroad can endanger the patient's health. The clinical condition may not be fully known to the patient and/or his/her family members, and urgent clinical attention is sometimes delayed. Any delay in travel arrangements may lead to a progression of the disease; this in turn leads to an increased burden of disease and a decline in performance status, both conditions decreasing the chances of successful treatment and a subsequent cure. A decline in performance status by a single grade is an adverse prognostic factor in almost all cases of cancer, and for some, this decline may occur within just a few weeks. Furthermore, the patient's selection of country or medical centre is often not informed by prior knowledge of expertise, excellence in the field or familiarity with the type of cancer, but rather by geographical proximity, convenience of travel or simply by a verbal recommendation. Some patients are known to have arrived at centres in which they have received less than adequate treatment or been the victim of experimental/investigational treatment without their knowledge. In both cases, the chances of any subsequent standard treatment being effective are reduced. Sometimes patients end up in good centres where standard treatment

is offered or advised for straightforward cases, but there are complications as a result of travel-related delays. Additionally, cancer treatment overseas is seldom cheaper.

In order to influence the behaviour of persons seeking a second opinion abroad, one needs to study the mechanisms underlying this phenomenon. First, it is important to understand the motives and expectations of the patients. Second, in a society where decision-making in health care is often shared, it is important to consider the point of view of all the decision-makers involved. Patients do not always make their own decisions. They are often influenced by the care-givers/well-wishers who, in some cases, are the only ones involved in important decisions.

Although many patients with cancer seek second opinions, there is a dearth of literature on the subject. Only a few have looked at the phenomenon, even fewer have tried to assess its incidence and outcomes.<sup>1,2</sup> The actual incidence of seeking a second opinion is likely to differ from country to country, and amongst different groups of patients. With an increase in the knowledge of disease and improvements in communication, an increasing number of patients seek second opinions. For example, 56% of more than 1,500 cancer patients in the United States sought a second opinion in a single year.<sup>3</sup> The incidence in Oman is unknown. It would be useful to know how often a second opinion has impacted upon the course of treatment. In a survey done in Holland of 403 patients, the majority with breast cancer, the investigators found that in 84% of cases the advice given was comparable. Not everybody had a review of either histological or radiological diagnosis and when this occurred, a major change in treatment was observed in only 3% of patients and a change in prognosis in just 2%.<sup>4</sup>

Who are the people more likely to travel abroad to seek a second opinion before the first? Are they the well-informed, the well-read or the wealthy? There is insufficient information on this subject. However, a common observation is that the phenomenon transcends the boundaries of information and financial resources as much as it transcends national boundaries. For example, Kangas reported on the behavior of not-so-rich Yemeni patients with various diseases seeking biomedical treatment in other countries, and noted that their behaviour did not differ significantly from that of relatively well-

off Saudis.<sup>5</sup>

In the absence of published data concerning Omani patients, the motives for seeking second opinions before the first remain hypothetical. The motives may be intrinsic or extrinsic, or a combination of both.<sup>6</sup> Intrinsic motives could include: seeking reassurance and more certainty about the diagnosis; seeking a treatment other than the conventional one 'usually' offered to cancer patients; the desire to be treated in a different environment - perhaps to maintain 'confidentiality'; or the belief that 'paying more' will produce better treatment. Extrinsic motives are more varied. These could include: experiences from the patient's past; doubts about the health care services in the home country; market forces, such as dynamic advertisements by external health care organisations; social and societal pressures; or merely word of mouth information that a 'cure' is available elsewhere, and hence borrowing or spending large amounts of money might bring positive results. Common extrinsic motivators for seeking a second opinion may not be applicable in the case of Omani patients, since a 'first' opinion has not yet been sought. These may include: the lack of effective communication by and with the oncologist; dissatisfaction with the primary oncologist; seeking an opinion on a rare cancer; concern about the side-effects of a particular type of treatment; an ambivalent attitude towards the care provided resulting in the need for more information, or the desire to participate in a clinical trial.

Is there a solution? First of all, the phenomenon needs to be studied, and the motives and expectations of the local population explored. This would provide a wonderful opportunity not only for examining patients' and families' motives, but also to investigate the health services offered. A lack of communication between health care providers, a delay in diagnosis (especially at the point of primary care), or simply the unavailability of resources (actual or perceived) may contribute to the need for a second opinion. In cases of the latter, these could be easily rectified by better utilisation of our material resources. On the other hand, if the major motivations are intrinsic (or social), then the solution may lie in sustained and concrete efforts aimed at enhancing public awareness and confidence-building through a process of education and information dissemination. The ultimate

winners should and would be the patients and society at large.

In conclusion, seeking a second opinion amongst cancer patients in Oman poses certain challenges for the health of our patients and provides the health care profession with opportunities to study the problem and to aim for practical solutions. First of all, it must be recognised that seeking a second opinion is not only justified, but also desirable in many situations. Oncologists themselves should support patients in their efforts to obtain an opinion. However, seeking a patient-initiated second opinion abroad, especially in the case of cancer management, may have an adverse effect on the outcome of the disease, both because of the delay it causes in diagnosis, and because of the chance of receiving sub-optimal treatment or advice elsewhere. In order to overcome the challenge, there is an urgent need to study patients' or their decision makers' motives and expectations. Meanwhile, it may help Omani patients diagnosed with cancer and their families, who are seeking a cure wherever it may be found, to know that the World Health Organization (WHO) has ranked Oman as the most efficient 'health care system in the world in terms of outcomes'.<sup>7</sup> Furthermore, patients should be advised that second opinions can be easily and quickly sought at little or no cost through fax, email, and telemedicine from places in Oman or abroad that are widely perceived to be centres of academic and clinical excellence. This will avoid the need for cancer sufferers to seek opinions from more profit-oriented health care centres which may not have the necessary expertise to provide the best advice.

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