An Insight about Management of Influenza virus

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Abstract

Influenza manifests with the abrupt onset of symptoms following an incubation period of 1 to 2 days. Mainly, these symptoms are systemic and consist of fever sensation, true chills, headache, severe myalgia, malaise, and anorexia. Mostly headache, myalgia, and fever determine the severity of the disease if they are more prominent. Most of the influenza cases are diagnosed by their clinical manifestations and there is no need for laboratory tests except in certain circumstances the diagnosis of flu needs laboratory confirmation using available tests such as nucleic acid tests (e.g., polymerase chain reaction (PCR) or rapid diagnosis kits or rarely virus isolation by culture methods. Amantadine was the first antiviral drug used in the treatment of influenza. It is effective against influenza A. This drug inhibits viral replication by blocking the A/M2 proton channel specific to influenza A virus. Neuraminidase inhibitors are now first line treatment for both influenza A and B worldwide. They competitively inhibit neuraminidase on the surface of influenza A and B. They act by preventing cleavage of sialic acid residues on budding newly formed virus particles thus preventing release of new virus particles from infected host cells. With a pandemic of a novel strain of influenza in 2009 new anti-influenza agents were approved for use initiating a new phase in the field of influenza treatment. The biggest feature of these new drugs is that a single intravenous dose or inhalation is sufficient to achieve efficacy. The challenge is how best to prescribe antibiotics and other agents to complement the use of these drugs. Recent recommendation for the management of influenza also provides the clinical indications for favipiravir (trade name: Avigan). Favipiravir exhibits a forceful antiviral effect owing to its inhibition of viral replication. More attention goes to this drug because of reports of its indication for the treatment of Ebola hemorrhagic fever and SARS-

CoV-2 which is caused by an RNA virus as well. As a result of its side effects such as hyperuricemia, strict adherence to its clinical indication on prescribtion shoyld be taken in consideration

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Introduction

Influenza manifests with the abrupt onset of symptoms following an incubation period of 1 to 2 days. Mainly, these symptoms are systemic and consist of fever sensation, true chills, headache, severe myalgia, malaise, and anorexia. Mostly headache, myalgia, and fever determine the severity of the disease if they are more prominent (1).

The patient has high grade fever and, on the second, and third days, the fever decreases and diminishes gradually. In the beginning of the course of the disease the patient's face is plethoric with watery and red eyes. A convalescent period of some weeks may occur with dry cough and malaise are the main complaints of the patient (1).

Myalgia is prominent in the calf muscle (especially in children) and the paravertebral and back even all muscles may be involved. These symptoms are mainly associated by the manifestations of respiratory tract illnesses such as dry cough, nasal discharge, and sore throat. The illness can range from afebrile respiratory illnesses similar to the common cold to diseases in which systemic signs and symptoms predominate with relatively little respiratory tract infection symptoms (2).

Cough is the most frequent respiratory symptom and associated with sub-sternal discomfort or burning. Illness in older adults and in immune-compromised can mainly be less dramatic because of a limited cytokine response. However, initial mild symptoms can progress to severe lower respiratory disease in these patients. The presentation can include fever, laziness and confusion without the characteristic respiratory complaints. Presentation in children can include febrile seizures but other prominent systemic complaints may not be present (3).

The major complication of influenza is pneumonia commonly in high-risk individuals. Primary pneumonia may occur as an extension of the acute influenza illness or secondary pneumonia may occur as a mixed viral and bacterial infection after a gap of a few days (3).

Primary influenza viral pneumonia occurs following the typical course of influenza with a rapid progression of fever, dyspnea, cough, cyanosis, and difficult breathing. It happens mostly among individuals with cardiovascular or underlying pulmonary diseases such as asthma. Physical examination indicates bilateral lung involvement and imaging findings in the lungs constitute reticular or reticulo-nodular opacities with or without superimposed consolidation. Radiographs may show focal areas of infiltration (5).

The incidence of secondary bacterial pneumonia ranged from 2% to 18% during the influenza pandemic in 1957. A threefold rise in the incidence of secondary *Staphylococcus aureus* pneumonia during the influenza pandemic of 1968 compared to a non-epidemic period of pneumonia etiologies was noticed **(4).**

Recently community acquired methicillin resistant Staphylococcus aureus (MRSA) and Streptococcus pneumonia are the most common causes of secondary bacterial pneumonia. The patient has a classic influenza disease followed by a convalescent period lasting maximally 2 weeks. The recurrence of the symptoms and findings of new consolidations in chest imaging can be found in patients. So biphasic pattern of signs and symptoms in influenza labeled patients should be considered as secondary superimposed bacterial pneumonia **(4).**

Commonly used pneumonia severity assessment tools such as the CURB65 (confusion-blood urea nitrogen-respiratory rate-blood pressure-Age 65 or older) scoring system or the Pneumonia Severity Index are of limited use in indicating patient hospitalization due to primary influenza pneumonia as they are not validated during an influenza pandemic **(5).**

Careful history taking and examination, determination of pregnancy or hypotension, and early identification of young patients with decreased oxygen saturation, respiratory rate >25 per minute, and concomitant diarrhea are critical for admission decision-making **(1).**

High resolution computed tomography (CT) shows multifocal peribronchovascular or subpleural consolidation with or without ground glass opacities. Severe cases progress rapidly to acute respiratory distress syndrome and multilobar alveolar infiltrations. These patients usually present with progressive dyspnea and severe hypoxemia two to five days after the onset of typical influenza symptoms. Hypoxemia increases rapidly and causes respiratory failure requiring intubation and mechanical ventilation, maybe after only one day of hospitalization **(6)**

Beside its respiratory effects the virus can affect other body systems such as the musculoskeletal, cardiac, and neurologic systems. Myocarditis and pericarditis constitute unusual but significant complications of seasonal or pandemic influenza. Significant myositis and rhabdomyolysis have rarely been reported with seasonal or pandemic flues. Mild myositis and myoglobinuria with tender leg or back muscles can mainly be seen in children as well as in adults accompanied by symptoms of painful walking or standing **(6)**

Other complications of influenza disease are Guillain–Barré syndrome, encephalitis, acute liver failure, and the Reye syndrome which may occur following influenza A infection especially in children with prolonged administration of aspirin in the previous 3 weeks **(6)**

Laboratory diagnosis:

Most of the influenza cases are diagnosed by their clinical manifestations and there is no need for laboratory tests except in certain circumstances the diagnosis of flu needs laboratory

confirmation using available tests such as nucleic acid tests (e.g., polymerase chain reaction (PCR) or rapid diagnosis kits or rarely virus isolation by culture methods **(1)**.

Specific diagnostic tests are essential for cases that needs management especially those with a severe critical illness requiring hospitalization, high risk groups, subtyping purposes, public health responses and surveillance efforts **(7)**.

The specimen submitted for testing is usually a nasopharyngeal swab, a nasal wash or a combined throat and nasal swab. As the sensitivity correlates with viral load, samples obtained within 3 days of symptom onset are favored **(7)**.

As influenza like illness can be caused by many viruses the gold standard laboratory tests used for influenza reverse transcription PCR (RT-PCR) and viral culture **(3)**.

Nucleic acid amplification assays including RT-PCR and loop isothermal amplification are highly sensitive and specific molecular test, rapid, can be incorporated into multiplex assays and can be used in subtyping. The nucleic acid amplification tests are clearly superior to virus culture in both sensitivity and specifity, as it can detect nonviable virus in samples, and speed in the context of clinical management **(8).**

The quality of the sample is important as irregularities in delivering can lead to degradation and false-negative results. The site sampled can also affect the sensitivity of the assay: nasopharyngeal swabs are preferred to throat swabs for detection of the virus during upper respiratory infection **(8).**

Viral culture can diagnose influenza with a high sensitivity and specificity. It is critical for detailed characterization and isolation of novel viruses, surveillance of sensitivity to antiviral drugs and monitoring of antigenic drift **(3)**.

It is a matter of time waste as it requires 3-10 days to get the results which is not accepted especially in severe illness and must be performed at public health laboratories. The length of the test can be reduced if shell vial cultures are used which detect virus positive cells within twenty-four to seventy-two hours by immunostaining before the occurrence of cytopathic effect **(3)**.

Rapid influenza diagnostic tests (RIDTs) provides point of care (POC) diagnosis that detect influenza viral antigens and screen patients with suspected influenza easily, provide results within 15 minutes, can be done in outpatient clinic and are cheap **(8).**

Rapid tests have low to moderate sensitivity and high specificity. These tests are not capable to subtype influenza A such as H1N1 and H3N2**(8).**

To overcome this limitation, a rapid molecular assay (based on nucleic acid amplification) has been developed and gets FDA approval in 2008 with results referenced to those of RT-PCR except in samples with low viral loads **(8).**

Depending on rapid influenza molecular diagnostic testing can result in better outcomes for patients and reduce the number of resources required for patients care in the emergency room (9).

Serological screening can be used to support clinical diagnosis of infection, herd immunity profiling and monitoring of vaccine compliance. Moreover, it is essential for seroprevalence based epidemiological studies (10).

Serological methods include hemagglutination inhibition (HI) assays, which measure antibody titers by inhibition of the agglutination of erythrocytes as well as enzyme-linked immunosorbent assay (ELISA) and virus neutralization (VN) assay that assess the presence of neutralizing antibodies (10).

Serology is not recommended for clinical decision making because timely results will not be available to inform clinical management. Serology requires obtaining paired acute and convalescent sera performed at specialized public health reference laboratories and results based on a single serum specimen are not interpretable (9).

The Infectious Disease Society of America (IDSA) guidelines recommend molecular influenza assays for testing respiratory specimens from all hospitalized patients with suspected influenza beside commercially available Food and Drug Administration (FDA) approved POC tests (9).

In Egypt, diagnosis is made by collecting samples of the oropharyngeal and nasopharyngeal mucosa taken during the first four days of illness. Samples can be processed for viral isolation, antigen detection or nucleic acid amplification. Suspected influenza cases are considered confirmed if the test sample test is positive by PCR or if the virus isolated from nasopharyngeal swab (11).

Treatment of Influenza virus:

Drugs Used for Influenza Treatment and Prophylaxis:

Amantadine:

Amantadine was the first antiviral drug used in the treatment of influenza. It is effective against influenza A. This drug inhibits viral replication by blocking the A/M2 proton channel specific to influenza A virus (12).

Naturally occurring point mutations in the transmembrane domain, which occur rapidly resulted in new amantadine resistant strains of influenza A (12).

Amantadine is a dose dependent drug with two active forms: amantadine hydrochloride for oral use and amantadine sulfate for oral and intravenous use. The first is used as antiviral treatment. In general, amantadine is well tolerated, but due to the risk of impaired excretion in the case of renal failure, it is recommended to start treatment with the lowest doses and doses adjusted enough for creatinine clearance (12).

The effectiveness of amantadine antiviral treatment is estimated to be a fifty percent reduction in the duration of symptoms if therapy is started in the first forty eight hours of infection with amantadine sensitive influenza A virus Due to upcoming global resistance, amantadine has not been recommended for the treatment of influenza since 2006 **(12).**

The primary adverse effects of amantadine may include orthostatic hypotension, syncope, peripheral edema, dizziness, delusions, hallucinations, falls, xerostomia, constipation and livedo **(13).**

Serious adverse effects include neuroleptic malignant syndrome, psychosis, suicidal ideation, and CNS depression. Doctors should caution patients against activities that require physical and mental alertness, such as driving and avoid combination with other CNS depressing agents, such as alcohol. Caution with usage and dosage adjustments may be necessary for those with heart disease, seizure disorder, hepatic impairment, and renal impairment **(13).**

Neuraminidase inhibitor:

Neuraminidase inhibitors are now first line treatment for both influenza A and B worldwide. They competitively inhibit neuraminidase on the surface of influenza A and B. They act by preventing cleavage of sialic acid residues on budding newly formed virus particles thus preventing release of new virus particles from infected host cells **(14).**

The neuraminidase inhibitors if administrated within 36 hours of infection have been shown to diminish the duration of illness by thirty percent as well as reduction in illness severity by forty percent and if given within twenty four hours of symptom onset even greater reductions in the duration of illness attributable to influenza (approximately forty four% reduction) have been noticed **(14).**

Secondary complications, such as otitis media, sinusitis and pneumonia were greatly diminished with the use of neuraminidase inhibitors **(14).**

When used as a chemoprophylaxis (before or shortly after exposure) neuraminidase inhibitors can decrease the incidence of infection by approximately 70–90% **(14).**

In the UK, oseltamivir (Tamiflu®), (oral agent: typically, first line for influenza A and B treatment) and zanamivir (Relenza®) (inhaled and also available as an aqueous solution which can be administered intravenously or via nebuliser) are licensed for the treatment of influenza A and B and also for prophylaxis **(14).**

Oral oseltamivir (Tamiflu) remains the antiviral drug of choice for the management of illness caused by influenza virus infections and is the only drug approved for treatment of hospitalized children **(15).**

Peramivir (a single-dose intravenous infusion) was licensed in the UK in 2018 but has not been marketed/launched (it is used in the USA, Japan and South Korea). Laninamivir (an inhaled neuraminidase inhibitor) is licensed for use in Japan **(14).**

Resistance develops much less in comparison with the adamantadine. In the NA gene of the H1N1 viruses a range of amino acid mutations are recognized to confer reduced inhibition by NA inhibitors Among these, two well characterized mutations are the H275Y mutation which results in viruses with highly reduced inhibition by oseltamivir and the I223R mutation which results in reduced inhibition by both oseltamivir and zanamivir. For these reasons and to optimize their use antiviral stewardship initiatives are necessary. These initiatives should target various sectors and levels of the medication prescription chain including the healthcare system, prescriber and patient education, prescription practices, patient monitoring and feedback, communication and diagnostics **(16).**

Novel antiviral drugs in Influenza:

With a pandemic of a novel strain of influenza in 2009 new anti-influenza agents were approved for use initiating a new phase in the field of influenza treatment. The biggest feature of these new drugs is that a single intravenous dose or inhalation is sufficient to achieve efficacy. The challenge is how best to prescribe antibiotics and other agents to complement the use of these drugs **(17).**

Recent recommendation for the management of influenza also provides the clinical indications for favipiravir (trade name: Avigan). Favipiravir exhibits a forceful antiviral effect owing to its inhibition of viral replication. More attention goes to this drug because of reports of its indication for the treatment of Ebola hemorrhagic fever and SARS-CoV-2 which is caused by an RNA virus as well. As a result of its side effects such as hyperuricemia, strict adherence to its clinical indication on prescribtion shoyld be taken in consideration **(17).**

The Japanese government and Taiwanese Centers for Disease Control (CDCs) decided to stockpile favipiravir for the people as a countermeasure for severe influenza **(17).**

In 2018 baloxavir marboxil (trade name: Xofluza), an anti-influenza agent with a new mechanism is also an important issue. It inhibits the endonuclease activity of the polymerase acidic (PA) protein found in influenza virus to ultimately inhibit virus replication As the emergence of low sensitive viruses has been a problem, its overwhelming antiviral activity has been demonstrated **(18).**

Alternative drugs:

Due to the limitations in the available therapeutic options for the treatment of influenza virus infections, additional treatment options with a different mechanism of action have been applied for use. A handful of monoclonal antibodies (mAbs) against influenza virus proteins are

currently in the early phases of evaluation for human infection control. These mAbs target the external portions (ectodomain) of the M2 protein (M2e) **(19).**

The M2e is a target for influenza vaccines and therapeutic antibodies because of the extremely conserved nature of the amino acid sequences of its domains among isolates from influenza A viruses subtypes **(19).**

Large amounts of broadly protective HA stalk- or M2e-specific IgG antibodies need to be administered parenterally to obtain a clinical benefit. Most likely, such huge amounts are required because less than 1% of a biological normally reaches the lung lumen, where the antibody could neutralize the virus and eliminate infected cells **(20).**

Pulmonary delivery of anti-influenza antibodies could reduce the required dose and perhaps result in a more pronounced clinical benefit **(20).**

Several broadly reactive human monoclonal antibodies directed against N1 and N2 NAs have been discovered recently **(20).**

These monoclonal antibodies were protective in H1N1, H5N1 and H3N2 mouse challenge models. Such broadly NA-binding and preferentially NA inhibitory antibodies could be developed as stand-alone therapeutics or combined with broadly protective HA-binding antibodies **(20).**

Many studies have reported that corticosteroid therapy adversely influences influenza illness. During the 2009 influenza pandemic 37% to 55% of the patients admitted to ICUs in Europe received corticosteroids as part of their treatment. However many observational suggested that corticosteroid therapy for influenza complications was associated with increased mortality **(20).**

Influenza viral infection is often complicated by bacterial pneumonia particularly in cases where the patient is elderly. Aggressive concomitant use of antibiotics should be prescribed in addition to antiviral drugs. Selection of appropriate antibiotics that target potential causative bacteria that are detected usually is preferable **(21).**

In spite of special care regards the antimicrobial activities against resistant *Streptococcus pneumoniae* and other bacteria, penicillin are considered the first line agents of antimicrobial treatment with a relative high dose recommended **(21).**

Prevention Strategies of Influenza virus:

Vaccination:

The main strategy for the prevention of influenza and its severe consequences is the annual vaccination targeting seasonal influenza. As influenza virus is characterized by frequent mutations affecting the function of immune system against new strains, new vaccines are produced annually to cope against circulating viruses. The selection of influenza antigens included in the vaccines is

based on the global surveillance of circulating influenza viruses and the dissemination of new strains of the influenza virus around the world (22).

Three types of influenza vaccines are now licensed for use worldwide: inactivated vaccines, live attenuated vaccines, and recombinant HA vaccines. All of them include dose of the seasonal influenza vaccine: influenza A (H3N2), A (H1N1), and influenza B strains or their HA proteins. These vaccines are called trivalent vaccines (22).

The seasonal vaccine for use in the 2010 Southern hemisphere influenza season contains anA/California/7/2009 (H1N1) like virus, an A/Perth/16/2009 (H3N2)-like virus and a B/Brisbane/60/2008-like virus (23).

Quadrivalent vaccines contain components of both influenza B strains were established as the trivalent one deficient the corresponding strain of influenza B (23).

Both vaccine platforms also met the requirements of the Committee for Human Medicinal Products for influenza vaccines. Currently both vaccine platforms are used annually with different recommendations for different groups of populations (23).

The WHO ensures that vaccination is especially essential for individuals at higher risk of serious influenza complications with the prioritization of pregnant ladies followed by children aged between 6 and 59 months, elderly, individuals with specific underlying chronic medical conditions and finally individuals at high risk (health care personel) (24).

In 2010, the United States Advisory Committee on Immunization Practices (ACIP) expanded the recommendation for annual influenza vaccination to enroll all individuals 6 months of age and older individuals who did not have contraindications without any priority (24).

The most commonly used of the three vaccine platforms are inactivated vaccines, which include whole virus, split-virus and subunit vaccines. Immunization with inactivated vaccines can start at 6–12 months of age with the need for an annual booster dose (23).

Live attenuated vaccines cause a weakened infection and can stimulate both immunoglobulin (Ig)A in the upper respiratory tract and IgG in tissues and serum. Live viruses have to replicate to induce immunity and their rate of replication is affected by the recency of a previous infection with a related strain in the host (23).

These vaccines simulate natural infection and usually induce vigorous immunity. However they are not recommended for children younger than two years old, pregnant females, or immune-compromised people due to the state of their immune Systems (23).

Recombinant HA vaccines depend on a protein expression system using insect cells and baculovirus. They have a similar mode of action to inactivated vaccines but are faster to manufacture and more scalable in production (23).

A single dose (0.5 cc) of an influenza vaccine should be injected to adults annually preferably by October in the northern hemisphere and May in the southern hemisphere. Children aged between 6 months and 8 years require 2 doses of influenza vaccine (with at least 4 weeks apart) during their 1st season of vaccination to achieve adequate immune response **(25).**

The efficacy of the vaccine is weighted by how much the seasonal influenza vaccine can prevent influenza virus infections in the given population during an influenza season. The documentation of the antigenic drift from the vaccine strain in the most of considered isolates gave attention that vaccine effectiveness might be suboptimal especially high-risk groups **(26)**

The Centers for Disease Control and Prevention (CDC) in the United States of America had an estimation of 23% of vaccine effectiveness for the northern hemisphere 2014–15 seasonal influenza vaccine due to a mismatch in the circulating viruses and vaccine contained viruses **(26)**

Chemoprophylaxis Strategy:

Available antiviral drugs play an important role for patients who have not been immunized or who are irresponsive to vaccines. Oseltamivir and zanamivir are the recommended drugs for the prevention of influenza based on their established efficacy and low rates of resistance in comparison to amantadines **(1).**

It should be emphasized on selecting a plan of antiviral chemoprophylaxis some limitations such as preventing complications in patients at high risk and reducing the risk of initiating antiviral drug resistance should be put in consideration. Some indications for this approach, as follows:

1) During influenza outbreaks in long term care centers in the elderly regardless of previous influenza vaccinations.

2) In unvaccinated individuals at high risk of influenza complications who have been in contact with infected individual within the preceding 48 hours.

3) Vaccinated persons at high risk of influenza complications who have had close contact with an infected individual within the preceding 48 hours when there is a mismatch between the vaccine and circulating viruses in a given year.

4) The United State (ACIP) recommends that antiviral chemoprophylaxis be considered in pregnant women and in women up to 2 weeks postpartum who have close contact with suspected or confirmed influenza A infected individuals. Zanamivir may be the drug of choice for prophylaxis due to its limited systemic absorption **(27).**

Prevention of zoonotic infection transmission from animal reservoirs to human:

The main risk factor for the emergence of viral reverse zoonotic diseases is the virus host range in an environment of human activities that facilitate viral zoonoses, which can be managed using a One Health approach. It estimates that the best way to mitigate the impact of reverse zoonosis of IAV infections is vaccinating humans and susceptible farmed and pet animals **(28).**

One Health, as defined by the One Health High Level Expert Panel (OHHLEP), includes collaborative concepts for experts and agencies working in human health, animal health, plant health, and ecosystems health to tackle complex issues that threaten the health and human-beings, animals, and ecosystems, recognizing the close link and interdependence of the health of all living species and ecosystems **(28).**

Good animal health management, biosecurity and hygiene practices are important on farms. However, efforts would also need to be exerted at other points of human animal connections, such as live animal markets, fairs, exhibits, and petting zoos **(29).**

Consequently, eradication programs should also include increased biosecurity, extensive surveillance, and a comprehensive education program for the public. Ongoing collaborations between organizations such as the World Organization for Animal Health (OIE), Food and Agriculture Organization of the United Nations (FAO) and the WHO are required to share expertiences in the animal health sector with the public health sector **(29).**

Infection prevention and control strategies of Influenza virus:

In addition to standard precautions, droplet precautions are necessary when a patient infected with a pathogen, such as influenza, is within three to six feet of the patient. Infections are transmitted through air droplets by coughing, sneezing, talking, and close contact with an infected patient's breathing. Droplets are about 30 to 50 micrometers in size. Patients should be isolated individualized rooms, if possible. Aerosol generating procedures such as bronchoscope, sputum induction, tracheal intubation or extubation, autopsy, and cardiopulmonary resuscitation have a risk of transmission of influenza through aerosols. So airborne precaution should be followed **(30).**

The WHO does not recommend travel restrictions related to pandemic influenza (H1N1) 2009 except for persons who are already diseased. However, the CDC recommends that travelers at increased risk of complications may need to postpone travelling. Based on mathematical modeling there is no reason to delay international travel to reduce the spread of infection **(31).**

Both the WHO and the CDC recommend social distancing from patients and basic hygienic measures to help prevent the spread of infection. Neither agency indicated vaccination for travel except for at least some groups of travelers **(31).**

Influenza in Egypt:

History and Epidemiology:

Seasonal infection of humans occurs commonly by H1N1 and H3N2 **(32).**

The first reported epidemic of human influenza in Egypt occurred sometime between 1650 BC – 1550 BC and resulted in thousands of deaths **(33).**

In the 19th century (1889–1892) two influenza epidemics were reported in Egypt. Seasonal influenza in human occurred in some regions in Egypt in 1952–1953, 1963–1965, 1966–1972, 1973–1974 **(33).**

In 2001–2002 H1N2 subtype was reported in over 41 countries in 4 continents including Egypt **(34).**

H3N2 was reported in Egypt in 2002–2007 with nonspecific details are available. The 2009 pH1N1 was first detected in Egypt in June and became the predominant influenza virus in human in the middle of November of the same year. To December 2010, less than 17,000 infected cases, among them 281 confirmed related fatalities were officially reported **(33).**

Zoonotic transmission of Influenza A virus in Egypt:

The only available report on transmission of Influenza A virus from animals other than birds in Egypt was from pigs in 1979–1980. As twenty out of two hundreds human sera (10%) reacted positive against the swine H1N1 virus **(35).**

Egypt, after Indonesia, is the country worst affected by H5N1 and the country with the highest reported human infections since 2009.over 90% of cases were linked to close contact with backyard birds. In 2014, the fatality rate of H5N1 in Egypt was 36% (63/173) compared to 59% (386/650) global fatality rate **(33).**

In 2004, H10N7 was isolated from 2 one-year old infants with fever and cough. Epidemiological investigations indicated that a father of one of them was a poultry vendor. The origin of the human infection was not unknown **(33).**

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